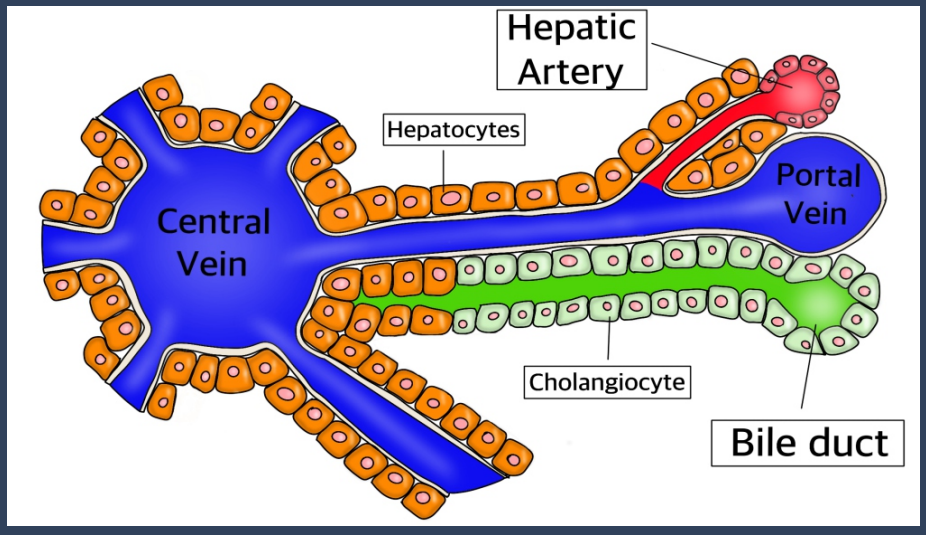
JILTI

The Official Journal of the Inonu Liver Transplantation Institute

Journal of Inonu Liver Transplantation Institute



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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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Journal of Inonu Liver Transplantation Institute

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.

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- 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;
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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.

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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.

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

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

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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;
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- 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.

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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.

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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.

JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

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CONTENTS

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JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

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J Inonu Liver Transpl Inst 2023;1(3):81–89

Review

Non-Alcoholic Fatty Liver and Periodontal Disease: Is there a Relationship? A Contemporary Review

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Abstract

Periodontal disease is a common inflammatory disease and is known to be related to other systemic diseases. This bidirectional relation between periodontal disease and other disease processes has led to outstanding research recently. In addition, periodontal disease has been advocated to exacerbate metabolic disorders including non-alcoholic fatty liver disease (NAFLD). In this traditional review, general characteristics of periodontal diseases, general characteristics of NAFLD/ Nonalcoholic steatohepatitis (NASH), and their causality were discussed for treatment providers. The collected data significantly corroborate a greater incidence of periodontal disease among individuals with NAFLD in comparison to the general healthy population. Healthcare professionals need to be aware of the association between NAFLD and periodontal disease thus patient management effectiveness can be enhanced.

Keywords: Periodontal diseases, non-alcoholic fatty liver disease, causality, steatohepatitis

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The Non-alcoholic fatty liver disease (NAFLD) it's a term used for several conditions caused by fat accumulation in the liver. One-fourth of the world's population is faced with this clinical situation. It is mostly seen in South America and the Middle East, and least in Africa.[1] Nevertheless, when considering its prevalence within the community, this malady emerges as one of the most frequently encountered liver diseases, demonstrating a notable association with elevated rates of liver-related mortality and morbidity.[2] By definition, NAFLD is a clinical picture in which insulin resistance, histopathological more than 5% steatosis of hepatocytes, or dense fat fractions by radiographic techniques are detected. This clinical situation is examined under two main headings non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (steatosis coexists with liver-cell injury and inflammation).[3, 4] NAFLD has 4 stages for developing; simple fatty liver (steatosis), non-alcoholic steatohepatitis (NASH), fibrosis and cirrhosis, and may liver cancer.[5] In advanced phases, this may result in liver transplantation. The patients with NAFLD show similar histological damage to alcoholic liver disease.[6] Oxidative and inflammatory responses play crucial roles in the shared pathogenesis of both NAFLD and nonalcoholic NASH.[7] Lifestyle is an important point for developing this disease.

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For an exact definition of these diseases, NAFLD/NASH necessitates the exclusion of viral, autoimmune genetic, and so on liver diseases (alcohol abuse, hepatotoxic medications, etc.).[8]

The definitive diagnosis of NASH is established through a liver biopsy. The accurate characterization of NAFLD necessitates the consideration of daily alcohol consumption, which should be less than 30 grams for men and less than 20 grams for women. Physical examination often reveals no discernible local or systemic signs. However, manifestations such as fatigue, right upper quadrant pain, or dullness may be evident. Conversely, mild to moderate hepatomegaly may be observed.[9] NAFLD generally shows insulin resistance as an important clinical finding. In addition to this, obesity, hyperglycemia, low HDL (high-density lipoprotein), cholesterol, hypertension, and hypertriglyceridemia levels are symptoms that occur in metabolic syndrome.[6]

NAFLD patients often present with increased liver function tests. It is detected incidentally. Although hepatic transaminases are normal in two-thirds of patients, transaminase levels are increased in one-third of patients, typically higher alanine aminotransferase (ALT). However, for diagnosis, conditions that cause toxic hepatitis such as viral hepatitis that increases hepatic transferases, autoimmune hepatitis, alcoholic hepatitis, Wilson's disease, hemochromatosis, alpha-1 antitrypsin deficiency, corticosteroids, antiretroviral therapy, and tamoxifen use must be excluded.[10]

Periodontal diseases may be important in the formation and development of some systemic diseases/conditions. A robust correlation is probable to exist between periodontal diseases and systemic diseases/conditions. Periodontal diseases are often affiliated with cardiovascular problems adverse pregnancy outcomes diabetes, respiratory system disorders, metabolic syndrome, osteoporosis, rheumatoid arthritis, neurological disorders gastrointestinal disorders, urological (e.g., prostatitis), and renal diseases.[11-13]

This review aims to delineate the features of periodontal disease and impairments associated with NAFLD/NASH for healthcare providers and explore potential interrelationships between them. Relevant citations were identified through searches on PubMed, Google Scholar, and the Cochrane Library databases, encompassing references in the English language from January 2010 through December 2023. The search strategy incorporated Medical Subject Headings (MeSH) for the following: Fatty liver-periodontal, hepatic steatosis-periodontal, liver steatosis-periodontal, and non-alcoholic steatohepatitis-periodontal. Only English papers were included. After determining the articles the current review was performed.

Periodontal Problems and the General Systemic Health

It is always useful to examine the health status of the periodontal tissues since periodontal diseases can be a sign of systemic diseases. Bleeding on probing, erythema, edema, attachment, and bone loss were not observed in the clinically healthy periodontium.[14] Periodontal disease formation be related to microbial dental plaque (sub-, supragingival plaque), host-related local factors (periodontal pocket, existing restorations, tooth position-anatomy), and general factors (host response, genetic and systemic conditions)] and environmental factors (relates to smoking, drugs, etc.) as presented by "Lang et al".[15] Periodontal diseases are examined under two main topics. In the case of gingivitis, only the gingival tissue is affected. Gingivitis may persist for years without progression to periodontitis, especially when inflammatory events are prevented.[16] Periodontitis, is an inflammatory clinical disease in which in addition to the gingiva the periodontal ligament and alveolar bone are affected resulting in their destruction.[17] The main clinical findings of periodontitis are characterized by attachment loss, alveolar bone destruction (radiographic), periodontal pocket formation, and bleeding on probing.[18] Microorganisms in dental plaque are an essential component in the progression of periodontitis.[19] Although bacteria are required for periodontal disease, a susceptible host is also required for the disease to occur.[20]

Periodontal disease is common in the community. In the evaluations, it was stated that periodontal disease is not present in 9.3% of adults, 9.7% of elderly individuals, and 21.2% of adolescents.[21] In research conducted in Saudi Arabia, it was shown that 100% of individuals aged 18-40 years had plaque-related gingivitis. A systematic review and meta-regression analysis (which was conducted between 1990-2010) showed that 11.2% of the world population had advanced periodontitis.[22] Again, in the studies performed on individuals over the age of 65 in the USA, differences were observed in cases in different states, and the incidence of periodontitis was found between 62.1% and 74.2% in some states. Severe periodontitis cases were observed in ~12% nationwide.[23]

Oral hygiene plays a major role in the progression of the periodontal disease. In the treatment of periodontal disease, considerations include factors such as oral hygiene and dental care. Periodontal therapy can be managed through effective mechanical periodontal therapy, including surgical procedures, and regular professional care, especially the control of biofilm and modifiable risk factors.[24] There are surgical and non-surgical periodontal treatments available based on the etiologic factor. The efficacy

of antimicrobials, probiotics, and host modulation-based treatments in the treatment of periodontal diseases are currently periodontal treatment research topics.[25]

The primary etiological factor in periodontal diseases is microbial dental plaque. Generally, periodontal disease is caused by a dysbiosis of the commensal oral microbiota and the activation of the host's immune mechanisms.[26] In individuals, especially with advanced periodontitis bleeding lesions show an ulcerated and inflamed pocket epithelium.[27] Inflamed and ulcerated pocket epithelium is considered to be a place where microorganisms enter the body.[28] It was stated that proinflammatory cytokines produced in periodontal tissues may increase in pathogenic amounts and affect the systemic state by participating in the circulation.[29]

The concept of focal infection should be mentioned hereby. Mechanisms that may cause focal infection were described by Thoden van Velzen et al.[30] These mechanisms encompass metastatic infection resulting from transient bacteremia, metastatic inflammation induced by immunological injury, and metastatic damage initiated by microbial toxins.

Periodontal Problems and Non-Alcoholic Fatty Liver Disease

The systemic effect of the oral cavity through the different pathways mentioned above is remarkable. Periodontal diseases share common risk factors and systemic diseases/conditions with NAFLD/NASH. Possible associations with several disorders of NAFLD have been explored in a review. Within this framework, NAFLD has been associated with a spectrum of health conditions, encompassing chronic kidney diseases, colorectal cancer, psychological dysfunction, gastroesophageal reflux disease, obstructive sleep apnea syndrome, hypothyroidism, adult growth hormone deficiency, polycystic ovarian syndrome, urolithiasis, and periodontitis.[31] Clinical studies revealed some collected works that investigate the possible relationship between fatty liver, periodontitis, and periapical (endodontic) lesions.[32-34]

There is enough data to suggest that periodontitis is associated with a higher incidence of NAFLD. Treatment and prevention of periodontal disease may be important in reducing the risk of NAFLD.[35] Data on the treatment of periodontitis in studies has shown promising results for obesity, diabetes, and NASH, but the data are not yet at the desired level for humans.[36] Further to that it was stated that the presence of hepatobiliary pathology in substance abusers and smokers enhances the risk of periodontal disease.[37] A meta-analysis revealed a noteworthy association between periodontitis and NAFLD. However, this relationship lost its significance when various metabolic parameters were taken into account. Predisposing factors for NAFLD were metabolic conditions, not periodontitis itself.[38]

Liver abnormalities with metabolic syndrome (MetS) were together examined with periodontal parameters [Probing pocket depth (PPD), clinic attachment loss (CAL), and oral hygiene index (oral hygiene index-simplified)] in a study. Deep pocket depth and the coexistence of elevated alanine aminotransferase (ALT) and MetS in males with low alcohol consumption were shown.[39]

G-glutamyl transferase (GGT) and ALT levels were increased in persons with periodontal pockets. Additionally, Morita et al. observed a significant correlation between periodontal pockets and GGT. It was underlined that periodontal disease is associated with liver function, independently of alcohol-using habits.[40] It was shown that elevated ALT is a potential risk hallmark for periodontitis in healthy young men. Fruta et al. suggested that to prevent cases of periodontitis, liver abnormalities should be monitored and better understood, particularly in the young adult population.[41] Nevertheless, the previously reported associations between periodontitis and NAFLD, particularly concerning ALT levels, were not replicated in Hispanic/Latin men and women. The inconsistency in findings was attributed to the utilization of transaminases to characterize NAFLD in the study.[42]

Periodontitis was associated with incident liver disease independent of different factors in a study with additional adjustments for alcohol use, smoking, metabolic risk, serum GGT, dental care habits, lifestyle, and socioeconomic status. Periodontal disease can be considered a modifiable risk factor for chronic liver disease.[43] It was suggested that chronic periodontitis may play a role in hepatic damage and liver steatosis, and its mechanism may be related to the oral-intestinal-liver axis and SCD1/AMPK signaling activation in the liver.[44] In a study group aged 35-64 years the presence of liver fibrosis and periodontitis were addressed. After a follow-up period, the development of liver fibrosis was %10.6. The periodontal parameter CAL was significantly associated with liver fibrosis and obesity.[45] Representative data of the Korean population showed that "Fatty Liver Index (FLI)" was higher and related to a higher prevalence of periodontitis which was diagnosed on the "Community Periodontal Index (CPI)".[46] In a study conducted on a Korean population periodontal status was determined by the CPI. NAFLD was detected with FLI and hepatic steatosis index (HSI). A statistical evaluation was made between the existing pocket depths and indices in individuals. In conclusion, periodontal pocket was found to be independently associated with NAFLD.[47] Results shown in another study have suggested that hepatic steatosis is related to periodontitis

in Japanese women.[48] In a US nominal study population, it was seen that NAFLD was significantly relevant with tooth loss, moderate-severe forms of periodontitis, and after adjusting some socio-demographic factors with dental caries.[49] Akinkugbe et al have reported that periodontitis showed a higher probability of NAFLD.[50] They have proposed that elevated serum C-reactive protein (CRP) levels and weighted CRP genetic scores exhibit a positive association with an increased prevalence odds of coinciding NAFLD and periodontitis. A Chinese study evaluated databases for periodontal and liver diseases. As a result, it revealed a positive association with NAFLD, increased transaminase level, liver cirrhosis, and liver cancer with tooth loss and periodontal disease.[51] A population-based survey and a patient-based study were performed to examine biopsy-proved NAFLD and underwent periodontal examination. Appreciations revealed an important association between periodontitis and NAFLD. Even when controlling diabetes, a connection was observed with significant liver fibrosis.[52]

Ultrasound diagnosed the NAFLD patient group, and periodontal parameters like PPD and number of teeth were recorded. The results have shown a possible risk factor for PPD≥4 mm. This was statistically significant.[53] Ultrasonic liver examination was performed in individuals in whom periodontitis was detected by the percentage, clinic attachment level, and pocket depth. Incidence of NAFLD, relative to participants without clinic attachment level ≥3mm, <30% of sites slightly increased and ≥30% of sites moderately increased in affected participants.[54] On the other hand, optical coherence tomography findings between the three study groups revealed that NAFLD could be an aggravating factor for inflammation in periodontal disease.[55]

A noteworthy correlation was established between elevated CAL and obesity among participants. However, such associations were not evident among non-obese individuals. The heightened CAL was conjectured to be linked with an elevated probability of liver fibrosis in obese adults with NAFLD.[45]

In an evaluation, it was seen that teeth loss in men was associated with NAFLD. The same relationship was not observed in female patients.[56] A similar tendency was shown in a distinctive study.[57]

A study revealed an inverse relationship between tooth brushing frequency (≥2 per day) and NAFLD. Oral hygiene habits as a modifiable factor can be considered as a method that can be applied to reduce the risk for NAFLD, especially in smokers and diabetic patients.[58] The findings from a particular study indicate that an exercise regimen may improve the oral environment of patients with NAFLD. This improvement is attributed to an increased diversity of oral microflora and a reduction in LPS-producing periodontal bacteria, along with their functional capacity.[59]

Aggregatibacter actinomycetemcomitans (Aa) administrations to mice reveal changes in gut microbiota. It's shown that Aa effects in NAFLD mice downregulation of fatty acid degradation and upregulation of fatty acid biosynthesis.[60] In additional review and studies the periodontopathogen *Porphyromonas gingivalis* (Pg) was considered as an extra risk factor for the development/progression of NAFLD/NASH.[61, 62] It's shown in a study that Pg has the potential to change the gut microbiota and initiate steatosis and metabolic disease.[63] Again Pg endotoxin-induced periodontal infection is believed to play an important role in the progression of NASH.[64] In a case report, a morbidly obese patient with cirrhosis due to NASH who died of sepsis due to a dental infection of Pg was reported. Oral care, including oral assessment and eradication of Pg may be important in patients with NAFLD.[65] A cross-sectional study suggested an involvement between Pg infection and alanine ALT levels in women.[66] Intravenous injection of sonicated Pg creates glucose tolerance, insulin resistance, and fatty liver in mice fed high-fat diets.[67] A new-dated trial has investigated current periodontal treatment results within the possible changes in endotoxin levels and treat Pg infection to show the improvement status in NAFLD patients.[68] Pg odontogenic infection exacerbates the disease of NASH by hepatic stellate cells (HSCs) activation by way of transforming growth factor-β1 (TGF-β1) and Galectin-3 [(Gal-3); a protein of the galectin family] boost the production from HSCs and hepatocytes.[69] Similarly, it was introduced that Pg derived lipopolysaccharide (LPS) may play an important role in the lipid accumulation in HepG2 cells (immortal cell line derived from the liver tissue) via activating nuclear factor kappa B (NF-κB) and c-Jun N-terminal kinase (JNK) pathways in the advancement of NAFLD.[70] Late elimination of Pg by intracellular lipid accumulation can cause long-term inflammation and cellular damage, suggesting that it's one of the risk coefficients for the progression and development of NAFLD.[71]

In a study, systemically and locally, macrolide (Azithromycin) was applied to the "high-fat-diet NASH" mouse model with Pg odontogenic infection, and markers such as TNFα, Il-1β, galectin-3, and phosphorylated Smad2 (pSmad2; key signaling molecule of TGF-β1), and the number of hepatic crown-like structures (hCLSs) were examined. The results showed that NASH progression was inhibited by Pg elimination.[72] It has been shown in the literature that consumed periodontopathic bacteria exacerbate NAFLD pathology due to dysregulation of gene expression and subsequent efflux of intestinal bacteria and/or bacterial products, possibly by inducing intestinal dysbiosis.[73]

Systemic effects of induced periodontitis caused by the increase in oxidative stress and lipid peroxidation were shown with differentiation in hepatic tissues (such as microvesicular steatosis). Findings show an association between ligature-induced periodontitis and liver disease with reduced pericytes in rats.[74] In a rat model one or two ligatures were enforced to generate periodontitis. The two models did not show differences from each other. Both were eligible to produce a similar amount of fatty liver.[75] It was shown that in ligature ligature-induced periodontitis rat model a high-fat diet provokes liver disease.[76]

Dos Santos Carvalho et al show that periodontitis-induced microvesicular steatosis in rats is reversible after ligature removal. It has been hypothesized that this may be related to the increase in oxidative stress and lipid peroxidation in the liver.[77]

A rabbit model that introduces an LPS-induced model of periodontal disease evaluates the effect of periodontal interventions on atherosclerosis, hyperlipidemia, and NASH. Poor periodontal health had the potential accompany to dyslipidemia and induce NAFLD progression.[78] The application of LPS and proteases to periodontal pockets has been demonstrated to induce a lesion reminiscent of NAFLD. In rats with periodontitis, elevated serum LPS levels led to increased levels of tumor necrosis factor-alpha (TNF-α) and 8-hydroxydeoxyguanosine (8-OHdG) in the liver.[79] Similarly, the localized application of LPS and proteases to the gingival sulcus has been shown to escalate liver deterioration and induce oxidative damage in rats subjected to a high-cholesterol diet.[80] Ahn et al. showed a streamed result with Pg on fatty liver disease in obese mice through the upregulation CD36-PPARγ pathway.[81]

Pg-LPS injected via the oral mucosa in the maxilla has been reported to induce the onset of NASH in the liver of rats fed a high-fat diet.[82] In general prevention and/or elimination of Pg infections with dental treatment may have a beneficial effect on NASH. This may happen through upregulation of the P.g.-LPS-TLR2 pathway and activation of inflammasomes.[83] The findings suggest that oral Pg administration directly causes NAFLD in mice, which causes dysregulated microbial metabolism and may be due to ferroptosis of liver cells, which also occurs through Th17/Treg imbalance. Therefore, optimizing periodontal health may be a new treatment strategy for the prevention of NAFLD.[84] Pg can cause ferroptosis and inflammation in hepatocytes, further aggravating liver damage. The mechanism of ferroptosis in hepatocytes is thought to depend on the NF-κB signaling pathway.[85] Pg. infected hepatocytes exhibited heightened cell proliferation and migration, coupled with reduced doxorubicin-mediated apoptosis. These alterations were impeded upon the knockdown of Integrin β1. The hypothesis posits that Pg.-related odontogenic infection could potentially advance the development of neoplastic nodules through integrin signaling and tumor necrosis factor-alpha (TNF-α)-induced oxidative DNA damage.[86] Tomofuji et al indicate in a rat model that tooth brushing decreased serum LPS concentrations and suppressed liver injury.[87]

Periodontitis probably affects the progression of NAFLD by increasing insulin resistance and hepatic inflammation in sphingolipid metabolism. Data also showed that acid sphingomyelinase with imipramine improved NAFLD by reducing insulin resistance and hepatic inflammation.[88]

One study found that food restriction in rats reduced oral damage as well as alveolar bone changes hepatic, blood, and associated with ligature-induced periodontitis.[89] In a ligature-induced periodontitis model study, bromelain was administrated to rats. It was shown that bromelain improved the steatosis scores. On the other hand, bromelain reduces oral inflammatory parameters (Gingival bleeding index, mobility, alveoli bone height, and probing depth) and some compounds like malondialdehyde, myeloperoxidase, and blood parameters.[90]

Conclusion

This review provides a comprehensive overview of the interplay between NAFLD and periodontal disease, suggesting the potential exacerbation of NAFLD by periodontal disease. The gathered data crucially confirm a higher prevalence of periodontal disease in NAFLD patients compared to the healthy population. The review underscores the significance of oral health in systemic well-being, particularly for individuals with NAFLD. Clinicians should be mindful of the relationship between NAFLD and periodontal disease, and dentists, equipped with this knowledge, can optimize periodontal treatment. Further research is imperative to elucidate the connection between periodontal disease and NAFLD, aiming to establish the overarching concept that oral health plays a pivotal role in systemic health, especially in individuals with NAFLD.

