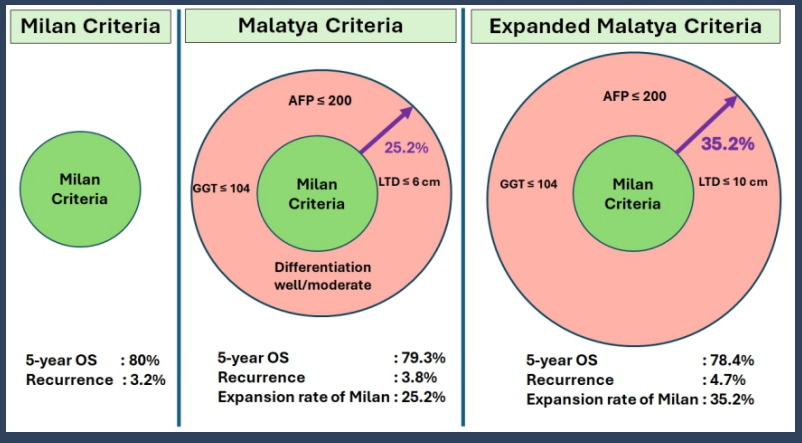
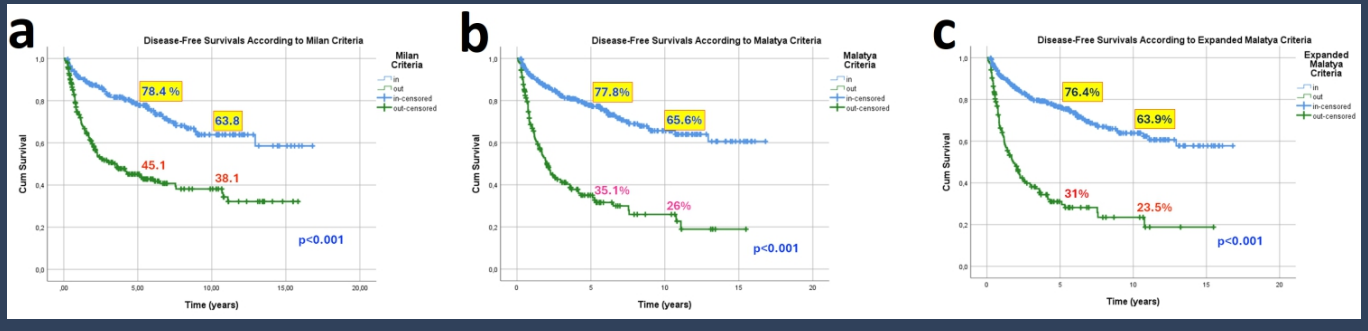
The Official Journal of the Inonu Liver Transplantation Institute

Journal of Inonu Liver Transplantation Institute





Liver Transplantation for Hepatocellular Carcinoma with Expanded Criteria: Malatya Experience

www.jilti.org

Volume: 2 Issue: 2 August 2024 E-ISSN 2980-2059

JILTI

Journal of Inonu Liver Transplantation Institute

JILTI

Journal of Inonu Liver Transplantation Institute

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
Editors-in-Chief: Sezai Yılmaz, MD, Prof. (sezai.yilmaz@inonu.edu.tr), Brian I. Carr, MD. Prof. (brianicarr@hotmail.com)
Publisher: Inonu University Liver Transplant Institute
Bulgurlu, 44000 Battalgazi, Malatya, Türkiye
+90 (0422) 341 06 60
sezai.yilmaz@inonu.edu.tr
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.
Paper Submission: Click here in order to submit your paper. https://jag.journalagent.com/jilti/

KARE

Publisher: KARE PUBLISHING
Address: Göztepe Mah. Fahrettin Kerim Gökay Cad. No: 200 Da: 2, Göztepe, Kadıköy, İstanbul-Türkiye
Phone: +90 216 550 61 11
Fax: +90 212 550 61 12
e-mail: kare@kareyayincilik.com
web: www.kareyayincilik.com

Yayın Turu: Uluslararası Sureli
Yayın Tarihi: August 2024
Basım: Yıldırım Matbaacılık, İstanbul
Tel: +90 212 629 80 37

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.

JILTI

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

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

JILTI

CONTENTS

E-ISSN 2980-2059 Volume 2 Issue 2 Year 2024

EDITORIAL

The Story of FK 506 Begins with Thomas E. Starzl

Yılmaz S 47

ORIGINAL ARTICLES

Examination of Genetic Background of Intrahepatic Cholangiocarcinoma by Bioinformatics Applications

Kucukakcali Z, Akbulut S 52

The new "Living Donor Liver Transplantation Program" Created by the Scientific Cooperation Between Malatya and Bishkek

Yılmaz S, Kizilay A 60

Determination of Burden of The Caregiver In Pediatric Liver Transplantation

Sonmez E, Barut B, Sahin TT, Yilmaz S 65

Liver Transplantation for Hepatocellular Carcinoma with Expanded Criteria: Malatya Experience

Ince V, Usta S, Carr B, Kutlu R, Dikilitas M, Harputluoglu M, Sagir Kahraman A, Temelli O, Akatli AN, Kekilli E, Isik B, Yilmaz S 72

CASE REPORTS

Gallbladder Cancer in a Liver Transplant Patient

Dalda Y, Ince V, Ozcan M, Dalda O, Sahin TT, Yilmaz S 78

Re-Transplantation in a Pediatric Patient with Hepatorenal Syndrome: A Case Report

Tuncer A, Sahin E, Ersan V, Ayyildiz Civan H, Taktak A, Dirican A, Unal B 82

Living Donor Liver Transplantation in Patients with Crigler-Najjar Syndrome Type 1: Report of Three Cases

Guzelaltuncekic E, Ayyildiz Civan H, Sari F, Sonmez Topcu F, Toprak HI, Tuncer A, Sahin E, Ersan V, Unal B, Dirican A 85

İNÖNÜ UNIVERSITY
LIVER TRANSPLANT INSTITUTE
2011

www.inonu.edu.tr/karaciger
karacigernakli@inonu.edu.tr
+90 422 341 0660
İnönü University, Battalgazi, Malatya, Turkey

JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2024.07379
J Inonu Liver Transpl Inst 2024;2(2):47–51

Editorial

The Story of FK 506 Begins with Thomas E. Starzl

Sezai Yılmaz

Department of Surgery and Liver Transplant Institute, Inonu University Faculty of Medicine, Malatya, Türkiye

Keywords: FK506, Liver transplantation, Thomas Starzl

Please cite this article as "Yilmaz S. The Story of FK 506 Begins with Thomas E. Starzl. J Inonu Liver Transpl Inst 2024;2(2):47–51".

Tsukaba University was founded in Tsukaba village, located at the foot of Tsukaba Mountain, 45 miles from Tokyo. As can be understood, the university and the village took their name from this mountain. Tsukaba Mountain is one of the most famous mountains in Japan. Since the surface color of the mountain turns purple in the morning and evening sun, the mountain was considered a sacred mountain and was called purple mountain. It is especially known for its twin peaks and is a place of spiritual worship. The two peaks are said to represent male and female deities. They are worshiped as husband and wife and couples visit here to pray for marriage and happiness.[1] Along with Mount Fuji, Mount Tsukaba is one of the famous mountains of Japan. According to folk legend, a god named Mioyano-Mikoto once asked these two mountains for a place to spend the night. Due to its size and grandeur, the proud Mount Fuji rejected this request. However, when the god approached the Tsukaba mountain, he was welcomed with warm hospitality. Since then, Mount Tsukaba has been blessed with rich vegetation, while Mount Fuji has remained a cold and arid mountain.[2]

While Tsukaba University was only in its second decade, it contained 10-15% of all scientists in Japan. Because in addition to more than 40 government institutes, about 100 private institutes were located on this university campus and were working with major corporations. Starzl mentions that Tsukaba village was a large farmland during his visit in 1977, but during his visit a decade later, he says that he saw that it was one of the fastest growing cities in Japan and even an intellectual hotbed.[3]

The chairman of the Department of Surgery at Tsukaba Medical Faculty in 1975 was Yoji Iwasaki, the founder of this department. While Iwasaki was a transplant fellow at the University of Colorado, he worked on anti-lymphocyte globulin, an important discovery in the field of transplantation, in 1964 and 1965.[4] In 1986, in addition to being chair of surgery, Iwasaki was appointed chair of the Institute of Clinical Medicine. Yoji was responsible for training in all clinical medical fields.

In the spring of 1986, there was news of a drug called FK900506 cod, discovered by scientists at an institute established by Fujisawa Pharmaceutical Corporation on the Tsukaba University campus. The aim of these scientists was to investigate natural substances in soil for their anticancer and antirejection features. The research was related to a fungus, which is a type of microorganism. It was found in the soil at the foot of Tsukaba Mountain, near Iwasaki's office. The substance produced from the fungus prevented

Address for correspondence: Sezai Yılmaz, MD. Department of Surgery and Liver Transplant Institute, Inonu University Faculty of Medicine, Malatya, Türkiye
Phone: +90 532 120 23 76 **E-mail:** sezai.yilmaz@inonu.edu.tr

Submitted Date: 05.09.2024 **Revised Date:** 05.09.2024 **Accepted Date:** 18.09.2024 **Available Online Date:** 09.10.2024

immune reactions in their test system. The substance has not yet been described in the scientific literature and has not been examined outside of Fujisawa Laboratories. Studies on this substance had not attracted much attention until Starzl went to a meeting of the biannual Transplantation Society in Helsinki in August 1986. In one of the small sessions, which was attended by 40-50 people at most, a Japanese surgeon named Takenori Ochiai from Chiba University would present a study with the mysterious code number FK900506 in its title. In a nearby amphitheater, which was filled with congress participants, cyclosporine treatment in kidney transplantation were being discussed. At this major meeting, the wonderful qualities of cyclosporine were praised, but the limitations associated with immunosuppression were noted. The most serious side effect, well known since 1980, was that while cyclosporine protected the kidney from rejection after kidney transplantation, it also damaged the kidney. The same kidney damage was also reported in liver and heart graft recipients. Additionally, high doses of cyclosporine caused high blood pressure, hirsutism, gingival hyperplasia and tremor. When the cyclosporine dose was reduced, the side effects disappeared, but the risk of rejection increased.

Roy Calne from Cambridge, along with Starzl, was one of those waiting for Ochiai's presentation. A Japanese surgeon named Satoru Todo was sitting next to Starzl. Starzl states that he met Todo in October 1980 in Fukuoka, a city on Kyushu Island at the southern tip of Japan. Kyushu was It was Todo's hometown and the city where the university where he received his surgical training was located. Todo was a 33-year-old surgeon who was extremely open to improvement and desired it. He was determined to get a master's degree in liver transplantation, an operation he only knew about from books and journals. This operation had not been performed in Japan until then. Brain death was not accepted in Japan and would not be accepted for many years, so cadaver liver donors were out of the question. He decided to come to Colorado to pursue his dreams, but he was unaware that the program would be moving to Pittsburgh. There was no position available for him in Pittsburgh, but he eventually landed a job in Pittsburgh in January 1984 and was willing to work without a salary for the first 12 months. He was ready to learn and perfect liver transplantation in dogs and rats, which allowed efficient testing of new drugs every day for 2.5 years. He also assisted more experienced transplant surgeons in the operating room almost every night. Ochiai began his speech with a summary of the properties and mechanisms of action of FR900506. He also reported results on heart transplantation in a small number of rats. Rejection was prevented, with remarkable reliability and safety. [5] Later during the discussion, Calne said he had tested the drug supplied to him by Fison Corporation, a British pharmaceutical company that obtained the drug through a trade agreement with Fujisawa. Calne was concerned about the drug's toxicity and the severe vomiting it caused, especially in dogs.[6] Over the following months, Calne became more convinced of the drug's shortcomings. However, according to Starzl, FR900506 was 100 times more potent than cyclosporin and seemed too promising not to abandon this drug. This was the beginning of a debate that would last for more than 3 years.

A trade agreement between Fujisawa and Fison prevented Starzl from supplying FR900506 for testing through normal channels. Thereupon, Starzl and Todo went from Pittsburgh to Japan and met with Fujisawa executives in Nagoya and discussed their laboratory research plans. In response to this meeting, FR900506 development executive director Hiroshi Imanaka flew to London for a meeting with Fison officials. During this trip to Japan, a celebration called Kanreki was held to mark Starzl's 60th birthday. Reaching age 60 is ignored in most American Institutes, but reaching this age is a major traditional event in Japan. A belated Kanreki ceremony was held, organized by approximately 100 former Japanese students, Shun Iwatsuki and Hiro Takagi (Head of the Department of Surgery at Nagoya University). In Japan, it is traditionally believed that after the age of 60, people's burden decreases and a new life begins. The timing of this ceremony was apt for Starzl, as the physical and emotional toll of the past decade had taken its toll on him. Fatigue always accompanied him. Maybe it would be better for him not to get the medicine and start a new discussion. Starzl and Todo waited in Japan for the outcome of the Fujisawa negotiations in London. During this time, they traveled from Nagoya to Tokyo and then south to Fukuoka, where Todo's house was located. A week later Dr. Imanaka returned from England and reported the outcome of the talks with Fison executives in the lobby of a hotel in Fukuoka. Translation was extremely slow, Todo was translating. In the end, Starzl was given a very small amount of FR900506, enough to fill the bottom of a small thimble. Adriana Zeevi and other cellular immunologists in Pittsburgh were able to test this extremely small amount of the drug. Within 1 month, more drugs arrived for testing. Thousands of transplantation experiments have been done on rats, dogs, monkeys and baboons. A research conference was held every Monday night. Initially, 8-10 people attended these meetings. At the end of 1986, the conference hall was not large enough for the crowd exceeding 100 people. Everyone was waiting with great curiosity for the weekly reports on tissue culture experiments. A pediatric surgeon named Nariko Murase was the subject of these meetings, where liver transplants on rats or the results of dog experiments

performed by Todo were the subject of these meetings. The excitement was increasing with each new information. FR900506 was more potent than cyclosporine and did not appear to be very toxic.

The findings in Calne's experiments in the British laboratory that FR900506 was intolerably toxic not only in dogs but also in mice and baboons reduced optimism for this drug. Reports describing these experiments were presented to the congress organizing committee for the ESOT June 1987 meeting to be held in Gothenburg, Sweden. Fearing that the presented abstracts would kill promising developments regarding this drug, Starzl arranged, through transplant surgeons Carl Groth (Stockholm), Hans Brynger (Gothenburg) and Walter Land (Munich), an afternoon symposium the day before the official congress, where all available information on FR900506 could be exchanged. No article about the drug has been published yet. Essentially all research took place in 4 centers: Fujisawa laboratories (Tsukaba and Osaka), Chiba University (Tokyo), University of Cambridge (England) and University of Pittsburgh. The Gothenburg symposium was published in a separate volume in Transplantation Procedings.[7] Anyone reading the papers, especially someone in the audience at the Gothenburg conference, might have wondered whether different researchers were discussing the same drug. Reports from Cambridge were bleak. Those from Pittsburg were optimistic, and those from Chiba were abstaining. The funeral ceremonies of controversial drugs are well known. If this was the fate of this drug, it would be easy to read its tombstone because the name of FR900506 was shortened to FK506.

Before the Gothenburg symposium, the work done in Pittsburgh laboratories was presented by six members of the team to a smaller, more critical group, scientists from the FDA's Oncology and Pulmonary Disease Section in Rockville, Maryland. The preliminary meeting in Rockville, Maryland, was held at Starzl's initiative to alert the FDA to a possible negative atmosphere towards FR900506 at the upcoming conference in Sweden in May 1987. Positive reports from Pittsburgh and negative reports from Cambridge were summarized. Starzl specifically clarified at this meeting that he had no financial connection with Fujisawa Corporation. The goal was to early apply with the FDA, get scientific advice from FDA scientists, and make sure what was being done complied with FDA regulations. In the end, they completed the deficiencies in the research, mostly related to toxicology, in accordance with the FDA's suggestions. It was soon announced that one of the FDA team members, physician oncologist Gregory Burke, had been appointed to lead the FK 506 project and would be the contact person for further questions and discussions. Burke was friendly and hardworking, and was promoted to FDA director for the evaluation of FK 506. His suggestions for FK 506 were always creative, and the last one, almost 2 years later, prevented a tragedy that might have occurred when it was first introduced to humans as a drug. The studies of these medically carefully studied healthy young men and women provide preliminary information about how the drug affects the body when the human body encounters new drugs. Likewise, all over the world, these people are selected from people who do not have alcohol or substance addiction. Such volunteers may have abnormal liver or other organ function tests during and after test doses of new drugs. These people are paid generously and given informed consent. This first step in drug development can be neglected in dangerous drugs used for cancer chemotherapy. When Burke gave the Pittsburgh team a new drug registration for the FK 506 study, steps had not been taken. How to proceed is left to the Institutional Review Board of the University of Pittsburgh (IRB). Then, examples from cyclosporine trials 8 years ago were shown. Richard Cohen, professor of pediatric psychiatry, was chairman of the IRB throughout the development of FK 506. His energy, grasp of complex issues in transplantation, and despite disagreements with him inspired the trust of IRB members and investigators. His initial decision regarding FK 506 was so shrewd that no further escape was possible. The therapeutic superiority of FK 506 was demonstrated almost from the beginning. Since preliminary testing of FK 506 was not done in healthy volunteers, Cohen wanted to give FK 506 for the first time to patients who lost their organs, even though transplanted liver patients were given the most powerful anti-rejection drug (cyclosporine). In other words, FK 506 was given to this patient group for the first time, not to volunteers. These patients were facing death and retransplantation and had nothing to lose. Burke was willing to follow this strategy. However, when the first patient was selected for rescue treatment, Burke immediately called the team to tell them that the initial IV dose was too high. He came to such a conclusion based on what we learned from the laboratory experiences. According to his recommendation, the dose was reduced. If Burke's recommendation had not been followed, the first patient could have died from overdosage. The person whose life was spared with Burke's recommendations was a 28-year-old woman named Robin Ford, who slowly rejected her third liver graft 8 months after her liver transplant. Rescue treatment with FK 506 started on February 28, 1989. Robin recovered. The next patient, a 38-year-old man who had received five liver grafts over the previous 4 years, was a more difficult test for FK 506. Just 3 months after the last transplant, he was rejecting his fifth liver graft. As with Robin, rejection was controlled. Many more patients were treated this way.

From February to July, 1989, in the first 10 liver recipients switched from cyclosporine to FK 506, 7 of the grafts were saved and the livers were functioning well over 2 years of follow-up.[8]

The surgeon who would lead these investigations had to have skills, ideas, and techniques that would allow the flowers to direct or force light through the cracks in the concrete. John Fung was a halfway surgeon but a full-fledged immunologist when he arrived in Pittsburgh in June 1984, a few months after Todo's arrival. In addition to his medical doctor degree, he earned a doctorate from the University of Chicago and took a 2-year leave of absence for laboratory work while in the middle of his general surgery residency at the University of Rochester. Fung helped Adriana Zeevi and Rene Duquesnoy develop tissue culture systems called "mini-transplant" models that in the past required months or years but now allow learning much about the efficacy and mechanisms of action of FK 506 in a matter of days.[9] Not yet 32 years old, he joined the program as a fully trained surgeon and professional researcher equipped with unique knowledge and skills.

The fact that FK 506 could save grafts that had been rejected despite all previously available treatments was known to only a handful of people in the early autumn of 1989. Two of them were Pittsburgh Post-Gazzette science reporter Henry Pierce and deputy editor-in-chief Mark Roth. Both had followed the development of FK 506 closely from the time the drug became interesting and promising. Even though they knew clinical trials had begun, they had promised not to publish the information until it was reported in a medical journal. Larry Altman, a New York Times reporter, arrived in Pittsburgh in late September, a few days after a phone conversation with Starzl about some new and controversial operative procedures involving the transplantation of multiple abdominal organs. There was a wind of criticism against these advanced surgical techniques, the use of which was abandoned some time ago. He was now questioning why operations were restarted and why such an approach was taken. After all attempts to evade telephone cross-examination failed, Starzl reluctantly told Altman that better anti-rejection therapy was available. Altman was an academic physician and the science editor of this newspaper. He realized that FK 506 was the real story, not the operations, and he was intrigued. He spent the next two weeks in Pittsburgh, where he wrote a report on FK 506 that was more expertly written than most and of a scientific quality rivaling that of medical reports. Altman insisted on seeing every patient and examined the records with the meticulousness of a born investigator. He postponed his article to be published in the New York Times, just like the Pittsburgh Post-Gazzette. Both newspapers knew that the first 10 cases were scheduled for publication in The Lancet on October 28, 1989. The voluntary news embargo was important to Starzl because it was feared that premature newspaper reports would jeopardize publication in the Lancet. While the entire team was holding their breath, the embargo lasted only until October 18, 1989, because advance copies of the Lancet article were routinely given to the media. Subsequently, Pierce called Starzl and informed him that the Post-Gazzette would not wait any longer and that the story they had been holding for 6 months would be published in the evening editions. Altman from the New York Times also told Starzl that they would include FK 506 in the morning edition of the Times. News about FK 506 competed with the San Francisco earthquake on the morning of October 19. The article in The Lancet was published as planned.[10]

ESOT's annual meeting was in Barcelona, and 1 week after the article was published, a 10-hour symposium on FK 506 was held in Barcelona. Overnight, FK 506 became the court of appeal (last resort) in the treatment of rejection of liver and other organ recipients that cannot be controlled with conventional treatments. As the news read, patients with failed grafts flocked to Pittsburgh from other centers. Meanwhile, not only rescue but also de novo FK 506 treatments were started in Pittsburgh. By the end of October, much experience and information had been gained regarding de novo immunosuppressive therapy with FK 506 in liver, kidney, heart and lung transplants.[11] Physicians treating all these different organ recipients quickly became convinced that FK 506 was superior to previously available drugs. The incidence of rejection was reduced, the amount of prednisone required was reduced, and the length and cost of hospitalization were reduced. Although side effects, including kidney damage, were similar to those caused by cyclosporine, they were not worse. The new treatment had a better margin of safety than the old one, or so it seemed to the treating physicians.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

References

1. Holtom DC. A new interpretation japanese mythology and is bearing on the ancestrol theary of shinto. J Relip 1926: 6: 58-77.
2. Yoshida T. The stranger as god: the place of the outsider in Japanese folk religion. Ethnology: An international journal of cultural and social anthropology 1981; 20: 87-100.
3. Starzl TE. The Drug with No Name. In: The Puzzle People. Memories of a Transplant Surgeon. 1st ed. Pittsburgh: University of Pittsburgh Press; 1992: pp288-308.

