Adult split liver transplantation

A PRISMA-compliant Chinese single-center retrospective case-control study

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Abstract

Although pediatric split liver transplantation (SLT) has been proven safe and the waitlist mortality rate has been successfully reduced, the safety of adult SLT has not been confirmed.

Using 1:2 matching, 47 recipients who underwent adult SLT were matched to 94 of 743 recipients who underwent adult whole graft liver transplantation (WGLT). Eventually, 141 recipients were included in the case-control study. Subgroup analysis of 43 recipients in the SLT group was performed based on the presence of the middle hepatic vein (MHV) in the grafts. No significant differences in 5-year survival (80.8% vs 81.6%, \( P = .465 \)) were observed between the adult SLT and WGLT groups. However, compared to recipients in the WGLT group, those in the SLT group had more Clavien–Dindo grade III–V complications, longer hospitalization duration, and higher mortality within 45 days. Furthermore, on multivariate analysis, 45-day postoperative mortality in recipients in the SLT group was mainly affected by hyperbilirubinemia within postoperative day (POD) 7–14, surgery time, and intraoperative blood loss. Subgroup analysis showed no significant differences in hyperbilirubinemia within POD 7–14, complications, and survival rate between SLT\(^{MHV}+\) and SLT\(^{MHV}–\).

Adult SLT is safe and effective based on long-term survival rates; however, a reduction in the incidence of short-term complications is required. Non-obstructive hyperbilirubinemia within POD 7 to 14 is an independent predictor of short-term mortality after SLT.

Abbreviations: HCC = hepatocellular carcinoma, LT = liver transplantation, MHV = middle hepatic vein, POD = postoperative day, SLT = split liver transplantation, WGLT = graft liver transplantation.

Keywords: donation after brain death, liver transplantation, split liver transplantation

1. Introduction

Since the first successful split liver transplantation (LT; SLT) in 1988,[1] this technique has theoretically doubled the donor pool and alleviated the shortage of donor livers. The significant value of this technique has attracted close attention from research centers worldwide. However, in the 20 years following the first successful SLT, many centers have found a high rate of graft mortality, high rates of complications, and low long-term survival. Most researchers believe that split livers should be considered marginal donor livers.[2] As LT has become a necessary treatment for congenital biliary atresia and some congenital metabolic diseases in children, the demand for donor livers in children has increased dramatically. The ethical problem regarding the conversion of an excellent organ into 2 marginal quality grafts exists, although many families have no alternative to living donor liver transplantation. The proportion of living donor livers for pediatric living donor liver transplantation in our center in China is about 75%, whereas that in other Asian countries, such as Korea, ranges between 66.6% to 80%.[3,4] To meet the growing demand for pediatric recipients, solving the safety problem of SLT has become the research focus of many transplantation centers. Presently, SLT has been confirmed by many centers to be safe in pediatric recipients and to reduce waitlist mortality rates.[5,6] Although negative evaluations of SLT in children are rarely reported, many centers for adult SLT have inconsistent views on its safety.[6] Because of its safety is questionable, many countries have not yet enacted SLT legislation, and a children-first allocation scheme still remains unresolved. This article discusses the experience of adult SLT in a single center.

2. Methods

2.1. Ethical approval and graft source

In this study, the grafts for LT were obtained from dead donors according to a new organ acquisition and distribution policy
established in China after 2012\textsuperscript{[27]} or brain death donation (DBD) before 2012. No prisoners were included as donors. The protocol was approved by the Ethics Committee of the West China Hospital of Sichuan University West China Hospital. Written informed consent was obtained from all recipients prior to surgery, and all donations were voluntary and altruistic and in accordance with the ethical guidelines of the Declaration of Helsinki.

### 2.2. Recipients

From September 2007 to October 2019, only recipients 18 years of age or older were included. The indications for LT in this study were end-stage liver diseases and malignant liver tumors.\textsuperscript{[8]} The exclusion criteria in this study were multiple organ transplantation (ie, combined liver-kidney transplantation), domino LT, double donor LT, and re-transplantation. The mean follow-up for the post matched groups was 774 days. Using 1:2 propensity score matching, 47 recipients who underwent adult SLT were matched to 94 out of a total of 743 recipients who underwent adult graft liver transplantation (WGLT). Eventually, 141 recipients were included in the case-control study. Subgroup analysis of 43 recipients in the SLT group was performed based on the presence of the middle hepatic vein (MHV) in the grafts. Every LT, whether for SLT or WLT recipients, was performed in vivo via an in-situ splitting surgery. Follow-up was routinely performed in the outpatient clinic. Measurements of alpha-fetoprotein and hepatitis B virus DNA and abdominal ultrasonography were performed every 3 months; a computer tomography scan was performed every 6 months. All hepatitis B virus DNA-positive patients were treated with antiviral therapy before and after surgery. When intrahepatic recurrence was difficult to ascertain, magnetic resonance imaging or contrast-enhanced ultrasonography were performed. Tumor recurrence was based mainly on radiographic evidence and/or alpha-fetoprotein level. Patients who showed tumor recurrence after surgery were treated with the following alternatives: resection, radiofrequency ablation, salvage LT, transcatheter arterial chemoembolization, or sorafenib. Recipients were monitored until August 2019 or until death, salvaged LT, transcatheter arterial chemoembolization, or sorafenib.

