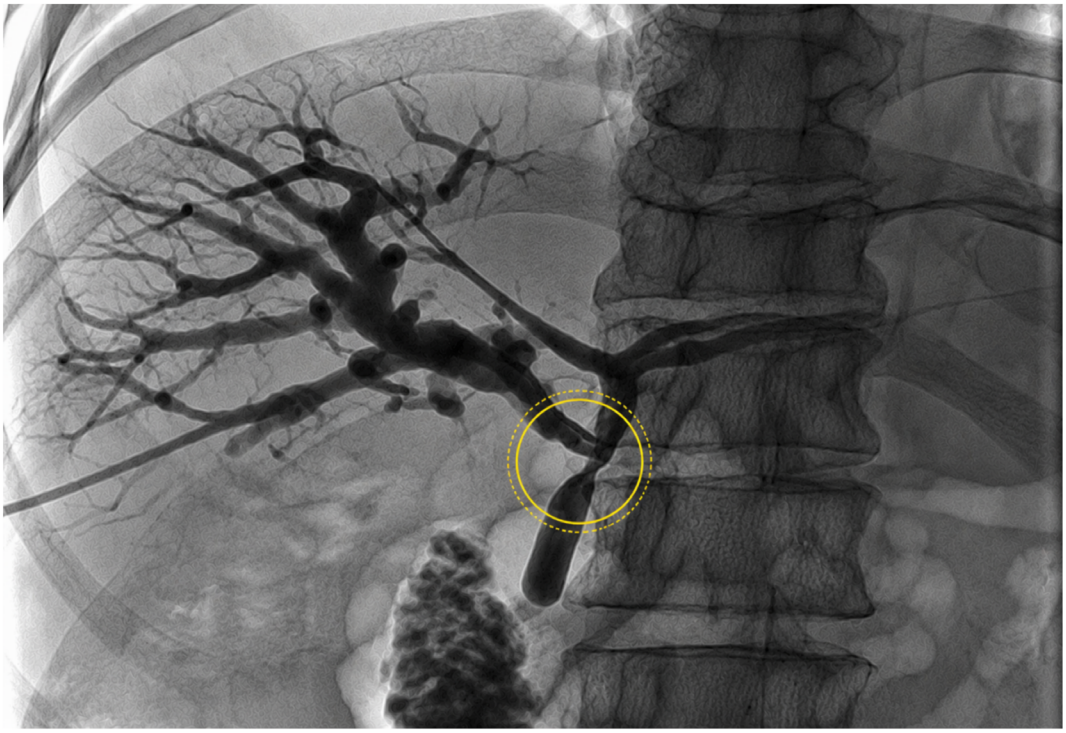
JILTI

The Official Journal of the Inonu Liver Transplantion Institute



Late Complication of Early Bile Leakage After Laparoscopic Cholecystectomy: Posterolateral Sectoral Duct Stricture with Elevated CA 19-9 Levels

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JILTI

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, Image
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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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

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Information for the Authors

THE JOURNAL

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

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

REVIEW PROCESS

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

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

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

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

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

Final approval of the version to be published; AND

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

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

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

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

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Image: Original and high-quality clinical or laboratory images are eligible for publication consideration. For images depicting identifiable patients, a completed and signed informed consent form must accompany the submission. The informed consent Form is available in the Forms section of the journal website. Authors are responsible for ensuring that all patient- and institution-identifying information, including names, dates, locations, hospital identifiers, and similar details, is removed from submitted images. Submissions are limited to a maximum of five authors and should consist of 200–400 words, including the case description and discussion sections. Authors may cite up to six references and submit a maximum of six figures/images..

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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.

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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).
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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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If an ahead-of-print publication is cited, the digital object identifier (DOI) number should be provided. Authors are responsible for the accuracy of references. Journal titles should be abbreviated in accordance with the journal abbreviations in the Index Medicus /MEDLINE/ PubMed. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six should be listed followed by "et al." In the main text of the manuscript, references should be cited using Arabic numerals in parentheses. The reference styles for different types of publications are presented in the following examples.
Journal article: van Erk MD, Dam-Vervloet AJ, de Boer FA, Boomsma MF, van Straaten H, Bosschaart N. How skin anatomy influences transcutaneous bilirubin determinations: an in vitro evaluation. Pediatr Res 2019;86:471-7.
Epub ahead-of-print article: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead-of-print].
Manuscript published in electronic format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlEID/cid.htm.
Book section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.
Books with a single author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.
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Original Research

Sociodemographic Profile of Recipients and Donors in Crossover Living Donor Liver Transplantation: A Public Health Perspective from a High-Volume Center

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Abstract

Objectives: Liver paired exchange (LPE) is an innovative strategy for expanding the living donor pool in liver transplantation, enabling compatible transplants between otherwise incompatible donor-recipient pairs. Despite its growing global adoption, the sociodemographic characteristics of LPE populations remain largely unreported. This study aimed to comprehensively characterize the sociodemographic profile of all recipients and donors who underwent crossover living donor liver transplantation at a single high-volume center and to contextualize the findings within a public health framework.

Methods: This was a retrospective, cross-sectional, descriptive epidemiological study. All 393 crossover living donor liver transplants performed at the İnönü University Liver Transplant Institute (IULTI), Malatya, Türkiye, between October 2021 and May 2026 through the Banu Bedestenci Sönmez Liver Paired Exchange (BBS-LPE) system were included. Variables analyzed included recipient and donor age, sex, blood group, primary diagnosis, exchange chain size (2-way through 7-way), geographic origin, MELD/PELD score, and graft weight. Descriptive and comparative statistical analyses were performed using IBM SPSS Statistics v27.0 (IBM Corp., Armonk, NY, USA). The Mann-Whitney U and Chi-square tests were used for between-group comparisons.

Results: A total of 393 recipient-donor pairs completed LPE through 132 exchange events ranging from 2-way to 7-way chains, the latter representing a world-first. Annual LPE volume increased from 2 transplants in 2021 to 155 in 2025 (R^2=0.94, p<0.001). Recipients comprised 64.9% males (mean age: 44.7±20.1 years); 14.8% were pediatric. The leading indications were cryptogenic cirrhosis (24.2%), HBV-related cirrhosis (13.5%), and HBV-associated hepatocellular carcinoma (8.4%). Male recipients were significantly older than females (46.4±19.4 vs. 41.5±21.1 years; p=0.042). Donors had a mean age of 30.7±8.0 years; 52.4% were under 30. Female donors constituted 41.2% of the total and were significantly more likely to donate to male recipients (p=0.039). Recipients originated from 68 Turkish provinces and 13 foreign countries; the southeastern Anatolian region contributed 35.9% of all domestic referrals. Şanlıurfa (8.4%), Gaziantep (7.6%), and Diyarbakır (6.1%) were the leading provinces of origin. International patients comprised 8.9% of the cohort (13 countries), with Syria as the most common country of origin.

Conclusion: This is the largest single-center sociodemographic analysis of an LPE population reported to date. Our data reveal pronounced geographic disparities, a consistent male predominance among recipients, a young donor population with a notable female contribution, and a broad disease spectrum spanning adult and pediatric indications. These findings underscore the critical public health role of high-volume LPE programs and highlight the need for targeted policies to address inequities in access to this life-saving modality. Sociodemographic profiling of LPE populations should become a standard component of transplant program reporting globally.

Keywords: Epidemiology, liver paired exchange, living donor liver transplantation, public health, sociodemographic profile, BBS-LPE system

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Liver transplantation (LT) remains the definitive treatment for end-stage liver disease, yet the persistent disparity between organ supply and patient demand continues to claim thousands of lives annually on transplant waiting lists worldwide. Globally, in 2021, 34,694 liver transplants were performed, representing only a fraction of the estimated need.[1] Living donor liver transplantation (LDLT) has emerged as a critical strategy to address this shortage, particularly in countries where deceased donor availability is limited. In Türkiye and across many Asian nations, LDLT constitutes 80–90% of all liver transplant procedures.[2,3]

Despite the surgical and logistical complexities involved, only 30–55% of potential living donors are ultimately eligible for donation due to factors such as ABO blood group incompatibility, inadequate graft-to-recipient weight ratio (GRWR), anatomical variations, or hepatic steatosis.[4,5] Liver paired exchange (LPE) provides an elegant solution to these incompatibilities by allowing donor-recipient pairs who cannot undergo direct transplantation to exchange donors with other incompatible pairs, thereby enabling compatible transplants across the entire chain.[6]

The concept of paired exchange was first introduced in kidney transplantation, where it now facilitates more than 18% of living-donor kidney transplants in the United States.[7] Its adaptation to liver transplantation has been considerably more challenging due to the greater surgical complexity of hepatic donation, technical constraints of lobe size and remnant volume, and the substantial logistical demands of performing multiple simultaneous operations.[8,9]

The Banu Bedestenci Sönmez Liver Paired Exchange (BBS-LPE) system, established at İnönü University Liver Transplant Institute (IULTI) in Malatya, Türkiye, in July 2022 through a collaboration between transplant surgeons and design economists from Boston College, has pioneered this field on a global scale. The program achieved successive world-firsts: the first 4-way LPE in July 2022, the first 5-way LPE in October 2023, and the first 6-way LPE in January 2024.[10,11] By 2023, LPE-facilitated procedures constituted 27.7% of all LDLTs at the institute—a rate more than an order of magnitude higher than any other reported LPE program.[10]

Despite the rapidly expanding clinical literature on LPE outcomes, there remains a striking absence of data concerning the sociodemographic characteristics of LPE recipients and donors at the population level. Understanding who benefits from LPE—their geographic origin, age distribution, sex, blood groups, and disease spectrum—is not only scientifically important but is critical for health policy planning, equitable program development, and identification of underserved populations.[12,13]

This study presents the first comprehensive sociodemographic analysis of all crossover living donor liver transplants performed at IULTI from program inception through May 2026, encompassing 393 recipient-donor pairs and 132 exchange events, including the world's first 7-way LPE. Our findings are contextualized from a public health perspective to inform global discussion on LPE program expans

Methods

Study Design and Setting

This was a retrospective, cross-sectional, descriptive epidemiological study. The study was conducted at IULTI, Turgut Özal Medical Center, Malatya, Türkiye—the highest-volume LDLT center in Europe, with more than 4,500 total liver transplants performed since 2002 and an annual output exceeding 300 LDLTs.[14] The BBS-LPE system has been operational since July 2022 and uses an optimal weighted matching algorithm developed in collaboration with economists at Boston College (USA) to identify compatible exchange configurations of up to 7 simultaneous pairs.[10,11]

Study Population

All recipients and their corresponding living donors who underwent crossover living donor liver transplantation at IULTI between October 2021 and May 2026 were included. Two 2-way exchanges performed prior to the formal launch of the computerized BBS-LPE system (October 2021 and January 2022) were included in the analysis. No exclusion criteria were applied; this represents a complete census of the LPE population during the study period (n=393 pairs).

Data Collection

Data were extracted retrospectively from the institute's prospectively maintained transplant registry database. All patient identifiers were removed prior to analysis in accordance with ethical standards. Variables collected for recipients included date of birth, age at transplantation, sex, ABO blood group and Rh factor, height, weight, transplant date, primary diagnosis, exchange chain size (2-way through 7-way), MELD/PELD score at transplantation, and geographic origin (province of residence or country of origin for international patients). Donor variables included age, sex, ABO blood group, height, weight, and graft weight (grams).

Ethical Considerations

This study was approved by the İnönü University Health Sciences Scientific Research Ethics Committee (Approval No: 2026/4412). As a retrospective registry study involving

no direct patient contact, an informed consent waiver was granted. All data were de-identified prior to analysis. The study adhered to the principles of the Declaration of Helsinki and was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as mean±standard deviation (SD) and range. Categorical variables are expressed as frequencies and percentages. The Shapiro-Wilk test was used to assess normality. Comparisons between two groups were performed using the Mann-Whitney U test for continuous variables and the Chi-square or Fisher's exact test for categorical variables. Temporal trends in LPE volume were assessed using linear regression analysis. Statistical significance was set at $p<0.05$.

Results

Program Volume and Exchange Chain Distribution

Between October 2021 and May 2026, a total of 393 recipient-donor pairs underwent crossover liver transplantation at IULTI through 132 discrete exchange events. The distribution of exchange chain types is presented in Table 1. Two-way exchanges accounted for the largest proportion (n=63 events, 126 recipients, 32.1%), followed by three-way (n=37 events, 111 recipients, 28.2%) and four-way chains (n=16 events, 64 recipients, 16.3%). Larger multipair exchanges included six 5-way chains (30 recipients, 7.6%), eight 6-way chains (48 recipients, 12.2%), and two pioneering 7-way exchanges (14 recipients, 3.6%), the latter representing a world-first achievement.

The annual transplant volume demonstrated a marked and progressive increase, from 2 LPE transplants in 2021 to 10 in 2022, 64 in 2023 (constituting 27.7% of all 231 LDLTs that year), 122 in 2024, 155 in 2025, and 40 in the first five months of 2026. Linear regression demonstrated a statistically significant increasing trend ($R^2=0.94$, $p<0.001$).

Table 1. Distribution of exchange chain types and corresponding transplant events

Exchange Type	No. of Events	No. of Recipients	% of Recipients
2-way	63	126	32.1%
3-way	37	111	28.2%
4-way	16	64	16.3%
5-way	6	30	7.6%
6-way	8	48	12.2%
7-way	2	14	3.6%
Total	**132**	**393**	**100%**

Recipient Sociodemographic Characteristics

The cohort comprised 255 males (64.9%) and 138 females (35.1%), with a male-to-female ratio of 1.85:1. Mean recipient age was 44.7±20.1 years (range: 0.5–76.8 years). The age distribution was bimodal, with a pediatric cluster in the first two decades of life and an adult peak in the fifth and sixth decades. By age group, 14.8% (n=58) were younger than 18 years, 18.6% (n=73) were 18–40 years, 38.2% (n=150) were 40–60 years, and 28.5% (n=112) were 60 years or older. Male recipients were significantly older than female recipients (46.4±19.4 years vs. 41.5±21.1 years, Mann-Whitney U, p=0.042). Key sociodemographic and anthropometric characteristics are summarized in Table 2.

Primary Diagnoses

The primary indication for LPE across the cohort was cryptogenic cirrhosis, accounting for 95 cases (24.2%), followed by HBV-related cirrhosis (n=53, 13.5%) and HBV-associated hepatocellular carcinoma (HCC) (n=33, 8.4%). Alcohol-associated liver disease represented 5.3% (n=21), Budd-Chiari syndrome 3.8% (n=15), and HBV-HDV co-infection 3.3% (n=13). Among the 58 pediatric recipients, the leading diagnoses were biliary atresia (n=10, 17.2%), progressive familial intrahepatic cholestasis (PFIC, n=8, 13.8%), cryp-

Table 2. Sociodemographic and anthropometric characteristics of recipients and donors

Characteristic	Recipient (n=393)	Donor (n=393)
Age (years), mean±SD	44.7±20.1	30.7±8.0
Age range (years)	0.5 – 76.8	18.1 – 57.4
Median age (years)	50.1	29.6
Age <18 years, n (%)	58 (14.8%)	—
Age 18–40 years, n (%)	73 (18.6%)	206 (52.4%)
Age 40–60 years, n (%)	150 (38.2%)	130 (33.1%)
Age ≥60 years, n (%)	112 (28.5%)	2 (0.5%)
Sex: Male, n (%)	255 (64.9%)	231 (58.8%)
Sex: Female, n (%)	138 (35.1%)	162 (41.2%)
Male:Female ratio	1.85:1	1.43:1
Height (cm), mean±SD	160.2±25.7	170.8±11.9
Weight (kg), mean±SD	70.3±25.2	71.8±12.2
MELD/PELD score, mean±SD	16.5±6.1	—
Graft weight (g), mean±SD	—	784±235

togenic cirrhosis (n=5, 8.6%), Wilson disease (n=3, 5.2%), and familial hypercholesterolemia (n=3, 5.2%), as well as rare metabolic disorders including Caroli disease, Alagille syndrome, Niemann-Pick disease, tyrosinemia type 1, and alpha-1 antitrypsin deficiency. The complete diagnostic distribution is presented in Table 3.

Donor Characteristics

All 393 donors underwent living donor right lobe (n=362, 92.1%), left lobe (n=22, 5.6%), or left lateral segment hepatectomy (n=9, 2.3%). Donors were predominantly male (58.8%, n=231), with a mean age of 30.7±8.0 years (range: 18.1–57.4 years). The majority of donors were young adults: 52.4% were under 30 years of age, 33.1% were 30–39 years, 14.0% were 40–49 years, and only 0.5% (n=2) were aged 50 or older. Male and female donors did not differ significantly in age (30.6±7.9 vs. 30.9±8.1 years, p=0.842).

An important sex-based finding emerged in the cross-tabulation of donor and recipient sex: female donors were significantly associated with male recipients (p=0.039). Of 255 male recipients, 95 (37.3%) received a graft from a female donor; conversely, of 138 female recipients, 71 (51.4%) received a graft from a male donor. This pattern may reflect familial donation dynamics in Turkish culture. The cross-tabulation is presented in Table 4.

Table 3. Primary diagnoses among crossover living donor liver transplant recipients

Diagnosis	n	%	Population
Cryptogenic cirrhosis	95	24.2%	Predominantly adult
HBV-related cirrhosis	53	13.5%	Adult
HBV + Hepatocellular carcinoma	33	8.4%	Adult
Alcohol-associated liver disease	21	5.3%	Adult
Budd-Chiari syndrome	15	3.8%	Adult/Pediatric
HBV + HDV co-infection	13	3.3%	Adult
Autoimmune hepatitis	11	2.8%	Mixed
Primary sclerosing cholangitis	11	2.8%	Adult
Wilson disease	11	2.8%	Predominantly pediatric
HBV + HDV + HCC	11	2.8%	Adult
Hepatocellular carcinoma (other)	11	2.8%	Adult
Biliary atresia	10	2.5%	Pediatric
PFIC (all types)	8	2.0%	Pediatric
NASH cirrhosis	7	1.8%	Adult
Familial hypercholesterolemia	3	0.8%	Pediatric
Glycogen storage disease	2	0.5%	Pediatric
Other diagnoses	27	6.9%	Mixed
Total	**393**	**100%**	—

Blood Group Distribution

Among recipients, the most common blood group was A Rh(+) (33.1%, n=130), followed by O Rh(+) (31.0%, n=122), B Rh(+) (15.3%, n=60), and AB Rh(+) (9.4%, n=37). Rh-negative recipients constituted 11.1% of the total cohort. Donor blood group distribution was broadly similar, with O Rh(+) as the most frequent (35.6%, n=140), followed by A Rh(+) (34.6%, n=136). The blood group distribution is detailed in Table 5.

Geographic Distribution

Recipients originated from 68 distinct Turkish provinces and 13 foreign countries, covering all seven geographic regions of Türkiye. The southeastern Anatolian region contributed the highest concentration of patients, accounting for 141 recipients (35.9%). The leading provinces of origin were Şanlıurfa (n=33, 8.4%), Gaziantep (n=30, 7.6%), and Diyarbakır (n=24, 6.1%). Ankara contributed 21 recipients (5.3%), while Kahramanmaraş (n=19, 4.8%), Malatya—the

Table 4. Cross-tabulation of donor and recipient sex

	Male Donor (n=231)	Female Donor (n=162)	Total
Male recipient	160 (62.7%)	95 (37.3%)	255 (100%)
Female recipient	71 (51.4%)	67 (48.6%)	138 (100%)
Total	**231 (58.8%)**	**162 (41.2%)**	**393 (100%)**

Chi-square test: p = 0.039

Table 5. Blood group distribution among LPE recipients and donors

Blood Group	Recipients n (%)	Donors n (%)
A Rh(+)	130 (33.1%)	136 (34.6%)
O Rh(+)	122 (31.0%)	140 (35.6%)
B Rh(+)	60 (15.3%)	55 (14.0%)
AB Rh(+)	37 (9.4%)	21 (5.3%)
A Rh(-)	21 (5.3%)	13 (3.3%)
O Rh(-)	10 (2.5%)	9 (2.3%)
B Rh(-)	10 (2.5%)	10 (2.5%)
AB Rh(-)	3 (0.8%)	9 (2.3%)

Table 6. Geographic distribution of LPE recipients by province and country of origin

Province / Country	n	%	Region / Type
Şanlıurfa	33	8.4%	Southeastern Anatolia
Gaziantep	30	7.6%	Southeastern Anatolia
Diyarbakır	24	6.1%	Southeastern Anatolia
Ankara	21	5.3%	Central Anatolia
Kahramanmaraş	19	4.8%	Mediterranean/SE
Malatya (local)	16	4.1%	Eastern Anatolia
İstanbul	15	3.8%	Marmara
Adana	13	3.3%	Mediterranean
Adıyaman	12	3.1%	Southeastern Anatolia
Muş	12	3.1%	Eastern Anatolia
Other domestic provinces	163	41.5%	All regions
Syria	14	3.6%	International
Kyrgyzstan	4	1.0%	International
Jordan	3	0.8%	International
Other international (10 countries)	14	3.6%	International
Total	**393**	**100%**	—

institute's home city (n=16, 4.1%)—and İstanbul (n=15, 3.8%) were also notable contributors.

International patients comprised 35 individuals (8.9%) from 13 countries. Syria was the most common country of origin (n=14, 3.6% of total), followed by Kyrgyzstan (n=4, 1.0%), Jordan (n=3, 0.8%), Azerbaijan (n=2, 0.5%), Afghanistan (n=2, 0.5%), Palestine (n=2, 0.5%), and Bulgaria (n=2, 0.5%). Single cases originated from Yemen, Cyprus, Russia, Turkmenistan, Pakistan, and the Netherlands. The geographic distribution is summarized in Table 6.

Discussion

Program Scale and Global Context

To the best of our knowledge, this is the largest and most detailed sociodemographic analysis of a liver paired exchange population reported in the international literature. The BBS-LPE system at IULTI has achieved a rate of growth unparalleled among LPE programs worldwide. Whereas LPE programs in high-volume Asian centers—including the pioneering program at Asan Medical Center in South Korea—typically generate 1–2% of LDLTs from exchange procedures,[15] our program reached 27.7% in its second full operational year. This achievement must be understood in the context of the institute's extraordinary logistical capacity and systematic recruitment of incompatible pairs. The consistent year-on-year growth in LPE volume reflects the program's sustained operational momentum and increasing national and international recognition.[10,11,14]

Sex Distribution: Recipients and Donors

The 1.85:1 male-to-female ratio among recipients is consistent with the global epidemiology of end-stage liver disease, in which males are more commonly affected by HBV-related cirrhosis, alcohol-associated liver disease, and HCC.[1,12] These three diagnoses collectively accounted for 27.0% of all cases and were predominantly represented among male recipients. However, this disparity may also reflect socioeconomic and cultural barriers to healthcare access that disproportionately affect women in underserved populations—a dimension that warrants dedicated future investigation.[16,17]

The statistically significant association between female donors and male recipients (p=0.039) reflects a well-established pattern in living donation programs in Türkiye and other Middle Eastern and Asian settings, where wives, daughters, and sisters frequently volunteer as donors for male relatives.[18,19] While altruistic and freely given, this gendered dynamic raises questions about whether implicit social pressures disproportionately direct donation toward male recipients—a concern that should be actively monitored through independent psychosocial evaluation of all donor candidates.

Age Distribution: Recipients

The bimodal age distribution of our recipient cohort reflects the breadth of pathology addressed by the LPE program. At one extreme, the youngest recipient was aged 0.5 years, underscoring the program's capacity to address pediatric liver disease, including biliary atresia, PFIC, and metabolic disorders. At the other extreme, recipients up to age 66.8 years were transplanted, consistent with established criteria for older recipient selection that carefully balance the tripartite equipoise of donor safety, recipient need, and expected outcome.[20]

The 14.8% pediatric recipient rate is notable. Including pediatric patients in LPE programs is critical, as their unique anatomical requirements—particularly for left lobe or left lateral segment grafts—serve as a catalyst for complex multipair exchanges by enabling donor-size matching configurations that would otherwise be impossible.[21] Male recipients were significantly older than female recipients (p=0.042), likely attributable to the predominance of male-specific diagnoses that tend to manifest clinically later in life.

