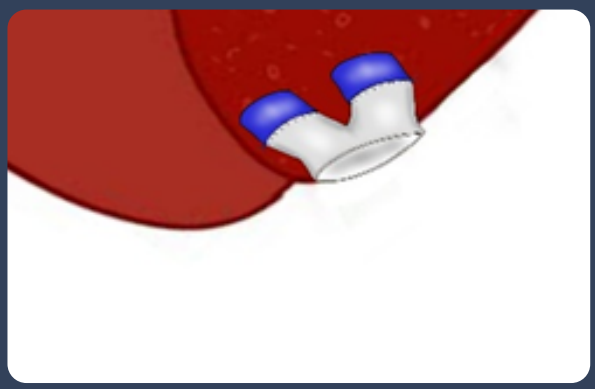
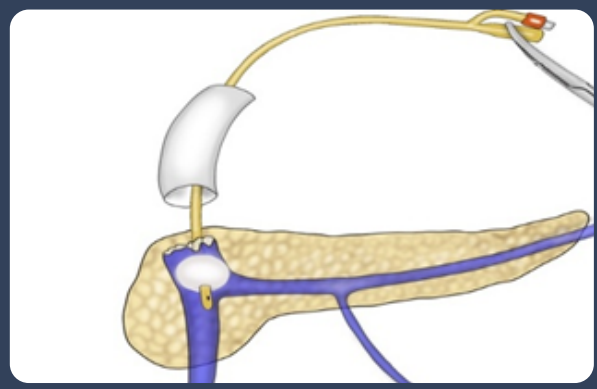
JILTI

The Official Journal of the Inonu Liver Transplantion Institute

A Rare Case in Living Donor Liver Transplantation: Graft-to-Graft of Portal Vein Anastomosis





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Journal of Inonu Liver Transplantation Institute

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

Aim and Scope

Aim

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

Overview

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

Scope

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

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

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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 provided a contribution but do not meet all four criteria should be recognized separately on the title page and in the Acknowledgements section at the conclusion of the manuscript.
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Ethics Policy

The Editorial Board of the Journal of Inonu Liver Transplantation Institute and the Publisher adheres to the principles of the International Council of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), the Council of Science Editors (CSE), the Committee on Publication Ethics (COPE), the US National Library of Medicine (NLM), the World Medical Association (WMA) and the European Association of Science Editors (EASE).
In accordance with the journal's policy, an approval of research protocols by an ethics committee in accordance with international agreements "WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects (last updated: October 2013, Fortaleza, Brazil)" , "Guide for the care and use of laboratory animals (8th edition, 2011)" and/or "International Guiding Principles for Biomedical Research Involving Animals (2012)" is required for all research studies. If the submitted manuscript does not include ethics committee approval, it will be reviewed according to COPE's guideline (Guidance for Editors: Research, Audit and Service Evaluations). If the study should have ethical approval, authors will be asked to provide ethical approval in order to proceed the review process. If they cannot provide ethical approval, their manuscript will be rejected and also their institutions and when needed, the related bodies in their country will be informed that such studies must have ethics committee approval. If they provide approval, review of the manuscript will continue.
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All authors are required to declare what support they received to carry out their research. Declaring funding sources acknowledges funders' contributions, fulfills funding requirements, and promotes greater transparency in the research process.
Each author must individually declare all sources of funding received for the research submitted to the journal. This information includes the name of granting agencies, grant numbers, and a description of each funder's role. If the funder has played no role in the research, this must be stated as well.
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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.

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

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

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

Final approval of the version to be published; AND

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

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

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

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

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Letter to the editor: A "Letter to the Editor" is a type of manuscript that discusses important or overlooked aspects of a previously published article. This type of manuscript may also present articles on topics within the scope of the journal that are of interest to readers, particularly educational cases. Additionally, readers may use the "Letter to the Editor" format to share comments on published manuscripts.

Key Features:

- The "Letter to the Editor" should be unstructured and should not include an abstract, keywords, tables, figures, images, or other media.
- The manuscript being commented on must be properly cited within the "Letter to the Editor."
- Our journal considers all feedback on published articles. However, we emphasize that comments should be scientifically relevant and meaningful to the discussion. Irrelevant or unfounded comments may be rejected.

ICMJE Guidelines:

Our journal adheres to the guidelines set forth by the ICMJE (International Committee of Medical Journal Editors). According to ICMJE, "Letters to the Editor" should be a platform for responsible debate, critique, and discussion. These letters may raise substantial criticisms or questions about previously published articles, and authors of the discussed articles are expected to respond to these criticisms.

ICMJE also notes that editors have the right to edit these letters for length, grammar, and style. However, all letters should contribute constructively to the academic discussion and critique, and those deemed irrelevant or unfounded may be rejected.

You can view the ICMJE guidelines on "Correspondence" here.

Table 1. Limitations for each manuscript type.

Type of manuscript	Wordlimit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	4000-5000	350-400	40-50	6	6
Review Article	5000-6000	350-400	50-60	6	10
Meta analysis	5000	350	50	6	10
Case 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 350*400 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.
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Limitations, drawbacks, and shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.
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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].
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Original Research

Evaluation of Correlation Between Pleth Variability Index and Blood Lactate Level in Living Liver Donors

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Abstract

Objectives: This study primary objective to compare simultaneous Pleth Variability Index (PVI) and blood lactate measurements taken during different surgical phases to determine whether PVI is a reliable parameter for fluid monitoring in this patient group. Our secondary objective is to monitor changes in PVI in fluid-restricted liver donors.

Methods: The study was conducted in ASA I–II living liver donors aged 18–55 undergoing right hepatectomy; patients with cardiovascular disease or drug allergies were excluded. PVI and PI were recorded noninvasively using the Masimo SET® device. Measurements were taken at surgical start (T1), 1 hour (T2), end of surgery (T3), postoperative 3 hours (T4) and 24 hours (T5): AST, ALT, BUN, creatinine and blood lactate; and at T1–T4: SpO2, heart rate, arterial pressures, CVP, urine output, blood loss, administered fluid volumes, PVI and PI. Anesthesia and surgery durations, graft weight, and transfused blood/products were recorded.

Results: Our study involved 51 living donors (31 males and 20 females) with a mean age of 28.78 ± 9.64 years. In the intra-group evaluation of PVI, no significant differences were observed across all time periods, but significant correlations in lactate levels were found at multiple time points ($p<0.05$). A notable correlation between PVI and lactate levels was identified during the T3 period. Additionally, significant changes in sodium and creatinine were observed in T3 and T4 ($p<0.05$), along with an increase in bleeding and a decrease in urine output during the first hour of surgery (T2) ($p<0.05$).

Conclusion: We found a correlation between lactate levels at the end of surgery and PVI values in liver transplant donors. Despite adequate hepatic blood flow, hepatocyte damage during surgery may impact lactate metabolism. Therefore, further studies are needed to explore the relationship between PVI and lactate levels in various surgical procedures.

Keywords: Liver translantation, living liver donor, pleth variability index, lactate

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During donor hepatectomy, goal-directed fluid therapy is implemented to reduce bleeding and limit the use of blood products. Close monitoring of fluid status is essential to ensure adequate tissue perfusion. In traditional fluid management regimens, fluid monitoring has been conducted using static parameters of cardiac preload, such as central venous pressure (CVP) measurements from central venous catheters or pulmonary artery wedge pressure (PAWP). However, nowadays, dynamic fluid monitoring can be performed non-invasively using

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the Masimo Radical-7 monitor to measure the Pleth Variability Index (PVI).[1] In fluid-restrictive regimens, invasive methods, such as monitoring blood lactate levels, can be used to closely track tissue oxygenation in a static and invasive manner.

With the advancement of monitoring methods today, many invasive techniques have been replaced by non-invasive measurement techniques. The Masimo Radical-7, through a finger probe, can non-invasively measure parameters such as blood hemoglobin levels, tissue fluid, and oxygenation levels, which can provide advantages in major surgeries like liver transplantation. Laboratory measurements of lactate from patient blood are a reliable method to assess tissue oxygenation and ensure adequate volume replacement. However, in live liver donors, the rapid increase in blood lactate levels following liver resection and manipulation makes it an inaccurate indicator of tissue perfusion adequacy. Additionally, this method is invasive and time-consuming.[2]

The accuracy and reliability of fluid monitoring using the PVI and its correlation with lactate levels have been tested. In major abdominal surgeries utilizing PVI for fluid monitoring, low lactate levels have been achieved, emphasizing its potential reliability.[3] The aim of this study is to compare the PVI and blood lactate values simultaneously obtained during different surgical phases in living liver transplantation donors and to investigate the reliability of PVI in this patient group.

Methods

This study was conducted after obtaining approval from the Malatya Clinical Research Ethics Committee (2015/121) and patient consent, involving living donors for liver transplantation undergoing right hepatectomy, classified as ASA I-II and aged between 18-55 years. Patients were selected by random assignment. Patients that were rejected for participation, had a history of cardiovascular disease, or had allergies to medications to be used during the operation were excluded from the study. The primary objective of these products is to determine whether there is a relationship between PVI and lactate levels. Our secondary objective is to monitor changes in PVI in fluid-restricted liver donors. This study was conducted prospectively and randomly in living liver donors.

Without the application of premedication, patients were brought into the operating room where electrocardiography (ECG), peripheral oxygen saturation (SpO_2), and non-invasive blood pressure monitoring were performed. All patients had a peripheral venous access established through the back of the hand using a 20-gauge intravenous catheter. After preoxygenation with 100% O2, induction was achieved with 1 mg/kg of 2% lidocaine, 1 µg/kg of fentanyl, 5 mg/kg of thiopental, and 0.1 mg/kg of vecuronium. After achieving adequate muscle relaxation, patients were intubated, and isoflurane (Forane Liquid Abbott 100 mL) was administered in concentrations ranging from 0.5% to 1.5% using a 50/50 mixture of oxygen and air. A second peripheral venous access was established using a 16-gauge intracath. Invasive arterial blood pressure monitoring was accomplished by catheterizing the radial artery on the non-dominant side. A three-way 7.5 French central venous catheter was placed in the right internal jugular vein for the purpose of monitoring CVP. A pulse oximeter probe (Masimo SET® Rainbow, Masimo Corp., Irvine, CA) was preferably placed on the ring finger of the left hand, with the surrounding area covered to prevent interference from ambient light. By connecting to a Masimo monitor equipped with PVI software, the perfusion index (PI) and PVI variables were automatically measured. Additionally, remifentanil (0.25 µg/kg/min) and cisatracurium (0.5 µg/kg/h) were added as infusions for maintenance.

During the liver dissection phase, IV crystalloids were administered in a restricted manner. When the CVP exceeded 10 mmHg and urine output was less than 0.5 ml/kg/hr, 5-10 mg of furosemide was given.

Blood tests were conducted and recorded at the beginning of the surgery (T1), after the first hour (T2), at the end of the surgery (T3), three hours postoperatively (T4), and 24 hours postoperatively (T5) for AST, ALT, BUN, creatinine, and blood lactate levels. Additionally, parameters such as SpO_2, heart rate, systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), CVP, urine output, blood loss, amounts of crystalloids and colloids administered, PVI, and PI were measured and recorded during the T1, T2, T3, and T4 periods.

Anesthesia and surgery durations, the weight of the graft obtained, and the administered blood and blood products, including noradrenaline, ephedrine, mannitol, and furosemide, were documented.

For postoperative analgesia, 0.05 mg/kg of IV morphine was administered following the removal of the liver graft. At the end of the operation, patients were extubated after the neuromuscular blockade effect was antagonized with neostigmine and atropine. In the postoperative recovery unit, a patient-controlled analgesia device was programmed with an infusion: no bolus of 15 mg and a lockout interval of 10 minutes. Patients with an Aldrete recovery score of 10 were transferred to the surgical intensive care unit.

Power Analysis

To achieve this aim, a theoretical sample size calculation was conducted using G*Power (version 3.1.9.3). This calculation, based on an assumed effect size of 0.50, an alpha error of 0.05, and a study power of 0.80, indicated that a minimum of 51 patients would be required for to determine the correlation between PVİ and lactate.

Statistical Analysis

The statistical analysis of the data was performed using the SPSS 16.0 (SPSS version 16.0 (SPSS Inc., Chicago, IL). software package. Data related to quantitative variables were presented as mean (± standard deviation, SD), while data related to qualitative variables were reported as frequency (n) and percentage (%). The normality of the quantitative variable data was assessed using the Shapiro-Wilk normality test ($p > 0.05$). The change of variables over time was analyzed using the Wilcoxon test, and the relationships between variables were evaluated using the Spearman Rank Correlation analysis. Fisher's Exact Chi-Square test and Pearson Chi-Square test were employed for the statistical evaluation of qualitative variables. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 51 cases, consisting of 31 male and 20 female living donors who underwent kidney transplantation, were included in the study. The distribution of the demographic characteristics of the donors is presented in Table 1. In the intra-group evaluation of PVI, there was no significant difference in correlation across all time periods.

In the intra-group evaluation of blood lactate levels, the correlations between T1 and T2, T4, and T5 values, as well as between T2 and T3, T4 values, and between T4 and T3, T5 values were found to be statistically significant ($p<0.05$).

In the inter-group evaluation of blood lactate levels, a statistically significant correlation was observed between PVI and lactate level during the T3 period (Fig. 1). The ALT, AST, and lactate values of the donors are provided in Table 2.

Table 1. Distribution of donors' demographic characteristics (mean±SD or number)

Gender (Female/Male)	20/31
ASA (I/II)	15/36
Age	28.78±9.64
Height (cm)	170.50±9.04
Weight (kg)	69.60±11.76
Body mass index	23.93±3.39
Duration of anesthesia (min)	439.31±98.09
Surgical duration (min)	370±96.48

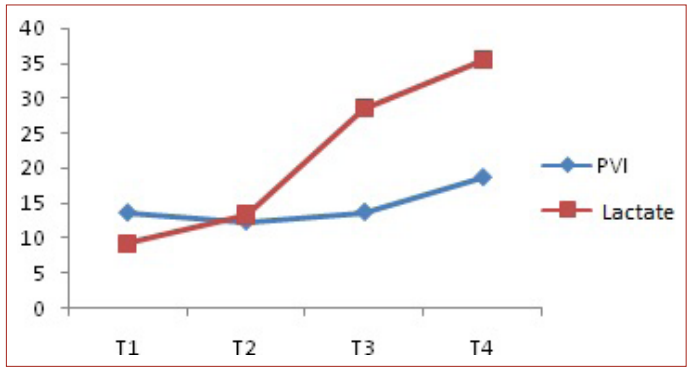

Figure 1. Start of surgery (T1), 1st hour of surgery (T2), End of surgery (T3), 3rd hour postoperatively (T4) change in PVI and lactate values over time.

Na, BUN, Creatinine values of donors are given in Table 3. The bleeding amounts of the donors and the amounts of crystalloid and colloid given are given in Table 4.

Hemodynamic data of the cases are given in Table 5. The liver graft weight of the donors, ICU and hospital stay conditions are indicated in Table 6.

Discussion

In our study aimed at comparing the correlation between PVI and lactate levels in kidney transplant donors, a correlation was found between the PVI measured at the end of the surgery (T3) and the lactate values. However, no correlation was detected between the PVI and lactate values measured at the beginning of the surgery (T1), at the first hour of the surgery (T2), and at the third hour postoperatively (T4).

Since intravenous lactate-containing solutions (such as Ringer's Lactate) can alter blood lactate levels during the operation,[2] they were not used in our study. Lactate levels provide an indirect yet sensitive measurement of organ perfusion. Lactate is clearly associated with energy deficiencies and tissue hypoxia due to intravascular volume adequacy and the redistribution of blood flow. Perioperative blood lactate levels can affect postoperative complications and the average length of hospital stay.[4] Hyperlactatemia is associated with morbidity and mortality risks in patients with liver failure.[2] Due to changes in hepatic blood flow and lactate metabolic capacity after surgery, lactate concentration tends to increase following donor hepatectomy. Increases in hepatic blood flow and lactate concentration may help predict the prognosis of patients undergoing liver resection due to hepatoma. However, the relationship between the liver profile post-liver resection and hyperlactatemia is less well understood.[2]

Shin et al.[2] assessing graft function in their study comparing changes in lactate and prothrombin time between cadaveric and living donor liver transplants during the early

Table 2. Donors' ALT, AST, Lactate values (mean±SD)

	T1	T2	T3	T4	T5
ALT	16.29±9.27	43.70±27.12	127.35±170.58	161.31±197.83	229.92±228.94
	p<0.001*	p<0.001*	p<0.001*	p<0.001*	
AST	20.96±8.00	45.86±23.48	130.09±145.67	169.92±189.59	201.82±171.33
	p<0.001*	p<0.001*	p<0.001*	p<0.001*	
Lactate	9.23±4.01	13.28±6.38	28.51±10.18	35.42±14.44	12.28±5.59
	p<0.001*	p<0.001*	p<0.001*	p<0.001*	

*p<0.05 Change relative to T1. (T1) Start of surgery, (T2) 1st hour of surgery, (T3) End of surgery, (T4) 3rd hour postoperatively, (T5) 24th hour postoperatively.

Table 3. Donors' Na, BUN, Creatinine values (mean±SD)

	T1	T2	T3	T4	T5
Na	138.62±2.35	138.27±2.39	140.39±2.27	138.68±2.44	135.92±2.55
	p=0.202	p<0.001*	p=0.963	p<0.001*	
BUN	13.11±3.89	13.03±3.77	13.23±3.66	12.60±3.75	11.84±3.89
	p=0.955	p=0.480	p=0.073	p<0.001*	
Creatinine	0.67±0.09	0.68±0.09	0.71±0.13	0.75±0.14	0.63±0.10
	p=0.092	p<0.001*	p<0.001*	p<0.001*	

*p<0.05 Change relative to T1. (T1) Start of surgery, (T2) 1st hour of surgery, (T3) End of surgery, (T4) 3rd hour postoperatively, (T5) 24th hour postoperatively.

Table 4. Donors' urine and bleeding volumes, crystalloid and colloid volumes administered (mean±SD)

	T1	T2	T3	T4
Urine	150.19±181.99	126.27±152.61	477.84±364.79	243.13±160.64
	p=0.522	p<0.001*	p<0.001*	
Bleeding	0.98±7.00	63.23±33.64	260.88±91.49	18.43±20.06
	p<0.001*	p<0.001*	p<0.001*	
Crystalloid	273.52±227.23	195.29±256.84	1137.05±660.63	462.78±173.79
	p=0.121	p<0.001*	p<0.001*	
Colloid	0±0	9.80±70.01	378.43±274.09	1.96±14.00
	p=0.317	p<0.001*	p=0.317	

*p<0.05 Change relative to T1. (T1) Start of surgery, (T2) 1st hour of surgery, (T3) End of surgery, (T4) 3rd hour postoperatively.

reperfusion period, reported that lactate and INR values normalized more rapidly in cadaveric recipients within one hour post-reperfusion. They attributed this to the larger size of the grafts in cadaveric cases. In contrast, our study focused on liver donors.

M. Feissel et al.[5] found that the PVI obtained automatically by the pulse oximeter is a reliable indicator of fluid responsiveness. It has been published that it can noninvasively predict fluid responsiveness in mechanically ventilated patients undergoing non-cardiac surgery under general anesthesia,[6] in mechanically ventilated patients undergoing major surgery,[1] in mechanically ventilated patients in the ICU,[7] in patients after cardiopulmonary bypass,[8] and in mechanically ventilated patients in early-phase septic shock.[9] Additionally, Tsuchiya et al.[10] reported that PVI could predict decreases in mean arterial pressure during anesthesia induction with propofol, suggesting that this measurement could be useful in identifying the occurrence of severe hypotension in high-risk patients during anesthesia induction.

Wenqing Lu et al.[11] reported that in patients undergoing mechanical ventilation under general anesthesia, extracellular fluid volume is beneficial when using noninvasive continuous hemodynamic monitoring with PVI. In line with these studies, our findings showed that PVI values were correlated with the CVP values of the patients.

