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Is it safe to expand the indications for split liver transplantation in adults? A single-center analysis of 155 in-situ splits

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[Correction added on 16 May 2022, after first online publication: CAUL funding statement has been added.]

Abstract

Introduction: Split liver transplantation (SLT) enables two recipients to be transplanted using a single donor liver; typically, an adult and a child. Despite equivalent long-term outcomes to whole grafts in selected adults, the use of these grafts in high-risk adult recipients with high model for end-stage liver disease (MELD) scores (≥30), a poor pre-transplant clinical status (ICU or hospital-bound), acute liver failure or retransplantation remains controversial.

Methods: We retrospectively analyzed all deceased donor adult liver transplants performed between July 2002 and November 2019 at a single high-volume center and performed a propensity score-matched analysis. A subgroup analysis was performed to assess utility of these grafts for high-risk recipients.

Results: A total of 1090 adult liver transplants were performed, including 155 SLT (14%). Graft survival at 1-, 3- and 5-years were comparable between recipients of split and whole liver grafts (82%, 79% and 74% vs. 86%, 81% and 77%, respectively, log rank $P = .537$), as was patient survival at 1-, 3- and 5-years. Recipients of split grafts were more likely to have biliary complications and hepatic artery thrombosis, but equivalent long-term survival. Recipients with high MELD scores or a poor pre-transplant clinical status had similar patient and graft survival and complication profiles irrespective of whether they received split or whole grafts.

Conclusions: SLT is an important method for addressing donor shortages and provides comparable long-term outcomes in adult recipients despite an increase in short-term complications. SLT use in high-risk recipients should be considered to allow for sickest-first allocation policies.

KEYWORDS
high MELD score, high-risk recipient, split liver transplantation, urgent indication

1 | INTRODUCTION

Split liver transplantation (SLT) addresses donor shortage by facilitating the transplant of two recipients from a single donor liver; an extended right graft (ERG) for an adult, and a left lateral segment graft (LLSG) for a child).[1] Despite increasing experience with SLT since its first description by Pichelmayr[2] and Bismuth[3] in the 1980s, the use of ERGs in adults has remained controversial. These grafts continue to be considered marginal by many and rarely used in high-risk recipients such as those with high model for end-stage liver disease (MELD) scores.[4,5] When groups have reported equivalent outcomes to whole liver graft (WLG) recipients, strict recipient and donor selection were universal.[6,7] This has generally restricted the use of SLT to the best donors (young, otherwise healthy, and hemodynamically stable), and the recipients with low risk (low MELD score, low urgency, first transplant).

With increasing waiting lists and allocation policies to transplant the sickest first, one potential solution is to broaden these selection criteria and utilize more "marginal" organs for splitting and permit transplant into more risky recipients. SLT has been used successfully in high MELD score recipients,[7,8] and with mixed results in recipients with acute liver failure.[9–11] With increasing experience, at our center, we have taken an increasingly liberal approach to recipient selection and routinely transplant risky recipients with a high MELD score or a poor pre-transplant clinical status (Intensive Care Unit (ICU) or hospital-bound) with an ERG if a suitable child has a high priority for transplantation. In this study, we aimed to analyze the outcomes at our center of adult SLT recipients compared to adult WLG recipients. A propensity score matched analysis was used to account for the effect of donor and recipient selection and provide a more comparable analysis. We particularly focused on high-risk recipients with a high MELD score (≥30), a poor pre-transplant clinical status, acute liver failure or requiring retransplantation to determine whether a more liberal approach to the use of split grafts such as this results in equivalent and acceptable long-term outcomes.

2 | PATIENTS AND METHODS

All deceased donor liver-only transplants performed in adults at Royal Prince Alfred Hospital, Sydney, Australia between July 2002 and November 2019 were included. Data were extracted from the prospectively maintained Australian National Liver Transplantation Unit database and supplemented by retrospective review of the medical records. The primary endpoints were graft and overall patient survival; and the secondary endpoints were vasculo-biliary complications occurring any time after transplant. To negate the effects of recipient selection and any era effect, a propensity score-matched analysis was performed. To assess the utility of SLT in high-risk recipients, we performed a subgroup analysis of recipients with a high MELD score (≥30), recipients with a poor pre-transplant clinical status (admitted to the ICU or hospital), recipients needing transplantation for acute liver failure (Status 1 or Status 2a)[12] and recipients requiring retransplantation. This study was approved by the Sydney Local Health District Ethics Review Committee (Royal Prince Alfred Hospital Zone, Sydney, Australia; HREC/EXCOR/19-12).

