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ORIGINAL ARTICLE

Retrospective Study

How to apply *ex-vivo* split liver transplantation safely and feasibly: A three-step approach

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Abstract

BACKGROUND

Given the current organ shortage crisis, split liver transplantation (SLT) has emerged as a promising alternative for select end-stage liver disease patients.

AIM

To introduce an *ex-vivo* liver graft splitting approach and evaluate its safety and feasibility in SLT.

METHODS

A retrospective analysis was conducted on the liver transplantation data from cases performed at our center between April 1, 2022, and May 31, 2023. The study included 25 SLT cases and 81 whole liver transplantation (WLT) cases. Total *ex-vivo* liver splitting was employed for SLT graft procurement in three steps. Patient outcomes were determined, including liver function parameters, postoperative complications, and perioperative mortality. Group comparisons for categorical variables were performed using the χ^2-test.

RESULTS

In the study, postoperative complications in the 25 SLT cases included hepatic artery thrombosis (n = 1) and pulmonary infections (n = 3), with no perioperative mortality. In contrast, among the 81 patients who underwent WLT, complications included perioperative mortality (n = 1), postoperative pulmonary infections

(*n* = 8), abdominal infection (*n* = 1), hepatic artery thromboses (*n* = 3), portal vein thrombosis (*n* = 1), and intra-abdominal bleeding (*n* = 5). Comparative analysis demonstrated significant differences in alanine aminotransferase (176.0 *vs* 73.5, *P* = 0.000) and aspartate aminotransferase (AST) (42.0 *vs* 29.0, *P* = 0.004) at 1 wk postoperatively, and in total bilirubin (11.8 *vs* 20.8, *P* = 0.003) and AST (41.5 *vs* 26.0, *P* = 0.014) at 2 wk postoperatively. However, the overall incidence of complications was comparable between the two groups (*P* > 0.05).

CONCLUSION

Our findings suggest that the total *ex-vivo* liver graft splitting technique is a safe and feasible approach, especially under the expertise of an experienced transplant center. The approach developed by our center can serve as a valuable reference for other transplantation centers.

Key Words: Split liver transplantation; Transplantation; Liver splitting; *Ex-vivo*; *In-situ*

Core Tip: Split liver transplantation has become a routine procedure at many transplant centers, and there are currently two main approaches for the generation of split-liver allografts: *In-situ* splitting and *ex-vivo* splitting. While *in-situ* splitting, which involves liver division within the organ donor's body before procurement, is the prevailing technique adopted by most transplant centers, the utilization of *ex-vivo* splitting, wherein the liver is divided after procurement, remains limited. Our findings suggest that the *ex-vivo* liver graft splitting technique is a safe and feasible approach, especially under the expertise of an experienced transplant center.

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INTRODUCTION

Given the current organ shortage crisis, split liver transplantation (SLT) has emerged as a promising alternative for select patients with end-stage liver disease[1-4], offering clinical outcomes akin to those achieved through whole liver transplantation (WLT)[5-7]. The techniques for SLT involve primarily splitting off the left lateral section and the right trisegment, followed by further partitioning into the left and right hemi-livers or liver segments, contingent on the compatibility conditions between the donor and recipient[8,9].

There are currently two main approaches for the generation of split-liver allografts: *In-situ* splitting and *ex-vivo* splitting. While *in-situ* splitting, which involves liver division within the organ donor's body before procurement, is the prevailing technique adopted by most transplant centers, the utilization of *ex-vivo* splitting, wherein the liver is divided after procurement, remains limited[4,10,11]. Despite its potential benefits, *ex-vivo* splitting is currently employed by only a few specialized centers. Ding *et al*[12] previously reported that out of 11 liver grafts, only 2 (18.2%) underwent *ex-vivo* splitting. Similarly, Xu *et al*[13] performed only 20 (14.3%) SLT procedures out of the 140 liver transplantations.

Interestingly, SLT has become a routine procedure at our transplant center, and the total *ex-vivo* liver graft splitting technique has become our preferred approach. Despite the significance of *ex-vivo* liver graft splitting, there are few detailed reports on this splitting technique. To address this knowledge gap, our present study presents a comprehensive summary of our center's practice and technical approach to *ex-vivo* liver graft splitting, aiming to evaluate its safety and feasibility and provide a reference for surgeons in other transplant centers.