4. Starzl TE, Marchioro TL, Porter KA, Iwasaki Y, Cerilli GJ. The use of heterologous antilymphoid agents in canine renal and liver homotransplantation and in human renal homotransplantation. Surg Gynecol Obstet 1967 Feb;124(2):301-8. PMID: 4163340; PMCID: PMC2675827.
5. Ochiai T, Nakajima K, Nagata M, Suzuki T, Asano T, Uematsu T, Goto T, Hori S, Kenmochi T, Nakagoori T, et al. Effect of a new immunosuppressive agent, FK 506, on heterotopic cardiac allotransplantation in the rat. Transplant Proc. 1987 Feb;19(1 Pt 2):1284-6. PMID: 2484094.
6. Collier DS, Thiru S, Calne R. Kidney transplantation in the dog receiving FK-506. Transplant Proc. 1987 Oct;19(5 Suppl 6):62. PMID: 2445077.
7. Starzl TE. First International Workshop on FK-506. A potential breakthrough in immunosuppression. Proceedings. Transplant Proc. 1987 Oct;19(5 Suppl 6):1-104. PMID: 2445066; PMCID: PMC3022438.
8. Fung JJ, Todo S, Jain A, McCauley J, Alessiani M, Scotti C, Starzl TE. Conversion from cyclosporine to FK 506 in liver allograft recipients with cyclosporine-related complications. Transplant Proc. 1990 Feb;22(1):6-12. PMID: 1689901; PMCID: PMC2903869.
9. Zeevi A, Yao GZ, Venkataramanan R, Duquesnoy RJ, Todo S, Fung JJ, Starzl TE. Comparative in vitro studies on the immunosuppressive effects of purine and pyrimidine synthesis inhibitors. Transplant Proc. 1993 Feb;25(1 Pt 1):781-3. PMID: 7679843; PMCID: PMC2953385.
10. Starzl TE, Todo S, Fung J, Demetris AJ, Venkataramman R, Jain A. FK 506 for liver, kidney, and pancreas transplantation. Lancet. 1989 Oct 28;2(8670):1000-4. doi: 10.1016/s0140-6736(89)91014-3. PMID: 2478846; PMCID: PMC2966318.
11. Todo S, Fung JJ, Demetris AJ, Jain A, Venkataramanan R, Starzl TE. Early trials with FK 506 as primary treatment in liver transplantation. Transplant Proc. 1990 Feb;22(1):13-6. PMID: 1689886; PMCID: PMC2903882.

JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2024.79663
J Inonu Liver Transpl Inst 2024;2(2):52–59

Original Research

Examination of Genetic Background of Intrahepatic Cholangiocarcinoma by Bioinformatics Applications

Zeynep Kucukakcali,[1] Sami Akbulut[2]

[1]Department of Biostatistics and Medical Informatics, Inonu University Faculty of Medicine, Malatya, Türkiye
[2]Department of Surgery and Liver Transplant Institute, Inonu University Faculty of Medicine, Malatya, Türkiye

Abstract

Objectives: Intrahepatic cholangiocarcinoma (ICC), the second most common primary liver cancer, is associated with a poor prognosis with a very low survival rate. Therefore, a comprehensive understanding of the molecular pathways involved in the disease is of great importance for the development of targeted therapies and personalised treatment strategies. The aim of this study was to identify possible biomarkers associated with ICC by analysing gene expression in ICC tumor and non-tumour liver tissues.

Methods: The dataset included in the study comprises gene expression data from ICC and non tumor liver tissue. The gene expression analysis of this data set was conducted using the capabilities provided by the limma package. The distribution of each tissue in the dataset is shown by the distribution graph. The UMAP graph represents the association of tissue types. The genes exhibiting different regulation are represented in the volcano plot.

Results: The UMAP analysis revealed a perfect separation of the tissues in the dataset into two distinct groups: ICC tumor tissues and non tumor liver tissues. The analysis showed that many genes differed in both groups under log2FC>1 p<0.05 and log2FC<-1 and p<0.05 conditions. The resultsshow that there are genes that are upregulated and down regulated in ICC tissues compared to non tumor liver tissues.

Conclusion: Genetic research has a pivotal role in enhancing investigate molecular pathways and treatment of ICC. Genes that have been identified can function as biomarkers, which can assist in the creation of medication therapies that are specifically targeted and enhance the quality of patient care and the efficiency of healthcare. As genetic research advances, the utilization of these biomarkers is anticipated to improve personalization.

Keywords: Intrahepatic cholangiocarcinoma, Tumor free liver tissue, Gene expression, Biological behavior

Please cite this article as "Kucukakcali Z, Akbulut S. Examination of Genetic Background of Intrahepatic Cholangiocarcinoma by Bioinformatics Applications. J Inonu Liver Transpl Inst 2024;2(2):52–59".

Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) account for approximately 85% and 15% of primary liver cancer, respectively.[1, 2] ICC show a rapidly increasing incidence, especially in western countries. The two types are quite different in terms of their morphology, metastatic capacity and response to cancer therapies.[1, 3] ICCs are composed of ductular, papillary, or solid tumor formations that are surrounded by a dense tumor stroma.[2] While HCC is invasive, the occurrence of metastatic tumours is more common in ICC. Interestingly,

Address for correspondence: Sami Akbulut, MD. Department of Surgery and Liver Transplant Institute, Inonu University Faculty of Medicine, Malatya, Türkiye
Phone: +90 422 341 06 60 **E-mail:** akbulutsami@gmail.com

Submitted Date: 09.09.2024 **Revised Date:** 17.09.2024 **Accepted Date:** 17.09.2024 **Available Online Date:** 09.10.2024

HCCs show a positive response to therapy with multikinase inhibitors, whereas ICCs are resistant to these medications. In contrast, ICCs exhibit positive therapeutic responses to traditional cytotoxic therapy, while HCC is characterised by its resistance to chemotherapy.[1, 3, 4]

ICC has a lower occurrence rate in comparison to other types of liver cancer, such as hepatocellular carcinoma. However, its prevalence is increasing worldwide, especially in areas with high rates of chronic liver illnesses, such as hepatitis C and cirrhosis.[5-7] ICC is also associated with a poor prognosis with a five-year survival rate of only 22-24% after curative resection.[8] The rising prevalence of ICC can be due to a combination of various risk factors, such as nonalcoholic fatty liver disease, chronic viral hepatitis, and primary sclerosing cholangitis.[6, 9, 10]

The clinical manifestation of ICC is frequently subtle, with a significant number of patients being discovered coincidentally during imaging examinations for other ailments. Common symptoms of this condition may encompass unintentional weight loss, yellowing of the skin and eyes (jaundice), discomfort in the stomach region, and elevated body temperature. However, it is important to note that these symptoms are sometimes vague and can result in delays in the identification of the underlying condition.[11] Imaging investigations, such as computed tomography (CT) and magnetic resonance imaging (MRI), usually show a mass with consistent low-attenuation and uneven enhancement at the edges. This may be accompanied by the shrinking of the outer layer and the widening of the ducts within the liver.[12, 13] The diagnosis is typically verified through histological examination after a biopsy or surgical removal of tissue.

The molecular composition of ICC is intricate, with multiple genetic changes and modifications involved in its development. Significantly, mutations in the KRAS, IDH1, and IDH2 genes have been found to be prevalent in ICC, especially in patients with pre-existing liver illness.[14, 15] The involvement of epithelial-mesenchymal transition (EMT) in the advancement of ICC has also attracted interest, as it is thought to contribute to the invasive properties of the tumor.[16, 17] Gaining a comprehensive understanding of these molecular pathways is of utmost importance for the advancement of targeted treatments and tailored treatment strategies. Although there have been improvements in diagnostic and treatment approaches, the outlook for individuals with ICC remains quite poor, especially for those who are discovered at a late stage. The significant frequency of reappearance after curative removal emphasizes the necessity for continuous monitoring and the investigation of additional treatments to enhance long-term results.[8, 18] Research into novel biomarkers and therapeutic targets is ongoing, with the aim of identifying patients who may benefit from specific treatment modalities based on their tumor's molecular profile.[19]

The latest developments in the field of bioinformatics have made it easier to identify precise genetic changes and biomarkers that play a critical role in the diagnosis, prognosis, and treatment approaches.[20, 21] Bioinformatics is crucial in the molecular profiling of ICC, enabling researchers to examine extensive databases of genomic and transcriptome information. For example, thorough analysis of molecules has shown that mutations in genes like IDH1, FGFR2, and BAP1 are common in ICC, and these changes can affect therapy choices and patient results.[20, 22, 23] In addition, the application of bioinformatics in examining gene expression patterns has resulted in the identification of prognostic biomarkers, such as CXCL12, that are linked to the spread of cancer to other parts of the body and unfavorable survival rates.[18, 21]

Ultimately, the incorporation of bioinformatics into the investigation of ICC is revolutionizing our comprehension of this cancerous condition. It aids in the detection of genetic changes, predictive markers, and immunological landscape features, all of which are crucial for enhancing diagnosis, therapy, and patient results. As research progresses, the utilization of bioinformatics is expected to have a growing significance in the management of ICC facilitating the development of more efficient and tailored therapeutic approaches.

Therefore, in this study, in order to understand the genetic background of ICC and to identify the associated biomarker genes by bioinformatic analyses, the data obtained from ICC tumour tissue and non-tumour liver tissue samples from 15 patients were examined by expression analysis. Genes showing differential regulation in ICC tumour tissues were identified.

Material And Methods

Dataset

The study utilised a dataset comprising of data collected from ICC tumour tissues and non-tumour liver tissues of 15 individuals. The purpose was to examine the alterations in RNA editing in ICC. The dataset was acquired through the utilisation of RNA-seq, employing Illumina HiSeq2000, on 15 pairs of ICC tumours and corresponding non-tumour liver tissues. The study utilised a data collection acquired from the National Centre for Biotechnology Information (NCBI). The current code assigned to the data collection at the NCBI is GSE119336.

RNA-Sequence Analysis (RNA-Seq)

RNA sequence analysis technologies, a widely recognized and efficient technology, have shown remarkable outcomes in characterizing all RNA transcripts produced by cells. RNA-seq is an innovative tool in the field of transcriptomics that allows for a thorough and precise study of complete transcriptomes in a quantitative manner. This strategy is the first of its kind to use sequencing technology to reveal the entire collection of RNA transcripts in an organism. In contrast to hybridization-based approaches, the RNA-seq method not only aims to identify known transcripts, but also seeks to discover and link new transcripts while examining and revealing the known ones. An important advantage of the RNA-seq technique is its capacity to evaluate expression levels throughout a wide and variable spectrum, rather than solely evaluating relative values. RNA-seq technologies provide substantial advantages, including little background contamination, resulting in very precise and dependable results. Moreover, these techniques enable accurate identification of exon and intron borders, as well as the detection of SNPs and other genetic variations within transcripts. RNA-seq offers multiple advantages, making it an ideal tool for most research projects aimed at discovery.[24]

Transcriptomics

The transcriptome encompasses all RNA molecules, such as mRNA, tRNA, rRNA, and non-coding RNAs, that are produced by the genome of a cell, tissue, or organism during a certain period. Transcriptomes have a constantly changing structure and experience ongoing modifications as a result of fluctuations in gene expression. Contrary to the largely unchanging genetic makeup of a cell, the transcriptome is vulnerable to changes produced by several environmental factors, such as changes in pH, differences in nutrient supply, fluctuations in temperature, and interactions with signals from nearby cells. Gene transcription related to these processes may differ in response to various cellular activities, resulting in alterations in the transcriptome, which includes all the messenger RNAs (mRNAs) found in the cell. Hence, the transcriptome offers a momentary and contextual representation of the genes that are now working. The detection of changes in gene expression induced by environmental factors has emphasized the importance of interactions between the environment and biological systems.[24, 25]

Transcriptomics is a scientific field that examines the entire array of mRNA transcripts generated by transcription within a cell's genome, offering insights on their expression patterns. Microarray and next-generation sequencing areadvanced technologies frequently utilized in transcriptomics applications. These technologies provide the analysis of precise alterations in the transcriptome that transpire at designated times and for certain purposes.[25]

Transcriptomics studies have become increasingly important and their prevalence has significantly increased in recent decades. These research efforts have specifically concentrated on clarifying the impact of changes in the expression of genetic variants, whether they increase or decrease, in the development of complex diseases like cancer. Moreover, these investigations seek to reveal the connections and expressions of these impacts. Furthermore, through these investigations, scientists and researchers can get supplementary data about the biochemical pathways and molecular mechanisms that regulate the life cycles of cells, and thus, the development of diseases.[25, 26]

Bioinformatics and Gene Expression Analysis

Bioinformatics encompasses the systematic collection, storage, organization, analysis, and presentation of data obtained via the application of theoretical and practical concepts in disciplines such as biology, medicine, behavioral sciences, and health sciences. The main objective of this project is to analyze and enhance computational tools and techniques in order to broaden the use and customization of data obtained from research efforts or the implementation of existing procedures. Obtained through careful and thorough intellectual inquiry or by following established procedures. Bioinformatic analyses are performed by selecting an appropriate database and utilizing a technology that enables the execution of bioinformatic analysis, depending on the particular biological inquiry, molecule, or structure being investigated. The collected data and the obtained insights from the studies are combined, and the ensuing assessments are carefully evaluated in relation to the available literature.[27]

Any alterations in the physiological state of an organism or cell will inevitably lead to corresponding modifications in the pattern of gene expression.Therefore, the assessment of gene expression is highly significant in all areas of biological investigation. The DNA microarray technology, now in the developmental stage, is employed for the examination of gene expression. This is accomplished by the process of hybridization, when mRNA molecules are attached to a tightly packed array of immobilized target sequences. Each of these target sequences corresponds to a unique gene. Studying the influence of chemical substances on the control of gene expression can offer valuable knowledge on both functional and toxicological characteristics. Conducting investigations on clinical samples, including both individuals who are in excellent health and those who are affected by diseases, has the potential to reveal previously unknown biomarkers.[28]

Bioinformatics Analysis Phase

In this study, gene expression analyses were performed at the transcriptome level to investigate the role of RNA editing on ICC. The data set of the study consisted of ICC tumour tissues and non-tumour liver tissues samples from paired 15 patients. The current study utilized the limma package, a software tool available in the R programming language that aids expression analysis.[29]

Limma is a software suite specifically developed for analyzing gene expression microarray data using linear models. The main goal is to utilize linear models to examine certain experiments and detect differential expression. The packet's functionalities can be utilized in many gene expression techniques, such as microarrays, RNA-seq, and quantitative PCR. The Limma software utilizes Empirical Bayes algorithms to obtain trustworthy results, especially in situations when there is a small number of sequences. The bioinformatic inquiry resulted in the identification of Lof2FC, a metric that measures the magnitude of differences in gene expression fold change. This metric arranges the genes in a descending order based on their level of importance. Genes with greater expression levels are determined by using a threshold of log2 fold change (log2FC) more than 1, whereas genes with lower expression levels are determined by using a threshold of log2FC less than -1.

The study utilized box plots to display the distribution of data. The graphs illustrate instances with comparable characteristics, denoted by the utilization of consistent colors. The study chose to employ the Uniform Manifold Approximation and Projection (UMAP) graph to visually depict the relationships between the samples being examined. The volcano plot was chosen as the optimal method for visualizing genes with differential expression, including both upregulation and downregulation. The volcano plot depicts the logarithmic relationship between the level of significance and the magnitude of fold-change. The y-axis denotes the level of significance, while the x-axis indicates the fold-change on a logarithmic scale with a base of 2. This graphical depiction enables the quick identification of genes that display differential expression. The graph depicts the levels of gene expression, where red represents genes that are up-regulated, blue represents genes that are down-regulated, and black represents genes that show no significant difference in expression. Furthermore, we employed the Mean Difference (MD) plot alongside the Volcano plot to visually depict genes that exhibit distinct expression patterns between various groups. The MD plot visually illustrates the log2 fold change of genes that exhibit differential expression, in comparison to the average log2 expression levels. The volcano plot use color coding to distinguish between up-regulated and down-regulated genes. The coloration in the volcanic graph exhibits a resemblance to that of this graph.

Results

Figure 1 displays the distribution plots of the samples from 15 pairs of ICC tumors and corresponding non-tumour liver tissues that were utilised in the investigation. The term 'cancer' is employed to symbolise the ICC tumour tissues, whereas 'non-tumour' is used to symbolise the corresponding non-tumour liver tissues. The graph depicted the distribution of values within the chosen samples. The graph utilizes colour coding to distinguish between different samples. The green colour indicates the presence of ICC tumour tissues, while the purple colour indicates the presence of matched non-tumour liver tissues. This graph is utilised to evaluate data normalisation prior to doing differential expression analysis.

Figure 2 displays the UMAP graph, which effectively depicts the relationships among the samples. The graph demonstrates that samples with comparable traits form

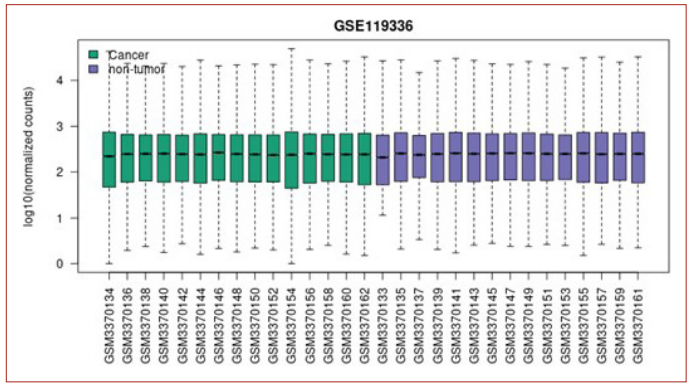


Figure 1. Distribution plot of the samples.

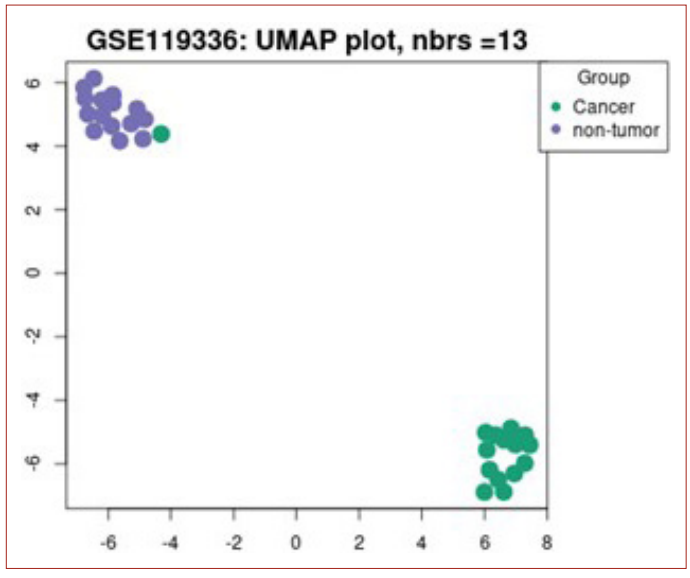


Figure 2. UMAP plot of the samples.

distinct clusters. The graph displays ICC tumor tissues as green dots and matched non-tumour liver tissue samples as purple dots. In the graph, "cancer" indicates ICC tumor tissues and "non-tumor" indicates non-tumour liver tissues.

The gene expression of 17327 genes in the dataset was analyzed, and the results of the top 10 genes exhibiting up- and down-regulation between the two groups are shown in Table 1 and Table 2. When evaluating the control of gene expression, conditions with an |log2FC| > 1.0 and a p-value less than 0.05 were considered.

Figure 3: Volcano plot of genes in ICC tumor and non-tumor liver tissues. (Red dots represent transcripts that increased, blue dots represent transcripts that dropped, and black dots represent transcripts whose expression level remained unchanged.)

Figure 4 displays the MD plot, which effectively demonstrates genes that show differential expression across the various groups. The MD plot graphically illustrates genes with differential expression by showing the log2 fold change in relation to the average log2 expression levels. The highlighted genes display a notable discrepancy in their levels of expression. The color red represents heightened levels of activity, whereas blue represents diminished levels of activity. This distinction is determined by utilizing a pre-established P-value threshold of 0.05.

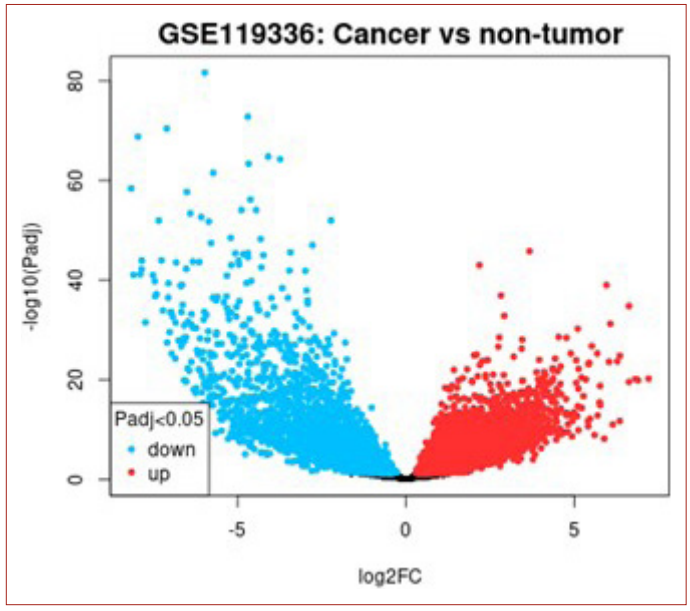


Figure 3. Illustrates the volcano plot, which visually portrays the genes that exhibit differential expression among the several groups.

Table 1. Transcripts found to be up-regulated in ICC tumor tissues samples relative to non-tumour liver tissues.

GeneID	padj	p	log2FoldChange	Symbol	Description
1311	6,54E-21	1,21E-22	7,201741	COMP	cartilage oligomeric matrix protein
5349	1,47E-20	2,87E-22	6,887498	FXYD3	FXYD domain containing ion transport regulator 3
5744	7,88E-21	1,48E-22	6,811435	PTHLH	parathyroid hormone like hormone
79574	2,99E-20	6,13E-22	6,618167	EPS8L3	EPS8 like 3
2810	1,73E-35	7,30E-38	6,617754	SFN	stratifin
4582	1,70E-25	2,01E-27	6,348982	MUC1	mucin 1, cell surface associated
131368	2,16E-12	1,27E-13	6,345546	ZPLD1	zona pellucida like domain containing 1
221416	2,20E-24	2,89E-26	6,272728	LINC03040	long intergenic non-protein coding RNA 3040
5266	1,11E-11	7,28E-13	6,136162	PI3	peptidase inhibitor 3
105371453	6,55E-32	3,82E-34	6,068467	BCAN-AS1	BCAN antisense RNA 1

Table 2. Genes found to be down-regulated in ICC tumor tissues samples relative to non-tumour liver tissues.