2.4. Statistical analysis

The R (version 3.6.2) was used for survival curve analysis. Overall, patient survival was estimated using the Kaplan–Meier method, and differences between groups were determined using log-rank test. To minimize the influence of other confounders on outcomes, a propensity score analysis was used to match the 2 cohorts using nearest neighbor matching and based on the variables listed in Table 1. Categorical data are presented as number (percent) and compared using the Pearson chi-Square method, and differences between groups were determined using t-test and repeated measure analysis of variance. Overall, survival was estimated using the Kaplan–Meier method, and differences between 2 groups were determined using log-rank test. $P < .05$ was considered statistically significant.

### 3. Results

#### 3.1. Baseline demographic characteristics, disease features, and surgical characteristics between SLT and WGLT

Baseline demographic characteristics and disease features in the experimental (SLT) and control (WGLT) groups in the post-matched samples are summarized in Table 1. The perioperative course of the post-matched samples is summarized in Table 2. The organs were preserved in 4°C perfusate, in which a thermometer was equipped to monitor the temperature. Compared with the traditional in vitro perfusion LT, the time period from the organ’s blood supply stops to its surface temperature drops to 4°C is greatly shortened. Because the difference of warm ischemia time between in situ perfusion and in vitro perfusion lies in this part of time. For an accurate comparison, we defined this part of time as partial warm ischemia time. Given that adult recipients in the SLT
Table 2

Perioperative course and postoperative outcome.

| Variables                          | SLT (n = 47) | WGLT (n = 94) | P     |
|-----------------------------------|-------------|---------------|-------|
| GRWR                             | 1.21 ± 0.24 | 2.01 ± 0.73   | <.001 |
| Partial warm ischemia time (min) | 4.0 ± 1.46  | 4.1 ± 2.01    | .146  |
| Cold ischemia time (min)          | 155.66 ± 52.7 | 160.07 ± 51.02 | 633   |
| Intraoperative blood loss (mL)    | 1129.79 ± 764.62 | 732.45 ± 546.87 | .002  |
| Blood transfusion (mL)            | 462.71 ± 313.89 | 380.59 ± 322.39 | .153  |
| Operation time (hours)            | 9.38 ± 1.88  | 7.49 ± 0.58   | <.001 |
| Postoperative hospital stays (days)| 13.85 ± 5.24 | 10.94 ± 3.14  | .002  |
| Postoperative infection (%)       | 10 (21.3%)  | 18 (19.1%)    | .765  |
| Hyperbilirubinemia (POD1-7, %)    | 24 (51.1%)  | 27 (29.7%)    | .009  |
| Hyperbilirubinemia (POD7-14, %)   | 17 (36.2%)  | 13 (15.8%)    | .002  |
| Vascular complication (%)         | 3 (6.4%)    | 5 (3.2%)      | .658  |
| Biliary complication (%)          | 9 (19.1%)   | 16 (17%)      | .755  |
| Intra-abdominal bleeding (%)      | 8 (17%)     | 6 (6.4%)      | .091  |
| Acute rejection (%)               | 8 (17%)     | 14 (14.9%)    | .743  |
| AKI (%)                           | 9 (19.1%)   | 8 (8.5%)      | .067  |
| EAD (%)                           | 3 (6.4%)    | 5 (5.3%)      | .898  |
| PNF (%)                           | 1 (2.1%)    | 2 (2.1%)      | .536  |
| Clavien-Dindo > Grade 3 (%)       | 12 (25.5%)  | 11 (11.7%)    | .036  |
| 30-d patient mortality            | 7 (14.9%)   | 4 (4.3%)      | .059  |
| 45-day patient mortality          | 8 (17%)     | 6 (6.4%)      | .091  |
| 1-yr patient survival             | 80.8%       | 82.2%         | .197  |
| 5-yr patient survival             | 80.8%       | 81.6%         | .465  |
| 1-yr graft survival               | 76.8%       | 82.2%         | .117  |
| 5-yr graft survival               | 76.8%       | 77.1%         | .328  |

**GRWR** = graft recipient weight ratio. **EAD** = early allograft dysfunction. **PNF** = primary nonfunction.

Postoperative hyperbilirubinemia is defined as total bilirubin value greater than 82.6 µmol/L, according to the peak value in the first week after donation.