MATERIALS AND METHODS

Study design and patients

Clinical data from 122 liver transplantation cases performed at Shenzhen Third People's Hospital were initially collected between April 1, 2022, and May 31, 2023. The study enrolled 81 cases of WLT, 16 cases of living-donor liver transplantation, and 25 cases of SLT. A total of 106 cases, comprising of SLT and WLT recipients, were eventually included in our study. Comprehensive data, including clinical records, surgical reports, laboratory findings, and imaging results, were obtained for each case. Liver function parameters, incidence of surgical complications, and perioperative mortality rate were independently analyzed for the SLT and WLT groups. All the patients provided informed consent before operation, and the study was approved by the ethics committee of Shenzhen Third People's Hospital (No. 2022-133).

Donor liver evaluation methods

Before organ procurement, all potential organ donors received comprehensive preoperative evaluations, including complete blood counts, liver function tests, renal function tests, infectious disease pathogen screening, and inflammation marker testing. Additionally, imaging studies, such as liver ultrasound or contrast-enhanced computed tomography (CT) scans, were performed.

Donor liver splitting procedure

The liver graft splitting procedure was performed using the total *ex-vivo* splitting technique. Following liver procurement, the donor liver was partitioned while immersed in a cold storage solution. The splitting of the left lateral section and the right trisegment involved three main steps: (1) Division of the first porta hepatis: The anatomical structures of the first porta hepatis were dissected, followed by the separate division of the left branch of the portal vein and the left branch of the hepatic artery. Next, the division site of the left hepatic duct was identified under biliary probe guidance. Following bile duct resection, the splitting line on the visceral surface of the liver was marked (Figure 1); (2) Division of the second porta hepatis: The suprahepatic inferior vena cava was gently elevated, and the root of the left hepatic vein was bluntly separated to fully expose the site where the left hepatic vein joins the inferior vena cava. After dividing the left hepatic vein, the surface splitting line of the liver on the diaphragmatic aspect was marked, connecting it to the visceral surface splitting line (Figure 2); and (3) Division of liver parenchyma: A clamp-crushing technique was utilized for dividing the liver parenchyma to avoid thermal injury to liver tissues. Smaller vessels were ligated with titanium clips, while larger vessels were ligated using silk or Prolene sutures. Throughout the procedure, continuous monitoring of anatomical structures with positional changes was performed to ascertain the precise division plane and avoid injuries to critical intrahepatic structures (Figure 3). After completing the division of the right trisegment and the left lateral section, the caudate lobe on the left side of the inferior vena cava was excised. The surgical procedure depicted above is further detailed in Figures 1-3.

Statistical analysis

All statistical analyses were performed using SPSS 24.0 statistical software. The descriptive statistics are expressed as frequencies (%) for categorical variables, and median (interquartile range) for continuous variables. Group comparisons for categorical variables were performed using the χ^2-test. For metric variables, the Mann-Whitney *U* test was used. A two-sided *P*-value < 0.05 was considered statistically significant.

RESULTS

Clinical data of donors

Between April 1, 2022 and May 31, 2023, 13 liver grafts were subjected to splitting. These grafts were procured from 13 brain-dead organ donors, with all exhibiting hemodynamic stability preoperatively, with minimal or no use of vasoactive drugs. The median age of the liver donors was 31 years, and they had a median preoperative total bilirubin (TB) level of 20.76 μmol/L, median alanine aminotransferase (ALT) level of 43.3 U/L, median aspartate aminotransferase (AST) level of 83 U/L, and median intensive care unit (ICU) stay duration of 4 d.

The liver graft splitting procedure was conducted using the total *ex-vivo* splitting technique, whereby both the left lateral section and the right trisegment were divided in all cases. Following the procedure, 26 liver segments were obtained (13 left lateral sections and 13 right trisegments). Among these liver segments, 25 were allocated to our transplant center by the China Organ Transplant Response System, while one right trisegment was given to another transplant center. During the liver graft splitting procedure for the 12 cases in which the right trisegment was utilized for liver transplantation, the caudate lobe located on the left side of the inferior vena cava was consistently excised. Further details regarding the donor liver information can be found in Table 1.