GeneID	padj	p	log2FoldChange	Symbol	Description
1549	4,31E-59	2,24E-62	-8,16581	CYP2A7	cytochrome P450 family 2 subfamily A member 7
641654	9,55E-42	2,48E-44	-8,09746	HEPN1	hepatocellular carcinoma, down-regulated 1
131669	1,71E-69	3,95E-73	-7,96448	UROC1	urocanate hydratase 1
1548	7,34E-42	1,86E-44	-7,894	CYP2A6	cytochrome P450 family 2 subfamily A member 6
10332	7,06E-43	1,67E-45	-7,85558	CLEC4M	C-type lectin domain family 4 member M
220296	1,43E-44	2,65E-47	-7,84927	HEPACAM	hepatic and glial cell adhesion molecule
1544	3,25E-32	1,86E-34	-7,74055	CYP1A2	cytochrome P450 family 1 subfamily A member 2
101928384	1,09E-41	2,91E-44	-7,51731	LOC101928384	uncharacterized LOC101928384
1543	1,73E-40	4,90E-43	-7,46271	CYP1A1	cytochrome P450 family 1 subfamily A member 1
319	1,76E-37	5,98E-40	-7,44875	APOF	apolipoprotein F

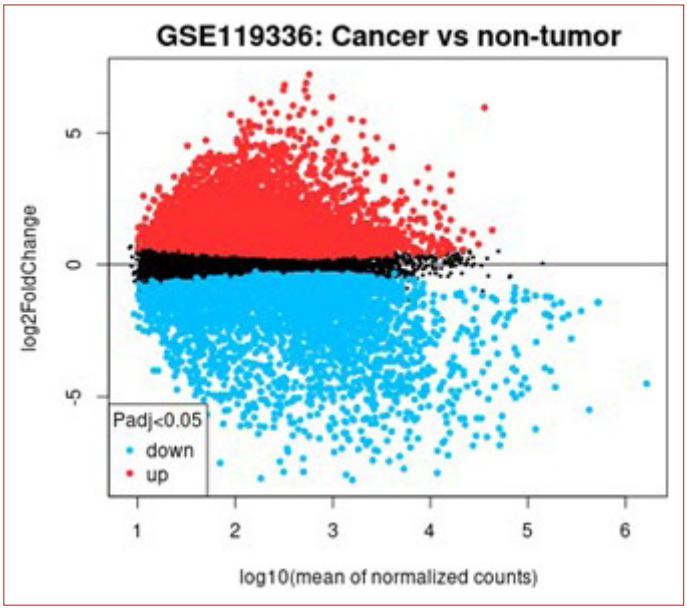


Figure 4. MD plot of genes in ICC tumor tissues and non-tumor liver tissues (Red dots represent transcripts that increased, blue dots represent transcripts that decreased and black dots represent transcripts whose expression level remained unchanged).

Discussion

ICC is a cancerous tumor that develops from the cells lining the bile ducts within the liver. It is the second most prevalent form of primary liver cancer, occurring after hepatocellular carcinoma, and makes up around 5-10% of all cases of primary liver malignancies.[30, 31] The global prevalence of ICC has been on the rise, especially in Western nations, and is linked to several risk factors such as chronic liver disorders, viral hepatitis, and bile duct stones.[31-33] The primary treatment for ICC is surgical excision, which aims to cure the disease, particularly in its early stages.[30, 31] Nevertheless, because ICC frequently lacks noticeable symptoms during its initial phases, a large number of patients are diagnosed with advanced disease. This greatly complicates the available treatment options and has a negative impact on the prognosis.[32, 34] When surgical removal is not possible, systemic chemotherapy, specifically with gemcitabine and cisplatin, has become a recognized treatment plan that has shown better results in terms of survival rates.[35, 36] Furthermore, ongoing research is investigating the effectiveness of targeted treatments and immunotherapy in treating ICC, but more examination is needed to determine their efficacy.[30, 37]

Genomic research has made great progress in improving our knowledge of the molecular basis of this disease. It has uncovered specific genetic changes that can affect the outlook and treatment approaches. Genomic research has discovered numerous crucial mutations linked to ICC, including changes in the KRAS, IDH1, and FGFR2 genes. The prevalence of KRAS mutations in ICC has been documented to vary from 8.6% to 25%, highlighting a significant frequency of this mutation among patients.[38] Furthermore, there is evidence that IDH1 mutations are associated with better survival rates, indicating that this genetic change could be used as a possible indicator for predicting prognosis.[39] Moreover, the existence of FGFR2 fusions has been identified as a crucial focus for therapeutic treatment. Studies have shown that these changes do not occur together with other important mutations, thus indicating the presence of discrete molecular subtypes of ICC.[22, 40] Recent study has emphasized the connection between changes in the genetic makeup and clinical characteristics, such as perineural invasion. This suggests that the specific genetic subtype of a tumor may provide more accurate information about prognosis compared to only considering tumor size.[41] This finding emphasizes the importance of comprehensive genomic profiling in guiding treatment decisions and improving patient outcomes.

The attention on ICC has extended beyond mutations to include the tumor microenvironment and immune response. Research has shown that natural immune mechanisms can affect the growth and spread of tumors, making the management of the condition more complex.[20, 42] Understanding these interactions may provide insights into novel therapeutic strategies aimed at enhancing the efficacy of existing treatments. To summarize, the genetic makeup of ICC is marked by a wide range of mutations and changes that have a substantial effect on prognosis and treatment approaches. Continued investigation into the molecular pathways that cause ICC is essential for the development of precise treatments and enhancing patient results. Therefore, in order to determine the pathophysiology of the disease and to personalise treatment modalities, it is very important to increase advanced bioinformatics and genetic-based studies and to approach the disease in the light of the results that can be obtained from these studies. In this study, it was aimed to determine the biomarkers that may play a role in the course of the disease by examining RNA seq data, which is very important in genomic studies, with bioinformatic analyses.

This study utilized an open access ICC dataset to conduct bioinformatic analysis. Through this analysis, genes that exhibited distinct regulation in ICC tumor tissues, as opposed to non-tumor liver tissue, were found. The volcano plot and MD plot were used to visualize these genes. Furthermore, the distribution of the samples in the data set was analyzed and represented using a scatter plot. The data samples were visualized using the UMAP graph, revealing a noticeable distinction between the two groups.

When the results of bioinformatic analyses were examined, it was determined that a lot of genes showed different regulation (up or down) in ICC tumor tissues compared to non tumor liver tissues. COMP gene showed 147,03 fold up-regulation in ICC tumor tissues compared to non tumor liver tissues. Likewise, FXYD3, PTHLH, EPS8L3, SFN, MUC1, ZPLD1, LINC03040, PI3,and BCAN-AS1 genes had up-regulated gene expression of 117.78, 112.20, 98.22, 98.15, 81.00, 79.98, 77.17, 70.03, and 66.71 fold, respectively. CYP2A7 gene showed 286.02 fold down-regulation in CRC tumor tissues compared to CRC normal tissues. Likewise, HEPN1, UROC1, CYP2A6, CLEC4M, HEPACAM, CYP1A2, LOC101928384, CYP1A1, and APOF genes had down-regulated gene expression of 272.47, 248.99, 237.20, 230.72, 229.12, 213.78, 182.27, 176.06, and 173.64 fold, respectively.

Additional analysis and research on the identified genes may reveal that these genes could serve as biomarkers that contribute to the development of successful treatment strategies for ICC. Biomarkers can be utilized to develop and implement drug therapy. The precise and efficient utilization of genetic biomarkers can enhance patient care and optimize the performance of healthcare systems. As genetic research progresses, an increasing number of genes are anticipated to serve as biomarkers, hence facilitating the wider adoption of personalized approaches in the field of medicine.

Genetic research into ICC, the second most prevalent primary liver cancer, is crucial for comprehending the illness. The unfavorable prognosis of the disease significantly impacts the choice of treatment techniques. Hence, comprehending the genetic foundation of ICC is vital for the prevention and management of the ailment. Genetic investigations in this context yield valuable information that enables the development of targeted prevention strategies and individualized treatment approaches. Genetic testing and screening programs for persons at high risk offer timely identification and prevention. In the future, as genetic research continues to progress, it is anticipated that more advanced and efficient approaches for preventing and treating ICCC will be created.

Disclosures

Ethics Committee Approval: This article was produced from 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.; Supervision – S.A.; Materials – Z.K., S.A.; Data collection &/or processing – Z.K., S.A; Analysis and/or interpretation – Z.K., S.A; Literature search – Z.K., S.A; Writing – Z.K., S.A; Critical review – S.A.

References

1. Llovet JM, Zucman-Rossi J, Pikarsky E, Sangro B, Schwartz M, Sherman M, et al. Hepatocellular carcinoma. Nature reviews Disease primers. 2016;2:16018.
2. Marquardt JU, Andersen JB, Thorgeirsson SS. Functional and genetic deconstruction of the cellular origin in liver cancer. Nature reviews Cancer. 2015;15(11):653-67.
3. Rizvi S, Gores GJ. Pathogenesis, diagnosis, and management of cholangiocarcinoma. Gastroenterology. 2013;145(6):1215-29.
4. Wu W, He X, Andayani D, Yang L, Ye J, Li Y, et al. Pattern of distant extrahepatic metastases in primary liver cancer: a SEER based study. Journal of Cancer. 2017;8(12):2312-8.
5. Poultsides GA, Zhu AX, Choti MA, Pawlik TM. Intrahepatic Cholangiocarcinoma. Surgical Clinics of North America. 2010;90(4):817-37.
6. Scott AJ, Shroff RT. Moving the Needle Forward With Locoregional Treatment in Unresectable Cholangiocarcinoma—The Jury Is Still Out. Jama Oncology. 2020;6(1):29.
7. Rizvi S, Khan SA, Hallemeier CL, Kelley RK, Gores GJ. Cholangiocarcinoma — Evolving Concepts and Therapeutic Strategies. Nature Reviews Clinical Oncology. 2017;15(2):95-111.
8. Schwenk L, Rohland O, Deeb AA, Dondorf F, Settmacher U, Rauchfuß F. Liver Transplantation for Incidental Cholangiocarcinoma or Combined Hepatocellular Carcinoma/Cholangiocarcinoma—Own Experiences and Review of the Literature. Cancers. 2023;15(14):3609.
9. Razumilava N, Gores GJ. Classification, Diagnosis, and Management of Cholangiocarcinoma. Clinical Gastroenterology and Hepatology. 2013;11(1):13-21.e1.
10. Nakanuma Y, Xu J, Harada K, Sato Y, Sasaki M, Ikeda H, et al. Pathological Spectrum of Intrahepatic Cholangiocarcinoma Arising in Non-biliary Chronic Advanced Liver Diseases. Pathology International. 2011;61(5):298-305.
11. Vijayan P, Hosapatna Laxminarayana KP, K JS, Shruthi S, K A. Sarcomatoid Cholangiocarcinoma: An Unusual Tumor Posing Diagnostic Challenges. Journal of Health and Allied Sciences Nu. 2024.
12. Rauchfuß F, Deeb AA, Rohland O, Dondorf F, Ardelt M, Settmacher U. Living Donor Liver Transplantation for Intrahepatic Cholangiocarcinoma. Current Oncology. 2022;29(3):1932-8.
13. Saurer A. Right Intrahepatic Cholangiocarcinoma. Journal of Diagnostic Medical Sonography. 2016;32(4):219-23.
14. Jang S-J, Chun S-M, Hong SM, Sung CK, Park H, Kang HJ, et al. High Throughput Molecular Profiling Reveals Differential Mutation Patterns in Intrahepatic Cholangiocarcinomas Arising in Chronic Advanced Liver Diseases. Modern Pathology. 2014;27(5):731-9.
15. Liau JY, Tsai J-H, Yuan R-H, Chang C-C, Lee HJ, Jeng YM. Morphological Subclassification of Intrahepatic Cholangiocarcinoma: Etiological, Clinicopathological, and Molecular Features. Modern Pathology. 2014;27(8):1163-73.
16. Yao X, Wang X, Wang Z, Dai L, Zhang G, Yan Q, et al. Clinicopatho-

logical and Prognostic Significance of Epithelial Mesenchymal Transition-Related Protein Expression in Intrahepatic Cholangiocarcinoma. Oncotargets and Therapy. 2012:255.
17. Zhao W, Zhao J, Guo X, Feng Y, Zhang B, Tian L. LncRNA MT1JP Plays a Protective Role in Intrahepatic Cholangiocarcinoma by Regulating miR-18a-5p/FBP1 Axis. BMC Cancer. 2021;21(1).
18. Miyata T, Yamashita YI, Yoshizumi T, Shiraishi M, Ohta M, Eguchi S, et al. <i><scp>CXCL</Scp>12</I> Expression in Intrahepatic Cholangiocarcinoma Is Associated With Metastasis and Poor Prognosis. Cancer Science. 2019;110(10):3197-203.
19. Rizvi S, Gores GJ. Emerging Molecular Therapeutic Targets for Cholangiocarcinoma. Journal of Hepatology. 2017;67(3):632-44.
20. Yang R, Song Y, Shakoor K, Yi W, Peng C, Liu S. Insights Into the Role of STAT3 in Intrahepatic Cholangiocarcinoma (Review). Molecular Medicine Reports. 2022;25(5).
21. Bañales JM, Marin JJG, Lamarca Á, Rodrigues PM, Khan SA, Roberts LR, et al. Cholangiocarcinoma 2020: The Next Horizon in Mechanisms and Management. Nature Reviews Gastroenterology & Hepatology. 2020;17(9):557-88.
22. Lowery MA, Ptashkin R, Jordan E, Berger MF, Zehir A, Capanu M, et al. Comprehensive Molecular Profiling of Intrahepatic and Extrahepatic Cholangiocarcinomas: Potential Targets for Intervention. Clinical Cancer Research. 2018;24(17):4154-61.
23. Zhou T, Mahn R, Möhring C, Sadeghlar F, Meyer CH, Toma M, et al. Case Report: Sustained Complete Remission on Combination Therapy With Olaparib and Pembrolizumab in BRCA2-mutated and PD-L1-positive Metastatic Cholangiocarcinoma After Platinum Derivate. Frontiers in Oncology. 2022;12.
24. Pertea M. The human transcriptome: an unfinished story. Genes. 2012;3(3):344-60.
25. Lee KJ, Yin W, Arafat D, Tang Y, Uppal K, Tran V, et al. Comparative transcriptomics and metabolomics in a rhesus macaque drug administration study. Frontiers in cell and developmental biology. 2014;2:54.
26. Mortazavi A, Williams BA, McCue K, Schaeffer L, Wold B. Mapping and quantifying mammalian transcriptomes by RNA-Seq. Nature methods. 2008;5(7):621-8.
27. Akalın PK. Introduction to bioinformatics. Molecular nutrition & food research. 2006;50(7):610-9.
28. van Hal NL, Vorst O, van Houwelingen AM, Kok EJ, Peijnenburg A, Aharoni A, et al. The application of DNA microarrays in gene expression analysis. Journal of biotechnology. 2000;78(3):271-80.
29. Smyth GK. Limma: linear models for microarray data. Bioinformatics and computational biology solutions using R and Bioconductor: Springer; 2005. p. 397-420.
30. Gong Y, Mao J, Liu M, Gao J. A Case of Toxic Epidermal Necrolysis Associated With Lenvatinib and Sintilimab Therapy for Intrahepatic Cholangiocarcinoma. Journal of International Medical Research. 2023;51(5):030006052311735.
31. Sulpice L, Rayar M, Boucher É, Pracht M, Meunier B, Boudjéma K. Treatment of Recurrent Intrahepatic Cholangiocarcinoma. British Journal of Surgery. 2012;99(12):1711-7.
32. Rizvi S, Gores GJ. Pathogenesis, Diagnosis, and Management of Cholangiocarcinoma. Gastroenterology. 2013;145(6):1215-29.
33. Florio AA, Ferlay J, Znaor A, Ruggieri D, Álvarez CS, Laversanne M, et al. Global Trends in Intrahepatic and Extrahepatic Cholangiocarcinoma Incidence From 1993 to 2012. Cancer. 2020;126(11):2666-78.
34. Kodali S, Shetty A, Shekhar S, Victor DW, Ghobrial RM. Management of Intrahepatic Cholangiocarcinoma. Journal of Clinical Medicine. 2021;10(11):2368.
35. Kabay KN, AkbaŞ CB, Cakcak İE. Management of a Patient With Difficult Cholangiocarcinoma. Turkiye Klinikleri Journal of Case Reports. 2023;31(4):127-9.
36. Kim YI, Park J-W, Kim BH, Woo SM, Kim TH, Lee K-H, et al. Outcomes of Concurrent Chemoradiotherapy Versus Chemotherapy Alone for Advanced-Stage Unresectable Intrahepatic Cholangiocarcinoma. Radiation Oncology. 2013;8(1).
37. Cantrell CK, White J. Successful Management of an "Unresectable" Intrahepatic Cholangiocarcinoma With Neoadjuvant Systemic Therapy, Chemoembolization, and Extended Hepatectomy With Portal Vein Reconstruction. Cureus. 2018.
38. Akita M, Fujikura K, Ajiki T, Fukumoto T, Otani K, Azuma T, et al. Dichotomy in Intrahepatic Cholangiocarcinomas Based on Histologic Similarities to Hilar Cholangiocarcinomas. Modern Pathology. 2017;30(7):986-97.
39. Prokopchuk O, Andres S, Becker K, Holzapfel K, Frieß H. Maffucci Syndrome and Neoplasms: A Case Report and Review of the Literature. BMC Research Notes. 2016;9(1).
40. Chauhan A, Likasitwatanakul P, Ahmed A, Sibley SD. A Case of Fibroblast Growth Factor Receptor Fusion-Positive Intrahepatic Cholangiocarcinoma With Humoral Hypercalcemia of Malignancy. Cureus. 2024.
41. Raghavan K, Jeffrey RB, Patel BN, DiMaio MA, Willmann JK, Olcott EW. MDCT Diagnosis of Perineural Invasion Involving the Celiac Plexus in Intrahepatic Cholangiocarcinoma: Preliminary Observations and Clinical Implications. American Journal of Roentgenology. 2015;205(6):W578-W84.
42. Sun W, Ge J, Zhang L, Zhou F, Liu J. Exploring the Role of Innate Immunity in Cholangiocarcinoma: Implications for Prognosis, Immune Infiltration, and Tumor Metastasis. Journal of Cancer. 2024;15(11):3547-65.

JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2024.29484
J Inonu Liver Transpl Inst 2024;2(2):60–64

Original Research

The new "Living Donor Liver Transplantation Program" Created by the Scientific Cooperation Between Malatya and Bishkek

Sezai Yılmaz,[1] Ahmet Kizilay[2]

[1]Department of Surgery and Liver Transplant Institute, Inonu University Faculty of Medicine, Malatya, Türkiye
[2]Rectorate, Inonu University, Malatya, Türkiye

Abstract

Objectives: In countries that do not have legal regulations regarding organ donation and brain death, only living donor liver transplantation (LDLT) centers can be established. LDLT is a very difficult operation and consists of a series of complex surgeries. Establishing an LDLT center in underdeveloped or developing countries is only possible with a long-term, patience and devoted cooperation of a developed transplant center.

Methods: In this study, LDLT training between the new LDLT center planned to be established in Kyrgyzstan and Inonu University Liver Transplantation Institute (LTI), one of the world's leading institutes in LDLT, and the first 2 LDLTs at the center in Bishkek were presented. LTI's mentoring process started 9 years ago. The training process continued intermittently, but an intensive training program was implemented for the last two years. During this process, a total of 74 doctors or nurses, mainly general surgeons, received training on LDLT.

Results: At the end of the training process, a team of surgeons from both centers performed 2 LDLTs on 2 separate days in Bishkek, on June 10 and 11, 2024.

Conclusion: The purpose of this cooperation is to plan and implement joint programs between states, universities and LT centers and to obtain good results for patients. This study focused on the implications, results, and future expectations of this cooperation, which was written as the first LDLTs in the history of Kyrgyzstan.

Keywords: Living donor, liver transplantation, surgical experience

Please cite this article as "Yılmaz S, Kizilay A. The new "Living Donor Liver Transplantation Program" Created by the Scientific Cooperation Between Malatya and Bishkek. J Inonu Liver Transpl Inst 2024;2(2):60–64".

Hepatocellular Liver transplantation (LT) is the most effective treatment method for end-stage liver disease, acute liver failure, and some hepatic malignancies. The first deceased donor liver transplantation (DDLT) was performed in 1988, and the first living donor liver transplantation (LDLT) was performed in 1990 in Türkiye.[1] More than 80% of the LTs that occur between 1500-2000 per year are LDLT, and the organ donation rate is unfortunately less than 4 per million people. Inonu University is located in Malatya, a province with a population of amount 1 million, located in the west of the Eastern Anatolia Region of the country. The university, which has a history of approximately 50 years, established the School of Medicine in 1987 and opened the Turgut Ozal Medical

Address for correspondence: Sezai Yılmaz, MD. Department of Surgery and Liver Transplant Institute, Inonu University Faculty of Medicine, Malatya, Türkiye
Phone: +90 532 120 23 76 **E-mail:** sezai.yilmaz@inonu.edu.tr

Submitted Date: 21.08.2024 **Revised Date:** 21.08.2024 **Accepted Date:** 30.09.2024 **Available Online Date:** 09.10.2024

Center (TOTM), one of the most expensive health investments in the country, in 1996. LT preparations at TOTM started in 1998, the first DDLT was performed in 2002, and the first LDLT was performed in 2005. The center, which exceeded its annual volume of 50 LTs in 2007, founded the Liver Transplantation Institute (LTI) in 2011 and built the Liver Transplantation Hospital in 2016. It is one of the only organ-specific university/institute hospitals in the world that has 156 patient beds, 36 intensive care beds, 12 operating rooms, conventional/interventional radiology, gastroenterology (endoscopy, ERCP etc.), and outpatient departments. It is the center that performs the most LDLT in Europe, including Türkiye, since 2008. Due to the transplantation team consisting of experienced and sufficient number of surgeons and anesthesiologists, medical tools, equipment and physical conditions, it is the center that performs the first 4-, 5-, 6-, 7-way liver paired exchange (LPE) transplants in the world.[2-4] The history of LT in Türkiye can be divided into 3 periods: initial stage (1988-1996), development stage (1997-2001) and rise and spread stage (2002-2023).[5] It is obvious that Inonu University Liver Transplantation Institute played the biggest role in the recent rise of LT activities in Turkey.

So far at LTI, a training was given to physicians from many centers such as Cambridge University, Warchaw University, Belgium Gent University, Giessen University, Russia St Petersburg University, and Novosibirsk State University. Among these countries, the Central Asian Turkish Republics have a special place due to the close origin of our nations. LTI has relations with Azerbaijan, Uzbekistan, Kazakhstan, Turkmenistan, and Kyrgyzstan in terms of training and operations related to LT. The Malatya - Bishkek story dealt with before but began mainly in September 2022, when Kyrgyz President Sadir Caparov requested the President of the Republic of Türkiye, Recep Tayyip Erdogan, to establish a LT program in Kyrgyzstan. Scientific cooperation began when President Erdoğan appointed the Rector of Inonu University, Prof. Dr. Ahmet Kizilay, through the Presidency of the Council of Higher Education, regarding this issue. In this study, the scientific, educational and operational aspects of Malatya-Bishkek cooperation were tried to be explained.

