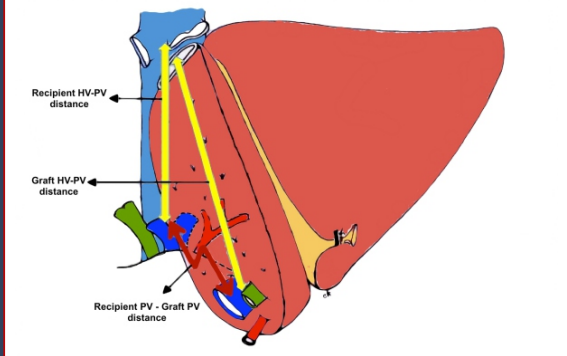
The Official Journal of the Inonu Liver Transplantation Institute

Journal of Inonu Liver Transplantation Institute



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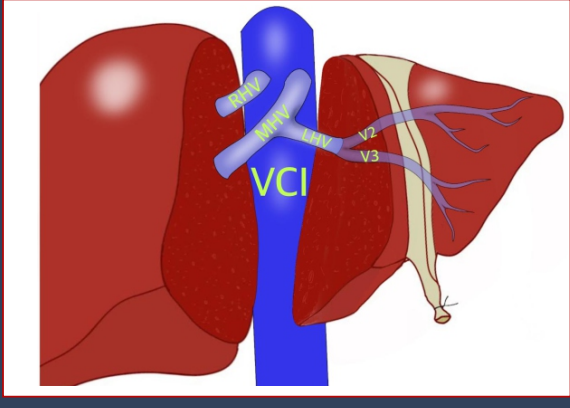

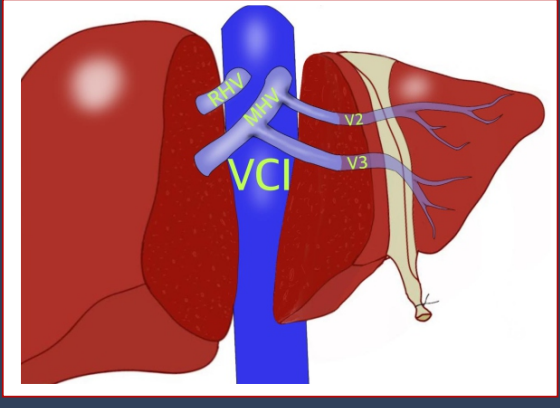

Anatomical Variations and Reconstruction Techniques of the Left Hepatic Vein in Pediatric Living Donor Liver Transplantation

www.jilti.org

Volume: 1 Issue: 2 August 2023 E-ISSN 2980-2059

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About the Journal

Main Title: Journal of Inonu Liver Transplantation Institute
Serial Key Title: Journal of Inonu Liver Transplantation Institute
Abbreviation: J Inonu Liver Transpl Inst
Serial Type: Journal
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Publisher: Inonu University Liver Transplant Institute
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Journal Description: Our journal is supported by Inonu Liver Transplantation Institute officially, and is a blind peer-reviewed free open-access journal, published three issue in a year (April, August, December).
Format: Electronic version E-ISSN 2980-2059. (online)
Start Year: 2022
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
Fee or Charges: This journal assesses NO submission fees, publication fees (article processing charges), or page charges.
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Publisher: KARE PUBLISHING
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Yayın Turu: Uluslararası Sureli
Yayın Tarihi: August 2023
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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.

Author's Responsibilities

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

Editor's Role and Responsibilities

General Duties

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

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

Reader Relationship

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

Author Relationship

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

Reviewer Relationship

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

Editorial Board Relationship

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

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

Relations with the Owner of the Journal and the Publisher

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

Editorial and Blind Review Processes

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

Quality Assurance

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

Protection of Personal Data

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

Ethics Committee, Human and Animal Rights

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

Measures Against Potential Misconduct

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

Maintaining Academic Publication Integrity

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

Protection of Intellectual Property Rights

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

Creativity and Openness

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

Complaints

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

Political and Commercial Concerns

Political or commercial factors will not affect editorial decisions.

Conflicts of Interest

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

Reviewer's Ethical Responsibilities

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

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

JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

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Information for the Authors

THE JOURNAL

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

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

REVIEW PROCESS

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

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

AUTHORSHIP

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

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

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

Final approval of the version to be published; AND

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

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

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

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

ORCID ID

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

PLAGIARISM DETECTION

All submissions are screened using similarity detection software at least two times: on submission and after completing revisions. In the event of alleged or suspected research misconduct, e.g., plagiarism, citation manipulation, or data falsification/fabrication, the editorial board will follow and act in accordance with COPE guidelines. Plagiarism, including self-plagiarism, that is detected at any stage will result in rejection of the manuscript.

PUBLICATION FEE - CHARGES

This journal assesses no submission fees, publication fees, or page charges.

MANUSCRIPT PREPARATION

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

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

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

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

MANUSCRIPT TYPES

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

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

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

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

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

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

Table 1. Limitations for each manuscript type.

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

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

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

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

Funding and other material support

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

REVISIONS

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

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

PUBLICATION PROCESS

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

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

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

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

SUBMISSION CHECKLIST

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

Formatting of text

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

Ensure that the following items are present:

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

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

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

JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

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E-ISSN 2980-2059 Volume 1 Issue 2 Year 2023

JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2023.07379
J Inonu Liver Transpl Inst 2023;1(2):29–30

Editorial

About the Book 'The Puzzle People' by Thomas Earl Starzl

Sezai Yilmaz,[1] Sami Akbulut,[1] Brian I Carr[2]

[1]Department of Surgery and Liver Transplant Institute, Inonu University Faculty of Medicine, Malatya, Türkiye
[2]Department of Translational Hepatocellular Carcinoma Research of Liver Transplantation Institute, Inonu University Faculty of Medicine, Malatya, Türkiye

Keywords: Thomas Earl Starzl, Father of Liver Transplantation, The Puzzle People, Memoriam of Starzl

Please cite this article as "Yilmaz S, Akbulut S, Carr BI. About the Book 'The Puzzle People' by Thomas Earl Starzl. J Inonu Liver Transpl Inst 2023;1(2):29–30".

"Journal of Inonu Liver Transplantation Institute (J Inonu Liver Transpl Inst)" will mainly include articles in the field of liver transplantation (LT). Based on this idea, It was planned to tell the story of LT in the period up to the pre-2000s, mainly by quoting from the book "Puzzle People", which describes the life of Starzl, a major pioneer of LT, and documents the historical origins of LT and making use of articles from that period.[1] Starzl stated that this book was about organ transplantation, or rather some people (scientists) whose work led to advances in the field of transplantation. In fact, the tendency to write his memoirs about the events that shaped the transplantation, which he tried to express in the book, was very weak, and recently the feeling of not writing predominated. However, the fact that he had two heart operations in the summer of 1990 motivated Starzl to write this book. Starzl states at the beginning of the book: "Now I think what I've been through might help someone who fears that their best efforts are going nowhere".

Readers who want documentation of some of the important events in the development of LT can also read the articles collected by Paul Terasaki, which reviews scientific progress of early work in this field.[2] Starzl's contribution to Terasaki's book has been to broadly describe the advances in transplantation over the past 35 years in which Starzl et al contributed so much. In fact, these were within the formal history, but the events described in the book made up the rest of the historical story in detail. These will be remembered with either a small smile or frown by those involved. It will even be remembered with tears by those who were involved in these events.

At a meeting in Capri, an Italian journalist asked Starzl the following question: Do you think a Puzzle People could be made with a heart, liver and pancreas taken from other people in the next 10 years? Starzl answered this question as follows: "There are now many examples of puzzle men or women who have received heart-kidney, pancreas-kidney, heart-lung, and heart-liver. More complicated combinations are possible in the near future". Starzl later thought how inadequate his answer was, that every patient who receives one or more of someone else's organs is a puzzle. It wasn't just the acquisition of new parts, the rest of the body also had to change in many ways for the gift to be ac-

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Submitted Date: 12.08.2023 **Revised Date:** 12.08.2023 **Accepted Date:** 13.08.2023 **Available Online Date:** 25.09.2023

cepted. And this was just the beginning. It was unpredictable how much the physical and mental parts would be put together in Puzzle people. Most patients died. Some have achieved a better world. Others also encountered a grim swamp, their vulnerabilities turned against them in ways they could not even imagine.

Over the years, transplantation has been such a great miracle that perhaps the least anticipated and potentially most important miracle in the history of medicine was not so easy to understand how it happened. Because we were led to stories written by doctors where someone's life could be summed up in a single sentence or a number in a table. In 1958, when Starzl started working on transplantation, this field was quite simple. There were no organ recipients in Boston, except for a few who had kidneys transplanted from identical twins as donors.[3] When John F Kennedy inaugurated his presidency three years later in 1961, transplantation was still a specialized field of study known to a few dreamers in surgical research laboratories. There was little that seemed realistic other than hopes that a successful transplant of a kidney or other life-supporting organ could be performed in humans. Until November 1963, when Kennedy was killed, kidney transplants were starting to be performed effectively, and the first cases were starting to be done for liver livers.[4,5] A new field in medicine was emerging. Many more years were needed to fulfill the inflated expectations of the early days. During these years, patients weren't just puzzle people who were remade. Surgeons and physicians in other specialties also changed, though not quickly. Their own lives were not in danger, but the lives of others were in their hands. Some were worn down as they gained experience, devastated, and some subjugated, but none remained the same. Many of the professional figures in the early days of transplantation are still in practical medicine. They are being pushed to the edge of the stage right now. One way to get there is at a conference where their past contributions and efforts are celebrated by that person's friends and former adversaries. These have happened frequently lately. These are like the city-by-city tours of old baseball stars. Some are modest, some are not, but they were all in the final season of the game. Meetings were not designed for what they were exploring or doing. The secrets were inside them. Starzl started writing this book, thinking that it would be best to retell his own story.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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

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JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2023.70298
J Inonu Liver Transpl Inst 2023;1(2):31–34

Review

Liver Transplantation for Severe Hepatic Trauma: Historical Review

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Abstract

Liver transplantation (LT) is rare in the context of liver trauma. There are no clear indications on which patients may benefit from LT, and what are the factors that may reduce or increase the success rate of LT for a trauma patient. We performed a review of the literature in order to better recognize indications and results in this setting.

A comprehensive review of the literature involving LT in the context of trauma using Pubmed and Google Scholar up to Dec 2022. As this is an uncommon event, we included all publications including case reports.

A total of 19 case reports and one retrospective trial were included in the review. Most past cases were performed in two stages including resection of the native liver with an anhepatic phase followed by liver transplant within a few days with availability of the donor liver. However, one stage was also performed successfully in hemodynamically stable patients with the presence of a donor organ. Bridge to transplantation by portocaval shunt and piggyback anastomosis to native vena cava demonstrated the best results. LT under conditions of infection resulted in increased mortality but can be feasible if there is a possibility of achieving source control of the infection. Auto-transplantation is an accepted option in cases of severe vascular trauma without extensive damage to the liver tissue and bile ducts.

LT in a trauma patient is valid option with accepted success rates. When performed, it is usually in grade 4 or higher liver trauma in an unstable patient, which has failed other treatment options or if there is irreversible damage to the liver tissue and bile ducts. A decision should be based on a multidisciplinary team discussion in an experienced LT center which should consider the chances of saving the patient with an acceptable quality of life in the face of wasting a costly liver graft.

Keywords: Autotransplantation, Hepatic trauma, Liver transplantation, Portocaval shunt

Please cite this article as "Zeid EEA, Netz U, Akbulut S. Liver Transplantation for Severe Hepatic Trauma: Historical Review. J Inonu Liver Transpl Inst 2023;1(2):31–34".

The liver trauma considered from the most common trauma and can reach up to 16 % from the total abdominal trauma.[1] The liver trauma can be divided by the mechanism to blunt and penetrating liver trauma, and by the severity according to the American Association for the Surgery of Trauma (AAST 2018 version) to five degrees.[2]

With the advancement of modern medicine techniques and the increase in therapeutic capabilities by means of intensive radiology, for example, the closure of a specific artery or vein to stop bleeding, operations of damage control strategies, perihepatic packing, and direct repair of vascular injuries, add to that an increase in understanding about

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Submitted Date: 05.05.2023 **Revised Date:** 05.05.2023 **Accepted Date:** 10.05.2023 **Available Online Date:** 25.09.2023

the possibilities of giving blood components and giving appropriate clotting factors have significantly reduced the needs for major liver surgeries in order to stop bleeding, or to repair the damage resulting from the injuries, at a time when researches have shownthe efficacy of these treatments may succeed in high rates and may reach 90%, also the failure of this treatment may not increase the risk.[3]

When the hepatic trauma was classified into grades 1-5 according to the AAST, it was mostly observed that the non-surgical treatment such as monitoring only or interventional radiologytreatment may be more effective with a grade of 1-3, and this of course refers to hemodynamically stable patients, while in cases of Grades 4-5 and unstable cases of patients may complicate matters further and the urgent need to resort to surgeries for damage control strategies such perihepatic packing, direct repair of vascular injuries, hepatectomies, and even liver transplantation.[4]

Over the past three decades, some case reports and retrospective trials have been published about liver transplantation in trauma situations. Despite this, there are no clear and explicit lines which patients may benefit from liver transplantation, and what are the factors that may reduce or increase the success rate of liver transplantation for a trauma patient. By looking at the history of liver transplantation in trauma cases, our aim to mark important points that may help, and to consider future research for a better explanation.

The Beginning of Liver Transplantation in Trauma Setting

For the first time in 1984, liver transplantation was done in patients who had suffered from liver trauma. It was published by Carlos O. et.al in the case report in which he talked about two cases of blunt trauma, the first transplant for a patient at the age of 24 years, the transplant took place after nearly two months due to liver failure and injury to the unrepairable bile ducts. The patient was discharged from the hospital after three weeks without significant complications. The second case, it occurred at the age of 17, and after three days from the injury only due to liver failure and damage to the bile ducts. He died after two weeks due to the CMV infection.[5] In all these cases in the 1980s, no long-term follow-up was mentioned.

The role of Two Stages Liver Transplantation, Anhepatic Phase and the Portocaval Shunt in Hepatic Trauma

In 1987 was mentioned first timethe possibility of two stages liver transplantation with anhepatic phase with the help of femoro-axial venous bypass. Severe lactate acidosis can be developed due to acute liver ischemia or due to reperfusion syndrome to prevent such cases, bicarbonate hemodialysis or continuoushemofiltration arteriovenous withreplacement fluids sodium bicarbonate-buffered was used prophylactically.

The possibility of liver transplantation with two stages hepatectomy and anhepatic phase which included bridge to transplantation by portocaval shunt also was described. The amounts of adrenalin and noradrenalin may increase in the anhepatic phase. It may decrease post-transplantation. By the substitution plasmatic coagulation was stabilized, showing higher values at 24 hours after transplantation than at 48 hours before transplantation. Under correct management the hepatic phase can be expended till 40 hours in some cases.[6-13]

Can Arterial Embolization or Surgical Packing in Liver Trauma setting lead to Liver Transplantation?

Since the nineteenth century, we are talking about liver transplantation in trauma in cases of failure of all attempts, such as observation, invasive radiology, and packing. It has been mentioned about the efficacy of these treatments, which may protect the patient from the need for liver transplantation, excessive bleeding, infection, post reperfusion syndrome, etc.

On the other hand,late complication as hepatic artery to portal veins fistulas which may lead to cholangiopathy due to ischemia, also in acute setting complication may develop a post-reperfusion syndrome, was mentioned as a result of perihepatic packingremoval. In some cases, the estimation of patient's situation, which can reach the maximum severity and may not be able to live for more than a few hours. Therefore, the liver should be removed and to perform a portocaval shunt. Also was mentioned a complete occlusion of hepatic artery proper,which resulted in irreversible liver ischemia, which also led to a relapse of the liver, but also to the bile ducts, which eventually led to the necessity of liver transplantation.[1, 14-16]

Is the Infection in Liver Trauma setting is Contraindication for Liver Transplantation?

The subject of infection in the pre-transplantation stage of the liver has always been considered as a relative contraindication. But if we talk about trauma cases, the possibility of an infection inside the abdomen due to intestinal rupture injuries or through penetrating injuries is very likely, so the exciting question may arise, are we exaggerating the liver The donor or the patient's traumatic life. Therefore, if we go back to some cases that have mentioned this subject directly or indirectly, liver transplantation is possible in the presence of infection, if we can control the infection or eradicate its basis with good and appropriate coverage of antibiotics.[3, 5, 8, 17, 18]

Liver Autotransplantation

In 2006, was mentioned for the first time in liver trauma about the attempt of extracorporeal repair and liver autotransplantation after total avulsion of hepatic veins and retro-hepatic Inferior vena cava injury. Liver transplantation in trauma is more susceptible to infection, especially after lowering immunity by immunosuppressing drugs, the chance of exposure to infection may increase, and since trauma is more of blood vessels without significant damage to the liver or bile ducts, the idea of removing the liver was mentioned while the patient is strapped on an extracorporeal bypass device between the left femoral vein and the left axillary vein using a centrifugal pump, the liver was transferred to the ex vivo team who washed the liver with 3 liters of the University of Wisconsin solution. Two liters through the porta and a liter through the main artery and liver transplantation again. It is true that the patient did not survive and died due to severe respiratory distress, but the liver from the data that was mentioned such as clotting factors, protein, liver enzymes and bilirubin was not liver failure, but rather the opposite. It was working and a significant improvement in its functions.[19]

What is the Best Technique to Perform the Liver Transplantation in Trauma setting?

In the largest retrospective study so far, from the European Liver Transplant Registry raised a very important point about the different ways in which the liver can be implanted such as piggyback, conventional with or withoutveno-venous bypass technique.

Statistically have been showed significant advantage in patients implanted with piggyback or conventionalwith veno-venous bypass in terms of patient and graft survival after surgery, and this despite the fact that in the normal transplants performed in the conventional way and a decrease in preload and afterload by almost 30% that the patient can still survive, still in a trauma patients this may lead to morbidity and mortality incidences increases without VVB, but it is still a point for deeper investigation and looking at the age of the patient, the age of the donor and comorbidities can be a point for prospective research.[3]

Discussion

There are around 30 case reports and series most of which spoke about theliver transplantation in trauma setting as a last option of treatment, and this is after all solutions have been tried or it will not be possible to offer them. It should be remembered that liver transplantation under conditions of infection showed a higher mortality according to the retrospective study, but we have witnessed several case reports that showed liver transplantation can be offered if there is an ability to resect the source of the infection.[3, 5, 8, 16-18]

The auto-transplantation option can be possible there's a trauma of the blood vessels only without extensive damage to the liver tissue and bile ducts.[19]

Most of the liver transplants in trauma setting was performed in the past are in two stages but there is still an option for one stage, and it depends on some factors like hemodynamic stability and the presence of a graft or a donor.[6-13, 20]

Liver transplantation techniques such as piggyback and conventional with veno-venous bypass showing the safest techniques in trauma setting.[3]

Conclusion

To summarize our words, liver transplantation in the context of trauma is supposed to be another option in the surgeon's pocket butconsidering the number of these cases and the high mortality, it is highly recommended to have a multidisciplinary committee for discussion and to consider a liver graft wasting in front of patient's life saving and the quality of life.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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

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JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2023.35744
J Inonu Liver Transpl Inst 2023;1(2):35–40

Original Research

Effect of Underlying Chronic Liver Disease on Lysosomal Acid Lipase Activity: Case-Control Study

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Abstract

Objectives: The goal of the current study is to examine the diagnostic usefulness of lysosomal acid lipase (LAL) activity in cirrhotic patients according to healthy control groups utilizing assessment methods including machine learning methods.

Methods: An open-access dataset was used in the current study and included 63 patients with cryptogenic cirrhosis (cryptogenic group), 88 patients with cirrhosis of known underlying causes (non-cryptogenic group), and 97 healthy individuals (control group). Mann Whitney U test was utilized for comparisons between cirrhosis groups and control group and for comparisons between cirrhosis groups. The Stochastic Gradient Boosting (SGB) method was utilized to model the patients with cirrhosis and the control group.

Results: LAL activity was observed to be reduced in cirrhotic patients (cryptogenic and known etiology cirrhosis) when compared to control groups. The machine learning modelling algorithm showed that the cirrhotic group and the control group were distinguished from each other with an accuracy of 93.2%. The platelets, LAL activity, ALT, AST, and white blood cells were obtained as the most important variables according to variable importance values.

Conclusion: LAL activity value can be evaluated diagnostic marker in cirrhotic patients. However, it is not a discriminative marker that differentiates different etiologies (cryptogenic and cirrhosis of known etiology).

Keywords: Chronic liver disease, Cirrhosis, Cryptogenic cirrhosis, Lysosomal acid lipase activity

Please cite this article as "Kucukakcali Z, Akbulut S, Sahin TT, Colak C. Effect of Underlying Chronic Liver Disease on Lysosomal Acid Lipase Activity: Case-Control Study. J Inonu Liver Transpl Inst 2023;1(2):35–40".

Cirrhosis is a common disease with high death and morbidity rate around the world.[1] Cirrhosis is caused by chronic liver inflammation, which proceeds to diffuse hepatic fibrosis. End-stage liver failure occurs when the normal hepatic structure is replaced by regenerating hepatic nodules.[2] Chronic liver inflammation does not usually result in cirrhosis; but, if it does, the time it takes to develop cirrhosis can range from weeks in individuals with severe biliary blockage to decades in persons with chronic etiologies such as viral hepatitis. Cirrhosis can have an asymptomatic (initial) phase followed by a symptomatic phase that might last months to years.