Disclosures

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Original Research

Large Hypovascular Hepatocellular Carcinoma: Non-Classical Type

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Abstract

Objectives: As the frequency of surveillance protocols increases in patients with chronic liver disease, the rate of detection of radiologically atypical lesions such as hypovascular hepatocellular carcinoma (HCC) increases. There is no concensus regarding the frequency, size, differentiation, relationship with biomarkers, treatment and survival of hypovascular tumors.

To examine the clinical characteristics and clinical outcomes of resected hypovascular HCCs with known pathology.

Methods: Data of 62 HCC patients treated with resection between January 2009 and December 2022 were retrospectively examined. Twenty-five of these patients had radiological hypovascular HCC and 37 had hypervascular HCC. Patient characteristics (age, gender, blood count and liver function tests, and AFP), tumor variables (differentiation grade, portal vein invasion, Milan Status), and outcome variables (survival, recurrence) were compared between the two radiological groups.

Results: Comparison of quantitative variables between the 2 groups, showed that only GGT values were significantly higher in the hypovascular HCC group. There were no significant differences between the qualitative variables. Overall survival at 1, 3, and 5-years was 79.2%, 55.9%, and 51.2% in the hypovascular group and 83.1%, 61.8%, and 32.4% in the hypervascular group, respectively (p=0.517). Disease-free survival at 1, 3, and 5 years was 58.5%, 46% and 46% in the hypovascular group and 60.3%, 36.5% and 18.2% in the hypervascular group, respectively (p=0.572).

Conclusion: Unlike smaller HCCs, large-dimension hypovascular HCC cases were found to be biologically similar to hypervascular HCC cases. This result may be due to the larger size of the hypovascular tumors. There is a need for studies on bigger series of large size hypovascular HCC cases.

Keywords: Cirrhosis, Hypovascular HCC, Resection

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Hypovascular HCCs have been reported to be smaller in size and show better differentiation[1,2] than typical hypervascular HCCs (HCC with arterial phase hyperenhancement and portal hepatic phase hypoenhancement - washout - findings).[3] The incidence of hypovascular HCCs is 18% in HCCs less than 3 cm in diameter and 24% in HCCs less than 2 cm in diameter.[4]

Questions regarding the frequency, size, differentiation, relationship with biomarkers, treatment and survival of hypovascular tumors have still not found a consensus answer. Additionally, large-dimention hypovascular HCC has not been a subject studied so far Therefore, in this study, we report our experience of 25 cases treated with resection and thus having pathological confirmation of HCC and who were diagnosed radiologically as hypovascular HCC.

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Methods

The data of 62 HCC patients treated with resection at our institute between January 2009 and December 2022 were retrospectively examined. Twenty-five of these patients had radiological hypovascular HCC and 37 had hypervascular HCC. None of them had a liver transplant. The data were accessed from hospital records. Patient characteristics (age, gender, neutrophil lymphocyte, platelet, AST, ALT, total bilirubin, GGT, AFP), tumor variables (differentiation grade, portal vein invasion, Milan Status), and outcome variables (survival, recurrence) were compared between two groups.

Radiologically suspicious hypovascular tumors were defined as hypovascular or isovascular tumors that did not show hyperenhancement compared with surrounding liver parenchyma in the arterial phase (Histopathologically, the characteristics of these tumors were that fibrous capsule formation was less common).

Before resection, extrahepatic metastases were excluded by CT/MRI or PET CT. For major resections, the ICG retention test was used and R15 was required to be below 15%. After resection, all patients were followed up with thorax and abdomen CT scans as well as blood tests every 3 months for the first 2 years and then every 6 months.

Statistical Analysis

All analyzes were performed using IBM SPSS Statistics 25.0 for Windows (New York; USA). Qualitative data from the variables included in the study were summarized as numbers (percentages). The suitability of quantitative data for normal distribution was evaluated with the Shapiro-Wilk test. Since quantitative data did not show a normal distribution, they were summarized with median values (95 % CI lower and upper limits). In statistical analyses, Mann-Whitney U test, Pearson chi-square test, Yates corrected chi-square test and Fisher's exact chi-square test were used where appropriate. In the statistical analysis applied, $p<0.05$ value was considered statistically significant.

Results

Of the 62 patients examined in this study, 25 were in the hypovascular (atypical) HCC group and 37 were in the hypervascular (typical) HCC group. The median age of the entire group was 60 (23-82) years, the median age in the atypical group was 58 (23-67) years, and in the typical HCC group it was 61 (27-82) years (p=0.156). While the male/female ratio was 37/5 in the atypical group, the male/female ratio was 25/6 in the typical group (p=0.731). Quantitative data of all patients, including age, neutrophil, lymphocyte, platelet, AST, ALT, bilirubin, GGT, MELD-NA and maximum tumor size, are shown in Table 1. Qualitative variables related to groups, gender, Milan status, pathological features, and PV invasion status of the entire cohort are shown in Table 2.

When quantitative variables were compared between the 2 groups, only GGT values were found to be significantly higher in the atypical group (Table 3). When the qualitative variables were compared between the 2 groups, there were no significant differences (Table 4).

The overall survival of the entire group was 755 (24-4589) days, 1252 days in the atypical group and 685 days in the typical group (p=0.062). Disease free survival was 574 days in the entire cohort, 383 (133-775) days in the atypical group and 205 (554-1093) days in the typical group (p=0.265). Overall survival (OS) for 1, 3, and 5-year was 79.2%, 55.9%, and 51.2% in the atypical group, respectively

Table 1. Qualitative variables for entire cohort

Parameters	Subparameters	Number	Percentage
Groups	Normal	37	60.7
	Suspicious	24	39.3
Gender	Female	11	18.0
	Male	50	82.0
Milan Status	Within	23	37.7
	Beyond	38	62.3
Pathological features	Well	15	24.6
	Moderately	30	49.2
	Poorly	16	26.2
PV Invasion	No	45	73.8
	Yes	16	26.2
Recurrence	No	25	41
	Yes	36	59
Outcome	Alive	32	52.5
	Dead	29	47.5

Table 2. Quantitative variables for entire cohort

Parameters	Median	IQR	95 % CI Lower	95 % Upper
Age	60	19	23	82
MELD.Na	8	4	6	21
Preop.AFP	32	481	1	30000
Preop.Neutrophil	3.8	2	1.1	17
Preop.Lymphocyte	1.8	1	0.6	6.5
Preop.Platelets	221	149	60	702
Preop.AST	34	31	10	140
Preop.ALT	30	31	12	178
Preop.TBilirubin	0.6	0	0.2	9.3
Preop.GGT	48	80	10	366
MTS	60	77	5	200
OS (days)	711	1441	24	4589
DFS (days)	574	990	24	3204

Table 3. Comparison of normal and suspicious groups in terms of qualitative variables

Parameters	Subparameters	Hypervascular		Hypovascular		p
		n	%	n	%	
Gender	Female	6	16.2	5	20.8	0.447
	Male	31	83.8	19	79.2	
Milan Status	Within	14	37.8	9	37.5	1.000
	Beyond	23	62.2	15	62.5	
Pathological features	Well	8	21.6	7	29.2	0.631
	Moderately	20	54.1	10	41.7	
	Poorly	9	24.3	7	29.2	
PV Invasion	No	30	81.1	15	62.5	0.189
	Yes	7	18.9	9	37.5	
Recurrence	No	15	40.5	10	41.7	1.000
	Yes	22	59.5	14	58.3	
Outcome	Alive	19	51.4	13	54.2	1.000
	Dead	18	48.6	11	45.8	

Table 4. Comparison of normal and suspicious groups in terms of quantitative variables

Parameters	Hypervascular			Hypovascular			p
	Median	95 % CI (Lower- Upper)		Median	95 % CI (Lower- Upper)		
Age	61	57	65	58	48	62	0.134
MELD.Na	8	8.00	10	8	7	11	0.636
Preop.AFP	22	11	250	84	4	400	0.724
Preop.Neutrophil	3.7	3.4	4.2	3.85	3.4	4.5	0.579
Preop.Lymphocyte	1.6	1.5	1.9	1.85	1.5	2.1	0.344
Preop.Platelets	205	184	247	255	194	296	0.535
Preop.AST	37	29	48	33	27	46	0.550
Preop.ALT	30	25	41	30	23	36	0.442
Preop.TBilirubin	.70	.70	1.10	.60	.60	1.0	0.206
Preop.GGT	43	38	57	86	47	128	0.039
MTS	60	55	85	98	45	140	0.154
OS	685	554	1093	1050	562	2194	0.118
DFS	685	554	1093	344	133	775	0.044

Mann-Whitney U test was used for comparison.

and 83.1%, 61.8%, and 32.4% in the typical group, respectively (p=0.517) (Fig. 1). Diseases-free survival (DFS) for 1, 3, and 5 year was 58.5%, 46% and 46% in the atypical group and 60.3%, 36.5% and 18.2% in the typical group, respectively (p=0.572), (Fig. 2).

Discussion

The incidence of hypovascular HCCs increases as surveillance programs increase in chronic liver patients. However, after such surveillance programs, mostly small-sized hypovascular HCCs are detected which is their purpose. Publications on hypovascular HCCs have always focused on small tumors.[4,5] In this study, the hypovascular types of resected large-dimension HCCs were reviewed and their characteristics were described.

Hypovascular HCCs are generally thought to have good biological behavior, with small tumor size (<3 cm), being well-differentiated tumors, and with low AFP levels.[4,6] The median maximum tumor size of the 25 hypovascular HCC cases in this study was 9.75 cm. Whether large-dimension hypovascular HCC cases have the same characteristics as small-dimension tumors is unexplored, to our knowledge.

We found that hypovascular HCC cases studied here had higher GGT values than hypervascular HCC cases. It has

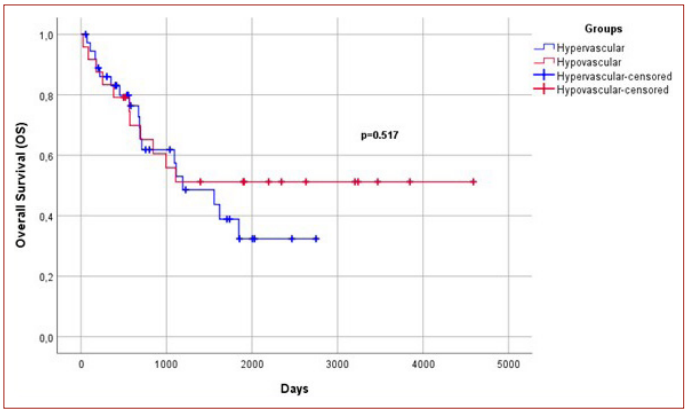

Figure 1. Comparison of overall survival (OS) of both group with Kaplan- Meier estimate.

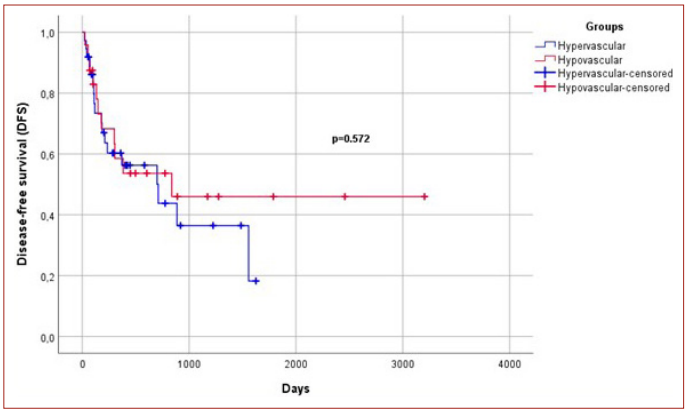

Figure 2. Comparison of disease-free survival (DFS) of both group with Kaplan- Meier estimate.

been shown in many studies how prognostically important high GGT levels have in large HCCs.[7,8] This result may indicate that large hypovascular HCC will have a similar survival rates with hyper vascular HCC.

Gammaglutamyl transpeptidase (GGT), has been thought to play a role in HCC growth and development and in resistance to drug toxicity,[9] being a cell surface enzyme that is involved in glutathione metabolism and is thus important in the maintenance of cellular cysteine levels. Furthermore, it is also considered to be a clinically useful prognostic factor, especially in HCC patients with low levels of AFP.

In the current study, hypovascular HCC cases were observed to have higher AFP values and a higher percentage of portal venous tumor invasion than hypervascular HCC cases. However, they had similar overall and disease-free survival. Although these differences between the two groups are not statistically significant, they may be due to the larger size of the hypovascular tumors as well as the small size of the case series. There is thus a need for studies on a larger series examining large hypovascular HCC cases.

Disclosures

Ethics Committee Approval: Since this study was prepared as a retrospective archive data review, ethics committee approval was not obtained.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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

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Original Research

Is Obesity a Risk Factor for Recurrence in HCC Patients Who Undergo Liver Transplantation?

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Abstract

Objectives: It is known that obesity is associated with increased complications and early recurrence after cancer surgery. This may also be the case in patients with hepatocellular carcinoma (HCC) who treated with liver transplantation (LT).

Methods: This retrospective observational study aimed to investigate the potential impact of pre-transplant body mass index (BMI) on tumor recurrence and disease-free survival (DFS) in patients who underwent LT for HCC. The study analyzed data from 423 HCC patients who underwent LT at the Inonu University Liver Transplant Institute between 2006 and 2023.

Results: The median age of the 423 patients included in the study was 56 years (range: 18-72), with 367 (86.8%) of them being male. The median BMI was 26 kg/m^2 (range: 16.4-46.9). The recurrence rates were 24.3% in the non-obese group, 18.3% in the overweight group, and 16.7% in the obese group (p=0.239). The mean DFS durations were 8.4 years ± 0.6 in the non-obese group, 8.7 years ± 0.5 in the overweight group, and 9.7 years ± 0.9 in the obese group (p>0.05).

Conclusion: This study suggests that obesity should not be considered a predictive factor for HCC recurrence when selecting candidates for liver transplantation.

Keywords: Body mass index, Hepatic malignancy, Hepatectomy, Recurrence, Survival

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Liver cancers are the sixth most common cancer worldwide, with approximately 1,000,000 annually new cases, and it ranks as the third most common cause of cancer-related deaths, accounting for 856,000 deaths.[1] Factors that increase the likelihood of developing hepatocellular carcinoma (HCC) comprise infections like hepatitis B virus (HBV) and hepatitis C virus (HCV), excessive alcohol consumption, obesity, and exposure to environmental toxins.[2] A common feature among these risk factors is their potential to cause liver injury and cirrhosis.

While treatment options for HCC vary depending on tumor progression and the functional status of the liver, LT has emerged as a curative treatment option as it can eliminate both malignancy and cirrhosis. Despite the development of criteria for transplant candidates, such as the Milan and Expanded Malatya criteria, tumor recurrence still occurs at rates of 15% to 20%.[3,4] Therefore, it is essential to identify risk factors for recurrence. Age, male gender, high alpha-fetoprotein levels, elevated gamma-glutamyl transferase (GGT) levels, portal vein invasion, and high-grade atypia

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in tumor cells have been identified as risk factors that increase the likelihood of recurrence following curative treatments.[5-9]

Obesity is known to be associated with various malignancies, including HCC.[10] Additionally, the accumulation of visceral fat tissue has been identified as a risk factor for both the development and recurrence of HCC.[11] However, the pathophysiology of the relationship between obesity and HCC recurrence remains unclear. It has been suggested that conditions associated with obesity, such as chronic inflammation and insulin resistance, may contribute to tumor growth. Elevated levels of vascular endothelial growth factor (VEGF) linked to obesity can enhance tumor angiogenesis and, consequently, increase recurrence. Moreover, obesity-related adiponectin and leptin have been reported to stimulate HCC proliferation, migration, and invasion.[12] The impact of obesity on post-LT outcomes for HCC is still a subject of debate.

The primary objective of this study was to examine the impacts of pre-transplant body mass index (BMI), a crucial determinant of obesity, on tumor recurrence and survival of individuals who underwent LT for HCC.

Methods

Patient Selection and Study Design

In this observational study, data from 517 patients those who have received living donor liver transplantation (LT) due to HCC between March 2006 and May 2023 at the Inonu University Liver Transplant Institute were retrospectively analyzed. The inclusion criterion for the study was the presence of HCC confirmed by explant pathology. After excluding 10 patients under 18 years of age and 84 patients with a follow-up duration of less than 90 days, data from the remaining 423 patients were analyzed. The treatment decisions for the patients were made during multidisciplinary meetings involving transplant surgeons, gastroenterologists, interventional radiologists, medical oncologists, nuclear medicine specialists, and radiation oncologists. Compliance with in Milan, Malatya, and Expanded Malatya criteria was primarily considered when deciding on transplantation. Post-transplant follow-up and immunosuppressive treatments were administered as previously described in another study.[13-18] Demographic information such as age, gender, and BMI was collected for the patients. Preoperative etiology, Child-Pugh groups, Model for End-Stage Liver Disease (MELD) scores (pre-transplant last labMELD, not exceptional MELD for HCC), bilirubin, creatinine, alpha-fetoprotein levels, recurrence status, and survival times were recorded. Tumor characteristics based on explant pathology, including tumor size, number of nodules, vascular invasion, and differentiation levels, were also noted. The patients were divided into three groups according to their BMI: <25 kg/m^2 (Group A), 25-30 kg/m^2 (Group B), and >30 kg/m^2 (Group C), based on the World Health Organization (WHO) classification.[13]

Statistical Analysis

The study assessed the normal distribution of numerical data using the Kolmogorov-Smirnov test. Continuous numerical variables were then subjected to analysis through the Mann Whitney U test, and the resulting data included median, minimum, and maximum values. Categorical variables underwent Chi-square analysis, with frequency and percentage values provided. Univariate logistic regression analysis was conducted for each variable, specifically those exhibiting statistically significant p-values within similar variables. To examine disease-free survival across different BMI groups (group A < 25 kg/m^2, 25 kg/m^2 ≤ group B < 30 kg/m^2, and group C ≥ 30 kg/m^2), the Kaplan-Meier method and log-rank test were utilized. Statistically significant results were defined as p-values less than 0.05. These analyses were carried out using SPSS version 23.

Results

The median age of the 423 patients included in the study was 56 years (range: 18-72), with 367 (86.8%) of them being male. The median BMI was 26 kg/m^2 (range: 16.4-46.9). The most common etiology of HCC was viral (80.4%) (Table 1).

The distribution of data among the three groups is presented in Table 2. Of the 423 patients, 169 were non-obese (BMI < 25 kg/m^2), 186 were overweight (30 kg/m^2 > BMI ≥ 25 kg/m^2), and 78 were obese (BMI ≥ 30 kg/m^2). The obese group tended to have a higher proportion of female patients.

Data on age, gender, Child-Pugh and MELD scores, albumin, bilirubin, serum creatinine, and alpha-fetoprotein levels can be found in Table 2. No notable distinctions were observed with in three groups regarding Child and MELD scores, albumin, bilirubin, serum creatinine, and alpha-fetoprotein values (p>0.05).

The data obtained from explant pathology, including the largest tumor diameter, vascular invasion, and tumor differentiation parameters, showed no significant differences among the groups (p>0.05). However, A disparity existed in the quantity of nodules among the groups (p=0.036). Additionally, while the largest tumor diameter was not statistically significant, it tended to be lower in the group with BMI >30 kg/m^2. Additionally, the likelihood of vascular inva-

Table 1. Demographic data and preoperative classification of HCC

Variables	Median (min-max)	n (%)
Age, years	56 (18-72)	
Gender		
Female		56 (13.2)
Male		367 (86.8)
Child		
A		147 (34.8)
B		185 (43.7)
C		91 (21.5)
MELD	13 (5-41)	
Etiology		
Viral		340 (80.4)
Cryptogenic		57 (13.5)
Ethanol		7 (1.7)
Budd Chiari		10 (2.4)
Metabolic		1 (0.2)
Another		8 (1.9)
Milan Cr.		
In		211 (49.9)
Out		212 (50.1)
Malatya Cr.		
In		263 (62.2)
Out		160 (37.8)
Exp. Malatya Cr.		
In		285 (67.4)
Out		138 (32.6)
BMI, kg/m^2	26 (16.4-46.9)	

HCC: Hepatocelluler Cancer; MELD: Model for End Stage Liver Disease; Child: Child-Pugh Classification; BMI: Body Mass Index.

sion was observed to be greater in patients with lower BMI. The recurrence rates were 24.3% in the non-obese group, 18.3% in the overweight group, and 16.7% in the obese group (p=0.239).