Forget et al.[3] demonstrated that when fluid management was guided by PVI in patients undergoing major abdomi-

Table 5. Donors' SpO_2 and Heart Rate SAP, DAP, MAP, CVP, PVI, PI values (mean±SD)

	T1	T2	T3	T4
SpO_2	99.07±1.33	99.35±1.09	99.62±0.91	97.94±1.89
	p=0.094	p<0.001*	p<0.001*	
Heart rate	84.52±20.13	80.92±14.17	97.88±12.44	98.41±15.88
	p=0.249	p<0.001*	p<0.001*	
SAP	109.52±18.36	109.96±16.09	111.09±16.38	142.00±20.96
	p=0.656	p=0.459	p<0.001*	
DAP	71.01±14.06	67.43±9.30	67.52±14.80	86.03±12.50
	p=0.170	p=0.123	p<0.001*	
MAP	85.47±16.19	83.58±12.09	83.21±14.90	103.92±13.90
	p=0.623	p=0.367	p<0.001*	
CVP	10.19±3.38	10.27±3.31	10.27±3.81	7.62±2.68
	p=1.00	p=0.754	p<0.001*	
PVI	13.59±8.43	12.29±5.61	13.68±6.75	18.74±9.42
	p=0.746	p=0.577	p<0.001*	
PI	4.74±3.22	2.83±2.57	1.27±1.67	3.46±2.31
	p<0.001*	p<0.001*	p<0.001*	

*p<0.05 Change relative to T1. (T1) Start of surgery, (T2) 1st hour of surgery, (T3) End of surgery, (T4) 3rd hour postoperatively.

Table 6. Donor liver graft weight, length of stay in the ICU and hospital (mean±SD)

KC graft weight (g)	736.56±149.30
Stay in ICU (days)	3.58±2.88
Hospital stay (days)	8.17±4.31

nal surgery, the volume of intraoperative fluid infusion significantly decreased, and both intraoperative and postoperative lactate levels showed a marked reduction during and 48 hours after surgery.

In our study, the lack of correlation between PVI and lactate levels at certain periods of the operation may depend on the type of surgery performed. This is because over 99% of lactate is cleared through the first-pass metabolism in a healthy liver,[12] and hepatocyte damage during liver resection may disrupt this metabolism. Therefore, even with adequate intravascular volume, lactate levels may still rise in patients.

AST and ALT, being hepatic cytoplasmic enzymes, are released into circulation due to cell membrane damage during parenchymal resection, leading to elevations in liver enzyme levels afterward. However, the extent to which this increase persists following human liver resection has not been clearly documented. In our study, we observed a rise in ALT and AST levels at the first hour of surgery (T2), at the end of the procedure (T3), and at three hours postoperatively (T4) compared to baseline at the start of surgery (T1).

Limitations

Our study had several limitations. First, it was conducted at a single center. In liver donors on fluid-restricted regimens, PVI and lactate changes may not be sufficient for target organ oxygenation. We believe that analyzing target tissue mediators would yield better results.

Conclusion

We found that the lactate levels at the end of the surgery in liver transplant donors were consistent with PVI values. Although hepatic blood flow may be adequate, we believe that hepatocyte damage occurring during liver surgeries could influence lactate metabolism. We also think that further studies are needed to investigate the correlation between PVI and lactate levels in other types of surgeries.

Disclosures

Ethics Committee Approval: This study was conducted after obtaining approval from the Malatya Clinical Research Ethics Committee (2015/121) and patient consent, involving living donors for liver transplantation undergoing right hepatectomy, classified as ASA I-II and aged between 18-55 years.

Peer-review: Externally peer-reviewed.

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Conflicts of Interest: The authors declare no conflict of interest.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data that support the findings of this study are not openly available for reasons of sensitivity but are available from the corresponding author upon.

Authorship Contributions: Concept – M.S.; Design – M.S., N.G.; Supervision – M.S., F.K., N.G.; Materials – M.S., F.K.; Data collection or processing – M.S., F.K., N.G.; Analysis and/or interpretation – M.S., F.K.; Literature search – M.S., N.G.; Writing – M.S., F.K., N.G.; Critical review – M.S., N.G.

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Original Research

Transcriptomic Profiling of Paired Tumor and Non-Tumor Biopsies Identifies Dysregulated Genes in Hepatocellular Carcinoma

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Abstract

Objectives: Hepatocellular carcinoma (HCC) is a highly heterogeneous malignancy with poor prognosis and limited biomarkers for early detection or targeted therapy. This study aimed to comprehensively analyze differential gene expression in paired tumor and adjacent non-tumor liver biopsies, in order to identify transcriptional alterations with potential diagnostic, prognostic, or therapeutic relevance.

Methods: We utilized the publicly available GSE64041 dataset, comprising 60 paired biopsies (120 samples in total) from HCC patients. Data preprocessing and normalization were conducted in R using the limma package. Differentially expressed genes (DEGs) were determined with thresholds of |log2 fold change| > 1 and adjusted p-value < 0.05. Visualization tools included box plots, density plots, Uniform Manifold Approximation and Projection (UMAP), volcano plots, and mean difference (MD) plots to ensure robust evaluation of expression patterns and biological clustering.

Results: The transcriptomic analysis revealed clear separation between tumor and non-tumor tissues. A total of 20 top-ranked DEGs were identified, including markedly upregulated genes such as REG3A, SPINK1, GPC3, SLC7A11, and AKR1B10, as well as downregulated genes including CRHBP, FCN3, OIT3, STAB2, and CLEC1B. Many of these genes are known to be involved in oncogenic signaling, ferroptosis regulation, immune evasion, and tumor suppression. UMAP clustering and DEG visualization confirmed distinct transcriptional landscapes, supporting the biological divergence of HCC tissues from normal liver.

Conclusion: This study highlights a panel of significantly dysregulated genes reflecting both oncogenic activation and tumor suppressor loss in HCC. The findings provide valuable insights into the molecular mechanisms of hepatocarcinogenesis and suggest potential biomarkers for diagnosis, prognosis, and therapeutic targeting. These results may contribute to improving early detection, guiding risk stratification, and supporting the development of precision medicine approaches in hepatocellular carcinoma.

Keywords: Biomarkers, Differentially expressed genes, Hepatocellular carcinoma, Paired biopsies, Transcriptomic profiling

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Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and accounts for approximately 75–85% of all liver cancers, representing a major cause of cancer-related mortality worldwide. According to the latest GLOBOCAN data, liver cancer is the sixth most frequently diagnosed cancer and the third leading cause

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of cancer-related death, with more than 900,000 new cases and 830,000 deaths reported annually.[1] The incidence of HCC shows marked geographical variation, with the highest burden observed in East Asia and sub-Saharan Africa, largely reflecting the prevalence of chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. In Western countries, increasing rates of non-alcoholic fatty liver disease (NAFLD) and alcohol-related liver disease are emerging as major risk factors.[2] Despite improvements in surveillance programs and therapeutic strategies, the prognosis of HCC remains poor, with a 5-year survival rate below 20% in most countries, primarily due to late-stage diagnosis, high recurrence rates, and limited treatment options.[3]

At the molecular level, HCC is recognized as a highly heterogeneous disease, both genetically and phenotypically. This heterogeneity arises from the interplay of genomic instability, somatic mutations, epigenetic modifications, and deregulated signaling pathways, including Wnt/β-catenin, MAPK, PI3K/AKT, and TGF-β.[3,4] Efforts to classify HCC into reproducible molecular subtypes have provided important insights into tumor biology. For example, expression-based classification studies have identified subgroups with distinct prognoses and associations with oncogenic signaling pathways.[5,6] However, these classification systems are still not integrated into routine clinical practice. One of the main limitations of existing studies is that they were primarily conducted on surgically resected tumor specimens, which are enriched for patients with preserved liver function and early-stage disease. This introduces a selection bias and does not adequately represent the molecular landscape of advanced HCC or cases associated with cirrhosis, which constitute the majority of the clinical population.

Gene expression profiling has emerged as a powerful approach for unraveling the molecular mechanisms of cancer and identifying potential biomarkers. Technologies such as microarrays and next-generation sequencing (RNA-seq) enable genome-wide evaluation of transcriptomic changes, providing valuable information on both protein-coding and non-coding RNAs.[7,8] In HCC, expression profiling has been applied to characterize dysregulated pathways, identify prognostic gene signatures, and explore therapeutic targets. For instance, several studies have demonstrated that transcriptomic signatures can predict patient survival, response to therapy, and risk of recurrence.[5,9] Despite these advances, the translation of gene expression signatures into clinical biomarkers remains limited due to variability in study design, patient cohorts, and analytical methods.

To address these gaps, the present study utilizes publicly available gene expression data from the GSE64041 dataset, which includes paired tumor and non-tumor liver biopsies from 60 patients with HCC. This study design provides several advantages: (i) paired sampling allows direct within-patient comparisons, reducing inter-individual variability; (ii) biopsy-derived material better represents real-world clinical scenarios, including patients with cirrhosis and various tumor stages; and (iii) integration of non-tumor liver tissue as a control enables the identification of truly tumor-specific alterations. Through differential expression analysis and visualization methods such as box plots, density plots, UMAP, volcano plots, and MD plots, we aimed to comprehensively characterize the transcriptional landscape of HCC.

By identifying the most significantly upregulated and downregulated genes, this study contributes to a deeper understanding of the molecular mechanisms underlying hepatocarcinogenesis. Moreover, the findings may highlight potential biomarkers for diagnosis, prognosis, or therapeutic targeting, supporting future translational applications and paving the way for integrative studies combining transcriptomic, genomic, and clinical data.

Methods

Dataset

The dataset used in this study was obtained from the NCBI Gene Expression Omnibus (GEO) under the accession number GSE64041. It consists of 60 paired liver biopsies collected from patients diagnosed with hepatocellular carcinoma (HCC), where each pair includes one sample from the tumor tissue and one from the adjacent non-tumor liver tissue. This design ensures direct within-patient comparisons, reducing variability caused by inter-individual differences and improving the reliability of identifying tumor-specific transcriptional changes.

The dataset provides a valuable resource for investigating the molecular features of HCC in a clinically relevant population. Since biopsies reflect the tumor microenvironment in situ, the expression profiles capture not only the intrinsic tumor cell signatures but also interactions with surrounding liver tissue. This makes the dataset particularly suitable for studying gene dysregulation patterns and for exploring potential biomarkers associated with disease progression and prognosis.

Gene Expression Analysis

Changes in the physiological or pathological state of an organism are reflected in corresponding alterations in gene expression patterns. Therefore, the systematic assessment of gene expression provides valuable insights into the underlying molecular mechanisms of health and disease. Among the available approaches, DNA microarray technology has become a widely adopted method for

transcriptome-wide analysis. This technique is based on the hybridization of complementary DNA (cDNA) derived from messenger RNA (mRNA) molecules to thousands of immobilized probes on a solid surface, each representing a specific gene sequence.[10] The resulting signal intensities allow for the simultaneous quantification of expression levels across the genome.

Such large-scale profiling enables the identification of differentially expressed genes between experimental or clinical groups, facilitating the discovery of molecular biomarkers, the characterization of disease subtypes, and the elucidation of signaling pathways involved in pathogenesis.[11] In biomedical research, microarray-based expression analysis has been successfully applied to clinical samples, including those from healthy individuals and patients with diverse disorders, providing a robust tool for both functional genomics and translational medicine.

Bioinformatics Analysis Phase

In this study, the gene expression profiles obtained from paired tumor and non-tumor liver biopsies of patients with hepatocellular carcinoma (HCC) were analyzed. Data preprocessing and normalization were carried out in R using the limma package, a widely used statistical framework for gene expression studies.[12] Limma applies linear modeling and empirical Bayes methods to improve variance estimation, making it particularly suitable for datasets with limited sample sizes. Differentially expressed genes (DEGs) were identified based on log2 fold change (log2FC) values and adjusted p-values. Genes with log2FC > 1 were classified as upregulated, while those with log2FC < –1 were considered downregulated.

To visualize the data, several complementary approaches were employed. Box plots were generated to assess the distribution and normalization of expression data across samples, ensuring comparability between tumor and non-tumor tissues. In addition, Uniform Manifold Approximation and Projection (UMAP) was applied to reduce dimensionality and provide an unsupervised overview of similarities and clustering patterns among the samples.

For the identification of significant DEGs, volcano plots were constructed, plotting log2FC against statistical significance (–log10 p-value). This visualization enables rapid recognition of the most strongly up- and downregulated genes, with red dots representing upregulated genes, blue dots representing downregulated genes, and black dots corresponding to non-significant changes. Alongside this, Mean Difference (MD) plots were used to illustrate the log2 fold change in relation to average expression values, offering an additional perspective on differential expression. The use of consistent color coding across these plots facilitated the interpretation of results and allowed clear differentiation between significantly dysregulated and non-significant genes.

Results

The study includes data from 60 hepatocellular carcinoma (HCC) patients, each contributing one tumor biopsy and one matched non-tumor liver biopsy, for a total of 120 tissue samples. To evaluate the distribution and normalization of the expression data, box plots were generated, as presented in Figure 1. These visualizations provided an overview of expression levels across all samples and confirmed that the data were properly normalized before further analysis. In the plots, tumor biopsies were labeled as cancer, while adjacent non-tumor tissues were labeled as normal, with color coding applied to distinguish the groups.

In addition, expression density plots were employed to further assess data quality. As shown in Figure 2, the density curves of cancer (green) and normal (purple) samples largely overlapped, demonstrating consistency in intensity distributions between groups. This overlap indicated that technical variation was minimized, ensuring that downstream differential expression analysis would reflect genuine biological differences.

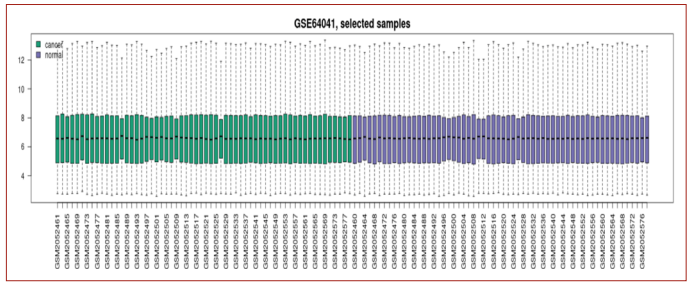

Figure 1. Box plot of gene expression values.

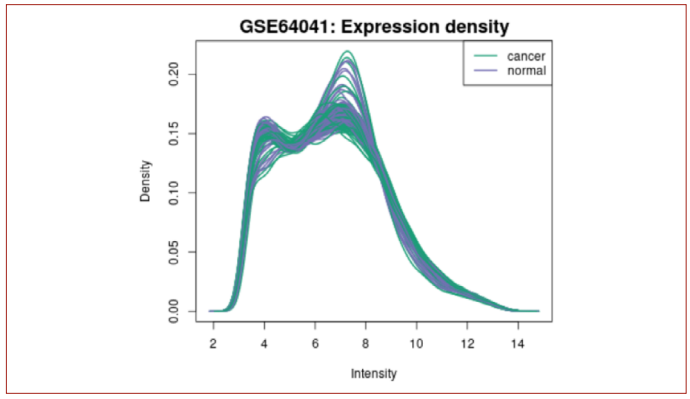

Figure 2. Expression density plot of samples (Density plot showing the distribution of expression intensities across cancer (green) and normal (purple) samples. The substantial overlap between the two groups confirms successful normalization and comparability of the datasets prior to differential expression analysis.).

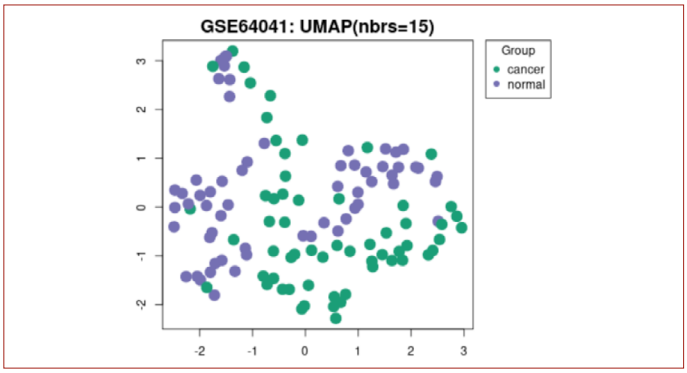

Figure 3. UMAP visualization of cancer and normal samples (UMAP plot based on expression data from 60 HCC patients (120 samples). Cancer (green) and normal (purple) tissues cluster separately, reflecting distinct transcriptional profiles.)

Figure 3 shows the UMAP plot generated from the expression profiles of the samples. This visualization demonstrates how samples with similar molecular characteristics cluster together in a reduced dimensional space. The distribution and clustering patterns provide important insights into the biological similarities and differences among the groups. In the graph, green dots represent cancer (tumor) tissue samples, while purple dots represent normal (non-tumor) liver tissue samples. The separation between these two groups highlights the distinct gene expression signatures of tumor and non-tumor tissues and illustrates the effectiveness of UMAP as a tool for visualizing heterogeneity and group classification within the dataset.

Based on the analysis of the GSE64041 dataset, the top 10 upregulated genes identified in the comparison between cancer (tumor) and normal (non-tumor) liver tissues are presented in Table 1. To ensure both statistical significance and biological relevance, threshold criteria were applied during differential expression analysis. Specifically, genes with an absolute log2 fold change (|log2FC|) greater than 1.0 and a p-value below 0.05 were considered significantly dysregulated.

These cut-off values provided a robust framework for distinguishing true biological differences from background noise. The upregulated genes identified under these conditions represent candidates of particular interest, as their consistent overexpression in cancer tissues may point to their involvement in tumor progression and carcinogenic pathways. Consequently, the results obtained from this analysis may offer valuable insights into potential biomarkers for diagnosis, prognosis, or therapeutic targeting in hepatocellular carcinoma.

Based on the analysis of the GSE64041 dataset, the top 10 downregulated genes identified in the comparison between cancer (tumor) and normal (non-tumor) liver tissues are presented in Table 2. For the identification of downregulated genes, the same statistical thresholds used for upregulation were applied. Specifically, genes with an absolute log2 fold change (|log2FC|) greater than 1.0 and a p-value below 0.05 were considered significantly downregulated.

These results highlight genes whose expression levels were consistently reduced in cancer tissues compared with normal liver tissues, suggesting potential roles as tumor suppressors or regulators of normal liver function that become impaired during hepatocarcinogenesis. The findings may provide further insight into molecular mechanisms underlying disease development and could support the identification of novel diagnostic or therapeutic biomarkers.

Figure 4 illustrates the volcano plot, which provides a comprehensive visualization of genes exhibiting differential expression between cancer (tumor) and normal (non-tumor) liver tissues. In this representation, the x-axis corresponds to the log2 fold change (log2FC), reflecting the magnitude and direction of expression changes, while the y-axis indicates statistical significance as –log10 (p-value). This dual-axis representation allows for the simultaneous evaluation of both the size and reliability of gene expression changes.