In the absence of a liver transplant, this symptomatic phase, known as decompensated cirrhosis, is associated with repeated hospitalizations, a decrease in patients' quality of life, and even mortality.[3, 4] Cirrhosis was responsible for 2.4% of global deaths in 2019.[5] Cirrhosis is mostly caused by HCV infection, alcoholic liver disease, HBV infection, and non-alcoholic fatty liver disease (NAFLD).[6] In other words,

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Submitted Date: 06.07.2023 **Revised Date:** 28.07.2023 **Accepted Date:** 29.07.2023 **Available Online Date:** 25.09.2023

etiologies can be classified into viral (HBV, HCV, HDV), alcohol-related (alcoholic liver disease), autoimmune (primary biliary cholangitis, autoimmune hepatitis, primary sclerosing cholangitis), biliary (biliary strictures, biliary atresia), vascular (veno-occlusive disease, Budd-Chiari syndrome etc.), metabolic and genetic (NAFLD, type IV glycogen storage disease, α1-antitrypsin deficiency, Wilson's disease, cystic fibrosis, lysosomal acid lipase deficiency, hemochromatosis, progressive familial intrahepatic cholestasis, tyrosinemia type 1), chronic drug-induced and unknown (cryptogenic) causes.[7]

Cryptogenic cirrhosis is a case of hepatic cirrhosis in which the exact etiology cannot be determined despite detailed clinical, laboratory, and histological evaluations. In fact, a diagnosis of exclusion is made to perform the diagnosis of cryptogenic cirrhosis and the diagnosis is made when the etiologies causing cirrhosis are ruled out. The incidence of cryptogenic cirrhosis decreases considerably by the development of new diagnostic tools and defining the factors causing cirrhosis.[8] Although it has been said that the prevalence of cryptogenic cirrhosis is 5%-30% in previous studies, there are no definite results since most of these results were obtained from studies conducted in single centers.[9, 10] When transplant databases are examined, it is reported that the prevalence of cryptogenic cirrhosis is around 10%.[11, 12]

The cause and severity of liver disease have changed dramatically during the last decade.[13, 14] The epidemiology and severity of cirrhosis are changing due to the increasing prevalence of obesity and alcohol consumption and due to advances in the management of HBV and HCV virus infections.[3, 14] For this reason, new markers and diagnostic criteria are needed to determine cirrhotic patients and also to discriminate among the different etiologies and stages of cirrhosis.

An enzyme called lysosomal acid lipase (LAL) controls the intra-lysosomal hydrolysis of triglycerides and cholesterol esters to create free cholesterol and fatty acids. A mutation in the LIPA gene results in the uncommon autosomal recessive genetic condition known as LAL deficiency, which is characterized by triglyceride and cholesterol ester buildup in a number of organs. In hepatocytes and macrophages (Kupffer cells), LAL deficiency causes a buildup of TG and cholesterol esters, which encourages chronic inflammation and fibrosis. Given the high incidence of severe liver fibrosis in the LAL deficient condition and the rapid development of cirrhosis, it is likely that the accumulation of lysosomal triglycerides and cholesterol ester is one of the main causes of liver fibrosis.[15, 16] According to a recent study, mice with hepatocyte-specific LAL deletion had increased transaminases as well as elevated levels of hepatic cytokines and chemokines, which led to Kupffer cell activation and liver damage.[17]

In the present study, it is aimed to evaluate LAL activity in patients with cirrhosis. Also, our secondary aim was aimed to compare LAL activity with cirrhosis patients of known etiology to check whether LAL activity can aid determine patients with cryptogenic cirrhosis by using machine learning methods.

Methods

Dataset and Patient Characteristics

An open-access data set was utilized in the study. In the data set used, the patients consist of three groups. There were 63 patients diagnosed with cryptogenic cirrhosis in the first group (cryptogenic group), 88 patients with cirrhosis of known etiology in the second group (non- cryptogenic group), and 97 healthy individuals without clinically important liver disease in the third group (control group). The patient groups in the study were matched in terms of gender and age.[18]

Modelling Phase

Stochastic Gradient Boosting (SGB), a tree-based technique from machine learning methods, was utilized in the modeling phase to model the control group and patients with cirrhosis and to explore the effect of LAL. Friedman invented stochastic gradient boosting by integrating randomization into the gradient boosting approach. A random subsample is chosen at each refresh in SGB using a permutation sampling approach. This subsample, rather than all learners, is used to generate the model update, lowering the correlation between trees.[19] This method, like other ensemble learning methods, does not produce massive trees; instead, each tree (approximately 100-200 trees) generated during the process is summed up, and each observation is classified based on the most common categorization across trees. These distinctions distinguish the SGB approach from other augmentation techniques and reduce its unbalanced data sets and sensitivity to outliers. This approach, which has a very high predictive power compared to other algorithms, is 5 times faster than other methods and incorporates a series of regularizations that can improve the overall performance of the model while decreasing overfitting and overlearning.[19, 20] The data are separated as 80% training 20% test data. To confirm model validity, the n-fold cross-validation method, one of the resampling methods, was used in this work. In this method;

The dataset is first separated into n pieces, after which the model is applied to those pieces. In the second step, one of

the n parts is used for testing, while the remaining n-1 parts are used for training. In the last stage, the cross-validation approach is evaluated using the average of the values collected from the models. Accuracy (Acc), balanced accuracy (bacc), sensitivity (se), specificity (sp), positive predictive value (ppv), negative predictive value (npv), and F1-score measures were utilized to assess the modeling performance. The graphical summary showing the method, analysis and modeling process applied in the study is shown in Figure 1.

Biostatistical Analysis

In the study, data were summarized as median (95 percent confidence intervals), and number (percentage). The Kolmogorov-Smirnov test was used to determine whether or not the data was normal. The Mann-Whitney U test was utilized for statistical analysis of non-normally distributed data. $p<0.05$ was regarded statistically significant. Analyzes were performed with IBM SPSS Statistics 25. Since the open access data set was used in this study, ethical approval was not required.

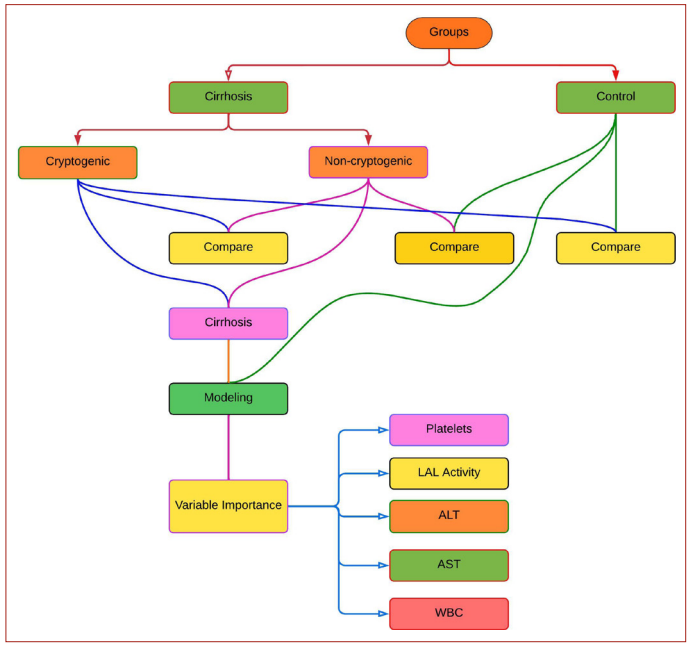

Figure 1. Method, analysis and modeling process.

Results

The mean age of all patients and healthy individuals utilized in the study was 66.24±9.51. When the mean age of the groups is examined, the mean age of the cryptogenic patients was 68±10, the mean age of the cirrhosis patients with known etiology was 65±10 years, and the mean age of the control group was 66±8 years.

Comparison of Control and Cryptogenic Cirrhosis Patients

When the total cholesterol, triglycerides, LDL cholesterol, AST, ALT, HDL cholesterol, platelets, white blood cells, and LAL activity variables were examined for the control and cryptogenic groups, a significant difference was found between the two groups in all variables except triglycerides. Table 1 shows the findings of the analysis.

Comparison of Control and Cirrhosis of Known Etiology

When the total cholesterol, triglycerides, LDL cholesterol, AST, ALT, HDL cholesterol, platelets, white blood cells, and LAL activity variables were examined for the control and non-cryptogenic groups, significant differences were obtained between the 2 groups in all variables. Table 2 shows the findings of the analysis.

Comparison of Cryptogenic Cirrhosis and Cirrhosis of Known Etiology

When the total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, AST, ALT, platelets, white blood cells, LAL activity and spleen volume variables were examined

Table 1. Comparison of control and cryptogenic cirrhosis groups in terms of variables

Variables [Median (95 % CI)]	Control group	Cryptogenic group	p*
Total Cholesterol (mg/dL)	200 (194-213)	145 (128-152)	<0.001
LDL Cholesterol (mg/dL)	123 (113-128)	72 (66-83)	<0.001
HDL Cholesterol (mg/dL)	50 (47-53)	36 (35-40)	<0.001
Triglycerıdes (mg/dL)	116.5 (108-125)	131 (115-159)	0.053
AST (IU/L)	17 (16-20)	39 (33-42)	<0.001
ALT (IU/L)	24.5 (23-27)	38 (34-45)	<0.001
Platelets (cells/mm^3)	225 (215-244)	105 (96-125)	<0.001
WBC (cells/mm^3)	6.02 (5.8-6.54)	4.89 (4.36-5.35)	<0.001
LAL activity (nmol/Spot/H)	0.96 (0.89-1.08)	0.62 (0.52-0.76)	<0.001

*:Mann Whitney U test.

Table 2. Comparison of control and non- cryptogenic cirrhosis groups in terms of variables

Variables [Median (95 % CI)]	Control group	Non-cryptogenic group	p*
Total Cholesterol (mg/dL)	200 (194-213)	148 (135-166)	<0.001
LDL Cholesterol (mg/dL)	123 (113-128)	85 (73-92)	<0.001
HDL Cholesterol (mg/dL)	50 (47-53)	45 (39-49)	0.012
Triglycerıdes (mg/dL)	116.5 (108-125)	94 (85-102)	0.012
AST (IU/L)	17 (16-20)	31 (27-46)	<0.001
ALT (IU/L)	24.5 (23-27)	29 (26-34)	0.036
Platelets (cells/mm^3)	225 (215-244)	114 (92-125)	<0.001
WBC (cells/mm^3)	6.02 (5.8-6.54)	5.34 (4.77-6.03)	0.002
LAL activity (nmol/Spot/H)	0.96 (0.89-1.08)	0.54 (0.48-0.67)	0.001

*: Mann Whitney U test.

for the cryptogenic and non-cryptogenic groups, only total cholesterol, HDL and triglyceride variables were statistically different. Table 3 shows the findings of the analysis.

Modelling Results

The results of the performance measurements obtained from the modeling using cirrhotic patients and control individuals in the test and training set are provided in Table 4. The graph of the significance of the variables obtained from the modeling is given in Figure 2. When the significance of the obtained variables is examined, it is seen that the most important variables that explain the dependent variable (control/cirrhosis) are platelet, LAL activity, ALT, AST, and white blood cells, respectively.

Discussion

Chronic liver disease (CLD) and cirrhosis cause a high burden of disability and increased healthcare costs, in addition to 2 million deaths worldwide each year. An accurate estimation of the burden of cirrhosis is vital for setting research and policy priorities. For this reason, worldwide studies have gained importance to provide early diagnosis and treatment of cirrhosis.[21] There is a need for new markers that can detect cirrhosis at early stages. Therefore, the current study focused on the changes in the LAL activity in patients with cirrhosis. Within the scope of the study, in addition to the LAL activity variable, total cholesterol, AST, ALT, LDL cholesterol, HDL cholesterol, platelets, triglycerides, and white blood cells variables were examined in cryptogenic cirrhosis, cirrhosis with a known etiology and control groups, and their changes between groups were determined. In addition, to determine the importance of the LAL activity in the cirrhosis and control groups, modeling was performed using the SGB method which is one of the machine learning technique.

When the results were examined, significant statistical differences were obtained in all the variables examined (except for the triglycerides variable) in the analyses performed in healthy control and cryptogenic cirrhosis patients. Variables that differ were total cholesterol, platelets, LDL cholesterol, AST, HDL cholesterol, ALT, white blood cells, and LAL activity.

Table 3. Comparison of cryptogenic and non- cryptogenic cirrhosis groups in terms of variables

Variables [Median (95 % CI)]	Cryptogenic group	Non-cryptogenic group	p*
Total Cholesterol (mg/dL)	145 (128-152)	147.5 (135-166)	0.139
LDL Cholesterol (mg/dL)	72 (6-83)	85 (73-92)	0.037
HDL Cholesterol (mg/dL)	36 (35-40)	45 (39-49)	0.023**
Triglycerıdes (mg/dL)	132.5 (115-159)	94 (85-102)	<0.001
AST (IU/L)	39 (33-42)	31 (27-46)	0.681
ALT (IU/L)	37.5 (32-44)	29 (26-34)	0.059
Platelets (cells/mm^3)	105 (96-130)	114 (92-125)	0.986
WBC (cells/mm^3)	4.93 (4.36-5.4)	5.34 (4.77-6.03)	0.095
LAL activity (nmol/Spot/H)	0.62 (0.52-0.76)	0.54 (0.48-0.67)	0.450
Spleen volume (cm^2)	70 (59-80)	59 (51-67)	0.151

*: Mann Whitney U test.

Table 4. Performance metrics values obtained after modeling

Performance Metrics	Training Stage Value (%)	Testing Stage Value (%)
Accuracy	98.9	93.2
Balanced Accuracy	98.7	93.4
Sensitivity	97.3	94.4
Specificity	100	92.3
Positive predictive value (PPV)	100	89.5
Negative predictive value (NPV)	98.2	96
F1-score	98.6	91.9

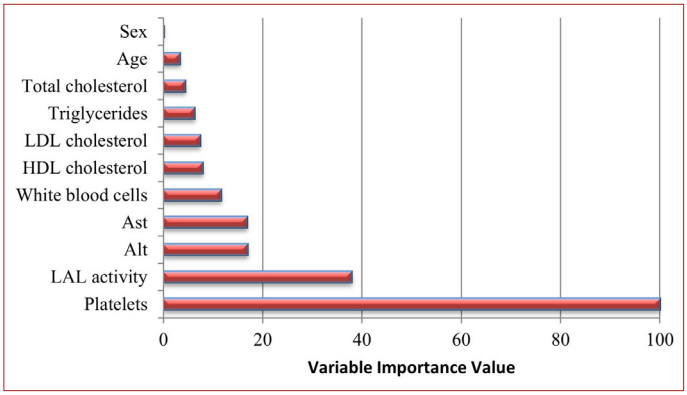

Figure 2. Variable importance plot.

The decrease of 0.34 units in LAL activity in the cryptogenic cirrhosis group is statistically significant compared to the control group. The LAL activity value is lower in cryptogenic cirrhosis patients than in the control group. In the analysis performed in control and cirrhosis with known etiology, significant statistical differences were obtained in all variables including total cholesterol, AST, LDL cholesterol, triglycerides, HDL cholesterol, ALT, platelets, white blood cells, LAL activity. The decrease of 0.42 units in LAL activity in cirrhosis with known etiology is statistically significant compared to the control group. The results of our study show that the LAL activity value is at a lower level in cirrhosis patients with known etiology compared to the control group. If the results obtained for the cryptogenic and known etiology cirrhosis group are compared , it was observed that significant differences are obtained in total cholesterol, HDL, and triglycerides variables. It was observed that the LAL activity did not differ significantly between both groups (cryptogenic and non- cryptogenic groups) with cirrhosis.

The LAL activity decreased in both cirrhosis patient groups (cryptogenic and non- cryptogenic) compared to the control group, while there is no differential effect between the cryptogenic and non- cryptogenic cirrhosis groups.

When the modeling results were conducted to determine the importance of LAL activity in the control and cirrhosis patient groups; accuracy (ACC), balanced accuracy (BACC), Sensitivity (SE), Specificity (SP), positive predictive value (PPV) and negative predictive value (NPV), and F1 score were 93.2%, 93.4%,94.4%, 92.3%, 89.5%, 96%, and 91.9%, respectively. According to the performance metric values obtained from here, we can assume that the control and cirrhosis patient group can be classified with high accuracy by modeling with the independent variables (total cholesterol, triglycerides, LDL cholesterol, platelets, AST, HDL cholesterol, ALT, white blood cells, and LAL activity). When the variable importance values produced from the modeling are reviewed, platelets are found to be the most important variable related to cirrhosis. In the second row, in accordance with the purpose of the study, we see that the LAL activity variable is among the most influential variables on the dependent group. The LAL activity variable is followed by ALT, AST, white blood cells, HDL cholesterol, LDL cholesterol, triglycerides, and total cholesterol variables, respectively.

Based on the results obtained in the cirrhosis patient group compared to the control group, when the studies conducted with the platelet variable with the highest variable importance value were examined, it was determined that the platelet value was lower in patients with cirrhosis compared to the control group.[22, 23] Similarly, in the current study, the platelet value was found to be lower in both cryptogenic and cirrhosis groups with known etiology compared to the control. However, no difference in platelet value was observed between cryptogenic and known etiology patients with cirrhosis. The decrease in LAL activity in the cirrhosis group compared to the control is striking. However, there is no significant difference in LAL activity between cryptogenic and cirrhosis groups with known etiology. It was reported that the LAL activity was low in the cryptogenic patients.[24] Another study showed reduced LAL activity in patients with cirrhosis.[18] In the current study, it was determined that LAL activity that is an important variable in cirrhosis and it was validated by machine learning methods in addition to basic statistical tests. Other predictive variables include AST and ALT, and the values of these markers increase in liver disease.

In conclusion, the LAL activity can be considered as a valuable parameter that can be examined in cirrhosis patients. Currently large sample size studies are required to evaluate the value of LAL activity to discriminate among the different etiologies of cirrhosis.

Disclosures

Ethics Committee Approval: This article was produced from open-access dataset (https://doi.org/10.1371/journal.pone.0156113.s001). Therefore, it has been reported by the institute that ethics committee approval is not required.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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

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JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2023.69775
J Inonu Liver Transpl Inst 2023;1(2):41–44

Original Research

Resection in Patients with Combined Hepatocellular-Cholangiocarcinoma

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Abstract

Objectives: Combined hepatocellular-cholangiocarcinoma (cHCC-CC) is a rare tumor that accounts for 2-3% of primary liver cancers. cHCC-CC mostly have a poor prognosis. There are publications reporting highly contradictory results regarding long-term survival after resection. The aim of this study is to examine the post-resection results of patients with cHCC-CC.

Methods: The data of 7 patients with histopathologically proven cHCC-CC collected prospectively at Inonu University Liver Transplantation Institute, between 2013-2023, were retrospectively analyzed. The preoperative variables examined were age, gender, underlying liver disease, alpha-fetoprotein (AFP) and carbonhydrate antigen (CA 19-9) levels. No patient was diagnosed with cHCC-CC in the preoperative tru-cut biopsies.

Results: Patients were predominantly male (M/F: 6/1) and median age 57 years. All patients had chronic hepatitis or cirrhosis. AFP levels were above 10 ng/dL in 5 cases (7-813 ng/dL) and CA 19-9 levels were normal in all cases. Perihilar lymph nodes resected during hepatectomy were involved with tumor in three patients. The maximum tumor diameter was 11 cm and the mean tumor diameter was 4.5 cm. Bisegmental resection was performed in four patients with cHCC-CC. Major hepatectomy was performed in two cases. Histopathologically, surgical margins were not tumor-free in two patients. The seventh case first underwent segment II-III resection for hepatocellular carcinoma (HCC), but left hemihepatectomy was performed 1.5 months later due to the presence of histopathological tumor in the surgical margins. Histopathological diagnosis confirmed HCC. After 27 months, the patient underwent salvage transplantation due to tumor recurrence within Milan criteria. Histopathological diagnosis was cHCC-CC. The patient who underwent right hemihepatectomy died on the 3rd postoperative day due to reasons other than hepatic failure (cardiac instability). One-year survival of the remaining 6 cases was 71.4%, 3-year survival was 14.3%, and 5-year survival was 14.3%.

Conclusion: cHCC-CC is an aggressive primary liver tumor associated with poor long-term oncological outcomes. Surgical resection is the only curative or palliative treatment option to improve the poor prognosis. In this study, we discussed the diagnosis, treatment and survival of 7 patients with advanced stage cHCC-CC. Studies that require a multidisciplinary approach for the treatment of these tumors are necessary to improve the survival of the patients.

Keywords: Combined hepatocellular cholangiocarcinoma, hepatocellular carcinoma, intrahepatic cholangiocarcinoma

Please cite this article as "Usta S, Karakas S, Yilmaz S, Ince V, Sagir Kahraman A, Akatli AN, et al. Resection in Patients with Combined Hepatocellular-Cholangiocarcinoma. J Inonu Liver Transpl Inst 2023;1(2):41–44".

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Submitted Date: 07.07.2023 **Revised Date:** 09.08.2023 **Accepted Date:** 09.08.2023 **Available Online Date:** 25.09.2023

Combined hepatocellular-cholangiocarcinoma (cHCC-CC) is a rare tumor that accounts for 2-3% of primary liver cancers.[1] This tumor is characterized by histological heterogeneity of both hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCC) elements. Preoperative demographic, clinical, and radiological features are not pathognomonic and may indicate either of the two tumors. Biopsy results are often inconsistent with post-resection pathological results. There are publications reporting highly contradictory results regarding long-term survival after resection.[2-4] The aim of this study is to examine the post-resection results of patients with cHCC-CC.

Methods

In this study, the data of 7 patients with cHCC-CC collected prospectively at Inonu University Liver Transplantation Institute, between 2013-2023, were retrospectively analyzed. The preoperative variables examined were age, gender, underlying liver disease, alpha-fetoprotein (AFP) and carbonhydrate antigen (CA 19-9) levels. Histopathological examination of the postoperative resection materials were reviewed in detail. All patients assessed with dynamic enhanced computed tomography (CT) and five patients revealed with upper abdominal magnetic resonance imaging (MRI) with hepatospecific contrast medium preoperatively. No patient was diagnosed with cHCC-CC in the preoperative tru-cut biopsies. In all 7 patients who underwent surgical resection, serum bilirubin was below 2 mg/dL, platelet levels were above 150.000 /mm^3, and nobody had splenomegaly, ascites, or esophageal varices. The patients were followed up postoperatively with imaging tools (CT and MRI) and serial tumor marker examinations.