Donor Age: A Young, Healthy Cohort

The donor population was considerably younger than the recipient population, with a mean age of 30.7±8.0 years. More than half of all donors (52.4%) were under 30 years of age, reflecting the ethical and logistical preference for younger donors who have a more robust regenerative capacity and lower comorbidity burden.[20,22] The absence of significant age differences between male and female donors (p=0.842) suggests that the decision to donate is not age-mediated by sex, with both sexes contributing across the same age spectrum.

Disease Spectrum and Diagnostic Insights

The predominance of cryptogenic cirrhosis (24.2%) as the leading indication likely reflects a combination of true cryptogenic disease and undiagnosed metabolic-associated steatohepatitis (MASH), given the increasing global prevalence of NAFLD and limitations in histopathological workup in some referral centers.[1,23] HBV-related disease—encompassing HBV mono-infection, HBV+HDV co-infection, and HBV-associated HCC—collectively constituted 28.0% of all indications, reflecting the substantial residual burden of hepatitis B in southeastern Türkiye and the countries from which international patients originate.[24,25]

The representation of metabolic and hereditary liver diseases underscores the program's established role in treating rare diseases for which LT is curative—often in pediatric patients who lack other therapeutic options. The diversity and rarity of some diagnoses among pediatric recipients highlights the program's position as a national and international referral center for complex cases.

Geographic Disparities and Public Health Implications

The pronounced geographic concentration of LPE recipients in southeastern Türkiye—a region characterized by lower socioeconomic development indices, higher rates of consanguineous marriage, and historically reduced access to specialized healthcare—is perhaps the most striking public health finding of this study. Şanlıurfa, Gaziantep, and Diyarbakır alone accounted for more than one in five referrals (22.1% combined), despite collectively housing approximately 6.5% of Türkiye's total population.[26] Including all southeastern Anatolian provinces, the region accounted for 35.9% of all domestic referrals—a striking overrepresentation that likely reflects both elevated disease burden and the concentration of transplant expertise at a single regional center.

The participation of 35 international patients from 13 countries raises important questions about global equity in access to advanced liver transplantation. From a global health policy perspective, initiatives to support development of LPE capacity in neighboring countries represent a potentially high-impact approach to expanding equitable access.

Limitations

This study has several limitations inherent to its retrospective, single-center design. The geographic data reflect province or country of residence rather than province of birth, which may underestimate the true southeastern origin of some patients. The study represents the experience of a single, exceptionally high-volume center; generalizability to smaller programs or different healthcare systems requires caution.

Conclusion

This study presents the first comprehensive sociodemographic characterization of a liver paired exchange population at scale. The BBS-LPE program at İnönü University Liver Transplant Institute has achieved an unprecedented volume of exchange-facilitated transplants, extending the benefits of LDLT to patients across a broad spectrum of age, sex, diagnosis, and geographic origin. Our data reveal significant geographic inequities in access, with southeastern Türkiye and multiple international countries disproportionately represented, reflecting concentrated disease burden and the absence of alternative options in these regions. The high proportion of pediatric recipients and the broad spectrum of rare diagnoses further demonstrate the unique public health role of high-volume LPE programs. Sociodemographic profiling of LPE populations should become a standard component of transplant program reporting to enable evidence-based health policy and equitable program expansion globally.

Disclosure

Ethics Committee Approval: This study was approved by the İnönü University Health Sciences Scientific Research Ethics Committee (Approval No: 2026/4412) and was conducted in accordance with the Declaration of Helsinki.,

Informed Consent: As a retrospective registry study involving no direct patient contact, informed consent waiver was granted.

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Original Research

Interpretable Machine Learning for One-Year Survival Prediction in Hepatocellular Carcinoma: A SHAP- and LIME-Based Explainable Artificial Intelligence Framework on the UCI HCC-Survival Cohort

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Abstract

Objectives: To develop and interpret machine learning (ML) models for predicting one-year survival in patients with hepatocellular carcinoma (HCC), and to characterize model behavior using an explainable artificial intelligence (XAI) framework combining global and local interpretability with calibration and clinical-utility analysis.

Methods: This was a secondary analysis of the publicly available, de-identified University of California, Irvine (UCI) HCC-Survival dataset (165 patients; 49 features; outcome, one-year survival coded as 1 = alive and 0 = deceased). Missing data (10.2% overall) were handled with multivariate imputation by chained equations (MICE), and class imbalance (102 alive vs. 63 deceased) was addressed with the synthetic minority over-sampling technique combined with Tomek links (SMOTE-Tomek); all preprocessing was performed within cross-validation folds to prevent leakage. Seven ML algorithms-logistic regression, random forest, extreme gradient boosting (XGBoost), light gradient boosting machine (LightGBM), categorical boosting (CatBoost), support vector machine (SVM), and k-nearest neighbors (KNN)-were trained under 10-fold stratified cross-validation. SHapley Additive exPlanations (SHAP) provided global interpretability and Local Interpretable Model-Agnostic Explanations (LIME) provided local interpretability. Platt scaling was used for calibration and decision curve analysis (DCA) for clinical utility.

Results: Random forest achieved the best discrimination (area under the receiver operating characteristic curve [AUC] = 0.808 ± 0.083; accuracy = 0.746; F1 = 0.716; Brier score = 0.176; Matthews correlation coefficient [MCC] = 0.446), followed by XGBoost (AUC = 0.795) and LightGBM (AUC = 0.783). SHAP analysis identified alpha-fetoprotein (AFP), alkaline phosphatase (ALP), serum iron, performance status, and hemoglobin as the most influential predictors of one-year survival, consistent with prior findings on this cohort. LIME provided concordant patient-level explanations. DCA indicated a positive net clinical benefit across a clinically relevant range of risk thresholds.

Conclusion: On a small, single-center cohort, an explainable ML framework yielded moderate but robust discrimination and, more importantly, transparent and clinically coherent explanations. Rather than maximizing performance alone, the framework emphasizes interpretability, calibration, and clinical utility, supporting its potential role as a transparent decision-support aid that warrants validation in larger, prospective cohorts.

Keywords: Hepatocellular carcinoma, machine learning, artificial intelligence, risk prediction, clinical decision support systems, prognosis

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Hepatocellular carcinoma (HCC) is the most common primary liver cancer worldwide and a leading cause of cancer-related death. According to GLOBOCAN 2022 data, with approximately 866,000 new cases and over 758,000 deaths annually, HCC remains a major public health problem. [1] Its heterogeneous etiology—chronic hepatitis B and C virus infection, alcoholic liver disease, aflatoxin exposure, and metabolic dysfunction-associated steatohepatitis (MASH; formerly nonalcoholic steatohepatitis, NASH)—and the diverse stages of the disease complicate the consistent assessment of patient prognosis and constitute a critical obstacle to individualized treatment planning. [2,3]

Traditional prognostic systems—the Barcelona Clinic Liver Cancer staging system, the Model for End-Stage Liver Disease score, and the Child-Pugh classification—provide a valuable framework but inadequately capture nonlinear interactions among variables and patient-level heterogeneity. Machine learning (ML) algorithms have therefore been increasingly applied in HCC prognosis research, with reported discrimination varying widely depending on cohort size, data quality, and validation rigor. [4,5]

A principal barrier to the clinical adoption of ML models is their "black-box" nature. Clinicians need to understand why a model makes a particular prediction, especially in high-risk decisions. To meet this need, explainable artificial intelligence (XAI) has emerged,[6] with SHapley Additive exPlanations (SHAP) and Local Interpretable Model-Agnostic Explanations (LIME) being the most widely used methods. SHAP quantifies the global contribution of each feature through game-theoretic Shapley values, whereas LIME explains individual predictions via local surrogate models.[7,8]

In this study, I applied a complete XAI framework to a single, well-characterized, publicly available clinical cohort (the UCI HCC-Survival dataset) to predict one-year survival. Rather than pursuing maximal discrimination, I prioritized transparency and clinical coherence. The contributions are: (i) a systematic, leakage-controlled comparison of seven ML algorithms; (ii) global SHAP and local LIME explainability; (iii) probability calibration; and (iv) a clinical net-benefit assessment using decision curve analysis (DCA).

Methods

Data Source and Outcome

This was a secondary analysis of the publicly available, fully de-identified UCI HCC-Survival dataset, compiled at Coimbra University Hospital, Portugal, and deposited in the UCI Machine Learning Repository.[9] The dataset contains real clinical records of 165 patients with HCC across 49 variables selected in accordance with the European Association for the Study of the Liver–European Organisation for Research and Treatment of Cancer clinical practice guidelines, spanning demographic, risk-factor, laboratory, tumor, and general health-status parameters. The outcome was survival at one year after initial diagnosis, coded as 1 = alive (n=102) and 0 = deceased (n=63). Missing values accounted for 10.2% of all data points, with only 8 patients having complete records. Because this was a secondary analysis of a fixed, publicly available cohort, no a priori sample-size or power calculation was performed; rather, the complete set of available records (n=165; 63 events) was analyzed in full. The consequent limits on statistical precision, including the low number of events per candidate variable and the resulting wide confidence intervals around performance estimates, are acknowledged in the Limitations.

Data Preprocessing

To prevent data leakage, all preprocessing steps were fitted on training folds only and applied to held-out folds. Missing data were imputed using multivariate imputation by chained equations (MICE) with up to 50 iterations.[10] Numerical variables were normalized with a robust scaler. Class imbalance (alive-to-deceased ratio ≈1.62) was addressed in the training folds with the synthetic minority over-sampling technique combined with Tomek links (SMOTE-Tomek); test folds retained their original distribution.[11] No external feature pre-selection was applied; all 49 variables were provided to each model, and feature importance was assessed post hoc via SHAP. Concretely, within each of the 10 outer cross-validation folds, the complete pipeline—MICE imputation, robust scaling, and SMOTE-Tomek resampling—was fit exclusively on the training partition; the held-out fold was then imputed and scaled using the parameters learned on the training data and was never resampled, so that no information from the test fold influenced any preprocessing step. The chained-equations imputer (scikit-learn's IterativeImputer, run for up to 50 imputation rounds) produced a single completed dataset per fold, which was carried forward for model training and evaluation; multiple imputed datasets with pooling were not generated. SMOTE-Tomek was configured to produce an approximately balanced (1:1) class distribution within the training partitions only.

Machine Learning Models

Seven classifiers were trained and compared under 10-fold stratified cross-validation: logistic regression, random forest (500 trees), XGBoost, light gradient boosting machine (LightGBM), categorical boosting (CatBoost), support vector machine (SVM) with a radial basis function kernel, and k-nearest neighbors (KNN).[12-16] All analyses were performed

in Python version 3.13.9 (Python Software Foundation, Wilmington, DE, USA) using scikit-learn, imbalanced-learn, and the respective gradient-boosting libraries.[17] Performance was summarized as the mean and standard deviation across folds for the AUC, accuracy, F1-score (macro average), Brier score, and Matthews correlation coefficient (MCC). The principal library versions were scikit-learn 1.7.2, imbalanced-learn 0.14.0, XGBoost 3.2.0, LightGBM 4.6.0, CatBoost 1.2.10, SHAP 0.51.0, and LIME 0.2.0.1. Rather than relying on library defaults, each model was trained with fixed, prespecified hyperparameters that were not selected through any data-driven search or optimization procedure: logistic regression (L2 penalty; maximum 2,000 iterations); random forest (500 trees); XGBoost (400 trees; maximum depth 6; learning rate 0.05; subsample 0.9); LightGBM (400 trees; 63 leaves; minimum 20 samples per leaf; learning rate 0.05); CatBoost (1,000 iterations; depth 8; learning rate 0.03); support vector machine (radial basis function kernel; C=10); and k-nearest neighbors (k=5). Because these configurations were fixed a priori and no tuning was performed, no nested inner optimization loop was required. Performance was characterized descriptively as the mean and standard deviation of each metric across folds. Because the analysis was predictive rather than inferential, no formal hypothesis testing was undertaken, and no parametric distributional assumptions (e.g., normality or homoscedasticity) were invoked; the tree-based learners are nonparametric and impose no distributional assumptions on the predictors.

Explainable Artificial Intelligence

Global interpretability of the best-performing model was assessed with SHAP using the TreeExplainer algorithm; the mean absolute Shapley value (mean $|\varphi|$) quantified each feature's global contribution.[7] Local interpretability was assessed with tabular LIME, which fits a locally interpretable surrogate model around individual instances.[8] The agreement between the two methods, measured as the Jaccard similarity of their top-10 ranked features, was reported as an indicator of interpretability consistency.

Calibration and Clinical Decision Analysis

Probability calibration was performed with Platt scaling (sigmoid calibration) and assessed using the expected calibration error (ECE) and reliability diagrams. Clinical net benefit was evaluated with DCA across a clinically relevant range of risk thresholds and compared with the "treat all" and "treat none" strategies.[18]

Ethical Considerations

This study used exclusively a publicly available, fully de-identified, open-access dataset and involved no new data collection from human participants; therefore, additional institutional ethics committee approval and informed consent were not required. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data Availability

The data analyzed in this study are publicly available from the UCI Machine Learning Repository (HCC-Survival data set; https://archive.ics.uci.edu/dataset/423/hcc+survival) and are described in the original data-source publication.[9] No new data were generated. The analysis code is available from the author upon reasonable request.

Results

Model Performance

The 10-fold cross-validation performance of the seven models is presented in Table 1. Random forest achieved the best discrimination, with an AUC of 0.808±0.083, an accuracy of

Table 1. Model performance under 10-fold stratified cross-validation (mean ± standard deviation for AUC; mean for other metrics)

Model	AUC	Accuracy	F1	Brier	MCC
Random forest	**0.808 ± 0.083**	**0.746**	**0.716**	**0.176**	**0.446**
XGBoost	0.795 ± 0.125	0.726	0.698	0.193	0.414
LightGBM	0.783 ± 0.120	0.727	0.686	0.213	0.409
Logistic regression	0.779 ± 0.112	0.733	0.718	0.199	0.463
CatBoost	0.779 ± 0.120	0.703	0.682	0.194	0.381
KNN	0.686 ± 0.073	0.661	0.646	0.256	0.314
SVM (RBF)	0.685 ± 0.121	0.623	0.566	0.233	0.161

Models are ordered by AUC; the best-performing model (random forest) is highlighted. All preprocessing (imputation, scaling, and SMOTE-Tomek resampling) was performed within training folds only. AUC: area under the receiver operating characteristic curve; MCC: Matthews correlation coefficient; XGBoost: extreme gradient boosting; LightGBM: light gradient boosting machine; CatBoost: categorical boosting; KNN: k-nearest neighbors; SVM: support vector machine; RBF: radial basis function.

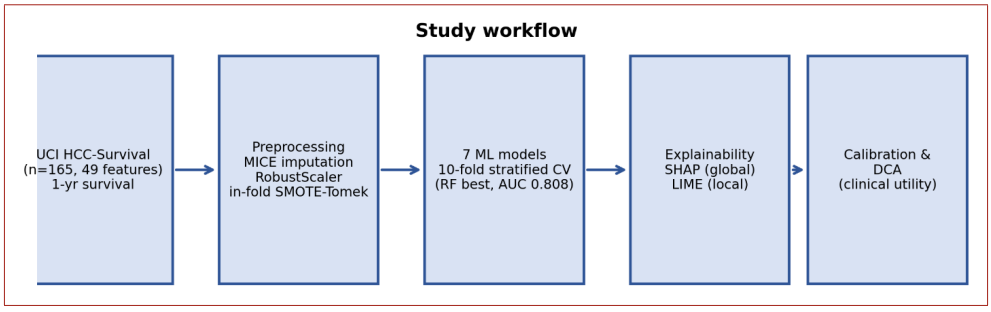

Figure 1. Study workflow, from the UCI HCC-Survival dataset through leakage-controlled preprocessing (MICE imputation, robust scaling, in-fold SMOTE-Tomek), 10-fold stratified cross-validation of seven models, and the SHAP/LIME explainability, calibration, and decision curve analysis pipeline.

0.746, an F1-score of 0.716, a Brier score of 0.176, and an MCC of 0.446. It was followed by XGBoost (AUC=0.795±0.125) and LightGBM (AUC=0.783±0.120). Logistic regression and CatBoost performed comparably (AUC=0.779 each), whereas KNN (AUC=0.686) and the SVM (AUC=0.685) yielded the lowest discrimination. Random forest also produced the lowest Brier score, indicating the most favorable overall probabilistic accuracy among the models evaluated. These values reflect moderate discrimination, in line with expectations for a small, single-center cohort with substantial missingness.

Global Interpretability (SHAP)

SHAP analysis of the random forest model identified the most influential predictors of one-year survival (Table 2). Alpha-fetoprotein (AFP) had the highest global importance (mean $|\varphi|$=0.067), followed by alkaline phosphatase (ALP; 0.044), serum iron (0.035), performance status (0.035), and hemoglobin (0.029). Direct bilirubin, the presence of symptoms, ascites, transferrin saturation, and ferritin completed the leading predictors. This ranking is clinically coherent and consistent with prior analyses of this cohort, in which ALP, AFP, and hemoglobin were reported among the most informative prognostic factors. The directions of effect were physiologically plausible: higher AFP, ALP, and direct bilirubin and the presence of ascites or symptoms were associated with reduced predicted survival, whereas higher hemoglobin was associated with improved predicted survival.

Table 2. Global feature importance for the random forest model (SHAP, TreeExplainer) and clinical interpretation

Rank	Feature	SHAP (mean $\|\varphi\|$)	Direction	Clinical meaning
1	Alpha-fetoprotein (AFP)	0.067	Higher levels associated with poorer survival	HCC tumor marker
2	Alkaline phosphatase (ALP)	0.044	Higher levels associated with poorer survival	Cholestasis / hepatic dysfunction
3	Serum iron	0.035	Non-monotonic association	Iron metabolism / liver status
4	Performance status	0.035	Worse status associated with poorer survival	General physiological reserve
5	Hemoglobin	0.029	Higher levels associated with better survival	General health status
6	Symptoms (present)	0.023	Presence associated with poorer survival	Clinical disease burden
7	Direct bilirubin	0.021	Higher levels associated with poorer survival	Hepatic-function impairment
8	Ascites	0.020	Presence associated with poorer survival	Decompensated cirrhosis
9	Transferrin saturation	0.019	Non-monotonic association	Iron metabolism
10	Ferritin	0.019	Non-monotonic association	Acute-phase / iron storage

Global importance is the mean absolute Shapley value (mean $|\varphi|$) across all patients. The outcome is one-year survival (1 = alive, 0 = deceased); the direction column summarizes how each feature related to the predicted probability of one-year survival in the SHAP dependence plots. A non-monotonic association denotes a feature whose effect on predicted survival was not consistently in a single direction. SHAP: SHapley Additive exPlanations; HCC: hepatocellular carcinoma; AFP: alpha-fetoprotein; ALP: alkaline phosphatase.

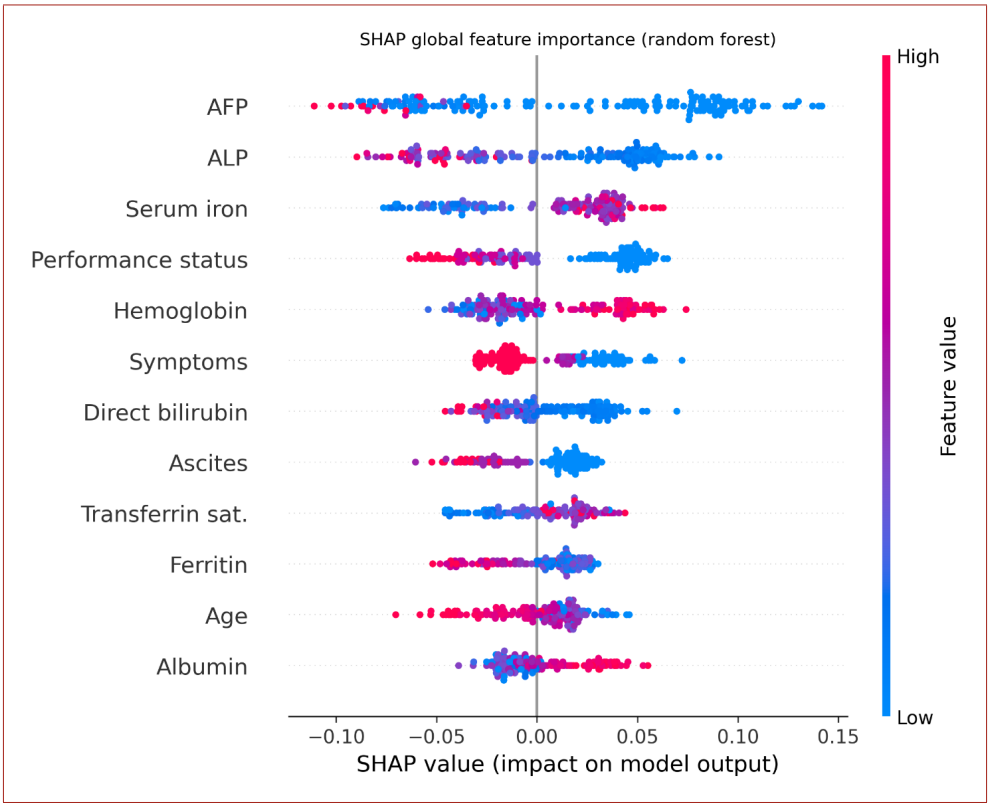

Figure 2. SHAP summary (beeswarm) plot for the random forest model, showing the global importance and directional effect of each feature on the predicted one-year survival. SHAP values were computed for the random forest, the best-performing classifier.

Local Interpretability (LIME)

LIME generated patient-level explanations that were broadly concordant with the global SHAP ranking, with the most influential features (AFP, ALP, iron, and hemoglobin) recur-

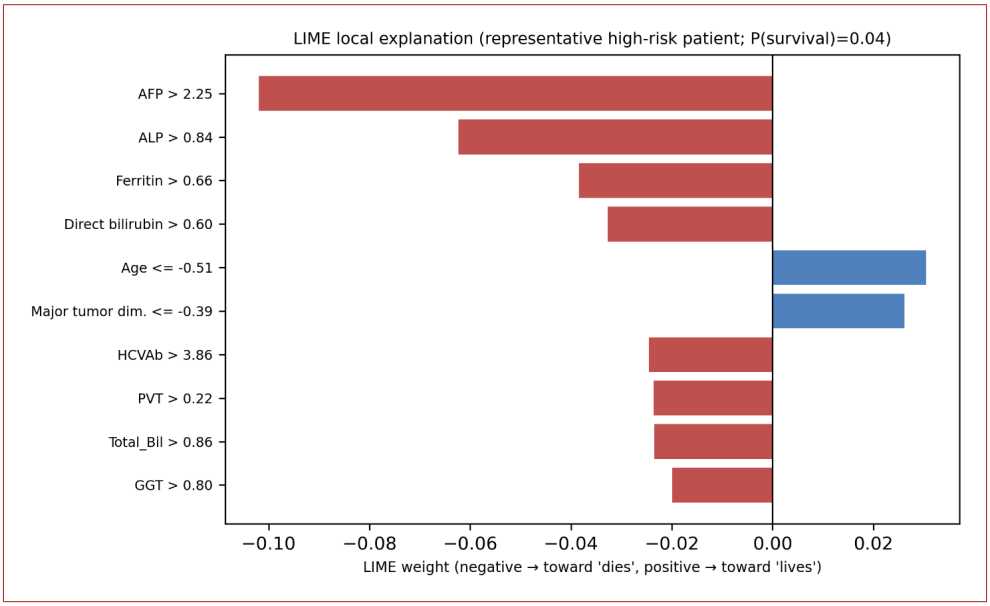

Figure 3. Representative LIME explanation for an individual high-risk patient, illustrating the local feature contributions to the predicted survival probability. This panel depicts a single, representative, de-identified patient and is shown to illustrate the local explanation method; it is not intended to be interpreted as a general or cohort-level result.