Material and Methods

Before the decision of the Presidents of both countries on the establishment of a LDLT center in Kyrgyzstan, 4 Kyrgyz general surgeons and 1 Kyrgyz gastroenterologist received LT training for various periods between 2015-2019 in LTI. However, the planned training program started in September 2022. During this period, 34 general surgeons, 14 operating room nurses, 5 anesthesiologists, 3 radiologists, 2 pediatricians, 2 biochemistry specialists, 1 gastroenterologist, 1 pathologist, and 1 anesthesia technician received LDLT training in Inonu University LTI until July 2024, each for at least 3 months. Kyrgyz physicians and nurses were trained on the preparation of patients requiring LT, follow-up and treatment before and after LDLT, ICU, normal ward, and outpatient clinic in LTI. Very few of the Kyrgyz surgeons had some experience in hepatobiliary surgery. Major operations in Kyrgyzstan were mainly hepatic resections for echinococcus alveolaris.[6] They had no experience with DDLT or LDLT. The importance of a multidisciplinary team was emphasized during the training process and efforts were made to form a team in this direction. Training programs for Kyrgyz physicians as a multidisciplinary and routine:

1. Hepatocellular Carcinoma Council every Monday at 16:00
2. Biliary and Vascular Council where postoperative complications of transplant patients are discussed every Tuesday at 12:30.
3. Transplantation Council, where patients who are candidates for liver transplantation are discussed every Thursday at 13:30
4. Discussion of a topic planned as a symposium, seminar, or panel once a month (biliary atresia, renal problems in LT patients, LT in HBV cirrhosis, or pushing the limits of LT in HCC, etc.)

Surgically, all Kyrgyz surgeons and nurses were allowed to undergo surgery. The surgical training process included:

1. Participating as a second assistant in at least 10 living donors and 10 recipients
2. Participating as first assistant to at least 10 living donors and 10 recipients
3. Using CUSA (cavitron ultrasonic aspiration) to divide hepatic parenchyma in at least 3 living donors
4. Assisting the perfusion and reconstruction of the liver graft removed from the donor at least 5 times at the back table
5. Participating of nurses in at least 10 living donor, 10 recipient and 10 back-table procedures

Before starting the program, faculty members of the LTI, including the rector, visited the centers in Bishkek and Ochi at least twice to check the facilities, existing infrastructure, necessary surgical instruments, and equipment to perform LDLT in Kyrgyzstan, and they held meetings with managers, including the Kyrgyz president.

LTI faculty members decided that the proposed hospitals for LT in Bishkek and Ochi were not very suitable. There-

upon, it was decided to perform LDLT at the Turkish Kyrgyz Friendship Hospital in Bishkek, which was planned to be a cardiology-heart surgery center and where kidney transplants had been performed before. However, in this hospital or others, the Thompson Retractor, CUSA, operation-specific surgical sets (including vascular clamps) and synthetic vascular grafts to be used in vascular reconstruction, which are important instruments for LDLT and which were repeatedly requested to be provided, were not available.

Five of the Kyrgyz surgeons who were training at LTI went to Kyrgyzstan at the beginning of May 2024 and started the patient and donor preparation process. During this multidisciplinary preparation period, close contact with the faculty members of the institute continued. Evaluation of the vascular and parenchyma of donor livers, volumetry, and LT indication in the recipient were all carried out under the supervision of institute faculty members.

This study was approved by the Ethics Committee of the Inonu University, School of Medicine and was conducted in accordance with the declaration of Helsinki of 1996.

Results

While the mentoring program continued, a total of 8 patients, 5 from Bishkek and 3 from Ochi, were prepared for LT from 2 separate centers in Kyrgyzstan as of the beginning of May 2024. These patients were discussed in online meetings. Finally, 2 patients with end-stage liver disease were selected for LT, which will be described in detail below. These patients had 2 suitable living donors. Five days before the operation, a faculty member transplant surgeon from the institute was sent to Bishkek to perform all the checks. Preparations were made for this surgeon's impressions there. The operations would be performed at the Turkish-Kyrgyz Friendship Hospital in Bishkek. Operating rooms and intensive care conditions (mechanical ventilators, hepafilter etc.) were suitable. However, surgical instruments, Thompson retractors, CUSA, and synthetic vascular grafts were not available. In other words, unfortunately, the essential elements of LDLT could not be provided.

This problem was solved with the initiatives of the rector of Inonu University (Prof. Dr. Ahmet KIZILAY) on the government. The Ministry of Customs and Trade and Turkish Airlines allowed the international movement of surgical sets, Thompson retractors, CUSA and other equipment weighing over 100 kg. In addition to the faculty member previously sent to Bishkek, a team of 7 people, including 3 transplant surgeons, 1 transplant anesthetist and 2 transplant nurses, headed by the rector, flew to Bishkek on June 9, 2024. The team arrived in Bishkek at 04.30 am on June 10, 2024. After a few hours of rest, the first LDLT operation was launched around noon. Donor and recipient informations for 2 separate LDLTs are presented below.

a. First LDLT (June 10, 2024)

Living donor: 20-year-old female, patient's daughter, height 155 cm, weight 65 kg, blood type: A Rh(+), right lobe: 500 cc, left lobe: 300 cc (remnant lobe 33%).

Recipient: 51-year-old female patient, height 147 cm, weight 52 kg, blood type: A Rh(+). The patient has severe tense ascite. Meld Na score was 20. ANA and ASMA are positive, with diagnosis cirrhosis due to otoimmune hepatitis. During the operation, 15 liters of ascitic fluid was drained from abdominal cavity of the patient. The liver was highly cirrhotic and atrophic. Right lobe LDLT was performed. Graft-to-recipient weight ratio was 0,96 %. Segment 5 hepatic vein was extended to the left hepatic vein stump with an 8 mm Dacron synthetic vascular graft. Right hepatic vein and portal vein anastomosis was normal. The graft hepatic artery had narrow diameter (<2mm). Hepatic artery anastomosis was repeated twice. The right hepatic artery of the graft was anastomosed to the arteria hepatica propria of the recipient with X8.5 magnitude loop and 8/0 prolene sutures according to the technique we described previously.[7] The bile ducts of the graft consisted of two ducts close to each other. Two duct to duct anastomoses were performed with interrupted, 6/0 prolene sutures. The patient's donor was discharged on the 12th postoperative day. On the 20th postoperative day, recipient's clinical and all laboratory parameters were normal and discharged. Triple immunosuppressive prophylaxis consisting of tacrolimus, mycophenolate mofetil, and corticosteroid is applied.

b. Second LDLT (June 11, 2024)

Living donor: Twenty six-year-old female, patient's daughter, height 161 cm, weight 50 kg, blood type 0 Rh(+), right lobe: 500 cc, left lobe 290 cc (remnant left lobe 32%).

Recipient: Fifty-years-old, female patient, height 148 cm, weight 50 kg, blood type 0 Rh (+). The patient had esophageal variceal bleeding twice and variceal ligation was performed for this. On CT, there were multiple nodules in the liver parenchyma, the largest of which was 2 cm in size. The liver had the appearance of chronic liver disease but was not severely cirrhotic. Nodules in the liver were evaluated as dysplastic nodules. MELD Na score was 10. During the operation, multiple nodular lesions were detected in the non-cirrhotic liver. Graft-to-recipient weight ratio was 1 %. Right lobe LDLT was performed. Hepatic vein and portal vein anastomoses were normal. The graft hepatic artery was anastomosed to the recipient arteria hepatica propria, as previously defined.

[7] The graft had one bile duct. Duct to duct anastomosis was performed and a transanastomotic feeding tube was placed through the cystic duct. At the end of the operation, cholangiographic images was normal. The patient's donor was discharged on the 10th postoperative day. On the 21th postoperative day, recipient's clinical and all laboratory parameters were normal and discharged. Triple immunosuppressive prophylaxis consisting of tacrolimus, mycophenolate mofetil, and corticosteroid is applied.

Kyrgyzstan Minister of Health Alim Kadir was involved in all of these operations at certain times. Because he was also a professor of general surgery.

On Wednesday, June 12, 2024, the patients' physical examinations, laboratory parameters and vascular anastomoses with Doppler US were normal. Subsequently, on Thursday, June 13, 2024, a meeting was held with the surgeons and anesthetists who would follow up the patients (Fig. 1), and the Turkish transplantation team of 8 people (Fig. 2) left Bishkek with the equipment brought.

Figure 1. The team that performed the first liver transplants in Kyrgyzstan.

Figure 2. Kyrgyz and Turkish physicians after transplantations.

Discussion

To put forward a model for establishing a new LDLT center through mentorship from an university with transplantation expertise is not an easy project. There are extremely heterogeneous publications on this subject.[8-10] It is obvious that Kyrgyzstan, with its population of 7 million, needs one or two liver transplant centers. Bishkek and Ochi are the 2 largest cities of Kyrgyzstan, and the infrastructure of health institutions is more developed in the capital Bishkek. However, in this country where there is no legal regulation regarding deceased donor organ donation, unfortunately there are no health institutions suitable for LDLT. Turkish-Kyrgyz Friendship Hospital in Bishkek was specially prepared in this regard, and 2 LDLTs were performed for the first time in the history of Kyrgyzstan. It is really difficult today to answer the question of whether this program will continue. This article will mainly focus on the rules, measures and remedies required for the continuity of this program.

Establishing a new LT program in underdeveloped countries will make significant contributions to better recognition of liver patients requiring LT in that country and the development of hepatobiliary surgery. However, since the learning curve tends to be long in complex surgeries such as LDLT, graft and patient survival rates may be low in the first LTs.[11] According to Addeo et al., surgeons performing LT have three learning curves. The first phase covers the first 70 procedures, the 2nd phase covers 70-100 LTs. After this, when the surgical time and blood transfusion requirement stabilize, the third stage is reached.[12] What path should be followed in LDLT? In Kyrgyzstan, it will take a long time to achieve even numbers of 10s rather than numbers of 70s and 100s.[13] For this reason, rather than the institutions' learning curve in Bishkek, the surgery and anesthesia team will need to complete the learning curve in an experienced center.

Multidisciplinary approach is the key to achieving good results in the new center. In the previous visits of Inonu University faculty members, they visited intensive care, operating rooms and patient wards and held many meetings with the teams there. In fact, these visits also revealed the obstacles to establishing such a program and led to studies on how to overcome these obstacles.

The structured training program for transplant surgeons in Türkiye is regulated by the Ministry of Health. The criteria that the responsible transplant surgeon must have for the opening of any new liver transplant center can be summarized as follows: Such as having at least 50 LTs per year for at least 1 year within the last 5 years and having articles on LT in journals within the scope of SCI. In addition, Inonu University LTI has 4-year doctoral programs under the name of LT surgery and anesthesia. However, it was impossible to

implement such programs for Kyrgyz surgeons or anesthesiologists. We focused on an accelerated training program in Malatya and the obligation to accompany transplants in Kyrgyzstan for approximately 1 year. We also suggested that 5-10 transplant surgeons and 2 transplant anesthetists should continue their education at Inonu University LTE for a more intensive training program. It would probably be necessary to train donor and recipient surgeons separately and more specifically. On the other hand, in some centers, donor and recipent surgery was given as training to the same surgeon. Training programs of over 40 hours for LT theory and over 100 hours for LT surgery have also been defined.[14]

Liver transplantation surgery requires to be highly skilled, with great expertise and vast experience. With accelerated training programs in a short time at Inonu University, efforts were made to help young Kyrgyz surgeons improve their surgical techniques and gain mastery and experience by teaching an optimized LT surgery.

Conclusion

Milan criteria can be expanded reasonably by Expanded Malatya criteria. Low GGT and low AFP are good prognostic biomarkers that predict survival following LT in patients with HCC. Patients Within Expanded Malatya Criteria had 78.4% 5-year OS, 4.7% post-transplant recurrence rate and Expanded Malatya criteria expanded the Milan by 35.2% which means 88 patients beyond Milan criteria were within Expanded Malatya criteria, giving them an opportunity for LT.

Disclosures

Ethics Committee Approval: This study was approved by Inonu University Ethics Committee (Date: 11/09/2024, Number: 2024/6397).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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

References

1. Karakayali H, Haberal M. The history and activities of transplantation in Turkey. Transplant Proc 2005;37(7):2905-8.
2. Yilmaz S, Kizilay A, Bayramov N, Tekin A, Emre S. Multiple Swaps Tested: Rehearsal for Triple and Five-Liver Paired Exchanges. Transplant Proc 2023:S0041-1345(23)00026-X.
3. Yilmaz S, Sönmez T, Ünver MU, Ince V, Akbulut S, Isik B, Emre S. The first 4-way liver paired exchange from an interdisciplinary collaboration between health care professionals and design economists. Am J Transplant 2023;23(10):1612-1621.
4. Yilmaz S, Sönmez T, Ünver MU, Ince V, Akbulut S, Sarici KB, Isik B. Enhanced role of multipair donor swaps in response to size incompatibility: The first two 5-way and the first 6-way liver paired exchanges. Am J Transplant 2024:S1600-6135(24)00338-1.
5. Akbulut S, Yilmaz S. Liver transplantation in Turkey: historical review and future perspectives. Transplant Rev (Orlando) 2015;29(3):161-7.
6. Toktogaziev B, Omorov K, Aitbaev S, Artisbekov B, Omorov R, Vityala Y, Tagaev T. A rare case of concurrent pulmonary and hepatic hydatid cysts treated by single-stage surgical management. Clin Case Rep 2022;10(5):e05897.
7. Yilmaz S, Kutluturk K, Usta S, Akbulut S. Techniques of hepatic arterial reconstruction in liver transplantation. Langenbecks Arch Surg 2022;407(7):2607-2618.
8. Praseedom RK, Madhavan KK, Akyol MA, Forsythe JL, Garden OJ. Training opportunities in liver transplantation surgery. Br J Surg 1999;86(12):1515-20.
9. Chaney AJ, Harnois DM, Musto KR, Nguyen JH. Role Development of Nurse Practitioners and Physician Assistants in Liver Transplantation. Prog Transplant 2016;26(1):75-81.
10. Pinheiro RS, Andraus W, Romeiro FG, de Martino RB, Ducatti L, Arantes RM, et al. Model for establishing a new liver transplantation center through mentorship from a university with transplantation expertise. PLoS One 2022;17(3):e0266361.
11. Marubashi S, Nagano H, Wada H, Kobayashi S, Eguchi H, Takeda Y, Tanemura M, Doki Y, Mori M. Donor hepatectomy for living donor liver transplantation: learning steps and surgical outcome. Dig Dis Sci 2011;56(8):2482-90.
12. Addeo P, Schaaf C, Noblet V, Faitot F, Lebas B, Mahoudeau G, Besch C, Serfaty L, Bachellier P. The learning curve for piggyback liver transplantation: identifying factors challenging surgery. Surgery 2021;169(4):974-982.
13. Khan AS, Garcia-Aroz S, Vachharajani N, Cos H, Ahmed O, Scherer M, et al. The learning curve of deceased donor liver transplant during fellowship training. Am J Transplant 2021;21(11):3573-3582.
14. Takagi K, Miura K, Nakanuma S, Sakamoto S, Yamamoto H, Yagi T, et al. Six National University Consortium in Liver Transplant Professionals Training (SNUC-LT) Program in Japan. Transplant Proc 2018;50(1):168-174.

JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2024.87587
J Inonu Liver Transpl Inst 2024;2(2):65–71

Original Research

Determination of Burden of The Caregiver In Pediatric Liver Transplantation

Erdem Sonmez, Bora Barut, Tevfik Tolga Sahin, Sezai Yilmaz

Inonu University Faculty of Medicine Department of Surgery and Inonu University Liver Transplant Institute, Malatya, Türkiye

Abstract

Objectives: We aimed to determine the burden of care of individuals caring for pediatric patients who have undergone liver transplantation.

Methods: The study was conducted at the Inonu University Liver Transplant Institute pediatric liver transplantation ward between May 2022 and February 2023. Data were the "Zarit Care Burden Scale," and the "Beck Depression Scale," and demographic characteristics of the patients and their caregivers.

Results: The average age of the caregivers was 38.35±11.82 years; 72.7% were women, 69.7% were the child's mother, and 81.8% reported that caregiving impacted their daily lives. The effect of caregivers' burden of care on their daily lives was found to be statistically significant (p = 0.021). Among the pediatric recipients, 42.4% were aged 13-18 years, 60.6% were female, 45.5% had been post-transplant for more than 25 months, and 54.5% developed complications. The burden of care was severe at 38.87±10.21, and the depression was mild at 10.81±8.65. A moderate positive relationship was observed between burden of care and depression level (r: .602, p: 0.000). Simple linear regression analysis showed that caregivers' depression levels significantly affected their burden of care, (R^2=0.363).

Conclusion: The study concluded that caregivers of pediatric liver transplant patients experience a very high burden of care and mild depression. This high burden of care negatively impacts their daily lives and leaves them with less personal time. Providing social support to these families can improve caregivers' quality of life by reducing their depression levels.

Keywords: Pediatric Liver Transplantation, Burden of care, Zarit Care Burden Scale, Beck Depression Scale, Complications, Rejection, Biliary complications, Infections

Please cite this article as "Sonmez E, Barut B, Sahin TT, Yilmaz S. Determination of Burden of The Caregiver In Pediatric Liver Transplantation. J Inonu Liver Transpl Inst 2024;2(2):65–71".

Hepatocellular Liver transplantation (LT) is the gold-standard treatment method for end-stage liver disease which is defined as the irreversible loss of liver functions beyond the physiologic limits.[1, 2] The patient who has end-stage liver disease and is confirmed to undergo liver transplantation is defined as the recipient. The individual who donates the liver is defined as the donor. The source of the liver graft may be from a deceased donor who is confirmed to have brain death. Under these circumstances, a whole liver graft is transplanted to the recipient. On the other hand, a partial left or right lobe liver graft can be transplanted from the living donors to the recipients. Living donor liver

Address for correspondence: Tevfik Tolga Sahin, MD. Inonu University Faculty of Medicine Department of Surgery and Inonu University Liver Transplant Institute, Malatya, Türkiye
Phone: +90 533 613 68 82 **E-mail:** tevfiktolgaa@gmail.com

Submitted Date: 22.09.2024 **Revised Date:** 22.09.2024 **Accepted Date:** 26.09.2024 **Available Online Date:** 09.10.2024

transplantation is usually performed between the next of kin and the recipient.[1, 2] The life expectancy following the LT procedure is prolonged because of the advancements in surgical technique and postoperative intensive care unit patient care.[3-5] The improved results have popularized LT, globally.[2, 3, 6]

The recipients need routine care after the liver transplant procedure and an increasing number of LT has resulted in an increased number of individuals requiring special care. The requirement for care is vital during the early postoperative period when patients cannot support themselves without their relative's care.[7] The values and the ethical standards of society determine the context of patient care requirements. In Turkey, patient care is the responsibility of the first-degree relatives of the patients.[8] Stone et al.[9] have defined the caregiver as the person who fulfills the care requirements of the patients and the person who is primarily responsible for their patient's care.

In LT recipients, the treatment period lasts a lifetime, which has detrimental effects on family members and caregivers. Furthermore, the caregivers may experience periodic psychosocial problems. Greenwood et al.[10] have shown that the caregivers experienced problems in sleep patterns, fatigue, and personality problems in addition to the difficulties encountered during the care of their patients. This was shown in direct relationship with the difficulty of the caregiving process.[10] It has been shown that the level of dependency of the patient on the caregiver was directly related to the burden of the caregivers.[11] The personal characteristics of the caregivers had a direct effect on the burden of the caregivers. Among these characteristics were the gender, age, and education status of the caregiver in addition to the presence of health problems, the degree of relation to the patient, the amount of time required for caring for their patient, and the amount of support provided by the peers to the caregiver.[12]

The LT recipient and their caregivers require psychosocial support. Studies have shown that nurses were expected to provide social support to patients.[13] Healthcare professionals focus on the physical, social, and psychological well-being of their patients; however, they should also provide the necessary support to their caregivers for a successful therapeutic outcome.[12] LT is a major abdominal surgery and caring for LT recipients is a demanding task. The nurses and other healthcare professionals must support the caregivers when they feel overwhelmed during the care of their patients. Only two studies have analyzed the burden of caregivers of LT recipients.[7,14] No studies analyze the caregivers' burden of pediatric liver transplant recipients.

In the present study, we aimed to evaluate the burden of caregivers in pediatric liver transplantation. Furthermore, we evaluated the relationship between the burden of the caregivers and the degree of depression of the caregivers. Our secondary aim was to determine the impact of the burden of the care for pediatric liver transplant recipients on the socioeconomic status of the relatives and we aimed to determine means of social support.

Methods

Study Design and Determination of the Study Population

The study is a descriptive and cross-sectional study. It is conducted between May 2022 and February 2023 in Inonu University Liver Transplant Institute pediatric inpatient ward. The power analyses were performed using the G-Power software (Düsseldorf, Germany). The power of the study was taken as 0.95 and the alpha-coefficient was determined as 0.05. The minimum number of participants was determined to be 33 in total. During the study period, 162 patients were admitted to the inpatient ward for various reasons. We included 33 of these patients and their caregivers in our study. All participants were informed by the researchers regarding the nature of the study and the patients who gave informed consent were included in the evaluation for our study. Initially, our study was approved by the Director of Inonu Liver Transplant Institute (Approval date: 23.02.2022, Approval number: E.148950). After the approval of the directorate of the Liver Transplant Institute, Institutional Review Board approval was obtained on 12.04.2022 (Approval number: 2022/1072).

Study Variables

All data are obtained using interview techniques to the patients and their caregivers in the pediatric inpatient ward. The study variables of the caregivers included age, gender, education level, occupation status, monthly income, degree of kinship to the patient, presence of any chronic illness, Zarit scale for burden of care, Beck's depression scale, and eight questions evaluating the degree of interference of caregiving to the daily activities. The study parameters of the recipients included the presence of any complications, the interval between hospitalization and liver transplantation, age, and gender.

The Zarit Scale for Burden of Care

Zarit, Reever, and Bach-Peterson developed the scale in 1980.[15] The Turkish version was validated in 2006 by Inci et al.[16] It was initially designed to determine the burden of caregivers caring for ill or old individuals. Twenty-two questions assess the burden of care and are answered

with a scale ranging between 0 to 4 (0=never, 1=occasional, 2=sometimes, 3=frequently, 4=always). Mainly, these questions evaluate the emotional and social aspects of the burden of care. The minimum score that can be obtained is 0 and the maximum score is 88. A higher score indicates the severity of the burden on the caregivers. The classification of the scores is as follows: a core ranging between 0 to 20 shows a low burden on caregivers, a score ranging between 21 to 40 indicates mild burden on the caregiver, a score ranging between 41 to 60 shows moderate burden on the caregiver, a score ranging between 61 to 88 indicates very severe burden on the caregiver.[17,18] The Cronbach alfa coefficient of the scale is 0.83.[17,18] The Cronbach alfa coefficient of scale in our study was 0.81. We used this scale to evaluate the burden of care for the relatives of the pediatric liver transplant recipients.