2.1 | Split liver transplantation procedures

SLT in Australia prioritizes the pediatric waiting list using an intention to split policy where all donor livers are split if suitable, to provide a LLSG for a pediatric recipient anywhere in the country. Therefore, all suitable livers are split if there is a suitable pediatric recipient on the waiting list. In general, SLT is performed if the donor is young (<50 years old), non-obese, without severe ischemic hepatitis, and hemodynamically stable. At the time of listing, all adult recipients are assessed for suitability for SLT. In this way, the ERG from the split is allocated by blood group to the sickest suitable recipient by MELD score and size compatibility similar to allocation for a WLG. Allocation occurs within the same state unless there is no suitable recipient or there is an urgent recipient in another state. As the only adult liver transplant center in New South Wales, almost all ERGs are retained for our recipients. Patients with acute liver failure (Status 1 and 2a) are given the highest priority and can direct the offer of suitable livers (whole or split) from another Australian state or New Zealand.[12]

A conventional in-situ splitting technique was used during procurement at the donor hospital. Hepatic parenchyma was divided 1cm to the right of the falciform ligament into a LLSG and an ERG, using available devices, often cautery and clamp crush. The coeliac trunk was preferentially kept in continuity with the LLSG unless donor vascular anatomy was prohibitive (multiple right hepatic arteries or small caliber right-sided donor vessels) or required by the recipient (poor arterial inflow vessels). An intraoperative cholangiogram was performed routinely to confirm biliary anatomy prior to splitting and segment IV was not removed. The adult recipient transplant procedure was performed with a preference for a bicaval over piggyback technique for caval reconstruction, and sequential reconstruction of the portal vein and hepatic artery with end-to-end anastomoses or an interposition graft if required. Biliary reconstruction was for both WLG and ERG preferentially a duct-to-duct anastomosis. In cases where this was not suitable, a Roux-en-Y hepaticojejunostomy was used. An abdominal drain was routinely placed.

Post-operative complications were recorded prospectively. Total biliary complications were divided into bile leaks, anastomotic strictures and non-anastomotic strictures. Strictures were only included if intervention was required rather than those found incidentally on cross-sectional imaging for a different purpose. Routine postoperative imaging was not performed. Hepatic artery thrombosis was included if it occurred within 90 days of transplant. Hepatic artery stenosis was defined by computed tomography or digital subtraction angiography demonstrating a stenosis of >70% as we have previously reported.[13] The highest grade morbidity for each transplant was classified using the Clavien-Dindo system.[14]

2.2 | Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows (Version 26; IBM Corp. Armonk, NY, USA) and *R* (Version 4.1.2). For continuous variables, normality was assessed using the Shapiro-Wilk test. Comparison of variables between groups was performed using an independent-samples t-test, Mann-Whitney U test or Pearson's chi-square test as appropriate. Kaplan-Meier survival curves were analyzed using the log rank test. Results were considered significant if $P<.05$. Propensity score matching of ERG and WLG recipients was performed to account for variability in recipient selection using *MatchIt* package (version 4.3.2). Relevant variables were identified on univariate analysis (pre-transplant characteristics that were significantly different between the groups) and used as covariates for logistic regression. Recipients were allocated in a 1:2 ratio using cardinality matching with a tolerance of .01.

3 | RESULTS

3.1 | Patient characteristics

Between July 2002 and November 2019, a total of 1090 adult liver transplants were performed at our center with 155 (14.2%) recipients receiving an ERG and 935 (85.8%) receiving a WLG. The median follow up was 60 months for ERGs (interquartile range (IQR) 17-130) and 56 months for WLGs (IQR 21-112). Baseline recipient, donor and operative factors are displayed in Table 1. When compared to recipients of ERGs, recipients of WLGs were significantly more likely to be male (73% vs. 64%, $P = .020$) and had a significantly higher mean body mass index (BMI) (27.3 +/-5.1, vs. 25.6 +/- 4.9, $P<.001$). This was most likely due to size-matching of split grafts such that females and recipients with a lower BMI were more likely to receive an appropriately sized smaller split graft. In the ERG group, donors were significantly more likely to be younger, non-obese and have a lower donor risk index, consistent with the criteria for splitting at our institution.

Overall, WLGs were used more commonly for high-risk recipients than ERGs. Specifically, WLGs were used more often in recipients with a MELD score ≥30 (19% vs. 12%, $P = .030$), a poor pre-transplant clinical status with the recipient ICU- or hospital-bound (31% vs. 19%, $P = .003$), acute liver failure (10% vs. 5%, $P = .035$) and for retransplantation (7% vs. 2%, $P = .018$). This reflects a relative reluctance to use ERGs for these recipients due to concerns about outcomes.

Across the time period, there was an increase in the proportion of MELD score ≥30 recipients of ERGs between 2002–2012 and 2013–2019 (5/80, 6% vs. 12/66, 18% $P = .025$). Cold ischemic time, warm ischemic time, and operative time were not significantly different between ERGs and WLGs in our population.

3.2 | Propensity score-matched analysis

Propensity score-matching was performed between ERG and WLG recipients to account for donor and recipient selection and to provide a more accurate assessment of outcomes utilizing matched groups. Relevant input variables associated with our outcomes on univariate analysis were included: recipient sex, recipient BMI, high MELD score (≥30), pre-transplant clinical status and donor BMI. Although donor age was identified as statistically significant, our routine is to only split donor livers <50, so it was not included in the propensity score model. Propensity score matching was performed in a 1:2 ratio, resulting in 140 ERGs and 280 WLGs. Comparison of recipient, donor and operative characteristics showed that propensity score-matched cohorts were well matched at baseline (Table 1). The differences between matched and un-matched WLG cohorts are displayed in Appendix Table 3.

