Original Article

Enhanced recovery after liver transplantation—a prospective analysis focusing on quality assessment

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Background: Enhanced Recovery After Surgery (ERAS) is a multimodal approach for almost all types of surgical procedures, including liver transplantation (LTx). We developed an ERAS protocol for LTx based on previous experience and assessed it using benchmarks from the German Institute for Quality Management and Transparency in Healthcare (IQTIG).

Methods: An ERAS protocol was developed and implemented in our center since 2018 for LTx, including preoperative, intraoperative, and postoperative procedures. From January 2021 to December 31st 2022, we conducted a prospective analysis including donor and recipient demographics, Model for End-Stage Liver Disease (MELD) score and medical history. Perioperative management, such as operative time, anhepatic phase time, intensive care unit (ICU) stay, morbidity and mortality as well as postoperative hospitalization, readmission and 1-year patient survival, were collected as outcome measures.

Results: Sixty-eight consecutive liver transplant recipients were included. Mean age of the donors was 47 (36–55.5) years old, type of donation was in 41 donation after brain death (DBD), 26 donation after controlled circulatory death (DCD) and 1 donation after brain and cardiac death (DBCD). Mean age of the patients was 49.6 years (range, 26–68 years), 81% were male. The mean body mass index (BMI) of the recipients was 24 kg/m^2 (range, 15–37 kg/m^2), mean MELD score was 15 (range, 6–39), 3 patients had a MELD score higher than 30. Fifty-three patients suffered from hepatitis B virus (HBV) related cirrhosis. Twenty-eight patients had hepatocellular carcinoma (HCC); 5 patients were diagnosed with alcohol related cirrhosis and primary biliary cirrhosis, autoimmune disease and drug induced cirrhosis, undefined cirrhosis, respectively. The mean operation time in our cohort was 6.73 hours, and the average anhepatic phase time

was 68 minutes. No patient had intraoperative hypothermia. Tracheal extubation was performed in the ICU department within 6 hours post operation and the average ICU/intermediate care (IMC) unit stay was 4.5 days (range, 2–14 days). None of the patients required re-intubation. Postoperative complications with a CDC classification > II were seen in 16 patients (23.5%). Mean hospital stay was 21.7 days and readmission rate was 13 (19%). Neither acute rejection nor postoperative mortality during the hospital stay was recorded. One patient died from acute myocardial infarction after discharge.

Conclusions: We developed an ERAS protocol in LTx, consisting of preoperative, perioperative and postoperative management and assessed the quality using benchmarks from IQTIG. Our study revealed that the proposed ERAS approach in LTx is feasible offering the opportunities of enhanced recovery and quality management.

Keywords: Enhanced Recovery After Surgery (ERAS); liver transplantation (LTx); quality management; IQTIG benchmarks

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Introduction

Enhanced Recovery Programs (ERP) or so called Fast-tracking or Enhanced Recovery after Surgery (ERAS) for complex liver surgery led to a significant reduction in perioperative stress, postoperative complications, faster functional recovery, shorter hospital stays and reduced costs (1). The successful application of ERP/ERAS in liver surgery evoked the application of ERAS in liver transplantation (LTx) (1,2). In the 1990s, elements of ERAS were introduced to LTx by Rossaint *et al.* (3,4). A key element in this development was the introduction of Fast-Track Liver Anesthesia using predefined criteria such as transfusion amount, baseline comorbidities and lab values to support individualized decisions for early extubation in order to achieve shorter intensive care unit (ICU) stays (5). Since then, several parameters, such as preoperative nutrition, anesthesia management, early mobilization, feeding and optimal analgesia of patients undergoing LTx, were introduced to ERAS programs (6). Meanwhile, a number of studies have demonstrated that ERAS in LTx is safe and effective and has potential in improving recipient outcomes and optimizing resource utilization, as well as improving patient satisfaction. For instance, Feizpour *et al.* reported that an ERP for LTx was associated with a shorter median ICU and hospital stay, as well as a significant reduction in median direct cost per case (7). A publication by Xu *et al.* reported a significant reduction of the postoperative hospital stay in favor of the ERAS group (14.5 *vs.* 16 d; P<0.001) (8). "*Guidelines for Perioperative Care for Liver Transplantation*: *Enhanced Recovery After Surgery (ERAS) Society Recommendations*", have been drafted by Brustia *et al.* in 2022 and reviewed by a wide international panel of experts applying the Delphi method (6,9). Due to the lack of a standardized ERAS protocol and inclusion criteria of LTx patients, the authors of the publication recognized that there lacks strong evidence in ERAS in LTx (6). Therefore, the value and potential developments of ERAS should be

Highlight box

Key findings

- The proposed Enhanced Recovery After Surgery (ERAS) protocol for liver transplantation (LTx) in this study can provide a safe management tool to monitor the patient and provide quality service with low morbidities and mortality throughout the observation period.

What is known and what is new?

- The ERAS protocol clearly indicated a benefit to measure and improved quality management for patients compared with benchmarks of the German Quality Assessment by the German Institute for Quality Management and Transparency in Healthcare.
- The study revealed that ERAS in LTx provides a safe management tool to monitor patients throughout the whole hospital stay providing quality service with low morbidities and absence of mortality.

What is the implication, and what should change now?

- The proposed ERAS approach for LTx in this study demonstrates that its use improves patient management and outcomes.

further investigated for liver transplant patients.

In this context, we describe an ERP/ERAS in LTx in our center in China based on previous experience in the past decades. There were several confounding factors in the introduction of an ERP/ERAS protocol, acknowledging the types of donors [donation after controlled circulatory death (DCD), donation after brain death (DBD), donation after brain and cardiac death (DBCD)], aspect of regional donation, training of anesthesia in order to provide Fast-Tracking Anesthesia, training of ICU staff as well as training of senior and junior members of the team becoming aware of rapid changes in patients after major surgery exposed to immunosuppression in recipients displaying different health and physiological features due to their primary disease as well as their comorbidities. In addition we applied bench marks (death during operation, in-hospital mortality, postoperative hospital stay, 1-year survival) used in the Quality Assessment of liver transplant patients as used and reported by the Institut für Qualitätssicherung und Transparenz im Gesundheitswesen (IQTIG) in Germany (10). We present this article in accordance with the STROCSS reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-24-349/rc).

Methods

ERAS protocol

An ERAS protocol had been previously developed and implemented, based on standard operating procedures (SOPs) generated in Halifax, NS, Canada, at the QEII Clinic and the UKE in Hamburg, Germany between 2003 and 2017. The ERAS Protocol was separated in (I) preoperative management, (II) perioperative management including donor, operation, anesthesia and intraoperative management. This protocol was developed and implemented for LTx in our center between 2018–2021. Likewise, we used this protocol in analogy in ultra-radical surgery for ovarian cancer in collaboration with the Department of Gynecology (11).

Donor and patients

All transplantations and organ donations were approved by the hospital ethics committee of The First Affiliated Hospital of USTC and in accordance with the Declaration of Helsinki (as revised in 2013) and the Declaration of Istanbul. Written informed consent of each patient was given before operation. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of the USTC, within University of Science and Technology of China (2024-RE-107). From January 1, 2021 to December 31, 2022, 73 adult orthotopic LTx were performed in our center. Sixty-eight were enrolled in the prospective evaluation. Five patients who received second LTx (n=1), living donor liver transplantation (LDLT) (n=1), split LTx (n=1) or were discharged from the hospital against medical advice (n=2) were excluded from this prospective analysis.

Preoperative management

The ERAS protocol includes preoperative, perioperative, and postoperative guidelines and SOPs, which are shown in *Tables 1-3*. For preoperative management, a structured evaluation protocol prior to listing for LTx is done. Briefly, all potential patients for LTx are evaluated in the clinic of hepatobiliary surgery and transplantation. The standard assessment items for patients are provided in *Table 1*, including demographic data, primary liver disease, medical history, past history, family history, routine laboratory test, imaging test, Model for End-Stage Liver Disease (MELD) score etc. Personalized assessment is carried out in patients with uncommon liver disease or complex disease status. After completion of the assessment, indication for listings is discussed by a multidisciplinary conference with participation of doctors from hepatobiliary surgery and transplantation, infectious disease, gastroenterology and anesthesia. The multidisciplinary conference decides regarding eligibility for LTx and the potential recipient is listed at the China Organ Transplant Response System (COTRS). Meanwhile, detailed preoperative counseling is given and informed consent is signed. Once a donor liver is available and allocated, the recipient will be hospitalized for actual lab work-up and if needed actual imaging, counseling with anesthesia, solid food and liquid fasting for no more than 6 hours and no intestinal preparations prior surgery.