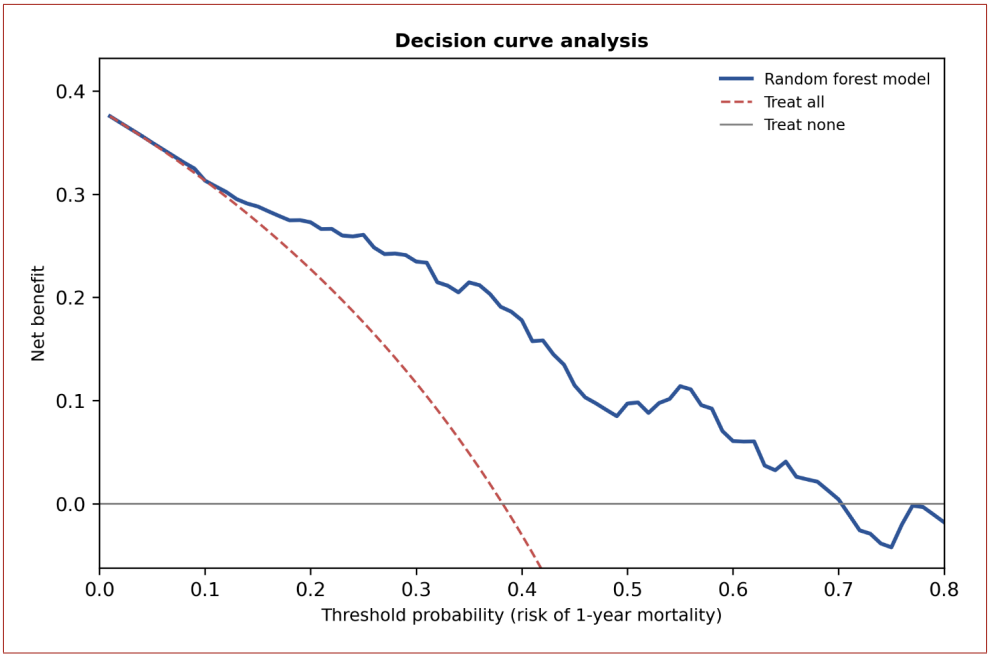

Figure 4. Decision curve analysis comparing the net benefit of the random forest model with the "treat all" and "treat none" strategies across clinically relevant probability thresholds.

ring in individual explanations. Quantitatively, the Jaccard similarity between the top-10 features ranked by SHAP and LIME was 0.43, with six predictors (AFP, ALP, iron, hemoglobin, direct bilirubin, and ascites) shared between the two rankings, indicating moderate agreement between the global and local explanations. This concordance between a global, theoretically grounded method (SHAP) and a local, perturbation-based method (LIME) supports the consistency and reliability of the model's reasoning at both the population and individual levels.

Calibration and Clinical Utility

After Platt scaling, the random forest model showed reasonable calibration (expected calibration error[ECE]=0.092), with predicted probabilities aligning reasonably with observed survival across risk strata. Decision curve analysis demonstrated a positive net clinical benefit relative to the "treat all" and "treat none" strategies across a clinically relevant range of threshold probabilities (approximately 0.02–0.74, read from Figure 4), indicating that model-guided decisions could add value over default strategies within this range.

Discussion

This study applied a complete explainable ML framework to a single, publicly available HCC cohort to predict one-year survival. Random forest provided the best discrimination (AUC=0.808), with tree-based ensembles (random forest, XGBoost, and LightGBM) generally outperforming the kernel- and distance-based methods (the support vector machine and k-nearest neighbors). The moderate discrimination is consistent with the inherent constraints of the dataset—small size, single-center origin, and substantial missingness—and these values are deliberately reported without optimistic inflation. This pattern is expected for heterogeneous, mixed-type clinical data marked by nonlinear interactions and residual missingness, for which ensembles of decision trees tend to be comparatively robust and require little manual feature scaling.[12]

These results are best read in the context of prior work on the same cohort and the broader HCC prognostic literature. The dataset was originally assembled to evaluate a cluster-based oversampling strategy for survival prediction,[9] and a later ensemble-learning analysis of the same patients reported similarly moderate discrimination while highlighting laboratory and tumor-marker variables as informative.[4] The present results are therefore consistent with what has been achievable on this cohort, and the wide spread of performance reported across HCC machine-learning studies more generally reflects differences in cohort size, end points, and validation rigor rather than any single benchmark. It is also worth noting that much recent machine-learning work in HCC has centered on radiomics and deep learning applied to cross-sectional imaging;[5] by contrast, the present model uses only routinely collected demographic, laboratory, and clinical variables, which may favor reproducibility and applicability in settings where advanced imaging or computational pathology is not readily available.

The principal value of this work lies less in raw discrimination than in the transparency and clinical coherence of the model. The SHAP ranking placed AFP and ALP at the top, in agreement with previous analyses of this cohort and with the established prognostic role of these markers in HCC; AFP is a well-recognized tumor marker, and ALP and bilirubin reflect cholestasis and hepatic dysfunction.[2] The prominence of ascites and the presence of symptoms is consistent with hepatic decompensation and a greater clinical disease burden, whereas hemoglobin and performance status align with the clinical understanding that general physiological reserve influences outcome. The recurrence of three iron-metabolism markers—serum iron, transferrin saturation, and ferritin—among the leading features, each with an association that appeared non-monotonic, is biologically plausible given the complex and frequently dysregulated role of iron handling in chronic liver disease and hepatocarcinogenesis, and this apparent non-monotonicity cautions against interpreting such markers through simple linear thresholds. The convergence of global SHAP and local LIME explanations provides a cross-checking mechanism that strengthens confidence in the model's reasoning at both the population and individual levels.[7,8]

Beyond ranking influential variables, the explainability layer speaks to a practical barrier to the clinical uptake of prognostic models. Opaque models, however accurate, are often met with justified clinician skepticism, and systematic reviews of machine learning in healthcare have observed that a large share of clinical prediction studies still provide little or no explanation of how their predictions are formed.[6] By pairing a model-agnostic local method (LIME) with a theoretically grounded global method (SHAP), the present framework allows each prediction to be examined in terms of the features that drove it, which is a prerequisite for accountability, error analysis, and meaningful clinician oversight. Such instance-level transparency is especially valuable when discrimination is only moderate, because it lets a clinician judge whether an individual prediction rests on coherent, clinically sensible signals rather than on spurious associations.

The DCA findings suggest that, despite moderate discrimination, the model may offer a net clinical benefit within a relevant range of decision thresholds, which is the more decision-relevant criterion for a prognostic aid than discrimination alone.[18] This distinction matters because measures such as the AUC quantify ranking ability but not whether acting on the model's predictions does more good than the default strategies of treating all or treating no patients. Combined with reasonable calibration after Platt scaling, which keeps the predicted probabilities interpretable as approximate risks rather than uncalibrated scores, these properties support the framework's potential as a transparent decision-support aid rather than an autonomous predictor. These observations are based on internal cross-validation in a small, single-center cohort and should be regarded as hypothesis-generating; they require confirmation in larger, external, and preferably prospective cohorts before any claim of clinical utility can be made.

This study has several limitations. First, the cohort is small (n=165) and single-center, which limits generalizability and yields wide confidence intervals around performance estimates. With only 63 events across 49 candidate variables, the number of events per variable is low; although no a priori sample-size calculation is applicable to a fixed secondary dataset, this further constrains statistical precision and motivated the use of ensemble and resampling-based methods together with strictly in-fold preprocessing. Second, the missing-data rate (10.2%) required imputation, which introduces uncertainty despite the use of multiple imputation. Third, no external validation cohort was available; the reported performance is therefore internal, and external, preferably prospective, validation is required before any clinical use. Fourth, because the outcome is dichotomized one-year survival, time-to-event information and the timing of death within the first year are not modeled. Fifth, although resampling and all preprocessing were confined to the training folds to prevent leakage, residual optimism arising from the modest sample size cannot be fully excluded, and the explanations—while internally consistent—describe the behavior of this particular model on this cohort rather than establishing causal relationships. Future work should pursue larger, multi-center, and prospective cohorts and time-to-event modeling, should prespecify and report calibration and net benefit alongside discrimination, and may explore the integration of molecular, proteomic, or imaging-derived data when such measurements are available for the same patients.

Conclusion

On the UCI HCC-Survival cohort, an explainable ML framework predicting one-year survival yielded moderate but robust discrimination, with random forest performing best (AUC=0.808). More importantly, SHAP and LIME produced transparent, mutually consistent, and clinically coherent explanations—identifying AFP, ALP, iron, performance status, and hemoglobin as leading predictors—while calibration and decision curve analysis supported clinical utility within a relevant range of thresholds. The framework prioritizes interpretability and honest reporting over performance maximization and provides a transparent basis for

prognostic decision support that warrants validation in larger, prospective cohorts.

Disclosures

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

Peer-review: Externally peer-reviewed.

Conflict of Interest: The author declares no conflict of interest.

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Data and code availability: The analyzed dataset is publicly available from the UCI Machine Learning Repository (HCC-Survival; archive.ics.uci.edu/dataset/423). The analysis code is available from the corresponding author upon reasonable request.

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Original Research

Depressive, Anxiety, and Post-Traumatic Stress Symptoms in Pediatric Liver Transplant Recipients: A Cross-Sectional Study

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Abstract

Objectives: Pediatric liver transplant recipients may experience depression, anxiety, and post-traumatic stress symptoms despite favorable medical outcomes. This study aimed to evaluate depressive symptoms, anxiety symptoms, and post-traumatic stress symptoms among pediatric liver transplant recipients and to examine the relationships among these psychological outcomes.

Methods: This cross-sectional study was conducted with 50 pediatric liver transplant recipients aged 8–18 years who were followed at a liver transplant center. Data were collected using the Child Descriptive Information Form, the Children's Depression Inventory (CDI), the Screen for Child Anxiety Related Emotional Disorders (SCARED), and the Children's Revised Impact of Event Scale (CRIES-13). The data were analyzed using descriptive statistics, Mann–Whitney U tests, Spearman correlation analyses, and multiple linear regression analyses.

Results: A considerable number of participants exhibited clinically relevant psychological difficulties. Anxiety scores differed significantly according to sex. Recipients of deceased-donor transplants had significantly higher post-traumatic stress symptom scores than recipients of living-donor transplants. Emotional and psychological distress levels decreased as the time elapsed since transplantation increased. Correlation analyses indicated significant associations among the measured mental health outcomes. Furthermore, trauma-related symptoms emerged as significant predictors of emotional difficulties after adjustment for age, sex, and post-transplant duration.

Conclusion: Psychological symptoms were observed among pediatric liver transplant recipients, and significant associations were identified among depression, anxiety, and trauma-related symptoms. These findings support the potential value of routine psychosocial assessment during post-transplant follow-up. Further longitudinal studies are needed to clarify the temporal relationships among these psychological outcomes.

Keywords: Anxiety, depression, mental health needs, pediatric liver transplantation, post-traumatic stress symptoms

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Liver transplantation is one of the major treatment approaches that can sustain life in children diagnosed with end-stage liver disease or acute liver failure. Recent progress in surgical procedures, immunosuppressive management, and post-transplant follow-up has been associated with improved long-term outcomes and a greater likelihood of survival in this patient population. [1] As survival outcomes have improved, attention has increasingly shifted beyond medical indicators to include children's psychosocial well-being, quality of life, and mental health. Previous research has indicated that children who have undergone liver transplantation may continue to experience challenges in psychosocial functioning, even when their physical health outcomes are generally favorable. [2] Moreover, following liver transplantation, children are confronted with numerous stressors, including lifelong immunosuppressive therapy, regular hospital follow-up visits, potential medical complications, fear of graft rejection, and the ongoing need for treatment adherence. [2] In addition, interruptions in school attendance, difficulties in peer relationships, changes in physical appearance, and family restructuring processes may also affect children's psychological well-being. For this reason, monitoring emotional and psychosocial adaptation alongside physical health status is considered an important component of follow-up care for children who have undergone liver transplantation. [2,3] Although liver transplantation is a life-saving intervention, it may be considered a potentially traumatic life event for children due to the diagnostic process, waiting period, surgical procedure, intensive care experience, and lifelong medical follow-up. Studies have shown that post-traumatic stress symptoms may persist in pediatric liver transplant recipients even years after transplantation. [4,5] The literature indicates that pediatric liver transplant recipients may experience some emotional, psychological, and behavioral problems. [3-5] In a study conducted by Düken and Yayan, clinically significant levels of anxiety, post-traumatic stress, and depression symptoms were reported among children who had undergone liver transplantation. [3] Similarly, Huang et al.[4] demonstrated that children who underwent living-donor liver transplantation may experience more emotional and behavioral problems than their healthy peers. Furthermore, psychiatric symptoms have been reported to negatively affect treatment adherence and may be associated with post-transplant clinical outcomes. [5]

Mental health needs refer to situations in which individuals may benefit from psychological assessment, counseling, or treatment services. [6] Unmet mental health needs, on the other hand, describe the gap in care that arises when existing psychological problems are not recognized, individuals are not referred to appropriate services, or necessary mental health support is not received. [6,7] Findings from a systematic review evaluating studies involving adolescents indicate that a substantial proportion of young people experiencing mental health problems do not have access to the services they need and that unmet mental health needs constitute a significant global public health concern. [6] Similarly, international studies have reported that many children experiencing psychological symptoms do not receive professional help and that utilization of mental health services remains considerably below the level of need. [7] Emotional, behavioral, and trauma-related difficulties observed in children and adolescents are considered important markers indicating the potential need for professional psychological support. [6] Therefore, although the assessment of psychiatric symptoms does not directly measure service utilization, it may provide important indicators suggestive of unmet mental health needs. [6,7] Nevertheless, evidence regarding psychiatric manifestations that may reflect unmet mental health needs among children who have undergone liver transplantation remains scarce. The present study was designed to assess depressive symptoms, anxiety symptoms, and post-traumatic stress symptoms among children who had undergone liver transplantation. The findings may contribute to understanding the psychological symptoms experienced by pediatric liver transplant recipients and may inform future research and post-transplant psychosocial care.

Research Questions

What are the levels of anxiety, depression, and post-transplant psychological impact symptoms among pediatric liver transplant recipients, and do these symptoms differ according to sociodemographic and clinical characteristics?

Is there an association among anxiety, post-traumatic stress, and depression symptoms among pediatric liver transplant recipients?

Do post-traumatic stress symptoms predict depression and anxiety symptoms among pediatric liver transplant recipients?

Methods

Study Design

This analytical cross-sectional study was conducted to evaluate depressive symptoms, anxiety symptoms, and post-traumatic stress symptoms among pediatric liver transplant recipients.

Population and Sample

The study population consisted of pediatric liver transplant recipients who were still being followed up and who had

applied to the İnönü University Liver Transplant Institute in June 2026. No sampling procedure was performed. Participant recruitment was based on eligibility and willingness to participate throughout the data collection period. By the end of the study, data had been obtained from 50 children with a history of liver transplantation.

Inclusion and Exclusion Criteria

Eligibility was limited to children between 8 and 18 years of age who were at least six months post-transplantation, had sufficient Turkish language proficiency to comprehend the study materials, possessed the cognitive ability required to complete the questionnaires, and expressed a willingness to participate. Children were excluded if they were hospitalized due to acute rejection or severe medical complications, had a diagnosed severe neurological disorder, or had cognitive impairment that prevented them from completing the questionnaires.

Measures Used in the Study

Child Descriptive Information Form: The Child Descriptive Information Form was developed by the researchers based on the study objectives and a review of the relevant literature. The form included questions regarding the participants' sex, age, family structure, educational status, donor type, time elapsed since transplantation, and other clinical characteristics.

Children's Depression Inventory (CDI): This scale, developed by Kovacs in 1985, was used to assess depressive symptoms in children and adolescents. [8] The scale consists of 27 items, each containing three statements reflecting varying levels of depressive symptom severity and scored as 0, 1, or 2. The scale allows for a total score between 0 and 54, with higher scores indicating a higher level of depressive symptoms. In the original version of the scale, the total score is primarily used for clinical evaluation, and no standard subscale scoring system has been established. The psychometric properties of the Turkish version of the CDI were examined by Öy in 1991. [9] Psychometric testing of the Turkish version demonstrated satisfactory internal consistency (Cronbach's α=0.80), supporting its use for the assessment of depressive symptoms in children. The scale does not contain any reverse-scored items. [9]

Screen for Child Anxiety Related Emotional Disorders (SCARED): This scale was used to evaluate anxiety symptoms in children and adolescents. It was originally developed by Birmaher et al.[10] and has been widely utilized in pediatric populations. SCARED is a self-report instrument designed to screen for DSM-based childhood anxiety disorders. The scale consists of 41 items that assess the frequency of anxiety symptoms experienced by children and adolescents. Each item in the assessment tool is scored between 0 and 2; higher scores indicate higher levels of anxiety symptoms. There are no reverse-scored items in the scale. The internal consistency coefficient of the original version ranges from 0.74 to 0.93 for the total scale. The Turkish validity and reliability study was conducted by Çakmakçı in 2004, demonstrating that the Turkish version is a valid and reliable instrument (Cronbach's alpha=0.81). [11]

Children's Revised Impact of Event Scale (CRIES-13): The CRIES-13 was administered to measure trauma-related stress symptoms among children and adolescents. Perrin, Meiser-Stedman, and Smith developed this instrument as a screening measure for traumatic stress reactions in children and adolescents. [12] It has been widely used to evaluate symptoms arising after traumatic experiences such as natural disasters, accidents, war, abuse, and severe illnesses. Çeri et al.[13] examined the psychometric characteristics of the Turkish adaptation of the scale. Higher total scores indicate more severe trauma-related symptomatology. The scale contains no reverse-scored items (Cronbach's alpha=0.80). [13]

Variables

Scores obtained from the CDI, SCARED, and CRIES-13 were used as the dependent variables in the analyses. The independent variables included the children's sociodemographic characteristics (e.g., age, sex, and educational status) and clinical characteristics (e.g., age at transplantation, time elapsed since transplantation, donor type, and other clinical variables).

Data Collection Procedure

Data were collected using a question-and-answer technique during face-to-face interviews when families brought their children for routine clinical check-ups. After participants were informed about the research in accordance with ethical principles, they began filling out the forms. All forms were completed under the supervision of the researcher. Most participants completed the study instruments within approximately 15–20 minutes.

Ethical Considerations

Prior to data collection, ethical approval was granted by İnönü University Health Sciences Scientific Research Ethics Committee (No: 2026/10316, June 2, 2026). Authorization to conduct the study was also obtained from the relevant institution. Participation was voluntary, and informed consent was secured from parents or legal guardians. In addition, age-appropriate assent was obtained from the children whenever applicable. The rights, safety, and well-being of the participants were protected in accor-

dance with internationally recognized ethical standards, including those described in the Declaration of Helsinki.

Statistical Analysis

The data obtained in this study were analyzed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was evaluated through examination of histograms, skewness and kurtosis values, and the Shapiro-Wilk test. Descriptive statistics were presented according to the characteristics of the data; continuous variables with normal distribution were expressed as mean±standard deviation, whereas those not meeting normality assumptions were summarized as median (Q1–Q3). Categorical variables were described as numbers and percentages. The prevalence of clinically significant anxiety symptoms, post-traumatic stress symptoms, and depressive symptoms was determined using the established cut-off values of the respective instruments. As the majority of the scale scores deviated from a normal distribution, non-parametric methods were preferred for comparative analyses. Differences between independent groups (e.g., sex and donor type) were assessed using the Mann-Whitney U test. Associations of age and post-transplant duration with psychological symptom scores were examined using Spearman's rank-order correlation analysis. The relationships among anxiety, post-traumatic stress, and depression symptom scores were also investigated using Spearman correlation coefficients. To examine the predictive role of post-traumatic stress symptoms on depression and anxiety symptoms, separate multiple linear regression models were constructed. Model performance was assessed using the coefficient of determination (R^2) and overall model significance statistics (F values). A p-value of <0.05 was considered statistically significant.

Table 1. Sociodemographic and clinical characteristics of the sample (n=50)

Characteristic	n (%)	Mean±SD / Median
Sex		
Male	28 (56.0%)	—
Female	22 (44.0%)	—
Age (years)	—	13.50±3.18/14.0
Transplant type		
Living donor	44 (88.0%)	—
Deceased donor	6 (12.0%)	—
Time since transplant (months)	—	80.9±59.2/66.3
Hospitalization in past year		
Yes	2 (4.0%)	—
No	48 (96.0%)	—
Psychiatric follow-up		
Yes	1 (2.0%)	—
No	49 (98.0%)	—

Results

Fifty children with a history of liver transplantation participated in the study. Participants ranged in age from 8 to 18 years, with a mean age of 13.50 years (SD=3.18). Boys accounted for 56% of the sample, whereas girls represented 44%. The majority had received a living-donor transplant (88%), with a mean post-transplant duration of 80.9 months (SD=59.2). At the time of assessment, only one participant (2%) was receiving psychiatric follow-up (Table 1).

Table 2 presents comparisons of depression, anxiety, and post-traumatic stress symptom scores according to sex and transplant type. Anxiety scores differed significantly by sex (p=0.035), whereas depression and post-traumatic

Table 2. Group Comparisons by Sex and Transplant Type (Mann-Whitney U Test)

Variable	Group	CDI Median	(Q1-Q3)	Z/p	SCARED Median	(Q1-Q3)	Z/p	CRIES Median	(Q1-Q3)	Z/p
Sex	Male (n=28)	29.00	26.00-29.00	-0.793/ 0.428	11.00	3.25-11.75	**-2.118/ 0.035***	7.50	2.00-16.50	-0.931/ 0.352
	Female (n=22)	29.00	27.00-31.00		7.50	7.00-16.00		4.00	3.50-14.75	
Transplant type	Living donor (n=44)	29.00	27.00-30.00	-0.606/ 0.545	9.00	6.00-12.00	-1.348/ 0.178	6.00	2.00-13.00	**-2.634/ 0.006****
	Deceased donor (n=6)	27.50	24.50-30.25		12.50	7.50-36.75		22.00	11.75-25.75	

* p<0.05 ** p<0.01

Table 3. Associations Between Age, Time Since Transplant, and Symptom Levels (Spearman)

Variable	CDI rho	p	SCARED rho	p	CRIES rho	p
Age	-0.131	0.364	-0.293	**0.039***	-0.126	0.383
Time since transplant (months)	-0.373	**0.008****	-0.473	**0.001****	-0.423	**0.002****
CDI (Depression)	—		0.337	**0.017***	0.444	**0.001****
SCARED (Anxiety)	0.337	**0.017***	—		0.484	**0.001*****
CRIES (Trauma impact)	0.444	**0.001****	0.484	**0.001*****	—	

*p<0.05; **p<0.01; ***p<0.001. Values below the diagonal mirror those above the diagonal (symmetric matrix).

Table 4. Prediction of Depression and Anxiety by Post-Transplant Stress Symptoms (Multiple Linear Regression)

Predictor variable	CDI B	p	SCARED B	p
CRIES total score	0.104	**0.020***	0.453	**0.004****
Age	0.108	0.386	0.083	0.844
Sex (female=1)	0.444	0.561	2.557	0.329
Time since transplant (months)	0.001	0.919	-0.043	0.087
Model fit statistics	**R^2 = 0.225** F(4,45) = 3.264, p = 0.020*		**R^2 = 0.288** F(4,45) = 4.546, p = 0.004**	

p<0.05; **p<0.01. B, unstandardized regression coefficient. Models were adjusted for age, sex, and time since transplant. In the simple regression models including CRIES total score as the sole predictor, R^2=0.178 (p=0.002) for CDI and R^2=0.217 (p=0.001) for SCARED.

stress scores did not. With respect to transplant type, recipients of deceased-donor liver transplants had significantly higher post-traumatic stress symptom scores than recipients of living-donor transplants (p=0.006). No significant differences were observed in depression or anxiety scores according to transplant type.

Time since transplantation was significantly and inversely correlated with all three symptom scales: depression (rho=–0.373, p=0.008), anxiety (rho=–0.473, p=0.001), and post-traumatic stress (rho=–0.423, p=0.002). This finding suggests that psychological distress tends to diminish over time following transplantation, possibly reflecting psychological adaptation and improved medical stability. Age showed a significant negative association only with anxiety (rho=–0.293, p=0.039), indicating that younger children may experience higher levels of anxiety symptoms (Table 3). All three scales were significantly and positively intercorrelated. The strongest association was observed between SCARED and CRIES (rho=0.484, p<0.001), followed by CDI and CRIES (rho=0.444, p=0.001), and CDI and SCARED (rho=0.337, p=0.017; Table 3).

CRIES total score significantly predicted both depression and anxiety after controlling for age, sex, and time since transplantation. The model explained 22.5% of the variance in depression scores (R^2=0.225, F(4,45)=3.264, p=0.020) and 28.8% of the variance in anxiety scores (R^2=0.288, F(4,45)=4.546, p=0.004). The larger regression coefficient for anxiety (B=0.453) than for depression (B=0.104) suggests that trauma-related symptoms may be more closely associated with anxiety symptoms than with depressive symptoms in this sample. These results highlight the clinical importance of screening for trauma-related symptoms as part of routine psychological assessment in pediatric transplant settings (Table 4).