3.3 | Outcomes

ERGs and WLGs resulted in similar long-term graft and overall patient survival (Log rank $P = .537$ and $P = .740$, respectively) (Figure 1). For recipients of ERGs and WLGs, the 1-, 3-, 5-, and 10-year graft survival was 82%, 79%, 74% and 66%; and 86%, 81%, 77% and 67%, respectively. The overall patient survival for recipients of ERGs and WLGs at 1-, 3-, 5- and 10-years was 85%, 82%, 80% and 74%; and 90%, 85%, 80% and 70%, respectively. The rate of mortality within the first 90 days post-liver transplant was also not significantly different between the groups (3.2% vs. 4.2%, $P = .580$).

Postoperative complications were common in recipients of both ERGs and WLGs, but not significantly different between the groups (63% vs. 56%, $P = .105$) (Table 2). Biliary complications, however, were significantly more common in recipients of ERGs than WLGs (32% vs. 21%, $P = .002$). Cut-edge bile leaks occurred in 13.5% recipients of ERGs, while the rate of anastomotic leak was not significantly different between ERGs and WLGs (11% vs. 9%). The rate of hepatic artery thrombosis was also higher in the ERG recipients when compared to WLG recipients in the unmatched cohort (14/155 (9%) vs. 24/935 (3%), $P<.001$). Anastomotic bile leaks, hepatic artery stenosis, portal vein and hepatic outflow complications were not significantly different between the groups (Table 2).

Propensity score-matching did not alter these findings. Biliary complications remained significantly more common in recipients of ERGs compared to WLGs (35% vs. 22%, $P = .005$). Similarly, hepatic artery thrombosis occurred at a significantly higher rate in recipients of ERGs than WLGs (9% vs. 3%, $P = .018$).

In the recipients of ERGs, there were five cases of graft failure requiring urgent retransplantation. Two were due to primary non function, another two due to hepatic artery thrombosis and one due to severe acute rejection. All were retransplanted with WLGs and are long-term survivors except for the recipient with severe acute rejection

TABLE 1 Recipient, donor and operative characteristics for recipients of extended right split grafts and whole liver grafts

	Split (ERG) $n = 155$	Whole grafts $n = 935$	*P*-value	Split (ERG) grafts (propensity-score matched) $n = 140$	Whole grafts (propensity-score matched) $n = 280$	*P*-value
Recipient factors						
Age at transplant (median, IQR)	53.8 (12.9)	54.4 (12.2)	$P = .267$	54.1 (12.3)	55.0 (12.2)	$P = .358$
Sex (Male (%))	99/155 (63.9%)	682/935 (72.9%)	$P = .020^*$	95/140 (67.9%)	191/280 (68.2%)	$P = .941$
BMI (median, IQR)	25.0 (5.4)	26.3 (5.9)	$P<.001^*$	25.0 (5.3)	24.4 (4.8)	$P = .346$