Clinical data of liver transplant recipients

All 106 Liver transplant procedures retrospectively analyzed in this study were successfully performed. The age of WLT cases was younger than that of SLT cases (49.00 *vs* 1.83, $P = 0.001$), and there were more decompensated cirrhosis recipients in WLT cases (48 *vs* 5, $P = 0.001$). Out of the 81 WLT cases, 66 were carried out using the classic *in-situ* liver transplantation technique, while the remaining 15 utilized the modified piggyback liver transplantation technique. As for the 25 SLT cases, 13 pediatric recipients received left lateral section grafts, and 7 adult and 5 pediatric recipients received right trisegment grafts. In the 12 patients who underwent SLT with the right trisegment graft, we conducted the removal of ischemic hepatic tissue from Segment IV while preserving the middle hepatic vein during the surgical procedure.

Postoperative results and complications

Among the 81 cases of WLT, one perioperative death occurred, while the remaining patients were successfully discharged. The postoperative complications primarily included pulmonary infections in 8 cases (9.9%), intra-abdominal infections in 1 (1.2%), incisional infections in 1 (1.2%), herpes zoster infection in 1 (1.2%), hepatic artery thrombosis in 3 (3.7%), portal vein thrombosis in 1 (1.2%), intra-abdominal bleeding in 5 (6.2%), graft-versus-host disease (GVHD) in 1 (1.2%), and acute kidney injury in 1 (1.2%). The patient with intra-abdominal bleeding underwent exploratory laparotomy to achieve hemostasis, while those with hepatic artery or portal vein thrombosis received surgical thrombectomy. The patient who experienced GVHD passed away on postoperative day 56 despite aggressive treatment.

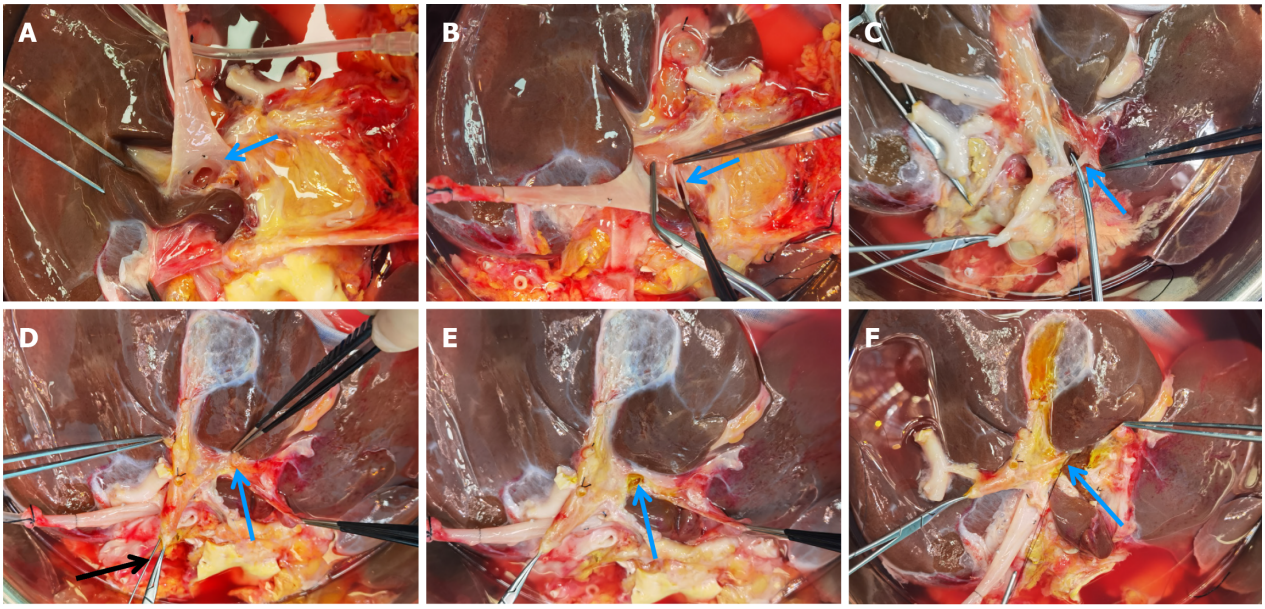

Figure 1 Procedure of splitting the first porta hepatis. A: Separation of the left and right branches of the portal vein (arrow indicating the left portal vein); B: Division of the left portal vein (arrow) followed by suturing of the proximal end; C: Identification and division of the left hepatic artery (arrow); D: Identification of the division site of the left hepatic duct (blue arrow) under biliary probe guidance (black arrow); E: Incision of the left hepatic duct anterior wall (arrow) and reconfirmation of the left hepatic duct, right hepatic duct, and suspected bile duct openings using the probe; F: Division of the left hepatic duct, confirming the landmark for the division of liver parenchyma in the first porta hepatis.