Biostatistical Analysis

Quantitative variables were summarized as median (95 % Confidence Intervals), and qualitative variables were given as number (percentage). The Kaplan-Meier estimate was used to calculate overall survival. Analyzes were performed using IBM SPSS Statistics 25.

Results

There were 7 patients with cHCC-CC who were diagnosed histopathologically following resection. Patients were predominantly male (M/F: 6/1) and median age 57 years (95% CI=38-77 years). All patients had chronic hepatitis or cirrhosis. Four patients were positive for hepatitis B virus and two were positive for hepatitis B plus D viruses. Despite another patient being negative for viral serology, she had histopathological findings of chronic hepatitis. AFP levels were above 10 ng/dL in 5 cases (7-813 ng/dL) and CA 19-9 levels were normal in all cases. Perihilar lymph nodes resected during hepatectomy were involved with tumor in three patients. Tumors had a single nodule in four patients and multiple nodules in three patients. The maximum tumor diameter was 11 cm and the mean tumor diameter was 4.5 cm (3.2-11 cm).

The tumors were not significantly different from 'conventional' HCCs on macroscopic examination. Most of the cases were unifocal, three of them were multifocal. On postoperative histopathological examination, the tumors showed a combination of the two components, either close to each other or deeply intermingled. The cholangiocarcinomatous component revealed an adenocarcinoma morphology with variable desmoplastic reaction. The hepatocellular carcinoma component demonstrated hepatocytic differentiation with the appropriate immunohistochemical features. Confirmation of a hepatocellular carcinoma component was shown by immunohistochemical cytoplasmic staining with HepPar-1, Arginase1, canalicular staining with polyclonal CEA or CD10 and sinusoidal capillarization pattern by CD34. The cholangiocarcinomatous component was stained positive for CK7 and CK19 immunohistochemically. In most of the cases, hepatocellular carcinoma was poorly differentiated and cholangiocarcinoma component was poorly or moderately differentiated in all cases.

The imaging features that favor ICC over HCC were present for most of the lesion at CT and MRI. The prominent features of the cases were the early rim enhancement and delayed central enhancement in the portal venous and delayed phase of contrast injection. The less common imaging features that favor the diagnosis of ICC were liver surface retraction, hypointensity on T2W images and target appearance of DWI. One lesion had imaging findings of HCC including arterial non-rim enhancement and portal venous washout. The only one lesion with the largest diameter that occupying right lobe of the liver had findings of right portal venous invasion.

Bisegmental resection was performed in 4 patients with cHCC-CC, which consisted of segments VI-VII in two cases, segments VI and VIII in one case, and segment II- III in one case. Major hepatectomy was performed in two cases consisting of right hemihepatectomy and central hepatectomy. In the patient who underwent right hemihepatectomy, there was tumor thrombus in the right portal vein branch extending to the left portal vein confluence (vP3). Histopathologically, surgical margins were not tumor-free in two patients who underwent bisegmental resection localized to the right lobe and in the patient who underwent central hepatectomy. In the seventh case, there was a different scenario. The 24-year-old male patient first underwent segment II- III resection for HCC, but left hemihepatectomy

was performed 1.5 months later due to the presence of histopathological tumor in the surgical margins. Histopathological diagnosis confirmed HCC. After 27 months, the patient underwent salvage transplantation due to tumor recurrence within Milan criteria. Histopathological diagnosis was cHCC-CC. This patient is alive for 10 years after the transplant. The patient who underwent right hemihepatectomy died on the 3rd postoperative day due to reasons other than hepatic failure (cardiac instability). The median follow up time of the remaining 6 cases was 380 days (95% CI: 112-3422). One-year survival was 71.4%, 3-year survival was 14.3%, and 5-year survival was 14.3% (Fig. 1). Six cases are currently not alive. The cause of death in all cases was tumor recurrence. The patients with tumor recurrence were treated with systemic chemotherapy.

Discussion

Although radical surgical interventions are the most emphasized treatments for patients with cHCC-CC, 5-year survival rates are about 30% due to the aggressiveness of the tumor. Major or segmental hepatic resections together with lymphadenectomy is the recommended treatment.[5-8] Age, male gender, elevated GGT, macrovascular invasion and hilar lymph node metastases are associated with poor prognosis after resection.[9] No effect of adjuvant treatments on recurrence or survival has been demonstrated.[10] The inability to draw a conclusion from the publications containing a small number of patients is a disadvantageous issue regarding the treatment of this tumor. In our study, seven cases were also reviewed. Despite surgical interventions that we consider radical, our survival rate was 71.4% at 1 year, but it was only 14.3% at 5 years, even with salvage liver transplantation. This result is a summary of how aggressive this tumor is.

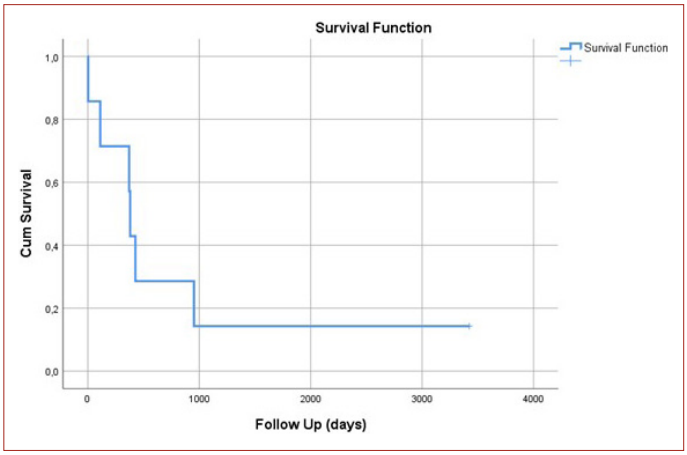

Figure 1. Survival curve of 7 patients with cHCC-CC treated with resection.

Radiologically findings suggestive of malignancy but atypical for HCC or CC should suggest cHCC-CC. In resectable tumors, the diagnosis of this tumor can be established by detailed histopathologic examination of the explant, but failure to diagnose it in unresectable cases cHCC-CC may be suggested by unresponsiveness to locoregional and systemic chemotherapy.[11] No radiological or histopathological preoperative diagnosis of cHCC-CC could be made in any of our cases, and even in the case that underwent to salvage LT, the histopathologic diagnosis was HCC even in the previous two hepatic resections. This raises the question of whether cHCC-CC diagnosed after LT develops as a separate tumor or after differentiation of the primary tumor.

Metastatic lymph nodes in the porta hepatis are predictors of long survival. The contribution of lymphadenectomy to survival in these cases is controversial.[12] Could it be a useful multidisciplinary treatment modality to consider surgical intervention after possible downstaging with systemic or local chemotherapy in these cases? Answering this question may contribute to survival in patients with cHCC-CC. Perineural invasion in liver tumors is a factor that adversely affects overall survival.[13] However, there is insufficient data on whether this is a prognostic factor in cHCC-CC. Metastatic porta hepatis lymph nodes in 3, lymphovascular invasion in 4, and perineural invasion in 2 of our cases were present. More importantly, all cases had signs of cirrhosis or chronic hepatitis, and all tumors were histopathologically undifferentiated. It is likely that these parameters, which negatively affect survival, explain the low survival rate in our cases.

It has been shown that anatomical resections in liver cancers are associated with better survival than non-anatomical resections.[14] However, cirrhosis or chronic hepatitis findings in our cases seem to lead us to parenchyma-preserving anatomic resections. Despite this strategy, we performed major hepatectomy in 2 cases with tumors larger than 10 cm. We believe that survival of more than 1 year despite positive surgical margins in the case who underwent central hepatectomy is an acceptable palliation in such an advanced stage tumor.

Extrahepatic portal vein invasion is rare in patients with cHCC-CC, but hepatic vein invasion is more common. One of our cases had portal vein invasion at vP3 level and we performed a right hemihepatectomy. It is known that these cases probably released tumor cells into the systemic circulation and their survival was not good.[15] The role of liver transplantation in cHCC-CC is controversial. It has been reported that cHCC-CC cases within the Milan criteria have similar survivals to HCC within the same criteria.[16] The survival over 10 years in our case, within the Milan criteria,

who underwent salvage LT seems to be a confirmation of this. This subject is out of the scope of the present article and will be presented in another study of our institute.

In summary, cHCC-CC is an aggressive primary liver tumor associated with poor long-term oncological outcomes. Surgical resection is the only curative or palliative treatment option to improve the poor prognosis. In this study, we discussed the diagnosis, treatment and survival of 7 patients with advanced stage cHCC-CC. Studies that require a multidisciplinary approach for the treatment of these tumors are necessary to improve the survival of the patients.

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.K., B.I.C; Design – V.I., S.A., S.Y.; Supervision – S.Y., B.I.C.; Materials – V.I., A.S.K., B.I., A.N.A.; Data collection &/or processing – V.I., S.K., S.Y.; Analysis and/or interpretation – T.T.S., S.A; Literature search – T.T.S., S.Y., S.A; Writing – Z.K., S.A; Critical review – S.A., S.Y., B.I., B.I.C.

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JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2023.68077
J Inonu Liver Transpl Inst 2023;1(2):45–51

Original Research

Selective Gene Up- and Down-Regulation as Potential Predictors of the Behavior of HBV-Associated Hepatocellular Carcinoma?

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Abstract

Objectives: The current study aimed to identify genes that show differential expression in tumor tissue by performing bioinformatic analysis from matched tumor and non-tumoral liver tissue samples obtained from HBV- HCC patients.

Methods: mRNA data from 21 HBV-HCC patients were used in this open-access database-based study. The mRNA sequence data were obtained from 21 pairs of tumors and non-tumoral liver tissue samples. Gene expression analysis was used in bioinformatics analyses and log2FC value was used to identify genes showing up- and down-regulation. To illustrate differentially expressed genes, the volcano plot was utilized.

Results: Our analysis showed that many genes showed quite different expression levels in tumor tissues. Among these genes, the genes that showed very high fold upregulation were GNG4, IGF2BP1, GPC3, PEG10, AFP, SPINK1, EPS8L3, MYCN, DUSP9, and DKK1 genes, respectively. The down-regulated genes were CNDP1, WAKMAR1, LINC01818, TH, LINC01093, MARCO, LOC101927078, LOC105372263, FCN2, and CLEC4M.

Conclusion: Our study defined various genes that might be utilized as potential biomarkers for HBV-related HCC. Targeted treatment for these genes can be developed and verified for efficacy in treatment.

Keywords: Biological behavior, Down-regulated genes, Hepatocellular carcinoma, Hepatitis B infection, Up-regulated genes

Please cite this article as "Kucukakcali Z, Akbulut S, Colak C. Selective Gene Up- and Down-Regulation as Potential Predictors of the Behavior of HBV-Associated Hepatocellular Carcinoma? J Inonu Liver Transpl Inst 2023;1(2):45–51".

Nearly two billion individuals worldwide are infected with the hepatitis B virus (HBV). At this point, there are around 350 million carriers, HBV is one of the most common public health problems, especially in the Middle East and Eastern Asia.[1] Even though the HBV vaccine is efficient and safe, and it has decreased the incidence of HCC to a certain extent, HBV infection remains the main etiologic factor for hepatocellular carcinoma (HCC) globally. More than half of all HCC cases are caused by HBV-related chronic liver disease.[2, 3] HBV surface antigen (HBsAg) carriers had a 25-37-fold higher lifetime risk of developing HCC than non-infected persons, according to recent research in Asia and North America.[4, 5] HCC risk is known to be increased by viral load;[6-8] however, other variables may be involved. Several studies in extremely prevalent areas, notably Mainland China and South Africa, have discovered a synergistic link between HBV infection and aflatoxin B1.[9]

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Submitted Date: 05.06.2023 **Revised Date:** 13.06.2023 **Accepted Date:** 19.06.2023 **Available Online Date:** 25.09.2023

HCC is the seventh most common cancer disease and the third main cause of cancer deaths globally. According to a recent epidemiological analysis, the incidence of liver cancer is rising and will continue to rise, globally. This is attributed to the rising incidence of fatty liver disease and Non-Alcoholic Steatohepatitis (NASH).[10] HCC has non-specific symptoms and the clinical diagnosis of the patients is difficult. The most important therapeutic approach is screening and treatment at an early stage.[11] However, there is no cost-effective screening protocol. For these reasons, the majority of the patients are diagnosed at a later stage, and these important results in poor prognosis for the patients. Advances in the molecular basis of HCC are of vital importance in these circumstances because it enables scientists to develop biomarkers for early diagnosis of the tumors and novel targeted therapeutics with higher potential for treatment.[12,13] The genetic and molecular characteristics of HCC are complex. There is a vast amount of intricate genetic changes that play a role in the pathogenesis of HCC. During hepatocarcinogenesis, point mutations, chromosomal amplification/deletions, gene methylations, and histone deacetylations contribute to hepatocarcinogenesis by disrupting the regulation of signal transduction pathways. Molecular studies on HCC have revealed that activation of cellular oncogenes, inactivation of tumor suppressor genes, and disruptions in signaling pathways such as PI3K/AKT, Wnt/-catenin, Ras, p53, pRB, , MAPK, STAT, JAK, and HGF/cMET all play important roles in the development, progression, and metastasis of HCC.

With the widespread use of genome-wide sequencing techniques, significant progress has been made in examining the genetic factors that play critical functions in diseases. Studies have focused on revealing the genetic mechanisms of diseases that have high mortality, are important public health problems, and have led to the determination of more efficient diagnostic biomarkers. Determining the prognostic importance of a new biomarker that plays a major role in carcinogenesis might inspire translational research to create targeted treatments against these new therapeutic indicators and their corresponding signaling pathways. In addition, such a biomarker can also help clinicians predict the success of transplantation and determine the nature of the immune response.

Global gene expression study provides quantitative information on the RNA types and quantity in the cells and tissues. It is a very effective research technique for investigating the fundamental biology of diseases, developing diagnostic markers, facilitating drug discovery and surveillance of response to therapy, and creating databases with information on biological processes. Consequently, expression analysis has become one of the most widely used methods in modern biology.[14] This study aims to determine the genes that may play a role in the genomic mechanism and are expressed differently in tumor tissues by mRNA sequence analysis of tumor and distant non-neoplastic liver tissues from HBV-related HCC patients.

Methods

Dataset

In the current study, we used an open-access dataset obtained by sequencing the mRNAs of 21 pairs of tumor and non-tumoral liver tissues obtained from patients with HBV-related HCC (HBV- HCC). These 21 pairs of tumors and non-tumoral liver tissues that were employed for RNA sequencing were obtained from HBV-HCC patients who underwent primary surgical resection between 2008 and 2013 at Mount Sinai Medical Center in New York, USA.[14] RNAs obtained from tissues were utilized for cDNA library preparation after quality control. The resulting library was subjected to purification. Before loading onto the sequencer, the size and concentration of the RNAseq collection were evaluated using a Bioanalyzer and Qubit fluorometry (Life Technologies, NY, USA) and compared to human transcript reference sequences from the ENSEMBLE database.[15]

Bioinformatics and Gene Expression Analyses

Bioinformatics generally includes collecting, storing, organizing, archiving, analyzing, and presenting the results by visualizing the data obtained based on both theory and practice in a field in biology, medicine, behavioral or health sciences. In addition, it is concerned with the research and development of computational tools and approaches to expand the use and processing of data obtained as a result of studies, or the application of known methods. In bioinformatics, analyses are made by selecting a database and a program that allows the performance of bioinformatic analysis following the biological question, molecule, or structure to be examined. The data and results obtained at the end of the analyses are blended in the light of the previously defined information about the subject in the literature and interpreted analytically.[16]

Changes in the physiology of an organism or cell will cause changes in the pattern of gene expression, making gene expression analysis significant in many disciplines of biological inquiry. By hybridizing mRNA to a high-density array of immobilized target sequences, each of which corresponds to a different gene, DNA microarray technology is used to examine gene expression. The impact of substances on gene expression, for example, can provide information on their functional and toxicological properties. Expression investigations on clinical samples, both normal and sick, may lead to the discovery of new biomarkers.[17]

Bioinformatics Analysis

In this study, gene expression analyses were performed on mRNA data obtained from 21 pairs of samples. In the investigation, the Limma package, which is accessible in the R coding language and enables expression analysis, was employed (18Limma (Linear Models for Microarray Analysis) is a library for analyzing gene expression microarray data, with a focus on using linear models to evaluate specific experiments and determine differential expression. The packet's functionalities apply to all gene expression methods, such as microarrays, RNA-seq, and quantitative PCR. The obtained results are displayed in the form of a table of genes ranked in order of importance and a graph depicting differentially expressed genes. Genes with the lowest p values are the most trustworthy, and the results table contains corrected P and log2-fold change (log2FC) values. Up-regulated genes were identified using log2FC >1 and a p-value of 0.05, whereas down-regulated genes were found using log2FC -1 and a p-value of 0.05. The volcano graph and Mean difference (MD) graph were used to show differentially expressed genes in the study. Uniform Manifold Approximation and Projection (UMAP) graphs were preferred to visualize the relations of the samples in the study with each other. In addition, a boxplot was used to show the distribution of each sample.

Study Protocol and Ethics Approval

The National Center for Biotechnology Information (NCBI) Gene Expression Omnibus open-access dataset was used in this work, which involved human participants and was established in compliance with institutional and national research committee ethical requirements. Since the open-access dataset was utilized, no approval from the local ethics commission was required.

Results

The mRNA sequence data used in the current study contains 26760 expressions. There were 21 pairs of samples which make up 42 in total, and the graph of the distribution of these samples is given in Figure 1. The UMAP graph that shows how the samples are related to each other is given in Figure 2. According to the gene expression analyses performed, statistically important differences were determined between both groups in the level of gene expression ($|log2FC| > 1.0$, $p<0.05$). According to the results of the bioinformatics analysis, the GNG4 gene has 165.42-fold higher gene expression in tumor tissues than in non-tumoral liver tissues. Likewise, IGF2BP1, GPC3, PEG10, AFP, SPINK1, EPS8L3, MYCN, DUSP9, and DKK1 genes had higher gene expression in the tumors of 143.01, 83.86, 62.24, 60.54, 53.81, 52.70, 42.25, 43.41, 40.22-fold, respectively. The CNDP1 gene, on the other hand, has 49.86-fold lower gene expression in tumor tissues than in non-tumoral liver tissues. Similarly, WAKMAR1, LINC01818, TH, LINC01093, MARCO, LOC101927078, LOC105372263, FCN2, and CLEC4M genes have 43.11, 40.22, 39.67, 38.85, 36.75, 36.50, 36.25, 35.01, 33.59-fold lower gene expression, respectively.

Information on the first 20 genes showing an increase and decrease in expression between the two groups is given in Tables 1 and Table 2. Figure 3 depicts the volcano plot utilized to display the differentially expressed genes between groups.

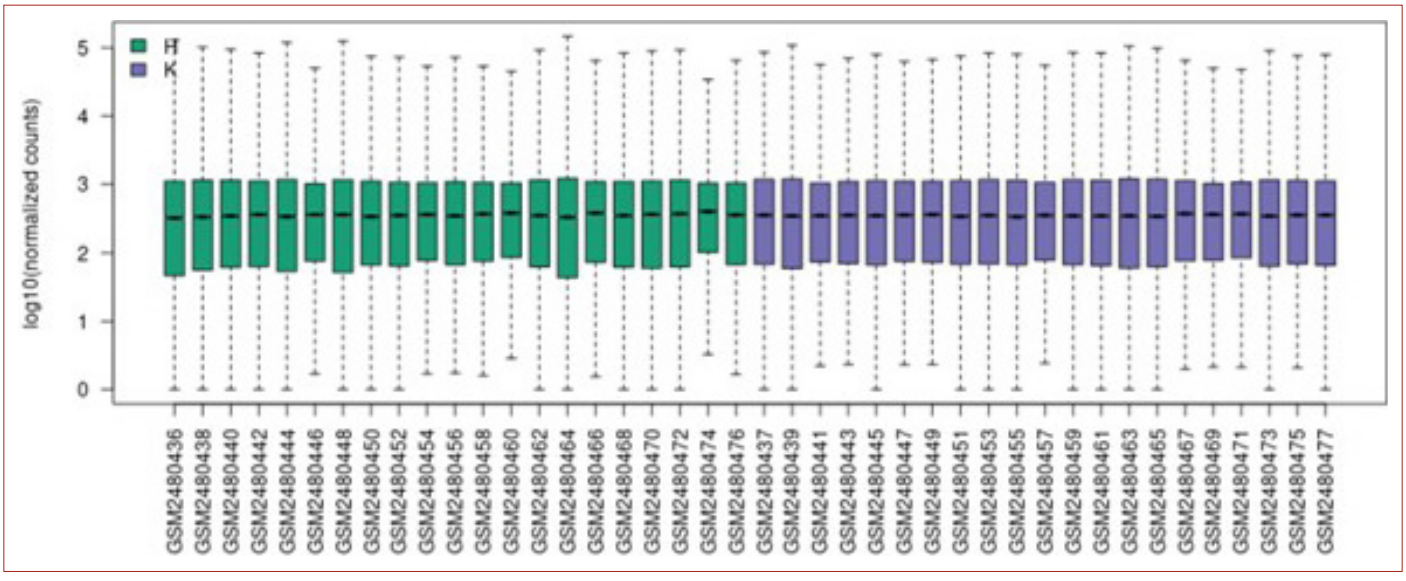

Figure 1. The distribution of the values of the selected Samples.