Beck's Depression Scale

Beck's depression scale was developed by Beck et al.[19] in 1961. Hisli et al.[20] validated the Turkish version of Beck's depression scale in 1989. Twenty-one questions are evaluating the severity of depression of the individuals. Each question is answered on a scale from 0 to 3. The minimum and maximum scores obtained from the scale are 0 and 63, respectively. The classification of the scores of Beck's depression scale is as follows: 0-9 points indicate no depression in the individuals, 10-16 points indicate mild depression in the individuals, 17-29 points indicate a moderate level of depression in the individual, and 30-63 points indicate a severe depression in the individuals.[21] The Cronbach alfa coefficient of the scale is 0.8. In the present study, we found the Cronbach alfa coefficient of the scale to be 0.86.

Statistical Analysis

Continuous variables are expressed as mean±standard deviation. Additionally, descriptive data such as gender and socio-economic status are presented as the number of individuals (n) and the percentage (%) in the study population. The normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov Test. For continuous variables, comparisons among multiple groups were made using the One-Way ANOVA test, and comparisons between two groups were made using the Student's T-Test. Furthermore, to investigate how caregiving burden and depression severity affect each other, Pearson correlation analysis was conducted, and R coefficients were calculated. An R coefficient between 0-0.3 indicates a weak relationship, 0.31-0.5 indicates a moderate relationship and >0.5 indicates a strong relationship. Differences identified in comparisons with p-values below 0.05 were considered significant. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS v27.0) software (IBM, USA).

Results

The average age of caregivers who took care of child transplant patients included in the study was 38.35±11.82 years. Additionally, 72.7% were women, and 51.5% had graduated from high school or higher. When looking at their income levels, it was found that 57.6% had an income above the minimum wage. 69.7% of the caregivers were the child's mother. It was observed that 72.7% of the caregivers were not working, 93.9% did not have a chronic illness, and 81.8% of the caregivers reported that the caregiving burden affected their daily lives (Table 1). The impact of the caregiving burden on the daily lives of caregivers was found to be statistically significant (p=0.021). However, when other variables were examined, no statistically significant difference was found for both caregiving burden and depression level (Table 1).

In our study, it was observed that 42.4% of the pediatric recipients were in the 13-18 age range, 60.6% were female, 45.5% had been more than 25 months since the transplant, and 54.5% had developed complications. Among those who developed complications, 24.2% had biliary complications, 84.8% did not develop rejection, and 93.9% did not develop an infection (Table 2). According to the results obtained between the transplant duration and the caregivers' caregiving burden and depression levels, it was observed that as time passed since the transplant, the caregivers' caregiving burden and depression levels statistically significantly decreased. However, when other variables were examined, no statistically significant difference was found for both caregiving burden and depression level (Table 2).

The average scores of caregiving burden and depression levels of caregivers and the correlation analysis between them are shown in Table 4.3. It was found that the caregiving burden level was severe with a score of 38.87±10.21, and the depression level was mild with a score of 10.81±8.65. Accordingly, it was observed that there was a moderate positive relationship between caregiving burden and depression level (r=0.602, p=0.000). In other words, as the depression level increases, the caregiving burden increases (Table 3).

A simple linear regression analysis was conducted to determine the effect of caregivers' depression levels on caregiving burden, and the model was found to be significant (F=17.649, p=0.000). The R^2 value, which expresses the explanatory power of the model, was found to be 0.363. This value indicates that 36.3% of the caregiving burden variable is explained by the independent variable depres-

Table 1. The burden of care and severity of depression in the caregivers in our study

Demographic characteristics of the caregivers	S	%	Burden of Care (Mean±SD)	Depression (Mean±SD)
Age				
18-30	5	15.2	40.20±8.52	12.80±12.27
31-45	20	60.6	38.35±11.82	9.55±8.81
46-60	8	24.2	39.37±7.32	12.75±5.84
Gender			F: .074, p: 0.929	F: .529, p: 0.595
Female	24	72.7	37.83±9.07	10.58±7.60
Male	9	27.3	41.66±12.97	11.44±3.84
			t: -.959, p: 0.432	t: -.251, p: 0.839
Education level				
Primary school or less	16	48.5	41.12±11.19	13.37±8.05
Highschool or more	17	51.5	36.76±9.01	8.41±8.73
		t: 1.236, p: 0.230	t: 1.697 , p: 0.100	
Income				
Minimum wage or less	19	57.6	40.52±9.54	13.36±7.15
More than minimum wage	14	42.4	36.64±11.00	7.35±9.55
		t: 1.059, p: 0.300	t: 1.980 , p: 0.060	
The degree of kinship				
Mother	23	69.7	38.34±8.91	10.56±7.78
Father	10	30.3	40.10±13.19	11.40±10.86
		t: -,384, p: 0.708	t: -.220, p: 0.829	
Occupational status				
Yes	9	27.3	38.44±12.84	10.55±11.17
No	24	72.7	39.04±9.35	10.91±7.80
		t: -.127, p: 0.901	t: -.089 , p: 0.931	
Chronic Illness				
Yes	2	6.1	51.00±5.65	21.50±3.53
No	31	93.9	38.09±9.98	10.12±8.45
		t: 2.943 , p: 0.143	t: 3.888, p: 0.067	
The effect on daily life				
Yes	27	81.8	40.77±9.14	11.66±8.87
No	6	18.2	30.33±11.20	7.00±7.01
		t: 2.434, p: 0.021*	t: 1.400 , p: 0.195	

*p<0.05; t: Independent Sample T test; F: One-way ANOVA; r: Pearson Correlation Test.

sion in the model. The Beta coefficient of the independent variable included in the regression model was (ß=0.602) (p=0.000). Accordingly, it is understood that the depression level has a significant effect on the caregiving burden of caregivers (p=0.000) (Table 4).

Discussion

Liver transplantation, a major surgical procedure, is quite complicated in the post-transplant period. For a helathy navigation of the process, patients and caregivers need professional support. After liver transplantation, patients may encounter problems such as infection, rejection, biliary complications, and bleeding. This process is especially stressful for families with pediatric liver transplants. If the liver transplant involves a living donor, the donor's health status is also a concern. Families of pediatric patients experience significant anxiety and worry about complications such as rejection and infection. These fears and concerns negatively impact the family and affect the caregiving burden.

A literature review revealed that there is only one study aimed at determining the caregiving burden of individuals caring for liver transplant patients.[7] Due to the lack of such studies in pediatric liver transplant patients, we designed current study.

In our study, consistent with the literature, the majority (72.7%) of caregivers were women. It is reported reported that 50.5% of caregivers were women.[22] According to the American Caregivers Association data, 75% of caregivers are women.[23] It is noted that, as in our country, most caregivers in foreign countries are also women.[23]

Table 2. The characteristics of pediatric liver transplant recipients.

Demographic characteristics	n	%	Burden of Care (Mean±SD)	Depression (Mean±SD)
Age				
0-3 years	2	6.1	45.00±2.82	8.00±2.82
4-6 years	9	27.3	38.88±11.48	7.11±6.58
7-12 years	8	24.2	42.37±8.17	14.75±10.76
13-18 years	14	42.4	36.00±10.80	11.35±8.61
		F: .916, p: 0 .446	F: 1.212, p: 0.323	
Gender				
Male	13	39.4	35.00±12.44	10.69±11.78
Female	20	60.6	41.40±7.79	10.90±6.20
		t: -1.655, p: 0.115	t: -.058, p: 0.954	
Post-transplant duration				
0-6 Months	10	30.3	45.00±10.11	18.00±8.76
7-12 Months	2	6.1	48.50±2.12	11.00±7.07
13-24 Months	6	18.2	38.16±6.73	7.66±6.12
25 months and longer	15	45.5	33.80±9.39	7.26±7.09
		F: 3.845, p: 0.020*	F: 4.523, p: 0.010*	
Complications				
Yes	18	54.5	38.61±11.52	10.77±10.30
No	15	45.5	39.20±8.77	10.86±6.51
		t: -.167, p: 0.869	t: -.030, p: 0.976	
Biliary Complications gelişme				
Yes	8	24.2	40.87±5.11	11.25±7.49
No	25	75.8	38.24±11.38	10.68±9.13
		t: .629, p: 0.534	t: .177, p: 0.862	
Rejection				
Yes	5	15.2	37.40±14.53	8.80±4.76
No	28	84.8	39.14±9.58	11.17±9.19
		t: -.258, p: 0.807	t: -.865 , p: 0.407	
Infection				
Yes	2	6.1	37.00±1.41	14.5±7.78
No	31	93.9	39.00±10.53	10.58±8.77
		t: -.935, p: 0.365	t: .685, p: 0.604	

*p<0.05.

Table 3. Correlation analyses between the severity of depression and the burden of care

	(Mean±SD) (The minimum and maximum scores of the scale)	Burden of Care	Depression
Burden of Care	38.87±10.21 (0-88)	1	r: .602 p: .000
Depression	10.81±8.65 (0-63)	r: .602 p: .000	1

The average Zarit Burden Interview (ZBI) score of caregivers was found to be 38.87±10. Türe and colleagues[24] found the average ZBI score to be 47.64±15.31 in caregivers of children with chronic illnesses. Taşçıoğlu and colleagues[25] found the average ZBI score to be 45.74±1.03 in parents of hospitalized children. Similarly, another study reported the average ZBI score to be 30.58±13.09 in parents of children with chronic illnesses.[26] Bayır and colleagues[7] determined the average ZBI score to be 33.77±12.37 in caregivers of liver transplant patients.

Table 4. The regression analysis of the depression scale versus the burden of care

Dependent variable	Independent Variable	B	Std. Error	ß	t	p	R	R^2	F	Model p
Burden of Care	Constant	31.193	2.329		13.391	0.000	.602	.363	17.649	0.000
	Depression	0.710	.169	.602	4.201	0.000				

In our study, it was found that 81.8% of caregivers reported that their daily lives were affected. The caregiving burden of those whose daily lives were affected was found to be severe. The impact of caregiving burden on the daily lives of caregivers was statistically significant. Similarly, in a study by Karaaslan et al.[14] investigating the effect of caregiving burden on daytime sleepiness in caregivers of liver transplant patients, the caregiving burden score was found to be severe in individuals whose daily lives were affected.

According to the results obtained regarding the interval from the transplant and the caregiving burden scores of caregivers, it was found that the caregiving burden of caregivers decreased over time, and this decrease was statistically significant. It is thought that in the early post-transplant period, the presence of families in the hospital environment, the stress of new situations encountered in the postoperative period related to their children's illnesses, and similar factors increased the caregiving burden. As families became accustomed to living with liver transplantation in the post-transplant period, the caregiving burden was lower.

In our study, although there was no statistically significant difference, it was observed that depression scores decreased as the education level increased. In the literature, Çiftçi et al.[27] similarly found no significant difference in depression scores according to education level. The literature indicates that as education levels increase, depression scores decrease because individuals use more effective coping mechanisms and have better decision-making processes.[28]

When depression scores were examined according to income levels in our study, no statistically significant difference was found. However, when looking at the average depression scores according to income levels, it was observed that those with an income above the minimum wage had an average depression score of 7.35±9.55, while those with an income at or below the minimum wage had an average depression score of 13.36±7.15; but this difference did not reach statistical significance. The literature indicates that low household income is correlated to the severity of depression.[29] Based on this information, it can be said that our research findings support the literature.

When comparing the depression scores of caregivers with the transplant duration, the results were found to be significant. Similar to the comparison of caregiving burden with transplant duration, it is thought that the difficulties brought by the early post-transplant period increased depression levels, while as the post-transplant period extended, families' ability to cope with problems improved, and depression levels decreased.

It was found that the caregiving burden level was severe at 38.87±10.21, and the depression level was mild at 10.81±8.65. According to these results, a moderate positive relationship was observed between caregiving burden and depression level.

A simple linear regression analysis was conducted to determine the effect of caregivers' depression levels on caregiving burden, and the model was found to be significant. The R^2 value, which expresses the explanatory power of the model, was determined to be 0.363. This value indicates that 36.3% of the caregiving burden variable is explained by the independent variable depression in the model. Accordingly, depression level has a significant effect on the caregiving burden of caregivers. As the depression level increases, the caregiving burden score also increases.

In the literature, Karaaslan et al.[30] found a positive relationship between caregiving burden and depression in their study evaluating the psychological conditions and caregiving burden of parents with mentally disabled children. Similarly, Budak et al.[31] concluded that as the caregiving burden of mothers of children with chronic illnesses increases, their levels of anxiety and depression also increase.

Our study has various limitations. We did not evaluate the burden of caregivers and the level of depression in the relatives of the non-transplanted individuals. Furthermore, the sample consists only of patients hospitalized at Inonu University Liver Transplant Institute.

Conclusion

Our results showed that the majority of the caregivers are the mothers of the child. The burden of care has a major impact on the social status of the caregivers. There is a positive correlation between the burden of care and depression in caregivers. As the duration of the posttransplant period prolongs the burden and the severity of depression of the caregivers are reduced. For these reasons, we believe psychosocial support is required in the early postoperative period. This will increase the quality of care. Also, the burden of care should be shared with other members of the family.

Disclosures

Ethics Committee Approval: This study was apporved by the Inonu University Scietific Research Ethics Committee (Date: 12.04.2022, Approval Number: 2022/1072).

Peer-review: Externally peer-reviewed.

Conflict of Interest: The Authors decalre that they have no conflict of ineterst.

Authorship Contributions: Concept – E.S.; Design – E.S., T.T.S.; Supervision – B.B., S.Y.; Materials: E.S., B.B.; Data Collection&/or Processing – E.S., T.T.S., Analysis and/or interpretation – E.S., T.T.S.; Lietrature search – E.S., B.B., Writing – E.S., T.T.S.; Critical Review – S.Y.

References

1. T.C. Sağlık Bakanlığı. Kan, Organ ve Doku Nakli Dairesi Başkanlığı https://organ. saglik.gov.tr/0TR/70Istatistik/OrganNakilIstatistik-Kamusal.aspx 13 Nisan 2019
2. Gülen H, Karaca A. Organ transplantasyonu sürecinde donör eğitimi ve hemşirelik bakımı. Journal of Duzce University Health Sciences İnstitute 2018, 8(2): 23-88.
3. Kapıkıran G. Karaciğer Nakli Olan Hastalarda Ayak Refleksolojisinin Ağrı, Konfor ve Beta Endorfin Düzeyine Etkisi. Sağlık Bilimleri Enstitüsü, Hemşirelik Anabilim Dalı. Doktora Tezi, Malatya: İnönü Üniversitesi, 2020.
4. Yang LS, Shan LL, Saxena A, Morrıs DL. Liver transplantation: A systematic review of long time quality of life. Liver İnt 2014, 34(9): 1298-313.
5. Adam R, Hoti E. Liver transplantatıon: The Current Situation. Semin Liver Dis 2009, 29: 3-18.
6. İzveren A, Dal Ü. Abdominal cerrahi girişim uygulanan hastalarda görülen erken dönem sorunları ve bu sorunlara yönelik hemşirelik uygulamaları. Hacettepe University Faculty of Health Sciences Nursing Journal 2011, 36-46.
7. Bayır K, Sarıtaş Çıtlık S. Karaciğer Nakli Olmuş Hastalara Bakım Verenlerin Bakım Yüklerinin Belirlenmesi. Sağlık Bilimleri Enstitüsü, Halk Sağlığı Ana Bilim Dalı, Yükseklisans Bitirme Projesi, Malatya: İnönü Üniversitesi, 2013.
8. İnci H.F. Bakım Verme Yükü Ölçeği'nin Türkçe'ye Uyarlanması, Geçerlilik ve Güvelinirliği, Sağlık Bilimleri Enstitüsü, Halk Sağlığı Ana Bilim Dalı, Yüksek Lisans Tezi, Denizli: Pamukkale Üniversitesi, 2006.
9. Stone R, Cafferata GL, Sangl J. Caregivers of the frail elderly: A national profile. Gerontologist, 1987, 27:616-26.
10. Greenwood, N., Mackenzıe, A, Cloud, GC, Wılson N. Informal carers of stroke survivors–factors influencing carers: A systematic review of quantitative studies. Disability and Rehabilitation, 2008, 30(18),1329 –49.
11. Dyck DG, Short R, Vitaliano PP. Predictors of burden and infectious illness inschizophrenia caregivers. Psychosom Med, 1999, 61:411-19.
12. Koçak G. İnmeli Hastalarda Bakım Vericinin Yükü. Dahiliye Hemşireliği Ana Bilim Dalı, Yüksek Lisans Tezi, İstanbul: İstanbul Üniversitesi, 2011.
13. Vasquez EM, Tanzi M, Benedetti E ve Pollak R. Medication noncompliance after kidney transplantation. Am J Health-Syst Pharm, 2003, Vol 60, 266-9.
14. Karaaslan R. Karaciğer nakli olmuş hastaların bakım vericilerin bakım yükünün gündüz uykululuk durumuna etkisi. İnönü Üniversitesi Sağlık Bilimleri Enstitüsü Hemşirelik Anabilim Dalı Halk Sağlığı Hemşireliği Yüksek Lisans Tezi. 2019
15. Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: correlates of feelings of burden. Gerontologist. 1980;20(6):649-55.
16. İnci F, Erdem M. Bakım verme yükü ölçeği'nin Türkçe'ye uyarlanması geçerlilik ve güvenilirliği. Anadolu Hemşirelik ve Sağlık Bilimleri Dergisi. 2010;11(4):85-9
17. Koçak G. (2011). İnmeli Hastalarda Bakım Vericinin Yükü. İstanbul Üniversitesi, Yüksek Lisans Tezi, İstanbul.
18. Tülüce D. (2012) Kalp Yetersizliği Olan Hastalara Bakım Verenlerin Bakım Verme Yükünün İncelenmesi. Gaziantep Üniversitesi, Yüksek Lisans Tezi, Gaziantep.
19. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961; 4:561-71.
20. Hisli N. Beck Depresyon envanterinin üniversite öğrencileri için geçerliliği, güvenirliği. Psikoloji Dergisi. 1989;7(23):3-13.
21. Ardıç A. Fazla Kilolu ve Obez Adölesanların Depresyon, Anksiyete ve Stres Düzeyleri: İstanbul Örneği. TJFMPC, 2020;14(3): 384-390.
22. Bufton S, Emmett K, Byerly AM. Liver Transplantation. ed: Ohler L, Cupless S. Core Curriculum for Transplant Nurses. İnternational Transplant Nurses Society. Mosby Elsevier, 2008, 423-53
23. FCA. Caregiver Statistics: Demographics; Available from: https://www.caregiver. org/caregiver-statistics-demographics, 2016.
24. Türe E, Yazar A, Akın F, Aydın A. Kronik hastalık nedeni ile takip edilen çocukların bakım verenlerinin bakım verme yükünün değerlendirilmesi. Bozok Tıp Dergisi.2018; 8(3):46-53.
25. Taşçıoğlu G, Beyazıt U, Ayhan Bütün A. Hastanede tedavi gören çocukların ebeveynlerinde bakım verme yükünün incelenmesi. Adnan Menderes Üniversitesi Sağlık Bilim Fakültesi Dergisi. 2017; 1(1):10–19.
26. Ağkaya Alahan N, Aylaz R, Yetiş G. Kronik hastalığı olan çocuğa sahip ebeveynlerin bakım verme yükü. İnönü Üniversitesi Sağlık Bilimleri Dergisi. 2015; 4(2):1–5.
27. Çiftçi Karaca E, Aydın D, Karataş H. Cerrahi Girişim Uygulanaca Ebeveynlerin Endişe Nedenleri ve Anksiyete Durumlarının Belirlenmesi. J. Pediat Res. 2016;3(1):23-9.
28. Kayhan, C. (2003). Cerrahi Hastalarda Preoperatif Anksiyetenin Postoperatif Komplikasyonlarla İlişkisinin İncelenmesi. Yüksek Lisans Tezi, Afyon Kocatepe Üniversitesi Sağlık Bilimleri Enstitüsü, Afyon.
29. Potter LB, Rogler LH, Mościcki EK. Depression among Puerto Ricans in New York City: the Hispanic Health and Nutrition Examination Survey. Soc Psychiatry Psychiatr Epidemiol. 1995;30(4):185-93.
30. Karaaslan MM, Çelebioğlu A. Zihinsel Engelli Çocuğu Olan Ebeveynlerin Psikolojik Durumları ile Bakım Yükünün Değerlendirilmesi. Soc Sci Stud. 2018 (6):2, 188-200.
31. Budak MA, Geçkil E. Kronik hastalığı olan çocukların annelerinin bakım verme yükü ile anksiyete-depresyon düzeyinin belirlenmesi. ACU Sağlık Bil Derg. 2020, 11(3):391-9.

JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2024.03164
J Inonu Liver Transpl Inst 2024;2(2):72–77

Original Research

Liver Transplantation for Hepatocellular Carcinoma with Expanded Criteria: Malatya Experience

Volkan Ince,[1] Sertac Usta,[1] Brian Carr,[1] Ramazan Kutlu,[2] Mustafa Dikilitas,[3] Murat Harputluoglu,[4] Aysegul Sagir Kahraman,[2] Oztun Temelli,[5] Ayse Nur Akatli,[6] Ersoy Kekilli,[7] Burak Isik,[1] Sezai Yilmaz[1]

[1]Department of General Surgery, Inonu University, Liver Transplantation Institute, Malatya, Türkiye
[2]Department of Radiology, Inonu University, Liver Transplantation Institute, Malatya, Türkiye
[3]Department of Medical Oncology, Inonu University, Faculty of Medicine, Malatya, Türkiye
[4]Department of Gastroenterology and Hepatology, Inonu University, Liver Transplantation Institute, Malatya, Türkiye
[5]Department of Radiation Oncology, Inonu University, Faculty of Medicine, Malatya, Türkiye
[6]Department of Pathology, Inonu University, Faculty of Medicine, Malatya, Türkiye
[7]Department of Nuclear Medicine, Inonu University, Faculty of Medicine, Malatya, Türkiye

Abstract

Objectives: The aim of this study is to present updated data on liver transplantation (LT) for hepatocellular carcinoma (HCC) of Inonu University, Liver Transplantation Institute, one of the largest volume liver transplant centers in the world.

Methods: The data of 492 LT patients with HCC were analyzed retrospectively from the databank which is recorded prospectively and sequentially. Post-transplant recurrence rates and patient survival according to Milan, Malatya and Expanded Malatya criteria were calculated. Milan Expansion rate of the Malatya and Expanded Malatya criteria were also calculated.

Results: Median follow-up period of the total cohort was 11.1±1.6 years (8.0–14.2, 95% CI) and the recurrence rate was 18.5 % (91/492). 5-year OS according to Milan, Malatya and Expanded Malatya criteria in our cohort were 80%, 79.3% and 78.4%, respectively. Post-transplant recurrence rates within these criteria were 3.2%, 3.8%, and 4.7%, respectively. Milan expansion rates were 25.2% for Malatya criteria and 35.2% for Expanded Malatya criteria.