MELD score (median, IQR)	17.0 (11.3)	19.0 (13.0)	$P = .002^*$	17.0 (10.8)	18.0 (10.0)	$P = .823$
MELD score ≥20	57/146 (39.0%)	444/918 (48.4%)	$P = .036^*$	56/140 (40.0%)	107/280 (38.2%)	$P = .723$
MELD score ≥30	17/146 (11.6%)	175/918 (19.1%)	$P = .030^*$	16/140 (11.4%)	33/280 (11.8%)	$P = .914$
Indication for transplant						
Alcohol	17/155 (11.0%)	154/935 (16.5%)		17/140 (12.1%)	45/280 (16.1%)	
Hepatitis B or C	41/155 (26.5%)	284/935 (30.4%)		39/140 (27.9%)	87/280 (31.1%)	
HCC	33/155 (21.3%)	126/935 (13.5%)		31/ 140 (22.1%)	40/280 (14.3%)	
PSC	20/155 (12.9%)	69/935 (7.4%)	$P = .067$	19/140 (13.6%)	28/280 (10.0%)	$P = .272$
NASH	5/155 (3.2%)	57/935 (6.1%)		5/140 (3.6%)	8/280 (2.9%)	
PBC	7/155 (4.5%)	35/935 (3.7%)		7/140 (5.0%)	14/280 (5.0%)	
Other	32/155 (20.6%)	210/935 (22.5%)		22/140 (15.7%)	58/280 (20.7%)	
Pre-transplant clinical status						
1 – ICU	8/155 (5.2%)	102/931 (11.0%)		7/140 (5.0%)	14/280 (5.0%)	
2 – hospital bound	22/155 (14.2%)	186/931 (20.0%)	$P = .025^*$	21/140 (15.0%)	43/280 (15.4%)	$P = 1.000$
3 – occasional inpatient	29/155 (18.7%)	158/931 (17.0%)		26/140 (18.6%)	51/280 (18.2%)	
4 – at home	96/155 (61.9%)	485/931 (52.1%)		86/140 (61.4%)	172/280 (61.4%)	
Acute liver failure (Status 1, Status 2A)	7/155 (4.5%)	91/935 (9.7%)	$P = .035$	6/140 (4.3%)	11/280 (3.9%)	$P = .861$
Retransplant	3/155 (1.9%)	64/935 (6.8%)	$P = .018^*$	3/140 (2.1%)	16/280 (5.7%)	$P = .097$
Donor factors						
Age (median, IQR)	30.0 (19.0)	51.0 (26.0)	$P<.001^*$	30.0 (19)	49.0 (29)	$P<.001^*$
Sex (Male, %)	92/155 (59.4%)	518/935 (55.4%)	$P = .358$	85/140 (60.7%)	138/280 (49.3%)	$P = .027^*$
BMI (median, IQR)	24.2 (4.8)	25.4 (5.3)	$P<.001^*$	24.6 (4.9)	23.4 (4.4)	$P = .113$
Cause of death						
Trauma	60/155 (38.7%)	179/935 (19.1%)		55/140 (39.3%)	57/280 (20.4%)	
Cerebrovascular event	56/155 (36.1%)	485/935 (51.9%)		52/140 (37.1%)	144/280 (51.4%)	
Cardiac arrest	3/155 (1.9%)	62/935 (6.6%)	$P<.001^*$	3/140 (2.1%)	17/280 (6.1%)	$P = .002^*$
Respiratory hypoxia	27/155 (17.4%)	183/935 (19.6%)		22/140 (15.7%)	49/280 (17.5%)	
Other	9/155 (5.8%)	26/935 (2.8%)		8/140 (5.7%)	13/280 (5.7%)	
DRI (median, IQR)	1.76 (.39)	1.23 (.19)	$P<.001^*$	1.76 (.38)	1.20 (.18)	$P<.001^*$
DRWR (median, IQR)	1.02 (.37)	.96 (.32)	$P = .090$	1.0 (.37)	.97 (.30)	
Operative factors						
Cold ischemia time (mins, median, IQR)	383 (206)	414 (187)	$P = .165$	396 (214)	391 (194)	$P = .938$
Warm ischemia time (mins, median, IQR)	45 (17)	47 (20)	$P = .702$	45 (18)	46 (19)	$P = .420$
Packed cells (median, IQR)	3 (7)	5 (7)	$P<.001^*$	3 (7)	5 (7)	$P = .002^*$
Operative time (median, IQR)	354 (115)	356 (139)	$P = .799$	355 (115)	360 (130)	$P = .631$