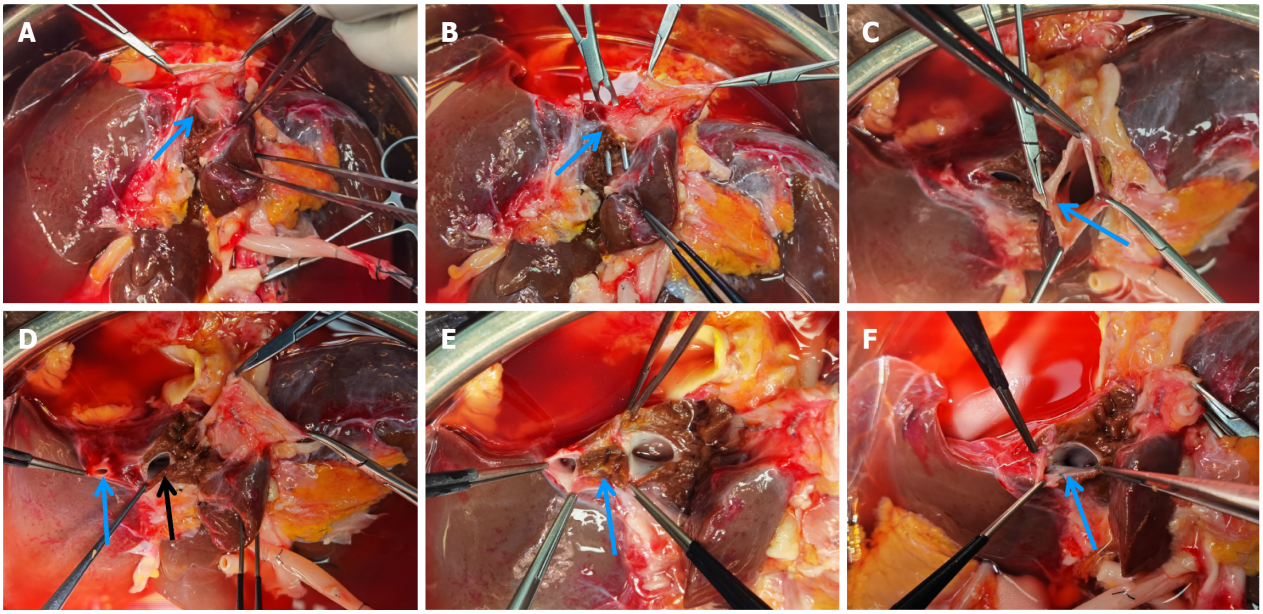

Figure 2 Step-by-step process involved in splitting the second porta hepatis. A: Elevation of the suprahepatic inferior vena cava followed by blunt dissection of the liver tissue at the junction of the left hepatic vein and the inferior vena cava (arrow) to fully expose the left hepatic vein; B: Separating and dividing the left hepatic vein (arrow) using a vascular occlusion clamp on the inferior vena cava side; C: Formation of the middle hepatic vein and the opening of the inferior vena cava (arrow points to the formed vessel opening); D: Identification of the two openings of the left hepatic vein in the left lateral segment (blue arrow and black arrow); E: Removal of the liver tissue between the two openings of the left hepatic vein (arrow) to form a single opening; F: Display of the formed opening of the left hepatic vein.

Subsequent follow-ups, ranging from 2 to 15 mo, revealed that 76 patients recovered well and had no abnormalities.

Among the 25 subjects that underwent SLT, one experienced hepatic artery thrombosis on postoperative day 3, which was successfully treated by surgical thrombectomy, leading to a favorable recovery. Another three patients developed postoperative pulmonary infections, but there were no instances of bile leakage or intestinal leakage, and no perioperative deaths were reported. All 25 patients were discharged without complications and showed no abnormalities during a follow-up period ranging from 4 to 15 mo.