The mean DFS durations were 8.4 years ± 0.6 (95% CI: 7.2-9.5) in the non-obese group, 8.7 years ± 0.5 (95% CI: 7.6-9.8) in the overweight group, and 9.7 years ± 0.9 (95% CI: 7.8-11.5) in the obese group (Table 3, Fig. 1) (p>0.05).

Discussion

The impact of preoperative BMI on post-LT HCC recurrence remains a subject of debate. The primary objective of this study was to examine the relationship between preoperative BMI and post-LT HCC recurrence and DFS in individuals who received LT for HCC. The study ultimately found that preoperative BMI did not significantly affect post-LT HCC recurrence and DFS.

While many criteria have been established for LT in HCC patients, recurrence still occurs in 15-25% of patients. In our study, the recurrence rates ranged from 16.7% to 24.3% among the BMI groups, with no significant differences. Siegel et al. reported that 25% of HCC patients who underwent LT were obese, and these patients had a higher rate of tumor recurrence and increased risk of death. They attributed this to higher vascular endothelial growth factor (VEGF) levels induced by adipose tissue.[19] Mathur et al. supported Siegel's findings with their results, suggesting that obesity increased the risk of tumor recurrence. They proposed that obesity promoted a pro-oncogenic state by reducing adiponectin and increasing leptin levels, thereby stimulating HCC proliferation and migration.[11] However, some studies argue that obesity does not have a significant effect on post-transplant outcomes, and high BMI should not be considered a contraindication for LT.[20] In our study, while there was no statistical significance, the group with a BMI >30 kg/m^2 had a lower recurrence rate compared to the other two groups.

We observed that 10-year DFS rates were similar within the categories of individuals who are not obese, those who are overweight, and those who are classified as obese. This finding aligns with studies suggesting that survival in patients with a BMI >30 kg/m^2 is comparable to non-obese groups.[21,22]

In our study, the three groups had comparable tumor characteristics based on explant pathology. While Siegel and colleagues argued that patients with microvascular invasion had a worse prognosis, and BMI >30 kg/m^2 was linked to greater frequency of vascular invasion, our study found no significant differences in tumor size, differentiation, and vascular invasion among the groups. Moreover, although not statistically significant, the obese group had lower rates of poor differentiation, vascular invasion, and low recurrence rate. On the other hand, the most common symptom of patients with HCC is weight loose which is one of a finding of advanced stage tumors, so, we believe that, in low BMI group had more aggressive behavior as in the explant pathology revealed. These findings emphasize the complex and multifaceted nature of the relationship between obesity and HCC recurrence.

Strengths of our study include a large sample size and even distribution of variables among the groups. However, its retrospective nature and the lack of knowledge about the patients' BMI during follow-up can be considered limitations. Overall, our study suggests that further research is needed to demonstrate the effectiveness of obesity on tumor recurrence, especially in patients with HCC.

Table 2. Outcomes of clinicopathological data between groups

Variables	BMI<25kg/m²		25kg/m²≤BMI<30kg/m²		BMI≥30kg/m²		p
	Median (min-max)	n (%)	Median (min-max)	n (%)	Median (min-max)	n (%)	
Age, years	55 (18-71)		56 (23-72)		57.5 (38-72)		0.014
Gender							
Female		15 (9.4)		21 (11.3)		20 (25.6)	0.001
Male		144 (90.6)		165 (88.7)		58 (74.4)	
Child							
A		62 (39)		61 (32.8)		24 (30.8)	0.699
B		65 (40.9)		83 (44.6)		37 (47.4)	
C		32 (20.1)		42 (22.6)		17 (21.8)	
AFP	14.8 (0.2-20179)		11.5 (0.4-10424)		14.6 (1.1-2324)		0.675
MELD	12 (6-41)		12.25 (5-34)		14 (6-26)		0.094
MTD	3.5 (0.1-24)		3 (0.1-24)		2.55 (0-20)		0.061
NOD	2 (1-36)		1 (1-20)		2 (1-21)		0.036
Differentiation							
WELL		62 (39)		79 (42.5)		32 (41)	0.735
INT		66 (41.5)		81 (43.5)		34 (43.6)	
POOR		31 (19.5)		26 (14)		12 (15.4)	
Venous Invasion							
ABSENCE		81 (50.9)		100 (53.8)		46 (59)	0.430
MIKRO		54 (34)		68 (36.6)		22 (28.2)	
MAKRO		24 (15.1)		18 (9.7)		10 (12.8)	
Milan Cr.							
IN		68 (42.8)		101 (54.3)		42 (53.8)	0.076
OUT		91 (57.2)		85 (45.7)		36 (46.2)	
Malatya Cr.							
IN		88 (55.3)		124 (66.7)		51 (65.4)	0.078
OUT		71 (44.7)		62 (33.3)		27 (34.6)	
Eks. Malatya Cr.							
IN		98 (61.6.)		133 (671.5)		54 (69.2)	0.139
OUT		61 (38.4)		53 (28.5)		24 (30.8)	
Etiology							
Viral		129 (81.1)		152 (81.7)		59 (75.6)	0.525
Cyriptogenic		19 (11.9)		24 (12.9)		14 (17.9)	
Ethanol		1 (0.6)		3 (1.6)		3 (3.8)	
Budd Chiari		6 (3.8)		3 (1.6)		1 (1.3)	
Metabolic		1 (0.6)		0 (0)		0 (0)	
Another		3 (1.9)		4 (2.2)		1 (1.3)	
Albumin, g/dL	2.9 (1.5-5.2)		2.95 (1.6-5.2)		2.8 (1.2-4.2)		0.358
Bilirubin, mg/dL	1.73 (0.23-20.7)		1.82 (0.3-44.7)		1.96 (0.32-17.3)		0.648
Creatinine, mg/dL	0.78 (0.5-13.8)		0.8 (0.4-2.8)		0.8 (0.47-1.8)		0.777
Recurrence		39 (24.3)		34 (18.3)		13 (16.7)	0.239
DFS, years	3.34 (0.08-15.08)		2.84 (0.08-14.86)		3.68 (0.33-15.78)		0.323

AFP: Alpha-feto protein; MELD: Model for end stage liver disease; MTD: Maximum tumor diameter; NOD: Number of nodules; DFS: Disease free survival.

Conclusion

The findings of this study align with existing evidence from the literature, indicating that the recipient's BMI at the time of liver transplant does not have a direct influence on the occurrence of HCC recurrence during long-term follow-up, regardless of the patients' condition and the characteristics of their tumors at the time of transplantation. In essence, this study strongly affirms that when choosing candidates

Table 3. Disease free survival of groups

	Mean (SD) DFS (years)	95%CI	p
BMI Status			
Group A	8.382(0.584)	7.237-9.527	0.287
Group B	8.719(0.542)	7.657-9.781	
Group C	9.702(0.943)	7.853-11.551	
Total	9.095(0.39)	8.33-9.86	

DFS: Disease Free Survival; SD: standart deviation; CI: Confidence Interval, p<0.05 was considered statistically significant.

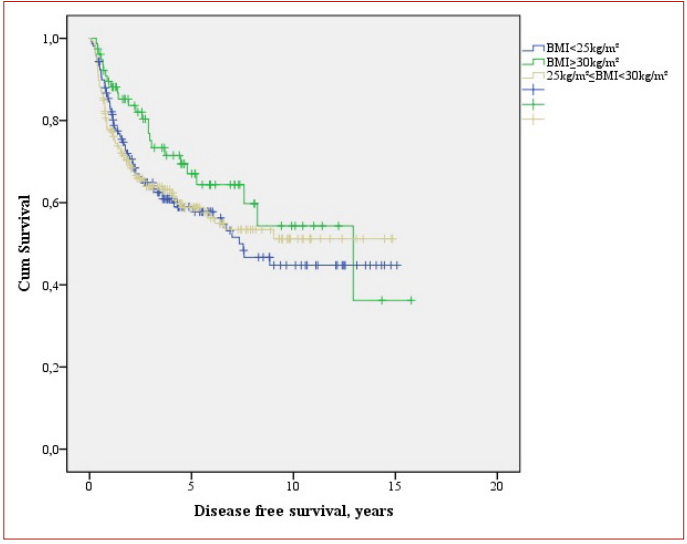

Figure 1. Kaplan-Meier DFS curves after liver transplantation for HCC according to BMI groups. BMI: body mass index.

with HCC for liver transplantation, obesity should not be regarded as a predictive factor for recurrence.

Disclosures

Peer-review: Externally peer-reviewed.

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Original Research

Histopathological Analysis of Gallbladder Specimens Obtained During Living Donor Hepatectomy

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Abstract

Objectives: Cholecystectomy is routinely performed during living donor hepatectomy and subsequently sent for routine histopathological examination. In this report, we reviewed the clinical and histopathological data of the resected gallbladders to give insight about the incidence of occult gallbladder pathologies among healthy adults.

Methods: The medical records of adult living liver donors between December 15th, 2017 and October 15th, 2023 were reviewed. Demographics, gallbladders gross and microscopic pathological data were collected. Male Vs. Female donors clinicopathological data were compared. A p value <0.05 was considered statistically significant.

Results: Two hundred-ninety five donors were reviewed. The median (95 % CI) age was 33 (32-35) years. The male/female ratio was 187 /108. The median (95 % CI) body mass index was 24.8 (24.2-26.0) kg/m2. The blood group were as follows: O (145; 49%), A (95; 32%), B (46; 16%) and AB (9; 3%). Topographically, the resected gallbladders showed a median length of 75 (75-80) mm, median width of 30 (30-35) mm while the median wall thickness was 2.0 (2.0-3.0) mm. The overall incidence of chronic cholecystitis was 41% (122/295) and normal gallbladder structure was found in 166 (56%) cases. No metaplastic or invasive pathologies were detected. Male donors were younger [32 (30-34) vs 34 (32-37); p=0.040], with higher median BMI [26 (25.5-27.1) vs 22.9 (21.6-24.3); p=0.002], with longer gallbladders [80 (80-85) vs 75 (75-80); p=0.002] and with more thick gallbladder wall [2.0 (2.0-3.0) vs 2.0 (2.0-3.0); p=0.034] than females. There was no statistically significant gender difference as regards the incidence of final histopathological diagnoses.

Conclusion: Resected gallbladders during living donor hepatectomy should be routinely sent for histopathological analysis for the detection of occult pathologies among healthy adults.

Keywords: Cholelithiasis, Cholecystitis, Gallbladder, Living donor hepatectomy

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Living donor liver transplantation is predominantly practiced in many regions in the world to overcome the problem of organ shortage and protracted waitlist.[1] Performing a safe donor surgery comes at the outset in all organ transplant centers.[2] Cholecystectomy and clear delineation of the hilar anatomy along with intra-operative cholangiography are integral steps in the donor procedure to ensure safety on both sides.[3] Since the resected gallbladder is being routinely sent for histopathological examination, it has become an interesting subject of research as regard the incidence and prevalence of different gallbladder pathologies in otherwise healthy adults.[4] In this study, we are providing a clinico-pathological review based upon a series of 295 resected gallbladders during living donor surgery.

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Methods

After obtaining the Institutional Review Board (IRB) approval the prospectively collected medical records of all healthy adults liver donors (≥18 years) who underwent partial hepatectomy between December 15th, 2017 and October 10th, 2023 were retrospectively reviewed. The demographics, as well as the topographic, gross and microscopic pathological information of the resected gall bladder were retrieved. Male and female donors were compared in terms of the incidence and prevalence of different gall bladder pathologies. All patients underwent open live donor surgery for harvesting of right hepaic lobe, left lobe or left lateral segment. Gallbladders were resected during the conventional donor surgery and all specimens are send routinely for histopathologic examination.

Study Protocol and Ethics Committee Approval

This study involving human participants was by the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval was obtained from the Inonu University Institutional Review Board (IRB) for Non-Interventional Clinical Research (Approval No: 2023/5337). STROBE (Strengthening the reporting of observational studies in epidemiology) guideline was utilized for considering the checklist related to the current study.

Statistical Analysis

Numerical variables were expressed using median and upper and lower bound of 95 % confidence interval (CI) and compared using t.test or Mann-Whitney U test as appropriate. Categorical variables were expressed as number (percent) and compared using Chi-square test or Fischer-exact test as approprite. P value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 22.0 (IBM SPSS Statistics, Amarok, NY, USA).

Results

Between December 15th, 2017 and October 15th, 2023 295 living donor hepatecotmy procedures were carried out at our transplant institution for living donor liver transplantation. The median (95 % CI) age of the living donors was 33 (32-35) years. The male/female ratio was 187 (36.6%) / 108 (63.4%). The median (95 % CI) height and weight were 164 (162-166) cm and 69 (67-71) kg, respectively. The median (95 % CI) body mass index was 24.8 (24.2-26.0) kg/m2. The blood group of donors were distributed as follows: O (n=145; 49%), A (n=95; 32%), B (n=46; 16%) and AB (n=9; 3%). Regarding the topographic details of the resected gall bladders: the median length measured vertically from the mid-fundus to the stump was 75 (75-80) mm, the median width taken transversely at the widest point on the fundus was 30 (30-35) mm while the median wall thickness at the midbody of gallbladders was 2.0 (2.0-3.0) mm. The incidence of cholelithiasis among our living liver donors was 8.1 % (24/295). The final pathological analyses were as follows: normal gallbladder structure (n=166, 56%), chronic cholecystitis (n=102; 35%), cholesterolosis (n=7; 2.5%) and double pathologies (n=20; 6.5%). Double pathologies included: chronic cholecystitis + cholesterolosis, chronic cholecystitis + gallbladder polyp and chronic cholecystitis + focal lymphangiectasis in 13, 6 and 1 specimens, respectively. So, the collective incidence of chronic cholecystitis was 41% (122/295). Detailed information was given in the Table 1.

Group Comparisons

Male living liver donors were at younger age [32 (30-34) vs 34 (32-37); p=0.040], with higher median BMI [26 (25.5-27.1) vs 22.9 (21.6-24.3); p=0.002], with longer gall bladders [80 (80-85) vs 75 (75-80); p=0.002] and with more thick gallbladder wall [2.0 (2.0-3.0) vs 2.0 (2.0-3.0); p=0.034] than females. There was no statistically significant gender difference as regards the incidence of cholelithiasis or final histopathological diagnoses. Likewise, no statistically significant difference among different blood groups in terms of aforementioned pathologies. Detailed information was given in the Table 2.

Table 1. Assessement of 295 living liver donors

Demographic and Clinicopathological Features	
Age (years)	33 (32-35)
Gender	
Male	187 (36.6)
Female	108 (63.4)
BMI (kg/m^2)	24.8 (24.2-26.0)
Blood Groups (%)	
A	95 (32.2)
B	46 (15.6)
AB	9 (3.1)
O	145 (49.2)
Gallbladder width (mm)	30 (30-35)
Gallbladder length (mm)	75 (75-80)
Gallbladder wall thickness (mm)	2.0 (2.0-3.0)
Cholelithiasis	
Yes	24 (8.1)
No	271 (91.9)
Histopathoical findings (%)	
Normal structure	166 (56.3)
Chronic cholecystitis	102 (34.6)
Cholestrolosis	7 (2.4)
Chronic cholecystitis + Cholesterolosis	13 (4.4)
Chronic cholecystitis + Polyp	6 (2.0)
Chronic cholecystitis + Focal lymphangectasia	1 (0.1)

Table 2. Comparison of male and female living liver donors

Parameter	Female Donors	Male Donors	p
Age (years)	34 (32-37)	32 (30-34)	0.04
BMI (kg/m^2)	22.9 (21.6-24.3)	26.0 (25.5-27.1)	0.002
GB length (mm)	75 (75-80)	80 (80-85)	0.002
GB width (mm)	30 (30-35)	30 (30-35)	0.294
GB wall thickness (mm)	2.0 (2.0-3.0)	2.0 (2.0-3.0)	0.034
Histopathoical findings (%)			0.812
Normal structure	61 (56.5)	105 (56.1)	
Chronic cholecystitis	35 (32.4)	67 (35.8)	
Cholestrolosis	3 (2.8)	4 (2.1)	
Double pathology	9 (8.3)	11 (5.9)	

Discussion

The routine histopathological assessment of gallbladder resected during cholecystectomy for CCC had been adopted in the recent literature for the purpose of detection of various adjoining occult pathologies especially invasive lesions.[5]

Cholecystectomy, being a routine step in living donor hepatectomy for safe delineation of hilar anatomy and subsequent liver resection,[6] has proven to be of no negative impact on the long term as regard donor GIT symptoms or quality of life.[7] Donor hepatectomy with gallbladder preservation had been proposed in previous reports[8] but its application is yet to be a standard of care.

From other perspective, the routinely removed gallbladder during donor hepatectomy surgery provides an endless source of clinical and histopathological insights about the incidence and prevalence of gallbladder pathologies among clinically healthy population.

Like the practice in almost all transplant centers, we send the gallbladder resected from 295 donors for routine histopathological examination. Overall, the prevalence of gallbladder pathology was 46% with the diagnosis of chronic cholecystitis being the most frequently encountered pathology in our donors' gallbladders reaching up to 41%. This incidence is much higher than the first series to address this concern by Akbulut and colleagues[4] who reviewed the gallbladders of 1009 donor and found 27% of them harboring incidental pathologies with the histological findings of chronic cholecystitis found among 19 % of the whole cohort.[4] In another study by Bhatti and colleagues,[9] around of 52 % of donors' gallbladders harbored chronic cholecystitis. The authors concurred with the concept of routine histopathological analysis of the resected gallbladder.[9]

As regard gender difference, male living liver donors in our series were younger and showed higher median BMI than females as well as longer longitudinal axis of their gallbladders. There was no statistically significant gender difference as regard the incidence of cholelithiasis or final histopathological diagnoses. In a larger updated series (n=2493) by Akbulut and colleagues,[10] they found a statistically significant gender difference, with male donors being younger, having lower median BMI and longer mean gallbladder length. Looking into gallbladder wall pathology, they found no gender difference among different pathologies.[10]

Cholesterolosis is a state of accumulation of cholesterol compounds in the gallbladder wall, that had been linked to the occurrence of idiopathic pancreatitis in previous reports. In our series, its incidence was 2.4 % and were all subtle clinically and radiologically before donor surgery.

In our study, no detected metaplastic or invasive pathologies in the resected gallbladder. In their early experience, Akbulut and colleagues. reported three cases with an area of metaplasia in the gallbladder mucosa. Our study has some limitations, being of small sample size and of retrospective nature.

Conclusion

The resected gallbladder from a healthy adult during living donor hepatectomy is an area of ongoing research to explore the incidence and clinical behaviour of subtle gallbladder pathologies. Although unusual pathological findings are rarely seen in young people such as living liver donors, all cholecystectomy specimens should be sent for histopathological examination.

Disclosures

Ethics Committee Approval: Inonu University Institutional Review Board (IRB) for Non-Interventional Clinical Research.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – S.A., S.S.; Design – S.A., AE.; Supervision – S.A.; Materials – A.E., S.A.; Data collection &/or processing – S.A.; Analysis and/or interpretation – S.A., AE.; Literature search – S.A., AE.; Writing – S.A., AE.; Critical review – S.S., S.A.

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Original Research

Can Split Liver Transplantation be a Solution for Organ Shortage in Türkiye?

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Abstract

Objectives: First split liver transplantation (SLT) which was performed by Rudolph Pichlmayr in 1988, a great hope has arisen to reduce organ shortage. Split liver transplantation is a challenging procedure. Increased perioperative complications and allocation of the split organ affect the results. Selection of both a suitable donor and an appropriate recipient is essential to achieve successful results. We aim to review SLT outcomes performed at our center.

Methods: We have performed 3611 liver transplantations between February 2007 and May 2023. During this period 75 split livers were transplanted. We retrospectively analyzed the 75 split liver transplanted patients data and recorded the age, gender, the reason for liver transplantation, and the survivals.

Results: There were 75 patients. The median age was 12 (0-64). The main reason for liver transplantation was fulminant hepatic failure (47 %, n=35) The 5-year overall survival rate before 2016 was 33 % (n=69). After 2016, the 5-year overall survival rate was 67 % (n=6).

Conclusion: The splittable deceased organ number in our country is extremely low, so SLT will not be a solution for organ shortage in Türkiye. We believe that successful outcomes can only be achieved by performing an in situ split in the same center.

Keywords: Split, insitu, liver transplantation

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After the first split liver transplantation (SLT) which was performed by Rudolph Pichlmayr in 1988, great hope has arisen to reduce organ shortage in the transplant community.[1] He has split a single cadaveric donor graft for a child and an adult. Same year Henry Bismuth performed full right and left SLTs for two adults.[2] Data published since this date have shown that SLT increases biliary and vascular complications compared to whole liver transplantation (WLT) but does not change overall graft and patient survival.[3] Although these efforts have the aim to increase the number of grafts needed to reduce waiting list mortality, it is a challenging procedure. Probably a good whole graft is converted into two marginal grafts which requires technical experience. Increased perioperative complications, the allocation, and the logistics of the split organ also affect the results. Selection of both a suitable donor and an appropriate recipient is essential to achieve successful results. We aim to review SLT outcomes performed at our center.