Perioperative management (donor, operation, anesthesia and intraoperative management)

All donor livers were from deceased donors (*Table 4*). LT was performed by full size orthoptic LTx. The anesthetic techniques were conducted as previously described (12). Briefly, propofol, fentanyl and succinylcholine were applied to facilitate rapid sequence induction of anesthesia and intubation; then, anesthesia was maintained with isoflurane.

Table 1 Preoperative management

1. Evaluation of liver transplant recipients
   a) Primary diagnosis: liver cirrhosis of all causes, acute liver failure, acute on chronic liver failure, Wilson disease etc.
   b) Medical history: including medication history (immunosuppressor or corticosteroid therapy etc.), operation history (especially abdominal operation, interventional therapy such as TIPS, splenectomy etc.), tuberculosis infection history
   c) Co-morbidity: hypertension, diabetes mellitus, tumor, ascites, hepatic encephalopathy, renal insufficiency etc.
   d) Past history: smoking, drinking, drug use, etc.
   e) Family history: liver disease, cancer, cardiovascular disease, mental disease, diabetes mellitus, etc.
   f) Physical examination: photograph from clavicle to symphysis pubis, chest circumference on the nipple level and abdomen circumference on the umbilicus level
   g) Routine laboratory test
      i. Complete blood count: including WBC, Hb, PLT, etc.
      ii. Biochemistry test; glycosylated hemoglobin test if elevated fasting glucose is detected
      iii. Coagulation function: INR, PT, etc.
   h) Virological test: including the serological test of HAV, HBV, HEV, HCV, HIV, CMV, EBV, HSV, and TORCH etc.; if the serological test of HBV, HBV or CMV is positive, then quantitative detection of indicated viral DNA will be given
   i) Tumor marker test: such as AFP, CA125, CA199, CEA etc. to exclude liver cancer or gastrointestinal tumors
   j) Twice blood type examination
   k) Blood culture: to rule out potential bacterial infection, especially for patients with dialysis treatments
   l) Urine test: including urine routine test, urine protein examination (such as proteinuria and albuminuria); if the patient with positive urine protein examination, consultation from nephrologist will be organized
   m) Stool test: including stool routine test and occult blood test
   n) Sputum test: including sputum culture and fungi examination; if the patients with a history of tuberculosis infection, then, acid-fast smear and tuberculin PPD or T-SPOT test, chest CT scan will be given
   o) Imaging tests
      i. Ultrasound: including hepatobiliary-pancreatic-splenic-abdominal ultrasound and evaluation of hepatic artery, portal vein and hepatic vein by ultrasound
      ii. CT and MRI scanning*: including chest CT scan; abdomen contrast CT or MRI (to evaluate liver cancers, such as HCC, CCA), CTA and CTV; if the patient with liver cancer, chest CT, PET-CT, bone scanning or brain MRI should be given to exclude extrahepatic metastasis or multiple lesions in liver. In addition, gastroscope and colonoscope examination should be given to exclude gastrointestinal cancer. If the patient with dialysis treatments, hepatic encephalopathy or Wilson disease, a head MRI or CT scan should be given to rule out potential infection or intracranial lesions
      iii. ERCP or MRCP: if the patient with hepatolithiasis, primary biliary cirrhosis, or primary sclerosing cholangitis, then, ERCP or MRCP will be given to check the biliary system
   p) Cardiac evaluation
      i. ECG and DCG
      ii. Echocardiogram: if the patient is older than 50 years or with cardiac insufficiency
      iii. If the patients with coronary heart disease, then, coronary arteriography, 24 h dynamic electrocardiogram, stress ECG should be given and consultation from cardiac physician should be organized

Table 1 (*continued*)

Table 1 (*continued*)

- q) Pulmonary evaluation: pulmonary function tests
- r) Dental examination: to prevent potential bacteremia infection from an oral source that could lead to systemic infection
- s) Other evaluation
  - i. Psychological evaluation
  - ii. Nutritional state evaluation
  - iii. Economical state evaluation
- t) MELD score

2. Detailed preoperative counseling and informed consent
3. Preoperative solid food and liquid fasting for 6 hours and no intestinal preparation

*, recommendations for dynamic contrast-enhanced CT and MRI of the liver is present in Tables S1,S2. TIPS, transjugular intrahepatic portosystemic shunt; WBC, white blood cell; Hb, hemoglobin; PLT, platelet; INR, international normalized ratio; PT, prothrombin time; HAV, hepatitis A virus; HBV, hepatitis B virus; HEV, hepatitis E virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HSV, herpes simplex virus; TORCH, toxoplasmosis, rubella, cytomegalovirus and herpes simplex virus; AFP, alpha-fetoprotein; CA125, carbohydrate antigen 125; CA199, carbohydrate antigen 199; CEA, carcinoembryonic antigen; PPD, purified protein derivative; T-SPOT, tuberculosis-specific enzyme-linked immunospot assay; CT, computed tomography; MRI, magnetic resonance imaging; CTA, CT reconstruction of abdominal artery; CTV, CT reconstruction of abdominal vein; PET, positron emission tomography; ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography; ECG, electrocardiograph; DCG, dynamic electrocardiogram; MELD, Model for End-Stage Liver Disease.

Muscular relaxation was maintained using cisatracurium. Fentanyl was reasonably administered so that the total dose did not exceed 10 μg/kg. The muscle relaxant was reversed with neostigmine and glycopyrrolate during closure of skin. During the operation, standard anesthesia monitoring was applied, including pulse oximetry, non-invasive blood pressure, temperature monitoring and warming devices were utilized to prevent hypothermia. The hemodynamic stability was continuously monitored, including the monitoring of invasive arterial blood pressure and central venous pressure (CVP) etc. Thromboelastography (TEG) test was carried out for viscoelastic testing and guiding effective utilization of blood product and antifibrinolytic agents. The detailed protocol for intraoperative management is presented in *Table 2*. The standard surgical technique is described elsewhere (13). During the anhepatic phase, 1.0 g methylprednisolone and 20 mg basiliximab were given. Basiliximab 20 mg was given again at postoperative day (POD) 4. On POD 1, a triple immunosuppressive regimen was started, consisting of tacrolimus bid (monitored according to C0 3–8 ng/mL), mycophenolate mofetil (MMF) (500 mg bid) and corticosteroids (100 mg qd, tapered to 5 mg at POD 7). Patients with hepatocellular carcinoma (HCC) were switched within one week following transplantation from MMF to sirolimus (C0 3–8 ng/mL).

Postoperative management

After operation, tracheal extubation was performed within 6 hours for all transplant patients in the ICU department. The gastric tube was removed within 48 hours after the transplant patients were transferred to the ICU department. During this course, the standard protocol of postoperative care, including physiological monitoring, food intake, laboratory, diagnostic imaging, stress ulcer prophylaxis, analgesia etc., was initiated the details of the postoperative management protocol are provided in *Table 3*.

Outcome

Assessment and comparison of outcome were done by using benchmarks from the German Institute for Quality Management and Transparency in Healthcare (IQTIG). These benchmarks were death during operation (0.89%), in-hospital mortality (11.01%), length of hospitalization (LOS) >41 days (24.86%), 1-year patient survival (82.02%) based on the year 2022 (14).