Table 1. Top 10 upregulated genes between cancer and normal tissue samples

ID	adj, P, Val	p	t	B	logFC	Gene symbol
8053341	4,18E-08	1,13E-09	6,603974	11,72321	2,624876	REG3A
8114964	1,41E-08	3,20E-10	6,856537	12,94729	2,350635	SPINK1
8084630	3,20E-12	1,48E-14	8,755112	22,65842	2,341945	NMRAL1P1
8175234	7,22E-09	1,42E-10	7,016854	13,73453	1,945761	GPC3
8102800	3,04E-11	2,16E-13	8,258221	20,04891	1,936128	SLC7A11
8167254	1,28E-07	4,10E-09	6,341416	10,47336	1,876775	SSX1
7927694	3,69E-11	2,71E-13	8,215627	19,82698	1,658532	PHYHIPL
8136336	2,05E-04	2,18E-05	4,418465	2,233265	1,61133	AKR1B10
7923086	5,02E-14	1,10E-16	9,651242	27,43665	1,5879	ASPM
8117054	7,79E-22	4,95E-26	13,56161	48,38471	1,574118	CAP2

Table 2. Top 10 downregulated genes between cancer and normal tissue samples

ID	adj, P, Val	p	t	B	logFC	Gene symbol
8106418	4,92E-19	1,48E-22	-12,0965	40,61003	-2,70026	CRHBP
7914075	6,18E-17	3,53E-20	-11,1056	35,27825	-2,61709	FCN3
7928330	2,82E-21	5,08E-25	-13,1323	46,12448	-2,52153	OIT3
8110183	5,99E-18	3,06E-21	-11,5475	37,6603	-2,42389	CDHR2
7958056	3,55E-22	1,07E-26	-13,8465	49,87529	-2,37671	STAB2
8148029	8,02E-16	7,76E-19	-10,5478	32,26708	-2,24046	COLEC10
7961102	1,47E-21	2,21E-25	-13,2856	46,93317	-2,23152	CLEC1B
7964183	5,60E-13	1,95E-15	-9,1272	24,63333	-2,21438	GLS2
8113369	2,54E-16	1,75E-19	-10,8162	33,71613	-2,19836	SLCO4C1
7968678	2,85E-16	2,40E-19	-10,7599	33,41227	-2,16527	FREM2

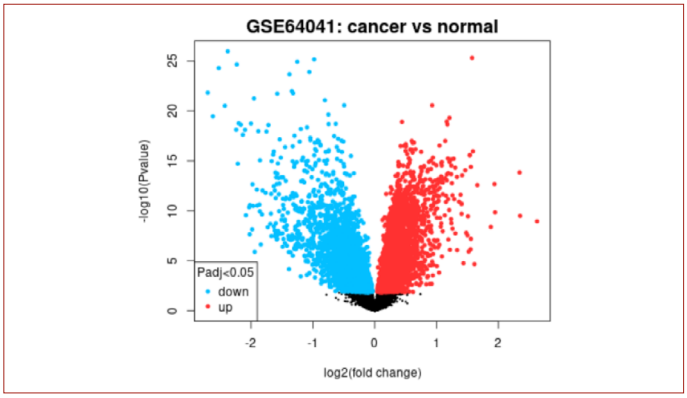

Figure 4. Volcano plot of differentially expressed genes between cancer and normal tissues.

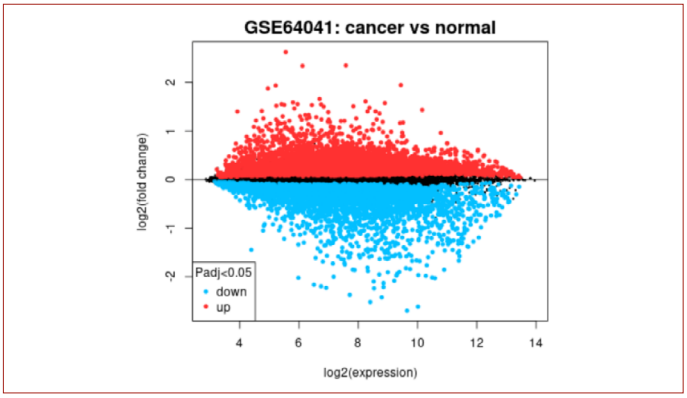

Figure 5. Mean Difference (MD) plot of gene expression between cancer and normal tissues.

In the plot, red dots represent significantly upregulated genes, while blue dots denote significantly downregulated genes. Genes that do not meet the established significance thresholds are shown in black, representing non-differentially expressed genes. The volcano plot therefore enables rapid identification of candidate biomarkers, as it highlights genes with both large fold changes and strong statistical support. This visualization is a widely used method in transcriptomic studies, as it effectively combines statistical significance with biological relevance, thereby providing an intuitive overview of the gene expression landscape within the dataset.

Figure 5 presents the Mean Difference (MD) plot, which provides a detailed visualization of the genes that display differential expression between cancer (tumor) and normal (non-tumor) liver tissues. In this plot, the x-axis corresponds to the average log2 expression level of each gene, while the y-axis represents the log2 fold change (log2FC), thereby combining both the baseline expression and the relative change in a single view. This dual representation makes the MD plot a powerful tool for detecting both subtle and pronounced alterations in gene expression.

Each point in the plot represents an individual gene. Red points indicate significantly upregulated genes, whereas blue points mark significantly downregulated genes, with color coding aiding in the rapid distinction of expression patterns. Genes that do not pass the significance threshold remain uncolored, providing a clear separation between relevant and background signals.

By visualizing expression levels in this way, the MD plot highlights not only global transcriptional trends but also emphasizes genes that deviate strongly from baseline expression, potentially serving as biomarker candidates. These dysregulated genes may be linked to critical pathways involved in hepatocarcinogenesis, offering valuable clues for understanding disease mechanisms and identifying possible therapeutic targets.

Discussion

In this study, we performed a comprehensive transcriptomic analysis of paired tumor and adjacent non-tumor liver biopsies from 60 hepatocellular carcinoma (HCC) patients using the GSE64041 dataset. This design, which incorporates matched samples from the same individuals, minimizes inter-patient variability and increases the robustness of the

findings by allowing direct comparison of tumor-specific transcriptional alterations against the background of the patient's own liver tissue. Differential expression analysis revealed distinct sets of upregulated and downregulated genes, highlighting not only known drivers of hepatocarcinogenesis but also novel candidates with potential diagnostic, prognostic, or therapeutic relevance. Importantly, the integration of multiple visualization strategies, including UMAP clustering, volcano plots, and mean difference plots, provided an intuitive overview of the transcriptional landscape and reinforced the biological separation between malignant and non-malignant tissues. Together, these results contribute to a more refined understanding of the molecular heterogeneity of HCC and may inform the development of precision medicine approaches aimed at improving early detection, risk stratification, and treatment outcomes in this highly lethal malignancy.

Among the most significantly upregulated genes, REG3A, SPINK1, GPC3, SLC7A11, and AKR1B10 emerged as key players. GPC3 has been widely validated as a diagnostic biomarker in HCC, with strong involvement in Wnt/β-catenin signaling and tumor proliferation.[13] SLC7A11, encoding the cystine/glutamate antiporter xCT, regulates glutathione synthesis and ferroptosis resistance, and its overexpression has been linked to poor prognosis and sorafenib resistance in HCC.[14] Similarly, AKR1B10 overexpression is consistently observed in HCC and has been associated with lipid metabolism, early carcinogenesis, and poor survival.[15,16] The upregulation of SPINK1 has also been implicated in promoting tumor growth and metastasis in HCC, potentially through EGFR pathway activation.[17] Collectively, the overexpression of these genes highlights their translational potential as biomarkers or therapeutic targets.

Conversely, several tumor suppressor candidates, including CRHBP, FCN3, OIT3, STAB2, and CLEC1B, were markedly downregulated. The reduced expression of STAB2, a scavenger receptor involved in hyaluronan clearance, has been linked to enhanced tumor progression and stromal remodeling.[18] CLEC1B, which contributes to platelet aggregation and immune regulation, has been reported as a prognostic marker, with lower levels associated with higher metastatic potential and poor outcomes in HCC.[19,20] Similarly, FCN3 and CRHBP downregulation may impair innate immune defense and stress response, thereby facilitating tumor development.[21,22]

The unsupervised UMAP clustering in this study clearly separated tumor and non-tumor tissues, underscoring the transcriptional divergence between groups. This observation aligns with prior large-scale transcriptomic classifications, such as those by Hoshida et al. and Boyault et al., which defined molecular subtypes of HCC with distinct signaling dependencies and clinical outcomes.[5,6] Importantly, the dysregulated genes identified in our dataset map onto pathways implicated in these molecular subclasses, reinforcing the robustness of our findings.

From a translational standpoint, the identified genes hold promise for both diagnostic and therapeutic applications. Serum-based detection of proteins such as GPC3 or AKR1B10 could facilitate earlier diagnosis, while expression status of SLC7A11 might guide ferroptosis-based therapies. Moreover, strategies aimed at restoring the expression of downregulated genes (e.g., CLEC1B or STAB2) may represent novel therapeutic directions.

Nevertheless, this study has limitations. First, it relied on a single dataset based on microarray technology, which does not capture the full spectrum of transcriptomic regulation, including non-coding RNAs and alternative splicing. Second, functional validation was beyond the scope of this analysis and is necessary to confirm the biological roles of the identified genes. Future studies integrating transcriptomic, genomic, and clinical data, along with experimental validation, will be crucial to translate these findings into clinical practice.

In summary, this transcriptomic analysis of paired biopsies highlights a panel of dysregulated genes that reflect both oncogenic activation and loss of tumor suppressor function in HCC. The results reinforce previously established molecular classifications while pointing to novel biomarker candidates that may improve diagnosis, prognosis, and therapeutic decision-making in hepatocellular carcinoma.

Disclosures

Ethics Committee Approval: Ethical approval was not required for this study, as all data were obtained from publicly available open-access datasets.

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Conflict of Interest: None declared.

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Original Research

Influence of Recipient Age on Outcomes After Liver Transplantation for Hepatocellular Carcinoma

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Abstract

Objectives: Liver transplantation (LT) is being performed with increasing frequency in elderly patients in parallel with the aging population worldwide today. In this study, we aimed to analyze the outcomes of LT for HCC in patients aged ≥65 (Older) versus those <65 (Younger).

Methods: In total of 535 HCC patients undergone LT at İnönü University Liver Transplantation Institute between April 2006 and March 2025 were retrospectively reviewed from a consecutively and prospectively recorded database and were analyzed.

Results: 68 out of 535 LT's age were ≥65 (12.7%). The percentage of older HCC patients receiving LT increased over time: it was 6.3% from 2002-2010, 11.3% from 2011-2020, and 17.5% from 2021-2025, showing a significant upward trend (p=0.039). 1-5-, and 10-years OS was 89.1%, 66.8%, and 53.9% in Younger group, and 81.5%, 52.8%, and 39.7% in Older group (p=0.012). Age≥65years was an independent predictor of mortality in patients undergoing LT for HCC (HR = 1.65, 95% CI: 1.11–2.46, p = 0.013). DFS, recurrence rate, tumor characteristics, demographics were similar. Only the last creatin level before LT (0.88 vs 0.8, p=0.003) and beyond Milan criteria rate were significantly higher (39.7% vs 60.2%, p=0.039) in the Older group.

Conclusion: Older age was independently associated with worse post-transplant overall survival among patients undergoing LT for HCC. This inferior survival cannot attribute to the tumor-related factors. Future studies focusing on sarcopenia, frailty, causes of death, and post-transplant complications, immunosuppressive regimens to better define the mechanisms underlying poor survival outcomes in elderly liver transplant recipients and to improve patient selection and post-transplant management in this growing population.

Keywords: Older, elderly, younger, hepatobiliary, neoplasm, survival, recurrence

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Liver transplantation is being performed with increasing frequency in elderly patients in parallel with the aging population worldwide today. According to data from the United Network for Organ Sharing (UNOS) and the European Liver Transplant Registry (ELTR), between 2000 and 2015, the rates of waiting list registration and liver transplantation (LT) for patients aged 65-70 doubled.[1] In our country, according to the data of the Turkish Statistical Institute (TÜİK), the population aged 65 and over, considered the elderly population, increased by 20.7% from 7.5 million in 2019 to 9.1 million in 2024.[2]

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In our center, the proportion of elderly patients among the number of liver transplants we have performed over the years has also increased significantly. In our program, which started in 2002, the rate of transplant patients aged 65 and over was 2.5% (13/512) between 2002 and 2010, while this rate increased to 5.1% (121/2378) between 2011 and 2020, and to 9.4% (127/1358) between 2021 and 2025, showing a significant increase (p<0.001).

LT outcomes in older patients have shown mixed results, with some studies indicating similar survival rates to younger individuals[3] and others reporting poorer outcomes.[4] Furthermore, hepatocellular carcinoma (HCC) is considered an independent risk factor for poor outcomes in older patients.[1] However, some studies[5] report similar LT results for HCC patients aged 65 and over compared to younger individuals.

In this study, we aimed to analyze the outcomes of LT for HCC in patients aged 65 and over (Older) versus those under 65 years of age (Younger).

Patients and Methods

Study Population

Data from patients who underwent liver transplantation due to HCC at İnönü University Liver Transplantation Institute between April 2006 and March 2025 were retrospectively reviewed from a consecutively and prospectively recorded database. To focus on oncological outcomes, patients with a follow-up period of less than 90 days after transplantation were excluded, and patients who have HCC in explant pathology were included in the study. In total of 535 transplant patients with HCC were analyzed.

Patients' demographic data, tumor characteristics obtained from explant pathology, pre-transplant last laboratory parameters, Milan criteria status, Malatya criteria status and expanded Malatya criteria status,[6] and post-transplant survivals and recurrence status were recorded.

According to the Turkish Statistical Institute's age classification,[2] patients were divided into two groups: under 65 years of age (Younger) and 65 years and older (Older). The distribution of the liver transplant numbers we performed for older HCC patients was calculated according to 3 time periods (2002-2010; 2011-2020; 2021-2025).

Post-transplant overall survival (OS), disease-free survival (DFS), and recurrence rates were calculated and compared for each group. The demographic and tumor characteristics of both groups were then compared to investigate the possible reasons for the difference in survival.

Statistical Analysis

The Kolmogorov-Smirnov test was used to assess the normality of the quantitative data. The Mann-Whitney U test was used for comparisons between two independent groups. Median, minimum, and maximum values were used to summarize the quantitative data. Distributions of the qualitative data were presented by count and percentage. Pearson chi-square test (asymptotic significance or exact significance) and the continuity-corrected chi-square test were applied for comparisons. The Kaplan-Meier method was used for survival estimations, and the Log-Rank test was used for survival comparisons between groups. Univariate Cox regression analysis was used to obtain the Hazard Ratios. In all analyses, the two-sided significance level was considered as <0.05. All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp, Armonk, NY).

Results

Patient Demographics

Patient demographics are presented in Table 1. The median age was 56 years (1–72), with 12.7% (68/535) of patients aged ≥65. Patients classified as CHILD B or C accounted for 63% (337/535). The proportion of patients within the Milan criteria was 51.4%, within the Malatya criteria was 63.6%, and within the Expanded Malatya criteria was 69%. The predominant underlying disease was viral hepatitis, accounting for 74.8% of cases.

Distribution of LT Numbers of Older Patients According to Time Periods

In our center, the proportion of elderly patients among the number of liver transplants we have performed over the years has increased significantly. In our program, which started in 2002, the rate of transplant patients aged 65 and over was 2.5% (13/512) between 2002 and 2010, while this rate increased to 5.1% (121/2378) between 2011 and 2020, and to 9.4% (127/1358) between 2021 and 2025, showing a significant increase (p<0.001).

The percentage of older HCC patients receiving LT also increased over time: it was 6.3% from 2002 to 2010, 11.3% from 2011 to 2020, and 17.5% from 2021 to 2025, showing a significant upward trend (p=0.039) (Table 2).

Overall Survival Functions of the Groups

Mean overall survival time for Younger group was 3793.5 days and 2497.5 days for Older group (Table 3). 1-5-, and 10-years OS was 89.1%, 66.8%, and 53.9% in Younger group, and 81.5%, 52.8%, and 39.7% in Older group. Survival difference was statistically significant with p=0.012 (Fig. 1).

Table 1. Patient demographics of all cohort

	n	Median (Min.-Max.)
AFP	530	12.1 (0.2-55000)
MTD (cm)	535	3 (0-26)
Number of nodules	535	2 (1-36)
BSA	535	1.92 (0.38-2.54)
BMI	535	26.1 (14.8-46.88)
NLR	535	2.59 (0.15-35.3)
PLR	535	84.15 (2.61-1092.31)
Platelets	535	101 (15-701)
INR	442	1.31 (0.82-4.1)
Albumin	534	3 (1.2-5.2)
Total Bilirubin	535	1.84 (0.23-44.7)
Creatin	535	0.8 (0.22-13.8)
Total protein	385	7 (1.01-9.4)
AST	533	58 (9-7789)
ALT	534	42 (7-3535)
ALP	533	118 (28-2327)
GGT	533	73 (11-1396)
LDH	451	232 (57-1538)
	n (%)	
Gender		
Female	69 (12.9)	
Male	466 (87.1)	
CHILD class		
A	198 (37)	
B	217 (40.6)	
C	120 (22.4)	
GGT		
≤104	343 (64.4)	
>104	190 (35.6)	
AFP		
≤200	450 (84.9)	
>200	80 (15.1)	
MELD		
<15	324 (60.6)	
≥15	211 (39.4)	
Recurrence		
None	441 (82.4)	
Yes	94 (17.6)	
TTD, cm		
≤8	390 (72.9)	
>8	145 (27.1)	
Differentiation		
Well/moderate	460 (86)	
Poor	75 (14)	
Venous invasion		
None	474 (88.6)	
Microscopic/Macroscopic	61 (11.4)	
Milan Criteria		
In	275 (51.4)	
Out	260 (48.6)	
Malatya Criteria		
In	340 (63.6)	
Out	195 (36.4)	
Expanded Malatya Criteria		
In	369 (69)	
Out	166 (31)	
Etiology		
Viral hepatitis	400 (74.8)	
Cryptogenic	88 (16.4)	
Ethanol	11 (2.1)	
Budd-Chiari	12 (2.2)	
Metabolic	11 (2.1)	
Others	13 (2.4)	
GRWR		
≥0.8	470 (90)	
<0.8	52 (10)	

AFP: Alpha fetoprotein; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; BSA: Body surface area; GGT: Gamma glutamyl transferase; GRWR: Graft to recipient weight ratio; LDH: Lactate dehydrogenase; MELD: Model for end stage liver disease; MTD: Maximum tumor diameter; NLR: Neutrophile to lymphocyte ratio; NN: Number of nodules; PLR: Platelet to lymphocyte ratio; TTD: Total tumor diameter.

Cox Proportional Hazards Regression Analysis for Age ≥65 Years

Age ≥ 65 years was an independent predictor of mortality in patients undergoing liver transplantation for hepatocellular carcinoma (HR = 1.65, 95% CI: 1.11–2.46, p=0.013), according to Univariate Cox regression analysis (Table 3).

Disease-Free Survival Functions of the Groups

Mean disease-free survival time for Younger group was 3711.4 days and 2483.6 days for Older group (Table 4). 1-5-, and 10-years OS was 84.2%, 63.9%, and 53.1% in Younger group, and 80%, 53.6%, and 40.3% in Older group. Survival difference was not statistically significant with p=0.066 (Fig. 2).

Tumor Recurrence

The overall HCC recurrence rate was 17.6% (94/535), with 13.2% (9/68) in the Older group and 18.2% (85/467) in the Younger group, showing no significant difference (p=0.404, Table 5). In the Older group, recurrences were liver-only 22% (2/11), extrahepatic-only 33% (3/11), or both 44% (4/11).

Table 2. Distribution of the LT numbers for HCC and all other indications according to time periods

Time period	All others n	All others Age <65 n (%)	All others Age ≥65 n (%)	p	HCC n	HCC Age <65 n (%)	HCC Age ≥65 n (%)	p
2002 – 2010	512	499 (97.5)	13 (2.5)	<0.001	63	59 (93.7)	4 (6.3)	0.039
2011 – 2020	2378	2257 (94.9)	121 (5.1)		301	267 (88.7)	34 (11.3)	
2021 – 2025	1358	1231 (90.6)	127 (9.4)		171	141 (82.5)	30 (17.5)	
Total	4248	3987 (93.9)	261 (6.1)		535	467 (87.3)	68 (12.7)	

Table 3. Overall survival and cox regression according to age 65

				Univariate Analysis	
OS	Survival (days) Mean±SE	Survival (days) Median±SE	Log-Rank p	HR (95% C.I.)	HR p
Age<65 (n=467)	3793.55±157.48	4451±762.33	0.012	reference	
Age≥65 (n=68)	2497.50±334.36	2184±919.77		1.653 (1.111-2.460)	0.013

HR: Hazard ratio; OS: Overall survival; SE: Standard error.