Abbreviations: BMI, body mass index; DRI, donor risk index; DRWR, donor-recipient weight ratio; ERG, extended right graft; HCC, hepatocellular carcinoma; ICU, intensive care unit; IQR, interquartile range; NASH, non-alcoholic steatohepatitis; MELD, Model for end-stage liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; SD, standard deviation.

*$P<.05$.

A propensity score-matched analysis was performed using recipient sex, recipient BMI, MELD score ≥30, urgency of transplant, and donor BMI.

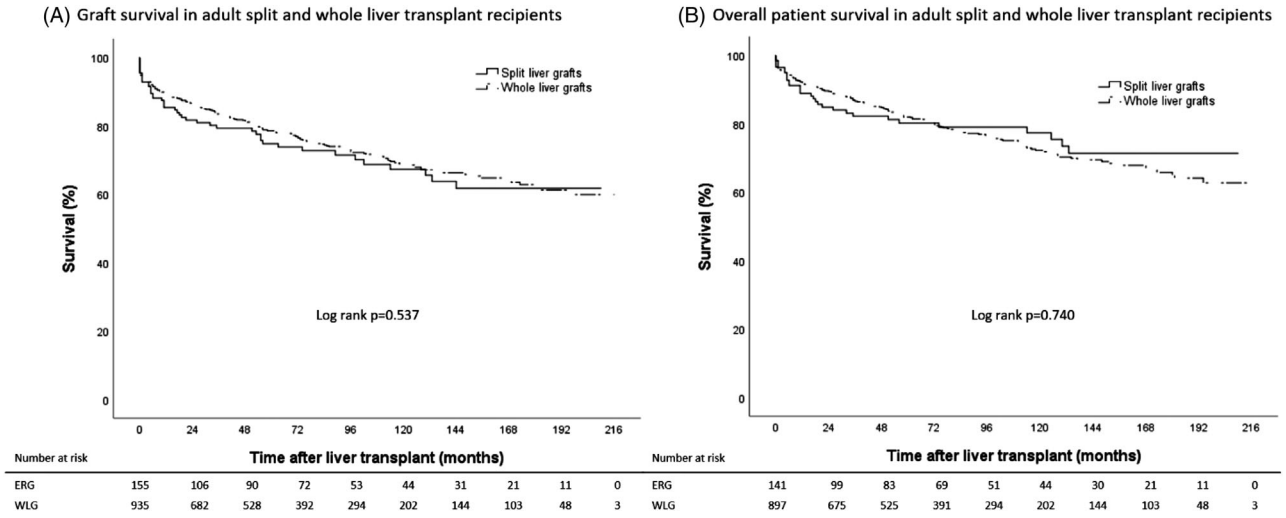

FIGURE 1 Graft and overall patient survival using a Kaplan-Meier survival analysis. Graft survival (A) and patient survival (B) were not significantly different between recipients of extended right grafts and whole liver grafts (Log rank $P = .537$ and $P = .740$, respectively). For recipients of extended right and whole liver grafts, the 1-, 3-, 5-, and 10-year graft survival was 82%, 79%, 74% and 66%; and 86%, 81%, 77% and 67%, respectively. The overall patient survival for recipients of extended right and whole liver grafts at 1-, 3-, 5- and 10-years was 85%, 82%, 80% and 74%; and 90%, 85%, 80% and 70%, respectively

who ultimately passed away after another retransplant due to rejection.

3.4 | High MELD score recipients

A total of 192 adults had a high-MELD score (≥30) at the time of transplant (18%). An ERG was used in 17 (9%) and a WLG used in 175 recipients (91%). The median follow-up in this high MELD score population was 60 months (IQR 29–85 months). In the group of patients receiving a split graft, high MELD score recipients were more likely to have a poor pre-transplant clinical status with admission to ICU or hospital than those with a low MELD score (13/17, 76% vs. 16/129, 12%, $P<.001$) (Appendix Table 1). They also had a higher median packed cell transfusion requirement and were more likely to be transplanted for decompensated cirrhosis rather than hepatocellular carcinoma (Appendix Table 1).

Comparison of high MELD score recipients of ERGs and WLGs demonstrated that the postoperative complication profiles were similar (Appendix Table 2). There were no significant differences between the rates of biliary anastomotic leaks or strictures or hepatic artery thrombosis. Similarly, rates of primary non function, return to theatre for bleeding and mortality rate <90 days were not different between the groups. There was a higher rate of infected collections in this group, presumably related to bile leaks from the cut-edge of the liver (6/17, 35% vs. 22/175, 13%, $P = .011$)

The long-term graft and overall patient survival of recipients of ERGs and WLGs with a MELD score ≥30 were similar (log rank $P = .472$ and $P = .264$, respectively) (Figure 2). Graft survival at 1-, 3- and 5-years for recipients of ERGs was 87%, 87% and 87%, compared to 95%, 85%, and 71%, for recipients of WLG, respectively. Overall patient survival for recipients of ERGs at 1-, 3- and 5- years was 93%, 93%, and 93%, and 95%, 87% and 76% for recipients of WLGs, respectively.

Recipients with a very high MELD score (≥35) were less likely to receive an ERG compared to a WLG, and a split graft was used for this purpose only on seven occasions (5% vs. 11%, $P = .029$). All seven recipients of ERGs with a MELD score of ≥35 remain alive, with a median follow up of 45 months (range 3–107 months).

3.5 | Poor pre-transplant clinical status, acute liver failure and retransplantation

During the time period, 318/1086 (29%) recipients had a poor pre-transplant clinical status (admitted to ICU, or hospital-bound). A total of 98/1090 (9%) recipients were transplanted for acute liver failure and 67/1090 (6%) were retransplant cases.

An ERG was used in recipients with a poor pre-transplant clinical status on 30 occasions (9%). Postoperative outcomes in these patients were generally equivalent to the use of WLGs (Appendix Table 2). Notably, there were no significant differences between recipients of ERGs and WLGs in the rates of biliary complications (23% vs. 19%, $P = .611$), hepatic artery thrombosis (3% vs. 2%, $P = .764$), primary non function (3% vs. 1%, $P = .329$) or bleeding (7% vs. 14%, $P = .285$). Long-term graft and patient survival for these patients with poor pre-transplant clinical status was also similar for recipients of ERGs and WLGs (log rank $P = .199$ and $P = .392$, respectively) (Appendix Figure 1).

For patients admitted to the ICU at time of transplant, an ERG was used eight times (8/110, 7%). In one recipient, graft failure occurred in 6 days and retransplantation was required. Two others died at 5 months and 3 years, respectively, due to chronic rejection and overwhelming

TABLE 2 Postoperative complications for recipients of extended right split grafts and whole liver grafts