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Methods

Patient Selection

We have performed 3611 liver transplantations between February 2007 and May 2023. There were 500 deceased donor liver transplantations in the same time frame. During this period 75 split livers were transplanted.

Study Design

We retrospectively analyzed the 75 split liver transplanted patients data and recorded the age, gender, the reason for liver transplantation, and the survivals.

Statistical Analysis

Continuous (quantitative) variables were expressed as Median (range), and Mean±SD. Categorical (qualitative) variables were expressed as numbers and percentages. Kaplan-Meier survival estimate was used to determine the overall survival and disease-free survival of the patients.

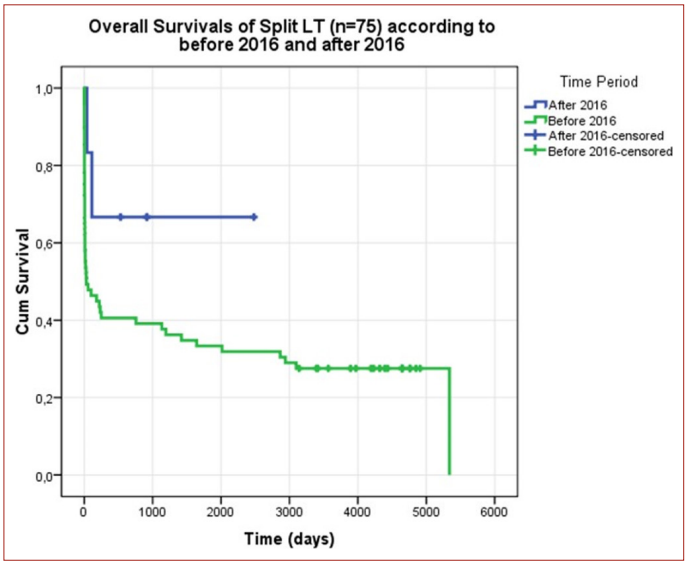

Figure 1. Overall survival of split LT.

Table 1. Demographic features and reason for liver transplantations

Parameters	n (%)
Age distribution, years (median)	0-64 (12)
Male/Female	36/39
Fulminant hepatic failure	35 (47)
Cryptogenic cirrhosis	13 (17)
Viral hepatitis	9 (12)
HCC	4 (0.5)
Biliary atresia	3 (0.4)
Alcoholic cirrhosis	2 (0.2)
Other reasons	9 (12)

The follow-up period was defined as the interval between LT until the date of the last visit to the outpatient department for living patients or until the date of death of the patient. Statistical tests were considered significant when the corresponding p-value was less than 5%. All statistical analyses are performed using Statistical Package for Social Sciences software version 25 (SPSS v25) (IBM, USA).

Results

There were 75 patients, 39 of them were female and the median age was 12 (0-64). The main reason for liver transplantation was fulminant hepatic failure (47 %, n=35). There were 44 pediatric and 31 adult patients. We lost 53 patients (30 pediatric and 23 adult) during the study period. Hospital mortality (< 90 days) was 50,6%. The 5-year overall survival rate before 2016 was 33 % (n=69). After 2016, the 5-year overall survival rate was 67 % (n=6) (Fig. 1).

Discussion

SLT can either be performed in situ or ex-situ (Fig. 2). Since Rogiers X. et al first described in situ liver spitting, published data has shown that the in situ splitting technique has some advantages over the ex-situ procedure.[4] These advantages are shorter cold ischemia time, better exposure of the transsection line, bleeding control, and prevention of bile leakage from the cut surface during the in situ splitting

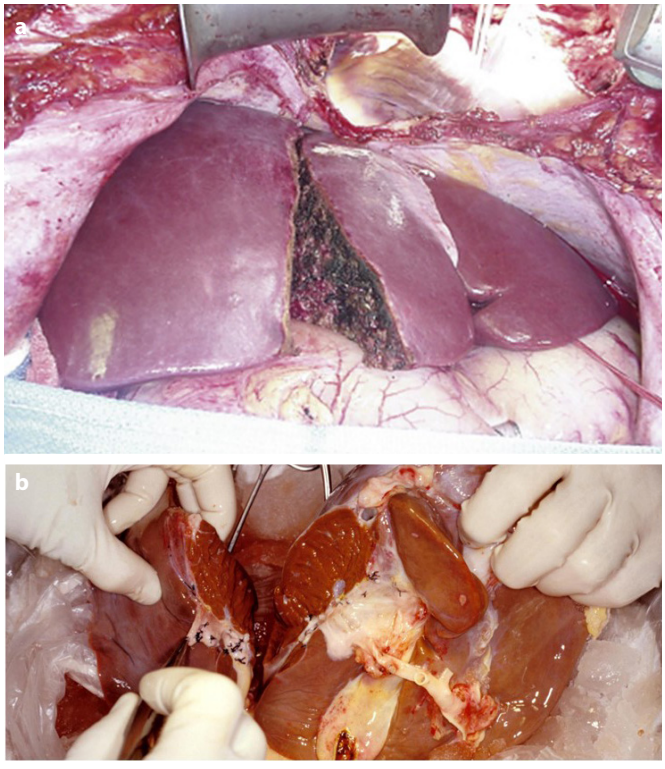

Figure 2. In situ **(a)** and Ex situ **(b)** splitting of the liver.

technique. Besides there are some disadvantages of in situ splitting such as longer procurement times (which is not suitable for unstable donors) and a lack of experienced surgeons in donor hospitals.[5] In an analysis by the European Liver Transplant Registry (ELTR), 221 in situ and 159 ex situ SLTs were evaluated. Median cold ischemia time was found to be significantly longer in ex-situ split. (9.3h vs 7.2h) Ex situ split was found to be associated with early graft failure and this was attributed to prolonged cold ischemia.[6] We believe that centers that perform living donor liver transplantations can easily achieve successful outcomes with in situ SLTs.

It is important to select a suitable donor for splitting. Ideal donors for splitting should have young age (<40 y), normal body weight (50-90 kg), length of stay in intensive care unit less than 5 days, no signs of sepsis, minimally impaired liver function tests (<2–3× normal), macrovesicular steatosis below 10% and low or no inotropic support.[7]

We know that SLT reduces waitlist mortality in pediatric recipients.[8] Meta-analyses have shown that SLT in adult patients increases biliary and vascular complications compared to WLT, but does not change overall graft and patient survival.[9] However appropriate recipient selection is a key factor to achieve successful outcomes. MELD score-based allocation system may restrict the widespread use of SLT. A split graft may not be suitable for potential recipients with high MELD scores. Prolonged cold ischemia time, perioperative biliary and vascular complications, and relatively small grafts may be associated with primary nonfunction and posttransplant graft loss for patients with high MELD scores. Even emergent liver transplantation and retransplantation may not be suitable for SLT.[10] Consequently, we believe that split liver transplantation may be more suitable for recipients with tumor or metabolic disease etiology, low MELD score, and without portal hypertension.

It is impossible to achieve better outcomes for ex-situ SLT in countries like ours with low deceased donation rates because none of these deceased organs meet the criteria for splitting. After 2016, we became very selective about performing SLTs. We became selective not only for donors but also tried to choose the appropriate patient for split grafts. We did not perform ex-situ splitting after 2016. We have performed in situ SLTs for only six patients. Thus, we achieved 67% 5-year overall survival rates in our series.

There are some limitations of our study. We did not meet all the splitting criteria both for donors and patients before 2016. Besides we can not reach all the data about the donors and grafts that we had split before 2016 for further investigation, because these donors and grafts were accepted from different centers.

Conclusion

We think that the splittable deceased organ number in our country is extremely low, so SLT will not be a solution for organ shortage in Türkiye. We believe that successful outcomes can only be achieved by performing an in situ split in the same center where the deceased organ came from.

Disclosures

Ethics Committee Approval: This study was approved by T.C. İnönü University Scientific Research and Publication Ethics Committee (Date: 26.12.2023, Number: 2023/5400).

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Conflict of Interest: None declared.

Authorship Contributions: Concept: F.O., S.Y.; Design: F.O., V.I.; Supervision: S.Y.; Data Collection: F.O.; Analysis and interpretion: V.I.; Writing: F.O.; Critical review: S.Y.

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Original Research

Predicting Early Post-Transplant Mortality: The Role of ICU Stay in Liver Transplant Recipients with HBV-Related Cirrhosis

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Abstract

Objectives: Liver transplantation is the only treatment option for patients with end-stage liver disease. Hemodynamic, respiratory, and metabolic monitoring in the intensive care unit (ICU) is a vital step after the transplant procedure. While most recipients are discharged from the hospital within postoperative two weeks, some patients stay longer, which increases both morbidity and the costs of liver transplantation. We aimed to explore the implications of ICU stay for post-transplant early mortality.

Methods: This is a retrospective analysis of the liver transplant recipients with Hepatitis B virus (HBV)-related cirrhosis between January 2017 and June 2022. Patients ≥18 years with HBV-related cirrhosis were included in the study. The patients were analyzed in two groups: patients who survived (n=167) and patients with early mortality (n=11) defined as mortality within postoperative 90 days. Various operative and clinical data were compared among the groups.

Results: Post-transplant ICU stay was significantly longer in patients with mortality (11 (7-21) versus 5 (4-7), p<0.001). Although it was not statistically significant, the MELD score (20 (17-25) versus 17 (14-22), p=0.051) and postoperative severe complication rate (63.6% to 34.1%, p=0.058) tended to be higher in the mortality group. We performed a ROC curve analysis and showed that cut-off value for the length of ICU stay was 10.5 days in terms of 90-day mortality. The sensitivity was 64% and the specificity was 94% (the area under the curve = 0.820, 95% CI = 0.651- 0.990, p<0.001). In univariate analyses, duration of operation (HR = 1.005, 95% CI = 1.002-1.009, p=0.002) and ICU stay ≥10.5 days (HR = 19.855, 95% CI = 5.796-68.011, p<0.001) were found as significant variables, but in multivariate analyses, only the ICU stay ≥10.5 days (HR = 17.204, 95% CI = 3.881-76.265, p<0.001) was found as an independent predictor of early post-transplant mortality.

Conclusion: The prolonged ICU stay is an independent predictor of postoperative 90-day mortality in living donor liver transplantation for HBV-related cirrhosis. By using length of ICU stay, high risk patients can be determined and closely monitored for early detection and management of serious complications that may lead to early post-transplant mortality.

Keywords: Complication, cirrhosis, survival, mortality, ICU, LDLT

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Liver transplantation is the only viable treatment option for patients with end-stage liver disease.[1] It is the only mode of therapy that provides acceptable survival and improved patient life quality.[2] Liver transplantation is a demanding major abdominal surgery but, establishment of hemodynamic stability, and metabolic monitoring in the intensive care unit (ICU) after the transplant procedure are equally important for a positive outcome of the patients.[3] ICU care of the patients has important implications in terms of the outcome of the liver transplant recipients.[4]

Most recipients are discharged from the hospital within two weeks following the operation. However, some patients stay longer, which increases both morbidity and the cost of liver transplantation.[5] The model for end-stage liver disease-sodium (MELD-Na) is a scoring system that characterizes the severity of the liver disease and enables physicians to prioritize critically ill patients for liver transplantation.[6] It has been shown that patients with higher MELD scores have longer ICU stays.[7] In addition, it was found that prolonged hospital stay is due to complications such as biliary strictures or leaks, early postoperative renal failure, sepsis, and multiorgan dysfunction.[8]

Our aim in the present study is to evaluate the effect of ICU stay on early post-transplant mortality after living donor liver transplantation (LDLT).

Methods

Patient Selection

This study was approved by the institutional review board (Approval number: 2023/4087). Between January 2017 and June 2022, a total of 178 adult patients received LDLT to treat Hepatitis B virus (HBV)-induced cirrhosis, a condition prevalent in Turkey that accounts for the majority of such liver complications. This selection criteria ensured a homogenous study group, focusing exclusively on individuals who received their first liver transplant (primary LDLT) due to chronic liver disease caused by HBV-related cirrhosis. We divided participants into two categories based on their postoperative outcomes: those who survived beyond the 90-day postoperative period (167 patients) and those who experienced mortality within this timeframe (11 patients). All patients gave written informed consent before the transplant procedure.

Study Parameters

Complications observed during the early postoperative period, which encompasses the first 90 days following surgery, were assessed and instances of death within this timeframe were categorized as early postoperative mortality. The complications were classified according to the Clavien-Dindo classification.[9] Clavien-Dindo grade 3 or higher complications were considered as severe complications. Demographic characteristics including age, and gender; clinical characteristics such as American Society of Anesthesiologists risk classification (ASA), MELD-Na; preoperative laboratory values including alanine aminotransferase (ALT), alanine aminotransferase (ALT), graft-to-recipient weight ratio (GRWR), type of liver graft, warm ischemia time (WIT), cold ischemia time (CIT), duration of ICU stay, operative time, intraoperative blood loss, length of hospitalization were all recorded for each patient.

Statistical Analysis

The Statistical Package for Social Sciences version 25.0 (SPSS v25.0) (IBM Corp., Armonk, N.Y., USA) was used for all statistical analyses. Kolmogorov-Smirnov test was used as the normality tests for the continuous variables. The continuous variables that distributed normally were given as mean±standard deviation (SD). The variables that did not distribute normally were expressed as median (interquartile range). Categoric variables were expressed as number of affected individuals and percentage (%) of the study population. Student t-test and Mann-Whitney U test were used for the comparison of the continuous variables between the study groups. Chi-square and Fisher's exact tests were used for the comparison of the categoric variables. Receiver operating characteristics (ROC) curve analysis was performed for the calculation of the cut-off value for the length of ICU stay. Univariate Cox regression analyses were performed for all variables. Multivariate Cox regression analyses were performed, using all variables with a $p \leq 0.10$ in the univariate analyses, for the determination of independent risk factors for early mortality. The Kaplan-Meier analysis was performed for survival analysis among the groups. Any p-value less than 0.05 was considered statistically significant.

Results

Table 1 summarizes the demographic, clinical, and preoperative laboratory data of the patients in the study groups. Only the duration of ICU stay was significantly higher in the patients with mortality [11 (7-21) versus (4-7), $p<0.001$]. The MELD-Na score among the patients who survived and patients with early mortality was 17 (14-22) and 20 (17-25); respectively ($p=0.051$). The incidence of severe complications in patients who survived and patients with early mortality was 34.1% and 63.6%; respectively ($p=0.058$). Although, patients with early mortality tended to have higher MELD-Na scores and higher serious complication rates, this did not reach statistical significance.

Table 1. Demographics and perioperative characteristics of the patients[x]

	Study group (n=178)	Survival group (n=167)	Mortality group (n=11)	P
Age, years	52 (44-59)	52 (45-59)	52 (39-58)	0.541
Gender, male	135 (75.8)	127 (76)	8 (72.7)	0.728
BMI (kg/m^2)	26.34±4.1	26.42±4.05	24.97±4.74	0.257
ASA score				
<3	22 (12.4)	22 (13.2)	-	0.364
≥3	156 (87.6)	145 (86.8)	11 (100)	
MELD-Na score	17 (15-22)	17 (14-22)	20 (17-25)	0.051
Preoperative ALT (U/L)	43.5 (27-71)	44 (28-71)	37 (18-76)	0.338
Preoperative AST (U/L)	63.5 (42-98)	64 (42-98)	56 (43-68)	0.422
Liver graft				
Right	171 (96.1)	160 (95.8)	11 (100)	1
Left	7 (3.9)	7 (4.2)	-	
GRWR (%)	1.02 (0.9-1.17)	1.02 (0.9-1.17)	0.97 (0.91-1.08)	0.781
WIT (minutes)	54 (42-63)	53 (42-63)	56 (45-64)	0.504
CIT (minutes)	80 (57-106.5)	80 (56.76-107)	84 (68-94)	0.931
Operation time (minutes)	504 (480-570)	502 (480-570)	540 (485-690)	0.155
Intraoperative blood loss (ml)	500 (400-700)	500 (350-700)	500 (500-800)	0.241
ICU stay, days	5 (4-7)	5 (4-7)	11 (7-21)	**<0.001**
Hospital stay, days	31 (25-41.26)	31 (25-41)	29 (15-51)	0.387

[x]Results are expressed as: mean±standard deviation, median (interquartile range), or frequency (%); Significant P values are in bold; BMI: Body mass index; ASA: American Society of Anesthesiologists; MELD: Model for End-Stage Liver Disease; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GRWR: Graft-to-recipient weight ratio; WIT: Warm ischemia time; CIT: Cold ischemia time; ICU: Intensive care unit.

We performed ROC curve analyses on the length of ICU stay in association with the occurrence of early mortality in the patients and the cut-off value was determined as 10.5 days. The sensitivity and specificity of the cut-off value were 64% and 94%; respectively. The area under the curve (AUC) was 0.820 (95% CI = 0.651- 0.990, p<0.001) (Fig. 1).

The univariate and multivariate Cox regression analyses for the predictors of early mortality are summarized in Table 2. Operative time (HR = 1.005, 95% CI = 1.002-1.009, p=0.002), length of ICU stay ≥ 10.5 days (HR = 19.855, 95% CI = 5.796-68.011, p<0.001) were significant risk factors of early mortality in univariate analyses. In the multivariate analyses only length of ICU stay≥ 10.5 days (HR = 17.204, 95% CI = 3.881-76.265, p<0.001) was the independent predictor of early mortality. The results of the Kaplan-Meier analyses are summarized in Table 3 and Figure 2. The early mortality rate of the patients with a length of ICU stay <10.5 days versus ≥10.5 days was 2.5% versus 41.2%, respectively (Log-rank Chi-Square = 45.111, p<0.001).

The causes of early mortality were peritonitis due to bile leakage in 3 (27%) patients, sepsis due to an intra-abdominal infected hematoma in 2 (18%)patients, prerenal acute renal failure in 1 patient (9%), SARS-CoV-2 infection in 1 patient (9%), acute cellular rejection and sepsis in 1 patient (9%), portal vein (PV) thrombosis and multiorgan dysfunction in 1 patient (9%), hepatic artery thrombosis (HAT) and intestinal ischemia in 1 patient (9%), and cardiac event in 1 patient (9%).

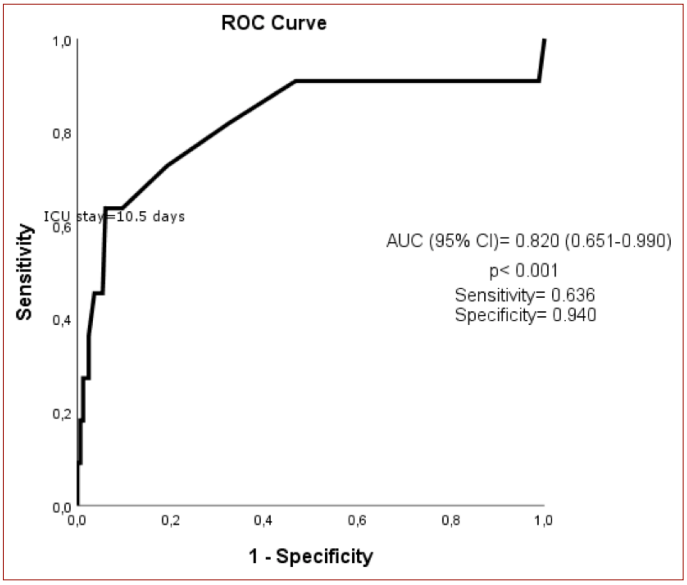

Figure 1. The receiver operating characteristics (ROC) curve for the cut-off value of the length of intensive care unit (ICU) stay in predicting 90-day mortality after living donor liver transplantation (LDLT) for Hepatitis B virus (HBV)-related liver cirrhosis.

Table 2. Cox regression analysis evaluating the predictors of 90-day mortality after LDLT for HBV related-cirrhosis.

Variable	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI Lower-Upper	p	Hazard ratio	95% CI Lower-Upper	p
Age, years	0.977	0.924-1.033	0.405	-	-	-
Gender, male	0.862	0.229-3.251	0.827	-	-	-
BMI (kg/m^2)	0.916	0.787-1.065	0.254	-	-	-
ASA score ≥3	24.741	0.011-57122.628	0.417	-	-	-
MELD score	1.089	0.992-1.194	0.072	1.049	0.951-1.157	0.340
Preoperative ALT (U/L)	0.996	0.984-1.007	0.466	-	-	-
Preoperative AST (U/L)	0.997	0.988-1.005	0.473	-	-	-
Graft type, right	0.047	0-28793.250	0.653	-	-	-
GRWR (%)	0.551	0.032-9.379	0.680	-	-	-
WIT (minutes)	1.004	0.975-1.034	0.786	-	-	-
CIT (minutes)	0.999	0.982-1.016	0.882	-	-	-
Operation time (minutes)	1.005	1.002-1.009	0.002	1.002	0.998-1.007	0.328
Intraoperative blood loss (ml)	1.001	1-1.001	0.081	1	0.999-1.001	0.753
ICU stay ≥10.5 days	19.855	5.796-68.011	<0.001	17.204	3.881-76.265	<0.001
Hospital stay, days	0.989	0.953-1.027	0.573	-	-	-

LDLT: Living donor liver transplantation; HBV: Hepatitis-B virus; CI: Confidence interval; BMI: Body mass index; ASA: American Society of Anesthesiologists; MELD: Model for End-Stage Liver Disease; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GRWR: Graft-to-recipient weight ratio; WIT: Warm ischemia time; CIT: Cold ischemia time; ICU: Intensive care unit.