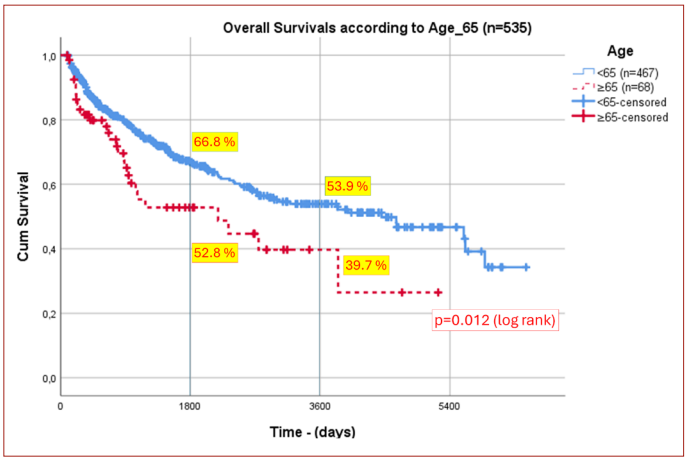

Figure 1. Overall survival function of LT patients with HCC according to age 65.

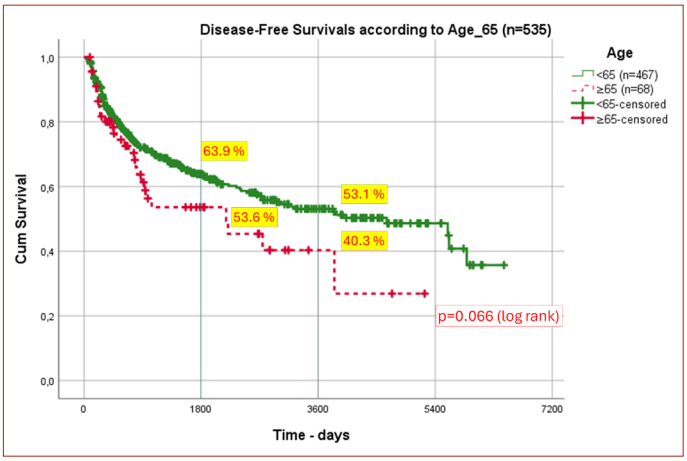

Figure 2. Disease-free survival function of LT patients with HCC according to age 65.

Table 4. Disease-free survival table according to age 65

DFS	Survival (days) Mean±SE	Survival (days) Median±SE	Log-Rank p
Age<65 (n=467)	3711.41±159.21	4655±918.12	0.066
Age≥65 (n=68)	2483.62±340.31	2184±871.69	

DFS: Disease-free survival; SE: Standard error.

In the Younger group, rates were 11.8% (10/85) liver-only, 48.2% (41/85) extrahepatic-only, and 40% (34/85) both.

Extrahepatic metastases occurred most frequently in the lungs (n=46), followed by bones (n=16), peritoneum (n=14), lymph nodes (n=12), adrenal glands (n=11), and brain (n=4).

Comparison of the Groups in Terms of Demographics and Tumor Parameters

Next, we made a comparison between the groups. Demographics, etiology, CHILD class, MELD score, recurrence rates, MTD, NN, differentiation grade, and vascular invasion status were similar between the groups. Only the last creatin level before LT (0.88 vs 0.8, p=0.003) and beyond Milan criteria rate were significantly higher (39.7% vs 60.2%, p=0.039) in the Older group.

Discussion

In our study, we demonstrated that the proportion of patients aged 65 years and older undergoing liver transplantation, both for all indications and specifically for HCC, increased significantly over time (Table 2). When analyzed by

Table 5. Comparison of the age groups

	Age<65		Age≥65		p
	n	Median (Min.-Max.)	n	Median (Min.-Max.)	
AFP	462	12.34 (0.2-55000)	68	10.5 (0.4-20179)	0.793
MTD (cm)	467	3 (0-26)	68	3.25 (0-16)	0.844
Number of nodules	467	2 (1-36)	68	2 (1-27)	0.072
BSA	467	1.92 (0.38-2.54)	68	1.92 (1.4-2.37)	0.972
BMI	467	25.96 (14.8-46.88)	68	26.85 (16.1-41)	0.125
NLR	467	2.59 (0.15-35.3)	68	2.59 (0.54-15.14)	0.997
PLR	467	82.7 (2.61-1092.31)	68	87.78 (34.06-298.68)	0.397
Platelets	467	96 (16-701)	68	110.5 (15-538)	0.152
INR	383	1.31 (0.82-3.67)	59	1.26 (0.9-4.1)	0.132
Albumin	466	3 (1.2-5.2)	68	3 (1.9-5.2)	0.242
Total Bilirubin	467	1.88 (0.23-44.7)	68	1.8 (0.3-10.7)	0.262
Creatin	467	0.8 (0.22-13.8)	68	0.88 (0.3-1.6)	0.003
Total protein	336	7 (1.5-9.4)	49	7 (1.01-9)	0.968
AST	465	59 (9-7789)	68	54 (14-268)	0.172
ALT	466	42.5 (10-3535)	68	40.5 (7-250)	0.281
ALP	465	121 (28-2327)	68	106.5 (46-367)	0.431
GGT	465	71 (11-1396)	68	88.5 (13-702)	0.070
LDH	391	235 (57-1538)	60	219 (149-401)	0.617
	Age<65 n (%)	Age≥65 n (%)	p		
Gender					
Female	60 (12.8)	9 (13.2)	1.000		
Male	407 (87.2)	59 (86.8)			
CHILD class					
A	171 (36.6)	27 (39.7)	0.763		
B	189 (40.5)	28 (41.2)			
C	107 (22.9)	13 (19.1)			
GGT					
≤104	306 (65.8)	37 (54.4)	0.067		
>104	159 (34.2)	31 (45.6)			
AFP					
≤200	391 (84.6)	59 (86.8)	0.782		
>200	71 (15.4)	9 (13.2)			
MELD					
<15	282 (60.4)	42 (61.8)	0.828		
≥15	185 (39.6)	26 (38.2)			
Recurrence					
None	382 (81.8)	59 (86.8)	0.404		
Yes	85 (18.2)	9 (13.2)			
TTD					
≤8	344 (73.7)	46 (67.6)	0.370		
>8	123 (26.3)	22 (32.4)			
Differentiation					
Well/moderate	400 (85.7)	60 (88.2)	0.699		
Poor	67 (14.3)	8 (11.8)			

Table 5. Comparison of the age groups (Cont.)

	Age<65 n (%)	Age≥65 n (%)	p
Venous invasion			
None	416 (89.1)	58 (85.3)	0.476
Microscopic/Macroscopic	51 (10.9)	10 (14.7)	
Milan Criteria			
In	248 (53.1)	27 (39.7)	0.039
Out	219 (46.9)	41 (60.3)	
Malatya Criteria			
In	300 (64.2)	40 (58.8)	0.386
Out	167 (35.8)	28 (41.2)	
Expanded Malatya Criteria			
In	327 (70)	42 (61.8)	0.169
Out	140 (30)	26 (38.2)	
Etiology			
Viral hepatitis	350 (74.9)	50 (73.5)	0.347
Cryptogenic	73 (15.6)	15 (22.1)	
Ethanol	9 (1.9)	2 (2.9)	
Budd-Chiari	12 (2.6)	0 (0)	
Metabolic	11 (2.4)	0 (0)	
Others	12 (2.6)	1 (1.5)	
GRWR			
≥0.8	409 (89.7)	61 (92.4)	0.636
<0.8	47 (10.3)	5 (7.6)	

AFP: Alpha fetoprotein; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; BSA: Body surface area; GGT: Gamma glutamyl transferase; GRWR: Graft to recipient weight ratio; LDH: Lactate dehydrogenase; MELD: Model for end stage liver disease; MTD: Maximum tumor diameter; NLR: Neutrophile to lymphocyte ratio; NN: Number of nodules; PLR: Platelet to lymphocyte ratio; TTD: Total tumor diameter.

indication, the proportion of elderly recipients was higher among patients transplanted for HCC compared with those transplanted for other indications. Advanced age is a well-established risk factor for the development of HCC; therefore, a higher proportion of elderly patients among those undergoing transplantation for HCC is an expected finding.

In the present study, we found that recipient age ≥65 years was independently associated with significantly worse post-transplant overall survival in patients undergoing liver transplantation for HCC (5-year OS 66.8% vs 52.8%, p=0.012). In the Cox regression analysis, the risk of mortality in the elderly group was found to be 1.65 times higher than that in the younger group (HR = 1.65, 95% CI: 1.11–2.46, p=0.013). These findings are highly consistent with the study by Xing et al.,[7] which compared locoregional therapy (LRT) in patients who underwent liver transplantation for HCC. In that study, advanced age (≥65 years) was identified as an independent risk factor for poor survival in patients with HCC (univariate analysis: HR 1.71, 95% CI: 1.44–2.94). Additionally, donor age, bridging LRT, and longer waiting time were identified as independent prognostic factors for survival.[7]

On the other hand, disease-free survival and recurrence rates were comparable between younger and older recipients. This finding suggests that the observed difference in overall survival among older patients cannot be explained by tumor recurrence. The impact of recipient age on liver transplantation outcomes has long been debated. While earlier studies suggested that chronological age alone should not preclude transplantation, more recent analyses indicate that selected elderly patients older than 65 and even 70 years benefit from LT as much as younger ones.[3, 5] But our findings are consistent with reports demonstrating inferior survival among elderly transplant recipients,[1, 4] even when tumor burden and transplant eligibility criteria are comparable between age groups.

When we compare the groups in terms of demographics, etiology, CHILD class, MELD score, recurrence rates, MTD, NN, differentiation grade, Malatya criteria status, Expanded Malatya criteria status and vascular invasion status we could not find significant difference. Only the last median creatin level before LT (0.88 vs 0.8, p=0.003) and beyond Milan criteria rate were significantly higher (39.7% vs 60.2%, p=0.039) in the Older group. In elderly

HCC patients with elevated creatinine levels, reassessing diuretic therapy, fluid status, and glomerular filtration rate during the pre-transplant preparation period to improve renal function may be beneficial in improving post-transplant survival outcomes. However, the significantly higher rate of beyond Milan criteria in elderly patients does not explain the current poor survival rate, as tumor recurrence rates, AFP levels, MTD, tumor differentiation, vascular invasion rates, and the rates of non-Milan criteria were similar in both groups. Age-related factors such as comorbidity, reduced cardiopulmonary reserve, frailty, and sarcopenia are well-recognized contributors to poor outcomes after major surgery. These conditions are not fully captured by conventional risk stratification tools or MELD-based allocation systems. Furthermore, immunosenescence in elderly recipients may predispose to infectious complications and impair long-term tolerance to immunosuppressive therapy, thereby contributing to late mortality independent of graft function or tumor recurrence. Comprehensive geriatric assessment, objective frailty indices, and detailed cardiopulmonary evaluation may help identify elderly patients who are most likely to derive long-term benefit from transplantation. In addition, individualized immunosuppressive regimens and closer post-transplant monitoring may be particularly important in this high-risk group. Further studies analyzing these parameters are needed.

This study has limitations inherent to its retrospective design, and age-related factors such as frailty, sarcopenia, or cause-specific mortality, immunosuppressive regimens, post-transplant complications which have potential contributors to poor outcomes were not analyzed.

The results of our study indicate that advanced age should be considered as a factor within risk stratification models for HCC transplant candidates, rather than used as an exclusion criteria.

Conclusion

In conclusion, the number of older patients (≥65 years) undergoing liver transplantation has increased significantly, both for HCC and for other indications. Older age was independently associated with worse post-transplant overall survival among patients undergoing liver transplantation for HCC. This inferior survival cannot attribute to the tumor-related factors. Future studies focusing on sarcopenia, frailty, causes of death, and post-transplant complications, immunosuppressive regimens to better define the mechanisms underlying poor survival outcomes in elderly liver transplant recipients and to improve patient selection and post-transplant management in this growing population.

Disclosures

Ethics Committee Approval: Ethical committee approval was not obtained because this study was retrospective in design.

Peer-review: Externally peer-reviewed.

Data Availability: The raw data used to support the findings of this study are available from the corresponding author upon request.

Informed Consent: No informed consent was requested from patients since this is a retrospectively designed study.

Conflict of Interest Statement: There is no conflict of interest

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Original Research

Surgical Management of Bile Duct Injuries During Laparoscopic Cholecystectomy: A Retrospective Analysis of 20 Cases

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Abstract

Objectives: This study aimed to retrospectively evaluate the clinical outcomes of surgical repair techniques applied in bile duct injuries occurring during laparoscopic cholecystectomy (LC).

Methods: A total of 20 patients who developed bile duct injury during laparoscopic cholecystectomy and subsequently underwent surgical reconstruction were retrospectively analyzed. Demographic characteristics, timing of injury recognition, type of injury according to the Strasberg classification, surgical techniques employed, postoperative complications, and length of hospital stay were evaluated.

Results: Thirteen patients were female (65%) and seven were male (35%), with a mean age of 57.6 years (range: 19–90). According to the Strasberg classification, the most common injury type was Type E2 (70%), followed by Type E1 (25%) and Type E3 (5%). Roux-en-Y hepaticojejunostomy was performed in 85% of cases. Concomitant vascular injury was present in two patients. The mean length of hospital stay was 7.2 days. Postoperative bile leakage developed in two patients and was successfully managed using interventional or conservative approaches.

Conclusion: Early diagnosis and appropriate surgical reconstruction are crucial in the management of bile duct injuries. Even in cases of delayed diagnosis, successful clinical outcomes can be achieved in experienced centers through a multidisciplinary approach.

Keywords: Bile duct injury, laparoscopic cholecystectomy, Strasberg classification, hepaticojejunostomy

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Laparoscopic cholecystectomy is the gold standard surgical treatment for benign biliary diseases. However, compared with open surgery, it is associated with a higher risk of bile duct injury.[1] The incidence of bile duct injuries following laparoscopic cholecystectomy has been reported to range between 0.4% and 0.6%.[2] Bile duct injuries develop due to multiple factors, including surgeon experience, anatomical variations, inflammation, and misidentification of biliary anatomy.

Bile duct injuries may lead to significant morbidity, prolonged hospital stay, and a marked deterioration in quality of life. In cases that are not recognized early or managed appropriately, serious clinical consequences may occur, including recurrent episodes of cholangitis, secondary biliary cirrhosis, development of portal hypertension, and ultimately the need for liver transplantation.

Bile duct injuries occurring after laparoscopic cholecystectomy should generally be managed using a multidisciplinary approach. Accordingly, the treatment of patients with bile duct injury should be performed in experienced

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centers that include general surgery, gastroenterology, and interventional radiology units.

In this study, we aimed to present the surgical management and clinical outcomes of bile duct injuries occurring during laparoscopic cholecystectomy.

Methods

This retrospective study included patients who were diagnosed with bile duct injury during laparoscopic cholecystectomy or in the early postoperative period and underwent surgical reconstruction at the Department of General Surgery, Harran University, between 2018 and 2025. Demographic characteristics, including age and sex, timing of injury recognition (intraoperative or postoperative), type of injury, referral status, presence of concomitant vascular injury, type of surgical reconstruction performed, postoperative complications, and length of hospital stay were recorded. All bile duct injuries were categorized according to the Strasberg classification (Fig. 1).

To determine the type of bile duct injury, intraoperative assessment was used in patients who underwent early reconstruction, whereas endoscopic retrograde cholangiopancreatography (ERCP) and magnetic resonance cholangiopancreatography (MRCP) were utilized in the remaining patients.

Early reconstruction was performed in patients who were referred to our center in the early period and in those whose injuries occurred at our institution. In the remaining patients, surgical treatment was performed after appropriate diagnostic evaluation and initial management. As part of the surgical treatment, T-tube cholangiography was performed on postoperative day 21 in patients who underwent T-tube repair or in whom an external stent was placed during hepaticojejunostomy. In cases with normal cholangiographic findings (Fig. 2), the T-tube and external catheters were subsequently removed.

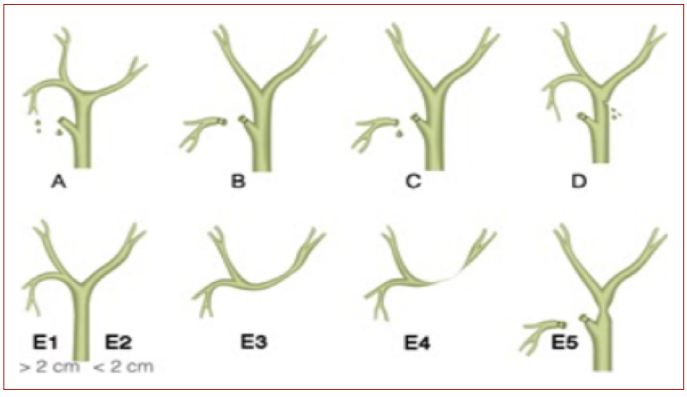

Figure 1. Strasberg Classification of Bile Duct Injuries.

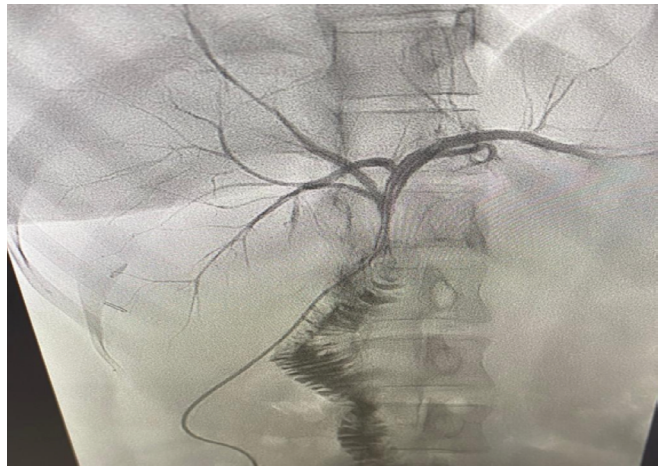

Figure 2. Postoperative MRCP Image of a Patient Who Underwent Surgery for Bile Duct Injury.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 27.0 (Armonk, NY: IBM Corp.). This study was designed as a descriptive analysis, and no comparative or inferential statistical tests were applied. Continuous variables were summarized as mean±standard deviation or median (minimum–maximum), as appropriate, based on data distribution assessed by visual inspection of histograms. Categorical variables were presented as numbers and percentages (%).

Results

Of the 20 patients included in the study, 13 (65%) were female and 7 (35%) were male. The mean age was 57.6 years (range: 19–90). Eighteen patients (90%) were referred from external centers, while bile duct injury occurred at our institution in two patients (10%). Bile duct injuries were identified intraoperatively in 19 patients and in the postoperative period in one patient (Table 1).

According to the Strasberg classification, the most frequently observed injury type was Type E2 (70%), followed by Type E1 (25%) and Type E3 (5%). Roux-en-Y hepaticojejunostomy was performed in 85% of cases, while portoenterostomy was performed in one patient and choledochal repair using a T-tube was performed in two patients (Table 2).

Concomitant vascular injury was present in two patients; injury to the right hepatic artery was identified in one patient, and injury to the proper hepatic artery was detected in the other. Reanastomosis with a graft was performed in the patient with proper hepatic artery injury, whereas no additional surgical intervention was performed in the patient with right hepatic artery injury.

Table 1. Demographic Characteristics of Patients

Characteristic	Value
Sex, n (%)	
Female	13 (65)
Male	7 (35)
Age, years (mean, range)	57.6 (19-90)
Referral status, n (%)	
External center	18 (90)
Same institution	2 (10)
Timing of diagnosis	
Intraoperative	19 (95)
Postoperative	1 (5)
Diagnosis	
Acute cholecystitis	14 (70)
Cholelithiasis	5 (25)
Gallbladder polyps	1 (5)
Hospital stay (mean, range)	7.2 days (5–11)

Table 2. The distribution of injuries according to the Strasberg classification and Surgical Procedure

Characteristic	Value
Type of Injury	
Type E1	5 (25)
Type E2	14 (70)
Type E3	1 (5)
Concomitant vascular injury	2 (10)
Surgical Procedure Performed	
Roux-en-Y hepaticojejunostomy	17 (85)
Choledochal repair with T-tube	2 (10)
Portoenterostomy	1 (5)
Biliary fistula following surgical procedure	2 (10)

The mean length of hospital stay was 7.2 days (range: 5–11). Postoperative bile leakage developed in two patients; one was treated with ERCP and percutaneous drainage, while the other was managed conservatively. No perioperative mortality was observed.