	Split (ERG) $n = 155$	Whole grafts $n = 935$	*P*-value	Split (ERG) grafts (propensity-score matched) $n = 140$	Whole grafts (propensity-score matched) $n = 280$	*P*-value
Any surgical complication	97/155 (62.6%)	520/935 (55.6%)	$P = .105$	91/140 (65.0%)	160/280 (57.1%)	$P = .122$
Biliary complication	50/155 (32.3%)	196/935 (21.0%)	$P = .002^*$	49/140 (35.0%)	62/280 (22.1%)	$P = .005^*$
Bile leak from cut-edge	21/155 (13.5%)	-		21/140 (15.0%)		
Biliary anastomotic leak	17/155 (11.0%)	87/935 (9.3%)	$P = .514$	16/140 (11.4%)	21/280 (7.5%)	$P = .181$
Biliary anastomotic stricture	24/155 (15.5%)	119/935 (12.7%)	$P = .346$	23/140 (16.4%)	46/280 (16.4%)	$P = 1.000$
Biliary non-anastomotic stricture	6/155 (3.9%)	40/935 (4.3%)	$P = .815$	6/140 (4.3%)	15/280 (5.4%)	$P = .635$
Hepatic artery thrombosis	14/155 (9.0%)	24/935 (2.6%)	$P<.001^*$	12/140 (8.6%)	9/280 (3.2%)	$P = .018^*$
Hepatic artery stenosis	17/155 (11.0%)	92/935 (9.8%)	$P = .665$	15/140 (10.7%)	35/280 (12.5%)	$P = .594$
Portal vein thrombosis	3/155 (1.9%)	25/935 (2.7%)	$P = .590$	3/140 (2.1%)	9/280 (3.2%)	$P = .534$
Primary non function	2/155 (1.3%)	13/935 (1.4%)	$P = .638$	2/140 (1.4%)	4/280 (1.4%)	$P = 1.000$
Bleeding	14/155 (9.0%)	103/935 (11.0%)	$P = .460$	13/140 (9.3%)	27/280 (9.6%)	$P = .906$
Infected collection	22/155 (14.2%)	103/935 (11.0%)	$P = .250$	22/140 (15.7%)	36/280 (12.9%)	$P = .424$
Wound complication	15/155 (9.7%)	127/935 (13.6%)	$P = .181$	15/140 (10.7%)	31/280 (11.1%)	$P = .912$
DVT/PE	6/155 (3.9%)	24/935 (2.6%)	$P = .358$	5/140 (3.6%)	4/280 (1.4%)	$P = .153$
Most severe Clavien Dindo grade <90 days						
I	23/155 (14.8%)	137/935 (14.7%)		19/140 (13.6%)	42/280 (15.0%)	
II	36/155 (23.2%)	219/935 (23.4%)		32/140 (22.9%)	71/280 (25.4%)	
IIIA	8/155 (5.2%)	39/935 (4.2%)		8/140 (5.7%)	17/280 (6.1%)	
IIIB	40/155 (25.8%)	203/935 (21.7%)	$P = .925$	38/140 (27.1%)	56/280 (20.0%)	$P = .861$
IVA	12/155 (7.7%)	89/935 (9.5%)		11/140 (7.9%)	24/280 (8.6%)	
IVB	3/155 (1.9%)	16/935 (1.7%)		3/140 (2.1%)	4/280 (1.4%)	
V	5/155 (3.2%)	39/935 (4.2%)		4/140(2.9%)	8/280 (2.9%)	
Mortality <90 days	5/155 (3.2%)	39/935 (4.2%)	$P = .580$	4/140 (2.9%)	8/280 (2.9%)	$P = 1.000$

Abbreviations: BMI, body mass index; DVT/PE, deep vein thrombosis/pulmonary embolism.
*$P<.05$.
A propensity score-matched analysis was performed using recipient age, recipient BMI, high MELD score, urgency of transplant, donor age and donor BMI.

sepsis. The remaining 5/8 remained alive with functioning grafts at the time of the study (Four of these were >4 years post-transplant).

In the time period, ERGs were used for patients with acute liver failure only on seven occasions. Four of these were for drug-induced liver injury and one was for an acute flare of chronic hepatitis B. The final two were acute retransplants for early graft failure. Graft failure occurred in 3/7 recipients and one of these did not survive to retransplant. The remaining patients were still alive at time of study analysis. In the three cases where an ERG was used for retransplantation, two were acute retransplants for early graft failure as discussed above and the other was for chronic biliary strictures. One of the acutely retransplanted patients is a long-term survivor (15 years), while the other succumbed to severe acute rejection after 6 days. The other recipient of an ERG for retransplantation died after 6 months due to complications of hepatic artery thrombosis and biliary sepsis. In general, ERGs were not commonly used for acute liver failure or retransplant cases due to our preference to avoid these grafts in these situations.

4 | DISCUSSION

Despite increasing experience with the technique worldwide, SLT remains controversial and ERGs are implanted into adults with caution.[5] In the present study, we report a large series of SLT recipients in adults with graft and patient survival that is equivalent to recipients of WLGs. We observed an increased rate of biliary complications and hepatic artery thrombosis in the recipients of ERGs. These finding are consistent with previous studies in this area, with multiple meta-analyses demonstrating this pattern of equivalent survival but increased complications.[5,15,16] In our population of ERGs, the increased rates of biliary complications, (50/155 32%) are attributed largely to cut-edge bile leaks (21/155, 13.5%), with similar rates of anastomotic strictures and anastomotic leaks to the WLG population. This is important to acknowledge since these cut-edge bile leaks constitute a relatively minor complication and are often managed non-operatively with good results.[17]