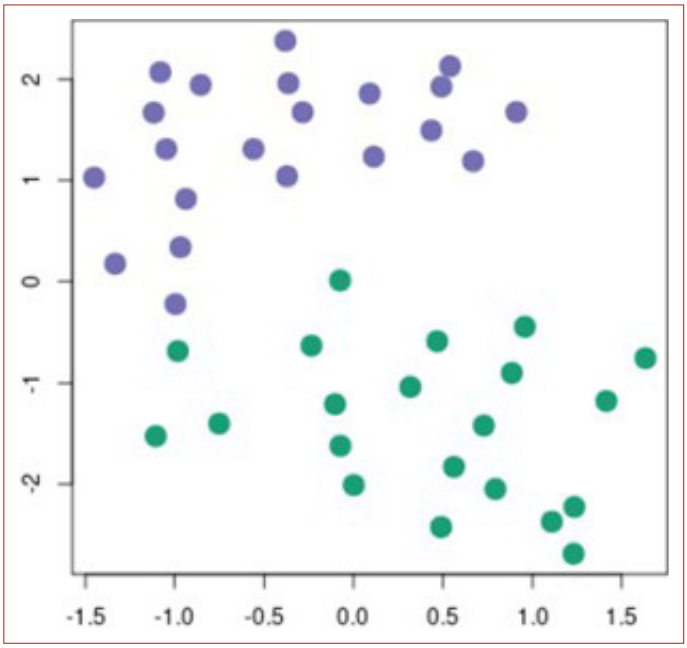

Figure 2. UMAP plot of the samples (Green Dots: Tumor specimens, Purple dots: non-neoplastic liver tissues samples).

Discussion

HCC is a frequent cause of cancer-related mortality which accounts for the fourth most prevalent cause of cancer-associated mortality.[19,20] The incidence and mortality of HCC vary significantly across the world. This can be attributed to regional variations in the duration and intensity of exposure to environmental and infectious factors. Also, accessibility to medical resources and the ability to identify HCC in its earlier stages. All these enable patients to receive potentially curative treatment. In Eastern Asia and Sub-Saharan Africa, low- and middle-income countries account for nearly 80% of all HCC cases.[21,22] Alcoholism, HBV, non-alcoholic fatty liver disease, HCV, and dietary toxins are all potential risk factors for HCC development.[20] HBV and HCV infection are the most common causes of HCC, accounting for 4 in 5 of all HCC cases globally. With the exception of Northern Africa, where HCV prevalence is highest, HBV infection is the leading cause of this cancer across Eastern Asia and the majority of African countries.[21,22] It is predicted that 257 million people globally are infected with chronic HBV. As a result of this condition, chronic viral liver disease and HCC are extremely common. Between 2015 and 2030, HBV is predicted to cause 20 million deaths due to cirrhosis, acute or chronic hepatitis, and HCC, with HCC alone accounting for 5 million deaths.[20]

The annual incidence of HCC in cirrhotic people due to chronic HBV or HCV infection is between 2 and 5%. HBV-related HCC can occur even in the absence of liver cirrhosis and accounts for 30 to 50% of HCC cases in HBV-endemic

Table 1. Up-regulated genes in tumor tissues relative to non-tumoral liver tissue samples

GeneID	PADJ	p	Log2FoldChange	Symbol	Description
2786	2,41E-30	1,29E-32	7,3706792	GNG4	G protein subunit gamma 4
10642	7,36E-32	3,58E-34	7,1650115	IGF2BP1	Insulin like growth factor 2 mRNA binding protein 1
2719	1,08E-38	3,12E-41	6,3956802	GPC3	Glypican 3
23089	1,56E-21	1,89E-23	5,9686012	PEG10	Paternally expressed 10
174	1,05E-15	2,74E-17	5,9220562	AFP	Alpha- fetoprotein
6690	1,76E-15	4,82E-17	5,753456	SPINK1	Serine peptidase inhibitor Kazal type 1
79574	2,47E-19	3,95E-21	5,7214354	EPS8L3	EPS8 like 3
4613	3,53E-21	4,48E-23	5,5005538	MYCN	MYCN proto-oncogene, bHLH transcription factor
1852	4,62E-22	5,39E-24	5,4477672	DUSP9	Dual specificity phosphatase 9
22943	4,78E-12	2,39E-13	5,3304587	DKK1	dickkopf WNT signaling pathway inhibitor 1
5865	8,46E-19	1,44E-20	5,2286698	RAB3B	RAB3B, member RAS oncogene family
4751	6,43E-46	6,05E-49	5,1911583	NEK2	NIMA related kinase 2
29944	3,08E-19	4,97E-21	5,0813647	PNMA3	PNMA family member 3
256714	9,87E-16	2,56E-17	4,952008	MAP7D2	MAP7 domain containing 2
2563	2,86E-30	1,56E-32	4,9170355	GABRD	gamma-aminobutyric acid type A receptor subunit delta
1063	6,85E-55	7,17E-59	4,8550639	CENPF	Centromere protein F
11082	1,11E-28	6,96E-31	4,8386647	ESM1	Endothelial cell specific molecule 1
114794	1,53E-14	4,84E-16	4,8192059	ELFN2	Extracellular leucine rich repeat and fibronectin type III domain containing 2
220134	2,74E-41	6,17E-44	4,8055116	SKA1	Spindle and kinetochore associated complex subunit 1
55872	1,04E-33	4,29E-36	4,7363249	PBK	PDZ binding kinase

Table 2. Down- regulated genes in tumor tissues relative to non-tumoral liver tissue samples

GeneID	PADJ	p	Log2FoldChange	Symbol	Description
84735	1,58E-26	1,23E-28	-5,64658	CNDP1	Carnosine Dipeptidase 1
105372576	4,04E-19	6,60E-21	-5,43271	WAKMAR1	wound and keratinocyte migration associated lncRNA 1
105373684	5,16E-36	1,73E-38	-5,33103	LINC01818	long intergenic non-protein coding RNA 1818
7054	5,59E-14	1,96E-15	-5,31748	TH	Tyrosine hydroxylase
100506229	9,32E-27	7,17E-29	-5,28676	LINC01093	long intergenic non-protein coding RNA 1093
8685	8,90E-20	1,32E-21	-5,2043	MARCO	macrophage receptor with collagenous structure
101927078	9,88E-38	2,95E-40	-5,19588	LOC101927078	uncharacterized LOC101927078
105372263	5,50E-16	1,37E-17	-5,18188	LOC105372263	uncharacterized LOC105372263
2220	2,38E-19	3,78E-21	-5,13387	FCN2	Ficolin 2
10332	5,38E-16	1,33E-17	-5,07029	CLEC4M	C-type lectin domain family 4 member M
3781	9,27E-42	1,99E-44	-5,01768	KCNN2	potassium calcium-activated channel subfamily N member 2
339390	2,76E-16	6,50E-18	-4,89947	CLEC4G	C-type lectin domain family 4 member G
5816	3,19E-40	8,01E-43	-4,80921	PVALB	Parvalbumin
51266	7,60E-20	1,11E-21	-4,72287	CLEC1B	C-type lectin domain family 1 member B
107985462	2,43E-14	8,00E-16	-4,68485	LOC107985462	uncharacterized LOC107985462
8547	1,61E-19	2,49E-21	-4,58575	FCN3	Ficolin 3
101928384	3,80E-19	6,18E-21	-4,58488	LOC101928384	uncharacterized LOC101928384
102724019	1,94E-12	8,99E-14	-4,55773	LOC102724019	uncharacterized LOC102724019
143941	6,83E-25	6,25E-27	-4,42997	TTC36	tetratricopeptide repeat domain 36
27302	2,80E-13	1,11E-14	-4,4283	BMP10	bone morphogenetic protein 10

areas.[23] HBV infection is responsible for 30% and 45% of people with liver cirrhosis and HCC, respectively, worldwide.[24,25]

The total survival of HCC patients is low, and prevention of exposure to the risk factors is important to reduce the global burden of the disease. There is a rising interest in identifying diagnostic and prognostic markers, and new and effective targeted treatments. Furthermore, research aimed at defining the mechanisms of hepatocyte carcinogenesis and means of increasing the clinical care of patients with HCC is also a very popular subject.[20,26]

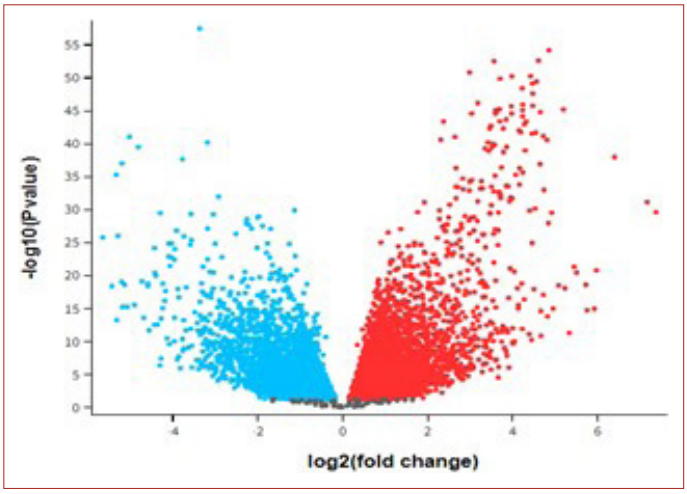

Figure 3. Volcano plot of genes with increased (red dots) and decreased (blue dots) gene expression among the group of tumorous and non-neoplastic liver tissues.

The current study examined liver tissues from HBV- HCC patients and utilized mRNA sequence data to identify genes with differences in gene expression between tumor tissues and non-neoplastic liver tissues. For this purpose, gene expression analysis was applied to the data set as a bioinformatic analysis, and the genes that differed between the two groups were determined. According to the results of the bioinformatics analysis, the GNG4 gene, IGF2BP1, GPC3, PEG10, AFP, SPINK1, EPS8L3, MYCN, DUSP9, and DKK1 genes had higher gene expression in the tumors. The CNDP1 gene had lower expression in tumor tissues than in non-tumoral liver tissues. Similarly, WAKMAR1, LINC01818, TH, LINC01093, MARCO, LOC101927078, LOC105372263, FCN2, and CLEC4M genes had lower expression in the tumors.

It has been shown that the abnormal expression of the GNG4 gene plays a significant role in the development of HCC.[27] GNG4 is upregulated in the HCC cells.[28] Further-

more, the GNG4 gene was shown to be among the differentially expressed genes for HBV-related HCC.[29] In a clinical study, IGF2BP1 was up-regulated in tumor tissues at a very high fold in the case of HCC.[30] Several studies have also been undertaken to examine the link between the IGF2BP1 gene and HCC.[31,32] Many studies on the GPC3 gene have also supported the idea that this gene can be a reliable biomarker for HCC, and this gene has shown upregulation in HCC.[33-35] Likewise, the PEG10 gene has been defined as the gene that plays a role in the development of HCC and is one of the genes that is upregulated in the case of HCC.[36,37] The CNDP1 gene is significantly downregulated in HCC.[38] It has been shown that downregulation of MORCO was associated with tumor progression in HCC.[39]

HCC, like all other cancers, has gene mutations and mutation-related mRNA expression alterations. As demonstrated by the findings of this study, the potential alterations in the expression of genes are highly related to HCC, and patients who have these genetic mutations are susceptible to HCC. Therefore, a surveillance program is required as well as preventive measures should be taken.

Conclusion

This study identified differentially expressed genes for tumor and non-tumoral liver tissue using genomic data from HBV- HCC patients. With further and comprehensive analysis of the target genes that we have defined, significant biomarkers for HCC can be developed. In addition, with the use of these biomarkers in clinical practice, the patient treatment approaches might be determined and personalized treatment strategies may be developed.

Disclosures

Ethics Committee Approval: This article was produced from the NCBI open-access dataset. Therefore, it has been reported by the institute that ethics committee approval is not required.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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

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JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2023.43531
J Inonu Liver Transpl Inst 2023;1(2):52–56

Original Research

A Novel Technique for Cadaveric Organ Procurement: Exposure with Internal Transverse Fascia and Vertical Skin Incision

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Abstract

Objectives: To describe a technique for retrieval of abdominal organs from a cadaveric donor and to report the outcomes of 59 cases at a single center.

Methods: We retrospectively analyzed data from 59 cadaveric organ retrieval operations between 2016 and 2021. The internal transverse fascia incision technique was used in all cases.

Results: Of the 59 patients 37 was male and 22 was female. Median intensive care unit stay was 10 days. The technique provided good exposure for abdominal closure, allowing for the retrieval of the liver, kidneys, and spleen. Aesthetic results and respect for the donor's body were also achieved.

Conclusion: Internal transverse fascia and vertical skin incision is a feasible and efficient method for abdominal organ procurement in cadaveric donors. Further studies are needed to validate and compare technique to other established methods.

Keywords: cadaveric, donor, technique, internal transverse fascia incision, procurement, transplantation

Please cite this article as "Cakir T, Aslaner A, Eyvaz K, Kazan MK. A Novel Technique for Cadaveric Organ Procurement: Exposure with Internal Transverse Fascia and Vertical Skin Incision. J Inonu Liver Transpl Inst 2023;1(2):52–56".

Organ transplantation is a definitive and inevitable solution for end-stage disease, fulminant liver failure or end-stage kidney disease. There is an organ shortage for patients suffering from end-stage diseases. Cadaveric and living donors are two primary sources of organs for transplantation. Cadaveric donors are deceased individuals whose organs are procured after brain or circulatory death confirmation. On the other hand, living donors are healthy individuals who voluntarily donate one of their organs, typically a kidney or a part of their liver, to a recipient in need.[1]

While living donor transplantation has the advantage of better graft survival rates and the possibility of pre-emptive transplantation, it is limited by the availability of suitable donors and the potential risks to the donor's health. Cadaveric transplantation allows for a more excellent pool of organs. However the quality of organs may be affected by various factors such as cause of death, donor age, and comorbidities.[1,2]

Xenotransplantation, which involves the transplantation of organs, tissues, or cells from one species to another, has emerged as a potential solution to address the shortage of organs for transplantation. However, despite promising advancements in the field, xenotransplantation is not yet widely applied due to unresolved issues such as immunological barriers, ethical concerns, and the potential for transmission of zoonotic diseases.[3,4]

A critical distinction between living and deceased donors lies in the incision method employed during the organ harvesting process. For obtaining organs from deceased donors, the thoracoabdominal cavities are typically opened using a midline incision that stretches from the supraster-

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Submitted Date: 02.10.2022 **Revised Date:** 06.08.2023 **Accepted Date:** 10.08.2023 **Available Online Date:** 25.09.2023

nal notch to the symphysis pubis. This procedure is known as the thoracoabdominal approach or the standard organ procurement technique (SOPT).[5] If intrathoracic organ extraction is not required, intraabdominal organs can be procured through abdominal incisions without requiring sternotomy. This method, called the modified standard organ procurement technique (MSOPT).

In this paper, we would like to present a novel MSOPT technique in cadaveric donors. This technique is favored for harvesting cadaveric organs and helps to ensure good exposure.

Methods

Patient Population and Data Collection

We retrospectively reviewed medical records from 121 cadaveric donors. 11 of them were allowed to be donor due to infection, sepsis and malignancy. 14 of the organ procurement operations performed by another transplantation team. Of 96 patients organ procurement performed by our team but 37 of them have some missing data and our described tecnich were not performed. Ultimately, the study enrolled 59 eligible patients between 2016 and 2021. (Fig. 1) An experienced surgical team performed all procurement procedures. Demographic and clinical characteristics, including sex, age, comorbidities, cause of death, cardiac arrest, cardiopulmonary resuscitation (CPR) duration, intensive care unit (ICU) stay duration, inotropic treatment, nationality, were collected from patient records. Laboratory parameters were also collected, including hemoglobin, white blood cell count, platelet count, sodium, potassium, creatinine, aspartate transaminase (AST), alanine transaminase (ALT), total and direct bilirubin, international normalised ratio (INR), and C-reactive protein (CRP) levels were also collected. The study was approved by University of Health Sciences- Antalya Education and Research Hospital's ethical committee with 188/2023 registration number.

Surgical Procedure

The organ retrieval procedure began with the detecting brain death, followed by meticulous donor care and family consent. Under general anesthesia, a midline incision was made from the xiphoid process to the suprapubic region. In our novel technique we make an incision to subcutaneous tissue, muscle, fascia, and parietal peritoneum using suitable energy devices lateral inner umbilicus level to Toldt's fascia bilaterally, while preserving the skin. The skin of the abdomen was temporarily sutured to the linea alba using

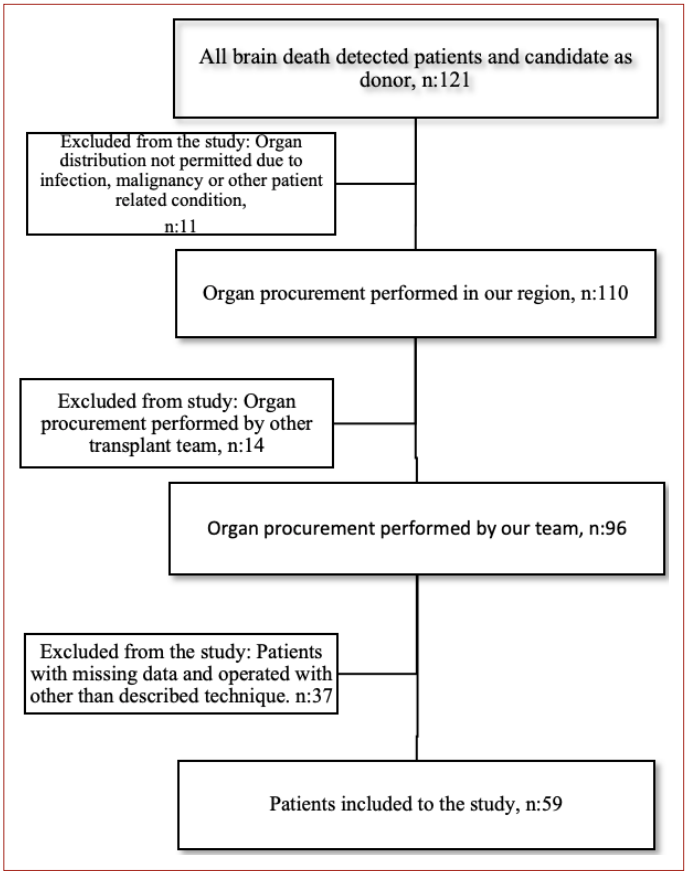

Figure 1. Flowchart of the patient selection enrolled in current study.

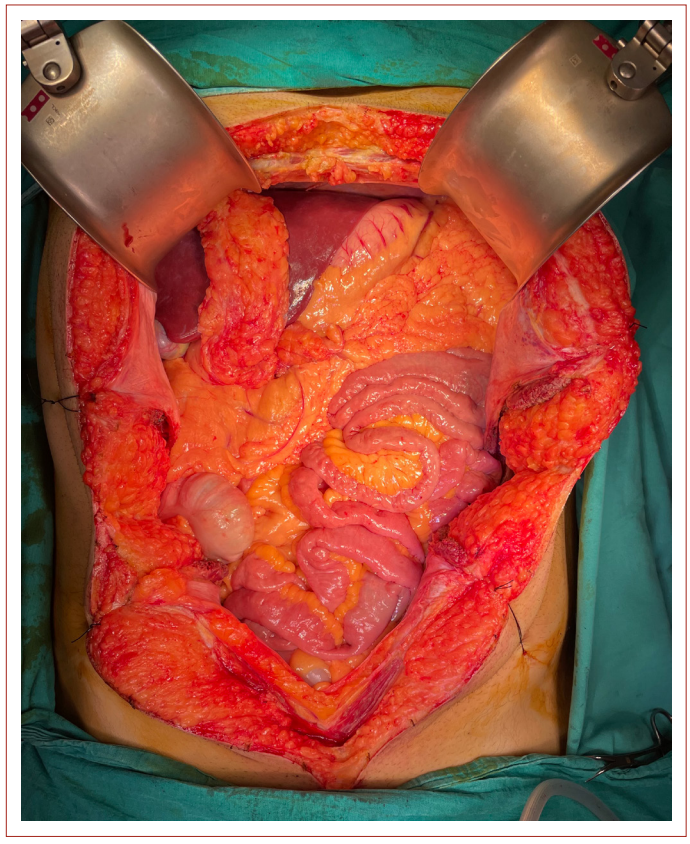

Figure 2. General appearance of the abdominal cavity after Internal Transverse Fascia and Vertical Skin Incision.

No. 1 silk suture for improved exposure (Fig. 2).

This abdominal opening allows us a great view of abdominal cavity and organs. Utilizing the Cattell and Braasch maneuver, the inferior vena cava was suspended superiorly to the left renal vein. The inferior mesenteric vein was secured, and a cannula was introduced. The distal abdominal aorta was exposed and suspended near the iliac bifurcation, allowing for the placement of an additional cannula. Both hemidiaphragms were incised anteriorly in a crescent-like shape close to the costochondral junction, providing access to the thoracic cavity. The inferior vena cava's opening in the right atrium was identified within the pericardial sac.

A cross-clamp was applied to the supraceliac abdominal aorta, and the right atrium was opened to prevent potential liver overdistention. All supportive medicine were discontinued at this point. The inferior vena cava was opened superior to the hepatic vein, and 3 L ringer lactate and 1 L of the University of Wisconsin solution were infused through the distal abdominal aortic cannula. Crushed ice was added to the abdominal cavity to maintain a cold environment.

An additional 2 L ringer lactate and 500 ml of the University of Wisconsin solution were introduced through the inferior mesenteric vein cannula to perfuse the portal vein. Upon completion of the perfusion process, the visceral organs were meticulously removed using en bloc dissection. Subsequently, the vascular pedicles of the organs were dissected on the back table for further analysis and preparation.

Following organ retrieval, the abdominal incision was closed anatomically. The lateral and midline fascia were approximated using No. 1 PDS or Prolene suture, and the skin was sutured subcutaneously with 3/0 Prolene or rapid Vicryl (Fig. 3).