Data collection

Information regarding patients' characteristics was

Table 2 Intraoperative management

Intraoperative management
(I) Maintenance of intraoperative normothermia
Monitoring temperature of the patients. Warm blanket and warm intravenous fluids are used to keep the temperature of the patients above 35.0 ℃
(II) Urine catheter intubation
Check diuresis hourly to ensure renal function, especially when the vena cava is clamped
(III) Nasogastric intubation
Nasogastric tubes placed during surgery and removed within 48 hours after LTx
(IV) Standard anesthesia
a) Induction of GA: intravenous induction with propofol
b) Maintenance of GA: utilizing inhalational anesthetics (sevoflurane), and non-depolarizing muscle relaxants (rocuronium)
(V) Hemodynamic monitoring
a) Establishing vein channels
i. A central line insertion for CVP monitoring and vasopressor infusion
ii. A large-bore peripheral cannula for rapid blood and fluid infusion
b) Invasive arterial blood pressure measurement via a catheter in the brachial artery
(VI) Intraoperative fluid management
a) Consistent invasive hemodynamic monitoring; applying balanced crystalloid solutions, avoiding massive transfusion and excessive amounts of normal saline
b) Administration of vasoactive substances
(VII) Coagulation management
a) Viscoelastic tests: TEG measurement
b) Avoid hyperfibrinolysis: utilizing antifibrinolytic agents such as administering fibrinogen 24 mg/kg, platelets transfusion, and tranexamic acid
(VIII) Others
a) Constant determination of hemoglobin, hematocrit, electrolytes, base excess and lactate etc.
b) Treat hypocalcemia and maintain K below 4 mEq/L

LTx, liver transplantation; GA, general anesthesia; CVP, central venous pressure; TEG, thromboelastography.

collected, including age at transplant, gender, body mass index (BMI), MELD score, primary diagnosis, blood type. The operative and post-operative characteristics, including anesthetic time, operative time, anhepatic phase time, the volume of intraoperative blood transfusion and fluid transfusion, postoperative blood transfusion and ICU stay, postoperative hospital stay, morbidity (classified as Dindo-Clavien Classification) and mortality, were collected. Discharge criteria included closed incision, tolerance for regular diet, stable vital signs, and no complications. All patients were followed-up for 1 year.

Statistical analysis

Continuous variables normally distributed data were expressed as mean ± standard deviation (SD). All measurements and calculations were analyzed using GraphPad prism 8 (GraphPad Prism Software Inc., San Diego, CA, USA).

Results

Donor demographics

Mean age of the 68 donors was 47 years (range, 36–55.5 years)

Table 3 Postoperative management

(I) Post-operative physiological monitoring for all operation patients

a) Vital signs monitoring: including body temperature, blood pressure, heart rate, respiratory rate, oxyhemoglobin saturation, CVP, blood glucose; 1 time every day

b) Daily wound and dressing check; the first dressing change is given on the second day post operation.

c) Observe and record the nature and amount of 24 hours' fluid drainage

d) Mobilization and respiratory training, for example, using a "Triflow" breath apparatus

e) Daily weight measurement

f) Physical therapy: especially for patients with sarcopenia

g) Daily input and output monitoring

(II) Food intake

a) Fast: e.g., kidney living donor

i. Drink, when the recipient is awake and oriented; if no nausea, provide with light food post operation

b) Minor operation: e.g., LapCHE, hernia, KTx

ii. 6 hours post operation, provide with 3 cups of water

iii. At post operation day 1, provide with fruit tea, broth (chicken etc.), rusk etc. (named TBR)

iv. At post operation day 2, light meal (e.g., rice, porridge, noodle, fish soup etc.)

c) Liver resection without BDA, and operations without intestinal involvement

v. Day 0–2: 2 cups of tea, plus infusion of 1 liter 5% glucose solution and 0.5-liter glucose and sodium chloride injection supplied with vitamin B6, vitamin C and proper potassium chloride

vi. Day 3: 3 cups of tea, plus infusion of 1 liter glucose and sodium chloride injection supplied with vitamin B6, vitamin C and proper potassium chloride

vii. Day 4: TBR

viii. Day 5: light meal

d) Segmental liver resection and operation with intestine intervention

ix. Day 0–4: 2 cups of tea, plus infusion of 1 liter 5% glucose solution and 0.5-liter glucose and sodium chloride injection supplied with vitamin B6, vitamin C and proper potassium chloride

x. Day 5: 3 cups of tea and 2 energy drinks (0.5 liter glucose and sodium chloride injection supplied with vitamin B6, vitamin C and proper potassium chloride.

xi. Day 6: TBR

xii. Day 7: light meal

(III) Diagnostic measures

a) During the first week after operation, monitor the count of blood cells, biochemistry and trough level of immunosuppression medication every other day

b) Monitor CMV PCR every 7 days

c) Monitor 24 hours of creatinine clearance once a week

Table 3 (*continued*)

Table 3 (*continued*)

(IV) Stress ulcer prophylaxis

a) PPI. For instance, administrate 40 mg pantoprazole orally or intravenously daily from the first day post operation

b) Administration of sucralfate for 6 days via gastric tube for Whipple with gastropancreaticostomy

(V) Analgesia

a) Minor procedure: administrate parecoxib 40 mg or flurbiprofen 50 mg intravenously for 2 times a day for 24 hours; if necessary, then, administrate codeine 15 mg orally for 4 times a day for 3 days

b) Large intervention: administrate codeine 15 mg orally for 4 times, together with 40 mg parecoxib or 40 mg flurbiprofen 2 times a day for intravenously 3 days

c) As an alternative to paracetamol, administration of 400 mg ibuprofen 3 times a day

(VI) Anticoagulation

a) Standard procedure: for patient at risk of thrombosis, administrate 40 mg clexane by subcutaneous injection on the day before surgery; if necessary, communicate with anesthetist and surgeon. In all significant liver procedures clexane begin before operation, no PD anesthesia

b) Remove thrombosis stockings up to thighs twice a day for 30 minutes

(VII) Immunosuppression

a) Start with administration of tacrolimus 3 mg every 12 hours orally and monitor the C-trough level of tacrolimus; maintain trough level between 3–8 ng/mL (aim to 5 ng/mL)

b) Administrate MMF 500 mg every 12 hours orally switch to sirolimus POD 7 in HCC patients, C-trough 3–8 ng/mL

c) Administrate simulect 20 mg during operation and at 4 days post of operation intravenously

d) Administrate methylprednisolone 500, 100, 80, 60, 40, 20 and 10 mg intravenously at postoperation day 0, 1, 2, 3, 4, 5 and 6, respectively; and 5 mg orally by postoperation day 7

(VIII) Antibiotics, antivirals and antimycotics

a) Administration of antibiotics for 10 days

b) Administration of valganciclovir 900 mg every day when the donor or recipient is CMV positive; check renal function of the recipient and adjust the dose of valganciclovir according the GFR of the recipient

c) Anti-hepatitis B virus treatment in HBV positive donor or recipient

i. Administration of 2,000 IU HBV immune globin intravenously during anhepatic phase and at 1st to 5th post-operation day; then, given 800 IU HBV immune globin intramuscular injection 2 times a week for 5 weeks

ii. Administration of entecavir 0.5 mg orally everyday beginning at post-operation day 1

d) Antimycotic medication is given upon individual indication

(IX) Rehabilitation training

a) Respiratory treatment: blow a balloon 10 minutes per hour

b) Ambulation starts at post-operation day 1

CVP, central venous pressure; KTx, kidney transplantation; TBR, tea, broth and rusk; BDA, biliodigestive anastomosis; CMV, cytomegalovirus; PCR, polymerase chain reaction; PPI, proton pump inhibitor; PD, peridural; MMF, mycophenolate mofetil; POD, postoperative day; HCC, hepatocellular carcinoma; GFR, glomerular filtration rate; HBV, hepatitis B virus.

Table 4 Donor demographics (N=68)

Donor characteristics	Values
Age (years)	47 (36–55.5)
Male	58 (85.0)
Cause of death	
Cerebral hemorrhage	37 (54.4)
Cerebral infarction	6 (8.8)
Craniocerebral trauma	21 (30.9)
Acute organophosphorus pesticide poisoning	1 (1.5)
Carbon monoxide poisoning	1 (1.5)
Hypoxic-ischemic encephalopathy	1 (1.5)
Other	1 (1.5)
Blood type	
A	17 (25.0)
B	16 (23.5)
AB	8 (11.8)
O	27 (39.7)
Donor type	
DBD	41 (60.3)
DCD	26 (38.2)
DBCD	1 (1.5)
Laboratory test	
AST (U/L)	101.8±174.3
ALT (U/L)	70.9±96.5
TBIL (μmol/L)	18.6±13.0
Alb (g/L)	33.6±8.0
INR	1.18±0.2
Crea (μmol/L)	122.6±134.0
Serum sodium (mmol/L)	148.8±9.2
Serum potassium (mmol/L)	4.2±0.7

Data are presented as mean (IQR) or n (%) or mean ± SD. DBD, donation after brain death; DCD, donation after controlled circulatory death; DBCD, donation after brain and cardiac death; AST, aspartate transaminase; ALT, alanine transaminase; TBIL, total bilirubin; Alb, serum albumin; INR, international normalized ratio; Crea, creatinine; IQR, interquartile range; SD, standard deviation.

and 58 were male (85%). Cause of death was in 37 donors' cerebral hemorrhage and in 21 craniocerebral trauma, in 6 cerebral infarction, acute organophosphorus pesticide intoxication, carbon monoxide inhalation, hypoxic-ischemic encephalopathy and one unknown were n=1 each. Blood type O was dominating with n=27 (39.7%) followed by A [17 (25%)], B [16 (23.5%)] and AB [8 (11.8%)]. Forty donors were DBD, 26 DCD and 1 donor was DBCD. Laboratory tests showed typical values for donors (*Table 4*).