Discussion

Although laparoscopic cholecystectomy (LC) is widely accepted as the gold standard treatment for symptomatic gallstone disease, it is associated with one of its most serious and potentially life-threatening complications, namely major bile duct injuries (BDIs).[3,4] The reported incidence of BDIs following LC ranges from 0.4% to 0.6%.[2] Despite a gradual reduction in these rates attributable to increased surgical experience and the adoption of standardized technical principles, BDIs continue to represent a major clinical challenge due to their association with considerable morbidity, mortality, and increased healthcare costs.[5] Notably, Sağlam et al. have reported cases progressing to liver transplantation after bile duct injury, highlighting the potentially devastating consequences of this complication.[6]

In the early period following the introduction of laparoscopic cholecystectomy, the incidence of bile duct injury was reported to be higher compared with open cholecystectomy. However, with increasing surgical experience and completion of the learning curve, these rates have gradually declined, and laparoscopic cholecystectomy has become the standard surgical approach in current practice. Nevertheless, despite improved surgical expertise, several studies have demonstrated that the incidence of bile duct injury remains higher in cases defined as difficult laparoscopic cholecystectomy. Advanced age, male sex, the presence of anatomical variations, and procedures performed in the setting of acute cholecystitis are considered risk factors associated with difficult laparoscopic cholecystectomy.[7] In our study, 35% of the patients were male, the mean age was 57.6 years, and 70% of the patients underwent surgery for acute cholecystitis. These findings are consistent with the existing literature and suggest that laparoscopic cholecystectomy performed during acute cholecystitis represents a significant risk factor for the development of bile duct injury. Due to the relatively limited sample size of our study, no statistically significant difference was observed with respect to male sex.

From a pathophysiological perspective, most injuries result from misidentification of the common bile duct as the cystic duct, leading to inadvertent transection, clipping, or ligation. This mechanism is closely related to inadequate achievement of the "critical view of safety" during dissection.[8] While previous studies have shown that approximately 20–30% of BDIs are recognized intraoperatively, the majority are diagnosed in the postoperative period based on clinical suspicion.[9] In the present study, bile duct injuries were identified intraoperatively in 19 patients, whereas only one patient was diagnosed postoperatively. In patients with delayed recognition, the most common warning signs include bile output from surgical drains, persistent abdominal pain, abdominal distension, clinical findings of biliary peritonitis, and unexplained elevations in cholestatic liver enzymes—particularly alkaline phosphatase and gamma-glutamyl transferase—as well as serum bilirubin levels.[10]

Appropriate imaging modalities are essential for confirming the diagnosis of major bile duct injuries (BDIs) and for accurately defining the type and anatomical level of injury, which are critical determinants of the subsequent treatment strategy. Among available imaging techniques, magnetic resonance cholangiopancreatography (MRCP) is currently

regarded as the preferred first-line modality owing to its non-invasive nature and high diagnostic accuracy.[10] MRCP enables detailed three-dimensional visualization of the biliary tree and allows precise identification of the presence, location, and extent of bile leakage. Consequently, it facilitates reliable classification according to the Strasberg system and supports appropriate therapeutic decision-making.[11] In the present study, MRCP, complemented by endoscopic retrograde cholangiopancreatography (ERCP) when indicated, was used to characterize the type of bile duct injury.

The Strasberg classification remains the most widely accepted framework for guiding management algorithms in patients with major BDIs. While minor injuries, classified as Types A–D, are generally amenable to minimally invasive interventions such as ERCP with biliary stenting or percutaneous drainage, Type E injuries—defined by complete transection of the main bile duct or extensive defects—typically necessitate surgical reconstruction, particularly in Types E1–E4.[12] In our cohort, approximately 70% of patients were diagnosed with Type E2 injuries. For these high-grade injuries, Roux-en-Y hepaticojejunostomy (HJ) is widely considered the gold standard reconstructive approach, as it provides a tension-free biliary-enteric anastomosis and is associated with favorable long-term patency and low stricture rates.[13] Consistent with these recommendations, HJ was performed as the primary reconstructive procedure in 17 patients in our series.

The management of major bile duct injuries (BDIs) requires a multidisciplinary approach and should ideally be undertaken in experienced hepatobiliary centers with the collaboration of specialists in gastroenterology and interventional radiology.[13] Such an integrated strategy is crucial for accurate diagnosis, prompt patient stabilization in the setting of acute biliary peritonitis or sepsis, and determination of the optimal timing for definitive surgical repair. Importantly, concomitant vascular injuries involving the hepatic arterial system—most frequently the right hepatic artery—or, less commonly, the portal vein, have been reported in approximately 10–25% of patients with BDIs.[14] In the present study, vascular injury was detected in two patients, involving the proper hepatic artery in one case and the right hepatic artery in the other. Given that associated vascular injuries substantially increase the risk of hepatic parenchymal ischemia and subsequent biliary strictures, their early recognition and repair, when technically feasible, are of paramount importance. Moreover, high-level bile duct injuries affecting the biliary confluence or proximal hepatic ducts (Strasberg Types E3, E4, and E5) represent the most technically demanding scenarios and, in rare instances, may ultimately necessitate liver transplantation following unsuccessful reconstructive attempts.[6,15]

The timing of intervention is another critical determinant of prognosis in patients with major BDIs. When the injury is recognized intraoperatively and the patient remains hemodynamically stable, immediate or early reconstruction—performed during the index operation or within the first 72–96 hours by an experienced surgical team—offers the highest likelihood of favorable outcomes.[9] In our series, bile duct injuries were diagnosed early in 19 patients, allowing for timely reconstruction. Conversely, in cases with delayed diagnosis accompanied by sepsis, intra-abdominal infection, or pronounced inflammatory changes, initial management should prioritize biliary decompression through interventional radiological techniques, effective infection control, and metabolic stabilization. Definitive reconstructive surgery in these patients is generally postponed for 4–6 weeks to permit resolution of inflammation and to facilitate repair under elective and more favorable conditions.[16]

This study has certain limitations, including its retrospective design and the relatively small sample size. Nonetheless, our results are in agreement with existing literature and further underscore the importance of multidisciplinary management, accurate injury classification, and appropriate timing of intervention in the treatment of major BDIs. In our clinical experience, early reconstruction in patients diagnosed intraoperatively was technically less challenging and associated with lower complication rates. Additionally, favorable outcomes were achieved in patients referred from external centers with delayed diagnosis through initial stabilization followed by carefully planned elective surgical reconstruction.

Conclusion

Early recognition and appropriately timed surgical reconstruction are fundamental to achieving favorable outcomes in the management of bile duct injuries. Importantly, even in patients with delayed diagnosis, successful clinical and surgical results can be attained when management is conducted within experienced hepatobiliary centers using a multidisciplinary approach.

Disclosures

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Original Research

Radioembolization Effects on Liver Function and Tumor Responses in Hepatocellular Carcinoma Patients

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Abstract

Objectives: Transarterial radioembolization with ^{90}Y (TARE) is used as neo-adjuvant therapy for resection, liver transplant down-staging, or frontline therapy for hepatocellular carcinoma (HCC) patients. There are few reports on its use from high-throughput liver transplant or HCC institutions in the developing world.

To evaluate responses of both the liver and tumor to TARE in patients awaiting living donor liver transplant (LDLT).

Methods: HCC patients received TARE, and suitable patients then received LDLT or otherwise continued TARE till disease progression. CAT scans, liver lobe volumes and liver function tests were assessed at baseline and 3 months.

Results: Less than 10% of patients developed decreased blood albumin or platelets, or increase in total bilirubin or ALBI grade at 3 months post TARE. Many patients with abnormal baseline liver values, had an increase in albumin (42.1% patients) and platelets (64.7% patients) or decrease in total bilirubin (71.4% patients) or ALBI grade (51.5% patients) at 3 months post TARE. To explain liver function improvements, lobar liver volumes were assessed and increased in the TARE-untreated, contralateral lobe (median 17.46%) pre-Tx. AFP levels decreased in 81.8% of patients with elevated baseline AFP levels. Survival was longer in the TARE-Tx compared with unrelated TARE-non transplanted patients.

Conclusion: Liver toxicities were low, and many patients had early improvement in liver parameters post TARE.

Keywords: HCC, lobar hypertrophy, liver function, radioembolization

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Transarterial radioembolization with ^{90}Y (TARE) has increasingly become part of the therapeutic armamentarium for locoregional therapy for patients with non-metastatic hepatocellular carcinoma (HCC) in recent years, owing to its effectiveness, relatively low toxicity[1-3] and comparable survival rates to transarterial chemoembolization (TACE).[4-6] In addition it is relative safe compared with TACE in patients with portal vein thrombosis (PVT).[7,8] Despite the burgeoning literature on its use, precise knowledge is still lacking concerning its mechanisms, predictors of response and resistance, optimal uses and combinations with other treatment modalities. There is also no accurate information on the speed to or durability of HCC responses.

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TARE has been shown to cause ipsilateral lobar or segmental atrophy, together with corresponding contralateral lobar hypertrophy, and is increasingly used as a safer substitute to portal vein embolization (PVE)[9, 10] for the preparation of patients for resection who have a potentially marginal future liver remnant (FLR) after resection.[11-14] We have explored these considerations in a series of patients who were treated with TARE for tumor control while being prepared for subsequent liver transplantation (LT). We performed targeted radioembolization therapy using either glass microspheres (Therasphere) or resin microspheres (Sirsphere), each containing radioactive ^{90}Yttrium (^{90}Y). A small proportion of these HCC patients had some expected liver toxicities[15, 16] post TARE, but we also unexpectedly found patients whose liver function improved compared with baseline values, in addition to a decrease in serum levels of alpha-fetoprotein (AFP) in patients who had elevated baseline AFP levels. We found contralateral lobar hypertrophy on routine follow-up CAT scans compared to baseline pre-TARE scans, which may explain the liver function improvement. We also consider other explanations and suggest new hypotheses for this, concerning tumor-microenvironmental interactions. If correct, this may enhance our ideas concerning the 2-way interactions between HCC and its microenvironment.

Methods

Thirty six unresectable patients with hepatocellular carcinoma (HCC) were treated with TARE to maintain tumor control while preparations were being made for living donor liver transplantation (LDLT), TARE-Tx were retrospectively analyzed.

Inclusion criteria: patients with an HCC diagnosis that was considered to be unresectable, age >18 years, absence of metastases, lung shunt <20%, prior informed consent for the radioembolization procedure and treatment; ECOG performance status <3 and adequate hematologic, renal and liver function tests for a safe interventional procedure.

Demographic and clinical characteristics of the HCC patients analyzed for this study were: age, gender, pre-TARE and last (pre-transplant) alpha-fetoprotein (AFP) and liver function values, maximal baseline tumor diameter, number of tumors (1 versus >1) and presence or absence of macroscopic portal vein invasion by tumor (PVT) on the CAT scan. The primary objective of this retrospective analysis was to examine the responses of the treated liver by liver function tests, as well as of the HCC to therapy by serum AFP level and CAT scan changes (RECIST criteria) and to identify the development of any liver toxicities. Since we unexpectedly found improved liver function in several patients, we then retrospectively looked for hypertrophy in the untreated contralateral liver lobe in the CAT scans. Radiographic liver volume and lobar assessment was performed by liver CAT scan at baseline and at 3 months post TARE, using Myrian imaging software, France.

The study protocol was approved by the ethical committee of the University institutional review board (IRB) for non-interventional studies (2025/8125) for data collection and analysis, and conducted in adherence to the Declaration of Helsinki. Since this was a non-intervention retrospective study, patient informed consent was not required for the study evaluation, although each patient signed an informed consent for the proceedure.

Diagnosis of HCC was established by percutaneous biopsy or noninvasively based on presence of a hepatic mass greater than 2 cm diameter with characteristic imaging findings in the setting of liver cirrhosis as per EASL guidelines. Treatment was performed on an inpatient basis, and patients were typically not discharged home for 24 hr after the procedure for post-TARE safety observations.

Radioembolization Procedures

Patients were treated as per published guidelines[15-17] and underwent pre-treatment angiographic mapping of the abdominal aorta and hepatic arteries. Planar scans of the lung and liver area in anterior and posterior views were acquired after injection of 99mTc-labelled albumin macroaggregated albumin (99mTc-MAA) into selected arterial branches followed by SPECT (until 2006) or SPECT/CT scans. Radioembolization was delivered using Yttrium-90 resin microspheres (SIR-Spheres; Sirtex Medical Limited, North Sydney, NSW, Australia) or glass microspheres Therasphere, Boston Scientific, Boston MA, USA). Dose calculating changed over time. Initially, the BSA method was used, but subsequently, personalized dosimetry planning, considering optimal absorbed doses by tumoral and non-tumoral volumes was used by the treating interventional radiologist.

Hepatic Volumetric Analysis

CT images (Somatom Definition, 256x256; Siemens Healthineers, GmbH, Erlangen, Germany) were used for volumetric evaluation. According to routine dynamic hepatic CT protocol, pre-contrast, thin-slice scanning and non-ionic, contrast-enhanced arterial, portal, and hepatic phase thin-slice scanning were performed. Automated volume calculation software used the data from the CT images to create estimated measurements.[17]

Clinical Evaluation

Serum laboratory analysis included complete blood count, international normalized ratio, AFP levels and comprehensive metabolic and liver panel were obtained at baseline and repeated at 1 and 3 months post TARE. Radioembolization-related toxicities were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v6.0 and the assessment of radioembolization-induced liver disease.[18] Tumor responses were evaluated by mRECIST (modified Response Evaluaton in Solid Tumors) criteria. Tumor necrosis was assessed by microscopic estimates in 5% increments.

Statistical Analysis

The normality of the quantitative data was assessed by Shapiro-Wilk test. Mann-Whitney U test was used to compare two independent groups and data were summarized by median (interquartile range). The distribution of the qualitative data was presented by count (percentage), and chi-square test was used for comparisons. Survival analyses were performed by Kaplan-Meier analysis, Log-rank test and univariate Cox regression analysis. The two-sided significance level was considered as 0.05 in all analysis. Software analysis was IBM SPSS Statistics for Windows, Version 26.0 (Armonk, NY: IBM Corp.).

Results

Liver Function Changes After TARE in Pre-transplant (TARE-Tx) HCC Patients

Liver function changes after TARE treatment are shown in Table 1, A-E. Results at 3 months post TARE showed a decrease in serum albumin levels in 8.3% percent of patients (Table 1A), all less than grade 3 toxicity by CTCAE criteria.[18] Stable levels were seen in 69.4% of patients. However, an improvement or increase in serum albumin levels was seen in 22.2% of the total patient cohort, or in 42.1% of those patients (8 of 19) who had low baseline <3.5 g/dL (abnormal) serum albumin levels (Table 1A, top row). There were similar findings for blood platelet levels, with 9.3% having decreased levels and 34.4% of the total cohort having increased platelet levels, or 64.7% of those patients (11 of 17) who had baseline thrombocytopenia <125 x103/μL, which is a reflection of portal pressure (Table 1B, top row) having increased platelet levels. Total serum bilirubin levels were increased in 9.3% of the total cohort at 3 months, all less than grade 3 toxicity, and 59.3% of patients had stable serum bilirubin levels. However, similar to the findings for albumin, 31.2% of the cohort had decreased (improved) total bilirubin levels, which was 71.4% of those patients (10 of 14) who had increased baseline serum total bilirubin levels of >1.5 mg/dL (Table 1C, bottom row). Similar results were seen for INR levels (Table 1D). ALBI levels were calculated, using MDCalc (www.mdcalc.com). A worsened (increased) grade was seen in 6% of patients at 3 months post TARE, while 51.5% (17 of 33 patients) had an improved (decreased) grade (Table 1E). Thus, there were some worsened liver function values, but a larger patient number had improvement in levels of albumin (increased), platelets (increased), total bilirubin (decreased), INR (decreased) and ALBI grade (decreased). The slight decrease in denominator patient numbers for INR and ALBI reflect some missing lab values.

Tumor Changes After TARE in Pre-transplant (TARE-Tx) HCC Patients

Baseline serum AFP levels were elevated in only 13 of 36 patients (36%) of the cohort, a figure close to what we and others have previously found.[20, 21] Two of 11 patients (18.2%) had increased AFP levels within 3 months of TARE (Table 2A), whereas 9 of 11 patients (81.8%) had decreased AFP levels, mostly by >90% at 3 months after TARE in pre-transplant patients. CAT scan-based tumor changes at 3 months (post 1 cycle of TARE) showed that 32.1% of the 36 patients had minor responses (RECIST criteria), with no partial or complete responses, but 60.7% of patients had decreased tumor vascularity (Table 2B). The transplant pathology showed an average of 58.7% necrosis in the treated HCC specimens, with 52% of patients having more than 75% of the tumor cells being necrotic (Table 2C). The variability of response by necrosis may also be a reflection of the wide time range between TARE and LDLT, being a mean of 6.3 months (range of 3 to 12 months) and a median of 5 months.

Changes in Liver Lobe Volumes in Response to TARE

TARE has previously been shown to cause atrophy in the treated liver lobe and compensatory hypertrophy in the non-treated, contralateral lobe,[11-14] which has being used to prepare for liver resection in those patients who have potential marginal future liver remnants (FLR) post resection. Since embolization- induced contralateral liver hypertrophy has been thought to be associated with improved liver function,[21, 22] we considered whether similar hypertrophy might explain the liver functional improvements found post TARE in our patients. Lobar volume changes in treated right lobes and untreated contralateral left lobe volumes are shown in Table 4. The median treated right lobe atrophy was a volume decrease of -16.4%, with a wide range from -49.01 to -5.22 percent decrease (data not shown). In contrast, hypertrophy in the untreated left lobe had a median increase of 17.46% in volume, with a similarly large range of 5.69 to 41.5% increase in the transplant (TARE-Tx) patients (Table 3).

Table 1. Blood parameter responses post TARE in pre-transplant (TARE-Tx) patients

A. Albumin. TARE-Tx	**Patients**	**Baseline – 1 mo. n (%)**	**Baseline – 3 mo. n (%)**
*Increased	Baseline low	9/21 (42.8)	8/19 (42.1)
Increased		9/36 (38.9)	8/36 (22.2)
No change	All	24/36 (66.6)	25/36 (69.4)
Decreased		3/36 (8.3)	3/36 (8.3)

*denominator reflects only those patients with abnormal baseline values.

B. Platelets. TARE-Tx	**Patients**	**Baseline – 1 mo. n (%)**	**Baseline – 3 mo. n (%)**
*Increased	Baseline low	10/17 (58.8)	11/17 (64.7)
Increased		10/36 (27.8)	11/32 (34.3)
No change	All	24/36 (66.6)	18/32 (56.2)
Decreased		2/36 (5.5)	3/32 (9.3)

*denominator reflects only those patients with abnormal baseline values

C. T. Bili. TARE-Tx	**Patients**	**Baseline – 1 mo. n (%)**	**Baseline – 3 mo. n (%)**
Increased		4/36 (11.1)	3/32 (9.3)
No change	All	19/36 (52.7)	19/32 (59.3)
Decreased		13/36 (36.1)	10/32 (31.2)
*Decreased	Baseline high	13/16 (68.7)	10/14 (71.4)

*denominator reflects only those patients with abnormal baseline values

D. INR. TARE-Tx	**Patients**	**Baseline – 1 mo. n (%)**	**Baseline – 3 mo. n (%)**
Increased		1/32 (3.1)	1/32 (3.1)
No change	All	28/32 (87.5)	27/32 (84.3)
Decreased		3/32 (9.3)	4/32 (12.5)
*Decreased	Baseline high	3/7 (42.8)	4/7 (57.1)

*denominator reflects only those patients with abnormal baseline values

E. ALBI TARE-Tx	**Patients**	**Baseline – 1 mo. n (%)**	**Baseline – 3 mo. n (%)**
Grade Increase		2/35 (5.7)	2/33 (6.0)
No change	All	18/35 (51.4)	14/33 (42.4)
Grade Decrease		15/35 (42.8)	17/33 (51.5)

ALBI - Increased: 2 to 3(1);1 to 2(1). Decreased: 2 to 1 (10); 3 to 1 (5); 3 to 2 (2). Albumin, Platelets (A, B), improvements = increased level post TARE as % of low baseline level. Bilirubin, INR (C, D), improvements = decreased level post TARE as % of elevated baseline level. ALBI (E), improvement = decreased grade post TARE compared with baseline grade.