Discussion

In the present study, anxiety, post-traumatic stress, and depression symptoms were evaluated simultaneously in pediatric liver transplant recipients, and a substantial proportion of the participants were found to continue experiencing a considerable psychological symptom burden. The most striking finding was that the majority of participants were classified as being at risk for depressive symptoms according to the cutoff score of the Children's Depression Inventory. However, this finding should not be interpreted as a diagnosis of clinical depression but rather as an indication of an elevated risk of depressive symptoms identified through a screening instrument. Previous studies have reported that anxiety, post-traumatic stress, and depression symptoms are more prevalent among pediatric liver transplant candidates and recipients than among healthy controls and that these symptoms are negatively associated with quality of life.[14] Similarly, a recent study reported clinically significant levels of anxiety, post-traumatic stress,

and depression symptoms among children who had undergone liver transplantation.[3] Taken together, these observations suggest that childhood liver transplantation should be viewed not only as a medical intervention but also as an experience with potential long-term psychosocial implications.

Although only one participant (2%) was receiving psychiatric follow-up at the time of assessment, a considerable proportion of participants exhibited elevated psychological symptom scores. This finding may suggest that some children with psychological symptoms were not receiving mental health care; however, the present study did not directly assess mental health service utilization or unmet mental health needs. Previous investigations have drawn attention to the need for ongoing mental health surveillance as part of comprehensive care for transplanted children. Huang et al.[4] reported that children who underwent living-donor liver transplantation were at greater risk for emotional problems, hyperactivity, and peer relationship difficulties than healthy controls. Their results further indicated that children's psychological well-being was influenced by parental psychological status, levels of physical activity, and characteristics of the family environment. Therefore, post-transplant follow-up in pediatric liver transplant recipients should include not only the assessment of graft function, immunosuppression, and medical complications but also systematic evaluation of depressive symptoms, anxiety, trauma-related symptoms, family functioning, and social adjustment.

Comparisons by sex revealed a significant difference in anxiety scores, whereas no sex-based differences were observed for depression or post-traumatic stress symptoms. This finding is consistent with the broader psychopathology literature reporting that anxiety symptoms are more prevalent among girls during childhood and adolescence. Similarly, studies conducted among pediatric liver transplant recipients have suggested that girls may be at greater risk for emotional problems and anxiety symptoms.[3,4] This difference may be associated with increased emotional sensitivity during adolescence, concerns related to body image, difficulties in social relationships, and uncertainty regarding the future. However, the present study did not identify sex-based differences in indicators of depression or traumatic stress. This finding suggests that the influence of sex on psychological adjustment may be more pronounced for anxiety symptoms than for other domains of psychological distress.

Analyses according to donor type revealed that children who received transplants from deceased donors had significantly higher post-traumatic stress symptom scores than those who received transplants from living donors. No significant differences were observed for depression or anxiety. One possible explanation is that deceased-donor transplantation may involve greater uncertainty and medical urgency. However, this interpretation should be considered speculative and requires confirmation in longitudinal studies. Interpretation of these findings warrants caution due to the relatively small sample size of the deceased-donor transplant group. Previous studies have shown that traumatic stress may negatively affect quality of life, treatment adherence, and psychosocial functioning in pediatric organ transplant recipients.[15,16] Therefore, it is important to comprehensively evaluate how children with a history of deceased-donor transplantation perceive and interpret the transplant process, their experiences during the waiting period, and the presence of medical trauma-related symptoms.

The present study found that the time elapsed since transplantation was negatively associated with anxiety, post-traumatic stress, and depression symptoms. In other words, psychological symptom levels decreased as the post-transplant period increased. This finding may reflect psychological adaptation over time; however, because of the cross-sectional design, no conclusions can be drawn regarding changes in symptoms over time or causal relationships. Longitudinal studies are required to confirm this interpretation. However, it also suggests that the period immediately following transplantation may represent a particularly vulnerable phase in terms of psychological well-being. The pediatric medical traumatic stress model emphasizes that serious illnesses and invasive medical procedures may lead to traumatic stress symptoms in children and that these symptoms may follow different trajectories over time.[17] Therefore, psychosocial screening during the early post-transplant period and close monitoring of at-risk children are of considerable importance.

Significant positive correlations were found among anxiety, post-traumatic stress, and depression symptoms. This finding suggests that psychological symptoms in pediatric liver transplant recipients do not occur independently but rather tend to manifest as an interconnected cluster of symptoms. Ünay et al.[14] also demonstrated interrelationships among psychological difficulties in pediatric liver transplant candidates and recipients, reporting that increased symptom severity corresponded to lower perceived quality of life. Likewise, Düken and Yayan reported a strong and significant relationship between anxiety and post-traumatic stress reactions.[3] These findings indicate that post-transplant psychological assessment should not focus on a single symptom domain but should instead in-

clude the simultaneous screening of anxiety, post-traumatic stress, and depression symptoms. Positive correlations were observed among depression, anxiety, and post-traumatic stress symptoms, suggesting that these psychological problems tend to co-occur in pediatric liver transplant recipients. The strongest association was observed between anxiety and post-traumatic stress symptoms, highlighting the close relationship between these psychological domains. This finding is clinically important because trauma-related symptoms may interfere with children's daily functioning and psychosocial adjustment, highlighting the need for routine psychological assessment following liver transplantation. Post-traumatic stress symptoms have been reported to affect not only psychological well-being but also treatment adherence among organ transplant recipients.[16,18] Therefore, trauma-related symptoms may represent an important target for early identification and intervention in pediatric transplant clinics.

Regression analyses revealed that post-traumatic stress symptoms significantly predicted both anxiety and depression after controlling for age, sex, and time elapsed since transplantation. This finding suggests that traumatic stress symptoms may play a central role in psychological adjustment following pediatric liver transplantation. Evidence from systematic reviews demonstrating that post-traumatic stress disorder can occur among organ transplant recipients and may have substantial effects on psychological outcomes further supports this interpretation.[19] In addition, traumatic stress symptoms have been reported to be associated with quality of life in pediatric organ transplant recipients and should therefore be considered during routine follow-up care.[15] Accordingly, the findings of the present study suggest that post-transplant psychological support should focus not only on anxiety and depressive symptoms but also on helping children process and cope with the experience of medical trauma.

Limitations

Certain characteristics of the research design should be considered when evaluating these results. This study was conducted at a single pediatric liver transplantation center. Therefore, center-specific clinical practices, patient characteristics, and the availability of psychosocial support services may have influenced the findings and may limit the generalizability of the results to other transplantation centers. The deceased-donor subgroup represented only a small proportion of the sample, which may have limited the ability to detect and interpret differences between donor groups. Furthermore, the snapshot nature of the data collection process does not allow conclusions regarding the sequence or direction of the relationships observed among the study variables. In addition, because the data were collected using self-report measures, the findings may have been influenced by individual differences in children's perceptions and reporting of symptoms. Furthermore, symptoms of depression, anxiety, and post-traumatic stress were not confirmed through clinical interviews; therefore, the findings should be interpreted in terms of symptom severity and risk rather than as clinical diagnoses. Despite these limitations, the study contributes to the existing literature by simultaneously examining anxiety, post-traumatic stress, and depression symptoms in pediatric liver transplant recipients and by demonstrating the predictive role of traumatic stress symptoms on depression and anxiety.

Conclusion

In conclusion, this study demonstrated that anxiety, post-traumatic stress symptoms, and depressive symptoms may be present at considerable levels among pediatric liver transplant recipients and that these symptoms are significantly interrelated. These findings support consideration of psychosocial monitoring during post-transplant follow-up. Moreover, the significant predictive effect of post-traumatic stress symptoms on anxiety and depression suggests that trauma-focused psychological screening and interventions should be integrated into the routine care of pediatric transplant recipients.

Disclosure

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Ethics Committee Approval: Inonu University Health Sciences Scientific Research Ethics Committee (No: 2026/10316, June 2, 2026).

Informed Consent: Participation was voluntary, and informed consent was secured from parents or legal guardians.

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RETRACTION NOTICE

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The Editorial Board of Journal of Inonu Liver Transplantation Institute hereby retracts the following article at the request of the author(s).

Following publication, the author formally requested the withdrawal of the article. After careful consideration of the request and the circumstances presented, the Editorial Board determined that retraction of the article was appropriate and approved the request.

This retraction is issued in accordance with the journal's editorial policies and recognized standards of publication ethics. The article's bibliographic record will remain part of the scholarly record; however, the article will be clearly marked as retracted in all available versions and records.

This retraction has been approved by the Editor-in-Chief and the Editorial Board of Journal of Inonu Liver Transplantation Institute.

Editor-in-Chief

Prof.Dr. Sezai YILMAZ

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Original Research

Celiac Trunk and Hepatic Arterial Variations in Pancreaticoduodenectomy: Surgical Outcomes and Hidden Risks

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Abstract

Objectives: Pancreaticoduodenectomy is a technically demanding procedure with considerable morbidity and mortality where detailed knowledge of vascular anatomy is essential. Variations of the celiac trunk and hepatic artery are relatively common and may influence surgical strategy, lymph node dissection and perioperative outcomes. However, their impact on operative and oncological parameters remains controversial. This study aimed to evaluate the impact of celiac trunk and hepatic artery variations on operative time, lymph node yield and early postoperative liver function in patients undergoing pancreaticoduodenectomy.

Methods: A single-center retrospective study was conducted including 117 patients who underwent PD between January 2016 and March 2025. Preoperative contrast-enhanced computed tomography angiography was used to assess hepatic arterial anatomy according to the Michels classification. Patients were grouped as normal anatomy (Type I) and arterial variation (Types II–X). Clinical, operative and pathological parameters were compared.

Results: Arterial variations were identified in 32.5% of patients. Operative time was significantly longer in the variation group compared to normal anatomy (315 vs 240 minutes, p=0.002). Total lymph node yield was significantly lower in patients with arterial variation (12 vs 21, p<0.001) whereas malignant lymph node count and lymph node ratio were similar between groups. No significant differences were observed in postoperative liver function tests, including ALT and AST levels. Subgroup analysis demonstrated that left sided variations were associated with the longest operative times. Regression analysis confirmed arterial variation as an independent predictor of prolonged operative time (B=55.763, p=0.001).

Conclusion: Celiac trunk and hepatic artery variations significantly prolong operative time and are associated with reduced lymph node yield in pancreaticoduodenectomy without adversely affecting early postoperative liver function. Preoperative identification of these variations is crucial for optimal surgical planning and may have implications for oncological adequacy.

Keywords: Arterial variations, pancreaticoduodenectomy, vascular pitfalls

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Pancreaticoduodenectomy (PD) is a technically complex surgical procedure used in the treatment of malignancies of the pancreatic head, ampulla of Vater, distal common bile duct, and duodenum and is associated with high morbidity and mortality rates. First described by Whipple and colleagues in 1935, this complex resection procedure has undergone significant technical refinement over the decades; however, it continues to be associated with mortality rates ranging from 1% to 6%, even at high-volume centers, as well as substantial morbidity.[1,2] The procedure involves extensive resection, lymph node dissection, and complex reconstruction, making accurate assessment of vascular anatomical structures during surgery of paramount importance.

The celiac trunk is one of the ventral branches of the abdominal aorta and typically divides into three main branches: the left gastric artery, the splenic artery, and the common hepatic artery. However, the celiac trunk is recognized as the structure among the ventral branches of the abdominal aorta in which anatomical variations occur most frequently. In the literature, the prevalence of the classic trifurcation pattern has been reported to range from 72% to 90%, while various other configurations have been documented at differing rates.[3] These variations include the absence of the celiac trunk, the formation of a hepatomesenteric trunk, bifurcation or quadrifurcation variants, and anomalous origins of its branches.

Hepatic artery variations also represent a significant factor in hepatopancreatobiliary surgery. Normal hepatic arterial anatomy has been reported in 52–80% of surgical cases, with various anatomical variants identified in the remaining cases.[4] One of the most frequently encountered variations is an aberrant right hepatic artery originating from the superior mesenteric artery, with a reported prevalence ranging from 11% to 21%.[5] Additional variations, such as the common hepatic artery arising from the superior mesenteric artery or the formation of a hepatomesenteric trunk, have also been described. The embryological origin of celiac trunk and hepatic artery variations is rooted in the differentiation that occurs during the development of the ventral segmental arteries. The variable persistence or regression of longitudinal anastomoses formed during this process gives rise to a spectrum of arterial variations. The presence of these anatomical variations may have significant implications for surgical technique, dissection planning, and intraoperative safety, particularly in hepatopancreatobiliary procedures such as pancreaticoduodenectomy. Vascular variations can increase the risk of arterial injury, potentially leading to serious complications, including hepatic ischemia, liver abscess, biliary fistula, and hemorrhage. Accordingly, accurate preoperative identification of arterial anatomical variations is of critical importance for optimizing surgical planning and minimizing complications.

Moreover, celiac trunk and hepatic artery variations have been reported to influence not only surgical technique but also lymph node dissection, resection margins, and surgical outcomes. Given that lymphadenectomy constitutes an indispensable component of curative resection in cancer and that the number of dissected lymph nodes is well known to affect both staging and survival, the question of whether vascular variations restrict adequate lymph node dissection is of considerable clinical relevance.[6] The superior mesenteric artery (SMA) margin is recognized as one of the most critical resection margins in pancreatic head adenocarcinoma surgery; in particular, an aberrant right hepatic artery arising from the SMA may increase the risk of R1 resection due to its close anatomical proximity to this margin. Indeed, several studies have reported a significantly higher rate of R1 resection at the SMA margin in patients harboring a replaced or accessory right hepatic artery.[7] Nevertheless, the effects of vascular variations on morbidity, operative time, and postoperative outcomes following pancreaticoduodenectomy have yielded variable results across different studies.

The aim of this study is to evaluate the impact of celiac trunk and hepatic artery variations on operative time, the number of dissected lymph nodes, and early postoperative liver function tests in patients who underwent pancreaticoduodenectomy.

Methods

Study Design

This study was designed as a single-center, retrospective, descriptive analysis. Data were obtained from patients who underwent pancreaticoduodenectomy for periampullary region malignancy or suspected malignancy at the Department of General Surgery, University of Health Sciences, Ankara Gülhane Research and Training Hospital. The study included patients treated between January 2016 and March 2025. This study was reviewed and approved by the Ethics Committee of Ankara Gülhane Research and Training Hospital (Date: 17.02.2026; Approval No. E-50687469-799-305797850). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Selection

The inclusion criteria were defined as follows: age 18 years or older, having undergone curative-intent pancreaticoduodenectomy for pancreatic cancer or suspected cancer, and availability of adequate preoperative contrast-en-

hanced abdominal computed tomography angiography (CTA) images for assessment of hepatic arterial anatomy. Patients who underwent palliative surgical intervention, patients with incomplete medical records, and patients whose preoperative CTA images could not be accessed were excluded from the study. A total of 117 patients who met the inclusion criteria were enrolled.

Data Collection

Clinical, laboratory, and radiological data were obtained retrospectively from patient files. The following variables were recorded for each patient: age, sex, tumor location, preoperative serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, postoperative day 2 ALT and AST levels, preoperative tumor marker results, hepatic artery variations detected by preoperative CTA, operative time, total number of lymph nodes dissected, number of malignant lymph nodes, positive lymph node ratio, and selected postoperative pathological data, primarily including pathological T stage.

Imaging Evaluation and Arterial Classification

All preoperative contrast-enhanced abdominal CTA images were reviewed to identify and characterize hepatic arterial anatomy. Hepatic artery variations were evaluated according to the Michels classification system, which defines hepatic arterial anomalies in 10 distinct subtypes (Types I–X) (Figure 1). Michels Type I, representing standard anatomy in which the common hepatic artery originates from the celiac trunk and divides into the right and left hepatic arteries, was considered normal anatomy. All other Michels subtypes (Types II–X) were classified as arterial variations. In subgroup analyses, arterial variations were further categorized into clinically meaningful groups based on their anatomical location and surgical significance: left-sided variations (Michels Types II and V) and right-sided/retropancreatic variations (Michels Types III, IV, VI, VII, VIII, and IX).

Outcome Measures

Primary outcome measures were operative time (in minutes), total number of lymph nodes dissected, and early postoperative hepatic function, as reflected by postoperative day 2 serum ALT and AST levels. Secondary outcome measures included the number of malignant lymph nodes, positive lymph node ratio, and ALT and AST ratios (calculated by dividing the postoperative day 2 value by the preoperative value). Delta values (ΔALT and ΔAST) were calculated as the difference between postoperative day 2 and preoperative enzyme levels. In a subgroup analysis restricted to patients with confirmed malignancy, additional pa-

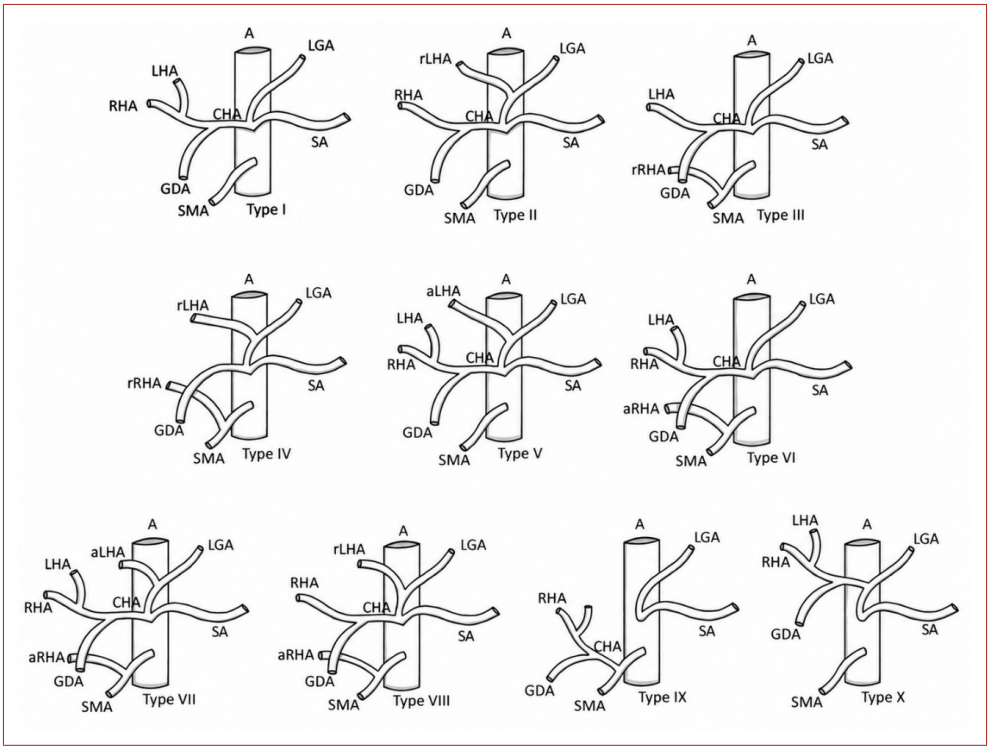

Figure 1. Classification of hepatic artery anatomy variation according to Michels.

LHA: Left hepatic artery; aLHA: accessory left hepatic artery; CHA: common hepatic artery; RHA: right hepatic artery; LGA: left gastric artery; SA: splenic artery; SMA: superior mesenteric artery; GDA: gastroduodenal artery; aRHA: accessory right hepatic artery; A: aorta.

rameters were assessed: pathological T stage distribution, total lymph node yield, number of malignant lymph nodes, positive lymph node ratio, and operative time.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). Prior to analysis, the distributional properties of continuous variables were assessed using the Shapiro–Wilk test and visual inspection of Q–Q plots. Variables demonstrating an approximately normal distribution were summarized as mean±standard deviation (SD), whereas non-normally distributed variables were reported as median [interquartile range (IQR)]. Categorical variables were expressed as number (n) and percentage (%). For comparisons between two independent groups (normal arterial anatomy vs. any arterial variation), the independent-samples t-test was used for continuous variables with an approximately normal distribution (e.g., age), while the Mann–Whitney U test was applied for non-normally distributed continuous variables (e.g., operative time, lymph node yield, and liver enzyme parameters). Pearson's chi-square test was used for categorical variables, including sex, tumor location, pathological T stage, and malignancy status. Effect sizes were calculated to quantify the magnitude of between-group differences. For continuous variables analyzed using parametric methods, Cohen's d with corresponding 95% confidence intervals (CIs) was reported. For categorical variables, Cramér's V was used as the measure of effect size. For comparisons involving more than two independent groups (normal anatomy, left-sided variation, and right-sided/retropancreatic variation), the Kruskal–Wallis test was used because of the non-normal distribution of variables. When the overall test was statistically significant, Bonferroni-adjusted pairwise comparisons were performed to identify group-specific differences. A malignancy-restricted subgroup analysis was conducted to evaluate oncological outcomes among patients with malignant pathology. In this subgroup, the Mann–Whitney U test was used for continuous variables and Pearson's chi-square test for categorical variables. To explore associations between arterial variation status and key clinical outcomes, univariable linear regression analyses were performed. Dependent variables included operative time, postoperative day 2 ALT, and postoperative day 2 AST. Regression results were reported as unstandardized coefficients (B), standard errors (SE), standardized coefficients (β), 95% confidence intervals (CIs), and p values. All statistical tests were two-tailed, and a p value<0.05 was considered statistically significant.

Results

Patient Characteristics

As shown in Table 1, the mean age of the overall cohort was 63.37±11.83 years. The mean age was 63.94±12.02 years in the normal anatomy group and 62.18±11.51 years in the arterial variation group, with no statistically significant difference between groups (p=0.456). We found no statistically significant difference in the distribution of sex according to arterial variation groups. Final malignant pathology was present in 104 patients (88.9%), including 72 patients (91.1%) in the normal anatomy group and 32 patients (84.2%) in the arterial variation group (Cramér's V=0.103, p=0.264). Tumor location did not differ significantly between groups (Cramér's V=0.097, p=0.775). Pancreatic head tumors were the most frequent overall (71/117, 60.7%), followed by ampullary tumors (34/117, 29.1%), distal common bile duct tumors (10/117, 8.5%), and duodenal tumors (2/117, 1.7%). Pathological T stage distribution was also comparable between groups (Cramér's V=0.182, p=0.424). According to Table 2, normal arterial anatomy (Michels Type I) was observed in 79 patients (67.5%). Among arterial variants, the most frequent pattern was Michels Type III, identified in 15 patients (12.8%). Michels Type II was present in 8 patients (6.8%), Type VIII in 5 patients (4.3%), Type V in 3 patients (2.6%), and Types VI, VII, and IX in 2 patients each (1.7%). Michels Type IV was observed in 1 patient (0.9%), whereas Michels Type X was not observed.

Operative and Pathological Outcomes of the Patients According to Arterial Anatomy Status

As presented in Table 3, operative time was significantly longer in patients with arterial variation than in those with normal anatomy (315.0 [150.0] min vs. 240.0 [120.0] min, p=0.002). Total lymph node yield was significantly lower in the arterial variation group than in the normal anatomy group (12.0 [4.25] vs. 21.0 [8.0], p<0.001). In contrast, malignant lymph node count did not differ between groups (1.0 [3.0] vs. 1.0 [3.0], p=0.913). Similarly, the positive lymph node ratio was not significantly different between the normal anatomy and arterial variation groups (0.0417 [0.1053] vs. 0.0556 [0.2125], p=0.276). As shown in Table 4, no statistically significant differences were observed between the normal anatomy and arterial variation groups with respect to liver enzyme profiles. Preoperative ALT levels were 40.0 [98.0] U/L in the normal anatomy group and 34.5 [91.0] U/L in the arterial variation group (p=0.677), whereas postoperative day 2 ALT levels were 55.0 [63.0] U/L and 44.0 [75.0] U/L, respectively (p=0.276). Preoperative AST levels were 37.0 [75.0] U/L in the normal anatomy group and 35.0 [40.0] U/L in the arterial variation group (p=0.646), and postoper-

Table 1. Baseline characteristics of the study cohort according to arterial anatomy status

Variable	Overall cohort (n=117)	Normal anatomy (Michels type I) (n=79)	Any arterial variation (Michels type II–X) (n=38)	Effect size	95% CI	p
Age, years	63.37±11.83	63.94±12.02	62.18±11.51	Cohen's d= 0.148	-0.240 to 0.535	0.456
Sex, n (%)						0.328
Male	78 (66.6)	55 (69.6)	23 (60.5)			
Female	39 (33.4)	24 (30.4)	15 (39.5)			
Final pathology, malignant, n (%)	104 (88.9)	72 (91.1)	32 (84.2)	Cramer's V = 0.103		0.264
Tumor location, n (%)				Cramer's V = 0.097		0.775
Pancreatic head	71 (60.7)	46 (58.2)	25 (65.8)			
Distal common bile duct	10 (8.5)	7 (8.9)	3 (7.9)			
Duodenum	2 (1.7)	1 (1.3)	1 (2.6)			
Ampulla	34 (29.1)	25 (31.6)	9 (23.7)			
Pathological T stage, n (%)				Cramer's V = 0.182		0.424
T0	5 (4.3)	3 (3.8)	2 (5.3)			
T1	17 (14.5)	11 (13.9)	6 (15.8)			
T2	42 (35.9)	32 (40.5)	10 (26.3)			
T3	44 (37.6)	29 (36.7)	15 (39.5)			
T4	9 (7.7)	4 (5.1)	5 (13.2)			

Data are presented as mean ± standard deviation (SD) for approximately normally distributed variables and as median [interquartile range (IQR)] for non-normally distributed variables. Categorical variables are expressed as n (%). Independent-samples t-test was used for continuous variables with approximately normal distribution, and Pearson's chi-square test was used for categorical variables. CI, confidence interval; SD, standard deviation

ative day 2 AST levels were 48.0 [49.0] U/L and 37.5 [34.75] U/L, respectively (p=0.132). Likewise, ΔALT, ΔAST, ALT ratio, and AST ratio were similar between groups (all p>0.05).