AKI = acute renal injury, defined as a consistent decrease in the absolute serum creatinine to less than 264 µmol/L, confirmed on 2 separate blood investigations at least 72 hours apart.

3.3. Surgical characteristics, postoperative course, and survival of SLT<sup>MHV(+)</sup> and SLT<sup>MHV</sup>−

The subgroups of SLT were analyzed according to MHV. Adult SLT [extended right lobe (n = 17), full left split (n = 10), and full right split grafts (n = 20)] were classified into 2 subgroups: SLT<sup>MHV(+)</sup>− (n = 27) and SLT<sup>MHV</sup>− (n = 20) based on the inclusion of the middle hepatic vein (MHV). No significant difference was observed in baseline demographic characteristics, disease features, and perioperative course between recipients in the SLT<sup>MHV(+)</sup>− and SLT<sup>MHV</sup>− subgroups [Supplemental Digital Content (table S2, http://links.lww.com/MD/F405)]. The recovery of TB in recipients in the SLT<sup>MHV</sup>− group was significantly slower than that of recipients in the SLT<sup>MHV(+)</sup>− group within POD3. However, the levels of aspartate aminotransferase and alanine aminotransferase were similar between the SLT<sup>MHV</sup>− and SLT<sup>MHV(+)</sup>− groups (Fig. 2). In addition, no significant difference was observed between the SLT<sup>MHV</sup>− and SLT<sup>MHV(+)</sup>− groups in terms of graft and overall survival (Fig. 1B). Furthermore, we made a detailed classification and comparison of complications between groups (Table 3). However, no significant difference in Clavien-Dindo grade III-V complications was observed between the groups (25.9% vs 25.0%, P = .943).

3.4. Univariate and multivariate analyses for 45-day postoperative SLT mortality

A high incidence of postoperative bilirubinemia was observed in recipients in the SLT group; therefore, univariate and multivariate analyses were performed for postoperative bilirubinemia. The results of the univariate analysis are shown in [Supplemental Digital Content (table S1, http://links.lww.com/MD/F404)]. Multivariate analysis revealed that only hyperbilirubinemia (POD7-14), surgery time ≥10 hours, and intraoperative blood loss ≥2000 mL were independently related to 45-day postoperative SLT mortality (Table 4).

4. Discussion

Recipients in the SLT group showed slow postoperative recovery and a high incidence of serious complications independent of MHV inclusion in the split graft. However, once recipients passed the period of high incidence of postoperative complications and successfully recovered, long-term survival outcomes were not significantly different from those of recipients in the WGLT group. SLT with MHV can reduce hyperbilirubinemia in the early postoperative stage; however, we did not observe that SLT with MHV significantly reduces complications, accelerates discharge time, or increases survival rates of grafts or recipients.
Reducing bleeding and surgery time by improving surgery skills may reduce short-term postoperative mortality in SLT. In addition, hyperbilirubinemia within POD 7-14 differed from hyperbilirubinemia within POD7 and can predict short-term mortality in SLT. In our study, SLT refers to the surgery using a split liver on a transplant recipient, rather than SLT is for 1 donor, 2 recipients.

4.1. Adult SLT is safe and effective based on long-term survival rates

SLT is different from WGLT, and the most important technical problem is the method of splitting. Inadequate graft volume might cause small-for-size syndrome, which mainly manifests as blood from the portal vein flowing into the small liver as a shunt.

4.2. Comparison of TB, AST and ALT levels after surgery

Figure 1. Five-year graft survival rates.