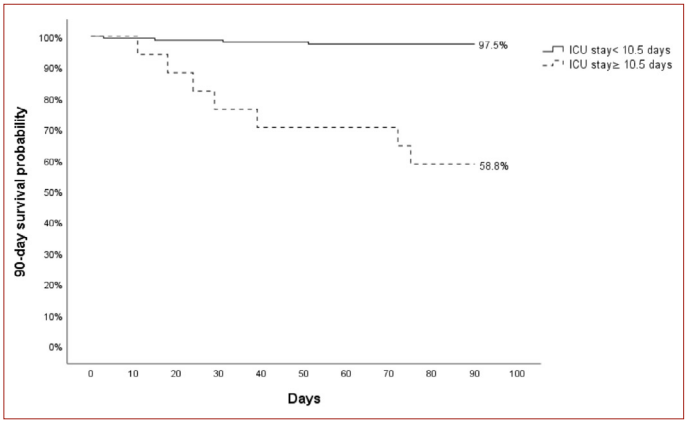

Figure 2. Kaplan–Meier 90-day survival graph of patients with living donor liver transplantation (LDLT) for Hepatitis B virus (HBV)-related liver cirrhosis according to the length of intensive care unit (ICU) stay with a cut-off value of 10.5 days.

Discussion

We have evaluated the duration of ICU stay and its implications in the post-transplant 90-day mortality in patients who received LDLT for HBV related cirrhosis. The study is unique in terms of the results for we have found that patients with an ICU stay longer than 10.5 days had higher early mortality in LDLT recipients.

Factors such as undiagnosed heart diseases prior to liver transplantation, high MELD score, Hepatitis C virus as the cause of end-stage liver disease, post-transplant infections, gastrointestinal bleeding, rejection, and renal failure cause prolonged hospitalization durations, and an increased risk of mortality.[8] Stratigopoulou et al.[4] showed that an ICU stay longer than 3 days affects the length of hospitalization, early mortality rates, and post-transplant survival. It is known that a high preoperative MELD score is a predictive factor that affects graft and recipient survival.[10] Furthermore, a high MELD score prolongs the duration of ICU care in the post-transplant period.[7] Bayrak et al.[1] stated that a MELD score of 19 can predict 30-day mortality of the recipients following the liver transplant. Niewińsk et al.[3] analyzed the results of 150 patients and reported that MELD scores greater than 16 were closely correlated with the length of postoperative ICU stay.

Transplant recipients are susceptible to infection and have a high risk of severe sepsis and infections that reduce graft and patient survival.[11, 12] The liver prevents sepsis induced tissues and organs damage.[13] It regulates the levels of the proinflammatory cytokines and chemokines in the circulation. Kupffer cells are the first line of defense against enteric bacteria, and microbial and environmental toxins originating from the intestinal tract.[14]

Pereira et al.[15] reported that there was a correlation between the 28-day mortality and the number of organ systems that failed during the ICU stay, the arterial lactate

Table 3. Results of Kaplan-Meier survival analysis for 90-day mortality in the patients with LDLT for HBV related-cirrhosis

	90-day mortality, n (%)	Log-rank Chi-Square	p
ICU stay <10.5 days (n=161)	4 (2.5)	45.111	<0.001
ICU stay ≥10.5 days (n=17)	7 (41.2)		

LDLT: Living donor liver transplantation; HBV: Hepatitis-B virus; ICU: Intensive care unit.

level on the postoperative third day in the ICU, and the INR. In LDLT, the duration of ICU stay in after the transplant procedure has high sensitivity and specificity in predicting the incidence of acute renal injury.[5] Postoperative renal dysfunction may occur due to the presence of hepatorenal syndrome before transplantation or post-transplant graft dysfunction, prolonged use of sympathomimetic agents, and the drugs that are used during the ICU stay that may cause acute tubular injury.[16]

The liver possess blood supply from the portal vein, hepatic artery, and inferior vena cava due to hepatic outflow. More than one vascular anastomoses are required in liver transplantation and complications can emerge at any anastomotic site.[2] Arterial complications are more common than venous complications.[2] HAT affects approximately 2-12% of patients with liver transplantation and can lead to graft loss and patient mortality.[2] This risk increases 5.76 times if hepatic artery anastomosis is performed to the supraceliac aorta via an interposition graft.[17] The mortality after re-transplantation for HAT was reported to be 40%.[18] In one of our patients, the reason for mortality was HAT. The hepatic artery anastomosis in this patient was performed using a graft extending from the supraceliac aorta. Portal vein complications have devastating results in LDLT and it is less frequently encountered.[2] The bile duct epithelium is supplied by the hepatic artery. For this reason, arterial complications may cause biliary ischemia that results in biliary strictures, bile leakage, and biloma.[19] Bile leakage constitutes 5-10% of early complications of transplantation.[2] Acute cellular rejection, another postoperative complication typically occurs within the first 90 days after transplantation,[2] and it causes high morbidity and mortality rates.[4] Three patients died due to peritonitis due to bile leakage, and 1 patient died due to acute cellular rejection in our series. In our clinic, the rate of bile leakage is 1.7% and the rate of bile complications is well below the rates stated in the literature.

The retrospective single-center design of our study and the low volume of the patients were the main limitations of our study. Although the MELD-Na score was close to significant in predicting 90-day mortality, it was not statistically significant. It may be meaningful in a larger case series study. Furthermore, we analyzed the effect of the duration of ICU stay on the early postoperative outcome of the recipients and we did not include the long-term outcome of the patients. It is important that we see long-term results to evaluate whether the transplanted liver is affected by the length of stay in intensive care.

Conclusion

In conclusion, our study indicated that the prolonged ICU stay was predictive for the determination of 90-day mortality risk following LDLT for HBV-related cirrhosis. The high-risk patients with an ICU stay longer than 10.5 days can be closely monitored for any complications and treated in the early period.

Disclosures

Ethics Committee Approval: Inonu University Review Board (Approval number: 2023/4087).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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

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Case Report

Varicella Zoster Fulminant Hepatitis in a Pediatric Patient with Leukemia: Recovery Without Liver Transplantation

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Abstract

Acute liver failure is a sudden and rapidly developing acute liver injury, with impaired metabolic-synthetic function of the liver, with or without encephalopathy that causes multi organ failure in a healthy person. Acute liver failure can develop due to many different reasons. In this report, we presented a child patient who received chemotherapy with the diagnosis of acute lymphoblastic leukemia and developed acute liver failure after Varicella-Zoster Virus infection.In this patient, liver transplantation could not be performed due to active viral infection, and she improved after acyclovir and supportive care with plasmapheresis. To the best of our knowledge, this is the only immunosuppressed child patient in the literature who improved from acute liver failure after Varicella-Zoster Virus infection without liver transplantation.

Keywords: Varicella-Zoster Virus, acute lymphoblastic leukemia, acute liver failure, plasmapheresis

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Acute liver failure (ALF) is a sudden and rapidly developing acute liver injury, with impaired metabolic-synthetic function of the liver with or without encephalopathy. Although there is no definitive description of ALF in children, it has been defined by the "Acute Liver Failure Study Group (ALFSG)" as the presence of biochemical findings indicating ALF, with or without encephalopathy and a coagulopathy that cannot be corrected (INR>1 and PT>15 seconds, in patients with encephalopathy and INR>2 and PT>20 seconds in patients without encephalopathy) in an individual without a previously known chronic liver disease.[1] ALF can develop due to many different reasons. The most common causes of ALF in children are viral hepatitis, drugs, chemicals, toxins, ischemia, venous thrombosis (hepatic vein, portal vein), autoimmune hepatitis, and metabolic diseases. In many cases, the etiology cannot be determined. Viral causes of acute liver failure include Hepatitis A-E, Varicella-Zoster Virus (VZV), Cytomegalovirus (CMV), Herpes Simplex Virus (HSV), Epstein-Barr Virus (EBV), and Adenovirus. VZV infections are potentially life-threatening in immunosuppressed patients, especially those with acute lymphoblastic leukemia (ALL).[2] In the literature, 9 cases (8

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adult, 1 child) of acute hepatic impairment due to hepatitis secondary to VZV has been reported. Of these patients, only 2 adult patients survived.[3]

In this report, we presented a child patient who received chemotherapy with the diagnosis of acute lymphoblastic leukemia (ALL) and developed ALF after VZV infection. In this patient, liver transplantation couldn't be done due to active viral infection, and she improved after acyclovir and supportive care. To the best of our knowledge, this is the only immunosuppressed child patient who improved from acute liver failure after VZV infection without liver transplantation.

Case Report

A 15-year-old girl, who was treated with chemotherapy with the diagnosis of ALL, admitted to the outer center with skin rash developed 15 days after receiving her last chemotherapy and was diagnosed with varicella. Laboratory tests were, AST 5500 U/L, ALT (alanine aminotransferase) 1200 U/L, total bilirubin 8.1mg/dl, direct bilirubin 6.7 mg/dl, and INR 7. The patient was referred to our center for evaluation of liver transplantation with the prediagnosis of ALF, which developed after the diagnosis of varicella. In the patients' history, it has been learned that the patient have not had varicella vaccine and varicella infection before. On physical examination, the patient had a poor general condition with icteric skin color and scleras, vesicular eruptions at different ages spread over entire body, and diffuse rales in the lungs. The liver was palpable 2-3 cm under the ribs. There was no encephalopathy. In the complete blood count, white blood cell was 8300/mm^3, hemoglobin 8 gr/dl, and platelet 11000/mm^3. INR was 4.32. In biochemical examination; Glucose 52 mg/dl, aspartate aminotransferase (AST) 7012 U/L, alanine aminotransferase (ALT) 2646 U/L, total bilirubin 8.48 mg/dl, direct bilirubin 6.21 mg/dl, gamma-glutamyl transpeptidase (GGT) 470 U/L, alkaline phosphatease (ALP) 275 U/L, sodium 132 mmol/L, phosphorus 2.8 mg/dl, and ammonia was 159 µg/dl. There was bilateral diffuse infiltration on chest X-ray. Serum VZV PCR revealed 1000 copy/ml. Other viral panel, metabolic and toxicological studies for hepatitis were negative. In abdominal ultrasonography revealed hepatomegaly, normal intrahepatic bile ducts, hepatic and portal veins. Administration of acyclovir 30 mg/kg/day iv, N-acetylcysteine 100 mg/kg/day infusion, ursodeoxycholic acid and fat-soluble vitamin supplements were started. The patient's MELD-Na score was 32, and an emergency liver transplant indication was established according to King's College criteria, but liver transplantation could not be performed because the possible high risk of transplant complications due to the disseminated varicella infection. On the third day of hospitalization, AST was 1044 U/L, ALT 443 U/L, total bilirubin 19.6 mg/dl, direct bilirubin 12.6 mg/dl, GGT 348 U/L, ALP 141 U/L, sodium 140 mmol/L, phosphorus 3.1 mg/dl, ammonia 257 ug/dl, and INR was 4.1. The patient with entered stage 2 encephalopathy and mannitol treatment was started for brain edema. Plasmapheresis (single-volume by centrifugation method) was applied to the patient twice a day with 12 hours of interval for a week until encephalopathy resolved. Then plasmapheresis was continued, once a day for a total of 1 month until bilirubin, ammonia and INR levels improved. On the 20th day of hospitalization, coagulation parameters returned to normal and liver biopsy was performed. The liver biopsy revealed parenchymal necrosis and steatosis, canalicular and hepatocellular cholestasis, fibrous enlargement, ductular proliferation, and degenerative changes in the ductus epithelium in most of the portal areas (Fig. 1a, b). Acyclovir was continued for three weeks until VZV PCR turned negative. On the 10th day of hospitalization, lung functions and in the first month liver function tests returned to normal, and signs of liver failure improved.

Discussion

VZV is a causative agent of varicella which is a highly contagious but generally a mild disease of childhood age. Its occurrence with acute liver failure is very rare and has high mortality.[4] A moderate increase in liver enzymes during VZV infection is usually seen whereas acute, severe hepatitis which leads to hepatic insufficiency is mainly seen in immunosuppressed patients.[3] Our patient had normal liver functions after the last chemotherapy session, and had negative viral panels except serum VZV PCR positivity, normal metabolic and autoimmune markers, absence of ischemia in the liver as shown by imaging methods, presence of vesicular rashes in physical examination. So, VZV was thought to be one of the causative factors in the development of ALF. However, toxic effects due to chemotherapy could not be excluded. Because, the patient was given

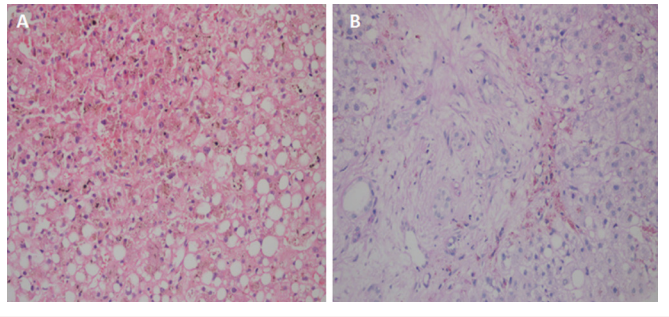

Figure 1. (a) Necrosis and steatosis in the liver parenchyma (HEX20). **(b)** Fibrosis and ductular proliferation in the portal area, steatosis in the liver parenchyma (PASX20).

peg-asparaginase (2500 U/m^2/day, single dose), high dose cytosine arabinoside (2 g/m^2/day, single dose), high dose methotrexate (5g/m^2/day, single dose) and cyclophosphamide (200 mg/m^2, 5 doses) 2 weeks before the development of ALF. Hepatotoxicity secondary to chemotherapy usually occur within 1-4 weeks.[5] Direct hepatotoxicity of chemotherapy agents have been reported, as rituximab and vincristine are associated with hepatocellular injury, cyclophosphamide and doxorubicin with venoocclusive disease (VOD), L-asparaginase, pegilated asparaginase, high-dose cytosine arabinoside, mitoxantrone and methotrexate with acute liver failure.[6]

VZV is common in immunosuppressed patients and may be mortal. In the literature, few patients with VZV-induced ALF have been reported to survive without liver transplantation.[3,4] The treatment of secondary acute liver failure involves early intravenous acyclovir, liver support systems, and liver transplantation.[3] Support systems save time for spontaneous recovery and serve as a bridge to transplantation in patients who need liver transplantation. Liver support systems include such as continuous renal replacement therapies, plasmapheresis and plasma replacement therapy, hemoperfusion, and liver replacement therapies.[7] Our patient benefited from single volume plasmapheresis with the intermittent centrifuge method for one month. In the literature, cases with ALF developed after chemotherapy have also been reported to have benefited from plasmapheresis.[8] Transplantation decision should be made considering the possibility of spontaneous hepatic healing in patients with ALF. As the degree of encephalopathy increases, the expected chance of spontaneous recovery decreases. It is difficult to predict which patient will recover without transplantation, and which will not. Many scoring systems have been developed to determine the time of liver transplantation in adults (King's College, Clichy, MELD, MELD-Na, BILE score). Currently, a scoring system for child patients hasn't been introduced and the indications for transplantation are not clear. In children, the diagnostic value of daily evaluation of important prognostic variables has been shown to be superior to King's College and MELD scoring systems.[9] The prognostic variables include the time between the onset of jaundice and encephalopathy, the degree of encephalopathy, bilirubin, PT/INR ratios, ALT and ammonia levels, and white blood cell count.[7] Our case was evaluated according to King's College Criteria, which is an adult scoring system, and indication for liver transplantaiton was established by considering that the jaundice period was 7 days before encephalopathy developed, the INR value was 3.5 and the serum bilirubin was above 17.5 mg/dl. In addition, our patient's MELD-Na score was 32 and indicating a poor prognosis. However, since our patient had disseminated VZV infection, the risk of complications after transplantation would be very high and liver transplantation could not be performed. Therefore supportive treatments have been applied and the patient was improved with these treatments. Although liver transplantation offers a treatment option for patients who cannot heal with medical treatment, it has a high mortality and morbidity. In addition, there are significant risks, including surgical complications and prolonged immunosuppression.[10] Comprehensive studies determining prognostic markers in children with ALF are needed to determine which patients will improve only with supportive treatments, and which will not survive without transplantation.

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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Inonu University Liver Transplant Institute
Biliary Atresia Symposium
22 December 2023

From the Symposium President

Dear Participants,

Biliary atresia is one of the most common liber transplant indications in pediatric patients. It is a complex disease that requires a multidisciplinary approach. Nutrition indices, complications of cirrhosis and portal hypertension, infections, and the extrahepatic organ systems should be closely monitored.

In the symposium, all aspects of patients with biliary atresia were discussed. In our opinion publication of the topics that were discussed during the symposium in our journal will contribute to the scientific armamentarium of our readers.

The president of the Symposium

Prof. Sezai Yilmaz, MD, FACS

Inonu University

Director of Liver Transplant Institute

Organizing Committee of the Symposium
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Fatma Ilknur VAROL
Sukru GUNGOR
Ayse Nur AKATLI
Sevgi TASOLAR
Ersoy KEKILLI

Symposium program

22 December 2023

Session I

Chairperson: Prof.Yasar Dogan; MD and Prof. Burak Isik; MD

Sezai Yilmaz

13.50-14.00 Historical Overview of Biliary Atresia

Fatma Ilknur Varol

14.05-14.20 Etiopathogenesis in Biliary Atresia

Sukru Gungor

14.30-14.50 Current Clinical Approach to Biliary Atresia

Ayse Nur Akatli

15.00-15.20 Liver Histopathology in Biliary Atresia

15.30-15.40 Tea/Coffee Break

Session II

Chairperson: Associate Prof. Fatma Ilknur Varol; MD and Associate Prof. Sukru Gungor; MD

Sevgi Tasolar

15.40-16.00 Diagnostic Radiological Findings in Biliary Atresia

Ersoy Kekilli

16.10-16.30 Diagnostic Nuclear Medicine Examinations in Biliary Atresia

Turan Yildiz

16.40-17.00 Kasai Portoenterostomy and Outcomes in Biliary Atresia

Tevfik Tolga Sahin

17.10-17.30 Liver Transplantation for Biliary Atresia

17.40 CLOSING REMARKS

Historical Overview of Biliary Atresia

Sezai Yilmaz

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Abstract

The last half century has been accompanied by significant advances in the diagnosis and treatment of infants with biliary atresia (BA). Kasai portoenterostomy and liver transplantation have changed the poor prognosis of infants with biliary atresia. In this article, historical developments regarding the diagnosis and treatment of BA were mentioned.

Key words: Biliary atresia, Kasai portoenterostomy, liver transplantation

BA is a serious neonatal disease that occurs with occlusion of the intra or extrahepatic bile ducts. The first reference to BA comes from John Burns of the University of Glasgow in 1817.[1] Burns pointed out that jaundice in infancies with BA is an important disease and that the danger is great, especially if it occurs immediately after birth. He also emphasized that the absence of bile in the stool may mean the absence of the extrahepatic bile duct and the disease may be in an incurable state. The first review on this subject was written by John Thompson in 1892.[2] In this study, the author reviewed 50 cases collected from the literature, 1 of which was his own. He described the symptoms, pathology and natural course of the disease. According to Thompson, 16% of these cases could be corrected surgically. This idea was on a theoretical basis, and no surgical procedures were performed on patients with BA. In his article written in 1916, Holmes focused mostly on BA that could or could not be corrected surgically, but he did not mention any surgical procedure.[3] He examined 120 cases collected from the literature (1 of which was his own). He stressed about the diseases caused by fat malabsorption and problems in the digestion of various foods in these patients. However, until those years, no surgical correction of BA had been reported. Cases of BA corrected surgically were first reported by Ladd in 1928. This information was obtained from Ladd's article in 1935.[4] He reported the first successful reconstruction of correctable BA, reporting good results with surgery in the first 4 months in 8 of 11 infants. Gross emphasized in 1953 that BA was the most common cause of obstructive jaundice in infants.[5] Most of these were of a nature that could not be corrected surgically. For many years, no serious progress has been made in the surgical treatment of BA. This general frustration led to numerous surgical maneuvers to restore bile flow, but these were unsuccessful. In those years, congenital atresia of the bile ducts constituted the darkest part of pediatric surgery.

Professor Morio Kasai is a pediatric surgeon who trained in surgery and pathology in Los Angeles in the 1950s. In BA according to Kasai, between 2-12 months after birth, there was a decreased pseudoductular proliferation in the portal tract and progressive destruction of intralobular bile ducts (Hering's ducts). There were fibrous residues of atretic bile ducts in the porta hepatis. He mentioned that there may be continuities between the ductal plate of the porta hepatis and the intrahepatic biliary system. In this case, if a portoenterostomy was performed, the progression of the disease could be stopped. Even the presence of bile pigments in the stool of 30% of infants with BA was an indication that the duct obliteration was not complete. In 1968, Kasai reported that he achieved "operative relief" with portoenterostomy in infants diagnosed with non-correctable BA, with his 10-year experience.[6] After Kasai's article, "hepatic portoenterostomy" was considered the treatment of choice for BA. With increased experience, it has become accepted that early diagnosis and timely operations are essential for successful restoration of bile flow. However, successful long-term results were still very rare.[7]

The presentation of liver transplantation as a treatment option by Starzl and his colleagues in 1963 opened a new horizon in the treatment of infants with BA.[8] The current surgical strategy for BA is initially Kasai portoenterostomy (first 2 months), then, if necessary, liver transplantation.