Recipient demographics

A total of 68 patients who underwent LTx were included into the prospective evaluation of the ERAS protocol. Demography and general characteristics of recipients are presented in *Table 5*. Mean age of the patients was 49.6 years (range, 26–68 years) and the majority of patients (81%) were male. Mean BMI was 24 kg/m^2 (range, 15–37 kg/m^2), mean MELD score was 15.4 (range, 6–39), 3 patients had an MELD score higher than 30. Hepatitis B virus (HBV) related cirrhosis was diagnosed in 53 recipients of whom 24 had in addition HCC; four more patients had HCC related to other primary diseases (*Table 5*). Five patients were diagnosed with alcohol related cirrhosis and primary biliary cirrhosis, autoimmune disease and drug induced cirrhosis, undefined cirrhosis, respectively. All patients with HCC were within the Milan criteria prior to transplantation and had received downstaging. Blood type A was present in 29, B in 17, AB in 9 and O in 13 recipients. The majority of recipients had cholecystolithiasis n=14 as comorbidity, hypertension was diagnosed in 7 patients and diabetes mellitus II in 6 patients. Spontaneous bacterial peritonitis had been diagnosed and treated prior to transplantation in 4 patients. At the time of transplantation none of the patients suffered from an infection.

Perioperative and postoperative outcomes

The perioperative and postoperative outcomes of patients are given in *Table 6*. All patients received blood products, such as packed red blood cells (PRBC) or fresh frozen plasma (FFP), to maintain circulatory stability intraoperatively in addition with crystalloids (mean 2,218.7 mL). A mean of 5.6 units of PRBC was given and 857 mL FFP. Twenty patients and 18 patients with platelet count less than 50×10^9/L and prolonged prothrombin time received intra- and post-operatively platelet transfusion, respectively. The mean operation time in our cohort was 6.73 hours, and the average anhepatic phase time was 67.51 minutes. None of the patient suffered from intraoperative hypothermia. Tracheal

Table 5 Recipient demographics

Recipient characteristics	Values
Age (years)	49.58±9.32 [26–68]
Gender	
Male	55 (80.9)
Female	13 (19.1)
BMI (kg/m^2)	24±4 [15–37]
MELD score	15.41±8.09 [6–39]
Primary diagnosis	
Alcohol-cirrhosis	5 (7.3)
HBV-cirrhosis	25 (36.7)
HBV-cirrhosis/CLF	1 (1.5)
HBV-cirrhosis/ACLF	2 (2.9)
HBV-cirrhosis/HCC	24 (35.3)
ACLF/HCC	1 (1.5)
Alcohol-cirrhosis/HCC	1 (1.5)
HCC	2 (2.9)
HBV-cirrhosis/Wilson disease	1 (1.5)
Primary biliary cirrhosis	1 (1.5)
Autoimmune liver disease	1 (1.5)
ALF	1 (1.5)
CLF	1 (1.5)
Drug-induced cirrhosis	1 (1.5)
Undefined cirrhosis	1 (1.5)
Co-morbidity	
Cholecystolithiasis	14 (20.6)
Hypertension	7 (10.3)
Diabetes mellitus	6 (8.8)
Spontaneous bacterial peritonitis	4 (5.9)
Hepatic encephalopathy	2 (2.9)
Nephrotic syndrome	1 (1.5)
Ankylosing spondylitis	1 (1.5)
Interstitial pneumonia	1 (1.5)
Infective endocarditis	1 (1.5)
Fungal septicemia	1 (1.5)
HCC staging—TNM (pathology)	
Tx[†]	8
T1a	1
T1b	4
T2	15
T3	0
T4	0
N0	28
M0	28
Gx[‡]	12
G2	11
G3	5
AFP (μg/L)	
Before transplantation	68.13±150.09
After transplantation[§]	6.33±11.47

Data are presented as mean ± SD [range] or n (%). [†], no tumor found; [‡], n=4 patients without classification, n=8 no tumor; [§], patient with HCC recurrence and AFP 29,703.6 μg/L not included. BMI, body mass index; MELD, Model for End-Stage Liver Disease; HBV, hepatitis B virus; CLF, chronic liver failure; ACLF, acute-on-chronic liver failure; HCC, hepatocellular carcinoma; ALF, acute liver failure; TNM, tumor-node-metastasis; AFP, alpha-fetoprotein; SD, standard deviation.

extubation was performed in the ICU department within 6 hours post operation and subsequently the patients were transferred to the intermediate care (IMC) unit. Average stay in ICU/IMC was 4.6 days (range, 2–14 days), only one patient stayed longer than 9 days on the ICU. None of the patients required re-intubation. The immunosuppression was started on POD 1 with tacrolimus (3.8 ng/mL C0) in combination with MMF and rapid tapering of steroids by POD 7 to 5 mg/d. Basiliximab was given on POD 0 and 4, 20 mg intravenous (iv). One-week post-operation Tac C0 was 7.4±2.9 and at time of discharge 6.7±1.8 ng/mL. No episode of acute rejection was observed within the first 365 days. Sixty-six patients were discharged within 40 days after transplantation with a mean stay of 21.7 days in hospital, 2 patients [biliary stricture and portal vein (PV)

Table 6 Intraoperative and postoperative variables

Variables	N	Values
Intraoperative		
PRBC (U)	68	5.7±3.7 [1.5–16]
FFP (mL)	68	857.1±425.6 [200–2,150]
PLT (U)	20	1.3±1.5 [1–5]
Crystalloids (mL)	68	2,118.7±793.7 [500–4,850]
Skin to skin time (hours)	68	6.7±1.2 [5–10.3]
Anhepatic phase time (min)	68	67.5±10.3 [43–95]
Hypothermia	0	
Average CVP (mmHg)	68	
High		13.3±2.1 [–7 to 26]
Low		4.2±3.3 [–16 to 9]
Average artery BP (mmHg)	68	
High		118.1±23.3 [80–180]
Low		50.9±9.7 [30–70]
Postoperative		
PRBC (U)	38	2.1±2.4 [1.5–10]
FFP (mL)	32	278.4±379.5 [100–1,600]
PLT (U)	18	0.7±1.9 [1–10]
Reintubation	0	
Postoperative ICU/IMC stay (days)	68	4.6±1.7 [2–14]
<4	38	
>4–8	29	
>9	1	
Length of hospitalization (days)	68	21.7±8.1 [9–53]
<41	66	
≥41	2	
Immunosuppressive drugs C0 level		
Tacrolimus (ng/mL)		
1 week post operation	68	7.4±2.9
At time of discharge	68	6.7±1.8
Sirolimus		
At time of discharge	28	7.9±5.6
Acute rejection	0	
Readmission (POD <365 days)	13 (19%)	
Acute myocardial infarction	1	22
Pneumonia	1	22
HCC recurrence	1	28
PV and BD stenosis	1	33
PV and BD stenosis	1	35
ITBL	1	44
BD stenosis	1	46
Cholangitis	1	48
PV stenosis	1	57
COVID-19 infection	1	75
BD stenosis	1	78
Craniocerebral trauma	1	106
BD stenosis	1	126

Values are presented as mean ± SD [range] or value (POD). PRBC, packed red blood cells; FFP, fresh frozen plasma; PLT, platelet; CVP, central venous pressure; BP, blood pressure; ICU, intensive care unit; IMC, intermediate care; POD, postoperative day; HCC, hepatocellular carcinoma; PV, portal vein; BD, bile duct; ITBL, ischemic-type biliary lesions; COVID-19, coronavirus disease 2019; SD, standard deviation.