Results

Of the 96 cadaveric donors we have the data of 59 patients and 37 (63%) were male, and 22 (37%) were female. The median age was 51 years (IQR, year: 38-65). Cardiac arrest occurred in 16 (27%) cases, with a median CPR duration of 10 minutes (IQR, minute: 5-15). The median ICU stay duration was 4 days (IQR, day: 2-7). Nationality distribution showed 51 (86%) were citizens and 8 (14%) were foreign. Blood group A is most frequently observed one (Table 1). The leading cause of brain death was listed and the most common cause of death was cerebrovascular accident (75%), followed by multiple trauma (6%) and intracranial lesions (8%) (Table 2). The various laboratory data of the patients were given in Table 3.

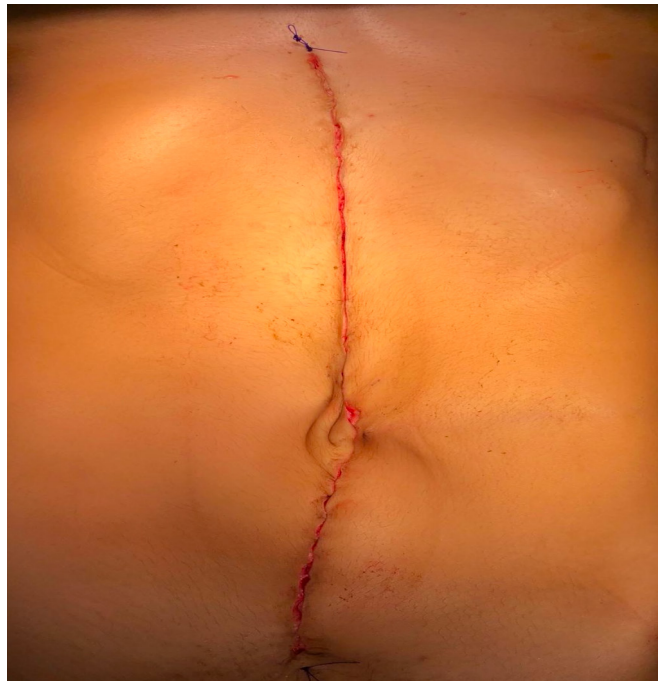

Figure 3. Appearence after organ procurement.

Discussion

Since Starzl first described the multiorgan procurement procedure the technique has been modified[6,7] SOPT and MSOPT[1] are examples of the described techniques. Here we modified the abdominal incision of these both methods. The extensive exposure and comfortably preperation and disection of donated organs are important issue for postoperative results after implantation. The inner transverse incision technique presented in this study offers several advantages over traditional methods of organ retrieval from cadaveric donors. By providing an extensive working area, easy implementation, and a respectful approach to the donor's body, this technique may contribute to improv-

Table 1. Demographic data of all patients, n:59

Sex, Male/Female, n (%)	37 (63)/22 (37)
Age, Median (IQR)	51 (38-65)
Blood Group (n)	
A Rh+/-	23/1
B Rh+/-	15/3
O Rh+/-	12/1
AB Rh+/-	3/1
Nationality; Citizen/Foreign, n (%)	51 (86)/8 (14)
ICU stay, days, Median (IQR)	4 (2-7)
CPR, min, Median (IQR)	10 (5-15)

IQR: Interquartile Range; ICU: intensive care unit; CPR: cardiopulmonary resuscitation.

Table 2. Causes of brain death n:59

	n	%
Cerebrovascular accident	44	75
Multiple trauma	4	6
Intracranial lesion	5	8
Cardiac arrest	2	3
Methil alcohol intoxication	1	2
Multi organ dysfunciton	1	2
Status epilepticus	1	2
Drowning in water	1	2

ing the organ retrieval process.

One of the main benefits of the inner transverse incision technique is the ability to reduce the risk of organ damage during the retrieval process. As organ quality is crucial for the success of transplantation, any technique that minimizes damage to the graft holds significant potential. By offering a wider working area and reducing the need for additional incisions, this technique allows the surgical team to work more comfortably and efficiently. This point may result in shorter operative times, which has been shown to impact organ quality and transplantation outcomes positively. In the existing literature, two predominant dissection methodologies are delineated.[8] In our study, we consistently employ cold dissection techniques to mitigate excessive hemorrhaging and subsequently reduce the overall duration of the surgical procedure.

Another critical aspect of the inner transverse incision technique is its respectful approach towards the donor's body. In many cultures, how a deceased person's body is treated carries significant emotional and spiritual implications for the bereaved family. By preserving the skin and ensuring a satisfactory cosmetic outcome, this technique demonstrates respect for the donor's body and aligns with the wishes of the relatives. This, in turn, may foster a more positive attitude towards organ donation, potentially increasing the number of donors and helping to address the organ shortage crisis.

Despite the encouraging results of this study, some limitations need to be acknowledged. As previously mentioned, the study's single-center and retrospective nature may limit the findings' generalizability. Moreover, a direct comparison with other established techniques would provide a better understanding of the advantages and potential drawbacks of the inner transverse incision technique. Future research could also explore the use of this technique in various clinical settings and its potential impact on donor family satisfaction and overall organ transplantation outcomes.

Table 3. Laboratory parameters of donors

Hemoglobin, Mean±SD (SEM)	11.2±2.17 (0.28)
White Blood Cell x 10^3, Mean±SD (SEM)	19.45±11.3 (1.49)
Platelets x 10^3, Mean±SD (SEM)	212±110.5 (14.7)
Sodium, Mean±SD (SEM)	153.8±13.8(1.8)
Potassium, Mean±SD (SEM)	4.37±3.61 (0.47)
Creatinin, Mean±SD (SEM)	1.61±1.78 (0.23)
AST, Mean±SD (SEM)	84.4±182(23.9)
ALT, Mean±SD (SEM)	100±407 (53.5)
Total Billirubin, Mean±SD (SEM)	1.05±1.22 (0.16)
Direct Billirubin, Mean±SD (SEM)	0.53±0.73 (0.17)
INR, Mean±SD (SEM)	1.29±0.48 (0.06)
CRP, Mean±SD (SEM)	128±124 (17.8)

AST: aspartate transaminase; ALT: alanine transaminase; INR: international normalised ratio; CRP: C reactive protein; SEM: standart error of mean; SD: standart deviation.

In summary, the inner transverse incision technique offers a promising alternative to traditional methods of organ retrieval in cadaveric donors. By providing a wide working area, easy implementation, and a respectful approach to the donor's body, this technique can potential to improve the efficiency and outcomes of the organ retrieval process. Further studies are needed to validate these findings and explore the potential applications of this technique in different clinical contexts.

Disclosures

Ethics Committee Approval: The study was approved by University of Health Sciences- Antalya Education and Research Hospital's ethical committee with 188/2023 registration number.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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

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JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2023.13007
J Inonu Liver Transpl Inst 2023;1(2):57–62

Original Research

Heterotopic Reversed Position Technique in Pediatric Liver Transplantation

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Abstract

Objectives: Many challenges persist, especially when transplanting large grafts into small pediatric patients in liver transplantation (LT). In this study, we will discuss the details of the "heterotopic reversed position technique" in LT, which is applied to prevent complications and allows primary closure of the abdomen in the initial surgery without causing an increase in intra-abdominal pressure.

Methods: From March 2002 to December 2021, our institution performed 3121 LT of these 691 (22.1%) were pediatric LT. We present the outcomes of 11 pediatric patients who underwent LT using this method.

Results: In the postoperative phase, none of the 11 cases had vascular complications. Five of the cases were alive for an average of 9.2 years. The causes of mortality in the three cases were due to persistent hepatic encephalopathy after surgery in one case, another due to hemodynamic instability in the early postoperative period, and the third due to graft-versus-host disease that manifested two months after surgery.

Conclusion: The reversed positioning technique offers a promising solution to the challenges of pediatric liver transplant, especially in cases of acute fulminant liver failure.

Keywords: Pediatric living donor liver transplantation, heterotopic reversed position, large for size syndrome

Please cite this article as "Ersan V, Varol FI, Kayaalp C, Yilmaz S. Heterotopic Reversed Position Technique in Pediatric Liver Transplantation. J Inonu Liver Transpl Inst 2023;1(2):57–62".

The evolution of liver transplantation (LT), especially in the pediatric population, has been marked by significant milestones and innovations. With the increasing demand for organs, attention was shifted towards living donor liver transplantation (LDLT). The first LDLT was performed in the late 1980s, and over the years, surgical techniques were refined, making LDLT a valuable procedure for pediatric patients, especially in regions with limited organ donation from deceased donors.[1, 2]

Despite these advances, challenges persist, especially when transplanting large grafts into small pediatric patients. Technical difficulties, such as increased intraabdominal pressure and challenges in abdominal closure, have been significant concerns.[3] Primary closure of the abdomen may lead to elevated intra-abdominal pressure. This can result in inflow or outflow obstructions in the implanted graft, an extended need for mechanical ventilation due to increased intrathoracic pressure, the development of abdominal compartment syndrome, associated renal

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Submitted Date: 05.09.2023 **Revised Date:** 05.09.2023 **Accepted Date:** 24.09.2023 **Available Online Date:** 25.09.2023

failure, graft loss, infection, and wound dehiscence.[4, 5] To address these challenges, innovative techniques, such as the use of monosegment or reduced-size grafts, have been introduced.[6] However, even if vascular complications are partially prevented by reducing the volume of the graft with these techniques, the challenges to closing the abdomen remain unchanged, since the anterior-posterior diameter of the graft remains the same and there is no effect on the vascular anastomosis difficulties, since the distance between the hepatic vein and the portal vein of the graft remains unchanged (Fig. 1).

In this study, we will discuss the details of the "heterotopic reversed position technique" in liver transplantation, which is applied to prevent the complications and allows primary closure of the abdomen in the initial surgery without causing an increase in intra-abdominal pressure and present the outcomes of 11 pediatric patients who underwent LT using this method.

Methods

This is a retrospective analysis of prospectively collected data, and no patient can be identifiable through the manuscript, the consent form was not obtained from the patients. We reviewed the medical records of pediatric patients who underwent heterotopic liver transplantation between March 2002 and December 2021.

Patients aged 0-18 years diagnosed with end-stage liver disease and who underwent heterotopic liver transplantation were included. Exclusion criteria included patients with incomplete medical records, those who were older than 18 years of age, and those who underwent orthotopic liver transplantation.

All statistical analyzes were performed using the Statistical Package for Social Sciences software version 24 (IBM SPSS Statistics for Windows/Mac, Armonk, NY: IBM Corp.). Continuous variables were presented as mean±standard deviation or median (min-max, range) and categorical variables were presented as numbers and percentage.

Surgical Technique

Donor selection criteria are described elsewhere.[7] All potential living donors were evaluated, including CT angiography for graft size, future remnant liver size of the donor, and evaluation of vascular anatomy. Informed consent was obtained from all donors.

The technique prerequisites are as follows:

- Graft-to-Recipient Weight Ratio (GRWR) >4%
- The anterior-posterior diameter of the graft is 1.5 times the diameter of the recipient's abdominal cavity.
- The distance from the portal vein (PV) to the hepatic vein (HV) of the graft is double that of the recipient.
- A graft that curving under the diaphragm due to an extended left lateral liver segment was seen as a relative contraindication.

For living donors, we used a reverse T incision followed by a left lateral segmentectomy. Full-sized grafts from deceased donors were split and prepared for transplantation upon arrival at our center. Since the order of anastomosis could change due to graft rotation, we meticulously examined the topographic placement of the hilar structures (Fig. 2) Additionally, we used a saphenous vein graft as a circumferential fence for the left hepatic vein of the grafts. After rotating the left lateral segment graft 180° in the sagittal plane, it was placed on the right side of the inferior vena cava (IVC) similar to the right lobe LDLT (Figure 3a,b). The subsequent anastomosis was performed between the left hepatic vein

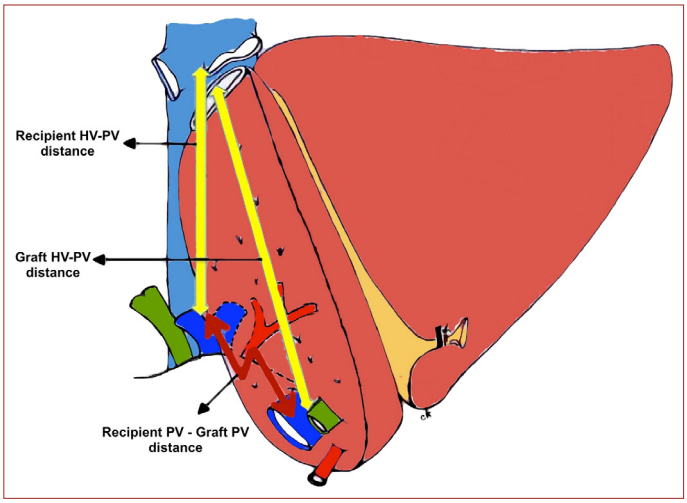

Figure 1. Difference distance between the hepatic vein and the portal vein of the graft and recipient.

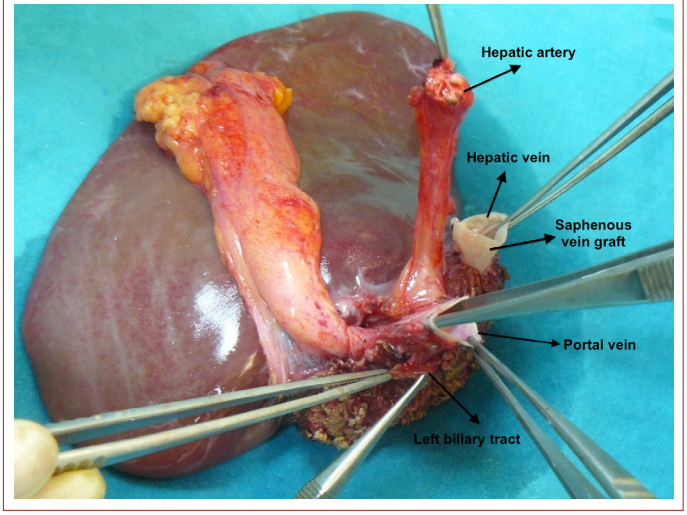

Figure 2. Topographic placement of the hilar structures.

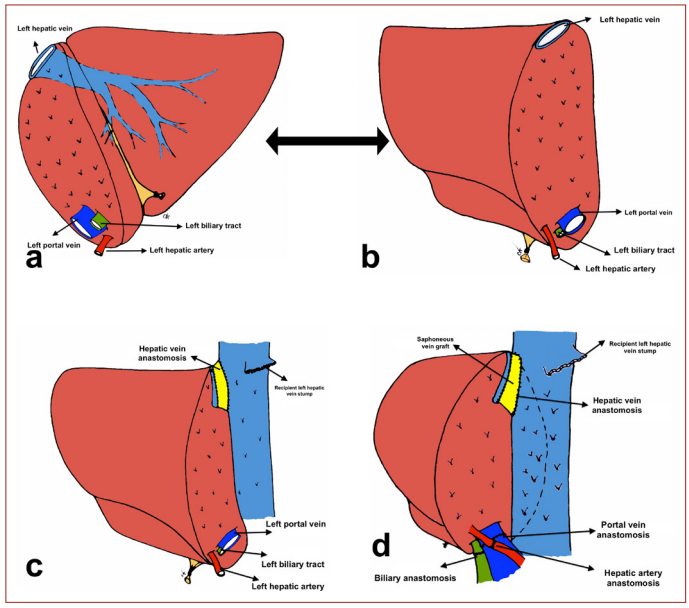

Figure 3. (a) Normal position of segment 2-3 graft, **(b)** Position after rotating the left lateral segment graft 180° in the sagittal plane, **(c)** It is placed on the right side of the inferior vena cava (IVC) similar to the right lobe LDLT. The subsequent anastomosis is performed between the left hepatic vein of the graft and the orifice of the recipient's right hepatic vein, **(d)** Subsequently, anastomoses of the bile duct, portal vein, and hepatic artery were performed in sequence.

of the graft and the orifice of the recipient's right hepatic vein (Fig. 3c). Subsequently, anastomoses of the bile duct, portal vein, and hepatic artery were performed in sequence (Fig. 3d). Rotation of the graft repositioned the bile duct posterior to the portal vein, necessitating a modification in the sequence of anastomosis (Fig. 4a, b).

Results

From March 6, 2002 to December 31, 2021, our institution performed 3121 LT of these 691 (22.1%) were pediatric LT. Eleven of these pediatric patients underwent the heterotopic reversed position technique for LT.

The median age at the time of transplantation of this subgroup was 31 months (range: 12-64 months), with an average weight of 13.5 kg (range: 9-20 kg). There were six males and five females. Indications for LT included fulminant liver failure (9 patients), cholestatic liver disease (1 patient), and chronic rejection (1 patient). Six received left lateral segment grafts from living donors, four from deceased donors. And a 16-year-old patient underwent retransplantation using a left lobe graft from a deceased donor (segment 2-3-4) graft. The heterotopic reversed position technique was used due to significant adhesions in the region corresponding to the left lobe of the liver in this patient. Demographic and intraoperative data are summarized in Table 1.

The average GRWR for the ten pediatric patients, excluding the retransplantation case, ranged from 1.5 to 3.4. The anterior-posterior diameter of the grafts averaged 8.3 cm, contrasting with the 4.3 cm anterior-posterior diameter of the orthotopically transplantable abdominal cavity. The distance between the portal vein (PV) and the hepatic vein (HV) in the grafts was 8.2 cm on average, while the corresponding distance in the recipients was 3.7 cm on average. Nine out of the ten cases had fulminant liver failure in which the liver is normal in size and ascites is usually absent.

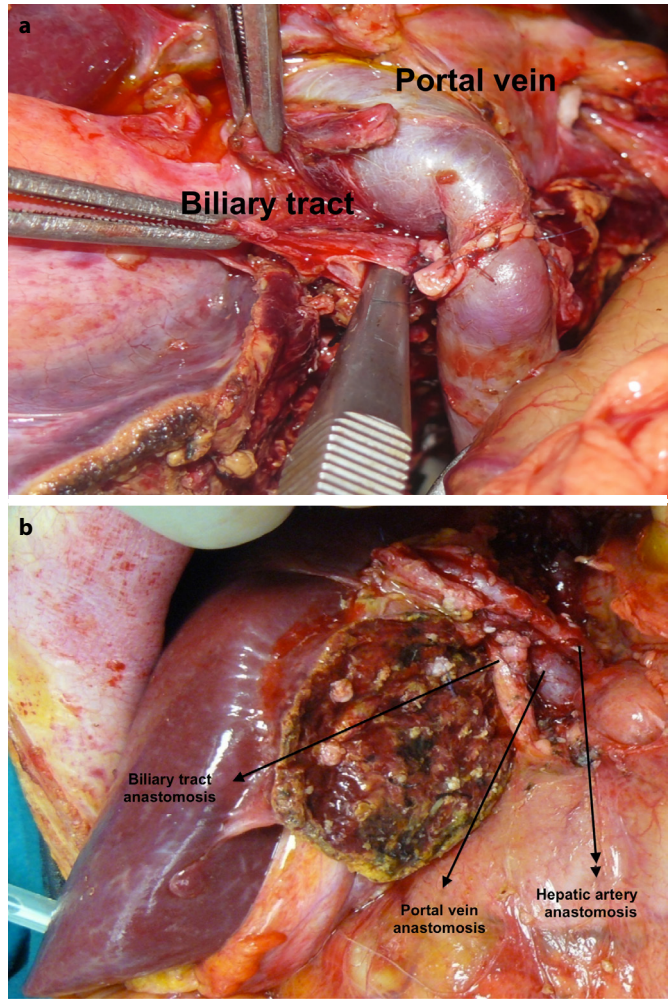

Figure 4. (a) Rotation of the graft repositioned the bile duct posterior to the portal vein, necessitating a modification in the sequence of anastomosis. **(b)** Appearance of hilar structures after completion of anastomose.

In the postoperative phase, none of the 11 cases had vascular complications (Fig. 5a, b). Five of the cases were alive for an average of 9.2 years. The biliary stricture that occurred in two of them was treated with percutaneous biliary interventions (Fig. 6a, b, c). The causes of mortality in the three cases were due to persistent hepatic encephalopathy after surgery in one case, another due to hemodynamic instability in the early postoperative phase, and the third due to

Table 1. Demographic and intraoperative data

Case	Age (months)	Indication	Donor	Graft (segment)	Patient Weight (kg)	Graft weight (gr)	GRWR (%)	Total bilirubin (mg/dL)	Child / PELD
1	22	HAV	Mother	2-3	13	236	1.8	3	B / 8
2	34	HAV	Mother	2-3	10	250	2.3	25	B / 34
3	25	HAV	Mother	2-3	12	240	2.0	18	C / 27
4	23	HAV	Uncle	2-3	12	269	2.2	14	B / 24
5	39	HAV	Father	2-3	18	275	1.5	24	C / 59
6	48	HAV	Mother	2-3	16	270	1.6	24	C / 48
7	37	HAV	Deceased	2-3	11	370	3.3	25	C / 18
8	64	HAV	Deceased	2-3	20	450	2.2	16	C / 25
9	28	Biliary atresia	Deceased	2-3	10	345	3.4	4	B / 10
10	12	HAV	Deceased	2-3	9	270	3.0	16	B / 30
11	192	Chronic rejection	Deceased	2-3-4	50	550	1.1	35	C / 19 *

*The MELD score was calculated because the patient was over 12 years old. GRWR: Graft-to-recipient weight ratio; PELD: Pedatric end-stage liver disease; MELD: Model for end-stage liver disease; HAV: Hepatitis A virus.