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Etiopathogenesis in Biliary Atresia

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Abstract

Biliary atresia (BA) is a progressive, idiopathic, fibro-obliterative disease of the intra and/or extrahepatic biliary tree that presents with biliary obstruction, particularly in the neonatal period. The general incidence of this condition is approximately 1 in 10,000 to 20,000 live births. Biliary atresia is the most common indication for liver transplantation in children. It is observed more frequently in girls and non-white children. Low birth weight term babies (<2500 g) have a higher risk of developing biliary atresia compared to normal birth weight term babies. Familial transmission and occurrence in twins are rare. The cause of biliary atresia is currently unknown. The etiopathogenesis is thought to be influenced by various factors, including genetics, immunology, viral infections, toxicology, environment, and vascular causes.

Definition

Biliary atresia (BA) is a progressive, idiopathic, fibro-obliterative disease of the intra and/or extrahepatic biliary tree that presents with biliary obstruction, particularly in the neonatal period.[1]

History

Dr. John Burns from Glasgow University first mentioned it as 'an incurable condition of the biliary apparatus' in a textbook published in 1817.[2] In 1891, John Thomson, an Edinburgh physician, published a case report and review defining congenital obliteration of the bile ducts.[3]

Embryogenesis

The biliary system primarily develops during the first trimester. The extrahepatic bile duct is the first visible structure in the embryo. It arises from an outgrowth of the foregut endoderm, specifically the liver bud, beginning at about day 20 of gestation. By about day 45, it is essentially complete, with a funnel-shaped proximal segment in close contact with the gallbladder, lumen, and liver outline. The cholangiocytes within it appear to originate from the foregut endoderm. [4]

Epidemiology

The general incidence of this condition is approximately 1 in 10,000 to 20,000 live births. Biliary atresia is the most common indication for liver transplantation in children.[5]

It is observed more frequently in girls and non-white children. Low birth weight term babies (<2500 g) have a higher risk of developing biliary atresia compared to normal birth weight term babies. Familial transmission and occurrence in twins are rare.[6]

Classification

Babies with biliary atresia (BA) are classified into three categories.[7]

1. Biliary atresia without any other anomaly or malformation:

This group is also known as perinatal biliary atresia, which occurs in 70 to 85 percent of infants with BA. These infants are usually born healthy but develop jaundice within the first two months of life, and their stools become increasingly pale.

2. Biliary atresia associated with malformations of laterality:

This pattern is also known as biliary atresia splenic malformation (BASM) or 'embryonic' biliary atresia. It occurs in 10 to 15 per cent of infants with BA. Laterality abnormalities include situs inversus, asplenia or polysplenia, malrotation of the interrupted inferior vena cava and cardiac abnormalities. Data suggest that children with BASM have worse outcomes than children with perinatal BA, possibly because of the associated cardiac anomalies.

3. Biliary atresia in combination with other congenital malformations:

It accounts for 5-10% of BA cases. Associated congenital malformations include choledochal cyst, intestinal atresia, anal atresia, renal anomalies and cardiac malformations.

The classification of biliary atresia according to the site of involvement is shown in Figure 1.[6]

Biliary atresia is also divided into 2 types, correctable and uncorrectable. Correctable is the condition in which the proximal common hepatic duct is open, which accounts for 10-15% of cases and allows primary anastomosis of EHBDs to the bowel, whereas uncorrectable is the condition in which the common hepatic duct is not open.[6]

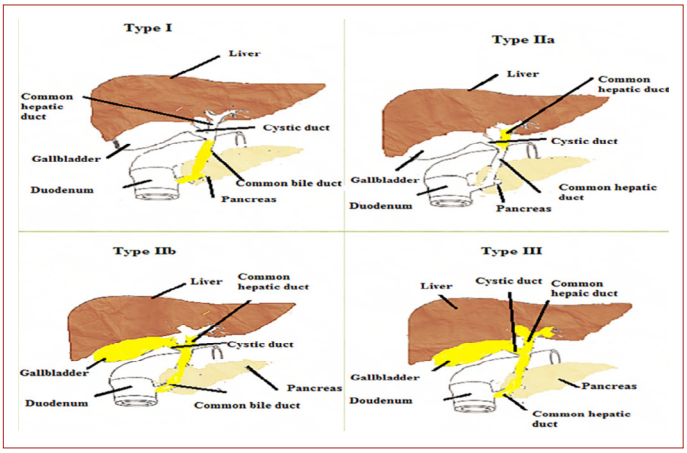

Figure 1. Classification of biliary atresia according to the site of involvement (yellow areas).

Etiopathogenesis

The cause of biliary atresia is currently unknown. However, it is believed to be associated with genetic defects in the formation of ductal plaque and bile ducts, or intrauterine ductal inflammation caused by viral or autoimmune factors. Although the exact trigger is uncertain, evidence suggests that biliary atresia begins in utero.[8]

Genetic Factors

BA is caused by mutations in the Jag1 gene, which plays an immunoregulatory role by suppressing the production of inflammatory cytokines such as IL-8.[9]

Some patients with sporadic BASM have been found to have mutations in the CFC1 gene, which is thought to act as a cofactor in the pathways determining the left-right axis. However, CFC1 mutations may predispose to BASM but are not sufficient to cause the disease.[10]

There is a contradiction about the relationship between HLA and BA. Some authors support this relationship,[3] while others do not.[11]

A new theory proposes that somatic mutations occurring after zygote formation affect only a subset of cells, leading to different phenotypes depending on the timing of the mutation. An earlier occurrence may result in de novo dominant disease, while later mutations can cause whole-body mosaicism or be limited to specific tissues. This concept also applies to BA phenotypes. The success rate of Kasai portoenterostomy (KPE) may be attributed to the rate of mosaicism in various regions of the liver.[12]

Imminological Damage

Initial studies published in the 1990s identified abnormal expression of ICAM-1 and, less frequently, VCAM-1 in the livers of seven infants with biliary atresia (BA), suggesting a trigger for an inflammatory reaction.[13] A larger cohort of 28 infants confirmed significant abnormal expression of ICAM-1, VCAM-1, and E-selectin on sinusoidal and biliary epithelium at rates of 50%, 25%, and 10%, respectively.[14]

Maternal chimeric cells were found in high concentrations in the portal and sinusoidal regions of patients with BA. This indicates that maternal lymphocytes cause bile duct damage through a graft-versus-host immune response.[15]

Liver samples obtained from infants with BA showed coordinated activation of genes related to lymphocyte differentiation, particularly those related to T helper 1 immunity.[6]

Polymorphisms that increase CD14 gene expression, which plays a role in bacterial endotoxin recognition, have been associated with biliary atresia (BA) and idiopathic neonatal cholestasis.[17]

Viral infections

In the 1970s, American paediatrician Benjamin Landing suggested a possible common factor in the etiology of choledochal cysts, neonatal hepatitis, and biliary atresia. He pointed to the action of a hepatotropic virus that can cause bile duct damage, also known as 'infantile obstructive cholangiopathy'.[18]

Rachel Moreki et al. initially provided evidence supporting this hypothesis by demonstrating higher antibody titres against REOvirus type 3.[19]

Hepatotropic and non-hepatotropic viruses have been identified as causes of biliary atresia (BA). An analysis of 249 cases of BA over a 16-year period in New York State revealed that the risk of BA was highest in babies born in spring in New York City, while the risk was higher in babies born in autumn outside New York City.[20] Although seasonal clustering of the disease has also been reported, a large participatory study in Japan did not find such a distribution. Multiparity and advanced maternal age have been identified as risk factors for BA.[21]

Reo Virus

Reovirus type III infection of mice causes biliary and liver damage similar to that seen in human biliary atresia (BA). Neonatal infection with reovirus in this animal model results in hepatitis, intra- and extra-biliary epithelial necrosis, bile duct oedema, inflammation, and irreversible luminal obstruction.[22]

Cytomegalovirus (CMV)

Cytomegalovirus is a double-stranded DNA virus that can infect epithelial cells of the common bile duct. Babies with biliary atresia (BA) who are CMV IgM positive exhibit more jaundice and lower survival rates without liver transplantation, in addition to higher aspartate aminotransferase and aspartate aminotransferase-to-platelet ratio index levels.[23]

Rota Virus

Intrahepatic cholangiocytes from patients with both syndromic and non-syndromic BA have a reduced number of primary cilia that are morphologically abnormal. The number of cilia is reduced in rotavirus-infected primary cholangiocytes, suggesting that ciliary abnormalities are part of the pathophysiology of BA.[24]

Toxic Etiologies

The strongest evidence for this hypothesis comes from three reported outbreaks of BA in lambs in Australia in 1964, 1988 and 2007 In each outbreak, during a period of drought, ewes giving birth to affected lambs grazed on previously flooded land. A significant number of lambs were weak, jaundiced, had acolic faeces and eventually died and were diagnosed with BA at autopsy. The putative mechanism is that pregnant ewes ingested a toxin while grazing on previously flooded land.[25]

A new isoflavonoid toxin was isolated from the Dysphania plant harvested in a recent outbreak area in Australia. This toxin caused severe damage to the extrahepatic biliary tree in a zebrafish model and also loss of cilia in neonatal mouse cholangiocytes. This evidence suggests that an environmental toxin may play a role in some cases of BA.[26]

Environmental Factors

Environmental factors that may trigger biliary atresia include drugs used during pregnancy (amphetamines and alcohol), agricultural and industrial toxins, phytotoxins and mycotoxins.[27]

Vascular Abnormalities

The biliary tree receives its blood supply mainly from the arterial system and impaired arterial flow leads to necrosis in the biliary tree. When compared with healthy infants and other infants with cholestatic diseases, tortuous hepatic artery branches and thickened wall with medial hypertrophy are observed in all patients with BA.[28]

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Current Clinical Approach to Biliary Atresia

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Abstract

Biliary atresia (BA) is a leading cause of liver transplantation in children, characterised by neonatal fibroobliterative disease of the extrahepatic biliary tree. BA may be associated with laterality anomalies and congenital malformations that affect prognosis. Clinical findings include jaundice, acholic stools and organomegaly. The differential diagnosis includes several cholestatic diseases.

Diagnostic biomarkers such as interleukin-33 and matrix metalloproteinase-7 are promising in the detection of BA. Imaging modalities such as ultrasonography and hepatobiliary scintigraphy aid in the diagnosis. Liver biopsy and intraoperative cholangiography are essential to confirm BA and guide the Kasai procedure, the gold standard intervention.

Postoperative markers of successful hepatoportoenterostomy (HPE) include colicky stools, decreased bilirubin, weight gain and decreased pruritus. Patient management includes choleretics (UDCA), nutritional support, prevention of cholangitis and monitoring for complications such as portal hypertension. Liver transplantation may be indicated in certain cases.

Timely and accurate diagnosis of biliary atresia is crucial for effective intervention. The Kasai procedure, if performed promptly, may improve outcomes. Continuous monitoring, nutritional support and appropriate management of complications contribute to a better prognosis. In cases where liver transplantation is indicated, preparation should begin, taking into account the patient's age and weight for optimal outcome.

Key words: Child, biliary atresia, liver transplantation

Introduction

Biliary atresia (BA) is the most common cause of childhood liver transplantation, presenting as a progressive, idiopathic, fibro-obliterative disease of the extrahepatic biliary tree in the neonatal period. Biliary atresia may be associated with laterality anomalies such as situs inversus, asplenia and other congenital malformations (10-15%). The prognosis of BA associated with these malformations is worse.[1-4]

Clinical Findings

Babies with biliary atresia are usually born at term with a normal birth weight. Initially, they show a healthy development. Jaundice develops in the first 8 weeks. It is unlikely to occur later. Total and direct bilirubin levels should be checked in every baby with prolonged neonatal jaundice. On physical examination, acholic stools, dark urine and organomegaly are frequently found. The family is usually not aware of acholic stools. It should be analysed in the anamnesis. Stool colour scales can be used in the evaluation of acholic stools. The sensitivity and specificity of stool colour scales in the detection of BA are 76.5% and 99.9%, respectively.[5-8]

A direct bilirubin (D.bil) value >0.45mg/dL in the first 3 days of life has low specificity (15.4%) and high sensitivity (100%). A D.bil value >1 mg/dL between 3-60 days has 100% sensitivity and 77% specificity for BA. Serum aminotransferases (AST, ALT) are mildly or moderately increased, while alkaline phosphatase (ALP) and gamma glutamine transferase (GGT) are disproportionately increased. In the late period, impairment in liver synthesis functions [hypoalbuminaemia, prothrombin time (PT) and International Normalised Ratio (INR)]may be found to be high.[9-11]

Differential Diagnosis:

Other cholestatic diseases of the newborn should be considered in the differential diagnosis.

Alagille syndrome should be considered in the presence of atypical facial appearance (wide nasal root, triangular face), congenital heart disease and butterfly vertebrae. Galactosemia should be considered in the presence of cataract with cholestasis.

Familial intrahepatic cholestasis (PFIC) should be considered in the presence of cholestasis, excessive pruritus, xanthomas and skin abrasions.

Peroxisosomal diseases, hypothyroidism and genetic metabolic diseases should be considered in the presence of hypotonicity and cholestasis.

In cholestasis developing after total parenteral nutrition, TPN-associated cholestasis should be considered. Infectious diseases should be considered in the presence of fever and weaning.

ARC syndrome should be considered in the presence of limb anomalies, renal pathology and cholestasis, and Aagenez syndrome should be considered in the presence of angioedema and cholestasis.

Tyrosinaemia should be considered in a patient with cholestasis in the presence of marked elevation in INR and AFP, tubulopathy and consanguinity. Neonatal haemochromatosis should be considered in the presence of cytopenia and high ferritin in a newborn with cholestasis.

Diagnostic Biomarkers

Interleukin-33: A study conducted among 30 healthy groups with 60 cholestasis (BA + Other) reported to be able to detect BA with 95% specificity and 96.7% sensitivity.

Matrix metalloproteinase-7 (MMP-7)

In 135 cholestatic and healthy infants, the diagnostic sensitivity and specificity were 98.67% and 95.00%, respectively. The negative predictive value was reported as 98.28%.

In a study of 288 patients with cholestasis, the sensitivity, specificity, positive predictive value and negative predictive value for BA were 95.19%, 93.07%, 97.27% and 91.43%, respectively.

Recommended threshold values differ between these studies.

Levels are affected by conditions such as age, gender and infection.

More comprehensive studies are needed to include these markers in the cholestasis algorithm.[12-17]

Imaging Methods

Abdominal USG

Ultrasonography (USG) may be guiding in the diagnosis of BA. Specific USG findings for BA are as follows.[5,18-23]

- Absence, irregularity, contractility of the gallbladder
- Absence of choledochal
- Triangular cortical sign (specificity 0.95 and sensitivity 0.68)

Hepatobiliary Scintigraphy

Visualisation of the biliary tract can be achieved by using the radioactive substance HIDA (99mTc-hepatic iminodiacetic acid).

The likelihood of BA is very low in patients in whom the passage of the radioactive substance into the small intestine has been demonstrated.

If the patient has absence of gallbladder and choledochal duct on USG and has acholic faeces, it will be more appropriate to give cholangiography without wasting time with scintigraphy.[24,25]

Liver Biopsy

It is done for two reasons

- Demonstration of pathological findings consistent with biliary obstruction supporting BA
  - Bile duct proliferation, enlarged portal ducts, portal duct oedema, fibrosis and inflammation. Canalicular and bile duct plugs are involved.[26,27]
- To differentiate BA from other intrahepatic biliary tract pathologies that do not require surgical intervention.
  - Bile blood deficiency (Alagille syndrome), periodic acid-Schiff (PAS) positive diastase-resistant granules (compatible with alpha-1 antitrypsin deficiency), loss of MDR3 staining (suggestive of PFIC3) or giant cell hepatitis without duct proliferation.[26,27]

Intraoperative Cholangiography

- It is the gold standard diagnostic method in the diagnosis of BA.
- Simultaneous liver biopsy is recommended if not previously performed.
- If BA is confirmed, Kasai procedure should be performed.

Babies with suspected BA should be evaluated rapidly. Because the success of surgical intervention gradually decreases with advancing age. Therefore, necessary investigations for differential diagnosis should be performed within 3-4 days in infants older than 6 weeks and intraoperative cholangiography should be performed. Kasai hepatoportoenterostomy (HPE) is recommended for all infants diagnosed with biliary atresia. It should preferably be performed before <2 months. While success increases in younger children, the chance of success gradually decreases with advancing age >2 months.[28]

Markers of successful HPE[29]

- The patient's colicky defecation,
- D.bil values of 2 mg/dL 3 months after the operation,
- Ensuring weight gain,
- Regression of itching.

Patient management after HPE

Choleretics (UDCA)	It is a hydrophilic bile acid and has been shown to stabilise membranes, reduce free radical formation and increase bile viscosity. In several large, randomised, double-blind, placebo-controlled studies in patients with primary biliary cholangitis, UDCA has been shown to reduce plasma levels of aminotransferases and improve liver histology and quality of life. It has also been reported to reduce the risk of death and the need for liver transplantation.[30-32]
Nutrition and vitamin support	Hypercaloric and MCT-containing nutrition and fat-soluble vitamin supplementation are recommended. Growth should be ensured as it is better in babies weighing >10 kg compared to smaller babies.[33,34]

Prevention of cholangitis	Although the success of prophylactic treatment has been emphasised in randomised controlled trials, we recommend antibiotic prophylaxis until at least 1 year after HPE, although a recent meta-analysis failed to show a cholangitis-reducing effect of prophylaxis.[35-37]
Glucocorticoid use	Clinical evidence does not recommend the routine use of glucocorticoids after HPE in patients with BA.[38,39]
Management of portal hypertension (PHT) and late sequelae	PHT may develop in approximately one-third of patients after successful HPE. Therefore, it should be closely monitored for ascites, peritonitis, and variceal bleeding, and an endoscopic evaluation should be performed annually. Endoscopic ablation of varicose veins should be started after the first variceal bleeding.[40]

Indications for liver transplantation in patients with biliary atresia;[38,41-43]

- Primary failure of HPE
- Total bilirubin >6 mg/dL three months or more after HPE
- Malnutrition
- PHT complications (Recurrent variceal bleeding, ascites, subacute bacterial peritonitis)
- Hepatopulmonary syndrome
- Portopulmonary HT
- Persistent itching
- Refractory coagulopathy
- Recurrent cholangitis
- Hepatocellular carcinoma

Since the results of liver transplantation are better in babies weighing >10 kg compared to younger babies and the chance of success is higher over the age of >2 years, liver transplantation can be postponed if the patients can grow and are clinically and laboratoryly stable.[44]

Prognosis

Most patients with biliary atresia (60-80%) eventually need a liver transplant. A minority of patients who undergo Kasai portoenterostomy survive to age 20 or longer. In most of these patients, complications of cirrhosis and portal hypertension develop and the need for liver transplantation arises.

Conclusion

As a result, acholic stools should be questioned in every patient complaining of jaundice during the neonatal period. If GGT is elevated and there are findings supporting BA on abdominal USG, intraoperative cholangiography should be performed without wasting time. Kasai procedure should be performed immediately in patients with cholangiographic findings compatible with biliary atresia. After the HPE, patients should be closely monitored clinically and laboratoryly. If the HPE is unsuccessful, it should be closely monitored for complications of portal hypertension. Necessary nutritional support should be given for growth, vaccinations should be done regularly, and if possible, the patient should be made to weigh >10 kg or grow up to >2 years of age. Liver transplantation preparation should be made in patients with liver transplantation indication.

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Liver Histopathology in Biliary Atresia

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Abstract

Biliary atresia is an idiopathic, progressive fibroinflammatory cholangiopathy involving the extrahepatic biliary tree in infants. It is one of the most important causes of neonatal cholestasis. If left untreated; can progress to micronodular biliary cirrhosis and death can occur in very early years. Therefore, early diagnosis and timely administration of Kasai portoenterostomy are important for the long-term functioning of the native liver.

Liver biopsy is the most reliable tool for the prelaparotomy diagnosis of biliary obstruction. The diagnostic histopathological features are mild to moderate portal edema with mixed inflammation, ductular reaction, and bile plugs .

The ethiological spectrum of neonatal cholestasis is wide and there are more than 100 diseases identified. Because early diagnosis and treatment is crucial, distinguishing biliary atresia from other causes of neonatal cholestasis is very important. For this reason, the diseases included in the differential diagnosis should be examined correctly with a multidisciplinary approach.