Conclusion: Milan criteria can be expanded reasonably by Expanded Malatya criteria. Low GGT and low AFP are good prognostic biomarkers that predict survival following LT in patients with HCC. Patients within Expanded Malatya Criteria had 78.4% 5-year OS, 4.7% post-transplant recurrence rate and Expanded Malatya criteria expanded the Milan criteria by 35.2%. Thus, 88 patients were beyond Milan criteria and were within Expanded Malatya criteria and so had an opportunity for LT.

Keywords: Liver tumor, live donor, hepatic transplantation

Please cite this article as "Ince V, Usta S, Carr B, Kutlu R, Dikilitas M, Harputluoglu M, et al. Liver Transplantation for Hepatocellular Carcinoma with Expanded Criteria: Malatya Experience. J Inonu Liver Transpl Inst 2024;2(2):72–77".

Hepatocellular carcinoma (HCC) is the 6th commonest cancer globally with 866.136 new cases and the 3rd global cause for cancer related deaths, with 758.725 deaths in the world.[1] It seems that it will continue to be one of the leading cancers in the future with an estimated number of annual new HCC cases of 1.52 million and deaths of 1.37 million by 2050.[2] Liver transplantation (LT) has an important role in the treatment of HCC patients by providing a chance of cure by removing both the underlying liver disease and as well as the tumor.

Address for correspondence: Volkan Ince, MD. Department of General Surgery, Inonu University, Liver Transplantation Institute, Malatya, Türkiye
Phone: +90 505 326 04 62 **E-mail:** volkanince@outlook.com

Submitted Date: 22.09.2024 **Revised Date:** 27.09.2024 **Accepted Date:** 30.09.2024 **Available Online Date:** 09.10.2024

Milan criteria were the first to be accepted globally for HCC patients for LT. We defined Malatya and Expanded Malatya criteria from Türkiye. In Türkiye, one of the countries with a cadaveric organ shortage, the patient selection criteria for deceased donor liver transplantation (DDLT) in patients with HCC are still the Milan criteria.[3] On the other hand, the search for criteria that will predict the best outcomes in LT for HCC continues.

In this study, we aimed to share the outcomes of patients with HCC who underwent LT in our institute, which is one of the largest transplantation centers in the world.

Methods

Inonu University Ethics Committee approved this study by approval no: 2024/6410. No informed consent was requested from patients since this is a retrospectively designed study.

Study Population

Between March 2002 and July 2024, 3784 LTs were performed at the Liver Transplantation Institute of Inonu University. We retrospectively analyzed the data of LT patients from the database which is recorded prospectively and sequentially. Patient demographics, tumor morphology (according to explant pathology report), etiology of the underlying liver disease, pre-transplant laboratory values, CHILD-Pugh class, MELD Na score, graft to recipient weight ratio (GRWR), overall (OS) and disease-free survival (DFS) years post-transplant and recurrence rate were recorded. Patient survivals were then calculated according within or beyond Milan criteria,[4] Malatya[5] and Expanded Malatya criteria.[6] Finally, the rate of expansion which the Malatya and Expanded Malatya criteria expanded the Milan criteria, were calculated.

Patient Inclusion and Exclusion Criteria

- Inclusion criteria
- Patients whose HCC was confirmed pathologically at the explant specimen
- Exclusion criteria
- Patients who had combined HCC and cholangio carcinoma
- Patients with post-transplant follow up period of less than 90 days

Definition of Milan Criteria[4]

- Patients with HCC who had no macrovascular invasion, no extrahepatic disease, for single nodule, maximum tumor diameter should be less than 5 cm; for multiple nodules, number of nodules should be less than 3 nodules and maximum tumor diameter of all nodules should be less than 3 cm.

Definition of Malatya Criteria[5]

- Patients with HCC should not have macrovascular invasion and extrahepatic metastasis
- If patient is within Milan criteria, its accepted as also within Malatya criteria
- If patient is beyond Milan criteria, should meet all the following 4 parameters
  - Largest tumor diameter ≤ 6 cm
  - AFP ≤ 200 ng/ml
  - GGT ≤ 104 IU/ml
  - Well or moderately tumor differentiation

Definition of Expanded Malatya Criteria[6]

- Patients with HCC should not have macrovascular invasion and extrahepatic metastasis
- If patient is within Milan criteria, its accepted as also within Expanded Malatya criteria
- If patient is beyond Milan criteria, should meet all the following 3 parameters
  - Largest tumor diameter ≤ 10 cm
  - AFP ≤ 200 ng/ml
  - GGT ≤ 104 IU/ml

Surgical Technique and Management of Immunosuppressive Treatment

- Our patient selection criteria, surgical method in LT for HCC, and immunosuppressive treatment protocol have been described in our previous studies.[5, 7-10]

Statistical Analysis

- The normal distribution of quantitative variables was tested using the Shapiro-Wilk test and summarized by median, minimum, and maximum values. For comparisons of two independent groups, the Mann-Whitney U test was used.
- The distribution of qualitative variables was presented by count (percentage), and chi-square tests (Pearson or continuity-corrected, where appropriate) were used for comparisons. Different superscript letters indicate significant differences between column proportions in tables as appropriate.
- Survival analyses were performed using the Kaplan-Meier method, Log-Rank test, and Cox regression analysis. The two-tailed significance level was set at 0.05.
- Overall survival defined as the time between the transplant day and death and calculated as years and death patients were censored by Kaplan-Meier method.
- Disease-free survival defined as the time between the

transplant day and the recurrence day and calculated as years and recurred patients and death patients were censored by Kaplan-Meier method.

- All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp, Armonk, NY).

Between March 2002 and July 2024, 3784 LTs were performed at the Liver Transplantation Institute of Inonu University, of which 592 (15.6%) were due to HCC. Following the inclusion and exclusion criteria, data of remaining 492 HCC patients were analyzed.

Annual LT numbers for HCC patients at our institute were shown at Figure 1. We thus perform an average of 35 to 40 LT for patients with HCC annually.

Median age was 56 (1–72 years), rate of male gender was 86.6% (n=426). Median AFP 12.3 (0.2–55.000 ng/ml), MELD/PELD 13 (6–41), Largest tumor diameter 3 (0.1–26 cm), number of nodules 2 (1–36). Demographics, laboratory parameters, and tumor data were summarized at Table 1.

Median follow-up period of the total HCC cohort was 11.1±1.6 years (8.0–14.2, 95% CI) and recurrence rate was 18.5% (91/492) (Table 1).

Survivals of the Total HCC Cohort (n=492)

1-, 5- and 10-year overall and disease-free survivals of the total cohort were 87.6%, 65% and 52.9% and 82.8 %, 62.3 %, and 51.4 % respectively, and recurrence rate in total cohort was 18.5 % (n=91).

Survivals According to Milan Criteria (Figs. 2a, 3a)

When we dichotomized the total cohort according to Milan criteria by pathology report, 250 patients were within Milan and 242 were beyond.

1-, 5- and 10-year overall and disease-free survivals of patients within Milan criteria were 91.3%, 80% and 66.1 % for overall and 90.9 %, 78.5 %, and 63.8 % for disease-free, respectively, and the recurrence rate in patients within Milan

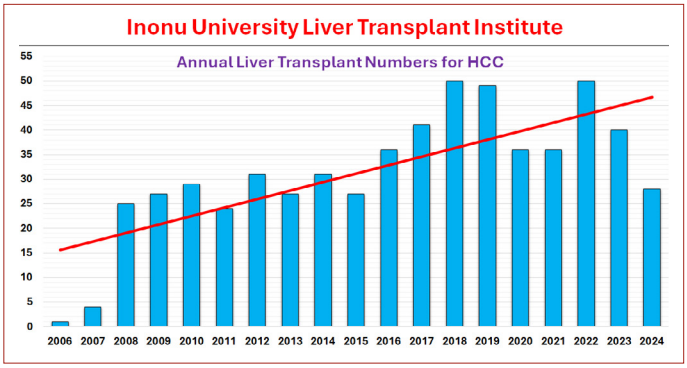


Figure 1. Annual liver transplant numbers for HCC at Inonu University, Liver Transplantation Institute.

Table 1. Demographics, tumor features, and laboratory parameters of all cohort

Parameters	Median	Minimum	Maximum
Age, years	56	1	72
AFP, ng/ml	12.3	0.2	55000
LTD, cm	3.0	0.1	26,00
NN	2.00	1	36
BSA	1.92	0.38	2.54
BMI	26.0	14.80	46.90
NLR	2.6	0.10	35.30
PLR	81.8	2.60	1092.30
Platelets, x10^3/uL	96	15	701
INR	1.31	0.82	4.10
Albumin g/dl	3.0	1.20	5.20
Total Bilirubin, mg/dl	1.87	0.23	44.70
Creatinine, mg/dl	0.8	0.22	13.8
AST, U/L	59	9	7789
ALT, U/L	42	10	3535
ALP, U/L	118	28	2327
GGT, IU/L	73	11	1396
MELD Na	13	6	41
	n	**%**	
Recurrence			
Yes	91	18.5	
No	401	81.5	
Milan criteria			
In	250	50.8	
Out	242	49.2	
Malatya criteria			
In	313	63.6	
Out	179	36.4	
Malatya criteria			
In	338	68.7	
Out	154	31.3	
Gender			
Male	426	86.6	
Female	66	13.4	
CHILD class			
A	175	35.6	
B	205	41.7	
C	112	22.8	
AFP, ng/ml			
≤200	410	83.3	
>200	77	15.7	
Missed	5	1.0	
GGT, ng/ml			
≤104	318	64.6	
>104	172	35	
Missed	2	0.4	
Differentiation			
Well	210	42.7	
Moderate	208	42.3	
Poor	73	14.8	
Missed	1	0.2	

Table 1. Demographics, tumor features, and laboratory parameters of all cohort (Cont.(

	n	%
Venous invasion		
None	270	54.9
Microvascular	165	33.5
Macrovascular	57	11.6
Etiology		
Viral hepatitis	374	76.0
Cyrptogenic	74	15.0
Budd-Chiari	12	2.4
Ethanol	10	2.0
Metabolic	8	1.6
Others	14	2.8
GRWR		
≥0.8	428	87
<0.8	51	10.6
Missed	13	2.6

criteria was 3.2 % (n=8).

1-, 5- and 10-year overall and disease-free survivals of patients beyond Milan criteria were 83.7 %, 49.2 % and 38.9 % and 74.2 %, 45.1 %, and 38.1 % respectively, and recurrence rate in patients beyond Milan criteria was 34.3 % (n=83).

Survivals According to Malatya Criteria (Figs. 2b, 3b)

When we dichotomize the whole cohort according to Malatya criteria by pathology report, 313 patients were within Malatya and 179 were beyond.

1-, 5- and 10-year overall and disease-free survivals of patients within Malatya criteria were 91.6%, 79.3 % and 67.6 % and 91.3 %, 77.8 %, and 65.6 % respectively, and recurrence rate in patients within Malatya criteria was 3.8 % (n=12).

1-, 5- and 10-year overall and disease-free survivals of patients beyond Malatya criteria were 80.7 %, 40 % and 26.7 % and 68 %, 35.1 %, and 26 % respectively, and recurrence rate in patients beyond Malatya criteria was 44.1 % (n=79).

The rate of expansion which Malatya criteria expanded the Milan by 25.2% (n=63 beyond Milan patients were within Malatya criteria).

Survivals According to Expanded Malatya Criteria (Figs. 2c, 3c)

When we dichotomized the total cohort according to Expanded Malatya criteria by pathology report, 338 patients were within Expanded Malatya and 154 were beyond.

1-, 5- and 10-year overall and disease-free survivals of patients within Expanded Malatya criteria were 91.3%, 78.4 % and 65.6 %, and 90.7 %, 76.4 %, and 63.9 % respectively,

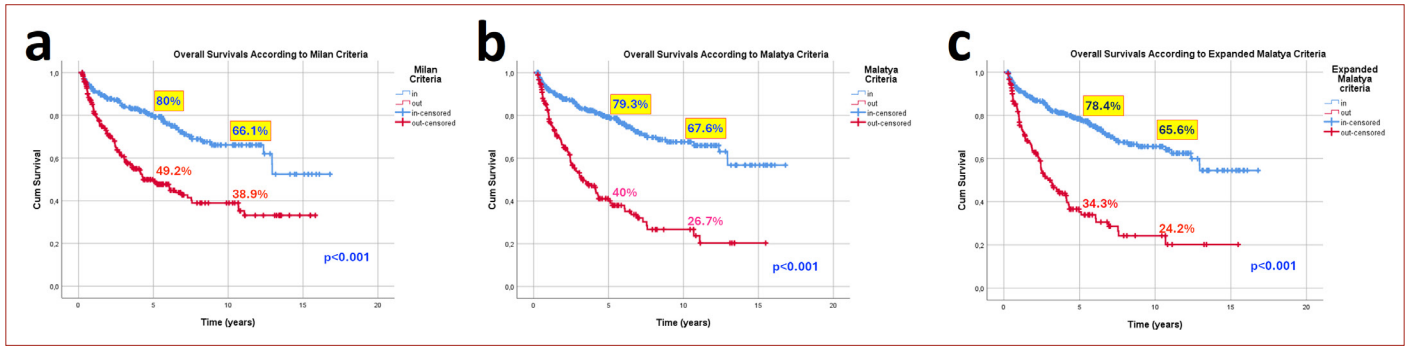


Figure 2. (a) Overall survivals according to Milan criteria, **(b)** Overall survivals according to Malatya criteria, **(c)** Overall survivals according to Expanded Malatya criteria.

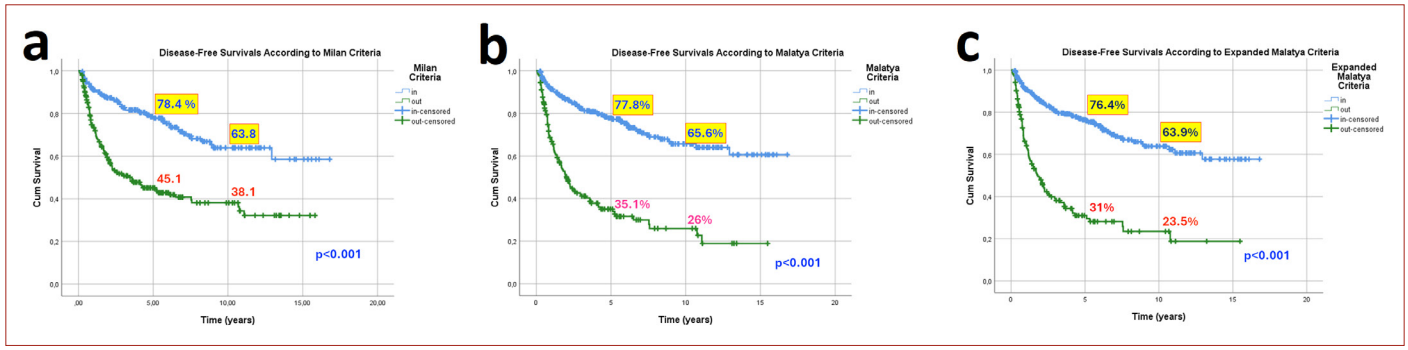


Figure 3. (a) Disease-free survivals according to Milan criteria, **(b)** Disease-free survivals according to Malatya criteria, **(c)** Disease-free survivals according to Expanded Malatya criteria.

and recurrence rate in patients within Expanded Malatya criteria was 4.7 % (n=16).

1-, 5- and 10-year overall and disease-free survivals of patients beyond Expanded Malatya criteria were 79.7 %, 35.3 % and 24.2 % and 65.5 %, 31 %, and 23.5 % respectively, and recurrence rate in patients beyond Expanded Malatya criteria was 48.7 % (n=75).

The rate of expansion which Expanded Malatya criteria expanded the Milan by 35.2% (n=88 beyond Milan patients were within Expanded Malatya criteria).

The OS and DFS, recurrence rates, and Milan criteria expansion rates of patients within the criteria are summarized in Figure 4.

Discussion

Efforts are ongoing to increase the donor pool through living donor liver transplantation and swap liver transplantation procedures in countries with organ shortage, such as Türkiye.[11, 12] However, the demand for organs is overwhelmingly higher than the donor organ supply. Therefore, using a valuable resource for patients with malignancy should be performed in accord with very strict criteria to choose patients who will benefit the most from transplantation. In patients with HCC, a 5-year overall survival more than 50 – 61% is considered as a target survival by LT,[13-16] but there is not any recommended data on the post-transplant recurrence rate.

Although 28 years have passed since its publication, Milan criteria which is very strict, is still used in cadaver organ distribution in Türkiye. As shown in many studies, when LT was performed in a group of patients beyond Milan criteria, survival outcomes were similar to Milan criteria.[3] In the present study, the 5-year overall survival rates of patients within Milan, within Malatya and within Expanded Malatya criteria were similar by LT, 80%, 79% and 78%, respectively (p=0.903). Additionally, the tumor recurrence rates after LT

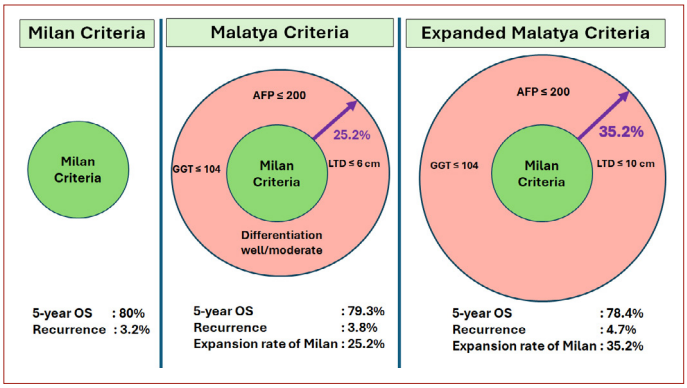


Figure 4 . Summary of OS and DFS, recurrence rates, and Milan criteria expansion rates of patients within the criteria.

in patients within these criteria were quite low, being 3.2%, 3.6% and 4.7%, respectively. On the other hand, the 5-year OS of patients with beyond Milan in our study is 49.2%. It is very close to the acceptable survival recommended in the guidelines. Thus, almost half of the patients with beyond Milan had a 5-year survival according to our study. These results are also evidence that the Milan criteria should be expanded reasonably.

There are more than 25 transplant criteria which are published in the literature from 10 different countries.[3] These criteria were called the expanded Milan criteria and each of them expanded the Milan criteria in different rates. Two of them were published from our institute in Türkiye, which are called Malatya criteria[5] and Expanded Malatya criteria.[6] The current study revealed that there were 250 patients within Milan, 313 patients within Malatya, 338 patients within Expanded Malatya criteria with similar 5-year OS. When we focused on the Milan expansion rates of the Malatya and Expanded Malatya criteria, Malatya criteria expanded the Milan by 25.2 % (n=63 beyond Milan patients had a chance to LT), while expanded Malatya criteria expanded Milan by 35.2 % (n=88 beyond Milan patients had a chance to LT).

Tumor morphological features such as number of nodules and largest tumor diameter as a selection criteria for LT in patients with HCC were insufficient to predict post-transplant survival. In addition to tumor morphology, biomarkers that predict tumor biological behavior are needed. We used low serum levels of alpha-fetoprotein (AFP) plus low serum levels of gamma glutamyl transpeptidase (GGT) as a good prognostic biomarker, in addition to largest tumor diameter in Expanded Malatya criteria and we expanded the Milan criteria by 35.2% with a similar 5-year OS 78.4%.

There are many studies on the diagnostic and prognostic usefulness of GGT and GGT-II which is its hepatoma-specific isoform. Several studies have also shown the prognostic usefulness of GGT in various treatments of HCC, including chemoembolization, radiofrequency ablation, resection, and LT.[17] We also have an ongoing study on GGT-II in our institute.

The retrospective design of the study and the fact of 80% of the cases being caused by viral hepatitis are among the limitations of the study. The strength of this study are the prospectively collected data and the relatively large number of patients.

Conclusion

Milan criteria can be expanded reasonably by Expanded Malatya criteria. Low GGT and low AFP are good prognostic biomarkers that predict survival following LT in pa-

tients with HCC. Patients Within Expanded Malatya Criteria had 78.4% 5-year OS, 4.7% post-transplant recurrence rate and Expanded Malatya criteria expanded the Milan by 35.2% which means 88 patients beyond Milan criteria were within Expanded Malatya criteria, giving them an opportunity for LT.

Disclosures

Ethics Committee Approval: Inonu University Ethics Committee approved this study by approval no: 2024/6410.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – V.I., S.U.; Design – V.I., S.U., B.I.C., S.Y.; Supervision – B.I.C., B.I., S.Y.; Funding – None; Materials – R.K., A.S.K., M.D., M.H., A.N.A.; Data Collection and/or Processing – O.T., E.K.; Analysis and/or Interpretation – V.I., S.U., E.K.; Literature Review – V.I.,A.S.K, A.N.A.; Writing – V.I., S.U.; Critical Review –B.I.C., B.I., S.Y.

References

1. Global Cancer Observatory: GLOBOCAN 2022. https://gco.iarc.who.int/media/globocan/factsheets/cancers/11-liver-and-intrahepatic-bile-ducts-fact-sheet.pdf
2. Global Cancer Observatory: Cancer Tomorrow https://gco.iarc.fr/tomorrow/en/dataviz/isotype?cancers=11&single_unit=50000&years=2050&types=1
3. Ince V, Sahin TT, Akbulut S, Yilmaz S. Liver transplantation for hepatocellular carcinoma: Historical evolution of transplantation criteria. World J Clin Cases 2022;10(29):10413-10427.
4. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–699.
5. Ince V, Akbulut S, Otan E, Ersan V, Karakas S, Sahin TT, et al. Liver Transplantation for Hepatocellular Carcinoma: Malatya Experience and Proposals for Expanded Criteria. J Gastrointest Cancer 2020;51:998–1005.
6. Ince V, Carr BI, Bag HG, Ersan V, Usta S, Koc C, et al. Liver transplant for large hepatocellular carcinoma in Malatya: The role of gamma glutamyl transferase and alpha-fetoprotein, a retrospective cohort study. World J Gastrointest Surg 2020;12:520–533.
7. Karakaş S, İnce V, Elkıran ET, Yılmaz S. Hepatoselüler Karsinomada Cerrahi ve Transplantasyonun yeri. Turk Klin Hepato-Pankreato Biliyer Sist Kanserleri 2021;1:23 31.
8. Kayaalp C, Ince V, Ersan V, Karakas S, Kahraman AS, Yilmaz S. Liver transplantation for hepatocellular carcinoma at Inonu University. J Gastrointest Cancer 2017;48(3):268-271.
9. Carr BI, Ince V, Bag HG, Ersan V, Usta S, Yilmaz S. Microscopic vascular invasion by hepatocellular carcinoma in liver transplant patients. Clin Pract (Lond) 2020;17(3):1497-1505.
10. Yilmaz S, Ince V. The importance of the immunosuppressive regime on hepatocellular carcinoma recurrence after liver transplantation. J Gastrointest Cancer 2021;1:1 6.
11. Yilmaz S, Sönmez T, Ünver MU, Ince V, Akbulut S, Isik B, Emre S. The first 4-way liver paired exchange from an interdisciplinary collaboration between health care professionals and design economists. Am J Transplant 2023;23(10):1612-1621.
12. Yilmaz S, Sönmez T, Ünver MU, Ince V, Akbulut S, Sarici KB, Isik B. Enhanced role of multipair donor swaps in response to size incompatibility: The first two 5-way and the first 6-way liver paired exchanges. Am J Transplant 2024:S1600-6135(24)00338-1.
13. Neuberger J, James O. Guidelines for selection of patients for liver transplantation in the era of donor-organ shortage. Lancet 1999;354(9190):1636-9.
14. Bruix J, Fuster J, Llovet JM. Liver transplantation for hepatocellular carcinoma: Foucault pendulum versus evidence-based decision. Liver Transpl 2003;9(7):700-2.
15. Volk ML, Vijan S, Marrero JA. A novel model measuring the harm of transplanting hepatocellular carcinoma exceeding Milan criteria. Am J Transplant 2008;8(4):839-46.
16. Mehta N, Bhangui P, Yao FY, Mazzaferro V, Toso C, Akamatsu N, et al. Liver Transplantation for Hepatocellular Carcinoma. Working Group Report from the ILTS Transplant Oncology Consensus Conference. Transplantation 2020;104(6):1136-1142.
17. Ince V, Carr BI, Bag HG, Koc C, Usta S, Ersan V, Baskiran A, Sahin TT, Yilmaz S. Gamma glutamyl transpeptidase as a prognostic biomarker in hepatocellular cancer patients especially with >5 cm tumors, treated by liver transplantation. Int J Biol Markers 2020;35(2):91-95.

JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2024.79188
J Inonu Liver Transpl Inst 2024;2(2):78–81

Case Report

Gallbladder Cancer in a Liver Transplant Patient

Yasin Dalda,[1] Volkan Ince,[1] Mehmet Ozcan,[2] Ozlem Dalda,[2] Tevfik Tolga Sahin,[1] Sezai Yilmaz[1]

[1]Department of General Surgery and Liver Transplantation Institute, Inonu University Faculty of Medicine, Malatya, Türkiye
[2]Department of Pathology, Inonu University Faculty of Medicine, Malatya, Türkiye

Abstract

Gallbladder cancers are relatively rare malignancies. While early-stage cases can achieve good outcomes with cholecystectomy, the 5-year survival rate in advanced stages is extremely low. Primary sclerosing cholangitis is a progressive liver disease characterized by inflammation of the bile ducts and is associated with an increased risk of gallbladder cancers.

A 32-year-old male patient with primary sclerosing cholangitis was referred for liver transplantation. Imaging revealed a suspicious polypoid lesion, 2.5 cm in diameter, in the gallbladder. With a Meld score of 30, the patient was placed on the transplant waiting list. After waiting period of one month a deceased donor liver transplant was performed. The hepatectomy specimen revealed T2 gallbladder cancer. No recurrence or metastasis was detected during 1 year of follow-up.

There is no consensus on the management of suspicious gallbladder lesions in patients with primary sclerosing cholangitis. Cholecystectomy in these patients carries a risk of decompensation in cirrhosis. Considering the decompensated liver cirrhosis and high Meld score, we preferred transplantation over cholecystectomy. Therefore, liver transplantation can be considered as primary treatment option instead of cholecystectomy.

Keywords: Gallbladder cancer, primary sclerosing cholangitis, liver transplantation.

Please cite this article as "Dalda Y, Ince V, Ozcan M, Dalda O, Sahin TT, Yilmaz S. Gallbladder Cancer in a Liver Transplant Patient. J Inonu Liver Transpl Inst 2024;2(2):78–81".

Gallbladder cancer (GBC) is the most common malignancy of the biliary tract and the fifth most common malignancy of the gastrointestinal system.[1] Except for those detected incidentally during elective cholecystectomies, the prognosis is generally poor. While gallstones and polyps are considered possible etiological factors, the exact causes remain unclear. Early-stage curative resections are effective, but oncological treatments in advanced stages have limited impact on overall survival.

Primary sclerosing cholangitis (PSC) is a chronic and progressive liver disease that affects the bile ducts. It is characterized by inflammation, strictures, and fibrosis in the intra- and extrahepatic bile ducts.[2] PSC is associated with hepatobiliary malignancies, colorectal cancer, and inflammatory bowel diseases. Liver transplantation (LT) is the most effective treatment for patients with cirrhotic livers due to PSC.[3]

There are limited reports in the literature of liver transplant patients with coexisting PSC and GBC. In this report, we present a patient with PSC and GBC who underwent LT.

Address for correspondence: Yasin Dalda, MD. Department of General Surgery and Liver Transplantation Institute, Inonu University Faculty of Medicine, Malatya, Türkiye
Phone: +90 422 341 06 60 - 37 01 **E-mail:** yasindalda@gmail.com

Submitted Date: 17.09.2024 **Revised Date:** 22.09.2024 **Accepted Date:** 22.09.2024 **Available Online Date:** 09.10.2024

Case Report

A 32-year-old male patient who had been followed up in gastroenterology department due to PSC and ulcerative colitis for about 7 years was referred to our clinic for transplantation, with no history of other comorbidities or previous surgery with. He had a history of recurrent endoscopic retrograde cholangio pancreatography (ERCP) and stenting and was using ursodeoxycholic acid (UDCA) and azathioprine. Laboratory tests showed a Meld (Model for End-stage Liver Disease) score of 30. Ultrasonography (USG) showed an asymmetric increase in gallbladder fundus thickness up to 2.5 cm in addition to the findings of chronic liver disease. Computed tomography (CT) and magnetic resonance imaging (MRI) showed cirrhotic liver and suspicious polypoid lesions measuring 2.5 cm in size in the gallbladder (Fig. 1). A cholecystectomy was not considered because of the risk of decompensation due to high Meld score and poor liver parenchyma. The patient with an patent portal vein was placed on the deceased donor waiting list because of lack a living donor. After 1 month on the waiting list, the patient was hospitalized due to decompensation and was under medical treatment when a deceased donor organ was presented. With a Meld score 30, the patient underwent LT. The gallbladder appearance was normal. There were no early post-transplant complications and histopathologic examination of the liver revealed cirrhosis with an etiology compatible with PSC. The gallbladder showed adenocarcinoma with a size of 3.5x2.5x1.5 cm. The pathologic stage of the patient with clear surgical margins and no lymphovascular and perineural invasion was T2aN0Mx (Figs. 2 and 3). No distant organ metastasis was detected in the scans and no oncologic treatment was given. Due to malignancy, everolimus was started in addition to tacrolimus in immunosuppression treatment. The patient continued with dual treatment and no recurrence or metastasis was observed 1-year follow-up (Fig. 4).

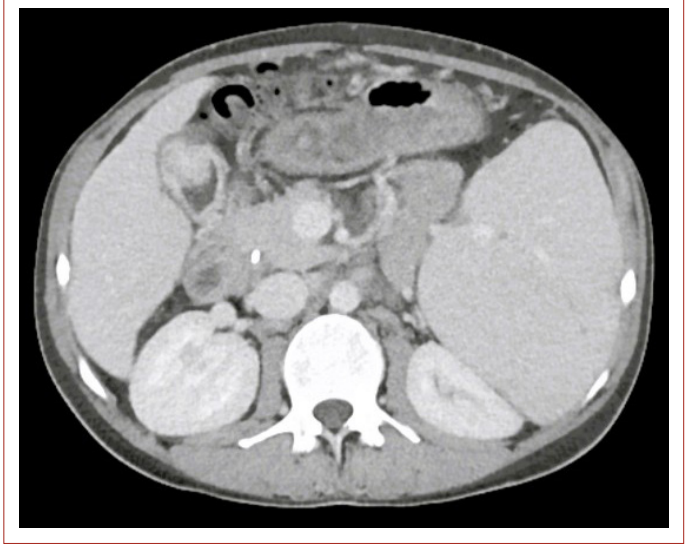


Figure 1. Preoperative polypoid lesion in the gallbladder.

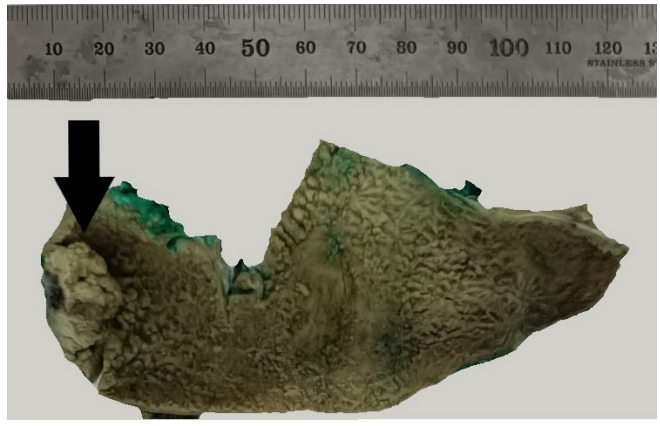


Figure 2. Polypoid tumoral lesion located in the fundus (arrow).

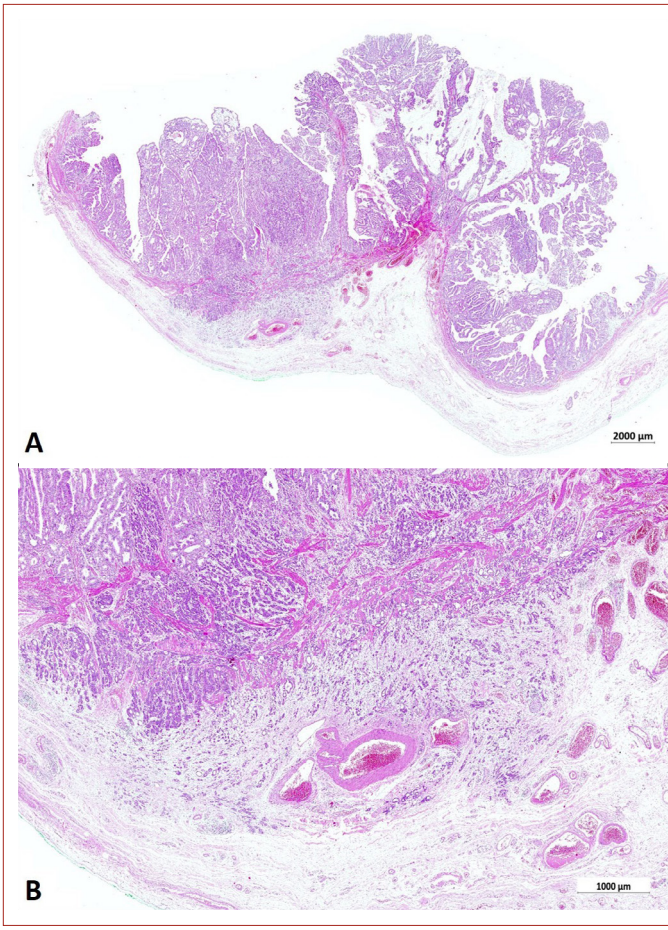


Figure 3. (a) Invasive adenocarcinoma (arrow) developing in the gallbladder on the background of intracholecystic papillary neoplasm with polypoid appearance (H&E; 10x). **(b)** Tumoral cells forming glandular structures invade the perimuscular connective tissue on the peritoneal side (H&E; 100x).

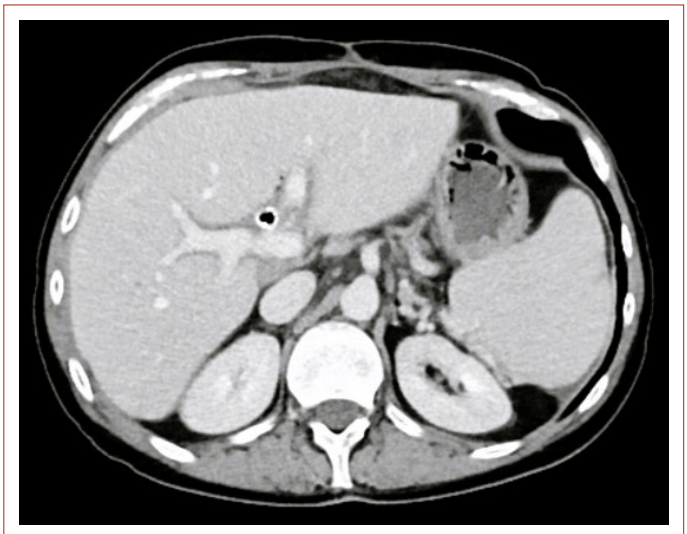


Figure 4. CT image of the patient 1 year after transplantation. Stent inserted due to biliary stricture.

Discussion

GBC is a malignancy with an aggressive course and poor prognosis. The 5-year survival of patients is between %5-15.[4] The worldwide incidence of this relatively rare disease is 2.5 per 100,000 people and is higher in women than in men. Gallstones are significantly associated with an increased risk of GBC. At the time of diagnosis, %90 of patients have stones.[5] Other risk factors include polyps and PSC disease. Especially in patients with PSC, the malignancy risk of gallbladder polyps has been found between %40-60.[6] In the early stage, patients mostly remain asymptomatic and are diagnosed as incidental in the imaging studies or elective cholecystectomies. Approximately %0.7 GBC has been reported in pathologic examination performed after cholecystectomy. The only curative treatment option for GBC is R0 resection.[7] While cholecystectomy is sufficient for T1 and T2 tumors, extensive resections and lymph node dissection are required for T3 and T4 tumors. It has been reported that depth of invasion and lymph node involvement are prognostic indicators for survival.[8]

PSC is a progressive liver disease involving the biliary tract and progressing to cirrhosis. It is known that the incidence of extrahepatic hilar cholangiocarcinoma and GBC are increased in PSC. The relationship between PSC and GBC has not been definitively established. Although the imaging studies performed at the diagnostic stage can put forth the diagnosis of GBC, the findings may be misleading due to the chronic cholecystitis in the background of PSC.

In the literature, cases who underwent LT due to PSC and incidentally found GBC have been presented. In the first report written in 1994, two patients underwent LT for PSC. They had T1N0M0 and T2N0M0 GBC.[9] Both patients survived for 2,5 years without the need for additional treatment. In another report, a 60-year-old patient who underwent LT due to PSC was found to have GBC and a 6-year disease-free survival was achieved.[10] The common point in the published reports is that cholecystectomy is avoided in patients with cirrhotic liver due to PSC in the diagnostic approach for suspicious masses in the gallbladder. On the other hand, in one report a cholecystectomy was performed in a 29-year-old patient who was followed up with PSC and an irregular mass of 11x13 mm in size was observed in the gallbladder. Histopathologic examination revealed GBC.[11] No distant metastasis was found and LT was performed 1 month later and a 24-month disease-free survival was reported. In another report, the association of LT and GBC was reported in four patients, three of whom had PSC and one had cryptogenic cirrhosis.[12] In one of the patients, cholecystectomy was performed before LT and T2N0M0 stage was diagnosed and the patient received radiotherapy and chemotherapy. LT was performed 11 months after cholecystectomy when liver function deteriorated. The other 3 patients were diagnosed in the hepatectomy specimen after LT. Disease-free survival was reported as the shortest 22 months and the longest 42 months.

LT seems to be the only option for these patients due to the risk of decompensation. And there have been no reports of early recurrence or metastasis after LT. One of the common features of these patients is the absence of nodal spread and early detection of tumors. Although lymph node involvement is an important prognostic factor in the literature, it has also been reported that residual disease in the lymph nodes of incidental GBCs has no effect on survival.[13] This makes the option of LT more attractive when a suspicious mass is seen in the gallbladder in patients with PSC. On the other hand, planning cholecystectomy because of the cirrhotic liver background in these patients is risky as it may lead to decompensation. In such a case, the patient's liver function should be well evaluated. Cholecystectomy should be avoided in patients with high Meld score.

Therefore, if early-stage GBC is considered in decompensated cirrhotic patients, LT should be done. There is no indication for LT in advanced-stage GBC. However, early-stage GBC should not be considered a contraindication for LT. The reported cases show favorable outcomes, making LT a viable treatment option for early-stage GBC, particularly in the setting of PSC or cirrhotic liver.

Conclusion

Since there is a risk of GBC in patients with PSC, the gallbladder should be examined especially in detail in perioperative imaging. As in our case, the result of LT in patients with T2 GBC are promising.

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.Y., V.I.; Design – Y.D., T.T.S.; Supervision – S.Y., V.I.; Materials – Y.D., T.T.S., M.O., O.D.; Data collection &/or processing – Y.D., M.O., O.D.; Analysis and/or interpretation – V.I., T.T.S.; Literature search – Y.D., V.I.; Writing – Y.D., V.I., S.Y.; Critical review – S.Y., V.I., T.T.S.

References

1. Misra S, Chaturvedi A, Misra NC, Sharma ID. Carcinoma of the gallbladder. The Lancet Oncology. 2003 Mar 1;4(3):167–76.
2. Cazzagon N, Sarcognato S, Catanzaro E, Bonaiuto E, Peviani M, Pezzato F, et al. Primary Sclerosing Cholangitis: Diagnostic Criteria. Tomography. 2024 Jan 7;10(1):47–65.
3. Shah YR, Nombera-Aznaran N, Guevara-Lazo D, Calderon-Martinez E, Tiwari A, Kanumilli S, et al. Liver transplant in primary sclerosing cholangitis: Current trends and future directions. World J Hepatol. 2023 Aug 27;15(8):939–53.
4. Sikora SS, Singh RK. Surgical strategies in patients with gallbladder cancer: nihilism to optimism. J Surg Oncol. 2006 Jun 15;93(8):670–81.
5. Roa JC, García P, Kapoor VK, Maithel SK, Javle M, Koshiol J. Gallbladder cancer. Nat Rev Dis Primers. 2022 Oct 27;8(1):1–22.
6. Buckles DC, Lindor KD, Larusso NF, Petrovic LM, Gores GJ. In primary sclerosing cholangitis, gallbladder polyps are frequently malignant. Am J Gastroenterol. 2002 May;97(5):1138–42.
7. Aloia TA, Járufe N, Javle M, Maithel SK, Roa JC, Adsay V, et al. Gallbladder cancer: expert consensus statement. HPB (Oxford). 2015 Aug;17(8):681–90.
8. Feo CF, Ginesu GC, Fancellu A, Perra T, Ninniri C, Deiana G, et al. Current management of incidental gallbladder cancer: A review. International Journal of Surgery. 2022 Feb;98:106234.
9. Washburn WK, Lewis WD, Jenkins RL. Liver transplantation with incidental gallbladder carcinoma in the recipient hepatectomy. HPB Surg. 1994;8(2):147–9.
10. Ortiz J, Reich D, Joon HB, Martinez O, Manzarbeitia C. Six year disease free survival after liver transplantation in a patient with T3 gallbladder carcinoma: case presentation and review of the literature. World J Surg Oncol. 2006 Jul 14;4:45.
11. von Schönfeld J, Lange R, Bug R, Erhard J. Liver transplantation in a 29-year-old patient with gallbladder carcinoma complicating primary sclerosing cholangitis. Z Gastroenterol. 1998 Nov;36(11):977–81.
12. Schmitt TM, Hughes CB, Bonatti H, Harnois DM, Nguyen JH, Dickson RC, et al. Gallbladder cancer and liver transplantation. Transplant International. 2005;18(1):52–5.
13. Đokic M, Stupan U, Licen S, Trotovsek B. Residual Disease in Lymph Nodes Has No Influence on Survival in Patients with Incidental Gallbladder Cancer – Institution Experience with Literature Review. Radiol Oncol. 2021 Dec 22;56(2):208–15.

JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2024.66375
J Inonu Liver Transpl Inst 2024;2(2):82–84

Case Report

Re-Transplantation in a Pediatric Patient with Hepatorenal Syndrome: A Case Report

Adem Tuncer,[1] Emrah Sahin,[1] Veysel Ersan,[1] Hasret Ayyildiz Civan,[2] Aysel Taktak,[3] Abuzer Dirican,[1] Bulent Unal[1]

[1]Department of General Surgery, Istanbul Aydin University, Istanbul, Türkiye
[2]Department of Pediatric Nephrology, Istanbul Aydin University, Istanbul, Türkiye
[3]Department of Pediatric Gastroenterology, Istanbul Aydin University, Istanbul, Türkiye

Abstract

Hepatorenal syndrome is common in patients with decompensated cirrhosis with severe ascites. Liver transplantation (LT) is the only viable option. Combined Liver-Kidney transplantation (CLKT) is recommended in cases with irreversible renal damage. Recovery of the renal functions following LT is common. We aimed to present a pediatric patient with biliary atresia with full recovery of renal functions after retransplantation for chronic rejection and biliary obstruction.

Living donor LT (LDLT) was performed on a 4-year-old female patient due to biliary atresia 6 years before the admission to our department. The patient suffered chronic anastomotic stenosis, cholangitis, and subsequent chronic rejection. On admission, the patient was severely icteric with massive ascites. The renal function was poor with no urine output and required hemodialysis. CLKT was planned but only LDLT could be performed due to deterioration of the patient's condition. However, the renal function improved dramatically in the postoperative period and the kidney transplant was not performed. The patient had an uneventful postoperative period.

Hepatorenal syndrome, can resolve following LT. The patients who have a high risk of chronic liver failure should be determined before the LT procedure to plant a CLKT and to allocate insufficient organ resources.

Keywords: Hepatorenal syndrome, liver transplantation, retransplantation.

Please cite this article as "Tuncer A, Sahin E, Ersan V, Ayyildiz Civan H, Taktak A, Dirican A, et al. Re-Transplantation in a Pediatric Patient with Hepatorenal Syndrome: A Case Report. J Inonu Liver Transpl Inst 2024;2(2):82–84".

Cirrhosis is the result of irreversible damage to the liver tissue that causes changes in the liver microarchitecture that is defined by extensive fibrosis. The only cure for end-stage liver disease is liver transplantation.[1] Hepatorenal syndrome (HRS) is a complication of severe decompensated cirrhosis. The physiopathological mechanisms that lead to HRS include splanchnic vasodilation, reduced systemic vascular resistance and central hypovolemia, inflammation, altered cardiovascular reflexes, and intraabdominal hypertension related to severe ascites. The prognosis of HRS is poor and mortality reaches 80%.[1,2]

Diagnosis depends on clinical suspicion since no definitive clinical and radiologic diagnostic test exists. HRS can be suspected in a patient with cirrhosis with elevated serum creatinine, oliguria, and low urinary sodium concentration.[4,5] There are no proteinuria or histologic changes and for this reason, the renal failure is reversible.[4,5]

Address for correspondence: Adem Tuncer, MD. Department of General Surgery, Istanbul Aydin University, Istanbul, Türkiye
Phone: +90 537 564 83 18 **E-mail:** ademtuncer89@hotmail.com

Submitted Date: 02.07.2024 **Revised Date:** 01.09.2024 **Accepted Date:** 02.09.2024 **Available Online Date:** 09.10.2024

Medical therapy of HRS includes treatment with a combination of albumin and posterior pituitary lobe hormone analogs such as terlipressin or vasopressin to obtain potent vasoconstriction. Medical treatment is a bridging therapy until definitive therapeutic options are performed. Definitive treatment includes liver transplantation (LT) or combined kidney and liver transplantation (CKLT).[2,5] Spontaneous recovery of the renal function following LT is common.[6] We need criteria to predict whether patients can recover from HRS after LT. This is very important for allocating scarce resources of deceased donor organs to patients who need them.