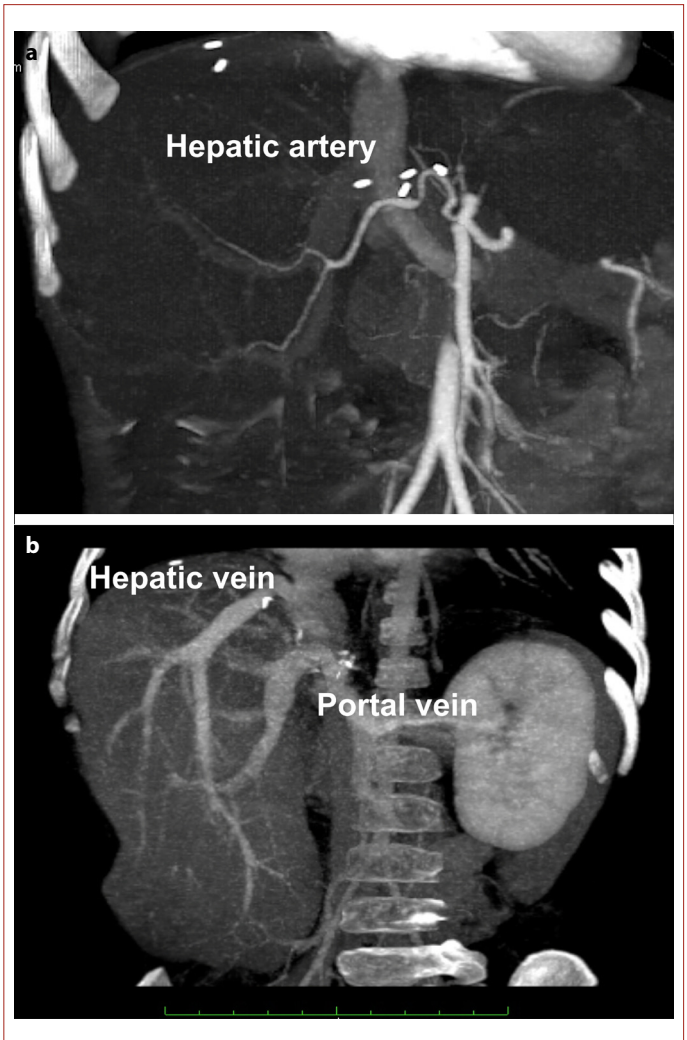

Figure 5. Radiological image of postoperative **(a)** hepatic artery, **(b)** portal vein and hepatic vein anastomoses.

graft-versus-host disease that manifested two months after surgery. The eleventh patient, the retransplantation case, died due to peritonitis resulting from postoperative duodenal ulcer perforation.

Discussion

Pediatric liver transplantation presents unique challenges, especially when there is a mismatch in age and body mass index (BMI) between the donor and the recipient. Ideally, if there is a perfect match, complications related to the size of the graft and the difficulties of anastomosis are minimized. However, in many pediatric cases, as observed in our study, transplantation involves a segment 2-3 from a living or deceased donor. If the anterior-posterior diameter of the graft exceeds that of the pediatric patient's abdominal cavity, it will invariably impede primary abdomen closure during orthotopic transplantation. Since the anterior posterior diameter of the graft remains the same, the use of reduced-size or monosegment grafts cannot solve this problem. Using the reversed position technique, the anterior-posterior diameter of the segment 2-3 graft, regardless of its size, remains considerably smaller than that of the right hypochondrium. Consequently, within the context of this technique, the size of the anterior-posterior diameter of the segment 2-3 graft does not hinder the primary closure of the abdominal cavity. The orthotopic position is always preferred for graft placement if it is technically feasible and allows primary abdominal closure. However, this is not possible in many cases. Therefore, the heterotopic reversed position technique was preferred in these cases.

In pediatric patients presenting with acute fulminant insufficiency, while the segment 2-3 grafts are not large enough

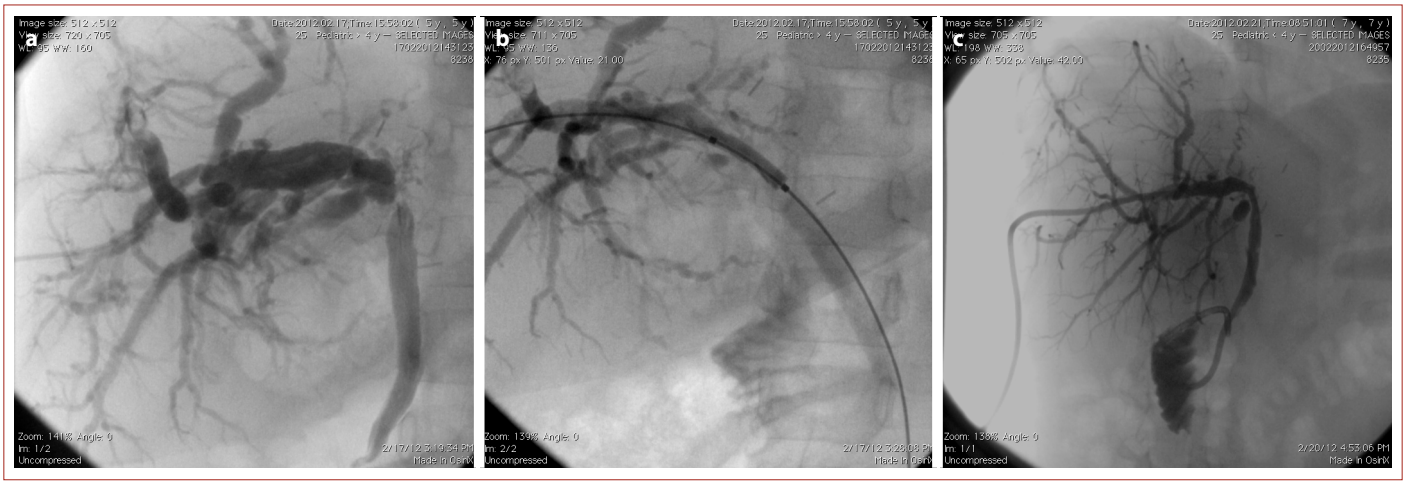

Figure 6. (a) The biliary stricture that occurred in two of the patients **(b)** was treated with percutaneous biliary interventions and **(c)** dilatation, external catheter, and stenting.

to induce the large-for-size syndrome, their orthotopic implantation remains notably challenging. Children with fulminant liver failure do not exhibit the manifestations typically associated with chronic liver disease. Conditions such as ascites or liver enlargement, which are prevalent in chronic liver failure, lead to expansion of the right hypochondrium and epigastric space.[8-11] Consequently, in pediatric cases of fulminant liver insufficiency, where the abdominal cavity has not had the opportunity to adapt or expand, orthotopic transplantation of segment 2-3 graft becomes a formidable challenge. In this case, rotating the segment 2-3 graft 180° in the sagittal plane and transplanting it heterotopically to the right hypochondrium allows the graft to fit into the abdominal cavity and the anterior wall of the abdomen to be closed primarily.

Another concern is the misalignment between the graft's hilar structures and those of the pediatric recipient. Specifically, the distance between the hepatic vein and the hilar structures of the segment 2-3 graft substantially exceeds the distance between the recipient's hepatic vein orifice and the hilar structures. Undertaking anastomosis of the portal vein and hepatic artery without tailored adjustments can result in pronounced kinking of these vascular structures, predisposing them to thrombotic events. Current best practices advocate for the recipient's portal vein to align with the coroner vein and the hepatic artery to align with the common hepatic artery level for optimal anastomotic outcomes.[12, 13] However, the inherent shortness of the pediatric recipient's vascular structures complicates this process. Even with meticulous alignment, the risk of vascular kinking and subsequent thrombosis remains palpable. Once the segment 2-3 graft is situated in the right hypochondrium, the elongated nature of the recipient's portal vein transitions from a perceived disadvantage to a beneficial attribute. As evidenced in our series, the extended portal vein maintains its physiological alignment. Similarly, the graft's hepatic artery's length in this technique ensures that the anastomosis remains relaxed, mitigating undue tension. It is worth noting that, in certain instances, the hilar vascular and ductal anastomoses within this technique may experience tension. To counteract this, supportive devices, such as expanders or balloons, which elevate the graft anteriorly and alleviate tension in the hilar structures, can be strategically positioned posterior to the graft.[14]

A meticulous examination of the graft's hilar structures is imperative, especially when considering a 180° sagittal plane rotation for heterotopic transplantation. In the standard transplantation procedure, the recipient's hilar structures follow a sequence from anterior to posterior: bile duct, hepatic artery, and portal vein. However, with the reversed position technique, this sequence for the graft's hilar structures is altered to portal vein, hepatic artery, and bile duct. Consequently, the anastomotic sequence shifts to prioritizing the bile duct, followed by the hepatic artery, and culminating with the portal vein. This specific sequence has been previously discussed in the context of dual lobe LT cases.[15, 16] Yet, it is crucial to note that this sequence is not universally applicable. Based on our observations, initiating with the portal vein anastomosis often does not compromise subsequent anastomoses of the bile duct and hepatic artery. Hence, it is imperative for an experienced transplant surgeon to meticulously evaluate the topographical arrangement of the hilar structures during the back-table preparations to determine the optimal anastomotic sequence.

Some segment 2-3 grafts are seen to extend more to the left and upwards than usual. In this case, when the graft is

rotated 180° in the sagittal plane and positioned to the right and the corner of the right diaphragm with the abdominal side wall of the parietal peritoneum, the long lateral edge of the graft and the liver parenchyma corresponding to the left triangular ligament will bend. Such placement may cause graft dysfunction in the postoperative period. Therefore, excessive extension of the segment 2-3 graft to the left may be considered a relative contraindication for this technique. Balci et al. suggested heterotopic implantation of reduced size monosegment or left lateral segment grafts.[17] The author suggested that the right lateral part of the graft can be resected in accordance with the preoperative right hypochondrium volume of the recipient.

In conclusion, the reversed position technique offers a promising solution to the challenges of pediatric liver transplantation, especially in cases of acute fulminant liver failure. However, further studies are needed to assess its long-term outcomes and establish its broader applicability.

Disclosures

Ethics Committee Approval: İnönü University Scientific Research And Publication Ethics Committee Health Sciences Non-invasive Clinical Research Ethics Committee 2023/4969-20-09-2023.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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

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JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2023.03208
J Inonu Liver Transpl Inst 2023;1(2):63–64

Case Report

Living Donor Liver Transplantation for a 78-Year-Old Recipient

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Abstract

Advanced age of the patient carries a higher risk after liver transplantation (LT) and may lead to worse outcomes. As people's life expectancy increases and advances in the medical treatment of chronic liver disease have increased the need for LTs in the older population. LT recipients over the age of seventy have acceptable survival rates after LT, provided certain criteria are met.

A 78-year-old male patient with cryptogenic liver cirrhosis and tense ascites. His MELD-Na score was 27. He underwent a right lobe living donor liver transplant and was discharged from hospital in good health after a month.

LDLT for elderly recipients might be suitable if the recipients does not have any co-morbidity, their outcomes are comparable to those for younger recipients which resulted in fairly acceptable long-term outcomes and if donor morbidity is acceptable.

Keywords: Elderly recipient, liver transplantation, living donor liver transplantation

Please cite this article as "Baskiran A, Carr B, Aloun A, Yilmaz S. Living Donor Liver Transplantation for a 78-Year-Old Recipient. J Inonu Liver Transpl Inst 2023;1(2):63–64".

Advanced age of the patient carries a higher risk after liver transplantation (LT) and may lead to worse outcomes.[1,2] As people's life expectancy increases and advances in the medical treatment of chronic liver disease have increased the need for LTs in the older population. LT recipients over the age of seventy have acceptable survival rates after LT, provided certain criteria are met.[3-5] Therefore, most transplant centers evaluate for LT patients over 70 years of age with less advanced liver disease and no cardiopulmonary comorbidity. There is no universally accepted upper age limit for LT candidates but the functional status of older patients is important in pre-LT evaluation. In this report, we aimed to present the living donor liver transplantation (LDLT) performed on one of the oldest liver patients in the literature.

Case Report

A 78-year-old male patient had cryptogenic liver cirrhosis with tense ascites. His blood laboratory values were total bilirubin 5.6 mg/dL, INR 2.86 IU, Na 134 mEq/dL, creatinine 0.9 g/dL, and MELD-Na score was 27. The general condition of the patient was moderate, he had difficulty in walking and slowness in speaking was remarkable. Physical examination, laboratory, and radiologic results of the elderly patient with high MELD score were considered. As a result of the evaluations in the LT council, the cardiopulmonary, neurological and GIT endoscopy findings of the patient who had 27 MELD-Na and 13 Child scores were completely normal. The patient's living donor was his 30-year-old nephew. The graft-to-recipient weight ratio was 1.01 and

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Submitted Date: 07.07.2023 **Revised Date:** 08.08.2023 **Accepted Date:** 08.08.2023 **Available Online Date:** 25.09.2023

remnant liver volume of the donor was 38 %. A right lobe LDLT was performed, operation time was about 7 hours, and the patient's blood loss was 250 ml during the operation.

The donor's postoperative course was uneventful and was discharged on the 7th day. Recipient was extubated on postoperative day 1, the ICU process was 3 days and there were no complications. The immunosuppressive regimen consisted of cyclosporine A and corticosteroid. Care was taken to keep C0 levels low, one week after LT, C0 levels were between 50-100 ng/dL. Recipient was discharged on day 38 post LT, late discharge due to patient's departure to hometown Jordan. The patient has been followed for 2 years without any complication.

Discussion

Three-quarters of LT in Turkiye consists of LDLTs.[6] LDLT differs from deceased donor liver transplantation (DDLT) in many ways. It does not use public deceased donor source, does not harm the rights of other recipients. Another is the risk of mortality and morbidity in healthy donors and this poses a huge ethical problem. Therefore, LDLT for elderly recipients might be suitable if the recipients does not have any co-morbidity, their outcomes are comparable to those for younger recipients which resulted in fairly acceptable long-term outcomes and if donor morbidity is acceptable.[3-5]

The advantages of the recipient presented in this article were that he had no co-morbidities, had a low BMI, and had a healthy living donor with adequate GRWR. The disadvantages consisted of high MELD score, presence of ascites for a long time, and advanced age. Considering these parameters, the LT decision was made and the result was successful with long-term follow up. Therefore, it is necessary to be very careful when making the LT decision in patients over 70 years of age, but it should not be deprived the appropriate recipients from LT.

So far, we have been able to find only one 78-year-old patient as the oldest recipient who underwent LDLT in the relevant literature.[7] This patient had a 23-month survival, but had a pre-LT MELD score of 12 and had LDLT for HBV-related HCC. The patient presented in our article had a high MELD score and tense ascites.

Interesting observation in the elderly LT recipients was the lower incidence of acute cellular rejection according to the younger recipients. Therefore, we started cyclosporine A , which is a less potent immunosuppressive agent, at a low dose in this patient. Another center recommends reducing the usual doses of tacrolimus by 60-80% as an immunosuppressive strategy.[7] A result of aging is a reduction of the cellular and humoral immune responses, but it is associated with an increased risk of infection and malignancy.[7,8] For this reason, the patient's clinical and laboratory observations were taken more frequently.

In conclusion, LDLT may be appropriate for low-risk elderly recipients with favorable long-term outcomes. This report presents one of the oldest recipients which were performed LDLT.

Disclosures

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

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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

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JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2023.25733
J Inonu Liver Transpl Inst 2023;1(2):65–69

Case Report

Bowel Perforation due to Complicated Meckel's Diverticulum in an Adult Living Donor Liver Transplant Recipient

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Abstract

Meckel's diverticulum is a rare cause of bowel perforation in liver transplant recipients. The aim of the present study is to discuss our management protocol in a 57-year old male liver transplant recipient with intestinal perforation due to complicated Meckel's diverticulum.

We report a case of 57 years old male liver transplant recipient who had abdominal sepsis on posttransplant 13th day. He was operated on and found to have Meckel's diverticulum that caused intestinal perforation due to volvulus around fibrous bands extending to the anterior abdominal wall. Segmental bowel resection with end-jejunostomy was performed. The patient had sepsis on the postoperative period and is followed in intensive care unit and treated with a combination of antibiotics.

Meckel's diverticulum is a rare cause of bowel perforation and this is the first case presenting with perforation in early post-transplant period. Stoma is beneficial for reduction of abdominal sepsis related symptoms. Preemptive diverticulectomy should be considered for prevention of serious complications such as perforation.

Keywords: Bowel perforation, Liver Transplantation, Meckel's Diverticulum

Please cite this article as "Sahin TT, Akbulut S, Ince V, Karakas S, Yilmaz S. Bowel Perforation due to Complicated Meckel's Diverticulum in an Adult Living Donor Liver Transplant Recipient. J Inonu Liver Transpl Inst 2023;1(2):65–69".

Liver transplantation (LT) is a major abdominal procedure. In addition, living donor liver transplantation (LDLT) is a technically demanding procedure where liver ischemia and reperfusion injury plays a critical role.[1] Meticulous tissue dissection during recipient hepatectomy, prolonged portal clamping, hepatic ischemia, and reperfusion in addition to the turmoil of inflammatory response that is induced during all these processes results in a hostile environment that is prone to gastrointestinal and hepatic complications. For these reasons, gastrointestinal complications ranging from mild nausea/vomiting to major issues such as gastrointestinal perforations can be observed in LT recipients.[2] Prolonged portal vein clamping, gastrointestinal mucosal injury, prolonged operative times, previous abdominal surgeries and need for post-transplant revisional surgeries are major risk factors for gastrointestinal system perforations.[3-6] The incidence of gastrointestinal system perforation rages between 1 to 5% in adults and 8 to 15% in pediatric liver transplant recipients.[2,3,7]

Meckel's diverticulum was first described by Wilhelm Fabry in 1598. In 1700, Alexis Littre defined the presence of Meckel's diverticulum in strangulated inguinal hernia sack. However, a detailed embryologic and anatomic explanation of the origins of this anomaly was done by Johann Friedrich Meckel in 1809 and thus this congenital malformation is named after this German anatomist.[8] It is the most com-

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Submitted Date: 05.07.2023 **Revised Date:** 27.07.2023 **Accepted Date:** 03.08.2023 **Available Online Date:** 25.09.2023

mon congenital defect of the gastrointestinal tract, it results from the persistence of the vitello-intestinal tract.[9] "The rule of the two" is defined for Meckel's diverticulum; i) it is present in 2% of the population, ii) it is seen within 2 feet from the ileocecal valve, iii) it is usually 2 inches in diameter, iv) it usually contains two kinds of ectopic mucosae (gastric and pancreatic).[10,11] The lifetime risk for Meckel's diverticulum to develop complications is nearly 7%.[12,13] The defined risk factors for occurrence of complications are male gender, age less than 40-50 years of age, diverticulum length longer than 2 cm and presence of ectopic mucosa.[14,15] The complications are complications are obstruction, bleeding, diverticulitis and perforation. Obstruction can occur either by volvulus around the fibrous bands or intussusception.[9] Bleeding occurs if the diverticulum contains ectopic mucosae such as gastric and pancreatic tissue. Bleeding can occur by erosion of the diverticular mucosa or the adjacent enteric mucosa by irritation of the secretions of the ectopic pancreatic or gastric tissue. Bleeding is more common in children and obstruction is more common in adults.[11,16] Perforation due to diverticulitis is a very rare event in all age groups and in all populations and it is not only specific for liver transplant recipients.

Meckel's diverticulum as the etiology of gastrointestinal perforation and abdominal sepsis is a rare event. Our literature search has shown that there is only one case that has been reported so far.[17] This was a case of 20 years of male patient who developed acute abdomen due to Meckel's diverticulum perforation three years after the transplant procedure. The cause was a migrated biliary stent that dislodged and perforated the diverticular wall far.[17]

In the present case report, we present a case of a 57 male liver transplant recipient that was operated for abdominal sepsis 13 following the transplant procedure. The cause of perforation was local intestinal volvulus due to Meckel's diverticulum. The aim of the present study was to discuss our approach for the management of the patient who is the first case in literature that presented with an early postoperative gastrointestinal perforation due to complicated Meckel's diverticulum.

Case Report

Fifty-seven years old male liver transplant recipient was in in his post-transplant 13th day when lethargy, hypotension, tachycardia and a fever of 38°C developed. He was transplanted for autoimmune hepatitis and in the last year he was hospitalized for the suspicion of mesenteric ischemia or acute pancreatitis and he underwent right lower limb amputation for peripheral vascular disease. The laboratory values are summarized in Table 1.

Table 1. Summary of the course of laboratory values of the patient before, during and after the exploratory surgery

Laboratory Parameters	Before Exploratory Surgery	The Day of The Exploratory Surgery	After The Exploratory Surgery
Leukocyte (cells/mm^3)	8.91	9.2	12.6
Hemoglobin (g/dL)	8.6	10.3	10.1
Hematocrit (%)	24.2	28.1	27
Platelet (x10^3 corpuscle/mm^3)	155	114	85
INR	1.3	1.4	2.2
Glucose (mg/dL)	164	179	98
BUN (mg/dL)	11.7	14.5	15.4
Creatinine (mg/dl)	0.5	0.4	0.4
Na (mEq/dl)	145	146	148
Potassium (mEq/dL)	3.1	2.81	2.9
Chloride (mEq/dL)	102	106	111
Albumin (mg/dL)	3.1	3.4	2.6
AST (IU/ml)	26	57	190
ALT (IU/ml)	32	49	109
ALP (IU/ml)	90	94	111
GGT (IU/ml)	30	71	31
Total Bilirubin (mg/dL)	11.9	12.8	18.2
Direct Bilirubin (mg/dL)	5.9	7.2	9.6
Ammonia (ug/dL)	51	22	78
Fibrinogen (mg/dL)	205.08	129.4	167.7

ALT: Alanine aminotransferase; ALP: Alkaline Phosphatase; AST: Aspartate aminotransferase; BUN: Blood Urea Nitrogen; GGT: Gamma Glutamyl Transferase; INR: International Normalized Ratio.