Table 1 Clinical data of 13 donor liver cases

No.	Gender	Age (yr)	Type of donation	Cause of death	Preoperative Na^+ concentration (mmol/L)	Preoperative TB (μmol/L)	Preoperative ALT (U/L)	Preoperative AST (U/L)	ICU stay duration (d)
1	Male	31	DBD	Craniocerebral injury	143	57.80	37.0	41.0	3
2	Female	12	DBD	Hypoxic-ischemic encephalopathy	140	13.40	42.0	53.0	4
3	Female	42	DBD	Craniocerebral injury	146	50.80	45.0	83.0	5
4	Male	44	DBD	Cerebral hemorrhage	143	45.30	18.0	37.0	4
5	Male	36	DBD	Craniocerebral injury	150	13.80	131.0	172.0	4
6	Male	34	DBD	Cerebral hemorrhage	156	23.40	267.5	293.2	2
7	Male	12	DBD	Hypoxic-ischemic encephalopathy	136	13.00	43.3	93.1	11
8	Male	31	DBD	Cerebral hemorrhage	150	26.80	15.0	25.0	10
9	Male	25	DBD	Craniocerebral injury	143	54.50	177.0	83.0	4
10	Female	9	DBD	Hypoxic-ischemic encephalopathy	148	3.05	103.0	227.0	10
11	Male	8	DBD	Hypoxic-ischemic encephalopathy	149	10.21	22.7	22.9	4
12	Female	29	DBD	Cerebral hemorrhage	148	20.76	37.0	42.0	7
13	Male	40	DBD	Cerebral hemorrhage	132	12.20	166.0	85.0	5

DBD: Donation after brain death; TB: Total bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; Na^+: Sodium ion; ICU: Intensive care unit.

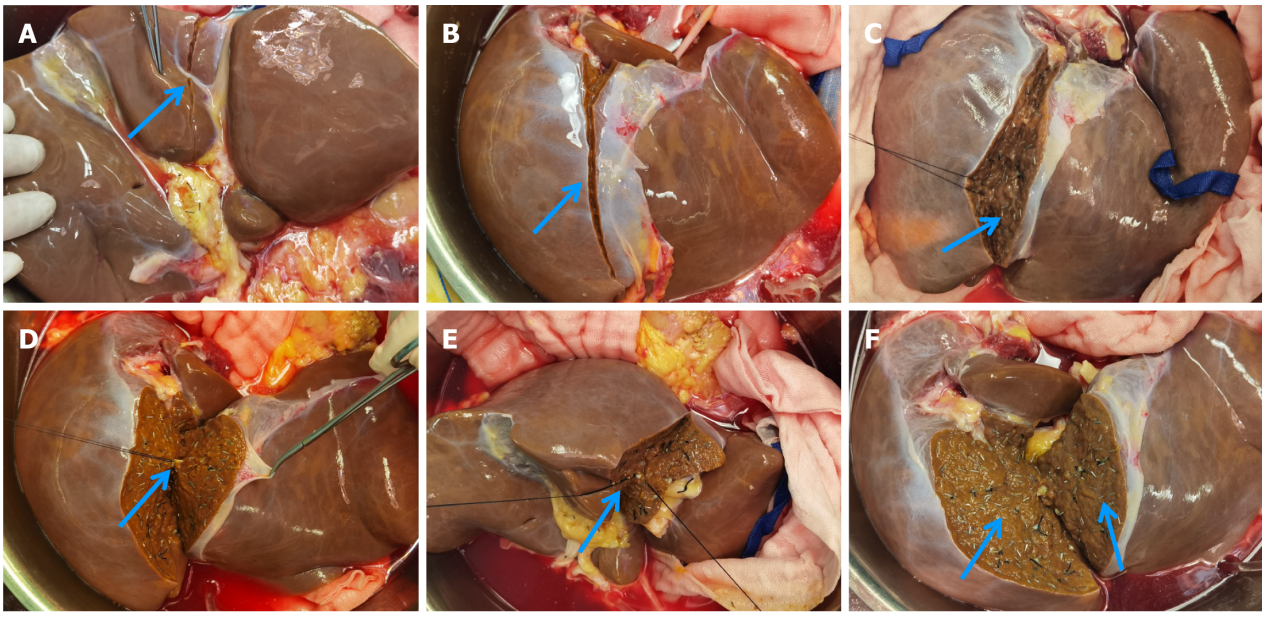

Figure 3 Procedure of liver parenchymal division. A: Identification of the landmark line on the visceral surface of the liver for liver parenchymal division (0.5-