Figure 2. Comparison of TB, AST and ALT levels after surgery. (A) SLT and WGLT; (B) SLT^MV+^ and SLT^MV-^. AST = aspartate aminotransferase.
and causing rapid swelling of the liver.[13] Considering inevitable preservation injuries, prolonged ischemia time, and reperfusion injuries, most transplant centers believe that a graft volume with ≥ 1% GRWR is necessary for SLT recipients.[14] S4 splitting is the main split method: extended right lobe (containing the MHV)/left lateral lobe split and full-left (containing the MHV)/full-right split. The average weights of adult Asian males and females are 66.2 kg and 57.3 kg, respectively. With the aforementioned methods of splitting, the GRWR for adult recipients is usually guaranteed to be >1.0. The full-left/full-right splitting mode may result in the congestion of residual S4 and a decrease in the effective liver volume. However, using the in-situ perfusion technique, the warm ischemia time during SLT was significantly shortened. In addition, using the in-situ splitting technique processes the cross-section of the liver without blocking the blood flow of the donor liver; thus, the bile duct and vascular tissue can be better recognized, thereby reducing the occurrence of hemorrhage and bile fistula. Concurrently, cold ischemia time was equally significantly reduced. The decrease in ischemia time can reduce the degree of liver injury and consequently reduce the effect of liver parenchymal loss caused by SLT. To some extent, it is equivalent to expanding the GRWR. Presently, in contrast to the fixed 5-year long-term survival rate (about 80%) of WLT,[15,16] the long-term survival rate of different SLT central receptors shows significant differences (63.8% - 90.8%).[17–20] The 5-year survival rate of SLT in our center was 80.8%. Furthermore, no significant difference was observed between WLT and SLT, a finding consistent with most central research results.[21] Based on the incidence of small liver syndrome, graft function, and graft survival rate, the data from our center reveals that in-situ S4 segment splitting and in-situ rapid organ acquisition are feasible.

### 4.2. Slow recovery and high incidence of serious complications concentrated within 45-day after surgery in SLT

Even if the long-term survival rate of recipients with SLT is acceptable with continuous technical improvement, it was observed that recipients who underwent SLT had a higher risk of intraoperative bleeding, longer postoperative hospital duration, and more grade III-V complications than those who underwent WGLT. The results of multicenter studies show that unlike WGLT, SLT is usually accompanied by resection of the bile ducts and blood vessels, which increases the incidence of postoperative bile leakage and bleeding.[22,23] In addition, bile leakage and bleeding may similarly respond to the bare cut surface and SLT-specific S4 vascular deprivation, which increase the risk of parenchymal necrosis of S4. Based on our experience, as long as the surgery is carefully performed and ligation is performed in a stepwise manner, bile leakage and bleeding after surgery are often transient. By prolonging the indwelling time of an abdominal drainage tube, recipients with S4-related complications can completely recover. However, arterial and venous embolisms are different from transient biliary leakage and often require re surgery. In this study, vascular complications, abdominal hemorrhage, and renal failure were the major causes of grade III-V complications and high 45-day mortality among recipients in the SLT group. Presently, there is no consensus on whether there is a difference in the short-term survival rate between SLT and WGLT.[21,22,24] Based on the survival curve, the data showed that WGLT and SLT showed the maximum difference in survival rate 30-45 days after surgery; however, the difference was not significant 6 months after the operation. Previous studies revealed that it usually takes at least 6 months for the donor liver to grow to 80% of the total liver volume.[23–30] In these 6 months, there may be a close balance between residual liver function after SLT and recipient requirements. Breaking this balance will significantly affect recipient prognosis. Specifically, during this time, because it takes a while for the split liver to recover its primary function, relatively weak liver function will be accompanied by coagulation disorder, further increasing the risk of bleeding. Massive hemorrhage and massive blood transfusion will subsequently aggravate the impairment in renal function. Therefore, improving the surgical techniques of transplantation and anastomosis, early detection of complications, timely treatment, and helping recipients survive past the first 6 months after surgery are important to improve the survival rate in SLT.

### Table 3

**Classification of postoperative complications.**

| Grades | Complications | SLT<sub>WLT</sub> (+) | SLT<sub>WGLT</sub> (+) |
|--------|---------------|----------------------|----------------------|
| 1      | Transient bile leak treated/Slight stenosis | 4                     | 5                     |
|        | Mild pleural effusion | 3                     | 1                     |
|        | Atelectasis | 2                     | 1                     |
|        | Intra-abdominal bleeding | 3                     | 5                     |
| 2      | Bleeding requires blood transfusion | 3                     | 2                     |
|        | Pneumonia managed with antibiotics | 2                     | 1                     |
|        | Fever (>38°C) managed with antibiotics | 5                     | 3                     |
|        | Wound infection | 1                     | 1                     |
|        | Hepatic artery embolism | 1                     | 2                     |
| 3a     | Bile leakage/strictures | 2                     | 1                     |
|        | Pleural effusion | 0                     | 0                     |
| 3b     | Intra-abdominal bleeding | 1                     | 1                     |
|        | Portal vein thrombosis | 0                     | 0                     |
|        | Hepatic artery embolism | 1                     | 1                     |
| 4a     | Single organ dysfunction | 1                     | 2                     |
| 4b     | Multiple organ dysfunction | 2                     | 0                     |
| 5      | PNF | 0                     | 1                     |

PNF = primary nonfunction.