We decided to continue with emergency exploratory laparotomy. There was 500 cc of enteric content and profound peritonitis in all quadrants of the abdomen. The peritoneal cavity was irrigated with 10 liters of warm saline. Our exploration revealed a conglomerated intestinal segment 160 cm distal to the Treitz ligament and 190 cm proximal to the ileocecal valve. Further adhesiolysis showed that there was perforated intestinal segment and a diverticular extension from the antimesenteric side that was fixated to the anterior abdominal wall with fibrous bands (Fig. 1). The possible cause the intestinal perforation was a volvulus of the intestinal segment because the perorated site of the intestine had pale ischemic mucosa. We performed a segmental small bowel resection with end jejunostomy. We avoided primary anastomosis because of the profound peritonitis and contamination and of the peritoneal cavity with intestinal content. The surgical specimen is shown in Figure 2.

The postoperative early course was very troublesome and as it can be seen from the laboratory values, patients was septic (Table 1). For this reason we switched his antibiotic treatment to tazobactam and piperacillin, teicoplanin and anidulafungin. He has minor biliary leakage from the bile duct anastomosis, and he is still recovering in the intensive care unit.

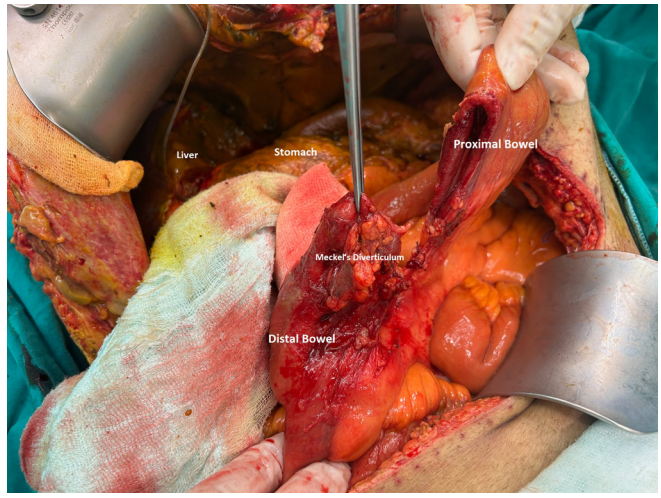

Figure 1. Intraoperative appearance of the of the perforation site showing the Meckel's diverticulum.

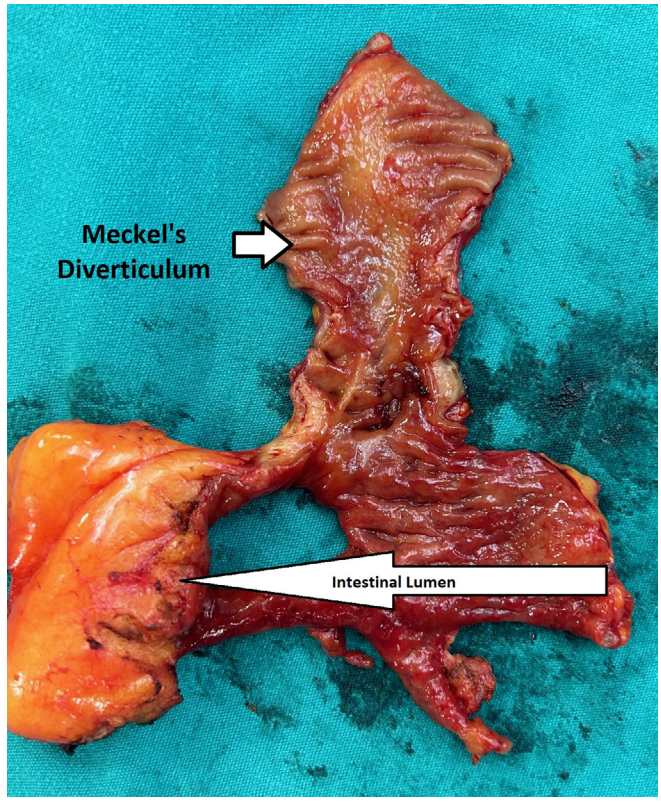

Figure 2. The surgical specimen is opened along the antimesenteric side. The long white arrow shows the intestinal lumen from proximal to distal direction. The white arrowhead shows the longitudinally opened Meckel's diverticulum.

Discussion

Gastrointestinal perforations can complicate the postoperative course of liver transplant recipients. Risk factors for occurrence of gastrointestinal system perforations are previous abdominal surgeries, prolonged portal clamping and need for post-transplant revisional surgery. All these factors show that the case is technically demanding and the procedure itself is complicated.[2,7] The present case is the first case of complicated Meckel's diverticulum causing gastrointestinal perforation in the early post-transplant period.

There have been only few report of complicated Meckel's diverticulum in solid organ transplant recipients.[17,18] Liu et al.[18] have reported a 51 years old male patient who received a multi-visceral transplant due to unresectable neuroendocrine tumor. The patient had recurrent gastrointestinal bleeding 3 months after the transplant procedure and ileoscopy revealed active bleeding from Meckel's diverticulum. The patients was treated with bowel resection. Topal et al.[17] have reported a Meckel diverticulum perforation in a liver transplant recipient in the postoperative third year which was due to a migrated biliary stent. The patient was treated with diverticulectomy. In the present case, our patient was re-operated to abdominal sepsis. We have diagnosed the presence of complicated Meckel's diverticulum intraoperatively. Since there was extensive peritonitis and contamination of the peritoneal cavity we performed resection and diversion end-ileostomy. We have previously published our experiences with gastrointestinal system

perforations in liver transplant recipients.[2,7] Also, we have shown the survival benefit of creating a stoma in pediatric liver transplant recipients with gastrointestinal system perforation[7] which, in our opinion, is valid for adult patients as well.

The operation of asymptomatic Meckel's diverticulum has a morbidity rate of 0-6%. However, operating on patients with complicated Meckel's diverticulum has a morbidity rate over 30% with a lifetime complication risk over 15%.[13-15,19,20] The delay in diagnosis has an adverse effect on the prognosis of the patients. In addition, the accuracy of preoperative diagnosis is as low as 5%.[21] This is because the low efficacy of computerized tomography and reduced accuracy of radionuclide scans in the diagnosis of Meckel's diverticulum.[22,23] Therefore, high grade suspicion of the attending physician and a low threshold for performing exploratory surgery has paramount prognostic importance. In our institute, we usually have a low threshold for operative intervention in clinical conditions such as acute abdomen and suspected abdominal sepsis in liver transplant recipients in our clinic. In the present case, we have seen the intestinal content in the drains and from the surgical incisions. Therefore, exploratory surgery was the only option for this patient.

Prevention is the best treatment option for any disease. In our case pre-emptive resection of incidentally discovered Meckel's diverticulum during the transplant procedure would have prevented this complication. However, we have not specifically searched the abdomen for any other gastrointestinal diseases since we have a detailed preoperative work-up for our patients. But since the pre-operative detection of a Meckel's diverticulum is very difficult, this was a didactic case for us and from now on, we intend to check the abdominal cavity for any other conditions during the transplant procedure. The efficacy and safety of pre-emptive diverticulectomy is the main question that should be answered. Unfortunately, the data regarding this subject is not available. However, as we have mentioned above, the intervention for symptomatic or complicated cases is associated with significant morbidity and furthermore, the lifelong risk of developing complicated in Meckel's diverticulum is high. Therefore, we believe that these arguments are enough to justify incidental diverticulectomy during the liver transplant procedure.

In summary, the present case has shown that complicated Meckel's diverticulum can be an underlying cause of perforation in liver transplant recipients. Therefore, attending surgeons should have a low threshold for operative intervention in patients and should decide whether to perform diverticulectomy or resection primary anastomosis versus creating a stoma according to the condition of the patient. In addition, the safety and efficacy of incidental diverticulectomy should be evaluated with further randomized controlled trials.

Disclosures

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

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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

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JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2023.54264
J Inonu Liver Transpl Inst 2023;1(2):70–72

Case Report

Spontaneous Rupture of Hepatocellular Carcinoma with Hemorrhagic Shock

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Abstract

Spontaneous rupture of hepatocellular carcinoma is a fatal and rare complication. Most of the patients admitted to the emergency department with abdominal pain and hemodynamic instability. After appropriate intravenous fluid therapy different treatment modalities can be chosen due to patient's functional liver reserve, clinical status and tumor's features.

A 48 years old male patient admitted to the emergency department with upper abdominal pain and severe hypotension. Dynamic contrast enhanced computerized tomography showed ruptured partially hypervascularized lesion at segment 4b and 5 in the liver. Also there were free hemorrhagic fluid densities at perihepatic and perisplenic areas. First of all transcatheter arterial embolization was performed at the interventional radiology department, then central hepatectomy including segment 5 and segment 4b was performed. The patient was discharged without any complication.

Ruptured hepatocellular carcinoma is an emergency clinical situation. Staged hepatectomy after transcatheter arterial embolization for ruptured hepatocellular carcinoma may be the best treatment option for patients who have acceptable liver functions and resectable tumor features.

Keywords: ruptured hepatocellular carcinoma, surgery, spontaneous

Please cite this article as "Ozdemir F, Kutlu R. Spontaneous Rupture of Hepatocellular Carcinoma with Hemorrhagic Shock. J Inonu Liver Transpl Inst 2023;1(2):70–72".

Spontaneous rupture of hepatocellular carcinoma (HCC) is a fatal and rare complication. The incidence rate of spontaneous rupture for HCC is between 2,6-26 %.[1] The incidence rate has reduced due to early diagnosis during the last decade, but mortality rates are still high like 25-100 % in most cases.[1] Most of the patients consulted at the emergency department with abdominal pain and hypotension. It is difficult to choose the right treatment modality for these clinically unstable patients. Studies have shown different treatment strategies such as emergency hepatectomy, hepatic arterial ligation, perihepatic packing and transcatheter arterial embolization (TAE). Liver functions and histopathologic features of tumor have the key role for choosing the right treatment option and also they affect the prognosis of the patient. We aimed to report a spontaneous rupture of hepatocellular carcinoma case that was treated successfully with central hepatectomy after TAE.

Case Report

A 48 years old male patient has applied to the emergency department with severe hypotension and tachycardia. (Ar-

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Submitted Date: 15.07.2023 **Revised Date:** 24.07.2023 **Accepted Date:** 24.07.2023 **Available Online Date:** 25.09.2023

terial blood pressure: 90/ 50 mmHg and heart rate: 120 b/min). He also had mild abdominal pain. Physical examination was revealed. There was abdominal tenderness at the epigastric region. The patient was monitored for the vital signs. Intravenous fluid resuscitation was started rapidly, and blood samples were collected for laboratory tests. Hemoglobin level was 5.5 g/dl. AFP level was 16,31 ng/ml. All the other biochemical test analyses were in normal range. (AST: 30 IU/L, ALT: 35 IU/L, Total bilirubin: 1.1 mg/dl, INR: 1.02) After fluid resuscitation and red blood cell transfusion, the patient's vital signs were stabilized. Dynamic contrast enhanced computerized tomography showed hypervascularized lesion at segment 4b and 5 with the dimensions of 6x4 cm in the liver. Also free hemorrhagic fluid densities were observed at perihepatic and perisplenic areas (Fig. 1). In order to stop active bleeding, transcatheter arterial embolization was performed at the interventional radiology department. Then elective surgery was planned. Central hepatectomy including segment 5 and segment 4b was performed. Post-operative course was uneventful and the patient was discharged without any complication. Final pathological examination revealed moderately differentiated ruptured hepatocellular carcinoma with the dimensions of 4x3,5x3 cm (Figs. 2-3).

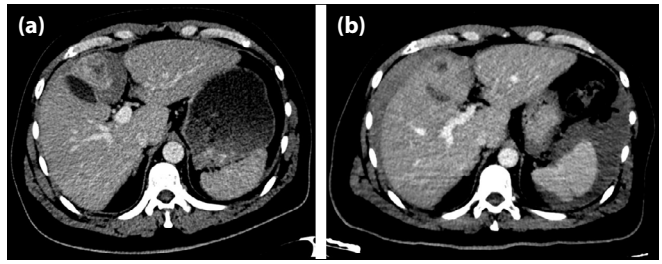

Figure 1. Contrast enhanced CT obtained one day before the admission **(a)** and at the day of admission **(b)** shows hypervascular tumor located in segment IV. An increase in the amount of perihepatic fluid consistent with hemorrhagic fluid is seen in these serial CT examinations.

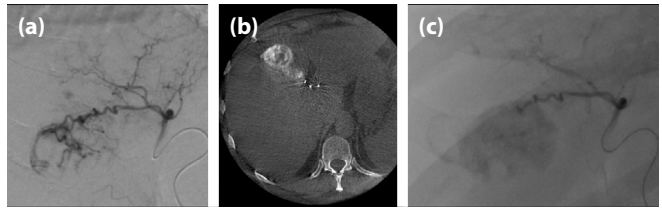

Figure 2. Superselective catheterization of the tumor feeding arterial branch of segment IV artery shows slight active contrast extravasation from the periphery of the tumor **(a)**. Cone-beam CT slice **(b)** shows the hypervascular tumor. After selective bland embolization with calibrated particles selective angiography image **(c)** demonstrates retained contrast in the tumor and cessation of active contrast extravasation.

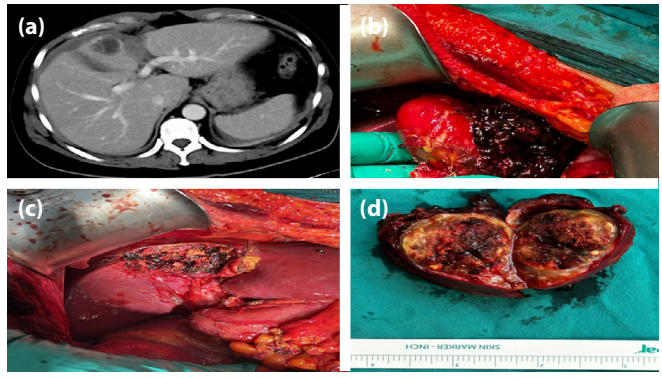

Figure 3. Post-embolization control CT slice **(a)** demonstrates necrosis of the tumor **(b)** and the decrease in the amount of perihepatic hemorrhage. Central hepatectomy **(c)** and macroscopy of the tumor **(d)**.

Discussion

Male gender and Child-Pugh A class patients' predominance has been shown in studies for ruptured HCC.[1] Our patient was a 48 year old male patient and his liver functions were fine at the admission. Hemodynamic instability, hemoperitoneum, and the degree of liver injury are the major factors affecting 30 day mortality.[1] Ruptured HCC with massive hemoperitoneum often results with hemorrhagic shock which should be treated urgently with intravenous fluid resuscitation in order to stabilize patients. We had treated our patient with intravenous fluids and red blood cell transfusion.

As we know that most of the HCC tumors' blood supply arises from the hepatic artery, conservative treatment strategies wouldn't be enough to decrease the risk of continuous or repeated bleeding. After hemodynamic stabilization of the patients TAE and/or surgery should be considered for ruptured HCC patients.[2] TAE is a better hemostatic method when compared with surgical hepatic arterial ligation.[3] Although TAE has an excellent hemostatic effect in ruptured HCC, Zhong et al observed that when TAE is compared with hepatectomy TAE has lower therapeutic effect. [1] Li et al suggested staged TAE followed by surgery in selected patients as a solution because due to hemodynamic instability the surgery may be difficult as a first choice.[4]

It should be considered that if TAE is a definitive or preliminary treatment modality case by case. Reevaluation of the patient after TAE; especially post TAE liver functions and patient's clinical condition are the main factors for choosing surgery after TAE as a definitive treatment. In a recent study liver failure after TAE was observed in 19 % patients who receive TAE after ruptured HCC, which suggests that patients with good reserved hepatic function should be se-

lected for TAE.[1] Liver functions and general clinical condition of our patient were excellent so we initially chose TAE for hemodynamic stabilization and afterwards surgery as a definitive treatment.

Patients who have ruptured HCC with stable hemodynamic parameters, acceptable liver functions and resectable tumor features may be considered for emergency hepatectomy. In a recent study spontaneous rupture independently predicted poor overall survival after hepatectomy but overall survival and recurrence free survival after hepatectomy for ruptured HCC in the emergency and staged subgroups were not significantly different in multivariable analyses.[5]

Conclusion

Ruptured HCC is an emergency clinical situation which should be evaluated by a multidisciplinary team consisted of surgeons, interventional radiologists, hepatologists and medical oncologists. Staged hepatectomy after TAE for ruptured HCC may be the best treatment option for patients who have acceptable liver functions, resectable tumor features and fine clinical conditions.

Disclosures

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

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – F.O.; Design – F.O.; Supervision – R.K.; Materials – F.O., R.K.; Data collection &/or processing – F.O., R.K.; Analysis and/or interpretation – F.O.; Literature search – F.O.; Writing – F.O., R.K.; Critical review – R.K.

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JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2023.57966
J Inonu Liver Transpl Inst 2023;1(2):73–76

Case Report

Compression of Left Portal Vein By Giant Hydatid Cyst Extending from the Caudate Lobe to the Foramen of Winslow

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Abstract

Hydatid disease may affect any organ or tissue, but the most involved organ is the liver. Despite the fact that it is an asymptomatic disease in most patients, about one-third of patients will have a complication. The most common complications of hydatid disease are cystobiliary communications, superinfection, cyst rupture, and mass effect induced complications. Primary aim of this study is to present this case study, 27 years old female patient, regarding a hydatid cyst originating from caudate lobe of the liver, extending to the foremen of Winslow and resulting in pressure on the left portal vein with heterogeneous liver parenchyma seen on computed tomography; as extensive, causing abdominal pain and treated before causing portal venous thrombosis or portal hypertension. The patient underwent cholecystectomy, pericystectomy and received preoperative and postoperative albendazole treatment. In the contrast enhanced computed tomography taken five months after the surgery, it was observed that the heterogeneity in the liver parenchyma completely resolved. After reviewing the literature, there were no studies showing early treatment of such cases before complications occurred.

Keywords: Caudate lobe, compression, hydatid cyst, liver, portal inflow

Please cite this article as "Akbulut S, Tuncer A, Aloun A. Compression of Left Portal Vein By Giant Hydatid Cyst Extending from the Caudate Lobe to the Foramen of Winslow. J Inonu Liver Transpl Inst 2023;1(2):73–76".

Hydatid disease is caused by a cestode class tainted family parasite; about 95% of humans hydatid disease is caused by echinococcus granulosus and the definitive host is sogged.[1] Infection of humans occurs by accidental ingestion of echinococcus granulosus from dog feces and results in hydatid disease. When eggs are ingested by an intermediate host like human, they are taken by the gastrointestinal system in humans to the portal vein and then to the liver developing the characteristic hydatid cyst.

Most cysts adhere to hepatic sinusoidal membranes, in most cases larva eggs bypassing those membranes can enter the systemic circulation and cause lung, splenic and brain cysts.[2,3] Asymptomatic diagnosed cysts may increase in size, collapse, calcify or remain asymptomatic in the same patients according to size, location and the relation to surrounding structures with a complication rate around 30%-50%.[4,5] The most common symptom is nonspecific abdominal pain. Other symptoms include itching and jaundice with diagnosis achieved by radiological studies, serological and immunological tests. Although liver function tests may be normal in biliary complications, cholestasis enzymes or transaminases are elevated; the ELISA test has 85% sensitivity.[6] The symptoms and signs of hydatid cyst are related to cyst size, site and surrounding structures. Average growth in cyst size is 10 mm in the first 6 months then 20-30 mm yearly.[7] Increasing cyst size may affect hepatic vein, portal vein, interahepatic or extrahepatic biliary structure, right diaphragm and kidney. The aim of this case report was to present a hydatid cyst originating from caudate lobe of the liver, extending to the foremen of Winslow and resulting in pressure on left portal

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Submitted Date: 05.07.2023 **Revised Date:** 21.07.2023 **Accepted Date:** 21.07.2023 **Available Online Date:** 25.09.2023

vein with heterogeneous liver parenchyma seen on magnetic resonance imaging; as extensive causing abdominal pain and treated before causing portal venous thrombosis or portal hypertension.

Case Report

A 27-year-old female patient applied to a private health institution with the complaints of nonspecific right upper quadrant pain and itching. Since hydatid cyst disease was detected in radiological analysis, albendazole (10 mg/kg/days) treatment was started. The patient, whose complaints did not resolve with anthelmintic treatment, was referred to our center for surgical treatment. In order to ensure the diagnosis of a hydatid cyst disease, contrast enhanced computed tomography was done and findings were 80x80 mm cyst with detached cystic membranes (lily sign) Gharbi II originating from segment 1 (caudate lobe) and extending to segment 7-8 superiorly and diaphragm anteriorly with portal confluence and heterogeneous parenchyma changes seen in the left lobe of the liver compressing left portal vein (Fig. 1). Echinococcus IgG ELISA was positive for hydatid disease. The patient was kept on preoperative anthelmintic treatment to prevent an postoperative recurrence and reduce intracystic pressure. Intraoperative findings consistent with 100x70 mm cystic lesion, displacing left portal vein, hepatic artery and common bile duct, superiorly. Periheptic area was surrounded with wet gauze 3% saline to prevent seeding. First hiller dissection, cholecystectomy and cholangiogram were performed. Cyst content was aspirated through an incision on the anterior wall of the cyst, followed by partial pericystectomy (Fig. 2). Cholangiogram was repeated to check if there is any biliary communication with the cyst cavity; after hemostasis drain

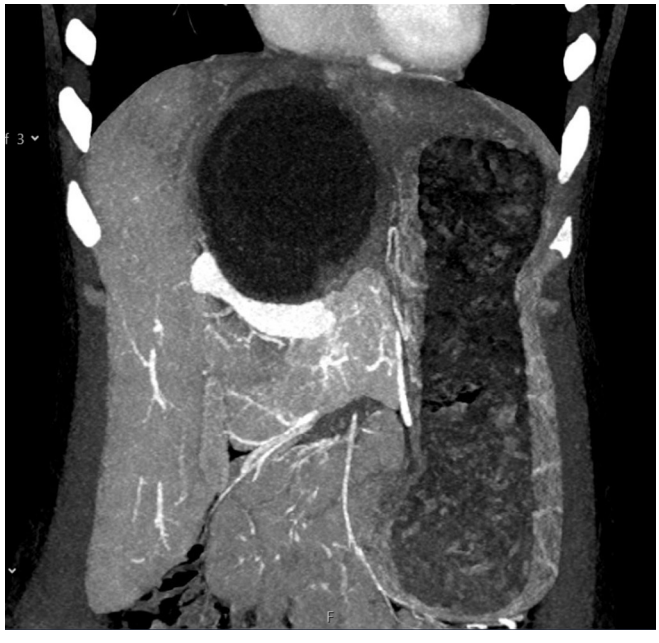

Figure 1. A cystic lesion located in the caudate lobe that disrupts the contrasting pattern on the left side of the liver by compressing the portal vein.