1.0 cm to the right of the liver round ligament); B: Landmark line on the diaphragmatic surface of the liver for liver parenchymal division (on the right of the falciform ligament); C: Liver parenchymal division in the flat position, using titanium clips for small vessels (arrow); D: Adjusting the position of the liver during parenchymal division (suprahepatic inferior vena cava facing upwards), using silk sutures or ligatures for larger vessels (arrow); E: Continued liver parenchymal division with the liver flipped (suprahepatic inferior vena cava facing downward); F: Display of the two smooth liver segment surfaces after completion of the splitting process (arrow).

A comparison of postoperative data between SLT and WLT revealed statistically significant differences in ALT (176.0 *vs* 73.5, $P = 0.000$) and AST (42.0 *vs* 29.0, $P = 0.004$) levels at 1 wk post-surgery. Additionally, at 2 wk post-surgery, there were statistically significant differences in TB (11.8 *vs* 20.8, $P = 0.003$) and AST (41.5 *vs* 26.0, $P = 0.014$) levels. However, no statistically significant difference was observed in the overall incidence of postoperative complications between the two groups ($P > 0.05$). Further details can be found in Table 2.

DISCUSSION

In the face of a critical shortage of available donor organs, SLT represents a valuable approach to address this pressing issue. SLT involves the division of a single high-quality liver into two parts, thereby saving the lives of two recipients [14]. The success of SLT hinges on ensuring that each split portion of the liver maintains intact anatomical structures, encompassing the inflow vessels (hepatic artery and portal vein), outflow vessels (hepatic veins), and biliary tract. Additionally, adherence to conventional criteria for SLT, such as the graft-to-recipient weight ratio (GRWR), is crucial. Typically, a GRWR greater than 1% for adults[8,15] and between 2% to 4% for children is recommended. In our study, all the 25 recipients of SLT met these criteria and did not experience postoperative complications such as large-for-size or small-for-size graft syndromes. However, some scholars reported that the ideal graft weight is approximately 1-3% of the recipient weight[16].

Different transplant centers primarily adopt either *in-situ* or *ex-vivo* splitting approaches. Reyes *et al*[17] previously reported that the survival rates of recipients undergoing *in-situ* and *ex-vivo* liver splitting were comparable and similar to the survival rates of WLT recipients, in line with the findings of our study. Our literature review revealed that the majority of transplant centers have a preference for the *in-situ* liver-splitting approach[8,12,18]. *In-situ* liver splitting involves performing the procedure within the donor's body for liver procurement. This approach offers several advantages[19,20], including shorter cold ischemia time, simultaneous hemostasis during liver parenchymal transection, and facilitated intraoperative cholangiography. However, it may also have certain drawbacks, such as potential delays in procuring other organs and the need for coordination between transplant centers. Recent literature has explored the use of normothermic perfusion devices for liver splitting, which holds the potential to mitigate some of the limitations associated with *in-situ* splitting. Although this technology shows promise, it has not yet been widely adopted in clinical practice, and its clinical effectiveness requires further observation and research[21].

By contrast, *ex-vivo* splitting, which we primarily use, avoids these drawbacks. However, it requires a skilled surgical team familiar with *ex-vivo* liver anatomy to prevent damage to critical structures. Although some literature reported a higher incidence of biliary and vascular complications in adult recipients undergoing *ex-vivo* splitting compared to *in-situ* splitting[22], in our study, out of the 25 cases of SLT, only one adult recipient suffered from hepatic artery thrombosis postoperatively. Besides, there was no incidence of other biliary or vascular complications in the remaining cases. Importantly, the overall incidence of postoperative complications showed no statistically significant difference between the SLT and WLT groups ($P > 0.05$). As mentioned in the Methods section, recipients undergoing liver right trisegment graft surgery had the caudate lobe and ischemic segment IV of the liver excised during the procedure, likely contributing to the absence of bile leakage and intra-abdominal infections postoperatively[23,24].