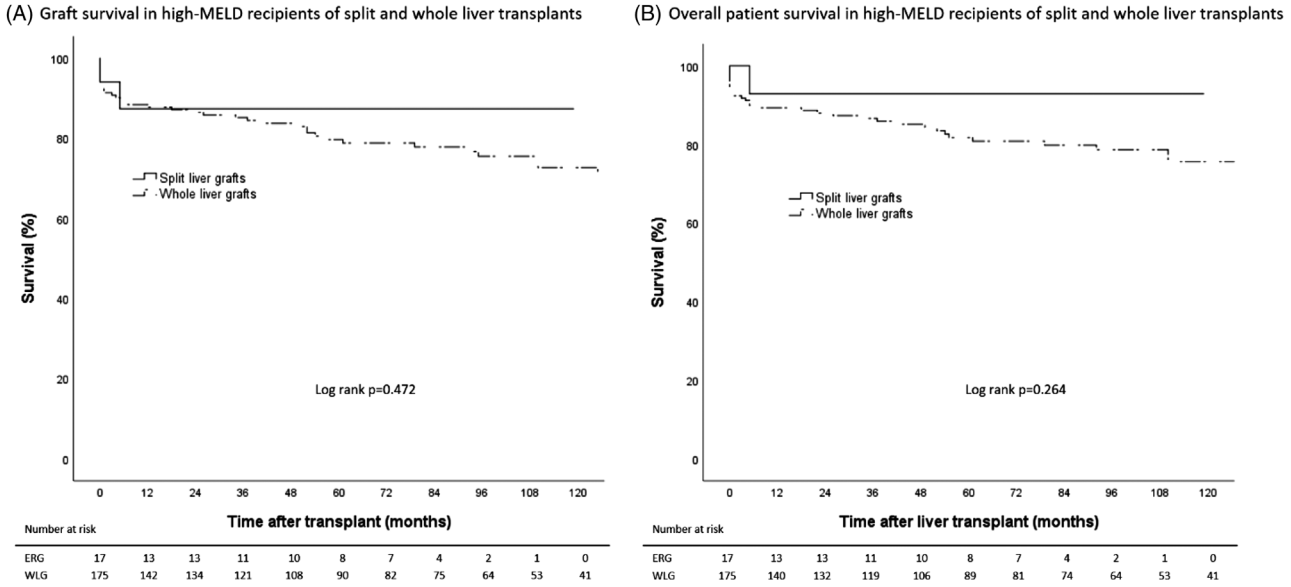

FIGURE 2 Graft and overall patient survival using a Kaplan-Meier survival analysis. Graft survival (A) and patient survival (B) were not significantly different between high MELD score (≥30) recipients of extended right split grafts and whole liver grafts (Log rank $P = .472$ and $P = .264$, respectively). Graft survival at 1-, 3- and 5-years for recipients of ERGs was 87%, 87% and 87%, compared to 95%, 85%, and 71%, for recipients of WLG, respectively. Overall patient survival for recipients of ERGs at 1-, 3- and 5- years was 93%, 93%, and 93%, and 95%, 87% and 76% for recipients of WLGs, respectively

An important point of difference in our study, compared to many others published, is the universal use of the in-situ splitting technique. Our practice is to split the liver at the donor hospital during native circulation, rather than in an ice-bath on the back-table. To our knowledge, this is the largest single-center series with the use of the in-situ technique. The advantages of this technique are: a shorter cold ischemia time and the opportunity for accurate, hemostatic splitting of the liver parenchyma. The disadvantages are an increased donor surgery time and the need for transplant surgeons with hepatobiliary expertise to travel to the donor hospital.[18] We find that using the in-situ technique is critical to minimize the cold ischemia time in a geographically large country like Australia where there can be large distances between donor and recipient hospitals. The largest previous single-center study of in-situ SLT reported 72 recipients of ERGs[10] and the largest overall reported 382 SLTs from nine transplant centres.[19] By comparison, the largest single-center study to date using the ex-vivo splitting technique included 212 SLTs.[20]

To account for differences in recipient and donor selection, a propensity score-matched analysis was used in this study. Variables chosen for the propensity score matching equation represented differences in baseline characteristics on univariate analysis and allowed us to account for donor and recipient selection utilized when choosing split grafts. In the matched cohort, the significantly increased rate of vasculo-biliary complications persisted between recipients of ERGs when compared to WLGs. The higher rate of hepatic artery thrombosis in the recipients of ERGs is likely due to the necessary anastomosis to a smaller right hepatic artery during implant of the split graft.[21] The caliber and length of this donor right hepatic artery can also necessitate an arterial interposition graft, which, by addition of a second arterial anastomosis, may also explain the increased rate of hepatic artery thrombosis. However, we have found that using interposition grafts liberally can make a technically challenging anastomosis easier and somewhat mitigate this risk.[22] As such, despite an increased rate of these short-term vasculobiliary complications in this cohort, the recipients of ERGs had equivalent long-term graft and overall patient survival.

Thus, although split grafts appear to be higher risk than WLGs in terms of early complications, the long-term survival data from our center and others' supports their continued use for adults and perhaps even an expansion of the indications.[15,16] While, SLT may benefit the pediatric waiting list in the context of donor shortages, it must also be acknowledged that it comes at the cost of an increased rate of short-term morbidity for the adult recipients.