In the present study, we report a case of a 10-year-old female patient with a prior history of LT due to biliary atresia. She lost the graft due to chronic rejection and had HRS that required hemodialysis at the time of retransplantation. Following the procedure, the renal function of the patient recovered completely.

Case Report

A 10-year-old girl was admitted to our department with abdominal distension, decreased urine output, and deterioration of her general health. The patient had undergone a Kasai procedure for biliary atresia and received a living donor liver transplantation when she was 4 years old. She suffered from stenosis of the biliary anastomosis for which multiple sessions of percutaneous transhepatic biliary catheterization were performed. She suffered from ascending cholangitis and received a broad spectrum of antibiotics. During these episodes, the immunosuppressive therapy was discontinued and she gradually developed graft rejection. Nevertheless, all attempts failed and the patient gradually developed fibrosis of the graft due to poor bile drainage and chronic rejection of the liver graft.

The physical examination upon admission showed that the condition of the patient was deteriorating, and she was severely icteric. The abdomen was distended due to severe ascites and caput medusae were observed. She showed severe sarcopenia and was almost immobile. The patient had severe renal failure with no urine output. She had to receive regular intervals of hemodialysis.

The computerized tomography scan showed that the bile ducts were severely dilated forming lacunar changes, and the liver parenchyma was destroyed (Fig. 1). The laboratory values at admission showed that she had severe renal failure (Table 1). A liver biopsy showed severe fibrosis and destruction of the microarchitecture of the liver parenchyma.

Initially, CKLT was planned. Her mother was a suitable candidate to be a partial liver donor. Her grandmother was a suitable kidney donor. The Child Pugh-Turcot score of the patient was 10 and the PELD score was 23. The perioperative of the patient deteriorated rapidly and our team decided to go through first with the liver transplantation and postpone the renal transplant after the condition of the patient improved. A left lateral lobe transplantation was successfully performed, and the patient required five sessions of hemodialysis in the postoperative period and renal

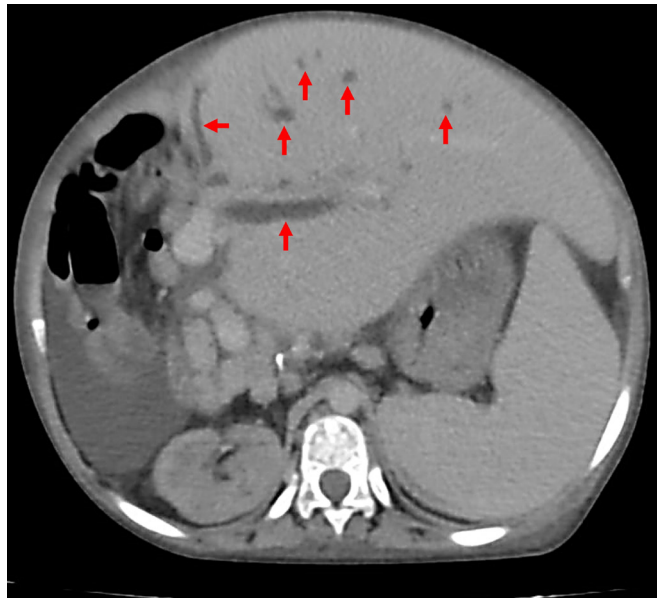


Figure 1. The computerized tomography sections of the liver showing dilated bile ducts and destruction of the normal architecture of the liver (The red arrows show the dilated bile ducts). The contours of the liver are rough indicating chronic liver disease.

Table 1. Laboratory values of the patient at admission and postoperative 9th month.

Laboratory values	Admission	Posttransplant 9th month
ALT	26	32
AST	37	19
GGT	127	29
ALP	194	245
T.Bil	14.8	1.1
D.Bil	11.3	0.22
Alb	2.9	3.9
PTT	15.7	14
INR	1.43	0.99
BUN	100	36
Cr	3.71	0.4

Abbreviations (normal value ranges) of the laboratory parameters: ALT: Alanine aminotransferase (1-40 IU/mL); AST: Aspartate aminotransferase (1-40 IU/mL); GGT: Gamma Glutamyl transferase (1-36 IU/mL); ALP: Alkaline Phosphatase (100-400 IU/mL); T.Bil: Total Bilirubin (<1.2 mg/dL); D.Bil: Direct Bilirubin (<0.2 mg/dL); Alb: Albumin (3-5 g/dL); PTT: Prothrombin Time (>12 sec); INR: International normalized ratio (0.8-1.5); BUN: Blood urea nitrogen (8-36 mg/dL); Cr: Creatinine (0.5-1.1 mg/dL).

functions gradually improved and urine output restored. Our team decided not to perform kidney transplantation. Her postoperative follow-up was uneventful and laboratory values on the postoperative 9th month are summarized in Table 1 showing full recovery of the renal functions. She is currently in the postoperative first year and there is no problem in her post-transplant controls.

Discussion

HRS is a serious complication of severely decompensated cirrhosis. If there is a strong suspicion of HRS, medical treatment should be started rapidly.[7,8] The interval between the diagnosis and LT is a risk factor for renal dysfunction. Prolonged periods of HRS that require renal replacement therapy may indicate permanent kidney damage.[7] LT is the gold-standard treatment for HRs, regardless of the response to medical therapy.[2,5,7] Impaired renal function while awaiting transplantation has been shown to increase morbidity and mortality after liver transplantation because ongoing renal dysfunction following LT is common in this case.[6-9] The risk factors for refractory HRS are resistance to medical therapy and the presence of underlying chronic renal disease that may be suspected in patients with diabetes, hypertension, anatomic problems in the kidneys observed during imaging, and the presence of proteinuria (>2 g/day).[10] Recovery of the renal functions following liver transplantation may be prolonged to a year after the procedure.[6,11] Determination of the patients that will recover is important for the allocation of the limited source of organs and also the prevention of unnecessary renal transplant procedures.

In the present study, our patient suffered from liver failure due to chronic rejection and she was also taking tacrolimus as an immunosuppressive therapy. A common side effect of tacrolimus is renal toxicity. Both liver failure and the use of tacrolimus played an important role in the development of HRS in our patient. We have performed a thorough literature search and have seen no information about concomitant chronic rejection and HRS in pediatric patients undergoing living donor liver transplantation. Our case report is unique because we report a pediatric patient suffering chronic rejection and HRS that resolved following liver retransplantation.

In conclusion, LT is the gold standard treatment for patients with end-stage liver failure and HRS. If the duration of HRS is prolonged, patients may suffer from irreversible renal damage. These patients require CLKT. The patients with refractory HRS should be determined before the LT procedure to plan the necessary therapeutic option.

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.A.; Design – T.A.; Supervision – E.V.; Materials – T.A., C.A.H.; Data collection &/or processing – S.E., D.A.; Analysis and/or interpretation –T.A., E.V.; Literature search – T.A.; Writing – T.A.; Critical review – D.A., U.B.

References

1. Ranawaka R, Dayasiri K, Gamage M. Combined liver and kidney transplantation in children and long-term outcome. World J Transplant. 2020;10(10):283-90.
2. Hasan I, Rashid T, Chirila RM, Ghali P, Wadei HM. Hepatorenal syndrome: pathophysiology and evidence-based management update. Rom J Intern Med. 2021;59(3):227-61.
3. Wadei HM, Mai M, Ahsan N, Gonwa T. Hepatorenal Syndrome: Pathophysiology and Management. Clinical Journal of the American Society of Nephrology, 2006;1(5): 1066–79.
4. Ginès P, Schrier RW. Renal failure in cirrhosis. N Engl J Med, 2009;361(13): 1279–90.
5. De Mattos ÁZ, de Mattos AA, Méndez-Sánchez N. Hepatorenal syndrome: Current concepts related to diagnosis and management. Ann Hepatol, 2016;15(4): 474–81.
6. Northup PG, Argo CK, Bakhru MR, Schmitt TM, Berg CL, Rosner MH. Pretransplant predictors of recovery of renal function after liver transplantation. Liver Transpl. 2010;16(4):440-6.
7. European Association for the Study of the Liver EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol. 2018;69(2):406–60.
8. Chiang CW, Lin YJ, Huang YB. Terlipressin-Induced Peripheral Cyanosis in a Patient with Liver Cirrhosis and Hepatorenal Syndrome. Am J Case Rep. 2019; 20:5-9.
9. Ruiz R, Kunitake H, Wilkinson AH, Danovitch GM, Farmer DG, Ghobrial RM et al. Long-term analysis of combined liver and kidney transplantation at a single center. Arch Surg. 2006;141(8):735–41.
10. Nadim MK, Sung RS, Davis CL, Andreoni KA, Biggins SW, Danovitch GM et al. Simultaneous liver-kidney transplantation summit: current state and future directions. Am J Transplant. 2012;12(11):2901-8.
11. Davis CL, Feng S, Sung R, Wong F, Goodrich NP, Melton LB et al. Simultaneous liver-kidney transplantation: evaluation to decision making. Am J Transplant.2007;7(7): 1702-9.

JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2024.35229
J Inonu Liver Transpl Inst 2024;2(2):85–87

Case Report

Living Donor Liver Transplantation in Patients with Crigler-Najjar Syndrome Type 1: Report of Three Cases

Esra Guzelaltuncekic, Hasret Ayyildiz Civan, Ferhat Sari, Feyza Sonmez Topcu, Huseyin I. Toprak, Adem Tuncer, Emrah Sahin, Veysel Ersan, Bulent Unal, Abuzer Dirican

Istanbul Aydin University, Florya VM Medical Park Practice and Research Hospital, Organ Transplantation Center, İstanbul, Türkiye

Abstract

Crigler-Najjar syndrome (CNS) type 1 is a rare autosomal recessive disorder caused by mutations in the UGT1A1 gene, leading to a complete deficiency of the enzyme uridine diphosphate-glucuronosyltransferase (UGT1A1). This enzyme deficiency results in severe unconjugated hyperbilirubinemia, which poses a high risk of neurological complications, particularly kernicterus, if left untreated. While phototherapy provides temporary relief in early childhood, its diminishing effectiveness over time requires liver transplantation (LT) as the only definitive treatment. In this report, we present three pediatric cases of CNS type 1 treated successfully with living donor liver transplantation (LDLT). The first case, an 11-year-old girl, presented severe jaundice and neurological impairment but showed significant improvement in bilirubin levels and neurological symptoms after transplantation. The second case, a 12-year-old boy, had persistently high bilirubin levels despite phototherapy, which normalized after LDLT. The third case, an 11- month-old infant without prior treatment, also achieved complete normalization of bilirubin levels after transplantation. These cases demonstrate that LDLT is highly effective in preventing kernicterus, normalizing bilirubin levels, and improving clinical outcomes in patients with type 1 CNS. Long-term post-transplant care, including immunosuppressive therapy and regular follow- up, remains essential for optimal management and patient well-being.

Keywords: Autosomal recessive, crigler-najjar syndrome, liver transplant, orthotopic liver transplantation, ugt1a1, unconjugated bilirubin.

Please cite this article as "Guzelaltuncekic E, Ayyildiz Civan H, Sari F, Sonmez Topcu F, Toprak HI, Tuncer A, et al. Living Donor Liver Transplantation in Patients with Crigler-Najjar Syndrome Type 1: Report of Three Cases. J Inonu Liver Transpl Inst 2024;2(2):85–87".

Crigler-Najjar syndrome (CNS) is a rare autosomal recessive disorder characterized by elevated levels of unconjugated bilirubin due to mutations in the UGT1A1 gene located on chromosome 2.

The syndrome is classified into two types: CNS type 1 and CNS type 2. CNS type 1, the more severe form of the CNS, manifests shortly after birth and leads to persistently high bilirubin levels throughout life. Patients with CNS type 1 are at high risk for bilirubin-induced neurological dysfunction (BIND), ranging from mild reversible impairments to severe irreversible encephalopathy known as kernicterus.

The primary cause of CNS type 1 is the complete absence of hepatic uridine diphosphate- glucuronosyltransferase (UGT1A1) activity, leading to accumulation of unconjugated bilirubin in the bloodstream. This condition is typically diagnosed by detecting elevated unconjugated bilirubin levels in serum or by genetic analysis that identifies mutations in the UGT1A1 gene.[4,5] The global incidence of

Address for correspondence: Hasret Ayyildiz Civan, MD. Istanbul Aydin University, Florya VM Medical Park Practice and Research Hospital, Organ Transplantation Center, İstanbul, Türkiye
Phone: +90 444 4 484 **E-mail:** hasretayyildiz@yahoo.com

Submitted Date: 23.08.2024 **Revised Date:** 18.09.2024 **Accepted Date:** 18.09.2024 **Available Online Date:** 09.10.2024

CNS type 1 is estimated at 1 in 1,000,000 live births, with a higher prevalence in populations where consanguineous marriages are common.[1,2]

Treatment Options

For patients with CNS type 1, daily phototherapy (PT) is the main initial treatment, particularly in the neonatal period. Phototherapy helps convert unconjugated bilirubin into a more water-soluble form, allowing it to be excreted through the bile. However, the effectiveness of phototherapy decreases as the skin thickens with age, leading to a reduced ability to lower bilirubin levels. Plasmapheresis and exchange transfusions can provide temporary relief by mechanically removing unconjugated bilirubin from the circulation, but these are not long-term viable options. Pharmacological approaches, such as enzyme inducers such as phenobarbital, are ineffective in CNS type 1 due to a complete lack of enzyme activity.

Liver transplantation (LT) is the only definitive treatment for CNS type 1.[3] Transplanted livers provide the missing UGT1A1 enzyme, allowing for proper conjugation and excretion of bilirubin. Studies have shown that liver transplantation not only normalizes bilirubin levels, but also reduces the risk of long-term neurological complications. However, LT is associated with lifelong immunosuppressive therapy and the risk of posttransplant complications.

This report presents three cases of pediatric patients with CNS type 1 who successfully underwent living donor liver transplantation (LDLT), resulting in significant clinical improvements.

Case Report

Case 1 — An 11-year-old Palestinian girl, weighing 30 kg and measuring 131 cm in height, presented persistent jaundice, delayed speech, and walking difficulties. Laboratory results showed an indirect bilirubin level of 21.1 mg/dL, while liver function tests, thyroid function tests, and urinalysis were normal. No glucose-6-phosphate dehydrogenase (G6PDH) or pyruvate kinase deficiency was detected, and there was no ABO or Rh incompatibility between the mother and the patient. Genetic analysis revealed a homozygous mutation in the UGT1A1 gene, confirming the diagnosis of Crigler-Najjar syndrome type 1 (CNS1).

The patient had been receiving 8 hours of home phototherapy daily for 10 years, but bilirubin levels remained elevated at 24.7 mg/dL (indirect bilirubin: 24.1 mg/dL, direct bilirubin: 0.6 mg/dL) when admitted for liver transplantation. Abdominal CT and brain magnetic resonance imaging did not show pathological findings. She underwent a living donor left lobe liver transplantation (LDLT) from her mother. The surgery involved duct-to-duct anastomosis of the bile duct and placement of a 5F trans-cystic feeding catheter. The patient was discharged on postoperative day 11. She experienced postoperative bacterial cholangitis, which was successfully treated with antibiotics. At the 4-month follow-up, the biliary catheter was removed and her total bilirubin level had decreased to 0.5 mg/dL (direct bilirubin: 0.2 mg/dL, indirect bilirubin: 0.3 mg/dL). Her bilirubin levels remained stable under immunosuppressive treatment.

Case 2 — A 12-year-old Turkish boy, weighing 37 kg and standing 153 cm tall, presented with an indirect bilirubin level of 28.2 mg/dL. Liver and thyroid function tests were normal, and no G6PDH or pyruvate kinase deficiency was found. There was ABO and Rh incompatibility between the patient and his mother. Despite long-term phototherapy, patient bilirubin levels remained elevated. Genetic testing revealed a homozygous mutation in the UGT1A1 gene, confirming the diagnosis of CNS1.

The patient underwent LDLT from his aunt, a blood-matched donor. During surgery, two arteries and a single bile duct were identified. The bile duct was duct-to-duct anastomosed, and a trans- coledochal 5F feeding catheter was placed. He was discharged on postoperative day 8. At 4 months of follow-up, the biliary catheter was removed and his total bilirubin level had decreased to 0.9 mg/dL (direct bilirubin: 0.3 mg/dL, indirect bilirubin: 0.6 mg/dL). His bilirubin levels remained stable under immunosuppressive treatment.

Case 3 — An 11-month-old Jordanian boy, weighing 9.8 kg and measuring 72 cm in height, had a history of persistent indirect hyperbilirubinemia since birth. The older sister of the patient had died at the age of 6 years due to jaundice, although the cause was not determined. Liver enzymes were normal, but total bilirubin was elevated at 28 mg/dL (direct bilirubin: 0.8 mg/dL). The patient had not received phototherapy or plasma exchange therapy prior to transplantation. Genetic testing identified a homozygous mutation in the UGT1A1 gene, confirming CNS1.

He underwent a reduced-size LDLT from his father. The surgery was uneventful, and the patient was discharged on postoperative day 10. At 4 months of follow-up, the biliary catheter was removed and his total bilirubin had decreased to 0.5 mg / dl (direct bilirubin: 0.3 mg / dl, indirect bilirubin: 0.2 mg/dL). His bilirubin levels remained stable under immunosuppressive treatment.

Discussion

Crigler-Najjar syndrome (CNS) is a rare congenital condition that results in severe unconjugated hyperbilirubinemia due to the absence or severe reduction of UGT1A1 enzyme activity. The distinction between CNS type 1 and type

2 is critical, as it dictates treatment approaches. CNS type 1 patients lack any UGT1A1 enzyme activity, leading to dangerously high levels of bilirubin that can cause irreversible neurological damage if not managed appropriately. In contrast, patients with CNS type 2 retain partial enzyme activity and respond well to pharmacological treatments, such as phenobarbital, which effectively reduces bilirubin levels in CNS type 2 but does not have an effect in CNS type 1.

The management of CNS type 1 is complex, with phototherapy being the mainstay of treatment during early childhood. Although phototherapy can significantly reduce bilirubin levels, its efficacy decreases as the skin thickens with age, making it less effective in older children. Furthermore, prolonged use of phototherapy is not without its complications, including skin damage and the risk of developing resistance to phototherapy.[6,7] For these reasons, liver transplantation (LT) is the only definitive treatment for CNS type 1, providing the missing enzyme necessary for bilirubin conjugation and excretion.

All three cases presented in this report underwent living donor liver transplantation (LDLT) with favorable outcomes. Posttransplant, bilirubin levels normalized in all patients and none required further phototherapy. Although LT is curative for the metabolic defect, long-term management of CNS type 1 patients includes monitoring for potential complications related to immunosuppressive therapy, such as infection and graft rejection. It is important to note that while LT corrects the metabolic defect, the underlying genetic mutation remains and affected individuals may pass the mutation to their offspring.[8,9]

Neurological outcomes in CNS type 1 patients who developed kernicterus prior to transplantation remain a topic of debate.[10] In some cases, LT has been shown to stop the progression of neurological symptoms, while in others, existing neurological damage may persist despite successful transplantation. In our 11-year-old patient, mild improvement in speech and gait was observed after transplantation, suggesting some degree of neurological recovery. However, more research is required to fully understand the potential for neurological improvement in patients with CNS type 1 after LT.

Conclusion

Crigler-Najjar syndrome type 1 is a rare but severe genetic disorder that requires early diagnosis and intervention to prevent irreversible neurological damage, such as kernicterus. While phototherapy provides temporary relief in early childhood, liver transplantation remains the only definitive treatment, as it restores the enzyme necessary for bilirubin conjugation.

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 – E.G.; Design – H.A.C.; Supervision – A.D.; Materials – F.S.; Data collection &/or processing – F.S.T.; Analysis and/or interpretation – H.İ.T.; Literature search – A.T., E.Ş.; Writing – V.E., E.G., H.A.C.; Critical review – B.Ü.

References

1. Kovačić Perica M, Todorić I, Marčinković N, Džepina P, Aničić MN, Mrzljak A, Vuković J. Case report: Crigler-Najjar syndrome type 1 in Croatia-more than a one in a million: a case series. Front Pediatr 2023;11:1276349.
2. Neeraj Kumar, Babli Kumari, Sarfaraz Ahmad. An Unusual Case of Type I Crigler–Najjar Disease in a Young Adult: A Case Report. Type I Crigler-Najjar Disease in Young Adult. Journal of Acute Care. September–December 2022:vol 1;3.
3. Alharbi FA, Al-Shammari NR, Aloqeely KM. Liver Transplantation in a Child With Crigler-Najjar Syndrome Type I: A Case Report With Review of the Literature. Cureus 2023;15(7):e42064.
4. Kadakol A, Ghosh SS, Sappal BS, Sharma G, Chowdhury JR, Chowdhury NR. Genetic lesions of bilirubin uridine-diphosphoglucuronate glucuronosyltransferase (UGT1A1) causing Crigler-Najjar and Gilbert syndromes: correlation of genotype to phenotype. Hum Mutat 2000;16(4):297-306.
5. Shevell MI, Majnemer A, Schiff D. Neurologic perspectives of Crigler-Najjar syndrome type I. J Child Neurol 1998;13(6):265-9.
6. Bosma PJ, Seppen J, Goldhoorn B, Bakker C, Oude Elferink RP, Chowdhury JR, Chowdhury NR, Jansen PL. Bilirubin UDP-glucuronosyltransferase 1 is the only relevant bilirubin glucuronidating isoform in man. J Biol Chem 1994;269(27):17960-4. Erratum in: J Biol Chem 1994;269(41):2542. PMID: 8027054.
7. Bach Knudsen K, Ebbesen F. Crigler-Najjars sygdom type 1 hos børn [Crigler-Najjar type 1 in children]. Ugeskr Laeger 2013;175(42):2489-91. Danish. PMID: 24629116.
8. Erlinger S, Arias IM, Dhumeaux D. Inherited disorders of bilirubin transport and conjugation: new insights into molecular mechanisms and consequences. Gastroenterology 2014;146(7):1625-38. Epub 2014 Apr 1. PMID: 24704527. 9
9. Rossi F, Francese M, Iodice RM, Falcone E, Vetrella S, Punzo F, De Vita S, Perrotta S. Disordini ereditari del metabolismo della bilirubina [Inherited disorders of bilirubin metabolism]. Minerva Pediatr 2005;57(2):53-63. Italian. PMID: 15985997.
10. Bhutani VK, Johnson-Hamerman L. The clinical syndrome of bilirubin-induced neurologic dysfunction. Semin Fetal Neonatal Med 2015;20(1):6-13. Epub 2015 Jan 7. PMID: 25577653.