stenosis (n=1), abdominal bleeding (n=1)] stayed longer than 41 days (*Table 7*) to a maximum of 53 days. Postoperative complications with a Clavien-Dindo classification (CDC) > II were seen in 16 patients (23.5%). Biliary strictures in terms of a stenosis of the anastomosis was documented in 9 patients and treated by endoscopic retrograde cholangiopancreatography (ERCP), dilatation and stenting. Pleural effusions were observed in 5 patients with associated atelectasis of the right lower lobe of the lung, followed by bronchoalveolar lavage (BAL) (n=1) and if necessary, antibiotic treatment based on antibiogram given by culture. Portal vein stenosis was observed in 2 patients and treated with angioplasty and stenting. Bleeding needing intervention (CDC IIIb) was diagnosed in two cases and controlled by surgical respectively radiological (coiling) intervention. No postoperative mortality was reported during the hospital stay, one patient was readmitted

Table 7 Postoperative complications (Clavien-Dindo classification)

No.	CDC	Complication	Intervention	POD
1	IIIb	Biliary stenosis	ERCP/stent	12
		Portal vein stenosis	Angioplasty/stent	
2	IIIa	Biliary stenosis	ERCP/stent	15
3	II	Thrombocytopenia	Blood transfusion	18
4	IIIb	Biliary stenosis	ERCP/stent	18
		Intra-abdominal hemorrhage	Operation	
5	I	Deep venous thrombosis of left leg	Anticoagulation	25
6	IIIa	Pleural effusion	Thoracic drainage	26
7	IIIa	Biliary stenosis	ERCP/stent	26
8	IIIa	Pleural effusion	Thoracic drainage	27
9	IIIa	Biliary stenosis	ERCP/stent	27
10	IIIa	Pleural effusion	Thoracic drainage	28
11	I	Leukopenia due to hypersplenism	–	30
12	IIIa	Pleural effusion and ascites	Thoracic and peritoneal drainage	30
13	IIIa	Biliary stenosis	ERCP/stent	32
14	IIIa	Biliary stenosis	ERCP/stent	33
		Pleural effusion	Thoracic drainage	
15	I	Pulmonary arterial hypertension	Sildenafil	35
16	II	Elevated level of liver enzymes at the 20th day post LTx and spontaneously decreased after 3 days	Liver biopsy shows lymphocyte infiltration and hyperplasia of fibrous tissue in the portal area	37
17	II	Abdominal bleeding	Blood transfusion	41
18	IIIb	Biliary stenosis	ERCP/stent	43
		Portal vein stenosis	Dilatation/angioplasty	
		Poor incision healing	Dressing change	
19	IIIb	Biliary stenosis	ERCP/stent	53
		Intrahepatic hematoma	Hepatic artery embolization	

CDC, Clavien-Dindo classification; LTx, liver transplantation; ERCP, endoscopic retrograde cholangiopancreatography; POD, postoperative day.

one week after an uneventful course and discharge due to an acute myocardial infarction of which he died. In his pretransplant workup, no evidence for cardiovascular disease had been diagnosed. In 28 patients with HCC histopathology confirmed Milan staging as T1–T2, N0, M0. Patients with HCC were switched from MMF to sirolimus at POD 7, maintaining C0 of 3–8 ng/mL with a C0 of 7.9±5.6 ng/mL at the time of discharge. These patients received in addition sulfamethoxazole prophylaxis for 3 months. Following discharge, 13 (19%) patients needed readmission (*Table 6*) for bile duct (BD) stenosis (n=3), PV and BD stenosis (n=2), acute myocardial infarction, pneumonia, HCC recurrence [increased alpha-fetoprotein (AFP)], cholangitis, PV stenosis, ischemic-type biliary lesion (ITBL), coronavirus disease 2019 (COVID-19) infection respectively craniocerebral trauma (each n=1).

Discussion

ERAS is by now a well-validated multimodal approach for almost all types of major surgical procedures, including liver surgery, colorectal surgery, thoracic surgery, urology, gynecology etc. (6). End stage liver diseases in China and western countries may differ in terms of underlying disease, comorbidities, metabolic stress response and organ-specific complications (15,16). To date, the application of ERAS in LTx is less reported in China. Therefore, it is unclear whether ERAS elements validated in western countries can be extrapolated and applied for LTx in China, hence we prospectively evaluated an ERAS protocol in our center with a focus on a patient related individualized approach and quality measures for outcome. One of the key factors in implementing ERAS protocols is the understanding of the philosophy behind ERAS by both patients and caregivers (17,18). The goal of the ERAS approach is to reduce the patients' reaction to surgical stress, promote better utilization of medical resources and thus improve patient recovery and safety. Introduction of Fast-Track Anesthesia and the successful application of ERAS in abdominal surgery promoted the utilization in LTx. Since the early 1990s, different ERAS protocols in LTx have been developed and compared to conventional cares, indicating clear benefits, but showing at the same time the need for a more comprehensive approach (19). Independent studies have validated that preoperative nutrition, early mobilization and feeding, and particular optimal analgesia are helpful to improve quality of care with shorter ICU stay and hospitalization, associated with lower total treatment costs of patients undergoing LTx.

LOS is one of the critical issues a number of ERAS protocols are aiming for. Here we put a patient centered treatment into the foreground, focusing on the opportunity to safely discharge the patient and keeping the readmittance rate low. Our readmittance rate was 19% and mainly related to postoperative complications, developing after discharge.

Measuring outcomes in LTx so far has been done by registries looking into patient and graft survival. Here we choose to compare outcome parameters with benchmarks of the quality assessment in LTx used by the IQTIG in Germany. These benchmarks in 2022 are death during operation (0% *vs.* 0.89%), in-hospital mortality (0% *vs.* 11.01%), LOS >41 days (2.9% *vs.* 24.86%), 1-year patient survival (98.25% *vs.* 82.02%) (14). The primary approach using an ERAS protocol was to improve quality service for patients in combination with acknowledging particular features of Health services in China resulting in LOS comparable to e.g., Germany: (I) the ideas among medical staff and patients are profoundly traditional; (II) medical administrations do not consider the application of ERAS protocols as the status quo in the hospital, including every involved department; (III) the medical treatment costs are very low in China; (IV) patients from the countryside would prefer not to travel home after surgery and then return for laboratory and particular C0 levels a few days later or weekly in the early phase; (V) the ward beds are cheaper than stays in a hotel and safer for the observation of their conditions until the completion of the initial postoperative care; (VI) patients do not have family physicians in China and if they go home, local hospitals would deny their admission in the presence of any complications; and (VII) insurance companies only pay for hospitalization but not for the costs related to regular visits in clinic (11). Taken together, setting up a transplant center and providing quality care needs modified approaches based on social and cultural backgrounds in order to serve patients in their best interest.

Preoperative evaluation of liver recipients is of paramount significance before LTx and should start with a detailed history (medication history, family history and past history etc.) and physical examination. It should include not only the etiology and status of liver cirrhosis or failure, but should include all major organ systems, particularly renal, cardiac and pulmonary function (20,21). Therefore, for patients with end stage liver disease being waitlisted, essential tests are performed to determine the etiology of liver disease. Additional diagnostic imaging tests, such as ultrasound and contrast-enhanced computed tomography (CT)/magnetic resonance imaging (MRI) particularly in HCC patients are essential and should follow Liver Imaging Reporting and Data System (LIRADS) procedures (19,22). In all 28 patients the radiology assessment was confirmed by pathology. A head MRI or CT scan should be given to rule out potential intracranial infection or bleeding, brain injury etc., especially for patients with previous extracorporeal liver support (23), or with a history of hepatic encephalopathy (24) or Wilson disease (25). Additionally, it has been reported that the prevalence of coronary artery disease in patients with liver cirrhosis is similar to those in the general population and cirrhotic cardiomyopathy shows a prevalence of approximately 50% in patients with chronic liver disease (26,27). Despite a specific evaluation we missed one patient being discharged at POD 15 after an uncomplicated postoperative course and readmitted with acute myocardial infarction one week later.

