Minimally Invasive Liver Resection in Liver Transplant: an International Multicenter Study

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LIST OF ABBREVIATIONS

ASA: American Society of Anesthesiologists Physical Status classification

BMI: body mass index

IHPBA: Scientific Committee of the International Hepato-Pancreato-Biliary Association

LT: Liver transplant

MILS: Minimally invasive liver surgery

E-AHPBA: European-African Hepato-Pancreato-Biliary-Association

1. PROTOCOL ABSTRACT

Background

Minimally invasive liver surgery (MILS) has revolutionized liver surgery. Despite promising outcomes in case reports, there is a lack of multicenter data to standardize the use of MILS in liver tansplant (LT) recipients and define its safety and efficacy.

Aim

This study aims to assess the feasibility, safety, and outcomes of minimally invasive liver resections in LT patients, focusing on perioperative and postoperative outcomes, complications, and survival. Additionally, it seeks to identify factors predicting complications and poorer outcomes.

Methods

This is a retrospective international multicenter study under the European-African Hepato-Pancreato-Biliary Association (E-AHPBA). All patients who underwent MILS after LT from January 2000 to December 2024 will be included. Data will be collected through predefined electronic case report forms (eCRFs) and anonymized by participating centers. Primary outcomes include feasibility and safety. Secondary outcomes include perioperative complications (classified by Clavien-Dindo), conversions to open surgery, and long-term survival.

Strengths

This is the first large-scale multicenter study addressing minimally invasive liver resections in LT patients, leveraging data from multiple centers to provide robust conclusions. It will establish evidence-based guidelines for MILS in this unique patient population.

Limitations

The primary limitations are inter-center heterogeneity in data collection, surgical protocols, and follow-up strategies, which may influence outcome measures. Retrospective design and variability in surgical indications across centers may also pose challenges.

Ethics

The study has been approved by the Ethics Committee of the lead coordinating center. All data will be anonymized to ensure patient confidentiality, and participating centers will link patient identifiers to unique study IDs for internal reference.

Planning

Data collection will be completed by early 2025, with analysis and manuscript preparation by the end of 2025. Results will be disseminated through publications in peer-reviewed journals and international conferences.

2. INTRODUCTION

Minimally invasive liver surgery (MILS) has transformed hepatic surgical care, offering reduced morbidity, quicker recovery, and shorter hospital stays compared to open surgery. These benefits are particularly relevant in patients with prior liver transplantation (LT), a group traditionally managed with open procedures due to the complexity and risks involved.

Recent reports highlight successful cases of MILS in LT recipients, demonstrating its feasibility and safety in managing post-transplant complications, reoperations, and graft explantation/reimplantation. Despite promising outcomes, robust data is lacking to establish standardized protocols and define its role in LT patients.

This study seeks to address this gap by collecting and analyzing multicenter data on minimally invasive hepatic resections in LT recipients to advance clinical understanding and develop evidence-based guidelines.

3. METHODS

3.1 Patients and Design

This is a retrospective, international multicenter study under the auspices of participating centers represented by members of the European-African Hepato-Pancreato-Biliary Association (E-AHPBA). All patients undergoing minimally invasive liver resections post-LT between January 2000 and December 2024 will be included. The study aims to evaluate surgical outcomes, complications, and conversions.

3.2 Inclusion criteria

Inclusion criteria

Patients with a history of liver transplantation.

Underwent minimally invasive liver resections during the study period. Including patients in whom a mini-invasive approach was attempted but conversion to open surgery was needed.

Exclusion criteria

Patients without a history of LT.

Procedures performed using open approaches.

Insufficient clinical or follow-up data.

3.3 Definitions

Patients' comorbidities are summarized according to Charlson Comorbidity Index. Intraoperative complications are categorized according to Satava's classification. Postoperative complications are scored and classified using the Clavien-Dindo classification of surgical complications. Major complications are defined as Clavien-Dindo grade IIIa or higher.