Key words: Biliary atresia, histopathology, neonatal cholestasis

Introduction

Biliary atresia (BA) is an idiopathic, progressive fibroinflammatory cholangiopathy involving the extrahepatic biliary tree in infants. It results in obliteration of the bile ducts leading to ineffective bile flow and chronic liver damage.[1,2] The damage begins in the extrahepatic bile ducts, but in the later stages of the disease, the intrahepatic bile ducts are also damaged. It manifests in the neonatal period, and accounts for approximately %30 of cases of neonatal cholestasis.[3] If left untreated; can progress to micronodular biliary cirrhosis and death can occur by 1-2 years of age.[4]

In infants with prolonged (>2 weeks) jaundice, acholic stools, and dark urine, an extensive investigation should be done.[3,5] In addition to laboratory investigation (conjugated hyperbilirubinemia with elevated GGT), ultrasound, hepatobiliary scintigraphy, liver biopsy and intraoperative cholangiography may be used.[3,4]

Early diagnosis and the correct timing of Kasai portoenterostomy are important for the long-term functioning of the native liver. Although Kasai procedure is not a definitive treatment method, it is important in terms of delaying the time to transplantation. Kasai operation was introduced to the medical literature by Japanese peadiatric surgeon Morio Kasai in 1955 and it is still the only accepted early treatment method.[4,6] Kasai portoenterostomy is based on resection of the fibrotic porta hepatis and then anastomosis of the hepatic hilum with the jejunal loop. Unfortunately, not all Kasai operations are successful. Failure to restore bile flow and/or late diagnosis leads to persistence of jaundice and hyperbilirubinaemia , and progressive cholestatic disease and cirrhosis of the liver. In this case, the only treatment method is liver transplantation.Biliary atresia is the most common cause of pediatric liver transplantation worldwide.[7,8]

Biliary atresia is classified as fetal and perinatal types according to whether it is congenital or acquired and morphologically as Type 1, Type 2a, Type 2b and Type 3 according to the location of obstruction of the extrahepatic bile duct.[9,10] Type 3 is the most common form (90%) and fibrosis in the porta hepatis and atresic/hypoplastic gallbladder are observed. There is also a classification consisting of 4 subgroups: isolated, syndromic, cystic and CMV-associated which was proposed by Davenport.[10]

Histopathology

Liver biopsy is the most common specimen submitted for pathologic evaluation of neonatal cholestasis.[1] It is the most reliable tool for the prelaparotomy diagnosis of biliary obstruction more than 90% of cases.[11,12] However some histopathological features may overlap with those of non-obstructive causes. Because of this a careful examination of the biopsy and clinical workup is necessary.

An adequate neddle-core liver biopsy should be at least 2 cm long, not fragmented, preferably 0.2 mm wide, and contain minimum 10 portal areas.[2] The diagnostic histopathological features are seen in the portal tracts. Mild to moderate portal edema with mixed inflammation, ductular reaction, (ductular proliferation consisting of anastomosing ductules at the peripheral portion of the portal tract accompanied by inflammatory cells) and bile plugs are the main characteristic findings. Fibrosis is observed in varying degrees according to the time of the biopsy. Lobular hepatocellular and canalicular cholestasis starting from the pericentral area is observed. In addition, focal hepatocellular giant cell formations, scattered extramedullary haematopoiesis and balloon degeneration may also be seen. Histopathological changes are typically milder when the sampling time is <30 days of age and may result in a falsely negative diagnosis.[3,4,13] False- negative diagnosis may also be the result of inadequate biopsies.[3] In this situation; repeated biopsies are advised if BA diagnosis persists in the clinical diagnosis. While mild fibrous portal expansion is seen in the early period; porto-portal fibrous bridging is seen especially after the 2nd month; advanced fibrosis and nodulation can be seen in biopsies taken in the later period (>90 days).[4] Immunohistochemical staining for CK7 or CK19 may be helpful in demonstrating the ductular proliferation.[3]

Pathologic examination of the Kasai specimen shows partial or complete fibrous obliteration of the extrahepatic bile ducts, periductular chronic inflammation, myofibroblastic proliferation, and ductal remnants focally may be lined with cubic or columnar epithelium.[4] Gall bladder is often hypoplastic/atretic and demonstrates partial or complete loss of the smooth muscle layer accompanied by mucosal chronic inflammation in the wall.[4]

Macroscopic examination of the explanted specimen shows two different scenarious. In patients who did not receive a Kasai operation or had an unsuccesful Kasai procedure, a firm, greenish liver with typical features of micronodular cirrhosis is seen. On the otherside , the ones who had a succesful Kasai operation and survived with their native livers for several years, prominent perihiler regenerative nodules can be present.[1,14] Microscopic examination of the specimens of the first group is consistent with the macroscopic findings demonstrating biliary cirrhosis with broad fibrous bands in a jigsaw patern.[1] Progressive loss of intrahepatic small bile ducts are seen in untreated cases and in most cases despite the treatment in the long term.[12] Majority of the patients with a succesful Kasai procedure develop portal hypertension in the long term which lead to transplantation. Microscopically a distinct pattern of fibrosis located peripherally can be obtained in the majority of patients . Hepatocellular regenerative nodules around the hilum, biliary cirrhosis and hepatoportal sclerosis features in the portal tracts can also be seen.[15] Dilated large ducts with ulceration of epithelium, bile sludge in the lümen, and bile lakes with inflammatory fibrous wall can be identified.[12] There are multiple theories for the formation of biliary cysts and lakes. One is the association with the ductal plate malformation. The others suggest that the ongoing inflammatory reaction results in cholangitis and bile cyst formation.[12]

Patel et al showed that biliary atresia patients with succesful Kasai portoenterostomy transplanted at adulthood show features of obliterative portal venopathy.[16] They demonstrated in this study that cholestasis and biliary cirrhosis are related to recurrent cholangitis. And in the absence of biliary cirrhosis portal hypertension may be secondary to obliterative portal venopathy.[16]

Differential Diagnosis

The ethiological spectrum of neonatal cholestasis has evolved over time and there are more than 100 diseases identified. The diseases other than biliary atresia with conjugated hyperbilirubinemia include genetic causes, infections, neonatal hepatitis, and structural disorders.[4] Prematurity, total parenteral nutrition, drugs and toxins also can lead to a similar clinical presentation.[4] Because early diagnosis and treatment is crucial, distinguishing biliary atresia from other causes of neonatal cholestasis is very important.

The obstructive ethiologies for cholestasis are choledochal cysts, tumors and stones. They can be differentiated on the clinical, laboratory and radiological data.[3] Cystic biliary atresia is a rare type of biliary atresia that is easily confused with choledochal cyst.[17] The patients with choledochal cyst usually have a regular gallbladder size, and a smooth wall with normal thickness. Lobeck et al. demonstrated that cystic BA cysts typically lacked epithelium and inflammation; cyst walls had an inner, dense cicatricial layer associated with myofibroblastic hyperplasia .On the other hand, choledochal cysts in patients had mostly preserved uninjured epithelium and did not have a subepithelial fibrous tissue.[18]

While the histopathological features of BA are well established, there is a significant histopathologic overlap with the non-obstructive causes of cholestasis.With the increasing use of molecular studies, there are lots of genetic diseases described which show the histopathological distal obstruction pattern seen in BA.

Alpha 1 antitrypsin (A1AT) deficiency is one of the most common genetic diseases of the liver in childhood. It is usually associated with PiZZ phenotype. In the infant period, a cholestatic picture mimicking neonatal hepatitis or BA such as jaundice, acholic stools and high GGT level is seen. Histopathological features are variable and may include damaged bile ducts, ductular cholestasis, ductular proliferation, portal chronic inflammation, ductular paucity, parenchymal giant cells and fibrosis. It should be kept in mind that the characteristic dPAS-resistant globules may not be very prominent in the first 3 months. If a liver biopsy showing an obstructive biliary pattern is from an infant, A1AT deficiency should always be considered in the differential diagnosis. In older children (>3 months), absence of fibrosis on biopsy and dPAS positive globules are useful in differentiation from BA.[3-5]

Progressive familial intrahepatic cholestasis is a group of autosomal recessive genetic disorders characterized by chronic cholestasis and variable progression to liver failure and cirrhosis.[4] There are 6 types identified; and all except type 3 have low GGT levels. So the type 3 mostly resembles the BA both on clinical and pathological features. The disease is characterized by abnormal canalicular transportation and secretion of the bile acids.[4] PFIC-1 , also called Bylers disease, is characterized by mutations in the ATP8B1 gene. Liver biopsy shows bland canalicular and hepatocellular cholestasis without a distinct obstructive pattern. PFIC-2, harbors a mutation on the gene(ABCB11) that encodes bile salt export pump (BSEP) protein. On histopathological examination of the liver biopsy, a giant cell hepatitis pattern and immunohistochemical loss of canalicular BSEP staining will be helpful. PFIC-3 is caused by mutations in the ABCB4 gene. This mutation results in the loss of function of phospholipid transporter MDR3 on the hepatocytes. Liver biopsy shows portal edema, mixed inflammation, ductular reaction and bile plugs that closely mimics BA's pathologic findings. But, MDR3 immunohistochemistry may be helpful for the diagnosis. In the clinical context it is very rare, that a PFIC-3 patient presented with a persistent neonatal cholestasis.[4]

Also it should kept in mind that weak or normal expression of BSEP and MDR3 can be seen in missense mutations; and it does not rule out functional deficiency.[19]

Paucity of intrahepatic bile ducts includes 2 groups; syndromic (Alagille) and non-syndromic variants. Alagille syndrome is an autosomal dominant disorder characterized by mutations in the JAG gene in more than %95 of the cases. It is associated with heart, vascular abnormalities, spinal abnormalities (butterfly vertebra), facial dysmorphism, ocular and renal abnormalities.[3-5] It is characterized by the reduced number of the bile ducts in the portal tracts. The loss of the bile ducts should be identified in >50% of portal tracts in an adequate biopsy consisting of 10 portal areas.[4] Histopathogical findings vary by the age of the patient and the progression of the disease. Ductular proliferation is usually lacking but it can be seen in early biopsies leading to confusion with BA. Progression to cirrhosis is slower than BA.[3]

There are lots of metabolic and genetic diseases including cystic fibrosis, bile acid synthesis defects, disorders of carbonhydrate metabolism, lipid metabolism, aminoacid metabolism, copper metabolism, mitochondropathies, etc. that can present with neonatal cholestasis mimicking BA.[4] The liver biopsy can be normal or show the features of the specific disorder.[4] The clinical and genetic investigations should be evaluated together.

Idiopathic neonatal hepatitis shows a giant cell hepatitis pattern on biopsy. Giant cell transformation of hepatocytes is a nonspesific reactive change.It can be seen due to very different aetiologies ranging from infectious diseases to genetic/metabolic diseases. Histopathologically, predominant lobular or canalicular cholestasis, extramedullary hematopoesis, and variable inflammation are seen. The histopathological features such as distinct ductular reaction, bile plugs, portal fibrosis, absence of sinusoidal fibrosis,and abnormal imaging findings of extrahepatic biliary tract support BA.[3,4,20]

One of the differential diagnosis of diseases with features of obstructive cholestasis is total parenteral nutrition – related hepatopathy. Cholestasis may occur within 2 weeks of TPN therapy and may mimick BA on histology. Liver biopsy shows portal edema, mixed inflammation, ductular reaction, bile plugs, lobular cholestasis and microvesicular steatosis.[4, 21] Increasing portal fibrosis may be seen in infants who receive TPN more than 6 weeks.[4] Clinical history of TPN should always be excluded before making a diagnosis of BA.

It has been shown that it is not possible to differentiate BA from TPN-associated hepatopathy and A1AT deficiency by biopsy alone without sufficient clinical information and the importance of clinical collaboration has been emphasized.[2]

Conclusions

BA is a neonatal disease characterised by idiopathic progressive fibroinflammatory obstruction of the extrahepatic biliary tract. Classical histopathological findings include portal edema, mixed inflammation, ductular reaction, biliary obstruction, and variable degrees of fibrosis in later stages. Early diagnosis and treatment contribute to prolonged liver survey. Recurrent episodes of cholangitis may lead to Kasai procedure failure. It should be kept in mind that obliterative portal venopathy and nodular regenerative hyperplasia are the features other than cirrhosis that may be seen in the explant specimens of transplanted patients after successful Kasai operation. Neonatal cholestasis has a wide spectrum of differential diagnosis and the diseases included in the differential diagnosis should be examined correctly with a multidisciplinary approach.

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Diagnostic Radiological Findings in Biliary Atresia

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Abstract

Biliary atresia (BA) is responsible for more than 90% of cases of obstructive biliary obstruction. It is of great clinical importance to rapidly and accurately differentiate biliary atresia from other causes of neonatal cholestasis. As it is a serious and progressive disease, early diagnosis is crucial for successful treatment. The ideal diagnostic tool for the differentiation of cholestatic jaundice in infants should be accurate, reliable, non-invasive and easily accessible. Among the diagnostic methods, USG is the first examination, MRCP is used as a problem solver. This presentation will review radiological imaging techniques and radiological findings used in the diagnosis of BA.

Keywords: Biliary atresia, pediatric, Ultrasound, MRCP

Presentation

Biliary atresia (BA) is the most common surgical cause of neonatal cholestasis. Its prevalence varies between 1/5,000-20,000 depending on the geographical region. Although the aetiology is unknown, viral infections, toxins and genetic factors have been implicated.[1] To improve outcomes in patients with BA, diagnosis and surgery should be performed as soon as possible.

The Kasai classification, also known as the Japanese and Anglo-Saxon classification, is an anatomical classification of the level and severity of obstruction in patients with BA.[2] In this classification, obliteration of the main bile duct (patent cystic duct and main hepatic duct) is observed in Type I, whereas obliteration of the main hepatic duct (patent cystic duct and main bile duct) is observed in Type II-a. In Type IIb, obliteration of the main hepatic duct, cystic and common bile duct is observed. In Type III, obliteration of the left and right main hepatic ducts is observed at the level of the porta hepatis. The most common type is type 3 and is seen in 90% of cases. BA is further divided into two types: non-syndromic form (80%) and syndromic form (20%). Syndromic BA may be associated with various congenital anomalies such as polysplenia or asplenia (100%), situs inversus (50%), preduo-

denal portal vein (60%), absence of retrohepatic inferior vena cava (40%) or cardiac anomalies (50%).[3]

Rapid and accurate differentiation of BA from other causes of neonatal cholestasis is of great clinical importance. Patients with BA should be operated on as soon as possible to improve surgical outcomes. Among radiological diagnostic methods, ultrasound (US) is used as a first-line screening method because it is cost-effective, does not use ionising radiation, is a real-time examination and generally does not require sedation. The use of microconvex or linear US probes with the highest frequency allows us to achieve good spatial resolution. The examination should be done after 4 hours of fasting.

Prenatal diagnosis of BA is extremely rare. Findings detected in fetuses with BA include inability to visualize the gallbladder, irregular gallbladder walls, cyst in the liver hilus, and heterotaxy syndrome. It is rare for the fetal gallbladder not to be permanently visualised. 15-43% have isolated gallbladder agenesis, a benign condition. The lack of visibility of the gallbladder lumen or the presence of an atretic gallbladder are the main findings on US in newborns with BA. Shape and wall abnormalities have been described for the atretic gallbladder. Reduced gallbladder size (less than 15-19 mm), irregular wall, unclear and irregular mucosa are findings known as the gallbladder ghost triad.[4,5] (Fig. 1) Lack of gallbladder contractility is another finding identified in BA, and it has been observed that the bladder volume measured before and after feeding decreases by 67-86%. It has been observed that this stenosis may be wider and some patients with LBP also have normal contraction.[6]

The triangular cord sign is in the form of a triangular or tubular echogenicity representing the fibrotic remnant of the extrahepatic biliary tree observed, just anterior distal right portal vein in the BA. The triangular cord sign has become accepted as an important diagnostic feature. If the echogenicity area is >3-4 mm, it is reported as positive. The triangular cord sign has been shown to be present in 17% of infants younger than 30 days and in 56% in the older group. This is thought to be due to the fact that the disease is a progressive disease.[7,8] Examining the accuracy of various ultrasound findings in the diagnosis of BA, it is known that the diagnostic accuracy increases when the triangle cord sign and gallbladder abnormalities are evaluated together.[9]

Cysts observed in BA are divided into two types. Macrocysts are observed in the hilus and vary between 0.5-4.0 cm in diameter, while microcysts are small cysts with dimensions less than 0.5 cm and are located at the junction of the intrahepatic bile ducts, at the porta hepatis, in the same region as the triangular cord sign. Macrocysts can also be seen in prenatal diagnosis. BA accompanied by macrocysts, also called cystic biliary atresia, is a relatively rare subtype.

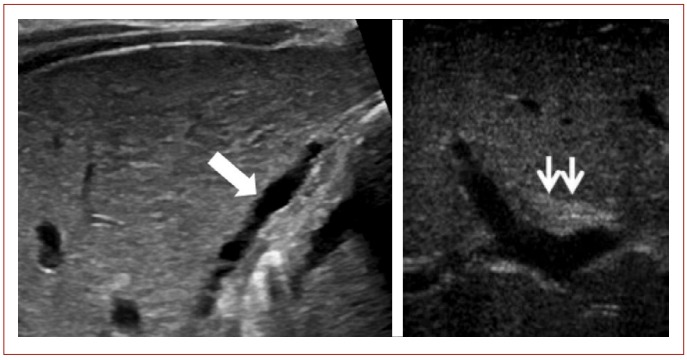

Figure 1. Irregular wall and triangular cord findings of atretic gallbladder on USG examination.

Common bile duct cyst is included in the differential diagnosis of cystic biliary atresia. The absence of intrahepatic ductal dilatation and the presence of a triangular cord sign or gallbladder abnormality in a patient with a cyst in the portal indicate a diagnosis of BA. Mud/stone within the cyst is more common in choledochal cysts.[10,11]

Studies have shown that the diameter of the hepatic artery increases in children with BA compared to normal controls or children with hepatitis. Hepatic artery diameter/portal vein diameter >0.45 or hepatic artery diameter greater than 1.5 mm predicts the diagnosis of biliary atresia. However, in the BA group younger than 30 days, the hepatic artery diameter was found to be significantly smaller than in older than 30 days with larger BA. It is thought that this is due to the fact that BA is a progressive disease and the portal flow is reduced over time due to the development of cirrhosis.[12,13] Additionally, hyperplastic and hypertrophic changes in the branches of the hepatic artery can be detected in the hepatic subcapsular area. This phenomenon has also been proposed as a diagnostic criterion for BA.[14] However, there is no measurement available for an objective evaluation. Although liver stiffness measurements by elastography are significantly higher in patients with BA compared to infants with other causes of cholestatic jaundice, there is no cut-off value to distinguish cirrhosis from other causes of cirrhosis. Elastography has been shown to improve diagnostic performance in prognostic assessment, especially in infants >30 days old. However, gray scale US is known to have better diagnostic performance than elastography for BA.[15]

Common bile duct visibility also contributes to the diagnosis of BA. However, it may not be visualised in ultrasound scans of newborn, even though it is usually normal. In particular, the absence of visualization of extrahepatic bile ducts by Magnetic Resonance Cholangiopancreatography (MRCP) is diagnostic of BA. Visibility of part of the extrahepatic bile duct does not exclude BA. It may not always be possible to see the entire extrahepatic biliary tree, from the right and left hepatic branches to the distal common bile duct.

MRCP is used as a problem solver in the diagnosis of BA due to its high cost and the need for sedation. It is recommended to fast for at least 4 hours before examination. Fast spin echo three-dimensional (3-D) taken with the fat suppression technique and coronal images allow smaller structures to be detected and evaluated without distortion. Real-time navigator gating is necessary to synchronize breathing. Field of view 18–24 cm and acquisition matrix 256×256 are adequate. Using a flexible surface coil according to the child's weight (minimum 12 channels) is suggest. The combination of MRCP and ultrasonography increases the diagnostic accuracy of BA. Again, failure to visualize the gallbladder identified on USG, bladder size and wall abnormalities, and a high signal area equivalent to the triangular cord finding in the porta hepatis can be detected on T2-weighted images (Fig. 2).

Differentiation of biliary atresia from neonatal hepatitis, which should

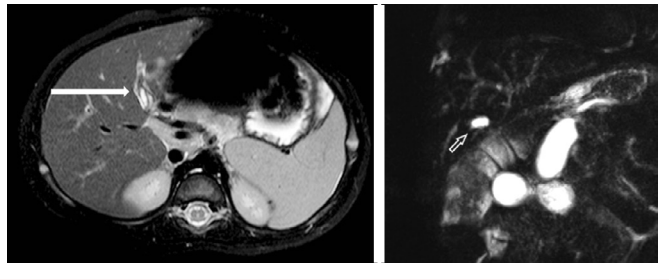

Figure 2. Atretic gallbladder in T2A axial and MRCP coronal sections.

be considered in the differential diagnosis, is made by a normal gallbladder length and morphology, the presence of post-feeding contraction, and the absence of other features suggestive of BA. Gallbladder wall thickening or periportal edema may occur. In addition to cardiac, ocular and skeletal abnormalities, a small gallbladder may be seen in Aagille syndrome, where interlobular bile ducts (PILBD) deficiency, typical facial appearance is observed, or the extrahepatic biliary tree may not be visualized on MRCP. It is distinguished by the absence of Triangular cord sign and hepatic artery dilatation, as well as the presence of systemic findings.