Postoperative liver function tests revealed statistically significant differences between the SLT group and the WLT group in ALT (176.0 *vs* 73.5, $P = 0.000$) and AST (42.0 *vs* 29.0, $P = 0.004$) levels at 1 wk postoperatively, as well as in TB (11.8 *vs* 20.8, $P = 0.003$) and AST (41.5 *vs* 26.0, $P = 0.014$) levels at 2 wk after surgery. Herein, the higher postoperative ALT and AST levels observed in the SLT group at 1 wk and the elevated AST level at 2 wk might be associated with ischemic necrosis on the transection plane of the liver. Although the difference in TB at 2 wk showed statistical significance, both groups had median values within the normal range, indicating good postoperative liver function.

The safety of SLT relies not only on a surgical team with extensive experience but also on a comprehensive evaluation and careful selection of the donor liver prior to the surgery. Several studies[12,14,25] have emphasized the importance of choosing relatively young donors with stable hemodynamics, short ICU stays, no significant steatosis or infections, and no apparent vascular or biliary anomalies. At our center, we adhere to specific criteria for selecting split liver donors, which include individuals under 45 years of age (with a median age of 31 years in this study) exhibiting stable hemodynamics, absence of significant steatosis or infections, and no apparent vascular or biliary anomalies. It has been reported that intraoperative cholangiography is a necessary examination[14,20], but we did not perform intraoperative cholangiography in this study, because no bile duct variation was found before surgery. However, it is essential to note that cholangiography should be considered if suspicious ductal structures are encountered during the surgery. In the study, all 25 recipients had no relevant biliary complications postoperatively.

Table 2 Clinical data comparison between split liver transplantation and whole liver transplantation cases

	Split liver transplantation (*n* = 25)	Whole liver transplantation (*n* = 81)	*P* value
Gender (male/female)	17/8	65/16	0.273
Age (yr)	1.83 (0.55, 43.00)	49 (40.50, 55.00)	0.001
Underlying diseases			
Decompensated cirrhosis	5	48	0.001
Liver cancer	2	15	0.210
One-week postoperative indicators			
TB	26.400 (12.950, 34.350)	28.250 (17.525, 48.925)	0.274
ALT	176.0 (81.5, 259.5)	73.5 (43.5, 115.5)	0.000
AST	42.00 (32.00, 79.00)	29.00 (20.25, 49.25)	0.004
GGT	139.0 (102.5, 227.5)	118.0 (64.0, 174.0)	0.117
Two-week postoperative indicators			
TB	11.80 (7.95, 20.55)	20.80 (15.20, 26.30)	0.003
ALT	63.0 (29.5, 82.5)	40.0 (21.0, 82.0)	0.154
AST	41.5 (20.5, 61.5)	26.0 (17.0, 41.0)	0.014
GGT	81.0 (54.5, 182.5)	114 (56.0, 201.0)	0.528
Postoperative complications			0.584
Intra-abdominal bleeding	0	5	
Hepatic artery thrombosis	1	3	
Pulmonary infections	3	8	
Abdominal infection	0	1	
Bile leakage	0	0	
Intestinal leakage	0	0	
30-d postoperative mortality	0	1	

TB: Total bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase.

CONCLUSION

In this retrospective analysis of consecutive *ex-vivo* SLT cases conducted over the past year, the methods and steps of *ex-vivo* liver graft splitting technique were summarized in detail, and our study demonstrated that the total *ex-vivo* liver splitting approach with three steps is safe and feasible, especially when performed in experienced transplant centers. Importantly, this approach has been found to address concerns associated with the geographical distance between organ donor hospitals and transplant centers, as well as potential risks of prolonged surgical duration during organ procurement and potential harm to other donated organs. However, follow-up studies with large samples are warranted due to the relatively small number of cases, in order to allow more donor livers suitable for cleavage to be split and to benefit more liver transplant recipients.

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FOOTNOTES

Author contributions: Zhao D contributed to study conception, design, and administrative support; Xie QH, Fang TS, Zhang KJ, Xie WG, and Tang JX contributed to provision of the study materials or patients; Jin X and Xie LJ contributed to collection and assembly of the data; Zhao D and Tang JX contributed to data analysis and interpretation; all authors contributed to manuscript writing and final

approval of the manuscript.

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Informed consent statement: All the patients provided informed consent before operation.

Conflict-of-interest statement: The authors have no conflicts of interests or disclosures to report.

Data sharing statement: If anyone needs relevant data, they can contact the corresponding author.

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