Perioperative variables for surgeries were analyzed, covering demographic information, preoperative assessments, surgical details, pathological findings, and short-term outcomes. Preoperative variables included age, gender, body mass index (BMI), American Society of Anesthesiologists Physical Status classification (ASA), Child-Pugh score, history of previous abdominal or hepatic surgery, or prior neoadjuvant therapy, along with the surgical indication. Intraoperative variables included type of hepatic resection, resected segments, concomitant surgery, Pringle maneuver, operation time, blood loss, and transfusions. Postoperative variables collected included postoperative length of stay and complications classified according to the Clavien-Dindo classification. The difficulty of hepatic resections was defined according to the revised IWATE scoring system presented at the Morioka consensus conference, where a score of 0-3 is classified as low difficulty, 4-6 as intermediate difficulty, 7-9 as advanced difficulty, and 10-12 as expert difficulty. The nomenclature for hepatic resections in this study was based on the Brisbane terminology approved in 2000 by the Scientific Committee of the International Hepato-Pancreato-Biliary Association (IHPBA)

3.4 Objectives

Primary objectives

Assess the feasibility and safety of minimally invasive hepatic resections in LT patients.

Secondary objectives

Evaluate perioperative outcomes, including morbidity, mortality, and hospital stay. Identify factors predictive of complications and poorer outcomes.

3.5 Data collection

Each participating center will appoint a coordinator responsible for study-related communication and collect anonymized patient data, including demographics, surgical details, complications, and follow-up information. Data will be submitted via a secure online platform (REDCap). Key variables to be collected

include patient demographics and comorbidities, surgical approach (laparoscopic/robotic), operative time, blood loss, transfusion requirements, postoperative complications, readmissions, and long-term outcomes.

3.6 Ethics

Approval from Ethics Committee of Clinic and University Virgen de la Arrixaca Hospital will be obtained. All data will be collected anonymously, without patient identifiers. Participating centres will be asked to link the patient's local medical record numbers to an anonymous study patient ID. This information will be stored locally at the responsibility of participating centres. In case additional data extraction is needed, participating centres may be asked to re-identify the patient based on the study patient ID.

All amendments to the protocol will be discussed with the Clinic and University Virgen de la Arrixaca Hospital. Advice will be taken on the regulatory approvals required for the amendments. Amendments submitted for regulatory review will not be implemented until the necessary regulatory approvals are received.

3.7 Statistical analysis

Data will be analyzed using R (R-2.14.1 2011 software (The R Foundation for Statistical Computing). Student's t, Mann Whitney U, Chi-square, or Fisher's exact tests will be used as appropriate. Categorical data will be expressed as frequency and percentage. Continuous data will be expressed either as mean and standard deviation or as median and interquartile range depending on the distribution of the data. Subgroups will be performed to compare characteristics and treatment outcomes, using Chi-square test, Mann-Whitney U test and Kruskal Walls test as appropriate. Alpha < 0.05 will be used to indicate statistical significance.

Long Term Data Storage

De-identified data will be stored on a secure password-protected database and for 10 years after study findings are published to ensure that findings are verifiable. We propose the duration of 10 years as this is very valuable data from an international collaboration of multiple centers, and we anticipate that elements of the data collected could be analysed again in the future for validation of any newer findings that emerge in the literature, to maximise the use of this precious resource and avoid duplication of effort to collect such data again.

4. AUTHORSHIP AND PUBLICATION POLICY

Authorships will be based on the International Committee of Medical Journal Editors (ICMJE) guideline (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html).

Centres providing at least 5 cases will be eligible for 1 authorship position, with eligibility for 2 authorship positions when providing at least 5-15 ASCP cases. These figures should be changed if recruitment levels are better/worse than expected.

Each participating centre will decide internally which local investigator will be listed as co-author. The first authorship position is reserved for the study coordinators (APC). Principal investigators (MSM and JMRA) will be listed as senior authors in the last position. All other authors will be listed according to the number of patients included. Any publication, presentation or abstract on collected data will be delegated to all authors. Each centre remains the possessor of their own data and additional reports on data collected will only be conducted in case of written author permission.