Therefore, for patients with any history of cardiopulmonary diseases or other chronic ailments (such as diabetes, hyperlipidemia, and severe obesity etc.), an extensive evaluation should include the identification of potential cardiology and pulmonology diseases to make sure the patient can stand the operation. Non-curable extrahepatic malignancies are a contraindication for LTx (28), selective tumor marker tests and positron emission tomography-computed tomography (PET-CT) examination should be performed in patients with a history of malignancies other than HCC. Taken together, listing for LTx should be decided by a multidisciplinary team, including doctors from departments of hepatobiliary surgery and transplantation, anesthesia, infectious disease, gastroenterology, and if necessary, consultation from oncology, cardiology and radiology should be included.

In conventional abdominal surgery, providing information regarding the procedure and details of the patients' postoperative tasks has been supportive in patient's collaboration regarding perioperative feeding, mobilization and respiratory physiotherapy, and thus being helpful to reduce complications after abdominal surgery (29,30). For our center we extrapolated this knowledge to our liver transplant population and performed routinely a detailed and comprehensive preoperative consultation and education. Preoperative fasting, for liquids no more than 2 h and for solid food no more than 6 h prior surgery, has proven to be safe and is recommended for digestive surgery (31). In addition, some research indicated that carbohydrate intake before operation had less perioperative insulin resistance which may facilitate liver regeneration (32). Hence, recipients are given oral bowel preparation by solid food fasting for no more than 6 hours and liquid fasting for less than 2 hours before operation in our center.

Anesthesia management for LTx follows fast tracking protocols as recently summarized in guidelines (33). Key elements (*Table 2*) are a focus on hemodynamic, normothermia and coagulation monitoring including standard monitoring [electrocardiogram (ECG), pulse oximetry, non-invasive blood pressure and temperature], hemodynamic monitoring (CVP, invasive arterial blood pressure, pulmonary capillary wedge pressure, intraoperative fluid management), and neurologic monitoring (bispectral index monitoring anaesthetic depth), etc. (34,35). Hemodynamic instability during LTx is difficult to manage and associated with postoperative morbidity and mortality (36,37). Patients with liver cirrhosis have an abnormal fluid distribution and impaired response to fluid therapy (34,38). Inappropriate fluid supply during operation can have substantial adverse effects, including pulmonary and graft oedema, dilutional coagulopathy and thrombocytopenia, hypovolemia, leading to abnormal gas exchange, disturbance of blood coagulation. Therefore, haemodynamic monitoring, strict intraoperative fluid management and coagulation management is crucial during the whole procedure. As for coagulation management, viscoelastic testing, which reflects the interaction of plasma, blood cells, and platelets, is recommended during a LTx procedure (39). In our center, the mean arterial pressure was maintained higher than 60–65 mmHg and in all cases volume replacement was within published ranges (2,218.7 mL crystalloids, 5.6 units of PRBC and 857 mL FFP). Additionally, a TEG test was used to monitor coagulation and to guide the use of antifibrinolytic agents (fibrinogen/tranexamic acid) and platelet transfusions when indicated. These facts indicated that in our center the use of FFP and PRBC reached a similar level as reported by Zoltan G. Hevesi *et al.* (40) and was no longer used as the main volume expanders. Our results support in addition the notion that the utilization of TEG leads to a significant reduction in blood transfusion as previously reported (41).

During the operative phase maintenance of intraoperative normothermia is strongly recommended. Hypothermia is defined as core body temperature below 36 ℃. Intraoperative hypothermia leads to unfavorable outcomes for patients, such as delayed recovery from anesthesia and increased intraoperative blood loss (42). The latter might be due to 'hypothermia-induced coagulopathy', so called oozing (42), a condition in which a decrease in body temperature below 35 ℃ causes platelet dysfunction and body temperatures below 33 ℃ further disrupt the blood coagulation cascade (43). There are many factors that put patients at high risk of developing hypothermia during LTx operation. These include low operation room temperature, exposure of large area of internal organs, longer surgery time and utilization of large number of unwarmed fluids or blood products. Clinical significance of intraoperative hypothermia is less evaluated in LTx. Paterson *et al.* reported that intraoperative hypothermia during LTx might be an indicator of CMV infection within the 1st month postoperatively and active warming seems to reduce this risk (44). Eun Jung Oh *et al.* showed that patients without prewarming did not recover blood fibrinogen level even after 3 h after graft reperfusion (45). Therefore, we kept the operation room temperature at not less than 26 ℃, and the patient is covered appropriately and supplied with forced

air warming (FAW) and body temperature monitoring is done every 30 minutes. Moreover, intravenous fluids of more than 500 mL are warmed to 37 ℃ in a temperature-controlled cabinet set between 38–40 ℃. Following these principles, we did not observe oozing in our patients.

Early endotracheal extubation is reported since the 1980'ies in cardiac and liver surgery (5,33). Improved technology in surgery and the utilization of faster elimination of anesthetic drugs shortens the duration of operation and patients to regain consciousness, which makes it possible to extubate early after LTx. LTx patients have a long course of disease or co-morbidities, and most of them have a poor basic physical condition; in addition, long duration of surgery and delayed correction of metabolic derangements may prevent early extubation. Physically, prolonged mechanical ventilation may increase right ventricular afterload and even induce venous congestion of the liver graft, while early extubation promotes spontaneously breathing could improve hepatic venous drainage, thereby facilitating early liver graft recovery and regeneration (46). Several studies have reported scoring systems to guide early endotracheal extubation following LTx in selected patients (46-48). The proposed criteria in these studies contain several variables, including the number of packed red cell transfusion, lactate at the end of surgery, duration of surgery, the use of vasoactive drugs at the end of surgery, the MELD score and hospital status of patients before LTx. These results have shown that in selected patients early extubation avoided the medical complications of prolonged ventilation and led to a shorter stay in ICU and significant cost saving (5). In our study, all patients were extubated within 6 hours in the ICU and then transferred to the IMC section stay. Mean total stay was 4.6 days. Our ERAS experience indicated that early extubation after LTx was safe and feasible. Postoperative pleural effusions, atelectasis and infections are common pulmonary complication following LTx (28). LTx patients with pleural effusions are associated with longer hospital length of stay and higher tracheostomy rates (49). Previously, it has been reported that severe pleural effusion may increase the incidence of lung infection in LTx (50) and recipients with pleural effusions had a higher rate of tracheostomy (49). Therefore, we performed a routine CT scan of the lung and sputum culture was routinely taken to rule out pulmonary complications; in addition, we initiated postoperative respiratory exercise and rehabilitation in ICU/IMC and general ward. The target exercise and respiratory frequency was 30 minutes every 2–3 hours and 10 minutes per hour, respectively. In addition, we performed BAL in case of left lower lobe atelectasis, increased white blood cell (WBC) and/or fever. We noticed that the early respiratory and exercise rehabilitation resolved the atelectasis and facilitated reduction in pleural effusions. In our center, only five patients needed pleural drainage due to effusion, but none of our patient's experienced pneumonia or the need for reintubation or tracheostomy. Our data indicate that a preemptive strategy as described fosters early rehabilitation for liver-transplant recipients, is safe, tolerable, feasible and supported functional outcomes.

Prolonged nasogastric intubation in abdominal surgery is associated with increased pulmonary complications and longer time to return of bowel function. Therefore, it is recommended that prophylactic nasogastric intubation should be abandoned in favor of selective use in abdominal surgery (51,52). A systematic review shows that early enteral nutrition may contribute to better immune function and lower rates of infectious complications (53). Currently, there is lack of consensual evidence related to nasogastric intubation in LTx patients. It is strongly recommended that normal food oral intake should be started 12–24 h after LTx, according to the patient's tolerance (9). In our study, we successfully removed the nasogastric tube within 48 hours after LTx and started oral intake training according to our SOP (*Table 3*) in order to facilitate bowel movement, reducing the time of flatus and the possibility of postoperative ileus, without any problems.

Prevention of thrombosis and bleeding complications are critical in postoperative management of LTx patients. Thromboprophylaxis is recommended in recipients at risk of hepatic artery and portal venous thrombosis, for example occlusive portal vein thrombosis (PVT) prior to LTx, complex physiological anastomosis, technical difficulties or non-physiological anastomosis (54). Preoperative evaluation of recipients and comprehensive communication with anesthetist and surgeon are necessary. We did not anticoagulated our patients instead stressed for fast ambulation after extubation. One patient developed a deep vein thrombosis on POD 25 and was put on anticoagulation.