Survival After TARE in Transplant (TARE-Tx) and Non-transplant (TARE-no Tx) Patients

Survival time for the TARE-Tx patients was significantly better than for the TARE-no Tx patients, as expected, with median survival in the transplant group not yet reached, but with a mean of 2211.29±168.97 days, compared to a mean of 1002.05±137.49 days for the non-transplant group (Table 4). The hazard ratio for death for the TARE-no Tx patients was 6.140.

Clinical Characteristics of TARE-Tx Compared with TARE-no Tx Patients

In order to try to understand the differences in the survival post TARE in the TARE-Tx versus the TARE-no Tx patients, we compared their blood biochemical and their tumor

Table 2. AFP and tumor responses post TARE in pre-transplant (TARE-Tx) patients

A.AFP.	TARE-Tx (n=13)	
	Baseline – 1 mo. n (%)	Baseline – 3 mo. n (%)
Increased	2/13 (15.4)	2/11(18.2)
No change	0	0
Decreased	11/13 (84.6)	9/11 (81.8)

B.Tumor response by CAT scan post TARE	TARE-Tx (n=28) n (%)
Minor	9 (32.1)
PR	0
CR	0
Stable	19 (67.8)
Progression	0
Vascular response	17 (60.7)

PR: Partial response; CR: Complete response.

C.Transplant tumor pathology (% necrosis)	TARE-Tx (%)
Range	5-100
Average	58.7
>75% necrosis	52

Table 3. Pre-transplant liver lobe volumes pre and post TARE (left lobe hypertrophy)

	Pre-TARE left	Post-TARE left	Change % left
Mean (mL)	552.3	657.6	20.29
Median (mL)	471	629	17.46
Min (mL)	241	312	5.69
Max (mL)	1203	1378	41.50

profiles (Table 5). The 4 tumor characteristics were all more aggressive for the TARE-no Tx versus the TARE-Tx patients. Thus, AFP levels (median 13.34 versus 64.55 IU/mL), maximum tumor diameter or MTD (median 7.5 versus 5.5 cm), percentage of patients with PVT (63.6 percent versus 33.3 percent) and tumor multifocality (66.6 percent versus 33.3 percent of patients), were all significantly worse in the non-transplant compared to the transplanted patients. These more aggressive tumor characteristic findings likely explain the reason why the TARE-no Tx patients could not be transplanted. Conversely, the liver function tests (total bilirubin, INR, GGT and platelets) were all significantly worse in the transplant group and liver transplantation is curative for liver failure. Interestingly, serum albumin levels were not significantly different, nor were the AFP levels significant, despite their similar median values, probably due to the wide range of individual values.

Discussion

TARE therapy has increasingly been used as a bridge to liver transplantation in the treatment of HCC.[24-27] Several reports have shown that contralateral hypertrophy of the non-irradiated liver occurs following TARE.[3-6] This effect has been considered useful because TARE has been shown by others to provide both tumor control as well as induction of contralateral hypertrophy, to enable improved liver function for possible planned resection surgery. TARE has superceded portal vein embolization[9, 10] for this purpose, in part for its enhanced safety compared with embolization, as well as for its concomitant tumoricidal actions. Although the current study did not involve resection, we were interested to see the rapid changes in lobar liver volumes and liver function tests post TARE, during the time these patients received TARE as a bridge to liver transplantation.

We found some grade <3, mainly transient liver toxicities, in line with the low percentage of these events reported by others[27-30] with less than 10% of patients having liver toxicities, mostly low grade and transient, as seen in changes in blood bilirubin, albumin, INR and ALBI score,[31-33] as well as platelets levels as a reflection of portal pressure (Table 1).

We also noted improvement in liver function, particularly in patients with baseline abnormal liver tests. This is shown in Table 1 as an increase with respect to baseline abnormal low values in blood levels of albumin or platelets, or a decrease in total bilirubin levels or INR, with respect to abnormal elevated baseline values. How might this improvement be explained? Others have shown an improvement in liver metabolic or other liver functions as a result of embolization- or TARE- induced lobar hypertrophy.[34-37] Therefore we used specific software (Methods) to measure pre- and post-TARE liver lobe volumes (Table 3) and found both treated

Table 4. Survival in TARE transplant (TARE-Tx) and TARE non-transplant (TARE-no Tx) patients

	Survival (days) Mean±SE	Survival (days) Median±SE	Log-Rank p	HR (95% C.I.)	HR p
TARE-no Tx (n=36)	1002.05±137.49	765.00±42.46	<0.001	6.140 (2.460-15.324)	<0.001
TARE-Tx (n=36)	2211.29±168.97	NA		reference	

Table 5. TARE pre-transplant (TARE-Tx) and TARE non-transplant (TARE-no Tx) patient characteristics

	TARE-Tx (n=36)		TARE-no Tx (n=36)		
Pre-treatment	**N**	**Median (IQR)**	**n**	**Median (IQR)**	**p**
AFP	36	13.34 (114.8)*	36	64.55 (994.05)*	0.110
ALB	35	3.3 (0.9)	36	3.2 (0.8)	0.645
T.Bili	36	1.46 (1.36)	36	0.77 (0.59)	0.001
INR	36	1.21 (0.37)	35	1.11 (0.2)	0.007
Platelets	36	118 (106.25)	36	159 (120.5)	0.025
GGT	36	105.5 (89.5)	23	144 (227)	0.033
MTD (cm)	36	5.5 (5.3)	36	7.5 (4.0)	0.008
MTD (cm) range		2-15		2.2-19.5	
PVT (Yes)	12	33.3%	21	63.6%	0.025
Multifocality (Yes)	12	33.3%	24	66.6%	0.002

*median AFP relates to those patients with elevated serum AFP levels. Tx: transplant; AFP: alpha-fetoprotein (IU/mL); ALB: albumin (g/dL); T. Bili, total bilirubin (mg/dL); GGT: gamma-glutamyl transferase (IU/mL); INR: international normalized ratio; platelets (109/L); MTD: maximum tumor diameter (cm); PVT: portal vein thrombosis (Yes).

right lobe atrophy (not shown) and contralateral untreated left lobe hypertrophy, the latter being a median of 17.46 percent expansion in untreated lobar volume. This is in line with the reported degree of hypertrophy within 3 months in the untreated lobe in 6 studies, with a range of 7-57%.[28] There has been discussion in the literature on the relationship between degree of liver hypertrophy versus liver functional increase, although any quantitative relationship is not yet clear.[35-36]

Tumor responses to TARE treatment were initially evaluated by measurement of serum alpha-fetoprotein levels, which have been shown to correlate well with TARE responses,[38, 39] and then by CT scan. Over 80% of the patients with elevated baseline AFP levels had a response by 1 month, which proved durable at 3 months in the transplant patients (Table 2). This is in line with the massive AFP responses reported by others, with 40-70% of patients showing a 90% decrease in AFP levels.[38, 40] However, only 36% of our cohort had elevated baseline AFP values and thus AFP responses could not be evaluated in the other 64% of the patients. A similar range of findings was found by others in relationship to AFP response and outcomes.[41] The CAT scans showed minor responses in 32.1% of the patients in the transplant group, but this low response rate is to be expected after a single TARE session and only 3 months post treatment.

Patients had a wide range of necrosis on transplant pathology. Despite this, with 5-100 percent of tumor cells in differing patients having necrosis, only 52 percent of patients had more than 75 percent of necrotic cells on pathology exam, similar to other reports.[27]

The fact of so much variability in liver enzymes after TARE, with some patients having (mainly minor) toxicities, whereas others showing an improvement in liver function, suggests that multiple factors could be at play. The simplest explanation is the documented contralateral lobar hypertrophy,[21, 22, 34, 35, 42] which permits a greater surgical margin of safety for planned resection in patients with otherwise uncertain post resection liver reserve/FLR. However, whether the observed 20 percent increase in untreated contralateral lobar mass is sufficient to explain an actual improvement in the liver function in some patients, has not yet been definitively addressed.

Accordingly, other explanations might be considered. It is possible that TARE kills invasive, parenchyma-destroying cancer cells. Another possibility is that HCC cells may be secreting factors that have a negative influence on liver parenchyma. The concept of the liver microenvironment secreting growth and inflammation factors that influence the tumor is now well accepted. Yet the reverse concept is also plausible, given that cancer cachexia has been recognized as a factor in advanced cancers[43-46] and cancer cells have been shown to secrete metabolic cytokines and other mediators of catabolism.[47] The speed of changes is also consistent with reports of decreases in peripheral lymphocyte levels within 24 hr of TARE.[48, 49] Hepatic immune cell changes within a few days of TARE have recently also been reported.[50] The improvement in liver function after regional liver radiation in a subset of patients reported here has also been observed by others.[34, 35, 51] Whole liver radiotherapy for liver metastases has also been reported to result in improved liver function.[52]

The heterogeneity in response does not currently have a satisfactory explanation, especially given reports of an

unclear correlation between degree of hypertrophy and relatvely greater improvements in liver function.[53, 54] This suggests the possibility of factors other than lobar volume expansion in explaining the liver function improvements post TARE.

The survival data show that TARE followed by transplantation resulted in better survival than TARE alone, as expected. TARE was used in a our transplant group because so many of this group were borderline or outside Milan criteria with respect to tumor size, levels of serum AFP or presence of branch PVT. TARE is also considered to be a relatively safe (toxicities) and effective (decreased AFP levels and presence of necrosis on pathological examination post transplant) therapy and as a bridge to liver transplantation. The variability in time from TARE to transplant was a reflection of need to downstage the tumor or the requirements for procuring a donor liver in a country in which cadaveric organs are uncommon. However, the differences in survival between the transplanted and untransplantable patients could also have been attributable to the more aggressive and larger tumors in the untransplantable group. Thus, even without transplantation, the median survival of over 2 years for TARE patients was superior to survival reported for Sorafenib in recent clinical trials.[23] However, the 2 groups were not entirely comparable (Table 5), as the non-transplant patients had more aggressive HCC characteriststics, which made them non-transplantable.

Strengths and Weaknesses

This study adds to the literature on the incredible potential of the liver for regeneration and repair and to reports that radiation can cause both hepatototoxicity and also repair of liver damage, despite unclear mechanisms. It also implies that radioembolization appears increasingly attractive as a method for maintaining or diminishing HCCs during the wait for liver transplantation, as well as the continued evaluation of TARE as a possible mode of tumor downstaging in patients who present beyond the current criteria for liver transplantation for HCC.

There are also several limitations to this report, including its retrospective nature and the small numbers of TARE-Tx patients involved in this single institution study (n=36). Our post TARE evaluations, including serum liver parameters and AFP levels, CAT scan changes and pathology were measured at quite short times post TARE and thus likely under-estimate responses to therapy. Also, most of our patients were HBV-based and it is unclear how applicable the findings are to HCCs of other etiologies. The fact that the AFP-positive patients were less than 50 percent of the total is a reminder that AFP positive and negative HCCs may have different biologies and reinforces the need for better and more generally applicable HCC biomarkers. Interestingly, the first follow up of all these patients was at 1 month post TARE, during which many of the TARE-induced changes had already occurred.

Conclusion

Radioembolization has become a relatively safe and effective treatment for patients with advanced non-metastatic HCC (the majority). It has also helped us to study the very complex dynamics of the human liver as a result of radioembolization and highlighted both radiation-induced toxicity and radiation-induced improvements in liver function.

Disclosures

Ethics Committee Approval: Inonu Transplant Institute database management conforms to Turkish legislation on privacy and this study conforms to the ethical guidelines of the World Medical Association, Declaration of Helsinki. university IRB approval was 2025/8125 for retrospective analysis of de-identified HCC patients.

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AI: no use was made of artificial intelligence (AI)– assisted technologies (such as Large Language Models [LLMs], chatbots, or image creators) in the production of submitted work.

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Original Research

Routine External Biliary Stenting via the Cystic Duct in Living Donor Liver Transplantation: Is it Always Safe?

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Abstract

Objectives: External biliary stenting via the cystic duct is widely used in living donor liver transplantation (LDLT) to reduce biliary complications, particularly bile leakage, and to facilitate postoperative biliary management. While some centers apply this technique selectively, others routinely use external biliary stents in all recipients. However, stent-related complications, including mechanical failure, remain a concern.

Methods: Between January-2009 and May-2025, a total of 365 adult LDLTs were performed at our center. In all cases, duct-to-duct biliary reconstruction was completed with routine placement of an external biliary stent via the cystic duct, planned for removal at 5–6 months postoperatively. This retrospective analysis focused on patients who required surgical re-exploration due to stent fracture. Clinical presentation, imaging findings, intraoperative observations, surgical management, and postoperative outcomes were reviewed.

Results: Among 365 LDLT recipients, seven patients(1.9%) required laparotomy due to stent fracture. Stent fracture occurred between postoperative months 3 and 6, prior to the planned stent removal. All patients presented with acute abdominal pain and signs of peritonitis. Imaging demonstrated retained stent fragments within the biliary tract in all cases, with findings suggestive of biliary irritation or leakage. Urgent laparotomy was performed in all patients. Intraoperatively, fractured stent segments were identified in the biliary system. In two patients, fragments were embedded in the biliary tract, necessitating meticulous dissection. No perioperative mortality occurred however, all patients experienced prolonged hospitalization and postoperative morbidity. No graft loss directly attributable to stent fracture was observed.

Conclusion: Routine external biliary stenting via the cystic duct in adult LDLT may reduce bile leakage but is not without risk. Although stent fracture is rare, it can result in severe complications requiring reoperation and significant morbidity. These findings support reconsideration of a routine stenting policy and suggest that a selective approach based on intraoperative and patient-specific factors may be safer.

Keywords: Living Donor Liver Transplantation, external biliary stent, risk, stent-related complication

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Biliary complications remain one of the most frequent sources of morbidity following living donor liver transplantation (LDLT), despite advances in surgical technique and perioperative management.[1,2] Bile leakage and biliary strictures can significantly affect graft function, prolong hospitalization, and increase the need for reintervention.[3]

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To mitigate these risks, various biliary reconstruction strategies and adjunctive measures have been proposed.

External biliary stenting via the cystic duct is one such technique, widely adopted with the intention of decreasing anastomotic tension, facilitating bile drainage, and allowing early detection of bile leakage.[4] While some transplant centers advocate selective use of external stents based on intraoperative findings or recipient risk factors, others employ routine stenting in all LDLT recipients.[5] However, the presence of a foreign body in the biliary system is not without potential drawbacks. Stent related complications including infection, dislodgement, obstruction, and fracture have been reported, though they are considered relatively uncommon. Among these, stent fracture represents a particularly serious complication, as retained fragments may cause biliary obstruction, bile leakage, or intra-abdominal contamination, often necessitating surgical intervention.[6,7]

In this study, we report our experience with routine external biliary stenting via the cystic duct in LDLT recipients, focusing on a subset of patients who developed stent fracture requiring laparotomy. By presenting these cases, we aim to reassess the safety of a routine stenting policy and to discuss whether a more selective approach may be warranted.

Methods

Between January 2009 and May 2025, a total of 365 adult living donor liver transplantations were performed at our center. In all cases, biliary reconstruction was completed with duct-to-duct anastomosis, and an external biliary stent was routinely inserted via the cystic duct at the end of the procedure. The stent was secured and externalized, with planned removal between 5 and 6 months postoperatively, provided no biliary complications occurred.

This retrospective study focused on patients who required surgical re-exploration due to stent-related complications, specifically stent fracture. Medical records were reviewed to identify patients who underwent laparotomy for this indication. Seven patients met the inclusion criteria.

Data collected included recipient demographics, indication for liver transplantation, timing of stent fracture, presenting symptoms, imaging findings, intraoperative observations, type of surgical intervention performed, and postoperative outcomes. All patients were evaluated using abdominal imaging modalities when clinically indicated. The study was conducted in accordance with institutional ethical standards.

Statistical Analysis

Statistical analyses were performed using descriptive methods. Continuous variables were summarized as mean±standard deviation or median (range), as appropriate, while categorical variables were presented as counts and percentages. The incidence of stent fracture was calculated as a proportion of the total number of adult living donor liver transplant recipients who underwent routine external biliary stenting via the cystic duct. To quantify the precision of this estimate, a 95% confidence interval (CI) for the proportion was calculated using the Wilson score method. Given the descriptive nature of the study and the limited number of events, no comparative or multivariable analyses were performed. A p-value was not calculated, as the primary aim was to report the incidence and clinical impact of stent fracture rather than to test a specific hypothesis.

Results

Among the 365 adult LDLT recipients who received routine external biliary stenting, seven patients (1.9%) (7/365; 95% CI: 0.9%–3.9%) required laparotomy due to stent fracture. Indications for liver transplantation varied among these patients and reflected the general transplant population of the center (Table 1).

Stent fracture occurred between postoperative months 3 and 6, prior to the planned time of elective stent removal. All patients presented with acute abdominal pain, accompanied by clinical signs of peritonitis. Laboratory findings were nonspecific, and imaging studies revealed retained stent fragments within the biliary tract, with associated intra-abdominal findings suggestive of biliary irritation or leakage.

All seven patients underwent urgent laparotomy. Intraoperatively, fractured stent segments were identified within the biliary system. In two patients, the stent fragments were found to be embedded in the biliary tract, making removal technically challenging and requiring meticulous dissection. In the remaining cases, fragments were retrieved without major technical difficulty.

Table 1. Overall characteristics of the study population and stent-related outcomes

Variable	Value
Total adult living donor liver transplant recipients	365
Routine external biliary stenting via cystic duct	365 (100%)
Patients with stent fracture	7 (1.9%)
Time to stent fracture (months)	3–6
Patients requiring laparotomy	7 (100%)
Mortality related to stent fracture	0

There was no perioperative mortality. However, all patients experienced prolonged hospitalization, and postoperative morbidity was notable, including delayed recovery and the need for additional supportive care. No long-term graft loss directly attributable to the stent fracture was observed during follow-up.

Discussion

External biliary stenting via the cystic duct has been widely regarded as a protective adjunct in LDLT, primarily aimed at reducing bile leakage and facilitating postoperative biliary management.[8] The rationale for routine stenting is rooted in the high incidence and clinical impact of biliary complications in living donor transplantation. Nevertheless, the findings of the present series highlight an important and often underemphasized aspect of routine stent use which is stent-related morbidity. Although the incidence of stent fracture was low, the clinical consequences were significant. All affected patients developed acute abdominal symptoms, required reoperation, and experienced increased morbidity and length of hospital stay.

Stent fracture represents a mechanical failure with potentially severe outcomes. Retained fragments may act as a nidus for infection, cause biliary obstruction, or lead to bile leakage and peritonitis, as observed in our patients. Notably, these complications occurred within the intended indwelling period of the stent, raising questions about material durability, mechanical stress, and long-term safety.[9]

In addition to mechanical failure, the clinical impact of stent fracture should be interpreted in the broader context of postoperative surveillance and intervention strategies in LDLT recipients. External biliary stents are often perceived as a safeguard that simplifies postoperative management; however, when stent-related complications occur, they may paradoxically complicate the clinical course. In our series, the diagnosis of stent fracture was prompted by acute clinical deterioration rather than by routine surveillance, underscoring that such events may not be predictable or preventable through standard follow-up protocols. This highlights an inherent limitation of routine stenting, namely that a complication designed to prevent biliary morbidity can itself become a source of emergent reoperation.