* Each patient may have more than 1 complication, and the low level of complication includes the high level with regard to the same complication.

### Table 4

**Independent variables in the multivariate analysis for 45-day postoperative mortality in SLT recipient.**

| Variables                  | B     | P     | 95%CI                        |
|----------------------------|-------|-------|-----------------------------|
| Hyperbilirubinemia (POD7-14) | 3.019 | .022  | 1.537 to 272.396            |
| Operation time ≥ 10 h       | 3.206 | .029  | 1.391 to 437.691            |
| Intraoperative blood loss ≥ 2000 mL | 3.165 | .016  | 1.799 to 312.194            |

CI = confidence interval, POD = postoperative day.
The risk factors for 45-day mortality were analyzed. Bleeding, surgery time, and hyperbilirubinemia within POD 7-14 were independent risk factors for high mortality. These factors are different from those reported by other LT centers with regard to short-term postoperative mortality. The explanation is that not only were SLT recipients selected as research participants, but the donor selection process was also considered. At present, there is no full legislation on SLT in China. The appropriateness of splitting a donor liver depends on the transplant hospital. Therefore, both donors and recipients are usually strictly chosen by doctors. For example, recipients with a high MELD score will not be selected as SLT recipients. Furthermore, a donor liver with abnormal pathological changes or potential diseases, such as high liver steatosis and viral hepatitis, will not be employed. Strict implementation of in-situ perfusion and in-situ split significantly reduces ischemia time. Therefore, most preoperative and intraoperative risk factors were not significant because they were avoided.

4.4. Hyperbilirubinemia and SLT reserved MHV

Complications and mortality were the focus of previous SLT studies, while few studies have considered liver function, such as non-obstructive hyperbilirubinemia, a postoperative complication that can lead to severe consequences and even death.[40] Abnormal liver function, such as hyperbilirubinemia, can lead to subsequent complications including postoperative biliary tract complications and acute rejection. Similarly, even vascular complications and bleeding can increase bilirubin levels. Eventually, the length of stay will increase and medical expenses will equally increase. Compared with WGLT, SLT usually has a higher bilirubin level within 7 days owing to liver resection; however, the level is not always high. The data show that this increase can often be reduced to the same level as WGLT on the 5th day after surgery, and this transient increase after surgery has no significant impact on short-term mortality. However, it was observed that the bilirubin levels of some recipients remained high 7 days after SLT or gradually increased after early decline. The risk of short-term postoperative death in SLT recipients will be significantly increased. The TB level of liver transplant recipients without MHV was higher and the retention of MHV could accelerate recipient recovery.[41] In subgroup analysis, SLT\(^{MHV}\) –\(^{1-3}\) showed a higher level of TB on POD3 than SLT\(^{MHV}\) \(^{4-7}\). However, no difference was observed in subsequent periods. No significant differences were observed in the hospital stay duration, grade III complications, and overall survival rate. In addition, there was no significant difference in the incidence of primary nonfunction and early allograft dysfunction. Consequently, although the split with the MHV might be helpful to relieve early hyperbilirubinemia, whenever the MHV was included, SLT recovery was slow after surgery. Thus, bleeding and surgery time are closely related to surgery techniques; this means that short-term postoperative SLT mortality may be reduced by improving surgical skills. Besides, for SLT recipients with hyperbilirubinemia within POD 7-14, prolonging the length of stay, early detection and treatment of related complications may reduce short-term mortality.

4.5. Limitations

Although we adopted propensity score matching and controlled for possible bias due to the various LT surgeries, the retrospective nature of the study should be acknowledged as a study limitation. In addition, data from a single center was used, which further limited the scope of the study. Therefore, multicenter studies must be conducted to verify the generalizability of the results to populations from other centers. Furthermore, the small sample size should be acknowledged as a limitation because only 47 recipients were undergoing SLT. Further studies with larger sample sizes are warranted to confirm our findings so that appropriate clinical decision making can be achieved.

5. Conclusions

Adult SLT is safe and effective based on long-term survival rates. However, the incidence of complications in SLT recipients is high and recovery is slow. The key to improving the survival rate of recipients with SLT is to help them safely pass through the high-incidence period of postoperative complications. Non-obstructive hyperbilirubinemia within POD 7-14 is an independent predictor of short-term mortality during SLT, and increased bilirubin within POD 7-14 may prolong hospital stay, lead to subsequent complications, and increase medical expenses.

Author contribution

LK and JY2 designed the study; LJ, JY1, TL, LK performed the research and collected the data; LK analyzed and interpreted the data; LK wrote the first draft of the manuscript; All authors edited and approved the final draft; The acquisition of funding is from J Y2.

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