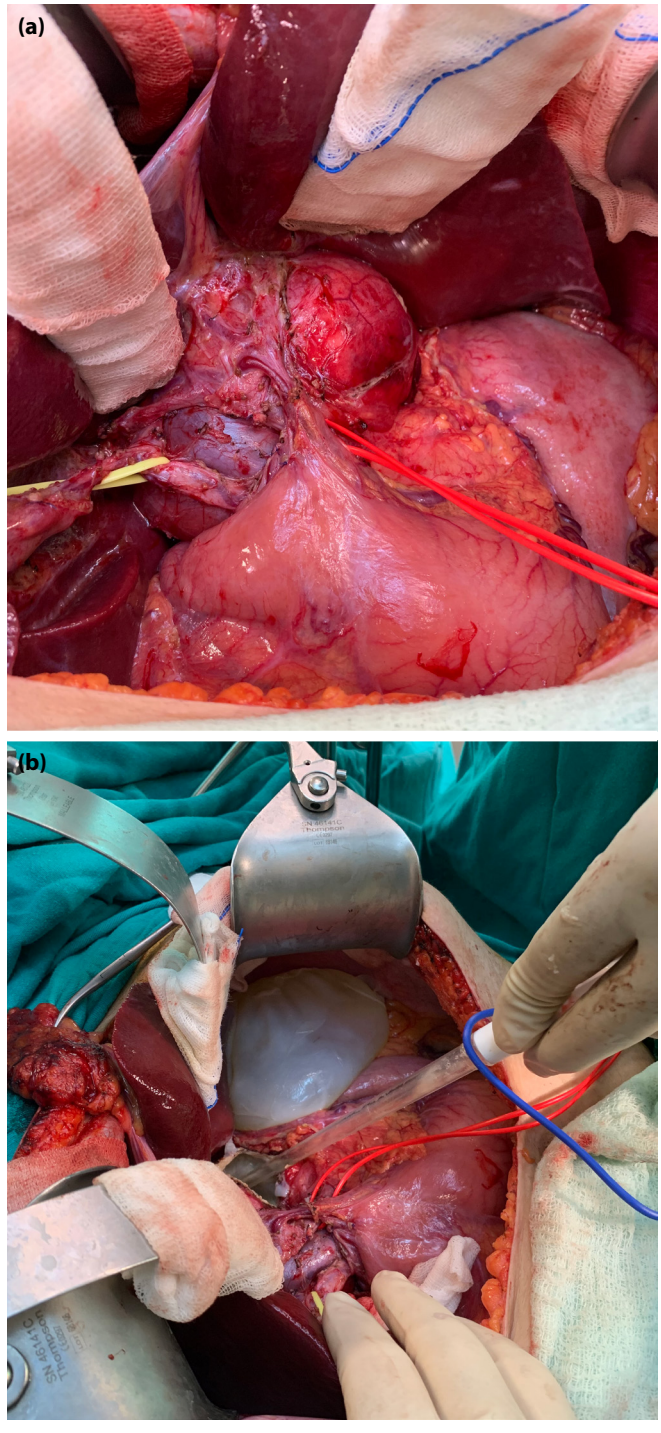

Figure 2. Images obtained from different stages during surgery. **(a)** The structure of the cyst that compresses the hilar structures posteriorly **(b)** Removal of the daughter vesicle in the cyst after the anterior wall is opened.

was inserted. Patient was discharged on the 4th postoperative days on albendazole for six weeks, 12 months later there were no signs of recurrence on computed tomography (Fig. 3), 36 months later patient was doing well without signs of recurrence or complications.

Discussion

Hydatid disease is an endemic disease in sheep and cattle raising countries like turkey, Spain Middle East, Africa and Greece.[8] As intermediate hosts, human beings are infected by ingested larva eggs through food contaminated by dog's feces. The first step in physical diagnosis is examination and patient history in which most patients with hydatid disease remain asymptomatic as the cyst grows slowly; some patients develop symptoms due to cyst size, number or location. These symptoms might be caused by the mass effect of the cyst on the biliary tree, vascular structures or surrounding organs. A common complication of hydatid Cyst is rupture of the biliary tree, secondary infection, anaphylactic shock, obstruction of the biliary tree or pressure on vascular structures. Cyst fluid contains antigens that could cause fever, urticarial or eosinophilic reactions. Anaphylactic shock, a well-known complication of hydatid disease, occurs 1-16% of patients who suffered form intraperitoneal ruptures,[9] although it is really common to see complications related to mass effect of the large hydatid cyst when the hydatid cyst is located on the hepatic hilum like portal vein thrombosis, Budd-Chiari syndrome, segmental atrophy secondary biliary cirrhosis and duodenal stenosis. In our case, exophytic hydatid cyst caused pressure on the left portal vein but was treated before causing any other liver complications. Hydatid cyst diagnosis was achieved by patient history, physical examination, laboratory investigations and radiological studies. Hydatid cyst was classified radiologically according to ultrasound findings in Gharbi classification: Type 1; pure cystic fluid collection, Type 2; fluid collection with membrane separation, Type 3; fluid collection with septa, Type 4; heterogeneous pattern, Type 5; completely calcified.[10] In our case, the most common was membranes separation, and we considered it as gharbi type II; symptomatic patients should be diagnosed and treated early to prevent complications; treatment modalities include medical percutaneous drainage and surgical interventions. Surgical interventions should be targeted at removing the cyst and preventing recurrence with minimal rates of morbidity and mortality. Cyst type and anatomical location should be considered when choosing treatments modalities. Medical treatment, open surgery, PAIR (punction- aspiration- injection- reaspiration) or laparoscopic surgery can be considered in the treatment of hydatid cyst disease.[11,12] In our case, the cyst was exophytic, and we opted for pericystectomy, surgical treatment was divided into Conservative and radical open and minimally invasive, and the choice was based on cyst size, type, Location, surgeon experience and institution's facilities; it should be mentioned that there is no difference between open and minimally invasive surgeries according to recurrence rate. The ideal treatment of a complicated hydatid cyst is preoperative medical treatment 1 to 2 weeks before any surgical intervention unless there is an emergency indication for an intervention. The best treatment of a complicated hydatid cyst is surgery and radical surgery for exophytic cysts; a radical approach like lobectomy, segmentectomy or pericystectomy has a higher morbidity and mortality rate compared to conservative treatment which is the best in regards to recurrence. As a result, in countries like turkey in which hydatid disease is considered endemic, hydatid disease should be one of the differential diagnoses when dealing with patients with vague abdominal pain. Radiological studies are cornerstone in devising a diagnosis and treatment plan for patients. It is preferable to keep

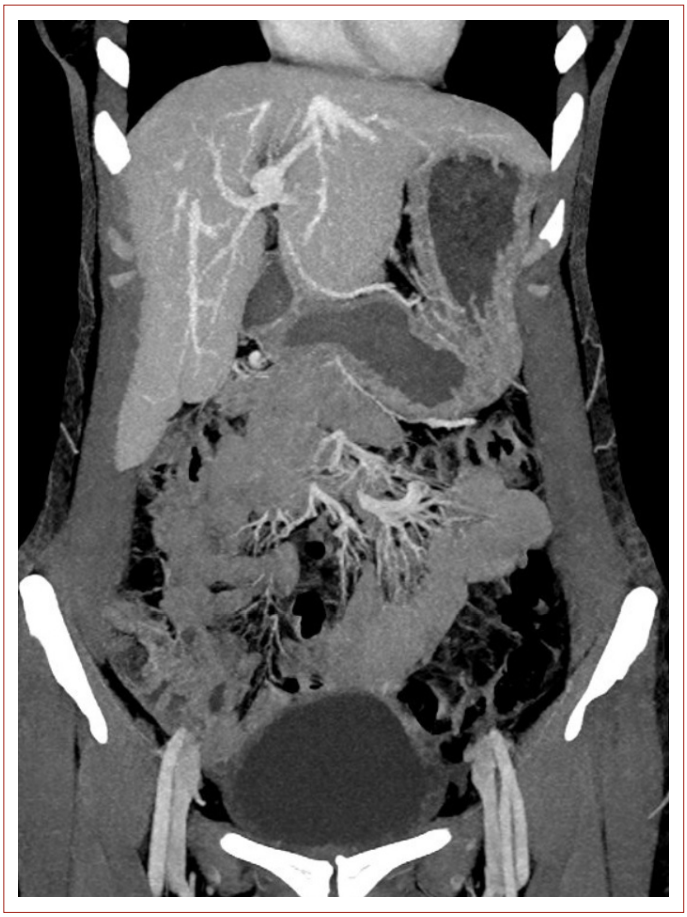

Figure 3. Control CT images taken at the sixth postoperative month. Heterogeneity in the left lobe of the liver appears to have disappeared.

patients on albendazole 10 -14 days preoperatively and 6-8 weeks postoperatively (continuous and cyclic). Conclusion after reviewing the literature, there were no studies showing early treatment of liver hydatid cysts with a high risk of complications before complications occurred.

Disclosures

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

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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

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JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2023.43534
J Inonu Liver Transpl Inst 2023;1(2):77–78

Letter to the Editor

Anatomical Variations and Reconstruction Techniques of the Left Hepatic Vein in Pediatric Living Donor Liver Transplantation

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Please cite this article as "Usta S, Yilmaz S, Akbulut S. Anatomical Variations and Reconstruction Techniques of the Left Hepatic Vein in Pediatric Living Donor Liver Transplantation. J Inonu Liver Transpl Inst 2023;1(2):77–78".

Dear Editor,

We read with interest the article by Shankar et al.[1] that was recently published in American Journal of Transplantation. This study was conducted on prospectively collected database of 296 left lateral segment (LLS) pediatric living donor liver transplantation. Aim of it was to identify different venous drainage patterns of segment 2 (V2) and segment 3 (V3) and to describe their proper reconstruction. We would like to make a few contributions by emphasizing that we appreciate great importance to this study.

The left hepatic vein (LHV) anatomy defined by the authors, which we encounter in a previous study of Mohamed Rela,[2] can be more comprehensive classification with addition of two different types, although the frequency is low. V2 and V3 may drain conjoin or separately into the middle hepatic vein (Fig. 1a, b).

In "modified triangular technique" frequently used in anastomosis to the vena cava inferior (VCI) of the recipient of the LHV, we do not recommend making a longitudinal slit in the anterior aspect of the inferior vena cava, as suggested in the article by Fukuda et al.[3] Because this incision will cause an excessive width on the inferior vena cava side of the anastomosis, adapting sutures will be used excessively to adapt the anastomosis, and inferior vena cava stenosis will occur as a result.

Regarding reconstruction techniques in grafts with multiple orifices:

- Unification venoplasty should be performed in type 1b and type 2. However, while doing this procedure, V2 and V3 orificies should be held together like an equilateral triangles (Fig. 2a). The closest edge of triangles should be joined with interrupted 7/0 absorbable monoflament sutures (Fig. 2b). The objective here is to apply a joining suture without narrowing or stretching both lumens. If the unifying includes half of the orificies of V2 and V3, that is half of the circles, it can be seen that both of the lumens narrow. Then an autologous saphenous vein that cut longitudinally or cryopreserved iliac vein graft is sutured around the joined vessel like a circumferential fence or venous conduit (Fig. 2c). This may also be called a funnel shaped extension.[4]
- In this article,[1] we see that a partial circumferential fence is made the named as "extension venoplasty" in Figure 4c. Such reconstructions will complicate anastomosis. A circumferential fence with saphenous vein or a venous conduit should always be made as 360 degree.

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Submitted Date: 29.05.2023 **Revised Date:** 29.05.2023 **Accepted Date:** 31.05.2023 **Available Online Date:** 25.09.2023

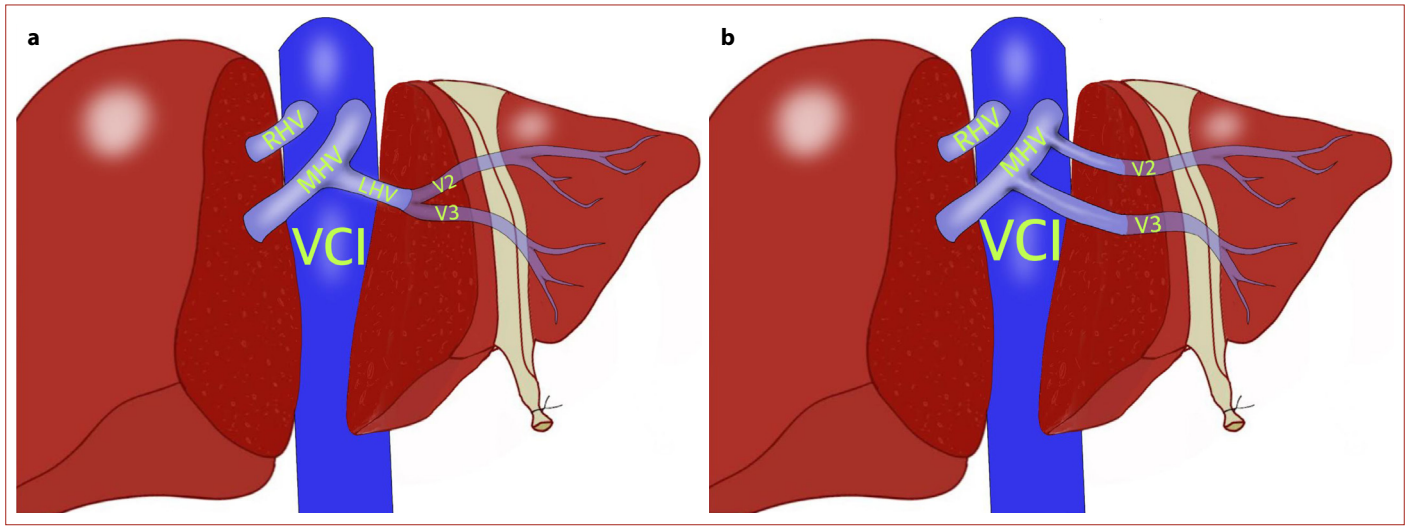

Figure 1. V2 and V3 may drain conjoin into the middle hepatic vein **(a)**; V2 and V3 may drain separately into the middle hepatic vein **(b)**.

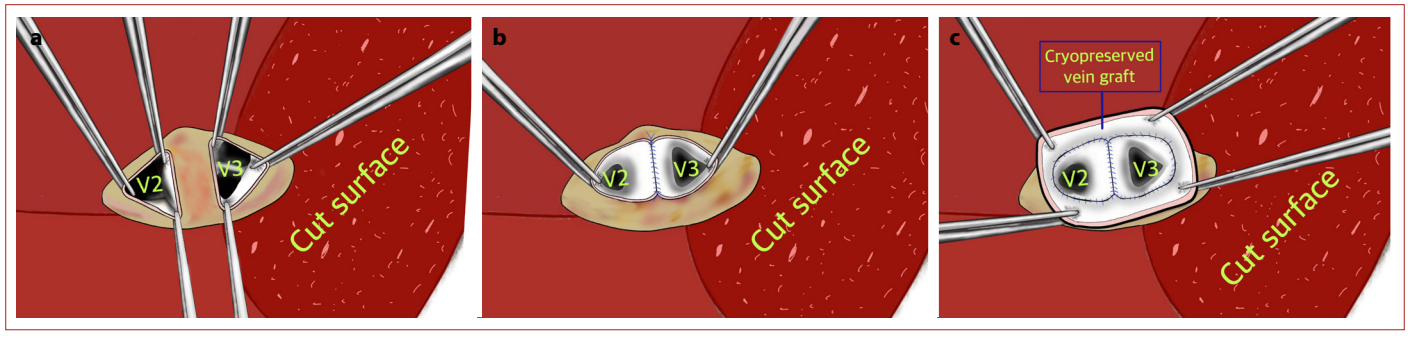

Figure 2. V2 and V3 orificies are held together like an equilateral triangles **(a)**; the closest edge of triangles are joined with interrupted sutures **(b)**; a cryopreserved ilia cvein graft is sutured around the joined vessel like a venous conduit **(c)**.

- We would like to state that we cannot make sense of the fact that the diameter of V3 below or above 7 mm in type 3 determines the type of reconstruction. In any case, the V3 orifice should be extended to V2 with a cryopreserved vein and unification should be done as described above. In the pediatric patients, especially under 10 kg, lengthening and anastomosis of the V3 into the inferior vena cava with an already very narrow diameter will invite inferior vena cava complications. Also, since the extension of V3 into the inferior vena cava will partially change the flow direction, thrombosis will be inevitable in a low-flow venous system.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declare that they have no conflict of interest.

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

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JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2023.54254
J Inonu Liver Transpl Inst 2023;1(2):79–80

Letter to the Editor

Comment on Respiratory Complications Among Living Liver Donors: A Single-Center Retrospective Observational Study

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Please cite this article as "Akbulut S. Comment on Respiratory Complications Among Living Liver Donors: A Single-Center Retrospective Observational Study. J Inonu Liver Transpl Inst 2023;1(2):79–80".

Dear Editor;

We read with great interest the recent article "Respiratory Complications Among Living Liver Donors: A Single-Center Retrospective Observational Study" published by Elbeialy and colleagues.[1] The authors stated that despite the low incidence of significant respiratory complications among their living liver donor cohort, close monitoring and early management are essential to achieve better prognosis, especially in donors older than 35 years or those with previous surgery. We would like to draw attention to a few points.

Authors state that they routinely use conventional angiography to evaluate the suitability of the living liver donor candidates. In the earlier times of living donor liver transplantation, the imaging techniques had an insufficient quality and conventional angiography was routinely used to avoid unnecessary laparotomy. However, in the last decade, there is a great number of advancements in the accuracy and quality of the non-invasive imaging techniques that resulted in the abandonment of the conventional angiography for the evaluation of the living liver donors.[2] Currently, conventional angiography is only used for the evaluation of vascular anatomy under certain exceptional conditions. In our institute, we use conventional angiography in less than 0.1 % of living liver donor candidates. Similarly, if preoperative ultrasonography, dynamic computerized tomography, and dynamic magnetic resonance imaging are performed appropriately, the fibrosis and hepatosteatosis can be evaluated accurately and occasionally there will be nor need for preoperative liver biopsy. In recent years, transient elastography (Fibroscan) can help determine the texture and steatosis of the liver, and together with using a specific formula, steatosis rates can be determined which is comparable with the histopathological evaluation.[3,4]

The authors have stated that they have used PASS software to calculate the sample size of 124 patients. In our opinion, there is no need for sample size and power analysis calculation in the present study because the authors have included all living liver donors' in the designated period which makes alpha value to be 0.05 at the minimum and the power would be 100%. If the authors were to use a statistical method, they should have performed propensity score matching analysis on the 10 patients with complications by choosing a 1:2 matched control group with similar demographic and clinical characteristics. This approach would

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Submitted Date: 11.04.2023 **Revised Date:** 11.04.2023 **Accepted Date:** 13.04.2023 **Available Online Date:** 25.09.2023

have reduced bias significantly in the present study.[5]

In the statistical methods section, the authors should clarify the criteria they have used to include the parameters to the logistic regression model, the accepted p values to include the variables to the analysis, the type of logistic regression model that is used (enter, backward, forward, etc.). In Table 1, the authors have expressed the age variable as mean±SD and have stated that there was no statistically significant difference between the groups in terms of the donors' age. However, in the logistic regression model, the authors have used age cut off value of 35 years. The authors should clarify the method of calculation of this cut off value (ROC etc.) and should express the sensitivity and specificity for this cut off value. Another method is to use the cut off values found in other studies that require referring to the specific studies. The authors should clarify the reason why they have not used this cut off value in Table 1.

There is not enough evidence in the literature regarding the relationship between the postoperative pulmonary complications and the right donor hepatectomies. Besides, the authors could not show such a correlation in their study. Nevertheless, our experience including 2250 donor hepatectomies and the review of the literature shows that pulmonary complications are more frequently encountered after the right lobectomies. In our opinion, the main reason for this is the dissection plane between the right lobe and the diaphragm which may lead to diaphragmatic paralysis and may lead to increased diffusion of ascites fluid to the pleural cavity. We have used the data provided by Dondero and colleagues[6] in their study, the risk of pulmonary complications was 47-fold higher in patients undergoing right lobectomy when compared to patients undergoing left lobectomy (OR=47; p=0.008). We have also analyzed the data provided in the study by Iwasaki and colleagues[7] the risk of pleural effusion following right lobectomy was 7.87-fold higher and the p-value was very close to being significant (p=0.051). We also reanalyzed the data of Ulubay and colleagues[8] and we found that the risk of overall pulmonary complications following right lobectomy was 1.4-fold higher but this did not reach statistical significance. Similarly, a re-analysis of the data of Ates and colleagues[9] has shown that overall complication risk was 1.31-fold higher but it did not reach statistical significance. Associating all these results with our experience, during the right lobectomy, we suggest that the dissection should be held close to the liver and far away from the diaphragm as much as possible to reduce the postoperative pulmonary complications that related with surgical procedure.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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