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Diagnostic Nuclear Medicine Examinations in Biliary Atresia

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Abstract

Early diagnosis and initiation of treatment are very important in biliary atresia. Radiologic and nuclear medicine imaging is very crucial in the diagnosis. Tc-99m iminodiacetic (IDA) derivatives are used in scintigraphic imaging. Tc-99m sestamibi (MIBI) is another radiopharmaceutical that can be used in wall biliary tract imaging. While it has the important advantage of having little effect on bilirubin level, caution should be exercised in false negative reporting due to direct secretion into the colon at the 2nd hour and beyond. We think that biliary scintigraphy remains important in the multidisciplinary approach in the diagnosis and follow-up of biliary atresia.

Key words: Biliary atresia, scintigraphy, radiopharmaceuticals

Biliary atresia (BA) is a disease that manifests itself with prolonged jaundice in infancy, significantly impairs life expectancy and quality of life, thus early diagnosis and initiation of treatment are important. Radiologic and nuclear medicine imaging is very crucial in the diagnosis.

Tc-99m-diisopropyl-IDA (DISIDA) and Tc-99m-trimethylbromo-IDA (mebrofenin), which are Tc-99m iminodiacetic (IDA) derivatives, are used in nuclear medicine imaging. Hepatic extraction of technetium-99m DISIDA is 88%, urinary excretion is 11% and hepatocyte uptake is 36% when bilirubin levels > 20 mg/dl. Hepatic extraction of Tc-99m mebrofenin is 98%, urinary excretion is 2% and hepatocyte uptake is 70% when bilirubin levels are > 20 mg/dl. Tc-99m mebrofenin should be preferred in cases with high bilirubin levels.[1]

Phenobarbital is given perorally at a dose of 5mg/kg/day for at least 3-5 days in order to increase bilirubin excretion by inducing microsomal enzymes in infants under 45 days of age. In preterm babies, this period can be extended up to 90 days. Sedation is not needed. It is preferred that the injection is given just before feeding time to initiate dynamic imaging.[2]

MR cholangiography is another noninvasive imaging method used in the diagnosis of biliary atresia. However, high cost and the need for sedation prevent its routine use. Failure to visualize extrahepatic bile ducts during MR cholangiography reveals biliary atresia[3] with 90% sensitivity and 77% specificity.[4]

During the study period, 93 patients aged 10 to 110 days with cholestasis and suspected Biliary Atresia underwent EHIDA. Sensitivity and NPV were 91.2% and 85.3%, specificity and PPV were 80.6% and 88.1%.[5] These results showed that EHIDA was sub-optimal in both the diagnosis and exclusion of BA 68Gallium-labeled tetrabromophthalein ([68Ga]Ga-BP-IDA) is a new radiopharmaceutical used in PET/CT and is promising due to its high resolution.[6]

Tc-99m sestamibi (MIBI) is a cationic lipophilic agent that is a sub-

strate of P-glycoprotein. This glycoprotein is normally expressed on the bile canalicular surface of hepatocytes. This feature provides a different mechanism of hepatic excretion from bilirubin excretion. While it has the important advantage of having little effect on bilirubin level, caution should be exercised in false negative reporting due to direct secretion into the colon at the 2nd hour and beyond.

Sdeghi et al. evaluated the value of Tc-99m BrIDA and Tc-99m MIBI in the differential diagnosis of neonatal cholestasis in 20 infants (10 with extrahepatic biliary atresia and ten with neonatal hepatitis) with a mean age of 2.41 months (range, 0.1-5 months). Tc-99m MIBI scintigraphy showed intestinal activity in all patients, including patients with biliary atresia.[7] Increasing small bowel activity in the area between the two renal pelvises corresponding to the jejunum in the early images leads away from the diagnosis of biliary atresia.

The hepatic extraction fraction value of Tc-99m IDA biliary tract scintigraphy in the first month after Kasai portoenterostomy can be used as a valuable parameter in long interval scintigraphic follow-up.

We think that biliary scintigraphy remains important in the multidisciplinary approach in the diagnosis and follow-up of biliary atresia.

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Kasai Portoenterostomy and Outcomes in Biliary Atresia

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Abstract

Biliary atresia is a progressive and obstructive kronik inflamatuar disease of the bile ducts. Kasai portoenterostomy has been used in its treatment since 1959. The most important factors in the success of the Kasai procedure are the age of the patient and the experience of the surgeon and whether complications occur in the early period. Staining the acholic stool with bile and decreasing bilirubin levels in the early postoperative period are considered success criteria. Studies have reported that the 5-year survival rate with native KC after the Kasai operation is around 50%.

Key words: Bilier atresia, Complications, Kasai portoenterostomi, Outcome

Biliary atresia is a bepatobiliary disease characterized by progressive inflammation and fibrous obstruction of the bile ducts. The gold standard method still for diagnosing biliary atresia is an intraoperative cholangiogram with concurrent liver biopsy. It should not be forgotten that the following diagnoses may be encountered during operative cholangiography: Biliary atresia, Biliary hypoplasia, Bile plug syndrome, Choledochal cyst, Intrahepatic bile duct dilatation (Caroli disease), Intrahepatic bile duct atresia (Alagille syndrome), Extrahepatic bile duct perforation.[1,2] Biliary atresia is characterized by progressive inflammatory obstruction of the extrahepatic bile ducts, and current therapeutic management is limited to two surgical approaches: Kasai hepatoportoenterostomy and liver transplantation.[3,4] Kasai portoenterostomy, which is the treatment of biliary atresia described by Morio Kasai in 1959, is still the main treatment method. Today, although there have been minor changes in the original Kasai portoenterostomy, satisfactory progress in surgery has not been achieved.[5]

How do we perform Kasai portoenterostomy?

The abdomen is entered through a subcostal incision on the right side of the abdomen. The initial dissection of the fibrous remnant is begun gall bladder and cystic duct. Next, forward dissection of the fibrous tissue proceeds just anterior to the portal vein and hepatic artery. Dissection should proceed until the fibrous remnant has come into approximation with the capsular surface of the liver within the bifurcation of the portal vein. Exised of the fibrous tissue is then performed. The ligament of treitz should be identified and a point about 15 cm from this should be transected to be the site of the jejunal anastomosis. The bowel is then divided, and a Roux loop, measured along the anti-mesenteric border at approximately 40 cm, constructed. The Roux limb is passed retrocolic and interrupted anastomosis to the transected porta hepatis is made using running absorbable monofilament 6/0 suture.[6]

The rate of complications in the early period (0-6 months) after Kasai portoenterostomy is 45-54.6%.[2,7] Complications of biliary atresia surgery can be evaluated as surgery-related or due to biliary atresia itself. Surgery-related complications include bleeding, anastomotic leak, small bowel obstruction, and internal hernia. Complications associated with biliary atresia include cholangitis, portal hypertension, malabsorption of fat-soluble vitamins A, D, E and K, intrahepatic bile lakes, liver failure, malignancy.[3]

In the literature, 5-year success rates of Kasai portoenterostomy have been reported in the range of 35-85%. The most important factors affecting success are; It is known that the child's age at diagnosis, early period camplications and the experience of the surgical clinic. The use of the stool color card in many countries, including Japan, Argentina, France and Taiwan, has proven to be effective in reducing the age of diagnosis and increasing the success rate of Kasai portoenterostomy.[4,8-10]

The earliest measurable result of the Kasai portoenterostomy is resolution of jaundice. Surgical success was defined as achievement of a total serum bilirubin ≤ 20 micg/dL. In experienced centers, biliary drainage can be achieved in up to 60-67.1% of children after Kasai portoenterostomy. Serum bilirubin of children with adequate bile drainage decreases to normal values within 6 months. 80% of these children can reach adolescence with a good quality of life without liver transplantation.[4,11]

It is reported in the literature that more successful results will be

achieved by lowering the age of diagnosis and collecting biliary atresia cases in a single center.

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Liver Transplantation for Biliary Atresia

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Abstract

Biliary atresia is the leading cause of liver transplantation in patients with biliary atresia. Biliary atresia is a complex disease that requires a multidisciplinary approach. Close monitoring of the patients in terms of nutritional indices, signs and symptoms of portal hypertension, and complications of cirrhosis is necessary. The two-step surgical therapy involving Kasai Porto-enterostomy followed by liver transplantation at an optimal time is the key to obtaining good patient and graft outcomes. The optimal timing is the most controversial point in the management of patients with biliary atresia. If porto-enterostomy results in good bile flow, the transplant-free survival of the patients is very good. However, things do not always go smoothly and there can be an early failure of the Kasai Porto-enterostomy, or cases may be complex and diagnosed later in infancy. In these cases, liver transplantation should be considered early to provide better graft and patient survival. Eventually, all patients with biliary atresia will develop end-stage liver disease and these patients will be transplanted later in life. As the patient's age is older, the success of liver transplantation will increase in this setting. The success of liver transplantation also depends on the nutritional status of the patients, the presence of recurrent cholangitis, and the presence of extrahepatic organ system failure. Physicians must have a good clinical perception to treat patients with biliary atresia.

Keywords: Liver transplantation, living donor liver transplantation, biliary atresia, reduced size grafts

Introduction

Biliary atresia (BA) is progressive inflammatory obliteration of the intrahepatic and extrahepatic bile ducts.[1] The incidence is 1 in 8000 to 18000 live births. Due to progressive obliteration of the bile duct and the recurrent cholangitis attacks the patients experience progressive liver failure and end-stage liver disease is inevitable at the early stages of childhood.[2] It has four main phenotypes:1) Isolated BA, 2) BA associated with laterality defects, 3) BA associated with major congenital malformations, and 4) BA associated with bile duct cysts; also named cystic BA.[1,2] The etiology is multifactorial but abnormal bile duct development, perinatal viral infections, perinatal toxin exposure, and abnormal immune response have been implicated as the main factors in the etiology of BA.[1,2]

The two-stage surgical approach is defined as Kasai porto-enterostomy followed by liver transplantation at an optimal time when liver failure develops. Currently, this is the preferred treatment that provides the longest survival for the patients.[3] Despite all efforts to restore the normal bile flow in patients with BA, it will eventually progress to end-stage liver failure and patients will require liver transplantation.[4] The present study aims to evaluate the role and efficacy of liver transplantation in pediatric patients with BA.

Indications of Liver Transplantation

Indications of liver transplantation for BA are summarized in Table 1.

Table 1. The summary of the main indications for liver transplantation in Biliary Atresia

Indications for Liver Transplantation in patients with Biliary Atresia
Failed Kasai Porto-enterostomy
Late diagnosis of Biliary Atresia
Failure to thrive
Recurrent bacterial cholangitis
Portal Hypertension and its complications
Treatment refractory pruritus
Hepatopulmonary syndrome and porto-pulmonary Syndrome
Hepatorenal syndrome
Development of hepatic malignancy

Failed Kasai Porto-Enterostomy

The prognosis of the patients with BA is poor unless the flow of bile is restored. Occasionally, despite a Kasai Porto-enterostomy, normal bile flow is not restored, and the faith of the patients is not different from patients who are not operated. The patients cannot live longer than two to three years unless liver transplantation is performed.[5-7] Early failure of Kasai Porto-enterostomy is defined as failure to restore normal bile flow in the patients within 3 months following the surgery.[8] A large-volume study from the United States of America has shown that patients who had bilirubin levels less than 2 mg/dL at the postoperative 3rd month following Kasai procedure had a 2-year transplant survival rate of 84% while the patients who had bilirubin levels more than 2 mg/dL had a 2-yea transplant-free survival of 16%.[8] In patients with BA who have undergone liver transplantation, if the bilirubin levels have not dropped below 2 mg/dL the patients should be evaluated for liver transplantation as early as 6 to 9 months of age.[2]

Late Diagnosis of Biliary Atresia

As it is known very well the complications that are encountered during liver transplantation caused by Kasai Porto-enterostomy include bowel perforation caused during adhesions that occurred due to Kasai Porto-enterostomy.[9-15] Some studies showed similar results regarding operative duration, blood loss, intraoperative complications, and duration of hospital and intensive care unit stay.[9-15] Late Kasai Porto-enterostomy is defined as performing the procedure at an age ranging between 90-120 days in patients with a confirmed diagnosis of BA. Studies have shown that the outcome of patients who have undergone late Kasai Porto-enterostomy have poor outcomes in terms of survival with native livers; survival rates at 1-, 5-, and 10-years were approximately 40%, 20%, and 15%, respectively.[16-19]

Failure to Thrive

Patients with BA have serious malabsorption of iron, zinc, lipids, and fat-soluble vitamins.[20] Furthermore, due to recurrent cholangitis attacks and the effects of systemic circulation, the patients experience a severe catabolic process leading to severe protein energy malnutrition.[20, 21] Protein-energy malnutrition and severe malabsorption can occur despite a successful Kasai Porto-enterostomy. Therefore, continuous surveillance of the anthropometric parameters is recommended to determine any growth retardation in early period.[21] Also, these patients experience metabolic bone disease which is defined as brittle bones despite the absence of calcium and vitamin D deficiencies. Patients with BA who develop failure to thrive, protein-energy malnutrition, or metabolic bone syndrome should be evaluated for transplantation.[2]

Bacterial Cholangitis

On average 60% of the patients with BA and who have undergone Kasai Porto-enterostomy develop at least one episode of cholangitis. And nearly 30% of the patients will experience more than one episode of cholangitis.[22,23] Cholangitis reduces transplant-free survival of patients with BA. Furthermore, cholangitis increases the failure rate of Kasai Porto-enterostomy by three years.[24] Liver transplantation should be considered in patients with recurrent cholangitis despite adequate antibiotic therapy, the emergence of multidrug-resistant microorganisms, patients with a history life-threatening sepsis, and patients suffering from cholangitis that severely impairs the quality of life due to frequent hospitalizations and invasive therapeutic interventions.[25]

Portal Hypertension

Portal hypertension is the most frequent complication of end-stage liver disease.[26] Definitive findings of portal hypertension are splenomegaly, hypersplenism, ascites, and varices and the complications related to these spectra of events. Some of the patients show only the complications of splenomegaly and hypersplenism which is also suggestive of portal hypertension.[2] Studies have shown that nearly 70% of the patients with BA have some form of portal hypertension. The causes of portal hypertension are the progressive inflammatory fibrosis of the liver and recurrent cholangitis contribute to the rapid development of portal hypertension in patients with BA. Furthermore, 60% of the patients with BA have one episode of variceal bleeding and nearly 20% suffer from recurrent variceal bleeding.[27] A large-volume study from France analyzed the patients with BA who could survive till adulthood and the results of the study showed that almost all the patients had cirrhosis, nearly 80% had signs and symptoms suggesting portal hypertension.[28] The presence of signs and symptoms of portal hypertension as well as its complications is an indication for portal hypertension.

Pruritus

Pruritus is a common complication of congenital disorders such as Alagille syndrome and Progressive Familial Intrahepatic Cholestasis. However, patients with BA can suffer from in severe pruritus that may have an impact on the quality of life of the patients. First step during the decision-making process is to rule out other causes of pruritus and maximum medical therapy should be performed.[29] In patients with BA and intractable pruritus that have a severe impact on the quality of life, liver transplant should be considered as the preferred treatment.

Extrahepatic Organ Systems Involvement

Hepatopulmonary syndrome results in hypoxia in a patient with portal hypertension and is caused by abnormal intrapulmonary shunting of the blood from right to left side. It can be seen in up to 20% of the patients with BA.[30,31] On the other hand, *porto-pulmnonary hypertension* is defined as increased mean pulmonary artery pressure and increased pulmonary vascular resistance in a patient with portal hypertension. It causes exertional dyspnea, hypoxia, and right-sided heart failure.[32] It is observed in less than 1% of the patients with BA. Hepatopulmonary syndrome is a definitive indication for liver transplantation. On the other hand, mean pulmonary arterial pressure is measured in patients with BA and who suffer from porto-pulmonary hypertension. Mean arterial pressure should be less than 50 mm-Hg to perform liver transplantation.[32]

Hepatorenal syndrome is defined as acute renal failure in a patient with end-stage liver failure who does not have intrinsic renal disease.[33] Liver transplantation should be considered in a patient who develops hepatorenal syndrome.[34]

Hepatic Malignancies

Hepatocellular carcinoma (HCC) develops in the setting of liver cirrhosis.[35] HCC can be observed in less than 1% of the patients with BA and can even be observed in infants. *Cholangiocarcinoma* is very rare in patients with BA.[36] HCC is suspected or confirmed by imaging and pathological analysis, the patients should be enlisted for liver transplantation provided that there is no distant metastasis and macrovascular invasion.[37,38]

Pretransplant Management

Pretransplant management of pediatric patients with BA requires a multidisciplinary approach. *Nutritional surveillance and support* have paramount importance. Anthropometric parameters, biomarkers of nutritional status (albumin, retinol-binding protein, and transferrin), and fat-soluble vitamins, iron, and zinc should be monitored regularly.[39]

For patients with BA who have signs and symptoms of portal hypertension, 90% have *esophagogastric varices* and 30% of the patients experience recurrent variceal bleeding. The mortality of recurrent variceal bleeding is nearly 5%.[40,41] Surveillance endoscopy enables determining patients who progress rapidly from early-stage esophageal varices to advanced-stage esophagogastric varices. Preemptive band ligation and sclerotherapy are effective in treating esophageal varices.[42] However, preemptive variceal treatment in patients with variceal bleeding refractory to band ligation and sclerotherapy should be considered for liver transplantation.[43]

Thrombocytopenia is the most common manifestation in patients with portal hypertension causing splenomegaly and hypersplenism. Platelet replacement is only necessary in patients with variceal bleeding and a platelet count between 20-60x10^3 corpuscles/mm^3.[2]

Another consequence of portal hypertension is *ascites* and *hyponatremia* (<130mEq/L). Ascites is observed in 30% of the patients with BA. The initial step in the medical treatment of ascites is sodium restriction. This may be followed by the use of diuretics such as spironolactone as a single agent or in combination with furosemide. In patients who have a low albumin level 20-25% albumin infusion combined with furosemide may be effective in the treatment of ascites. In cases that do not respond to adequate medical therapy (intractable ascites), large-volume paracentesis can be used (should be less than 200 mL/kg or no more than 680 mL/hr). Paracentesis can be combined with albumin infusion to increase the effective plasma volume.[44]

Fluid restriction is used for the treatment of hyponatremia. In cases with severe hyponatremia (115-120mEq/L) or moderate hyponatremia with neurologic symptoms should be treated with an infusion of normal or hypertonic saline. The increase in the sodium levels of the patients should not increase 9mEq/L per day.[45]

Spontaneous bacterial peritonitis (SBP) can develop in patients with ascites and physicians should have a high grade of suspicion to diagnose SBP in the pediatric population. The most common etiologic agent is Streptococcus pneumonia. Patients with recurrent SBP require prophylactic antibiotics.[46] Prophylactic trimethoprim-sulfamethoxazole therapy may prevent bacterial cholangitis episodes and prolong the transplant-free survival of patients with BA who have undergone Kasai Porto-enterostomy.[46]

Redo-portoenterostomy can be attempted in patients with BA who initially showed a good bile flow following Kasai's procedure but suddenly deteriorated. However, redo-surgeries may complicate future liver transplantation.[47]

Vaccination programs should be completed as much as possible because vaccine-preventable infectious disease is still a major problem in pediatric transplant recipients. The live vaccines should only be performed if the time to transplant is more than 4 months. Tuberculosis surveillance should be performed in high-risk areas.[48]

Timing of Liver Transplantation

According to the United Network for Organ Sharing (UNOS) data pediatric patients with BA who have a pediatric end-stage liver disease score (PELD)≥17 had the best outcome following liver transplantation.[49] However, if the waiting period is too long or if the patients are enlisted at a late stage, the physical condition of the patient deteriorates and may not undergo a major procedure such as liver transplantation and mortality on the waiting list is 25%.[50] Living donor liver transplantation (LDLT) is effective and safe in pediatric patients with BA who have a PELD score between 15 to 25.[51]

We have searched the global literature regarding pediatric patients who undergo liver transplants for BA and the studies have shown that the patients have a mean age of 0.8 to 3.7 years, a mean body weight of 8 to 18.6 kg, and studies report a 10-year graft survival of 70-90%.[52-58] The factors that affect graft survival are donor body mass index, ABO incompatibility, graft type, recipient age, and the experience of the center.[4]

The left lobe liver grafts have poor overall survival when compared to the right lobe liver grafts.[4] Patients older than 18 years of age have better overall graft survival than adolescents and younger children.[4] Centers performing 50 cases of liver transplantation for BA annually are considered experienced centers. The graft and patient survival in experienced centers are better than the inexperienced centers.[4] The age of the patients with BA who undergo liver transplantation in centers performing LDLT is younger age (<5 years) when compared to centers that perform deceased donor liver transplantation (DDLT).[4]

Although Kasai Porto-enterostomy postpones liver transplantation by providing a good liver function, failed Kasai procedure is a risk factor for poor outcomes after liver transplantation.[59]

Comments

Biliary atresia is one of the most common indications for liver transplantation in the pediatric population. A two-step surgical approach including Kasai Porto-enterostomy followed by liver transplantation at an optimal time provides the best outcome for the patients. However, when optimal patient response is not obtained after the initial step of this approach, controversial points arise regarding the possible therapeutic options. However, since the results are discouraging otherwise, liver transplantation should be considered early in these cases. In patients who respond to Kasai's procedure, liver transplantation can be postponed until the patient is in adolescence or early adulthood.

A multidisciplinary approach is necessary to treat these patients. Nutritional support is of paramount importance.

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