Furthermore, the fact that stent fracture occurred within the planned indwelling period suggests that duration alone may not be the sole determinant of stent safety. Factors such as bile composition, local inflammatory response, graft regeneration, and dynamic changes in biliary anatomy after transplantation may contribute to mechanical stress on the stent over time. Although the present study was not designed to identify material or patient specific risk factors for stent fracture, the observed morbidity emphasizes the need for critical re-evaluation of the "one-size-fits-all" approach to external biliary stenting in LDLT.[10,11]

This study has several limitations that should be acknowledged. First, its retrospective design inherently limits the ability to control for confounding variables and precludes causal inference. Second, the analysis focuses on a small number of events, as stent fracture requiring surgical re-exploration was a rare complication, which restricts the performance of robust comparative or multivariable statistical analyses. Third, the study was not designed to evaluate the overall incidence of biliary complications, such as bile leakage or biliary strictures, in the entire transplant cohort; therefore, a comprehensive assessment of the net protective effect of routine external biliary stenting could not be performed. In addition, this represents a single-center experience, which may limit the generalizability of the findings to other institutions with different surgical techniques, patient populations, or postoperative management protocols. Finally, potential factors contributing to stent fracture—such as stent material properties, mechanical stress, and patient-specific biliary dynamics—could not be systematically analyzed and warrant further investigation in future prospective studies.

Taken together, these findings support a shift in focus from routine stent placement toward individualized decision-making. A selective strategy, guided by intraoperative assessment of biliary anatomy, anastomotic quality, and recipient risk profile, may help balance the potential protective effect of external stenting against the risk of stent related complications. Table 2 presents the potential benefits and risks of routine external biliary stenting via the cystic duct in living donor liver transplantation. Future studies comparing routine versus selective stenting protocols, ideally in multicenter settings, are warranted to better define which patient subgroups derive true benefit from external biliary stents without incurring disproportionate risk.

Table 2. Potential benefits and risks of routine external biliary stenting via the cystic duct in living donor liver transplantation

Potential Benefits	Potential Risks
Reduction in bile leak risk	Stent fracture
Controlled external bile drainage	Retained intra-biliary stent fragments
Early detection of biliary leakage	Biliary tract injury
Decompression of biliary anastomosis	Bile leakage and peritonitis
Simplified postoperative biliary monitoring	Need for reoperation Prolonged hospitalization and increased morbidity

Conclusion

Although routine external biliary stenting via the cystic duct is widely employed to mitigate biliary complications after adult living donor liver transplantation, our findings demonstrate that this strategy is not without clinically meaningful risk. Stent fracture, while infrequent, represents a severe complication that may precipitate acute abdominal pathology, necessitate urgent reoperation, and result in substantial postoperative morbidity. Importantly, these events occurred within the intended indwelling period of the stent, underscoring that the complication is not merely a consequence of prolonged or neglected stent use.

Taken together, our experience challenges the safety of a universal, routine stenting policy and highlights the need to reconsider a "one-size-fits-all" approach. A selective stenting strategy, guided by intraoperative biliary anatomy, anastomotic quality, and recipient-specific risk factors, may offer a more balanced means of maximizing protective benefit while minimizing the potential for serious stent-related harm.

Disclosures

Ethics Committee Approval: Ethical committee approval was not obtained because this study was retrospective in design.

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Case Report

A Rare Case in Living Donor Liver Transplantation: Graft-to-Graft of Portal Vein Anastomosis

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Abstract

In RL-LDLT, both APVB and PVT are associated with adverse operative outcomes. Portal vein thrombosis surgical planning depends on the type and extent of portal vein thrombosis. While completely occlusive portal vein thrombosis is associated with higher morbidity and an unfavorable postoperative course, long-term outcomes may be comparable to those of patients without portal vein thrombosis when physiological portal venous inflow can be achieved. In this report, we present a successful liver transplantation in which a living donor graft with APVB was reconstructed on the back table using a homolog portal Y-graft. This reconstructed graft was then anastomosed to a cadaveric interposition graft of the recipient with Yerdel grade 3 portal vein thrombosis, resulting in a graft-to-graft portal vein anastomosis.

Keywords: Jump graft, Jump graft and Y-graft anastomosis, Liver transplantation, Portal vein reconstruction

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Local or systemic pro-thrombotic conditions play a significant role in the pathogenesis of portal vein thrombosis (PVT).[1] PVT is a common complication occurring in 5–26% of cirrhotic patients listed for liver transplantation (LT). Although previous studies suggest that anticoagulant therapy may achieve portal vein recanalization, the timing and choice of anticoagulant therapy in these patients have not yet been clearly established.[2] When necessary, transjugular intrahepatic portosystemic shunt (TIPS) can be used as a minimally invasive option for PVT.

In advanced PVT cases, complex vascular reconstructions may be required to achieve a successful LT.[3] The commonly used classification was defined by Yerdel et al.[4] Early PVT (Yerdel grade I/II) can generally be managed by thromboendovenectomy, whereas grades III–IV may require a jump graft from the superior mesenteric vein (SMV).

Completely occlusive porto-mesenteric thrombosis poses major surgical challenges. Historically, LT was considered contraindicated in such patients, with multivisceral transplantation accepted as the only alternative.[5] Today, the main goal in PVT management for transplant candidates is to restore portal inflow through anatomical end-to-end portal vein anastomosis by achieving recanalization whenever possible.[6]

Our patient required both portal venous reconstruction with homolog portal Y-graft on the donor graft and a jump graft from the portal confluence due to PVT. This case involves highly complex procedures. In this report, we aim to emphasize that when physiological reconstruction pathways are used, long-term outcomes can be favorable and this case represents an encouraging example.

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Case Report

A 68-year-old Middle Anatolian female patient presented with clinical features consistent with chronic liver disease. She reported abdominal distension, fatigue, and weakness. Her MELD-Na score was calculated as 16. Preoperative dynamic liver CT demonstrated PVT with minimal residual flow. The patient underwent right-lobe living donor liver transplantation for cryptogenic liver failure and Yerdel type 3 PVT (Fig. 1).

This original has been confirmed and approved in writing by the legal guardian/relative of the person(s) included.

Surgical Technique

The recipient hepatectomy was performed using standard surgical procedures. Prior to graft implantation, thromboendovenectomy was attempted. However, during the procedure, a bleeding occurred at the portal vein confluence. Hemostasis was achieved by inflating a Foley catheter balloon at the confluence, and a cadaveric vein graft was anastomosed outfluence of SMV-Splenic vein for extension[15] (Fig. 2).

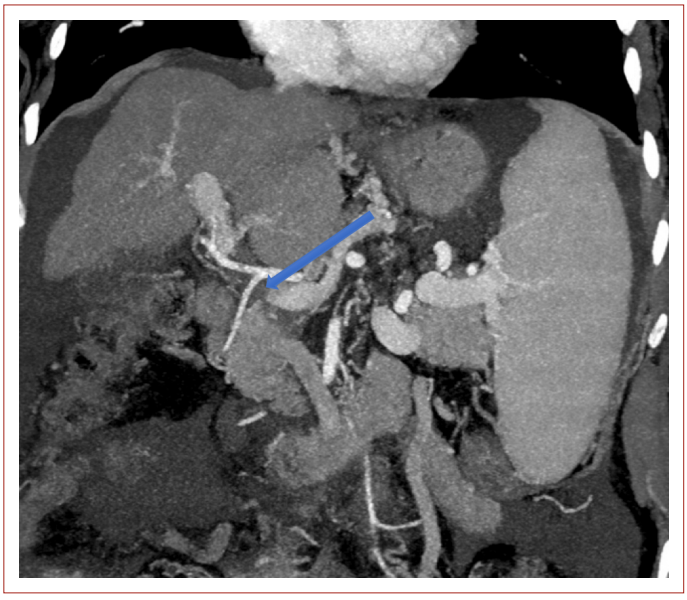

Figure 1. Preoperative imaging of Yerdel type 3 portal vein thrombosis.

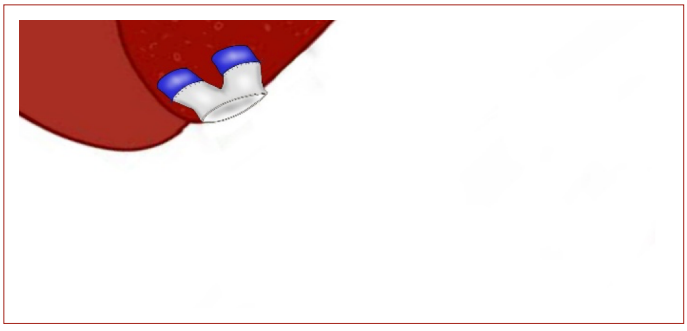

Figure 2. Back-table Y-graft reconstruction of double portal veins.

After clamping the vena cava, the right-lobe graft was implanted. The donor graft had anomalous portal venous branching (APVB); therefore, a homolog portal Y-graft interposition was performed on the back table (Fig. 3). The reconstructed right-lobe portal vein was then anastomosed to the recipient's extension graft (Fig. 4), ensuring continuous and physiological portal flow and successful graft perfusion.

The patient was discharged after routine intensive care and ward monitoring following the postoperative period. They are currently continuing with outpatient follow-up appointments (Figs. 3-5).

Discussion

Physiological reconstructions of the portal vein are associated with better postoperative outcomes. Physiological reconstruction techniques include primary anastomotic thrombectomy, interposition vein grafting, SMV jump grafting, and collateral vein interposition grafting. For non-physiological portal vein reconstructions, methods such as cavoportal hemitransposition, renoportal anastomosis, portal vein arterialization, and multiple organ transplantation have been described.

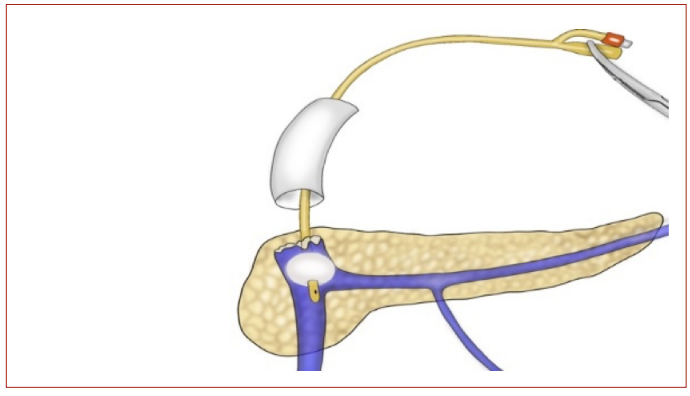

Figure 3. Extension graft anastomosis facilitated by Foley catheter inflation at the confluence.

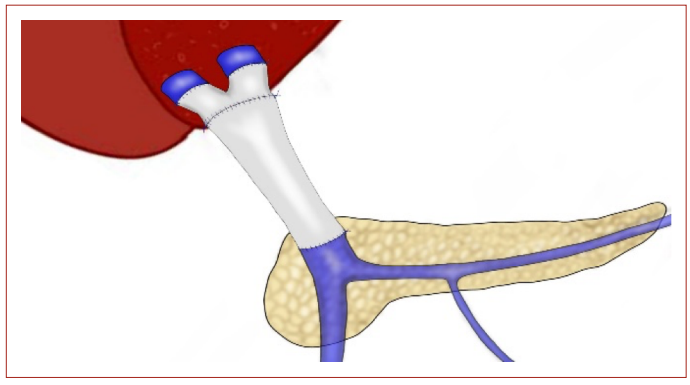

Figure 4. Graft-to-graft portal vein anastomosis.

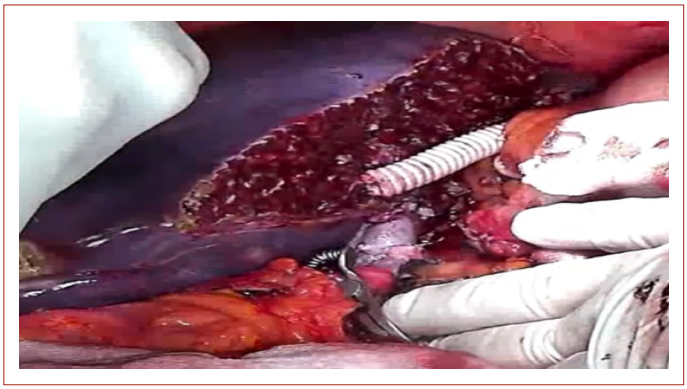

Figure 5. Intraoperative image of graft-to-graft anastomosis.

Various solutions for PVT have been described in the literature. Magistri et al. proposed an extra-anatomic jump graft from the right colic vein using an iliac vein graft.[7] Hwang et al. used a PTFE jump graft from the IMV to the portal vein in patients with portomesenteric thrombosis.[8] Mori et al. reported that when the SMV is patent but the thrombus extends to the confluence, iliac or jugular vein grafts can be used as a jump graft between the SMV and graft portal vein.[9] Ozdemir et al. emphasized that renoportal anastomosis can provide adequate portal inflow even in patients with prior proximal splenorenal shunt and splenectomy.[10]

Portal system reconstructions may also be required due to donor-related anatomical variations. In APVB, direct anastomosis may not be feasible, necessitating reconstruction. Several techniques have been described, including portal Y-graft interposition, which has demonstrated good long-term outcomes.[11] Yoo and Hwang later developed the conjoined unification venoplasty (CUV) technique to prevent stenosis sometimes seen with Y-grafts.[12]

Yilmaz S. et al. described a large-series technique known as the Malatya Approach, which combines APVB into a single outflow using a saphenous vein conduit, significantly reducing postoperative PVT and improving survival.[13]

Attempts to create a single portal vein orifice during donor surgery for APVB may also lead to complications, including stenosis and thrombosis of the remnant portal vein,[14] further emphasizing the importance of reconstruction.

Complex cases requiring combined portal vein reconstruction pose significant challenges in living donor transplantation. In our case, a right-lobe graft with APVB was transplanted into a recipient with PVT.

Although multiple reconstruction techniques have been described,[7–9] the goal remains achieving the most physiological flow with minimal anastomotic complexity. In this case, the right lobe graft APVB was reconstructed using a Y-graft, while an extension graft was used for recipient PVT. A graft-to-graft anastomosis was successfully performed.

Two major technical problems were encountered:

1. Restoring portal flow after thromboendovenectomy:

Endothelial injury at the confluence prevented direct anastomosis. When bleeding occurred during clamped anastomosis, the previously described balloon tamponade technique from our center[15] was used to safely complete the extension graft anastomosis.

2. Reconstruction of right lobe APVB:

Cadaveric iliac Y-grafts were used to solve the APVB. This allowed the graft-to-graft anastomosis to be performed safely.

The patient continues to be followed without any vascular complications (Figs. 6, 7). No similar graft-to-graft anastomosis technique was found in the literature.

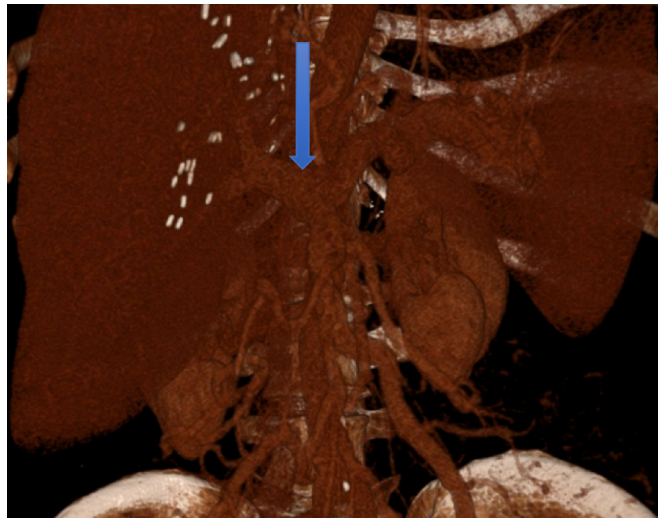

Figure 6. Dynamic CT (portal phase) performed 11 months post-transplant showing patent portal reconstruction.

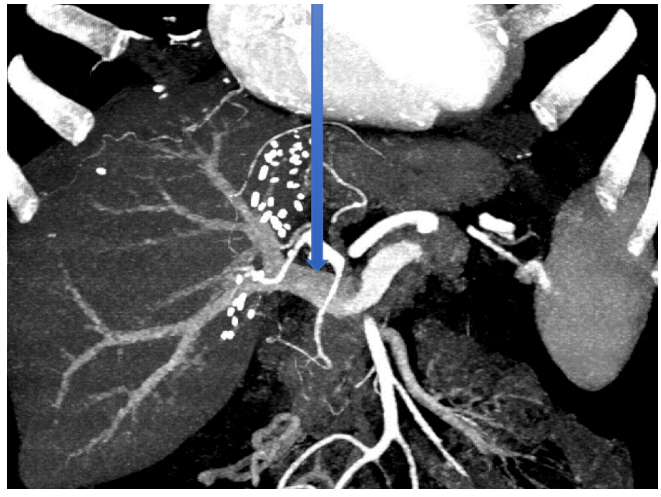

Figure 7. Dynamic CT (portal phase) performed 11 months post-transplant showing patent portal reconstruction.

Conclusion

In right-lobe living donor liver transplantation with APVB, successful outcomes can be achieved using appropriate surgical techniques. This case demonstrates that in living donor liver transplantation with PVT, a combined portal Y-graft and extension graft, completed with graft-to-graft anastomosis, can be safely used for portal vein reconstruction.

Disclosures

Informed consent: Written, informed consent was obtained from the patient's family for the publication of thís case report and the accompanying images.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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

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Case Report

Living Liver Donor with Gallbladder Agenesis

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Abstract

Gallbladder agenesis (GA) is a rare congenital condition with a reported incidence of 10–65 per 100,000 (1), though its true prevalence is likely underestimated due to frequent asymptomatic presentation. Symptomatic individuals may experience manifestations related to associated biliary tract disorders. We report a case of a living liver donor with GA, with particular emphasis on intraoperative considerations and surgical awareness required during donor hepatectomy.

Keywords: Gallbladder agenesis, living liver donor, living donor liver transplantation

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Gallbladder agenesis (GA) is a rare congenital condition with a reported incidence of %0.01-0.02,[1] though its true prevalence is likely underestimated due to frequent asymptomatic presentation. Symptomatic individuals may experience manifestations related to associated biliary tract disorders.[2] We report a case of a living liver donor with GA, with particular emphasis on intraoperative considerations and surgical awareness required during donor hepatectomy.

Case Report

The recipient of the living liver donor described in this report, a 38-year-old male patient presented with chronic liver disease. His Model for End-Stage Liver Disease (MELD) score was 15. He weighed 75 kg, with a body mass index (BMI) of 24.2 kg/m^2 and a body surface area (BSA) of 1.91 m^2. Dynamic computed tomography (CT) demonstrated a severely cirrhotic liver with moderate ascites. Following evaluation by a multidisciplinary liver transplantation committee, the patient was deemed an appropriate candidate for liver transplantation.

The donor was the patient's 25-year-old male nephew, he volunteered as a living liver donor candidate. His body weight was 73 kg, BMI 23.8 kg/m^2, and BSA 1.89 m^2. All laboratory investigations were within normal limits, and cardiopulmonary evaluation revealed no contraindications to living donation. On dynamic CT imaging, the gallbladder was not visualized, whereas both intrahepatic and extrahepatic bile ducts were present (Fig. 1). Volumetric analysis revealed a right lobe graft (segments V–VIII) volume of 750 cc, with a future liver remnant of 35%. Two segment VIII hepatic veins and two segment V hepatic veins were identified draining the right lobe. Hepatic arterial and portal venous anatomies were normal. Given the radiological findings consistent with GA, the donor evaluation and living donor liver transplantation were planned with specific consideration of this anatomical anomaly (Fig. 2).

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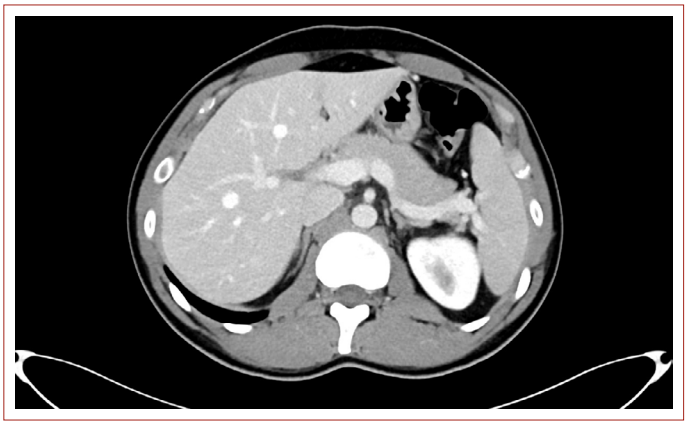

Figure 1. CT image of the donor with no gallbladder.