5. REFERENCES

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Appendix 1

Baseline and outcome variables

Table 1. Variables to identify

VARIABLE	FORMAT
1. GENERAL DATA	
1.1 Hospital	Hospital Name
1.2 Case ID	Hospital ID
2. PATIENT DEMOGRAPHICS	
2.1 Gender	M/F
2.2 Ethnic	Asian/Caucasian/African/Latin/Other
2.3 Date of Birth	DD/MM/YYYY
2.4 Age at Operation	Calculation
2.5 Height	cm
2.6 Preoperative Weight	kg
2.7 BMI	Calculation
2.8 ASA Score	I/II/III/IV/V/Unknown
2.9 Pre-transplant Diagnosis	Free text
2.10 Transplant Date	DD/MM/YYYY
2.11 Comorbidities (CCI)	See details below
2.11.1 Prior myocardial infarction	N/Y
2.11.2 Chronic liver disease	N/Y
2.11.3 Diabetes	N/Y
2.11.4 Renal disease	N/Y
3. PREOPERATIVE DATA	
3.1 Preoperative Symptoms	Abdominal pain/Nausea/Jaundice/Other
3.2 Preoperative Lab Results	
3.2.1 Bilirubin	mg/dL
3.2.2 INR	Ratio
3.2.3 Platelets	$x10^3/\mu L$
3.2.4 Liver enzymes (ALT/AST)	U/L
4. INTRAOPERATIVE DETAILS	
4.1 Surgical Approach	Laparoscopic/Robotic
4.2 Type of Resection	Segmentectomy/Wedge resesction/LLS/Hemihepatectomy/Other
4.3 Intraoperative Complications	None/Satava Grade 1-3
4.4 Conversion to Open Surgery	N/Y
4.4.1 Reason for Conversion	Bleeding/Adhesions/Insufficient overview/Other (Free text)
4.5 Iwate	Score
5. POSTOPERATIVE DATA	
5.1 ICU Admission	N/Y
5.2 Length of ICU Stay	Days
5.3 Hospital Stay	Days

5.4 Postoperative Complications	Clavien-Dindo (I/II/III/IV/V)
5.4.1 Specific Complications	
5.4.1.1 Bile Leak	No/Grade A/B/C
5.4.1.2 Postoperative Hemorrhage	No/Grade I/II/III
5.4.1.3 Infections (UTI/Pneumonia)	N/Y
6. HISTOPATHOLOGY	
6.1 Tumor Location	Segment/Region
6.2 Size of Lesion	mm
6.3 Margin Status	R0/R1/R2
6.4 Vascular/Lymphatic Invasion	N/Y
7. FOLLOW-UP	
7.1 Date of Last Follow-up	MM/YYYY
7.2 Survival	Alive/Deceased
7.2.1 Cause of Death	Free text
7.3 Recurrence	Local/Extrahepatic/Both
7.3.1 Location of Recurrence	Free text
7.4 Adjuvant Therapy	N/Y
7.4.1 Type of Adjuvant Therapy	Free text

Appendix 2

Classifications

1) Charlson Comorbidity Index *(Roffman C, Buchanan J, Allison G.T. Charlson Comorbidities Index. J Physiother. 2016; 62(3): 171).*

COMORBIDITY	SCORE
Prior myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Rheumatologic disease	1
Peptic ulcer disease	1
Mild liver disease	1
Diabetes	1
Cerebrovascular (hemiplegia) event	1
Moderate- severe renal disease	1
Diabetes with chronic complications	2
Cancer without metastases	2
Leukemia	2
Lymphoma	2
Moderate or severe liver disease	3
Metastatic solid tumor	6
Acquired immuno- deficiency syndrome (AIDS)	6

2) Surgical complications. Clavien- Dindo classification *(Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004; 240(2): 205-13).*

CLAVIEN-DINDO	DESCRIPTION
Grade I	Any deviation from the normal preoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs such as antiemetics, antipyretics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade IIIa	Surgical, endoscopic or radiological intervention that is not under general anesthesia.
Grade IIIb	Surgical, endoscopic or radiological intervention that is under general anesthesia.
Grade IVa	Life- threatening complication requiring intermediate care or intensive care unit management, single organ dysfunction (including dialysis, brain hemorrhage, isquemic stroke, and subarrachnoidal bleeding).
Grade IVb	Life- threatening complication requiring intermediate care or intensive care unit management, multi-organ dysfunction (including dialysis).

Grade V	Death of a patient.

3) Iwate Model for Predicting the Difficulty of Laparoscopic Liver Resection

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