According to Table 5, operative time differed significantly across clinically grouped arterial variation patterns (p=0.006). Median operative time was 240.0 [120.0] min

Table 2. Distribution of Michels-classified arterial anatomy in patients undergoing pancreaticoduodenectomy

Michels type	Anatomical definition	n	%
Type I	Normal anatomy	79	67.5
Type II	Replaced left hepatic artery from left gastric artery	8	6.8
Type III	Replaced right hepatic artery from superior mesenteric artery	15	12.8
Type IV	Combined replaced right and left hepatic arteries	1	0.9
Type V	Accessory left hepatic artery from left gastric artery	3	2.6
Type VI	Accessory right hepatic artery from superior mesenteric artery	2	1.7
Type VII	Accessory right and left hepatic arteries	2	1.7
Type VIII	Mixed accessory/replaced right hepatic artery pattern	5	4.3
Type IX	Common hepatic artery from superior mesenteric artery	2	1.7
Type X	Common hepatic artery from left gastric artery	-	-

Arterial anatomy was classified according to Michels. CHA, common hepatic artery; LHA, left hepatic artery; RHA, right hepatic artery; SMA, superior mesenteric artery.

Table 3. Operative and pathological outcomes according to arterial anatomy status

Variable	Normal anatomy (n=79)	Any arterial variation (n=38)	p
Operative time, min	240.0 [120.0]	315.0 [150.0]	0.002
Total lymph node yield, n	21.0 [8.0]	12.0 [4.25]	<0.001
Malignant lymph node count, n	1.0 [3.0]	1.0 [3.0]	0.913
Positive lymph node ratio	0.0417 [0.1053]	0.0556 [0.2125]	0.276

Data are presented as median [interquartile range (IQR)] because these variables were non-normally distributed. CI, confidence interval; IQR, interquartile range.

Table 4. Preoperative and postoperative day-2 liver enzyme profiles according to arterial anatomy status

Variable	Normal anatomy (n=79)	Any arterial variation (n=38)	p
ALT, preoperative, U/L	40.0 [98.0]	34.5 [91.0]	0.677
ALT, postoperative day 2, U/L	55.0 [63.0]	44.0 [75.0]	0.276
AST, preoperative, U/L	37.0 [75.0]	35.0 [40.0]	0.646
AST, postoperative day 2, U/L	48.0 [49.0]	37.5 [34.75]	0.132
ALT change (ΔALT), U/L	-3.0 [59.0]	-3.5 [72.25]	0.900
AST change (ΔAST), U/L	3.0 [53.0]	-3.0 [45.5]	0.648
ALT ratio (POD2/preop)	0.8824 [1.8295]	0.8194 [1.8918]	0.633
AST ratio (POD2/preop)	1.0588 [1.7483]	0.9277 [1.2744]	0.580

Data are presented as median [interquartile range (IQR)] because these variables were non-normally distributed. ΔALT was calculated as postoperative day-2 ALT minus preoperative ALT, and ΔAST was calculated as postoperative day-2 AST minus preoperative AST. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; IQR, interquartile range; POD, postoperative day.

in the normal anatomy group, 360.0 [120.0] min in the left-sided variation group, and 300.0 [150.0] min in the right-sided/retropancreatic variation group. Bonferroni-adjusted pairwise comparisons showed a significant difference between the normal and left-sided variation groups (p=0.025), whereas the comparison between the normal and right-sided/retropancreatic variation groups did not reach statistical significance (p=0.067). Total lymph node yield also differed significantly across groups (p<0.001), with medians of 21.0 [8.0], 12.0 [4.0], and 12.0 [5.0], respectively. Bonferroni-adjusted pairwise comparisons showed significant differences between the normal and left-sided groups (p=0.001) and between the normal and right-sided/retropancreatic groups (p<0.001). By contrast, ALT on postoperative day 2, AST on postoperative day 2, ALT ratio, and AST ratio did not differ significantly among the three groups (all p>0.05). As shown in Table 6, univariable linear regression analysis identified arterial variation status as a significant predictor of operative time, with an unstandardized coefficient of 55.763 (95% CI, 23.012–88.514), standardized β=0.300, and p=0.0010. Age was not associated with operative time (B=0.010, 95% CI, −1.355 to 1.374, β=0.001, p=0.989), nor were sex (B=−9.468, 95% CI, −43.317 to 24.382, β=−0.052, p=0.581), final pathology malignancy (B=25.962, 95% CI, −24.972 to 76.895, β=0.094, p=0.315), tumor location (B=0.099, 95% CI, −11.930 to 12.129, β=0.002, p=0.987), or pathological T stage (B=8.665, 95% CI, −8.108 to 25.438, β=0.095, p=0.308). Univariable linear regression analysis demonstrated that arterial variation status was the only variable significantly associated with operative time. Arterial variation status explained approximately 9.0% of the variance in operative time (R^2=0.090). None of the other variables included in the analysis showed a statistically significant association with operative time in the univariable analyses. Therefore, no additional candidate variables met the predefined criterion for inclusion in a multivariable regression model. Accordingly, a multivariable analysis was not performed. Nevertheless, residual confounding by unmeasured variables cannot be completely excluded because of the retrospective observational design. Univariable linear regression analyses for postoperative day 2 ALT showed no significant association with arterial variation status (B=−29.922, 95% CI, −75.837 to 15.993, β=−0.120, p=0.199), preoperative ALT (B=0.013, 95% CI, −0.162 to 0.188, β=0.014, p=0.880), age (B=0.299, 95% CI, −1.538 to 2.137, β=0.030, p=0.747), or final pathology malignancy (B=−7.760, 95% CI, −76.657 to 61.137, β=−0.021, p=0.824). Similarly, postoperative day 2 AST was not significantly as-

Table 5. Outcomes according to clinically grouped arterial variation pattern

Variable	Normal (n=79)	Left-sided variation (n=11)	Right-sided/retropancreatic variation (n=27)	Overall p value	Post hoc adjusted p values
Operative time, min	240.0 [120.0]	360.0 [120.0]	300.0 [150.0]	0.006	Normal vs Left-sided: 0.025; Normal vs Right-sided/ retropancreatic: 0.067
Total lymph node yield, n	21.0 [8.0]	12.0 [4.0]	12.0 [5.0]	<0.001	Normal vs Left-sided: 0.001; Normal vs Right-sided/ retropancreatic: <0.001
ALT, postoperative day 2, U/L	55.0 [63.0]	32.0 [36.0]	51.0 [100.0]	0.321	
AST, postoperative day 2, U/L	48.0 [49.0]	31.0 [14.0]	43.0 [49.0]	0.132	
ALT ratio (POD2/preop)	0.8824 [1.8295]	0.8387 [1.7365]	0.8000 [1.9000]	0.734	
AST ratio (POD2/preop)	1.0588 [1.7483]	0.9268 [0.8915]	0.9286 [1.5447]	0.776	

Data are presented as median [interquartile range (IQR)] because these variables were non-normally distributed. Bonferroni-adjusted pairwise comparisons are reported only for variables with a statistically significant overall Kruskal–Wallis test. ALT, alanine aminotransferase; AST, aspartate aminotransferase; IQR, interquartile range; POD, postoperative day.

sociated with final pathology malignancy (B=7.490, 95% CI, −83.958 to 98.939, β=0.015, p=0.871), arterial variation status (B=−45.072, 95% CI, −105.883 to 15.738, β=−0.136, p=0.145), preoperative AST (B=−0.079, 95% CI, −0.400 to 0.243, β=−0.045, p=0.629), or age (B=1.758, 95% CI, −0.660 to 4.176, β=0.133, p=0.152).

As presented in Table 7, among malignant cases, pathological T stage distribution did not differ significantly between the normal anatomy and arterial variation groups (Cramér's V=0.177, p=0.351). In this malignancy-restricted analysis, total lymph node yield remained significantly lower in the arterial variation group than in the normal anatomy group (12.0 [4.0] vs. 21.0 [7.75], p<0.001). Malignant lymph node

Table 6. Univariable linear regression analyses for operative time, postoperative day-2 ALT, and postoperative day-2 AST

Dependent variable	Predictor	B	SE	Standardized β	t	95% CI for B	p
Operative time	Arterial variation status	55.763	16.534	0.300	3.373	23.012 to 88.514	0.0010
	Age, years	0.010	0.689	0.001	0.014	-1.355 to 1.374	0.989
	Sex	-9.468	17.089	-0.052	-0.554	-43.317 to 24.382	0.581
	Final pathology malignancy	25.962	25.714	0.094	1.010	-24.972 to 76.895	0.315
	Tumor location	0.099	6.073	0.002	0.016	-11.930 to 12.129	0.987
	Pathological T stage	8.665	8.468	0.095	1.023	-8.108 to 25.438	0.308
Postoperative day 2 ALT	Arterial variation status	-29.922	23.180	-0.120	-1.291	-75.837 to 15.993	0.199
	Preoperative ALT	0.013	0.088	0.014	0.151	-0.162 to 0.188	0.880
	Age, years	0.299	0.928	0.030	0.323	-1.538 to 2.137	0.747
	Final pathology malignancy	-7.760	34.782	-0.021	-0.223	-76.657 to 61.137	0.824
Postoperative day 2 AST	Final pathology malignancy	7.490	46.167	0.015	0.162	-83.958 to 98.939	0.871
	Arterial variation status	-45.072	30.700	-0.136	-1.468	-105.883 to 15.738	0.145
	Preoperative AST	-0.079	0.162	-0.045	-0.485	-0.400 to 0.243	0.629
	Age, years	1.758	1.221	0.133	1.440	-0.660 to 4.176	0.152

Values are from univariable linear regression analyses. B denotes the unstandardized regression coefficient, β denotes the standardized regression coefficient, and 95% CI indicates the 95% confidence interval for B. ALT, alanine aminotransferase; AST, aspartate aminotransferase; B, unstandardized regression coefficient; β, standardized regression coefficient; CI, confidence interval; SE, standard error.

Table 7. Malignancy-restricted oncological analysis according to arterial anatomy status

Variable	Normal anatomy among malignant cases (n=72)	Any variation among malignant cases (n=32)	Effect size	p
Pathological T stage, n (%)			Cramer's V = 0.177	0.351
T1	7 (9.7)	4 (12.5)		
T2	32 (44.4)	9 (28.1)		
T3	29 (40.3)	15 (46.9)		
T4	4 (5.6)	4 (12.5)		
Total lymph node yield, n	21.0 [7.75]	12.0 [4.0]		<0.001
Malignant lymph node count, n	1.0 [3.0]	1.0 [3.75]		0.743
Positive lymph node ratio	0.0513 [0.1129]	0.0812 [0.2625]		
Operative time, min	240.0 [112.5]	330.0 [150.0]		0.001

Pearson's chi-square test was used for pathological T stage, and Mann–Whitney U test was used for continuous variables.

count did not differ significantly between groups (1.0 [3.75] vs. 1.0 [3.0], p=0.743). The positive lymph node ratio was 0.0812 [0.2625] in the arterial variation group and 0.0513 [0.1129] in the normal anatomy group. Operative time remained significantly longer in patients with arterial variation (330.0 [150.0] min) than in those with normal anatomy (240.0 [112.5] min, p=0.001).

Discussion

Celiac trunk and hepatic artery variations represent some of the most clinically significant anatomical variables encountered in hepatopancreatic surgery. The present study evaluated the impact of celiac trunk and hepatic artery variations on operative time, lymph node yield, and early postoperative liver function tests in a retrospective cohort of 117 patients undergoing pancreaticoduodenectomy (PD).

In our study, arterial variations classified as Michels Types II–X were identified in 32.5% of patients, a rate consistent with the 20–45% range reported in the broader literature. Balzan, evaluating 200 CT studies, identified an anomalous right hepatic artery (RHA) in 13% of cases, noting that the replaced RHA from the superior mesenteric artery (SMA) was the most common variant and that all anomalous vessels followed a retroportal course.[8] Li, in a high-volume center series of 238 minimally invasive PD patients, reported a hepatic artery variation (HAV) prevalence of 26.1% and a clinically relevant HAV (CR-HAV) prevalence of 18.9%.[9] Zhang identified aberrant hepatic arteries in 24.8% of 218 laparoscopic PD cases.[10] The slightly higher rate in our cohort likely reflects the comprehensive inclusion of all Michels variation subtypes (Types II–X).

The most frequently encountered variation in our series was Michels Type III (replaced RHA from the SMA, 12.8%), consistent with the systematic review by El Amrani, who, across 2,278 patients, found that 65.2% of aberrant RHA cases corresponded to this type.[11] Similarly, Alberici et al.[12] reported an SMA-origin aberrant RHA in 39 of 224 PD patients (17.4%) at a single Italian center. Cadaveric studies by Hemamalini and Juszczak further underscored that celiac trunk variations span a wide anatomical spectrum, including rarer forms such as the hepatomesenteric trunk and hepatosplenic trunk, all of which carry meaningful surgical implications.[13,14]

With respect to operative time, the arterial variation group in our study demonstrated a statistically significant prolongation compared with the normal anatomy group (315.0 [150.0] min vs. 240.0 [120.0] min; p=0.002). Univariable linear regression analysis identified arterial variation status as a significant predictor of operative time (B=55.763; 95% CI, 23.012–88.514; β=0.300; p=0.001). This finding is consistent with the existing literature. Li demonstrated that HAV was associated with an approximately one-hour longer median operative time (6.72 vs. 5.80 h; p=0.013), with only operative duration differing significantly between groups, while other perioperative parameters remained comparable.[9] Zhang reported a significant increase in surgical resection time in patients with aberrant hepatic arteries (121.46 vs. 105.64 min; p<0.001).[10] The systematic review by El Amrani observed a general trend toward prolonged operative time in the RHA group without reaching statistical significance across all included series.[11] Alberici reported a significantly longer operative time in the unmatched aberrant RHA cohort (+25 min; p=0.039), a difference that resolved after entropy balancing.[12] Chierici, in their systematic review on aberrant RHA management during minimally invasive PD, also noted that some series reported significantly lon-

ger operative times in the presence of aberrant vascular anatomy.[15] This prolongation is attributable to the additional technical demands of careful dissection to preserve the variant artery, management of potential hemorrhagic complications, and the need to ensure hepatic arterial perfusion integrity throughout the procedure.

One of the most novel and clinically significant findings of this study was the significantly lower total lymph node yield observed in the arterial variation group compared with the normal anatomy group (12.0 [4.25] vs. 21.0 [8.0]; p<0.001), a difference that was consistently reproduced in the malignancy-restricted subgroup analysis. Despite this reduced yield, malignant lymph node count and positive lymph node ratio did not differ significantly between groups. To date, the literature specifically addressing the impact of hepatic artery variations on the adequacy of lymph node dissection during PD remains limited. Li found no significant differences in harvested lymph node counts between HAV-positive and HAV-negative patients, attributing this to the standardized dissection technique maintained at their high-volume center.[9] Similarly, Zhang reported no statistically significant differences in lymph node-related pathological parameters according to variation status.[10] The significant reduction in lymph node yield observed in our study may reflect the anatomical constraints imposed by aberrant arteries coursing through the mesopancreas and retroportal lamina, potentially limiting the extent of lymphadenectomy in the vicinity of the SMA. A possible explanation for this finding is that preservation of aberrant hepatic arteries, particularly those originating from the superior mesenteric artery, requires more careful dissection around the SMA and mesopancreatic region. Consequently, surgeons may adopt a more cautious approach to tissue dissection in close proximity to these vessels to reduce the risk of vascular injury. This may limit the extent of lymphadenectomy in this region and, consequently, result in a lower total lymph node yield. Alberici et al.[12] were the first to specifically demonstrate that the presence of an aberrant RHA significantly increases the R1 resection rate at the SMA margin (OR=2.3; 95% CI, 1.1–5.2; p=0.045), attributable to this same anatomical relationship. The mechanistic overlap between reduced lymph node yield and elevated SMA margin positivity in the presence of a variant RHA deserves prospective investigation, given its potential impact on both staging accuracy and long-term oncological outcomes.

Regarding early postoperative liver function tests, no statistically significant differences were detected between groups for any of the assessed parameters, including preoperative and postoperative day 2 ALT, AST, ΔALT, ΔAST, ALT ratio, or AST ratio. These findings corroborate existing evidence. Li reported no significant differences in postoperative outcomes, morbidity, mortality, or hospital stay between HAV-positive and HAV-negative patients.[9] The systematic review by El Amrani similarly found comparable postoperative mortality, overall morbidity, pancreatic fistula, delayed gastric emptying, and hemorrhage rates between RHA and non-RHA groups.[11] Chierici confirmed that conservative management of aberrant RHA during minimally invasive PD did not significantly increase major postoperative complication rates.[15] Zhang reported that, among their cohort of 218 patients undergoing laparoscopic PD, only one patient in the variant group sustained a partial rupture of the CHA during isolation, which was successfully managed laparoscopically with end-to-end anastomosis and an uneventful recovery.[10] Ye, in a case report of an exceptionally rare absence of the celiac trunk with a hepatomesenteric trunk, demonstrated that, with appropriate intraoperative management, the compensatory contribution of an accessory left hepatic artery and intact portal blood supply allowed gradual normalization of liver function.[16] Collectively, these findings suggest that, with experienced surgical teams and sound preoperative planning, vascular preservation can largely maintain hepatic functional integrity irrespective of arterial variation status.

Regarding preoperative imaging, our findings further support the critical role of multidetector CT angiography (MDCTA) as a standard component of the PD workup. Balzan demonstrated that preoperative CT can clearly identify hepatic arterial variants and facilitate safer pancreatic head dissection through proper surgical planning.[8] Zhang reported that MDCTA achieves sensitivity, specificity, and accuracy values of 94%, 100%, and 97%, respectively, for characterizing hepatic arterial anatomy prior to PD.[10] Chierici specifically emphasized that the inability to palpate arterial pulses in minimally invasive approaches makes preoperative contrast-enhanced CT indispensable.[15] Hemamalini noted that, while preoperative imaging can aid surgical preparation and planning, not all arterial variations may be detectable (detection rate of only 60–80%), making intraoperative awareness equally important.[13] Ye vividly illustrated how an undetected celiac trunk variation can present as an intraoperative surprise, underscoring the challenges and limitations of preoperative assessment even with modern imaging.[16]

In terms of variant management strategies, arterial preservation remains the primary approach, with reconstruction reserved for selected cases. El Amrani reported that conservative dissection and preservation were adopted in 87% of patients with RHA variants; only 8% underwent sacrifice

without reconstruction, and 4% required resection with reconstruction.[11] Zhang successfully preserved the aberrant artery in all variation cases in their laparoscopic PD series.[10] Chierici proposed that preoperative embolization of a replaced RHA may be considered in cases where arterial sacrifice appears likely as a strategy to stimulate hepatic arterial collateral shunts and reduce the risk of right lobe ischemia.[15] Juszczak emphasized that comprehensive knowledge of celiac trunk anatomical variations is essential not only for PD but also for liver transplantation, hepatic artery infusion chemotherapy, and transarterial chemoembolization (TACE).[14]

This study has several limitations. Its retrospective design and the inclusion of patients from a single tertiary referral center may limit the generalizability of the findings. In addition, because only patients with available preoperative CT angiography were included, a degree of selection bias cannot be excluded. Although arterial variation status was the only variable significantly associated with operative time in the univariable analyses, the possibility of residual confounding should be acknowledged, as unmeasured factors may also have influenced the observed associations. Furthermore, differences in surgical approach and surgeon experience were not evaluated systematically, and long-term oncological outcomes were beyond the scope of the present study.

Conclusion

The present study demonstrates that celiac trunk and hepatic artery variations have a significant impact on operative time and total lymph node yield in patients undergoing pancreaticoduodenectomy. The prolonged operative time observed in patients with arterial variations most likely reflects the increased technical complexity of dissection and vascular preservation in the presence of aberrant arterial anatomy. More importantly, the consistent reduction in lymph node yield across both the overall cohort and the malignancy-restricted subgroup suggests that arterial anatomy may influence the extent of lymphadenectomy during pancreaticoduodenectomy. This finding suggests that the anatomical proximity of aberrant arteries to the SMA margin and mesopancreatic territory may constrain the completeness of lymphadenectomy. Early postoperative liver function tests, however, did not differ significantly between groups, indicating that experienced surgical teams are largely able to maintain hepatic functional integrity through meticulous vascular preservation.

These findings highlight the importance of routine high-quality preoperative CT angiography as a standard component of the PD workup and underscore that preoperative identification of vascular variants strengthens surgical planning. Our results further suggest that a surgical team with expertise in managing arterial variations should be available when such anomalies are anticipated. The oncological implications of the observed reduction in lymph node yield and its underlying mechanisms warrant validation in larger prospective studies.

Disclosures

Ethics Committee Approval: This study was reviewed and approved by the Ethics Committee of the Ankara Gülhane Research and Training Hospital (Date:17.02.2026 and Approval No. E-50687469-799-305797850).

Informed Consent: As the present study only collected retrospective clinical data and does not pose a risk to the participants, written informed consent was not required.

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Original Research

Evaluation of Physical and Cognitive Outcomes in Liver Transplant Recipients Following Participation in a Post-Transplant Physiotherapy Program

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Abstract

Objectives: Although liver transplantation is the most effective treatment for end-stage liver disease, many recipients still experience impairments in physical performance, balance, cognitive function and fatigue, even after a successful transplant. While physiotherapy has been shown to be effective during the early postoperative period, evidence regarding its longer-term benefits is limited. This study investigated the long-term effects of routine physiotherapy and rehabilitation on physical performance, balance, functional capacity, cognitive function and fatigue in liver transplant recipients approximately one year after transplantation.

Methods: This cross-sectional comparative study enrolled 106 adult liver transplant recipients who had undergone transplantation at least one year previously. Participants were divided into two groups: a control group of 53 participants who had not participated in a postoperative physiotherapy programme, and a routine physiotherapy group of 53 participants who had completed the routine postoperative physiotherapy programme. Functional mobility was evaluated using the Timed Up and Go Test (TUG), static balance using the Single-Leg Stance Test (SLST), functional exercise capacity using the Six-Minute Walk Test (6MWT), cognitive function using the Montreal Cognitive Assessment (MoCA) and fatigue using the Fatigue Severity Scale (FSS). Between-group comparisons were performed using independent samples t-tests and chi-square tests, with statistical significance set at $p<0.05$.

Results: Baseline demographic and clinical characteristics were comparable between the groups (all $p > 0.05$). Recipients who had completed the routine physiotherapy programme demonstrated significantly better functional mobility (TUG, p=0.001), static balance (SLST, p=0.003), cognitive performance (MoCA, p=0.003) and lower fatigue levels (FSS, p=0.006) than the control group. No significant difference between the groups was observed in functional exercise capacity, as measured by the 6MWT (p=0.454).