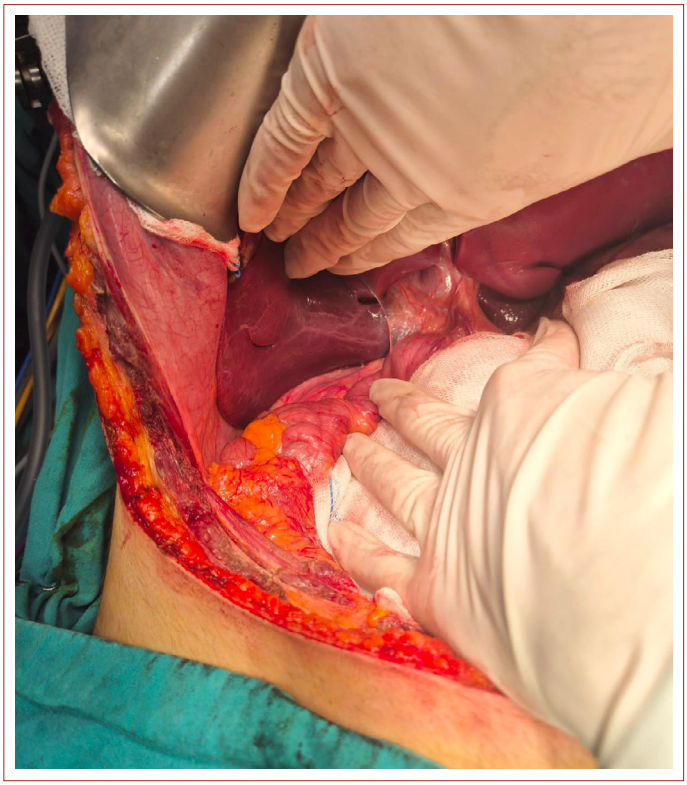

Figure 2. Operative appearance of the liver with gallbladder agenesis.

During donor surgery, GA was confirmed intraoperatively. Despite thorough exploration of all potential ectopic locations (intrahepatic, positioned on the left side, beneath the posteroinferior surface of the liver, between the omentum leaves, within the falciform ligament, retrohepatic, retroperitoneal, or in the retroduodenal and retropancreatic areas) no ectopic gallbladder was identified intraoperatively.[3] The hepatic parenchyma appeared macroscopically normal. Intraoperative histopathological examination (frozen section) of the liver parenchyma was consistent with <10% hepatic steatosis. Because standard intraoperative cholangiography (IOC) via the cystic duct was not feasible, cholangiography was performed by injecting contrast through an insulin needle introduced into the distal common bile duct. The cholangiography demonstrated three distinct bile ducts draining the right hepatic lobe, while the intrahepatic biliary anatomy of the entire liver was otherwise normal (Fig. 3). A right lobe donor hepatectomy was performed using Cavitron Ultrasonic Surgical Aspirator The three bile duct stumps of the right lobe graft were individually closed using 6-0 Prolene sutures. In addition, the puncture site used for IOC was closed with 7-0 Prolene sutures. A routine post-hepatectomy IOC was performed and normal (Fig. 4).

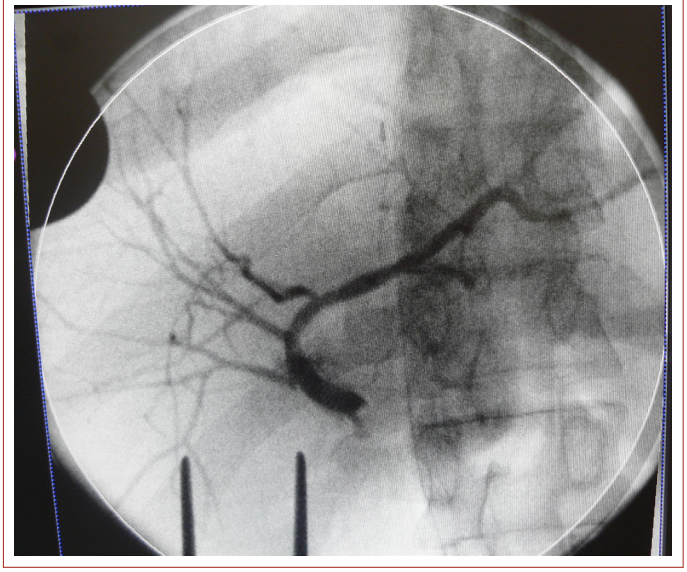

Figure 3. Intraoperative cholangiography in the beginning of the operation.

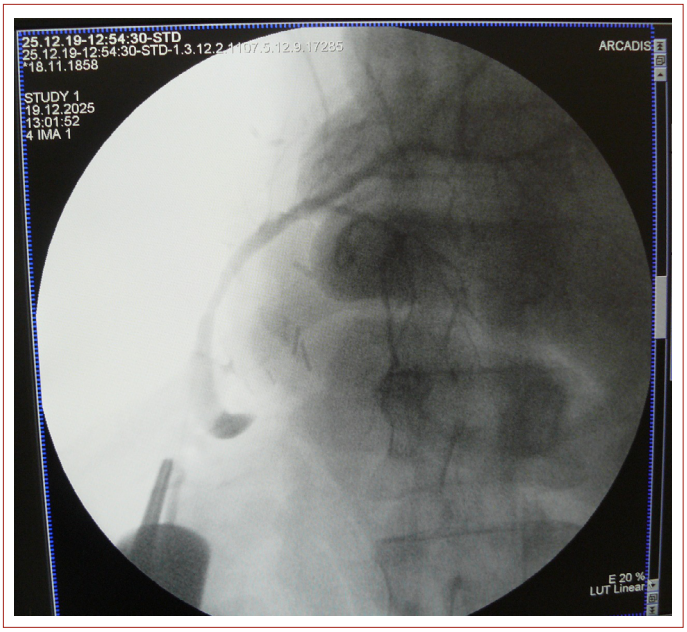

Figure 4. Completion cholangiography after the hepatectomy.

A right lobe living donor liver transplantation was performed. Two segment VIII hepatic veins, 1 segment V hepatic vein, and 1 right hepatic inferior vein were reconstructed. Other anastomoses were normal. Three bile ducts were anastomosed in duct-to-duct fashion, separately. One biliary anastomosis had a feeding catheter.

On postoperative day 2, the patient developed clinical signs of peritonitis, including severe abdominal pain, accompanied by elevated inflammatory markers and increased serum bilirubin levels. An emergency relaparotomy was therefore performed. Intraoperatively, a localized bile collection was identified, predominantly within the operative field. Minimal bile leakage was observed from the previously closed bile duct stumps as well as from the puncture site on the common bile duct used for IOC. All repair sites were carefully re-evaluated, and additional reinforcing sutures were placed. A choledochotomy was performed on the distal common bile duct, and a 6-Fr feeding catheter was advanced into the intrahepatic bile ducts. Cholangiography performed through the catheter demonstrated normal intrahepatic biliary anatomy, with no evidence of obstruction or leakage (Fig. 5). Leak testing using a lipid solution was negative.

The patient's subsequent postoperative course was uneventful.

Discussion

GA is defined by the complete absence of the gallbladder in the presence of normally developed intrahepatic and extrahepatic bile ducts, a key feature that distinguishes it from biliary atresia. In some patients, dilatation of the proximal common bile duct with a normal-caliber distal segment may be observed. This finding is thought to result from biliary stasis within the common hepatic duct, which often becomes dilated and may function as a compensatory bile reservoir in the absence of the gallbladder.[4]

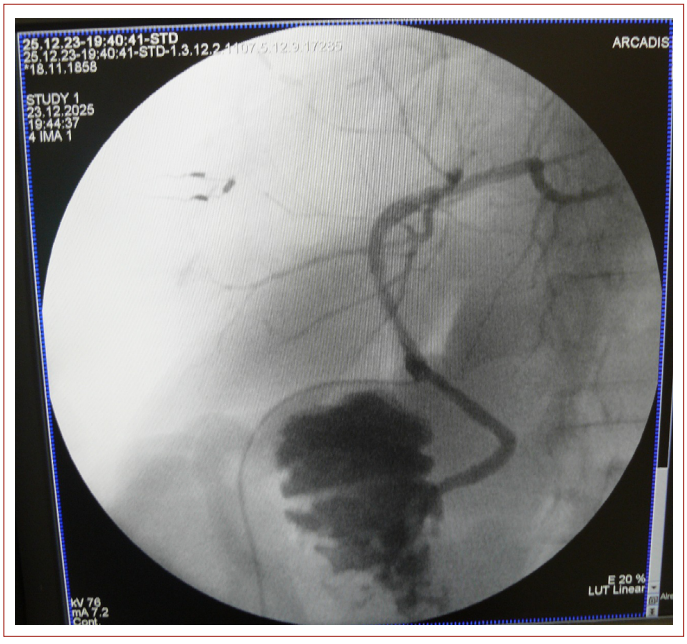

Figure 5. Intraoperative colangiography via feeding catheter in relaparotomy.

It is important to emphasize that IOC remains the gold standard diagnostic modality for confirming GA, particularly in cases where preoperative imaging is inconclusive. If GA is encountered intraoperatively, a systematic and meticulous exploration should be undertaken to exclude the presence of an ectopic gallbladder. This exploration should include careful inspection of the falciform ligament, the region between the leaves of the lesser omentum, the posterior surface of the duodenum, the retropancreatic region, and the retroperitoneum. In addition, IOC should be performed to definitively exclude the presence of an intrahepatic or ectopically located gallbladder and to accurately delineate the biliary anatomy.[5,6]

In this case, GA was suspected on preoperative CT imaging, and taking into account the extensive experience of our institute in living donor liver transplantation, the donor operation was considered feasible. Intraoperatively, GA was confirmed, and IOC demonstrated normal intrahepatic biliary anatomy, with no evidence of an ectopic gallbladder.

A routine completion cholangiography was performed in the same manner via the distal common bile duct that had been previously punctured with an insulin needle. However, three bile duct stumps and the additional puncture site of the bile duct were closed following hepatectomy and the risk of bile leakage from these sites was considered high, as biliary dyskinesia has been reported in the literature in association with GA.[6] This underlying functional abnormality may contribute to increased intraductal pressure and impaired bile flow dynamics, thereby predisposing to bile leakage from biliary suture lines and puncture sites. Based on the postoperative course observed in this case, we believe that whenever IOC is performed via the distal common bile duct in donors with GA, a biliary catheter should be placed into the biliary tree to allow completion cholangiography. Because biliary dyskinesia secondary to sphincter of Oddi dysfunction has been described in these cases. Although postoperative ERCP and sphincterotomy can be performed to address this issue, placement of an intraoperative biliary catheter provides a more immediate solution. Such temporary biliary drainage may reduce intraductal pressure in the postoperative period and thereby decrease the risk of bile leakage.[5,6]

Conclusion

Living liver donation in the setting of GA may be considered in highly experienced centers, provided that all other donor evaluation parameters are normal.[7] We believe that preoperative magnetic resonance imaging, particularly MR cholangiography, is essential to exclude an ectopic gallbladder and to delineate intrahepatic biliary anatomy in detail before proceeding with donor hepatectomy in these rare cases. Although preoperative MR imaging was not performed in our patient, a diagnosis of gallbladder agenesis had already been established on CT. Therefore, additional MR imaging was not obtained. IOC is important for visualizing the intrahepatic biliary anatomy and detecting an ectopic gallbladder and should be performed at both the beginning and the end of donor hepatectomy, and a biliary catheter should be placed into the biliary tree to reduce intraductal pressure and to facilitate postoperative cholangiographic imaging.

Disclosures

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

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Conflict of Interest: None declared.

Authorship Contributions: Concept - M.J., H.B., C.D.A.; Design - M.J., H.B.; Supervision H.B.; Materials - M.J., C.D.A., Data collection - C.Y.; Analysis and interpretation H.B.; Literature search - A.A.O, C.Y.; Writing A.A.O.; Critical review - M.J., H.B.

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Letter to the Editor

Late Recurrence of Lymph Node Micro-Metastatic Hepatoblastoma Following Living Donor Liver Transplantation

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Dear Editor,

Hepatoblastoma (HB) is the most common primary liver malignancy in childhood, and liver transplantation (LT) is the main curative treatment option in unresectable cases. The overall 5-year survival rate after LT is approximately 70%. According to the SIOPEL risk stratification, the presence of lymph node involvement and/or metastatic disease classifies patients as high-risk; approximately 20% of HB patients present with locally advanced or metastatic disease at diagnosis.[1,2] Recurrence after LT for HB is defined as biopsy-proven or radiologically confirmed mass lesions accompanied by three consecutive rises in serum alpha-fetoprotein (AFP) levels. Late recurrence is extremely rare and has been reported in only two separate cases in the literature.[3,4] Herein, we present a patient who underwent living donor liver transplantation (LDLT) at the age of six for unresectable HB, with lymph node (LN) micro-metastasis and local peritoneal invasion identified in the explant pathology, who developed recurrence 4.5 years post-transplant and survived more than five years post-LT.

A male patient presenting with abdominal distention was referred to our center for LT after receiving five cycles of cisplatin and doxorubicin for unresectable HB, achieving stable disease and classified as POSTTEXT stage III.[5] Upon admission, biochemical parameters were within normal limits, and AFP was 2615 ng/mL. LDLT was successfully performed using the donor's (20-year-old brother) left lateral segment (segments 2–3). The donor was discharged uneventfully on postoperative day 9. On postoperative day 2, the recipient developed hepatic artery thrombosis, necessitating urgent surgical revision; however, graft failure ensued, and emergency retransplantation with a reduced-size deceased donor graft (segments 2–3) was performed on postoperative day 5. The patient was discharged on postoperative day 37. Explant pathology revealed three foci (up to 5 cm) of epithelial-type HB. Of five lymph nodes dissected from the hepatic hilum, one contained a microscopic HB focus, and an additional microscopic HB lesion was identified in Gerota's fascia adjacent to an exophytic segment 5 lesion extending toward the kidney (Fig. 1). Based on these findings, adju-

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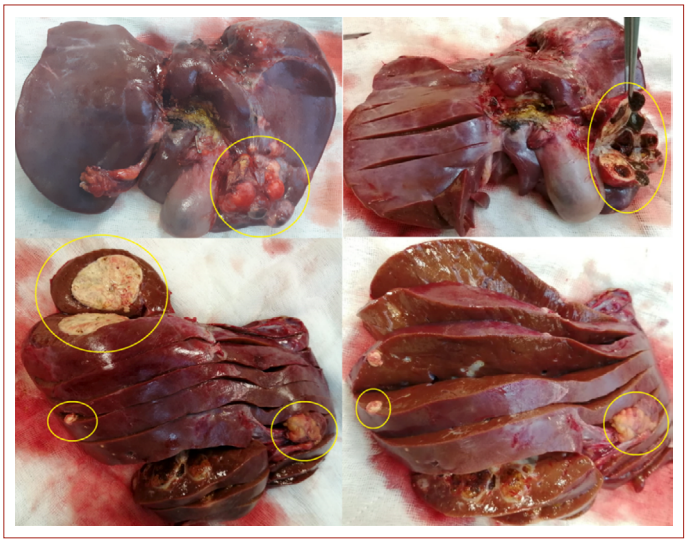

Figure 1. Explant specimen.

vant chemotherapy (etoposide + ifosfamide + carboplatin) was administered for two cycles due to advanced-stage/metastatic disease. Post-LT AFP remained within normal limits for two years but then showed mild elevation (AFP: 20 ng/mL; normal <9 ng/mL). Thoracic CT, abdominal CT, cranial MRI, and FDG PET-CT revealed no pathology. Viral serology demonstrated positivity for HBsAg, HBeAg, and HBV DNA, leading to a diagnosis of de novo HBV hepatitis; antiviral therapy with lamivudine was initiated, and the mild AFP elevation was attributed to HBV infection. During the following 2.5 years, no pathological finding was detected, and AFP fluctuated between 20–63 ng/mL. At 4.5 years post-LT, AFP abruptly increased to 918 ng/mL (from 63 ng/mL six months earlier). Imaging studies showed no metastatic lesions, though HBV DNA remained positive, and antiviral therapy was switched to tenofovir. Preemptive chemotherapy was not initiated. Three months later, AFP rose further to 6244 ng/mL, and imaging revealed multiple hepatic and left pulmonary metastatic lesions (Fig. 2). The multidisciplinary tumor board recommended systemic therapy; however, the patient developed massive ascites and hepatic decompensation, requiring palliative management. The patient died at 64 months post-LT (5.3 years) due to tumor recurrence.

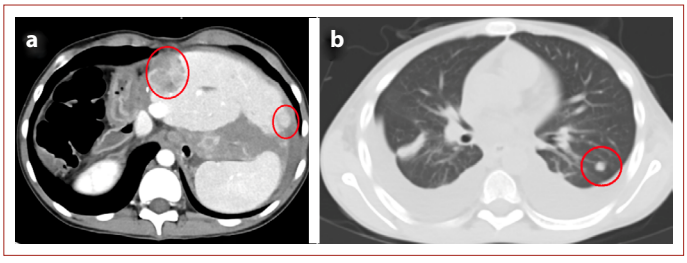

Figure 2. (a) Recurrences on the transplanted liver, **(b)** Lung metastases.

Overall and disease-free survival rates following LT for HB—whether performed as primary (pLT) or salvage LT (sLT)—exceed 60% at five years. In a study by Umeda et al., the 5-year overall survival was 69% for pLT and 73% for sLT, while Boster JM et al. reported 5-year disease-free survival rates of 78% for pLT and 62% for sLT. Thus, LT achieves favorable long-term outcomes for HB. Our patient underwent LT despite advanced-stage disease with lymph node metastasis and local invasion. Remarkably, no recurrent lesions were detected for 4.5 years post-transplant. AFP increased sharply thereafter, and hepatic and pulmonary metastases became radiologically visible once AFP exceeded 6000 ng/mL. During the period of rising AFP, persistent HBsAg, HBeAg, and HBV DNA positivity (under tenofovir therapy) suggested ongoing HBV replication. This raises the possibility that HBV reactivation might have triggered tumor cell proliferation.

Similarly, we previously observed a comparable scenario in a patient with hepatocellular carcinoma who exhibited unexplained AFP elevation post-LT without detectable recurrence on CT or PET-CT. Brain metastasis was subsequently discovered when the patient presented with neurological symptoms highlighting the limited sensitivity of PET-CT for detecting cerebral metastases and the importance of conventional cranial imaging in such cases. [6] In the current case, despite comprehensive imaging including cranial and genitourinary evaluations—no lesion was detected until AFP exceeded 6000 ng/mL. The gradual AFP rise (20–63 ng/mL) over 2.5 years, followed by a rapid increase to 918 ng/mL in six months and 6244 ng/mL within three months, correlated with detectable recurrence. We speculate that HBV replication and immunosuppressive therapy may have jointly promoted tumor progression. Bandopadhyay et al. previously demonstrated that the hepatitis B virus X protein (HBx) can contribute to hepatoblastoma carcinogenesis by suppressing miR-122 expression in HB cells,[7] supporting our hypothesis. Moreover, we believe that adjuvant chemotherapy administered post-transplantation may have contributed to delaying early recurrence.

In conclusion, during follow-up of HB patients after LT, both rapid and gradual increases in AFP should be considered potential indicators of tumor recurrence or metastasis, even in the absence of radiologically detectable lesions. Conventional imaging modalities may fail to identify early recurrence. Although data are insufficient to support preemptive adjuvant chemotherapy, given the propensity for microinvasion and metastatic spread, post-LT adjuvant chemotherapy protocols may warrant reevaluation.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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