Due to increased risk of bacterial, fungal, and viral infections of patients with end stage liver disease, postoperative prophylaxis of these pathogenic microorganism after transplantation is recommended. Hence, in our center, universal antibiotic prophylaxis of bacterial infections was administrated for 4 days. Meanwhile, body

temperature, cultures and drug sensitive tests of blood, sputum culture, abdominal drainage fluid are routinely performed in patients with risk of infection to guide the anti-bacterial therapy. Five patients had pleural effusion, treated with drainage and a CT was performed to rule out an atelectasis of the right lower lobe. In case of atelectasis, we choose BAL as early intervention including culture of samples (n=1). Cytomegalovirus (CMV) prophylaxis was administrated to recipients in case of DR+/R– constellations, no infections were observed. For recipients with HBV infection before LTx, HBV immune globin was intravenously administrated for 2 times every week for 5 weeks and entecavir was orally taken every day beginning at POD 1. Fungal infections are associated with immune deficiencies and immunosuppression and patients with liver transplants are at high risk of invasive fungal infections (IFIs). The mortality of IFIs in liver recipients ranges from 25% to 67% (55). MELD scores higher than 25, post-transplant acute kidney injury and pre-transplant fungal colonization seem to be potential risk factors for IFIs (56,57). Currently, using 1.3-beta D glucan (BDG) and galactomannan (GM) can be helpful in diagnosis of fungal infection, it remains challenging to distinguish between colonization and true infection. Therefore, diagnosis of fungal infection and antifungal prophylaxis should be given carefully and upon individual indication, and clinical manifestations. None of our patients suffered from a fungal infection.

Standardized and individualized immunosuppressive therapy is the key to guarantee the efficacy of transplantation (58). In principle, primary immunosuppression is started at the time of LTx to prevent any forms of rejection (58). Nevertheless, several studies have shown that complications related to overimmunosuppression, such as chronic kidney disease, *de novo* malignancies, diabetes, dyslipidemia and hypertension, compromised long-term patient survival rather than immunological graft loss (59-61). Therefore, achieving stable trough levels within a target range is important, particularly early after LTx. Here, we choose a well-developed concept already published with AR rates below 10% which was highly efficient (62-64). No acute rejections neither adverse effects were observed, and we followed a daily monitoring during the hospitalization phase. Moreover, did our patients stay within the aimed therapeutic range. In 28 patients with HCC, we switched from MMF to sirolimus. Only one patient demonstrated a very early recurrence, while the other patients at 1 year after transplantation demonstrated no recurrence. These data are in line with recent findings by Kang *et al.* (65), demonstrating that patients on minimized Tacrolimus and Everolimus had a significant better outcome compared to SOC (Standard of Care—Tac, MMF).

Conclusions

In conclusion, ERAS is feasible in LTx, consisting of preoperative, intraoperative and postoperative procedures. Comparison of outcome using benchmarks from the German quality assessment in liver transplantation (IQTIG reference) demonstrated excellent outcomes in terms of in-house mortality, LOS, 1-year patient survival and readmission rates, clearly indicating the benefit of an ERAS protocol to measure and improve quality management for patients. Our study revealed that ERAS in LTx can provide a safe management tool to monitor the patient throughout the whole hospital stay, providing quality service with low morbidities and absence of mortality throughout the observation period.

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Footnote

Reporting Checklist: The authors have completed the STROCSS reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-24-349/rc

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Ethical Statement: The authors are 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. All transplantations and organ donations were approved by the hospital ethics committee of The First Affiliated Hospital of USTC and in accordance with the Declaration of Helsinki (as revised in 2013) and the Declaration of Istanbul. The study protocol was approved by the Ethics Committee of The First Affiliated Hospital of the USTC, within University of Science and Technology of China (2024-RE-107). Written informed consent of each patient was obtained before operation and for the publication of this study.

References

1. Melloul E, Hübner M, Scott M, et al. Guidelines for Perioperative Care for Liver Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations. World J Surg 2016;40:2425-40.
2. Coolsen MM, Wong-Lun-Hing EM, van Dam RM, et al. A systematic review of outcomes in patients undergoing liver surgery in an enhanced recovery after surgery pathways. HPB (Oxford) 2013;15:245-51.
3. Rossaint R, Slama K, Jaeger M, et al. Fluid restriction and early extubation for successful liver transplantation. Transplant Proc 1990;22:1533-4.
4. Golder HJ, Papalois V. Enhanced Recovery after Surgery: History, Key Advancements and Developments in Transplant Surgery. J Clin Med 2021;10:1634.
5. Aniskevich S, Scott CL, Ladlie BL. The Practice of Fast-Track Liver Transplant Anesthesia. J Clin Med 2023;12:3531.
6. Katsanos G, Karakasi KE, Antoniadis N, et al. Enhanced recovery after surgery in liver transplantation: Challenges and feasibility. World J Transplant 2022;12:195-203.
7. Feizpour CA, Patel MS, Syed MA, et al. Enhanced recovery in liver transplantation: A value-based approach to complex surgical care. Surgery 2021;170:1830-7.
8. Xu Q, Zhu M, Li Z, et al. Enhanced recovery after surgery protocols in patients undergoing liver transplantation: A retrospective comparative cohort study. Int J Surg 2020;78:108-12.
9. Brustia R, Monsel A, Skurzak S, et al. Guidelines for Perioperative Care for Liver Transplantation: Enhanced Recovery After Surgery (ERAS) Recommendations. Transplantation 2022;106:552-61.
10. Lebertransplantation (LTX). 17th February, 2024. Available online: https://iqtig.org/qs-verfahren/qs-tx/
11. Li M, Zhang T, Zhu J, et al. Risk factors of perioperative complications and management with enhanced recovery after primary surgery in women with epithelial ovarian carcinoma in a single center. Oncol Lett 2022;23:155.
12. Bulatao IG, Heckman MG, Rawal B, et al. Avoiding stay in the intensive care unit after liver transplantation: a score to assign location of care. Am J Transplant 2014;14:2088-96.
13. Guo Y, Wang J, Wu W, et al. Incidence of Ischemia Reperfusion Injury Related Biliary Complications in Liver Transplantation: Effect of Different Types of Donors. Transplant Proc 2022;54:1865-73.
14. Bundesauswertung. 14th, November, 2023. Available online: https://iqtig.org/veroeffentlichungen/bundesauswertung/
15. Mi S, Jin Z, Qiu G, et al. Liver transplantation in China: Achievements over the past 30 years and prospects for the future. Biosci Trends 2022;16:212-20.
16. Ling S, Jiang G, Que Q, et al. Liver transplantation in patients with liver failure: Twenty years of experience from China. Liver Int 2022;42:2110-6.
17. Herbert G, Sutton E, Burden S, et al. Healthcare professionals' views of the enhanced recovery after surgery programme: a qualitative investigation. BMC Health Serv Res 2017;17:617.
18. Alawadi ZM, Leal I, Phatak UR, et al. Facilitators and barriers of implementing enhanced recovery in colorectal surgery at a safety net hospital: A provider and patient perspective. Surgery 2016;159:700-12.
19. Taner CB, Willingham DL, Bulatao IG, et al. Is a mandatory intensive care unit stay needed after liver transplantation? Feasibility of fast-tracking to the surgical ward after liver transplantation. Liver Transpl 2012;18:361-9.
20. Thuluvath PJ. Evaluation of liver transplant recipients. J Clin Exp Hepatol 2011;1:199-203.
21. Fatima I, Jahagirdar V, Kulkarni AV, et al. Liver