Conclusion: Routine physiotherapy after liver transplantation was associated with improved functional mobility, balance, cognitive performance and reduced fatigue approximately one year after transplantation. While no significant improvement in functional exercise capacity was observed, these results suggest that the benefits of physiotherapy extend beyond the immediate postoperative period. Incorporating structured physiotherapy into long-term, multidisciplinary follow-up programmes could help to optimise functional recovery and improve overall patient outcomes after liver transplantation.

Keywords: Liver transplantation, physiotherapy, rehabilitation, functional mobility, cognitive function, fatigue

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Liver transplantation is the most effective treatment for end-stage liver disease, significantly improving survival rates and quality of life. In recent years, advances in surgical techniques, immunosuppressive therapy protocols, intensive care management and multidisciplinary patient care have substantially improved both short- and long-term survival rates following liver transplantation[1-4]. As survival rates have increased, the primary goals of treatment have expanded beyond merely prolonging life to include preserving functional independence, restoring daily living activities and improving quality of life. Consequently, the success of liver transplantation is now evaluated in terms of both graft survival and recipients' physical, cognitive, and psychosocial well-being.

Despite successful transplantation, physical performance does not fully recover in a significant proportion of liver transplant recipients. Pre-transplant conditions such as sarcopenia, prolonged physical inactivity, chronic inflammation, malnutrition and metabolic alterations associated with chronic liver disease may persist even after surgery. Furthermore, surgical trauma, prolonged hospitalisation, the adverse musculoskeletal effects of immunosuppressive therapy and postoperative complications may contribute to reduced muscle strength, impaired aerobic capacity, balance deficits and diminished functional capacity [3, 4]. These impairments can limit patients' ability to perform activities of daily living, delay their return to work and social participation, and negatively affect their overall quality of life. In addition to physical impairments, changes in cognitive function are another important clinical concern among liver transplant recipients. Although liver transplantation improves hepatic function, the effects of hepatic encephalopathy, chronic inflammation and metabolic disturbances that develop during end-stage liver disease may persist after transplantation. In particular, impairments in attention, memory, executive function and processing speed have been reported to have a negative impact on activities of daily living, adherence to medication and social participation [3-5]. Furthermore, many recipients continue to experience chronic fatigue, exercise intolerance and reduced physical activity levels, all of which increase the need for comprehensive rehabilitation even further.

To address these impairments, physiotherapy and rehabilitation have become integral components of postoperative care following liver transplantation. Previous randomised controlled trials and systematic reviews have demonstrated that aerobic exercise, resistance training, balance exercises and multicomponent rehabilitation programmes can improve functional capacity, muscle strength, walking performance, fatigue and health-related quality of life [6-8].

Recently, rehabilitation programmes that incorporate cognitive tasks have attracted a great deal of attention. Motor-cognitive exercise interventions and dual-task training have been shown to enhance executive function, attention and general cognitive performance in a variety of clinical groups. However, studies investigating cognitive rehabilitation and motor-cognitive exercise specifically in liver transplant recipients are scarce, and the available evidence is largely limited to short-term follow-up. Consequently, it is unclear whether the functional benefits of rehabilitation are maintained in the medium to long term. This highlights the need for studies that evaluate long-term outcomes, in order to optimise rehabilitation planning and follow-up strategies [7, 9, 10].

Although there is a growing body of evidence supporting rehabilitation after liver transplantation, studies evaluating physical performance, balance, functional exercise capacity, fatigue and cognitive function one year or more after transplantation are still limited. Consequently, it is unclear whether the benefits of routine physiotherapy are maintained beyond the early postoperative period, highlighting the need for studies investigating medium- and long-term outcomes.

This study compared the physical performance, functional exercise capacity, balance, fatigue and cognitive function of liver transplant recipients who had participated in a routine physiotherapy and rehabilitation programme with those who had not received physiotherapy approximately one year after transplantation. To the best of our knowledge, this is one of the few studies to evaluate the medium-term effects of routine physiotherapy and rehabilitation in liver transplant recipients using such a comprehensive assessment.

Methods

Study design

This cross-sectional comparative study evaluated the medium-term physical and cognitive outcomes of liver transplant recipients who participated in a routine physiotherapy and rehabilitation programme. It was carried out at the Liver Transplant Institute Hospital, Turgut Özal Medical Centre, İnönü University between October 2024 and June 2026.

Ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee at Hasan Kalyoncu University (Approval No: 2024/116; Date: 15 October 2024). Institutional permission was also obtained from the Liver Transplant Institute Hospital at the Turgut Özal Medical Centre at İnönü University. The study was conducted in ac-

cordance with the principles of the Declaration of Helsinki and was registered at ClinicalTrials.gov (NCT07694245).

Participants

Participants were allocated into two groups according to their post-transplant rehabilitation status

Control group: Liver transplant recipients who had not participated in any physiotherapy or rehabilitation programme following transplantation.

Routine physiotherapy group: Liver transplant recipients who had completed the routine physiotherapy and rehabilitation programme following transplantation.

Potential participants were identified in the outpatient follow-up clinic of the Liver Transplant Institute at İnönü University's Turgut Özal Medical Centre. Liver transplant recipients who had undergone transplantation at least one year previously were consecutively screened for eligibility during routine follow-up visits. Those who met the inclusion criteria were invited to participate in the study.

Liver transplant recipients who met the following inclusion criteria were recruited

- Age ≥18 years
- At least one year had elapsed since liver transplantation
- Spontaneous breathing
- Haemodynamic stability
- Ability to read and write
- Willingness to participate voluntarily in the study

Participants were excluded if they met any of the following criteria

- History of a neurological disorder
- Presence of a neuropsychiatric disorder
- Orthopaedic or rheumatological conditions that could interfere with the assessments
- Advanced cardiopulmonary disease
- Visual or hearing impairment preventing completion of the assessments
- Refusal to participate in the study

Sample size

The required sample size was determined by an a priori power analysis using version 3.1.9.4 of G*Power software. Based on a comparison of the means of two independent groups, the following assumptions were made: a medium effect size (Cohen's d = 0.55) was selected as a realistic and clinically meaningful estimate of the expected difference between groups in the primary outcomes; a significance level of 5% (α = 0.05) was assumed; and statistical power was set at 80%. The analysis indicated that a minimum total sample size of 106 participants (53 per group) was required.

To achieve this, 128 liver transplant recipients were screened for eligibility. Twenty-two individuals were excluded because they did not meet the eligibility criteria or declined to participate. Consequently, the study was completed with 106 participants, thus meeting the sample size determined by the power analysis.

Physiotherapy intervention

The routine postoperative physiotherapy programme was started while the patient was still in hospital after surgery. It was designed to prevent pulmonary complications after surgery, encourage early movement, improve physical fitness, maintain muscle strength and stamina, and help patients return safely to their daily activities. It was tailored to each patient's clinical condition, haemodynamic stability and functional status, and progressed alongside postoperative recovery.

It consisted of breathing exercises, postural training, active range-of-motion exercises, progressive mobilisation, muscle-strengthening exercises, balance training, sit-to-stand and transfer training, gait training and functional exercises targeting activities of daily living. Breathing exercises included diaphragmatic breathing, thoracic expansion exercises and effective coughing techniques. The mobilisation programme progressed gradually from in-bed exercises to sitting, standing and independent ambulation. Muscle-strengthening and balance exercises were prescribed according to each patient's functional status and were progressively intensified throughout the rehabilitation process.

The programme's primary objectives were to facilitate early recovery of physical function, prevent complications associated with prolonged immobilisation, promote independent mobility and support a safe return to activities of daily living following hospital discharge.

Assessment procedures

The participants' demographic and clinical characteristics were recorded, including their age, sex, height, body weight and body mass index (BMI). In addition, the following were documented using a standardised assessment form developed by the researchers: marital status, educational level, employment status, smoking and alcohol use, regular exercise habits, duration of liver disease before transplantation, presence of comorbidities, and donor type.

Montreal Cognitive Assessment (MoCA)

Cognitive function was assessed using the MoCA. This 30-point screening instrument evaluates several cognitive domains, including attention, concentration, executive function, memory, language, visual-spatial abilities, ab-

straction, calculation and orientation. Total scores range from 0 to 30, with higher scores indicating better cognitive performance. The Turkish version of the MoCA has been shown to be valid and reliable by Selekler et al [11].

Six-Minute Walk Test (6MWT)

Functional exercise capacity was evaluated using the 6MWT. The test was performed in accordance with the American Thoracic Society guidelines in a 30-metre straight corridor. Participants were instructed to walk as far as possible at their maximum self-paced speed for six minutes. Standardised verbal encouragement was provided throughout, and the total distance walked was recorded in metres at the end. A greater walking distance indicated better functional exercise capacity[12].

Timed Up and Go (TUG) test

Functional mobility and dynamic balance were assessed using the TUG test. Participants were seated in a standard-height chair and instructed to stand up on command, walk 3 metres, turn around a designated marker, walk back to the chair and sit down again. The time taken to complete the test was recorded in seconds using a stopwatch. Shorter completion times indicated better functional mobility [13].

One-legged standing test

Static balance was assessed using the Single-Leg Stance Test. Participants were instructed to stand on their dominant leg for as long as possible while maintaining balance. The duration of single-leg standing was measured in seconds and the best performance was recorded. Longer standing times were considered to be indicative of better static balance [14].

Fatigue Severity Scale

Fatigue severity was assessed using the Fatigue Severity Scale (FSS). The FSS consists of nine items, each of which is rated on a seven-point Likert scale ranging from 1 to 7; higher total scores indicate greater fatigue severity [15]. The Turkish version of the FSS has demonstrated satisfactory validity and reliability.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Kolmogorov–Smirnov test and visual inspection of histograms. Descriptive data are presented as the mean ± standard deviation (SD) or the number (percentage), as appropriate.

Comparisons between groups were performed using the independent samples t-test for continuous variables. Categorical variables were compared using the chi-squared test or Fisher's exact test, as appropriate. Statistical significance was set at $p < 0.05$.

Results

A total of 106 liver transplant recipients met the eligibility criteria and were included in the final analysis. Participants were classified into a control group (n = 53) and a routine physiotherapy group (n = 53). The mean age was 62.13 ± 3.68 years in the control group and 61.60 ± 3.80 years in the routine physiotherapy group. The respective mean body mass index (BMI) was 24.68 ± 3.17 kg/m^2 and 25.09 ± 3.43 kg/m^2.

Table 1 summarises the baseline demographic characteristics of the participants. No statistically significant differences were observed between the groups with respect to sex, marital status, educational level, employment status, smoking status, alcohol consumption (all $p > 0.05$). In both groups, the majority of participants were male, married, retired, had completed primary education and reported not currently smoking or consuming alcohol.

Table 2 summarises the baseline clinical characteristics of the participants. The mean duration of liver disease before transplantation was 7.55 ± 1.50 years in the control group and 7.15 ± 1.71 years in the routine physiotherapy group. The mean Charlson Comorbidity Index (CCI) score was 2.87 ± 1.85 in the control group and 3.04 ± 1.60 in the routine physiotherapy group. No statistically significant differences were found between the groups regarding the duration of liver disease before transplantation, the cause of liver transplantation, the type of donor, comorbidity status or the CCI (all $p > 0.05$). Hepatitis B was the most common indication for liver transplantation in both groups, followed by Wilson's disease. Living-donor liver transplantation was the predominant donor type (83.0%), and the majority of participants presented with at least one comorbid condition (67.9% in the control group and 71.7% in the routine physiotherapy group).

Table 3 presents a comparison of the physical performance outcomes after the intervention between the control group and the routine physiotherapy group. Participants in the routine physiotherapy group demonstrated significantly better performance in both the Timed Up and Go Test ($p = 0.001$) and the Single-Leg Stance Test ($p = 0.003$) than those in the control group. However, no statistically significant difference was observed between the groups in the 6-Minute Walk Test ($p = 0.454$).

Figure 1 shows the distribution of MoCA scores in the control group and the group that received routine physiotherapy. The raincloud plot shows an increase in cognitive

Table 1. Baseline demographic characteristics of the participants in the control and routine physiotherapy groups

Descriptive characteristics	Control Group (n=53)	%	Physiotherapy Group (n=53)	%
	n		n	
Gender				
Female	15	%28.3	17	%32.1
Male	38	%71.7	36	%67.9
Marital status				
Married	33	%62.3	36	%67.9
Single	20	%37.7	17	%32.1
Educational background				
Primary education	28	%52.8	25	%47.2
High school	20	%37.7	22	%41.5
University	5	%9.4	6	%11.4
Employment status				
Working	8	%15.1	11	%20.8
No-Working	15	%28.3	12	%22.6
Retired	30	%56.6	30	%56.6
Smoking status				
Yes	7	%13.2	9	%17
No	26	%49.1	23	%43.4
Quit Smoking	20	%37.7	21	%39.6
Alcohol consumption				
Yes	2	%3.8	3	%5.7
No	41	%77.4	37	%69.8
Quit Drinking Alcohol	10	%18.9	13	%24.5

BMI: body mass index; m: meters; SD: standard deviation.

performance in the routine physiotherapy group, which is consistent with the statistically significant difference between the groups observed in the quantitative analysis ($p = 0.003$).

Figure 2 shows the distribution of Fatigue Severity Scale (FSS) scores in the control and routine physiotherapy groups. As can be seen in the raincloud plot, participants in the routine physiotherapy group reported lower fatigue severity than those in the control group. This is consistent with the statistically significant between-group difference identified in the quantitative analysis ($p = 0.006$).

Discussion

Promoting functional recovery and improving quality of life have become key objectives of multidisciplinary care following liver transplantation. In the present study, we evaluated the effects of a routine physiotherapy programme on the physical performance, balance, cognitive function and fatigue levels of liver transplant recipients. Our findings showed that patients who participated in the programme exhibited significantly better functional mobility, balance and cognitive performance, and lower fatigue levels than the control group. Significant improvements were specifically observed in the TUG Test, Single-Leg Stance Test, MoCA and FSS. However, no statistically significant difference was found between the groups in the 6MWT. These results suggest that participating in a routine physiotherapy programme following liver transplantation was associated with better functional mobility, balance, cognitive performance and lower fatigue levels. These findings may be explained by several mechanisms. Progressive mobilisation, balance training and functional, task-oriented exercises are likely to improve neuromuscular coordination, postural control and movement efficiency. This would contribute to better functional mobility and balance. Additionally, regular physiotherapy participation may boost

Table 2. Baseline clinical characteristics of the control and routine physiotherapy groups

Variable	Control (n=53)	Routine Physiotherapy (n=53)	p
Duration of liver disease before transplantation (years), mean ± SD	7.55±1.50	7.15±1.71	0.208
Cause of liver transplantation, n (%)			0.747
Hepatitis B	28 (52.8%)	24 (45.3%)	
Wilson disease	18 (34.0%)	17 (32.1%)	
Hepatocellular carcinoma	4 (7.5%)	6 (11.3%)	
Toxic hepatitis	2 (3.8%)	3 (5.7%)	
Other	1 (1.9%)	3 (5.7%)	
Donor type, n (%)			1.000
Living donor	44 (83.0%)	44 (83.0%)	
Deceased donor	9 (17.0%)	9 (17.0%)	
Comorbidity, n (%)			0.672
Present	36 (67.9%)	38 (71.7%)	
Absent	17 (32.1%)	15 (28.3%)	
Charlson Comorbidity Index, mean ± SD	2.87±1.85	3.04±1.60	0.615

Values are presented as mean ± standard deviation (SD) or number (%). Continuous variables were compared using the independent samples t-test, whereas categorical variables were compared using the Pearson chi-square test. Statistical significance was set at $p < 0.05$.

Table 3. Comparison of post-intervention physical performance between the study groups

Outcome	Control (n=53) Mean ± SD	Routine Physiotherapy (n=53) Mean ± SD	Mean Difference (95% CI)	p
Timed Up and Go Test	12.13±1.66	11.00±1.89	1.13 (0.45 to 1.82)	**0.001***
Single-Leg Stance Test (s)	20.11±4.47	23.00±5.26	-2.89 (-4.77 to -1.01)	**0.003***
6-Minute Walk Test (m)	457.72±89.44	470.17±81.05	-12.45 (-45.33 to 20.43)	0.454

*Statistically significant difference between the control and routine physiotherapy groups ($p < 0.05$). Values are presented as mean ± standard deviation (SD). Mean differences, 95% confidence intervals (CI), and p values were obtained using the independent samples t-test.

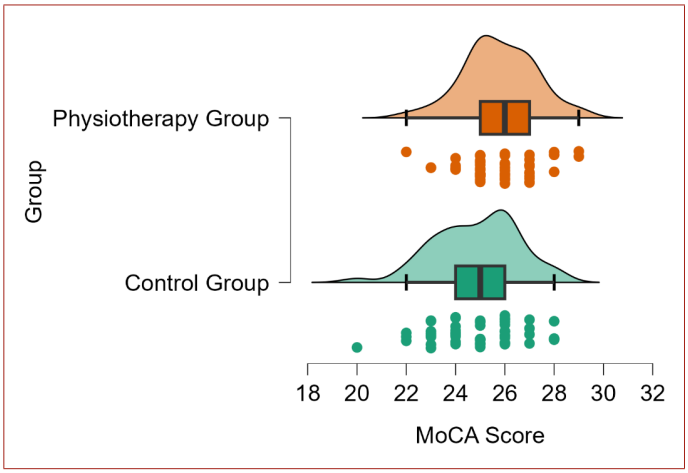

Figure 1. Distribution of montreal cognitive assessment (MoCa) scores in the control group and routine physiotherapy group.

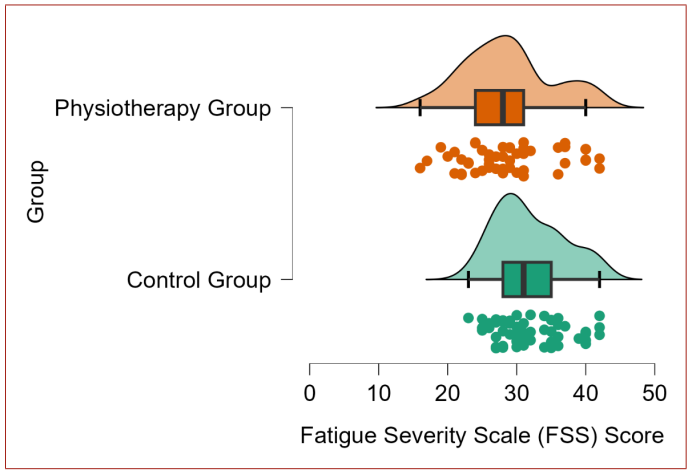

Figure 2. Distribution of fatigue severity scale scores in the control group and routine physiotherapy group.

self-confidence during movement, alleviate fear of physical activity and promote greater engagement in daily activities. The improvement in cognitive performance observed may be related to the cognitive demands of functional exercises, increased physical activity, and enhanced cerebral perfusion — all of which have been linked to improved cognitive function. Similarly, the reduction in fatigue may reflect improvements in physical conditioning, movement efficiency, and overall functional independence, which are achieved through regular rehabilitation.

One of the most notable strengths of the present study is that participants were evaluated approximately one year after liver transplantation. Therefore, our findings reflect not only early postoperative recovery, but also the functional status maintained during the medium-term post-transplant period. This provides valuable insight into whether the beneficial effects of routine physiotherapy persist over time. Our results imply that physiotherapy programmes designed appropriately may continue to contribute to functional recovery several months after transplantation, supporting the idea that rehabilitation should not be considered solely as an intervention for the immediate postoperative period.

Previous studies investigating rehabilitation after liver transplantation have predominantly focused on exercise and physiotherapy interventions implemented in the early post-operative period[16-18]. Programmes initiated during hospitalisation or within the first few weeks or months after discharge have been shown to consistently improve muscle strength, physical performance, exercise capacity and health-related quality of life. For example, Foroncewicz et al. found that starting a rehabilitation programme within the first two weeks after surgery significantly improved 6MWT performance and promoted early functional recovery[19]. Similarly, van den Berg-Emons et al. demonstrated that a 12-week programme resulted in significant improvements in aerobic capacity, muscle strength and fatigue[20]. More recently, systematic reviews and analyses have concluded that exercise-based rehabilitation yields promising improvements in physical function among liver transplant recipients[21]. However, these reviews have also emphasised that the available evidence is based on a limited number of randomised controlled trials, and that data regarding medium- and long-term outcomes remain insufficient [21, 22].

From this perspective, the present study differs from previous investigations in that it evaluates the functional outcomes of routine physiotherapy approximately one year after liver transplantation. Most published studies have primarily examined the early postoperative period[23-25]. As survival rates following liver transplantation have improved substantially, treatment success is no longer evaluated solely on the basis of graft function or patient survival[26]. Instead, there has been an increasing emphasis on maintaining long-term functional independence, preserving physical activity and improving health-related quality of life[22, 27]. Nevertheless, previous studies have shown that many liver transplant recipients experience reduced physical activity levels, persistent fatigue and incomplete recovery of physical function years after transplantation. Therefore, rehabilitation should be regarded as an essential component of long-term transplant care and follow-up, not merely as a short-term strategy to prevent postoperative complications. There are several possible explanations for the absence of a significant between-group difference in the 6MWT. Firstly, the participants were assessed approximately one year after liver transplantation. During this time, many recipients may have already regained an acceptable level of functional exercise capacity through spontaneous recovery and routine daily activities. This reduces the likelihood of detecting differences between groups. Secondly, exercise capacity is influenced by factors beyond postoperative physiotherapy, such as age, comorbidities, cardiovascular fitness, habitual physical activity, and long-term adherence to exercise after hospital discharge. However, functional mobility, balance, cognitive performance and fatigue may be more responsive to specific physiotherapy programme components, such as balance training, progressive mobilisation and functional, task-oriented exercises. Therefore, although routine physiotherapy appears to confer important functional benefits, these benefits may not necessarily be reflected in walking distance measured by the 6MWT during the medium-term follow-up period.

The present study has several limitations that should be considered when interpreting the findings. Firstly, as the study was conducted at a single centre, the results may not be generalisable to other liver transplant populations. Secondly, although participants were evaluated approximately one year after transplantation, no subsequent longitudinal follow-up assessments were performed. Therefore, it remains unclear whether the functional benefits associated with routine physiotherapy are maintained over a longer period. Additionally, objective physiological parameters such as muscle strength, body composition, cardiorespiratory fitness and habitual physical activity levels were not evaluated. Including these measures in future studies would provide a more comprehensive understanding of the mechanisms underlying the effects of rehabilitation. Furthermore, baseline measurements of physical performance, cognitive function, fatigue and functional capacity were not available before or immediately after transplantation. Therefore, the observed differences between groups

should be interpreted with caution, as they cannot be attributed solely to participation in the routine physiotherapy programme. The routine postoperative physiotherapy programme was delivered by experienced physiotherapists according to the institutional rehabilitation protocol. This included breathing exercises, airway clearance techniques (when indicated), early mobilisation, transfer training, progressive ambulation, range-of-motion exercises, muscle-strengthening exercises, balance training and functional activities appropriate to the patient's stage of recovery. Although all participants followed the same general rehabilitation protocol, the progression, intensity and selection of specific exercises were tailored to each patient's clinical status, functional capacity, ability to tolerate exercise and postoperative recovery. Finally, the absence of a statistically significant difference between groups in the 6MWT results should be interpreted with caution. This may be due to the participants' relatively preserved functional exercise capacity at the time of assessment and the multifactorial nature of post-transplant recovery. Future multicentre randomised controlled trials with larger sample sizes and extended follow-up periods are needed to determine the optimal duration, intensity and components of physiotherapy programmes following liver transplantation.

Conclusion

In summary, the results of this study suggest that participating in a regular physiotherapy programme improves functional mobility, balance, cognitive performance and reduces fatigue in liver transplant recipients. While no statistically significant difference was observed between groups in the 6MWT, the overall findings suggest that physiotherapy has a positive impact on several important aspects of postoperative recovery.

These results emphasise that the effectiveness of rehabilitation following liver transplantation should not be evaluated solely based on changes in aerobic exercise capacity. Instead, clinically meaningful outcomes such as balance, functional mobility, cognitive function and fatigue should also be considered, as these directly influence patients' independence in daily living and health-related quality of life.

Furthermore, our findings support the concept that rehabilitation should extend beyond the early postoperative period and continue after hospital discharge through structured, sustainable physiotherapy programmes to facilitate long-term functional recovery. Accordingly, physiotherapy should be considered an integral component of long-term multidisciplinary follow-up after liver transplantation, with rehabilitation programmes tailored to the individual needs and functional status of each recipient.