High MELD score recipients accounted for 12% of all SLT recipients in our study. Although not commonly reported, this is less than the use of split grafts for high MELD score recipients reported in studies of the United Network for Organ Sharing registry (36.4%) and the Korean Network for Organ Sharing registry (26.5% MELD >30).[7,8] This difference is likely due to our historical reluctance to use ERGs for high-risk recipients with our rate of high MELD recipients in this group as low as 5% prior to 2012. Our data and these registry studies all support the use of ERGs for high MELD score adult recipients. It has become our practice to not exclude potential recipients from using ERGs on the basis of MELD-score alone, as long as the graft will provide an adequate size-match. Although with a higher MELD-score, an inferior complication profile might be expected from the use of split grafts, our results demonstrate the safety of using these grafts in recipients with a high MELD score in the same way we might use a WLG.

In this study, ERGs were used relatively commonly for recipients with a poor pre-transplant clinical status (19%), but uncommonly for acute liver failure (4.5%). This is comparable to other centres with reported rates ranging from 10% to 58% depending on the definition used.[9–11] We have also demonstrated equivalent results for recipients of ERGs and WLGs in patients with a poor pre-transplant clinical status. Other groups seem to have had more mixed results. Hong et al reported inferior long-term survival in recipients of ERGs, possibly due to a significantly increased proportion of split grafts used for acute liver failure[10] while others have demonstrated comparable mortality and morbidity.[9,11] Ultimately, these findings are likely a reflection of local allocation policies and recipient selection but based on our findings, we support the use of ERGs for recipients with poor pretransplant clinical status.

Using ERGs for acute liver failure and retransplantation; however, is controversial. In general, we avoid allocating split grafts for these indications apart from exceptional circumstances. As a consequence, our study only identified seven SLTs for acute liver failure and three for retransplantation Therefore the conclusions that can be drawn are limited. Ultimately, 3/7 recipients with acute liver failure suffered graft failure and 2/3 retransplant recipients did not survive. These findings are consistent with the published literature, with retransplantation being a risk factor in ERG recipients for significantly worse graft and patient survival.[10,19]

Another strategy to expand the indications for SLT is full-left full-right splitting for two adult recipients. Transplant of WLGs tends to underserve female and small-sized recipients due to a lack of donors with a suitable size-match, and full-left full-right splitting represents a potential solution.[18,23] A higher proportion of our WLG compared to SLT recipients were male (73% vs. 64%) which highlights this disparity. However, results to date using this technique have been disappointing with only a few studies comparing full-left full-right SLTs to WLGs and most reporting inferior survival.[18,24–26] Using this strategy likely requires separate allocation, independent of a MELD-based system and allocation to recipients of an appropriate size and condition. Our experience is that small-sized recipients are often well-served by an ERG, and for this reason, we liberally assess them as suitable for SLT so that these grafts are available to them during the allocation process.

The main limitation of this study is its retrospective nature and despite propensity score matching, it is not equivalent to a prospective randomized controlled trial. Further, the subgroup analyses of high-risk groups resulted in small numbers which limited our ability to draw strong conclusions. However, retrospective data collection provided the opportunity to maximize our study cohort and follow-up time. This single-center report also limits the generalizability of our results to other countries and other centers. Nonetheless, our large sample size in a population with its own challenges (regional and distant donors and recipients) should provide some confidence in our liberal use of ERGs for adult recipients. In particular, we support the use of ERGs for high MELD score and poor pretransplant clinical status recipients based on a comparable outcomes profile.

To improve recipient waiting lists, future research should focus on improving the utilization of ERGs, particularly in high-risk recipients with high MELD scores or urgent indications. There may also be a role to expand the donor selection criteria for livers that are suitable for splitting. The advancement of machine perfusion technology could allow sophisticated assessment of marginal grafts for suitability for splitting, and then for viability testing of each graft prior to implant.[18] In this way, we will be able to better understand which livers are suitable for which recipients and thereby improve the utility of each donated liver.

5 | CONCLUSION

SLT is an effective way of reducing recipient waiting lists and can provide comparable results to WLGs when recipient-donor matching is performed. In this study, we present the largest single-center series to date of in-situ SLTs and have demonstrated equivalent graft and patient survival. ERGs can also safely be used in high MELD score and poor pre-transplant clinical status indication recipients without compromising long-term outcomes but at this stage we do not recommend their routine use for retransplantation, and the role in acute liver failure remains uncertain. Overall, we support the use of SLT, even for high-risk recipients, and encourage transplant surgeons to continue to push the boundaries for the use of these grafts in the future.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Ngee-Soon Lau participated in research design, performed the research, analyzed the data and wrote the paper. Mark Ly, Ken Liu, Avik Majumdar, Simone I. Strasser, Geoffrey W. McCaughan and Michael Crawford participated in research design and critically reviewed the manuscript. Raaj K. Biswas analyzed the data, performed statistical review and critically reviewed the manuscript. Carlo Pulitano participated in research design, analyzed the data and reviewed the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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