Transplantation: Protocol for Recipient Selection, Evaluation, and Assessment. J Clin Exp Hepatol 2023;13:841-53.
22. Dioguardi Burgio M, Garzelli L, Cannella R, et al. Hepatocellular Carcinoma: Optimal Radiological Evaluation before Liver Transplantation. Life (Basel) 2023;13:2267.
23. Qin J, Zheng H, Li X, et al. Successful, Combined Long-term Treatment of Cerebral Candidiasis and Aspergillosis in a Liver Transplant Recipient: A Case Report. Transplant Proc 2021;53:2588-93.
24. Bjerring PN, Gluud LL, Larsen FS. Cerebral Blood Flow and Metabolism in Hepatic Encephalopathy-A Meta-Analysis. J Clin Exp Hepatol 2018;8:286-93.
25. Shribman S, Bocchetta M, Sudre CH, et al. Neuroimaging correlates of brain injury in Wilson's disease: a multimodal, whole-brain MRI study. Brain 2022;145:263-75.
26. Kaur H, Premkumar M. Diagnosis and Management of Cirrhotic Cardiomyopathy. J Clin Exp Hepatol 2022;12:186-99.
27. McAvoy NC, Kochar N, McKillop G, et al. Prevalence of coronary artery calcification in patients undergoing assessment for orthotopic liver transplantation. Liver Transpl 2008;14:1725-31.
28. Feltracco P, Carollo C, Barbieri S, et al. Early respiratory complications after liver transplantation. World J Gastroenterol 2013;19:9271-81.
29. Cerantola Y, Valerio M, Persson B, et al. Guidelines for perioperative care after radical cystectomy for bladder cancer: Enhanced Recovery After Surgery (ERAS((R))) society recommendations. Clin Nutr 2013;32:879-87.
30. Lassen K, Coolsen MM, Slim K, et al. Guidelines for perioperative care for pancreaticoduodenectomy: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations. Clin Nutr 2012;31:817-30.
31. Gustafsson UO, Scott MJ, Schwenk W, et al. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS(®)) Society recommendations. World J Surg 2013;37:259-84.
32. Nygren J, Thacker J, Carli F, et al. Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced Recovery After Surgery (ERAS(®)) Society recommendations. World J Surg 2013;37:285-305.
33. Nguyen-Buckley C, Bezinover DS, Bhangui P, et al. International Liver Transplantation Society/Society for Advancement of Transplant Anesthesia Consensus Statement on Essential Attributes of a Liver Transplant Anesthesiologist. Transplantation 2023;107:1427-33.
34. Brezeanu, L.N., et al., Anaesthesia for Liver Transplantation: An Update. J Crit Care Med (Targu Mures) 2020;6:91-100.
35. Pollok JM, Tinguely P, Berenguer M, et al. Enhanced recovery for liver transplantation: recommendations from the 2022 International Liver Transplantation Society consensus conference. Lancet Gastroenterol Hepatol 2023;8:81-94. Erratum in: Lancet Gastroenterol Hepatol 2023;8:117.
36. Bezinover D, Mukhtar A, Wagener G, et al. Hemodynamic Instability During Liver Transplantation in Patients With End-stage Liver Disease: A Consensus Document from ILTS, LICAGE, and SATA. Transplantation 2021;105:2184-200.
37. Feng AC, Fan HL, Chen TW, et al. Hepatic hemodynamic changes during liver transplantation: a review. World J Gastroenterol 2014;20:11131-41.
38. Kashani A, Landaverde C, Medici V, et al. Fluid retention in cirrhosis: pathophysiology and management. QJM 2008;101:71-85.
39. Mallett SV. Clinical Utility of Viscoelastic Tests of Coagulation (TEG/ROTEM) in Patients with Liver Disease and during Liver Transplantation. Semin Thromb Hemost 2015;41:527-37.
40. Hevesi ZG, Lopukhin SY, Mezrich JD, et al. Designated liver transplant anesthesia team reduces blood transfusion, need for mechanical ventilation, and duration of intensive care. Liver Transpl 2009;15:460-5.
41. Rettke SR, Janossy TA, Chantigian RC, et al. Hemodynamic and metabolic changes in hepatic transplantation. Mayo Clin Proc 1989;64:232-40.
42. Sajid MS, Shakir AJ, Khatri K, et al. The role of perioperative warming in surgery: a systematic review. Sao Paulo Med J 2009;127:231-7.
43. Polderman KH. Hypothermia and coagulation. Crit Care 2012;16:A20.
44. Paterson DL, Staplefeldt WH, Wagener MM, et al. Intraoperative hypothermia is an independent risk factor for early cytomegalovirus infection in liver transplant recipients. Transplantation 1999;67:1151-5.
45. Oh EJ, Han S, Lee S, et al. Forced-air prewarming prevents hypothermia during living donor liver transplantation: a randomized controlled trial. Sci Rep 2023;13:3713.
46. Bhangui P, Bhangui P, Gupta N, et al. Fast tracking in adult living donor liver transplantation: A case series of 15 patients. Indian J Anaesth 2018;62:127-30.
47. Glanemann M, Hoffmeister R, Neumann U, et al. Fast

tracking in liver transplantation: which patient benefits from this approach? Transplant Proc 2007;39:535-6.
48. Aneja S, Raina R. Immediate postoperative extubation after liver transplantation at our centre: A report of two cases. Indian J Anaesth 2011;55:392-4.
49. Lui JK, Spaho L, Hakimian S, et al. Pleural Effusions Following Liver Transplantation: A Single-Center Experience. J Intensive Care Med 2021;36:862-72.
50. Xu C, Zhang W, Wang X, et al. Correlation Analysis of Pleural Effusion and Lung Infection After Liver Transplantation. Clin Lab 2021.
51. Nelson R, Edwards S, Tse B. Prophylactic nasogastric decompression after abdominal surgery. Cochrane Database Syst Rev 2007;2007:CD004929.
52. Pessaux P, Regimbeau JM, Dondéro F, et al. Randomized clinical trial evaluating the need for routine nasogastric decompression after elective hepatic resection. Br J Surg 2007;94:297-303.
53. Richter B, Schmandra TC, Golling M, et al. Nutritional support after open liver resection: a systematic review. Dig Surg 2006;23:139-45.
54. Kirchner VA, O'Farrell B, Imber C, et al. What is the optimal management of thromboprophylaxis after liver transplantation regarding prevention of bleeding, hepatic artery, or portal vein thrombosis? A systematic review of the literature and expert panel recommendations. Clin Transplant 2022;36:e14629.
55. Singh N, Wagener MM, Marino IR, et al. Trends in invasive fungal infections in liver transplant recipients: correlation with evolution in transplantation practices. Transplantation 2002;73:63-7.
56. Utsumi M, Umeda Y, Yagi T, et al. Risk Analysis for Invasive Fungal Infection after Living Donor Liver Transplantation: Which Patient Needs Potent Prophylaxis? Dig Surg 2019;36:59-66.
57. Raghuram A, Restrepo A, Safadjou S, et al. Invasive fungal infections following liver transplantation: incidence, risk factors, survival, and impact of fluconazole-resistant Candida parapsilosis (2003-2007). Liver Transpl 2012;18:1100-9.
58. Montano-Loza AJ, Rodríguez-Perálvarez ML, Pageaux GP, et al. Liver transplantation immunology: Immunosuppression, rejection, and immunomodulation. J Hepatol 2023;78:1199-215.
59. Watt KD, Pedersen RA, Kremers WK, et al. Evolution of causes and risk factors for mortality post-liver transplant: results of the NIDDK long-term follow-up study. Am J Transplant 2010;10:1420-7.
60. Rubín A, Sánchez-Montes C, Aguilera V, et al. Long-term outcome of 'long-term liver transplant survivors'. Transpl Int 2013;26:740-50.
61. Azhie A, Sheth P, Hammad A, et al. Metabolic Complications in Liver Transplantation Recipients: How We Can Optimize Long-Term Survival. Liver Transpl 2021;27:1468-78.
62. Herzer K, Strassburg CP, Braun F, et al. Selection and use of immunosuppressive therapies after liver transplantation: current German practice. Clin Transplant 2016;30:487-501.
63. Neuhaus P, Clavien PA, Kittur D, et al. Improved treatment response with basiliximab immunoprophylaxis after liver transplantation: results from a double-blind randomized placebo-controlled trial. Liver Transpl 2002;8:132-42.
64. Nashan B, Schemmer P, Braun F, et al. Early Everolimus-Facilitated Reduced Tacrolimus in Liver Transplantation: Results From the Randomized HEPHAISTOS Trial. Liver Transpl 2022;28:998-1010.
65. Kang I, Lee JG, Choi SH, et al. Impact of everolimus on survival after liver transplantation for hepatocellular carcinoma. Clin Mol Hepatol 2021;27:589-602.

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