Disclosures

Ethics Committe Approval: Ethical approval was received for the study from the non-interventional ethics committee of Hasan Kalyoncu University, numbered 2024/116. Additionally, permission was obtained from the Liver Transplant Institute Hospital.

Informed Consent: The purpose and details of the study were explained to the individuals who accepted to participate in the study in written and verbal form and signed consent forms were obtained from the individuals.

Conflict of Interest: The authors declare no conflicts of interest.

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Original Research

Prevalence of the Scissural Vein in Living Liver Donor Candidates and Its Association with Hepatic Venous Variants: A Single-Center Retrospective Study

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Abstract

Objectives: The scissural vein is an independent venous structure arising from segment IV or the umbilical fissure and draining directly into the inferior vena cava (IVC) without joining the middle hepatic vein (MHV) or left hepatic vein (LHV). This study aimed to determine its prevalence in living liver donor candidates and evaluate its association with hepatic venous variants.

Methods: This single-center retrospective study included 248 consecutive adult living liver donor candidates evaluated between January 2020 and January 2026. Three-dimensional volumetric reconstructions from preoperative multiphase contrast-enhanced computed tomography (CT) were reviewed for surgically significant scissural veins (≥4 mm). The same ≥4 mm diameter threshold was applied to the inferior hepatic vein (IHV), V5, and V8, in accordance with institutional reconstruction practice and published literature. Associations between the scissural vein and demographic, volumetric, and venous variables were statistically analyzed.

Results: A scissural vein was identified in 70 of 248 candidates (28.2%). No significant differences were observed between candidates with and without a scissural vein regarding age, sex, BMI, hepatic steatosis, liver volumes, remnant liver percentage, GRWR, or the presence of an IHV ≥4 mm (OR 1.03; p=1.000). However, V5 and/or V8 ≥4 mm were significantly more frequent in the scissural vein-positive group (42.9% vs. 28.1%; OR 1.92, 95% CI 1.08–3.41; p=0.037), and this association remained significant after adjustment for age, BMI, and liver volume (adjusted OR 1.89, 95% CI 1.04–3.42; p=0.037). Hepatic steatosis was associated with BMI (p<0.001), but not with age (p=0.820).

Conclusion: A scissural vein was present in 28.2% of living donor candidates. It was not associated with liver volume, sex, or IHV presence but was independently associated with V5/V8. This finding may reflect a shared developmental pattern of the anterior/periscissural venous system and warrants further prospective investigation.

Keywords: Hepatic venous anatomy, middle hepatic vein, scissural vein, segment IV venous drainage, umbilical fissure vein, Living donor liver transplantation

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Living donor liver transplantation (LDLT) has consolidated its place as an effective treatment for end-stage liver disease; however, because it requires major hepatic resection in healthy individuals, donor safety constitutes the principal priority of surgical planning.[1-3] Among the main determinants of donor safety are remnant liver volume, portal inflow balance, and preservation of hepatic venous outflow. Impaired venous outflow has been shown to lead to parenchymal congestion, heterogeneous regeneration, and functional liver loss.[4,5]

The middle hepatic vein (MHV) primarily drains segments V and VIII but also contributes to a variable degree to segment IV drainage.[6,7] In right lobe donor hepatectomy, the question of on which side the MHV should be left remains one of the controversial topics in transplant surgery.[8,9] Kishi et al.[10] showed that preservation of large-caliber MHV tributaries reduces congestion in the donor remnant, whereas Faitot et al.[11] demonstrated that preservation of the distal MHV branches is critical for segment IV regeneration.

The diameter threshold plays a decisive role in hepatic venous reconstruction decisions. Several centers and recent reviews report that venous branches ≥4 mm in diameter should be considered candidates for reconstruction.[2,12,13] Borhani et al.[12] defined this threshold as standard practice, and Jeng et al.[13] adopted the same approach in their technical review based on an experience of 619 LDLTs. The comprehensive review published by Goldaracena et al.[2] in 2025 also recommends a >4 mm anastomosis threshold for accessory hepatic veins.

In their 3D CT-based anatomical study, Zhang et al.[14] reported that the umbilical fissure vein (UFV) was present in 82.7% of cases but that the great majority drained into the left hepatic vein (LHV) or MHV. Similarly, Idrees et al.,[15] in a retrospective CT study of 186 cases, detected the UFV in 72.8% of cases and reported drainage into the LHV in 81.4%, into the MHV in 16.4%, and into the confluence of both veins in 2.2% of cases.

During liver surgery, this venous structure, which arises from the umbilical fissure region and drains directly into the inferior vena cava without joining the LHV or MHV, is observed in some cases and is commonly referred to as the "scissural vein" in surgical practice. To the best of our knowledge, no previous study has described this structure as a distinct venous entity or used the term "scissural vein." Therefore, we chose to use the term "scissural vein" as a descriptive anatomical designation reflecting its location within the umbilical fissure. Yang et al.[16] showed that mapping of the hepatic venous drainage territory is associated with clinical outcomes and emphasized the importance of reconstructing veins with a large drainage territory.

To our knowledge, the prevalence of the scissural vein under this specific definition and its association with hepatic venous variants have not been systematically investigated in a living donor population. The aim of this study was to determine the prevalence of the scissural vein in real-world donor data and to evaluate its association with IHV, V5/V8, and arterial anatomy variants.

Methods

Study Design and Patient Selection

This study was designed as a single-center, retrospective, descriptive-analytical cohort study. The study was conducted with institutional ethics committee approval (Approval No: 25.02.2026/2026-02-13). The records of a total of 390 individuals evaluated as living liver donor candidates at our center between January 2020 and January 2026 were screened. Demographic data were accessible for 361 of these candidates; however, because some of the radiological images had been deleted from the system, preoperative multiphase contrast-enhanced abdominal computed tomography (CT) could be evaluated in only 248 candidates. Accordingly, 248 consecutive donor candidates who were ≥18 years of age, had evaluable CT imaging, and had a documented scissural vein assessment were included in the analysis (the study flow is summarized in Figure 1). Cases with insufficient imaging quality or inaccessible radiological images were excluded from the study.

No a priori sample size calculation was performed because of the retrospective design of the study. Instead, all consecutive living liver donor candidates evaluated during the predefined study period who met the eligibility criteria and had accessible preoperative CT images were included. Therefore, the final sample size was determined by the number of eligible cases available for analysis.

Imaging and Definition of the Scissural Vein

Preoperative multiphase contrast-enhanced abdominal CT images (portal venous and hepatic venous phases) of all candidates were retrospectively reviewed using three-dimensional volumetric reconstruction software (Myrian software; Intrasense, Montpellier, France). Liver segmentation was performed according to the Couinaud classification.[17]

The scissural vein was defined as follows: a venous structure that originates from segment IV or the umbilical fissure region and drains directly into the IVC—or via an independent ostium into the MHV–LHV confluence—without joining the trunk of the MHV or LHV as a tributary. In both drainage patterns, the structure represents an independent third venous outflow pathway lying outside the MHV/LHV

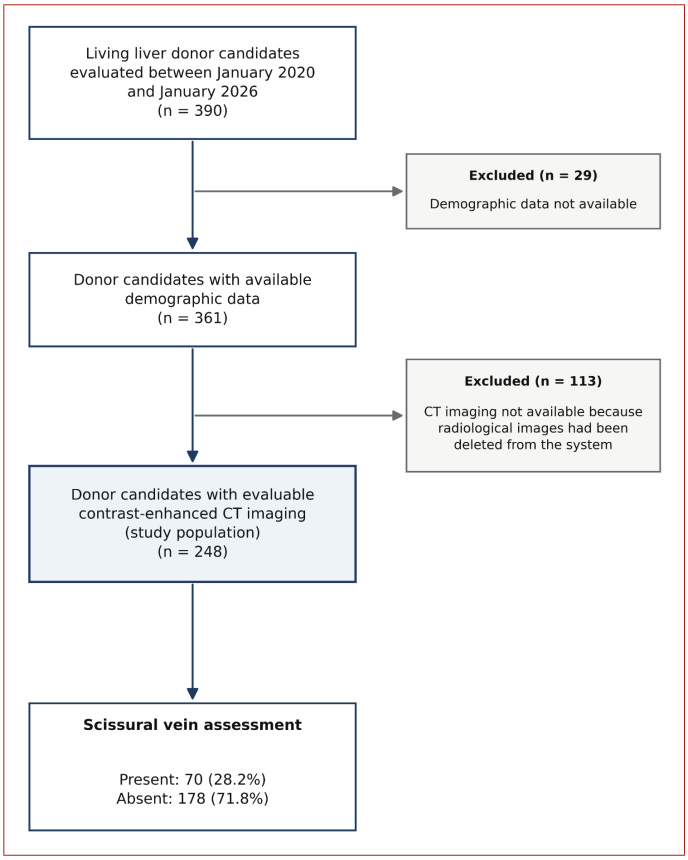

Figure 1. Study flow diagram (STROBE).

branching hierarchy. Scissural vein presence was defined as a diameter of ≥4 mm; veins with a diameter <4 mm were classified as absent. In the same assessment, together with the MHV, the IHV, V5, and V8 (each with a ≥4 mm diameter threshold) and the arterial anatomy were also systematically recorded; the ≥4 mm threshold was chosen in accordance with institutional anastomosis practice and the international literature.[2,12,13] CT examinations were performed using a 192×2-slice multidetector computed tomography scanner (SOMATOM Force, Siemens Healthineers, Forchheim, Germany) with a multiphase contrast-enhanced protocol, including arterial, portal venous, and delayed (hepatic venous) phases. Images were acquired with a slice thickness of 1 mm. All examinations were reviewed by the same radiology team experienced in hepatobiliary imaging.

Volumetric parameters included right lobe volume, left lobe volume, total liver volume (TLV=right + left lobe), remnant liver percentage, and GRWR.

Statistical Analysis

Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). The distributional normality of continuous variables was assessed by a combined evaluation of the Shapiro–Wilk test and visual inspection of histograms and skewness/kurtosis values; normally distributed variables were expressed as mean±standard deviation and non-normally distributed variables as median (interquartile range, IQR). Comparisons between the two groups were performed, as appropriate to the distribution, using the Student *t* test or the Mann–Whitney U test (continuous variables) and the chi-square or Fisher exact test (categorical variables). Odds ratios (OR) and 95% confidence intervals (CI) were calculated for bivariate associations. To assess whether the association between the presence of a scissural vein and the presence of V5 and/or V8 was independent of age, BMI, and total liver volume, a multivariable logistic regression model was constructed with the presence of a scissural vein (present/absent) as the dependent variable and the presence of V5 and/or V8, age, BMI, and total liver volume as independent variables. Because numerous pairwise comparisons were performed across the tables, the possibility that the significant finding was affected by multiple comparisons was additionally evaluated using the Benjamini–Hochberg false discovery rate (FDR) correction, and the results were interpreted within this framework. A complete-case analysis was used for variables with missing data, and the number of cases used in each analysis was indicated in the relevant table and text. $p<0.05$ was accepted as the threshold of statistical significance. The study was reported in accordance with the STROBE guideline.

Results

Cohort Characteristics and Scissural Vein Prevalence

A total of 248 living liver donor candidates were included in the study (153 men, 95 women; median age 36 years, IQR 29–42; mean BMI 27.4±4.4 kg/m^2). Hepatic steatosis was identified in 111 of 247 evaluable cases (44.9%). TLV was calculated in 243 cases, with a mean of 1366±325 mL. The mean GRWR was 1.17±0.41 (n=234).

A scissural vein was identified in 70 of 248 candidates; the prevalence was 28.2% (70/248).

Demographic and Volumetric Comparison

No significant difference was found between the groups with (n=70) and without (n=178) a scissural vein in terms of age (median 33 vs 36 years; $p=0.127$), sex (62.9% vs 61.2% male; $p=0.927$), BMI (26.9±4.5 vs 27.7±4.3 kg/m^2; $p=0.229$), or hepatic steatosis rate (40.0% vs 46.6%; $p=0.422$). No significant difference was found either in right lobe volume (891±234 vs 913±229 mL; $p=0.515$), left lobe volume (450±113 vs 462±129 mL; $p=0.457$), TLV (1341±305 vs 1375±332 mL; $p=0.445$), remnant percentage (33.8±5.5 vs 33.6±4.7; $p=0.826$), or GRWR (1.17±0.40 vs 1.17±0.41; $p=0.959$). The findings are summarized in Table 1.

Table 1. Demographic and volumetric characteristics according to the presence of a scissural vein

Variable	Total (n=248)	ScV present (n=70)	ScV absent (n=178)	p
Age (years), median (IQR)	36 (29–42)	33 (25–41)	36 (30–43)	0.127
Sex (male), n (%)	153 (61.7%)	44 (62.9%)	109 (61.2%)	0.927
BMI (kg/m^2), mean ± SD	27.4 ± 4.4	26.9 ± 4.5	27.7 ± 4.3	0.229
Hepatic steatosis, n (%)	111 (44.9%)*	28 (40.0%)	83 (46.6%)	0.422
Right lobe volume (mL), mean ± SD	907 ± 230	891 ± 234	913 ± 229	0.515
Left lobe volume (mL), mean ± SD	459 ± 125	450 ± 113	462 ± 129	0.457
TLV (mL), mean ± SD**	1366 ± 325	1341 ± 305	1375 ± 332	0.445
Remnant (% TLV), mean ± SD	33.7 ± 4.9	33.8 ± 5.5	33.6 ± 4.7	0.826
GRWR, mean ± SD	1.17 ± 0.41	1.17 ± 0.40	1.17 ± 0.41	0.959

* n = 247 evaluable cases. ** n = 243 evaluable cases. ScV = scissural vein; TLV = total liver volume; GRWR = graft-to-recipient weight ratio; BMI = body mass index; IQR = interquartile range. The Mann–Whitney U test (age), Student t test (continuous) and chi-square test (categorical) were used.

Association with Accompanying Hepatic Venous Variants

The IHV (≥4 mm) was identified in 37.1% (26/70) of the scissural vein-positive group and 36.5% (65/178) of the negative group, with no significant difference between the two groups (OR 1.03; 95% CI 0.58–1.82; p=1.000). V5 and/or V8 (≥4 mm) was significantly higher in the scissural vein-positive group (42.9% vs 28.1%; OR 1.92; 95% CI 1.08–3.41; p=0.037). The coexistence of IHV and V5/V8 did not differ between the two groups (10.0% vs 10.7%; p=1.000). The results are presented in Table 2. In the multivariable logistic regression model, the presence of V5 and/or V8 maintained its association with the presence of a scissural vein independently of age, BMI, and total liver volume (adjusted OR 1.89; 95% CI 1.04–3.42; p=0.037); none of the other variables in the model were significant (all p>0.40 for age, BMI, and total liver volume). However, when the Benjamini–Hochberg false discovery rate correction was applied for the multiple comparisons performed across the tables, this association lost its statistical significance (adjusted p=0.205); therefore, the finding should be regarded as hypothesis-generating.

Analysis of Steatosis, Sex, BMI and Age

In cases with hepatic steatosis (n=111), BMI was markedly higher (29.0±4.3 vs 26.2±4.0 kg/m^2; p<0.001). In contrast, the median age was 36 years in both groups and did not differ significantly (p=0.820). BMI in the presence of steatosis was similar in both sexes (29.0 kg/m^2 in male donors and 29.3 kg/m^2 in female donors). Male sex showed no statistically significant association with steatosis (OR 1.30; p=0.367). The presence of a scissural vein did not differ between the groups with and without steatosis (25.2% vs 30.9%; OR 0.76; p=0.422). The findings are presented in Table 3.

Arterial Anatomy Variants

Arterial anatomy could be evaluated in 247 cases (1 NA). Normal hepatic arterial anatomy was found in 155 cases (62.5%). The most common variant was the origin of the left hepatic artery from the left gastric artery (n=40; 16.1%). Origin of the right hepatic artery from the superior mesenteric artery (SMA) was identified in 47 cases (19.0%). Rare variants (origin of the CHA from the aorta or SMA) were observed in 5 cases (2.0%). No significant association was found between the presence of a scissural vein and any arterial anatomy variant (all p>0.05). The findings are presented in Table 4.

Discussion

In this real-world cohort of 248 living liver donor candidates, the prevalence of surgically significant scissural

Table 2. Association between the presence of a scissural vein and accompanying hepatic venous variants

Venous structure	ScV present n=70 (%)	ScV absent n=178 (%)	OR (95% CI)	p
IHV (≥4 mm)	26 (37.1%)	65 (36.5%)	1.03 (0.58–1.82)	1.000
V5 and/or V8 (≥4 mm)	30 (42.9%)	50 (28.1%)	1.92 (1.08–3.41)	0.037
IHV + V5/V8 combined	7 (10.0%)	19 (10.7%)	0.93 (0.37–2.34)	1.000

ScV = scissural vein; IHV = inferior hepatic vein; V5/V8 = segment V and/or VIII veins (≥4 mm); OR = odds ratio; CI = confidence interval. The chi-square and Fisher exact tests were used.

Table 3. Hepatic steatosis — association with BMI, sex, age and the scissural vein

Parameter	Steatosis (+) n=111	Steatosis (–) n=136	Difference / OR	p
BMI (kg/m^2), mean ± SD	29.0 ± 4.3	26.2 ± 4.0	+2.8	<0.001
Age (years), median	36	36	—	0.820
Male sex, n (%)	72 (64.9%)	80 (58.8%)	OR 1.30	0.367
ScV presence, n (%)	28 (25.2%)	42 (30.9%)	OR 0.76	0.422
Right lobe volume (mL), mean ± SD	935 ± 241	884 ± 220	+51 mL	0.083

ScV = scissural vein; BMI = body mass index; OR = odds ratio. The Student t test (continuous) and chi-square test (categorical) were used. n = 247 evaluable cases (1 NA).

Table 4. Distribution of hepatic arterial anatomy according to the presence of a scissural vein

Arterial anatomy	Total n (%)	ScV present n (%)	ScV absent n (%)	p
Normal	155 (62.5%)	45 (64.3%)	110 (61.8%)	0.843
LHA from left gastric artery	40 (16.1%)	10 (14.3%)	30 (16.9%)	0.785
RHA from SMA	47 (19.0%)	13 (18.6%)	34 (19.1%)	1.000
Other (CHA from aorta/SMA)	5 (2.0%)	2 (2.9%)	3 (1.7%)	0.616
Total evaluated	247	70	177	—

ScV = scissural vein; LHA = left hepatic artery; RHA = right hepatic artery; SMA = superior mesenteric artery; CHA = common hepatic artery. The chi-square and Fisher exact tests were used. n = 247 evaluable cases (1 NA).

veins (≥4 mm) was 28.2%. The scissural vein was identified as an independent venous structure draining directly into the inferior vena cava without joining either the middle or left hepatic vein, representing an anatomical variant that has not previously been systematically characterized. The primary aim of this study was not only to determine its prevalence but also to evaluate whether this venous variant is associated with other clinically relevant hepatic venous structures that may influence surgical planning in living donor liver transplantation. Therefore, our findings provide both an anatomical description and a clinically oriented assessment of this previously underrecognized venous structure.

Zhang et al.[14] reported the UFV in 82.7% of cases but showed that the great majority of these veins drained into the LHV or MHV system. The structure we defined—draining directly into the IVC (or via an independent ostium into the MHV–LHV confluence) without joining the MHV/LHV trunk—constitutes a distinct anatomical phenotype. Although the recent review by Goldaracena et al.[2] reports that hepatic vein variants are seen in approximately 40% of healthy donors, it does not address segment IV veins draining directly into the IVC as a separate category. This gap constitutes the original contribution of the present study. Therefore, the prevalence reported in the present study should not be directly compared with studies evaluating all umbilical fissure veins irrespective of size or drainage pattern. Our study specifically focused on surgically significant scissural veins (≥4 mm) draining independently into the inferior vena cava, reflecting a clinically relevant anatomical subset rather than the overall prevalence of segment IV venous branches. This distinction is important because the objective of the present study was to identify venous structures that could potentially influence surgical planning in living donor liver transplantation.

One of the notable findings of this study is that the presence of a scissural vein was unrelated to liver volume, sex, age, and steatosis. No significant difference was found between the groups in terms of TLV, right/left lobe volumes, remnant percentage, and GRWR. This finding indicates that the scissural vein has the characteristics of an anatomical variant independent of liver size. Similarly, in the hepatic steatosis analysis, the presence of steatosis showed a strong association with BMI but no significant association with the scissural vein or sex.

The only significant association of the presence of a scissural vein was with the presence of V5 and/or V8 (≥4 mm) (OR 1.92; p=0.037). This finding is biologically plausible. Both the scissural vein (draining segment IV from the left side) and V5 (draining the anterior sector of the right lobe) receive blood from the peri-scissural region in close proximity to the main portal scissura. It may be postulated that, during embryological hepatic venous remodeling, the peri-scissural sinusoidal

network develops more prominent direct IVC tributaries in some individuals. Nevertheless, the mechanism of this association was not functionally tested in this study. These findings suggest that the presence of a surgically significant scissural vein may serve as an additional anatomical marker of complex hepatic venous anatomy, emphasizing the importance of meticulous preoperative three-dimensional imaging assessment in living donor liver transplantation.

The absence of a significant association with the IHV (p=1.000) is noteworthy. The IHV drains the posterior sector and lies outside the anterior/peri-scissural region shared with the scissural vein. This finding supports the hypothesis that the association arises not from a general tendency toward hepatic venous hypertrophy but from a developmental pattern specific to the anterior/peri-scissural region. Similarly, the lack of association between hepatic arterial anatomy and the presence of a scissural vein indicates that this venous variation is a process independent of arterial development. From a surgical perspective, the coexistence of a scissural vein and an inferior hepatic vein may indicate a more complex venous drainage pattern that warrants careful evaluation during preoperative imaging. Recognizing these venous variations before donor hepatectomy may facilitate surgical planning and help reduce unexpected intraoperative findings.

The clinical significance of the scissural vein could not be directly evaluated in this study, since postoperative data, the MHV decision-making process, and patient follow-up information were not available in the data set. The debate over on which side the MHV should be left in right lobe donor hepatectomy is one of the long-standing surgical dilemmas of living donor liver transplantation.[8,9] Preservation of segment IV venous drainage is central to this decision; Faitot et al.[11] showed that this drainage is largely dependent on the distal branches of the MHV. Precisely because of this dependence, the presence of a sufficiently large scissural vein draining segment IV independently of the MHV could theoretically reduce the need to leave the MHV with the donor, thereby facilitating the surgical decision.[10,18-20] Nevertheless, confirmation of these inferences requires prospective studies incorporating postoperative volumetric and functional endpoints. Future studies integrating detailed intraoperative findings and postoperative outcomes are warranted to determine whether preservation or reconstruction of these veins influences donor safety, graft function, or recipient outcomes. Such data would further clarify the clinical relevance of this anatomical variant in living donor liver transplantation.

The main limitations of this study are as follows. First, the retrospective design carries a risk of selection bias. Second, the presence of a scissural vein was recorded as present/absent; because drainage territory and drainage volume were not available in the data set, its functional significance could not be evaluated. Third, intraoperative correlation was not performed. Fourth, numerous pairwise comparisons were performed across the tables, and the only significant finding—the association with V5/V8—does not retain its statistical significance after correction for multiple comparisons (Benjamini–Hochberg false discovery rate); therefore, this association should be regarded not as an established relationship but as a hypothesis requiring confirmation. Finally, in the comparisons that were not significant (volume, IHV), the width of the confidence intervals indicates that small true effects cannot be excluded; accordingly, these results should be interpreted not as the definite absence of an association but as the absence of a significant association in the present sample. For all these reasons, the present findings are hypothesis-generating and require confirmatory studies.

Conclusion

A scissural vein was identified in 28.2% of living donor candidates. It showed no significant association with liver volume, sex, age, BMI, steatosis, or the presence of an IHV. An association with the presence of V5 and/or V8 was observed; however, this finding should be considered hypothesis-generating and requires prospective confirmation. This observation may reflect a distinct venous developmental pattern in the anterior/peri-scissural region. These findings contribute to the current understanding of hepatic venous anatomy in living liver donors and may be relevant for preoperative venous assessment. Further prospective studies incorporating intraoperative observations and postoperative outcomes are needed to clarify the clinical significance of the scissural vein and its implications for MHV management.

Disclosure

Ethics Committee Approval: This study was approved by the Demiroğlu Bilim University Medical Research Ethics Committee (Date: 25.02.2026, Decision no: 25.02.2026 / 2026-02-13).

Informed Consent: Written informed consent was waived owing to the retrospective design of this single-center study.

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terials: A.T., N.A., E.S., S.A., N.I.G., A.D., B.U.; Data collection and/or processing: A.T., N.A., E.S., S.A., N.I.G., A.D., B.U.; Analysis and/or interpretation: A.T., N.A., E.S., S.A., N.I.G., A.D., B.U.; Literature review: A.T., N.A., E.S., S.A., N.I.G., A.D., B.U.; Writing: A.T., N.A., E.S., S.A., N.I.G., A.D., B.U.; Critical review: A.T., N.A., E.S., S.A., N.I.G., A.D., B.U.

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Case Report

Elevated CA 19-9 After Laparoscopic Cholecystectomy: A Case Report

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Abstract

Although laparoscopic cholecystectomy is one of the most frequently performed operations in general surgery, its complications may be clinically serious. Management may range from minimally invasive interventional procedures to complex surgical strategies, including liver transplantation in selected cases. Correct management of these complications requires careful exclusion of an overlooked preoperative malignancy. In this case report, we present the clinical course of a patient with postcholecystectomy biliary complications accompanied by marked elevation of carbohydrate antigen 19-9 (CA 19-9).

Keywords: Laparoscopic cholecystectomy, complications, elevated CA 19-9, biliary stricture, ERCP

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Cholecystectomy is among the most commonly performed operations in general surgical practice. The main indications include symptomatic gallstones, complications of gallstone disease, and gallbladder polyps. For these indications, laparoscopic cholecystectomy is currently accepted as the gold-standard approach. Although the frequency of complications decreases with increasing experience, some complications may result in substantial morbidity and mortality. Bile duct injuries remain the most serious complications of laparoscopic cholecystectomy.[1] In the management and follow-up of postcholecystectomy biliary leaks, interventional radiological procedures and endoscopic interventions are currently used successfully. Endoscopic retrograde cholangiopancreatography (ERCP) is the first-line minimally invasive method for diagnosis and effective treatment of biliary leaks.[2] Although endoscopic interventions are prioritized during the initial treatment phase, percutaneous radiological interventions remain important and are successfully performed in many situations in which anatomy does not permit endoscopic access. These percutaneous approaches may also be completed with subsequently placed stents.[3] Carbohydrate antigen 19-9 (CA 19-9) may increase in benign conditions; however, elevated CA 19-9 may raise suspicion for malignancy and lead to unnecessary diagnostic work-up.[4] CA 19-9 is the most widely used and best-validated serum tumor marker for the diagnosis of pancreatic cancer in symptomatic patients and for monitoring treatment in patients with pancreatic adenocarcinoma. CA 19-9 is normally synthesized by pancreatic and biliary ductal cells, as well as gastric, colonic, endometrial, and salivary epithelia, and is present in serum at low levels. Although CA 19-9 has been introduced as a reliable marker for pancreatobiliary malignancy, elevated serum CA 19-9 levels may also be observed

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in obstructive jaundice.[5] In this study, we aimed to present the complication management and clinical significance of elevated CA 19-9 in a patient who underwent elective laparoscopic cholecystectomy and subsequently developed postoperative complications.

Case Report

A 60-year-old male patient had previously undergone laparoscopic cholecystectomy at another center for symptomatic cholelithiasis. No conversion to open surgery was required, and no intraoperative complication was reported. On postoperative day 2, bile drainage was observed from the surgical drain, and the patient was referred to a tertiary center. The patient had no evidence of biliary peritonitis or acute abdomen. Laboratory values at admission were as follows: leukocyte count, 5.3 × 10^3/μL (reference range, 4.3-10.3); aspartate aminotransferase, 15 U/L (5-34); alanine aminotransferase, 38 U/L (0-55); gamma-glutamyl transferase, 57 U/L (9-64); alkaline phosphatase, 64 U/L (40-150); total bilirubin, 0.7 mg/dL (0.2-1.2); and CA 19-9, 7.3 U/mL (0-35). ERCP was performed, and a leak from the cystic duct was detected. A stent was placed across the proximal aspect of the leak. The stent was removed 3 months later. After an approximately 9-year disease-free interval, the patient presented again with right upper quadrant pain and jaundice. Laboratory values at this admission were as follows: leukocyte count, 10.1 × 10^3/μL (4.3-10.3); aspartate aminotransferase, 18 U/L (5-34); alanine aminotransferase, 37 U/L (0-55); gamma-glutamyl transferase, 307 U/L (9-64); alkaline phosphatase, 166 U/L (40-150); total bilirubin, 0.9 mg/dL (0.2-1.2); and CA 19-9, 58,977.06 U/mL (0-35). Other tumor markers were within normal limits. During follow-up, CA 19-9 levels varied as shown in Figure 1. Imaging revealed dilatation of the posterior intrahepatic bile ducts (Fig. 2). Because dilatation was limited to the posterior sector, percutaneous catheterization was planned. A catheter was placed from this sector extending toward the common bile duct, and the radiological interpretation suggested the possibility of segmental Caroli disease. However, segmental Caroli disease was subsequently ruled out after the biliary abnormality was determined to represent an acquired postoperative biliary stricture. Two months later, a stent was inserted over the catheter, and the patient was discharged with normalized laboratory values. During follow-up visits every 3 months, cholestatic parameters remained normal, and CA 19-9 levels showed a decreasing trend, as shown in Figure1. Malignancy was excluded on the basis of the progressive decline in CA 19-9 levels following biliary drainage and the absence of any mass or suspicious lesion on magnetic resonance imaging. One year after stent placement, the stent was removed by ERCP. At the final follow-up, all blood parameters were normal and the patient was asymptomatic; therefore, routine follow-up was discontinued. The patient was ultimately evaluated as having a postoperative biliary stricture. Written informed consent was obtained from the patient for publication of this case report and the accompanying clinical images.

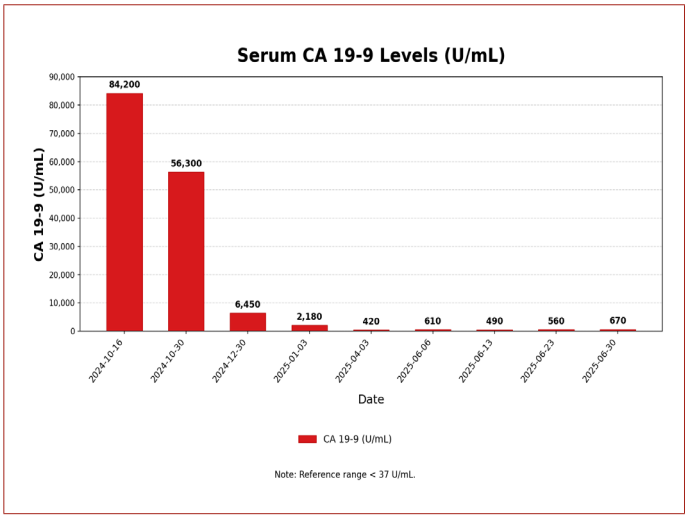

Figure 1. CA 19-9 values at presentation and after treatment.

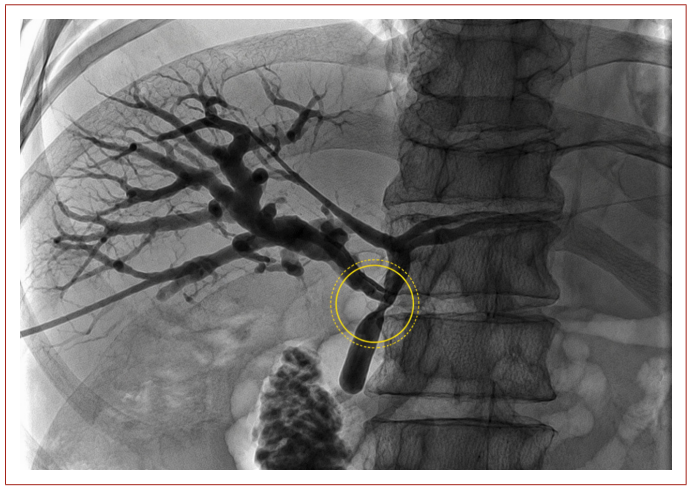

Figure 2. Dilated posterior sector on cholangiographic imaging.

Discussion

To prevent bile duct injuries during laparoscopic cholecystectomy, the principles of the Critical View of Safety should be followed, and no tubular structure should be divided before the cystic duct and cystic artery have been definitively identified. In addition, electrocautery should be used carefully and at low energy settings to reduce thermal injury. Although postcholecystectomy biliary leaks can be successfully treated with ERCP, early control of the leak does not completely eliminate the risk of late biliary complications. Mechanical, thermal, or ischemic bile duct

injury may lead to fibrosis and biliary stricture over time.[6] In the present case, the biliary leak that developed after cholecystectomy was treated with ERCP; however, the patient presented years later with biliary stricture. This clinical course highlights the importance of long-term clinical and biochemical follow-up in patients with a history of biliary leakage. Despite preventive measures, bile duct injuries are reported at rates ranging from 0.3% to 0.8%.[7] Bile duct injuries have been described using several classification systems, including the Bismuth, McMahon, Strasberg, Amsterdam Academic Medical Center, Stewart-Way, Neuhaus, and Csendes classifications. In our patient, the initial injury was classified as Strasberg type A, and the complication was treated with ERCP at presentation. However, in subsequent years, the patient re-presented with jaundice and markedly elevated CA 19-9 due to biliary stricture. CA 19-9 is normally synthesized by pancreatic and biliary ductal cells and by gastric, colonic, endometrial, and salivary epithelia, and is present in small amounts in the blood of healthy individuals. However, dramatic increases may occur in some malignant diseases.[8] Therefore, CA 19-9 is regarded as a tumor-associated antigen rather than a tumor-specific antigen.[9] Particularly in obstructive jaundice, CA 19-9 levels may be substantially affected and increased, making it difficult to distinguish benign from malignant cholestasis.[10] Elevation of CA 19-9 in the absence of malignant disease is clinically important and requires follow-up; however, it may also lead to complex and invasive diagnostic procedures.[11] CA 19-9 remains an actively investigated tumor marker because biliary obstruction and other benign conditions may substantially distort measured levels and thereby lead to inappropriate clinical decisions; accordingly, dynamic changes after biliary drainage and correction approaches have been studied to improve its clinical interpretation.[12] As demonstrated in this case, elevated CA 19-9 may prompt clinicians to investigate many different diseases, particularly malignancy. Nevertheless, in accordance with one of the unwritten rules of surgical practice--that "a surgeon must follow his own footprints"--the patient's previous surgical history and possible late surgery-related complications should always be carefully considered.

Conclusion

This case of elevated CA 19-9 accompanying a bile duct stricture that developed years after laparoscopic cholecystectomy was evaluated in light of the literature. In conclusion, even when postcholecystectomy complications are initially resolved, late complications may present years later as biliary strictures, and such benign strictures may cause marked elevation of CA 19-9. Although CA 19-9 is widely used as a tumor marker in pancreatobiliary malignancies, elevation of this marker alone does not justify complex invasive procedures without appropriate clinical correlation. Through this case, we aimed to emphasize that a complication following laparoscopic cholecystectomy may elevate CA 19-9, an important tumor marker, and may consequently lead to invasive diagnostic and therapeutic procedures.

Disclosures

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

Conflict of Interest: None declared.

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Clinical Image

Extended Retroperitoneal Dissection and Retrohepatic Vena Cava Resection for Recurrent Retroperitoneal Liposarcoma

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Liposarcomas account for less than 1% of all human malignancies; however, they represent one of the most common soft tissue sarcomas, comprising nearly 50% of all retroperitoneal soft tissue tumors. Because the retroperitoneal space is expansive, these tumors often attain a tremendous size before becoming symptomatic.[1]

Histologically, liposarcomas are categorized into well-differentiated, dedifferentiated, myxoid, and pleomorphic subtypes. Myxoid and pleomorphic variants generally demonstrate greater responsiveness to chemoradiotherapy than well-differentiated and dedifferentiated forms.[2] Due to late diagnosis at advanced stages and large tumor volume, disease recurrence is common. Nearly 50% of patients with moderate- to high-grade liposarcoma develop local or distant recurrences, which significantly reduce overall survival. Tumor size, histological grade and subtype, male sex, and age at diagnosis are established risk factors for recurrence.[3] Complete (R0) surgical resection, with or without postoperative chemoradiotherapy, has been shown to reduce post-treatment recurrence rates.[4]

Here, we describe our surgical strategy in a 69-year-old male presenting with a second recurrence of retroperitoneal dedifferentiated liposarcoma requiring retrohepatic inferior vena cava (IVC) resection and reconstruction.

A 69-year-old male presented to our institution with a 4-cm retroperitoneal mass adjacent to the IVC, located superior to the right kidney (Figure 1). His surgical history was notable for a primary retroperitoneal liposarcoma resected 3 years previously. At initial presentation, the primary tumor measured 22 cm in maximum diameter and was adjacent to the right psoas muscle and right kidney. The patient received only chemotherapy after the index operation. A local recurrence occurred 18 months following the primary resection. The recurrent tumor measured 19 mm in diameter and was located near Gerota's fascia of the right kidney. The recurrent mass was prepared for resection together with the right renal Gerota's fascia and segments 6 and 7 of the liver. The patient received massive transfusion during the operation (15 units of packed erythrocytes). Although the patient's condition was relatively stable, we decided to terminate the operation with packing and complete the resection and reconstruction in a second session. Forty-eight hours after the primary operation, the patient was taken back to the operating room, and depacking was performed. The mass, together with the right adrenal gland and retrohepatic vena cava, was resected, and the inferior vena cava was reconstruct-

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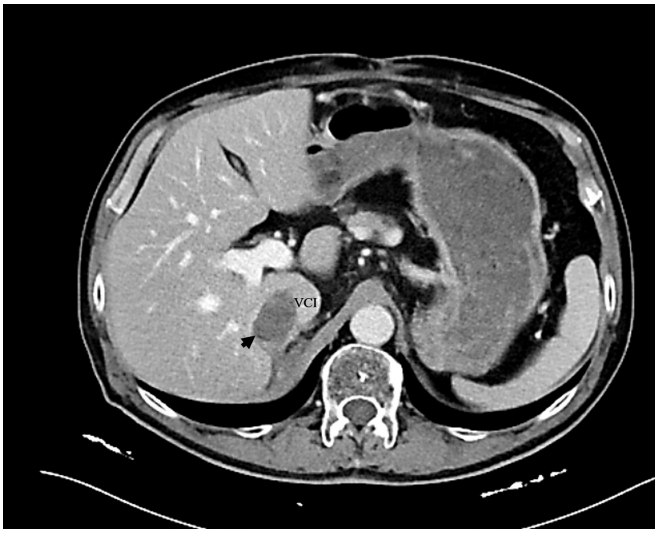

Figure 1. The recurrent mass adjacent to the retrohepatic vena cava (arrow head). VCI: Vena cava inferior.

ed using a synthetic polyester vascular graft made of polyethylene terephthalate (PET) (Figure 2a, b). The patient had an uneventful postoperative course and was discharged on postoperative day 20. We obtained informed consent from the patient for the publication of the clinical information presented in this study.

The present study shows that the treatment of recurrent retroperitoneal liposarcoma can be challenging. However, consensus dictates that resection of recurrences with adequate safety margins increases complete remission rates in retroperitoneal liposarcoma.[5] Up to seven resections have been reported in a single patient.[1] Furthermore, a multidisciplinary approach, including chemoradiotherapy in the adjuvant or even neoadjuvant setting, has been reported to be effective in preventing recurrences.[6] The common iliac artery and inferior vena cava are the two major vessels that may be involved in retroperitoneal liposarcoma. Concomitant organ resection rates increase when major vascular structures are resected. Although complication rates increase, major vascular structures may need to be resected to achieve R0 resection.[6] In accordance with the current literature, our patient received adjuvant chemoradiotherapy following the primary surgery and targeted therapy after the first recurrence. In conclusion, we would like to share our experience in treating a challenging case of recurrent retroperitoneal liposarcoma to demonstrate that a dedicated center for advanced hepatobiliary surgery can facilitate the treatment of such diseases requiring multiorgan and major vascular resections together with complex reconstruction, even in fit elderly patients such as the patient presented in this study.

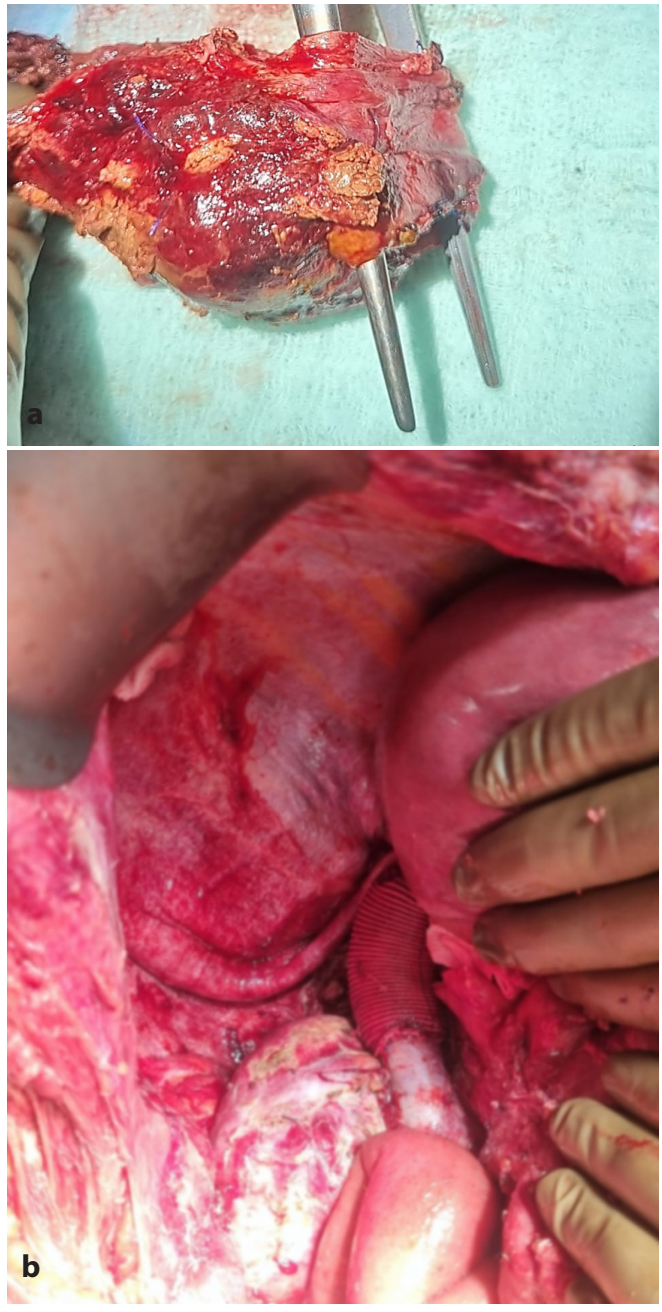

Figure 2. The surgical specimen **(a)** and the reconstruction of the retrohepatic vena cava is shown **(b)**.

Disclosures

Informed Consent: We have obtained informed consent from the patient regarding sharing of the clinical information for the present study.

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Letter to the Editor

Severe Trismus Developing After Liver Transplantation: A Rare Sequela of Oral Pathology Rendering ERCP Impossible

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Dear Editor,

Oral cavity lesions encountered during long-term follow-up after liver transplantation are generally reported as mucositis, infections, or drug-related gingival hyperplasia associated with immunosuppressive therapy.[1,2] To our knowledge, no case has been reported in the literature of a patient who underwent living-donor liver transplantation for non-alcoholic steatohepatitis (NASH), subsequently developed progressive trismus due to recurrent oral lesions (actinomycosis and traumatic fibroma), and in whom this trismus completely prevented the treatment of common bile duct stones causing cholestasis by endoscopic retrograde cholangiopancreatography (ERCP). Here, we aim to present such a rare clinical scenario.

A 39-year-old woman underwent living-donor liver transplantation in April 2015 because of NASH. Following an uneventful postoperative course and discharge, an excisional biopsy was performed for an oral lesion that developed in her mouth. The pathology report was consistent with actinomycosis caused by Actinomyces species, and appropriate antibiotic therapy was administered. In March 2016, the patient developed an ulcerated, hyperemic lesion extending from the right buccal mucosa to the retromolar trigone. An incisional biopsy was performed, and the pathology report identified the lesion as a traumatic fibroma.

The patient, who had maintained stable liver function over the past ten years, developed progressive and painless trismus due to soft tissue damage caused by an oral lesion (Fig. 1). The patient's mouth was almost completely closed, and she could only consume liquid food using a pipette. Routine follow-up revealed elevated cholestatic enzymes (ALP: 715, GGT: 342). Magnetic resonance cholangiopancreatography showed numerous stones in the main bile ducts, and ERCP was planned (Fig. 2). However, since the

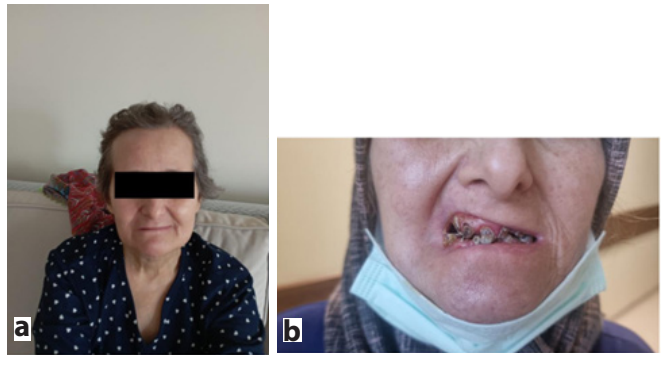

Figure 1. Photograph of the patient when the mouth opening was normal and the final state where the patient could be fed through a straw. **a)** The period after transplant when mouth opening is normal, **b)** The final period when the mouth cannot be opened.

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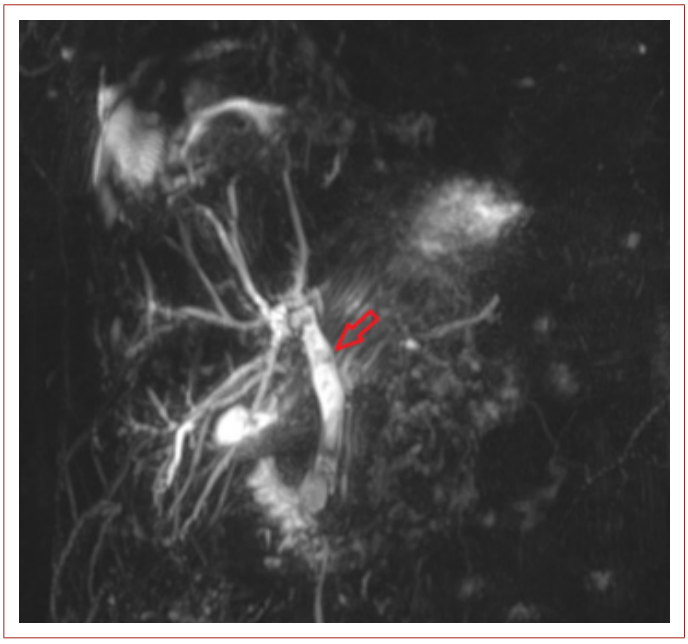

Figure 2. Magnetic resonance imaging showing stones in the patient's bile ducts.

* The stones in the common bile duct are indicated by red arrows.

patient's interincisal mouth opening was less than 4 mm, it was considered impossible to pass a standard flexible endoscope through the mouth and to safely perform anesthesia management, including endotracheal intubation. At the oral surgery and gastroenterology council, it was decided that the patient should first undergo surgery to correct the trismus, with the asymptomatic bile duct stones to be addressed after this procedure. The patient was transferred to the oral surgery department for treatment.

Trismus is a rare complication in liver transplant patients, usually developing after trauma to the corner of the mouth, myopathy of the masticatory muscles secondary to long-term steroid use, or oral mucositis.[3,4] However, to our knowledge, a case involving a buccal mucosal lesion complicated by actinomycosis, followed by a traumatic fibroma that progressed over the years and physically obstructed endoscopic access to the biliary tract, has not been previously described.

In conclusion, active monitoring of oral lesions, especially recurrent or scarring lesions, in liver transplant patients and early surgical correction, if necessary, can prevent future trismus and the associated obstruction of endoscopic interventions. This case highlights the critical importance of interdisciplinary collaboration among gastroenterologists, surgeons, and oral surgeons.

Disclosure

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