Original Article

A novel nomogram for prognosis stratification in salvage liver transplantation: a national-wide study with propensity score matching analysis in China

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Background: Salvage liver transplantation (SLT) has been reported to be an efficient treatment option for patients with recurrent hepatocellular carcinoma (HCC) after liver resection (LR). However, for recipients who underwent liver transplantation (LT) due to recurrent HCC after LR in China, the selection criteria are not well established.

Methods: In this study, data from the China Liver Transplant Registry (CLTR) of 4,244 LT performed from January 2015 to December 2019 were examined, including 3,498 primary liver transplantation (PLT) and 746 SLT recipients. Propensity score matching (PSM) analysis was used to minimize between-group imbalances. The overall survival (OS) and disease-free survival (DFS) between PLT and SLT in recipients fulfilling the Milan or Hangzhou criteria were compared based on the multivariate analysis, nomograms were plotted to further classify the SLT group into low- and high-risk groups.

Results: In this study, the 1-, 3- and 5-year OS and DFS of SLT recipients fulfilling Milan criteria (OS, P=0.01; DFS, P<0.001) or Hangzhou criteria (OS, P=0.03; DFS, P=0.003) were significantly reduced when compared to that of PLT group after PSM analysis. Independent risk factors, including preoperative transarterial chemoembolization (TACE), alpha fetoprotein (AFP) level, tumor maximum size and tumor total diameter were selected to draw a prognostic nomogram. The low-risk SLT recipients (1-year, 95.34%; 3-year, 84.26%; 5-year, 77.20%) showed a comparable OS with PLT recipients fulfilling

Hangzhou criteria (P=0.107).

Conclusions: An optimal nomogram model for prognosis stratification and clinical decision guidance of SLT was established. The low-risk SLT recipients based on the nomograms showed comparable survival with those fulfilling Hangzhou criteria in PLT group.

Keywords: Salvage liver transplantation (SLT); nomogram; primary liver transplantation (PLT); overall survival (OS); disease-free survival (DFS)

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Introduction

Liver resection (LR) is considered as a curative option for patients with hepatocellular carcinoma (HCC) with 5-year overall survival (OS) of 30–50%, whereas 2-year recurrence rates was still up to 76% (1). Within the Milan criteria, primary liver transplantation (PLT) is the most effective treatment to eliminate both tumors and potential liver lesion (2,3). However, the drop-out rates of waiting list exceed 20% for these recipients due to organ shortage (4). Thus, many centers attempt to perform LR first and then salvage liver transplantation (SLT) in case of recurrence (5). When compared with PLT, different centers report controversial results regarding SLT. In the previous studies, propensity score matching (PSM) analysis has not been examined and thereby introduced uncontrolled bias, which affected the veracity of the results. It also should be noted that all the studies regarding SLT and PLT lacked a large sample size. Furthermore, previous reports did not present any new classification of the recipients in SLT group when they found that the survival of SLT was inferior to PLT.

In the present study, based on the data from the China Liver Transplant Registry (CLTR), OS and disease-free survival (DFS) of recipients fulfilling Milan criteria and Hangzhou criteria with PSM analysis were compared to verify if the criteria for candidate assessment in SLT were applicable or not. Additionally, landmark OS and DFS, which were measured from the relevant time point to the time of the event of interest (death or recurrence), were compared between the two groups. Finally, the nomograms plotted based on the results of multivariate analysis were used to classify SLT group into low- and high-risk groups. And OS and DFS of low-risk recipients were compared with PLT recipients fulfilling Hangzhou criteria. We present this article in accordance with the STROBE reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-22-304/rc).

Highlight box

Key findings

- This study demonstrates that the overall survival (OS) and disease-free survival (DFS) of recipients fulfilling the Milan or Hangzhou criteria show a significant reduction in the salvage liver transplantation (SLT) group compared to primary liver transplantation (PLT) group.
- SLT risk stratification system based on nomogram can further classify SLT recipients into low- and high-risk groups.
- The low-risk SLT group show comparable OS and DFS to PLT group fulfilling Hangzhou criteria.

What is known and what is new

- PLT is thought to be the most optimal treatment strategy for hepatocellular carcinoma (HCC) recipients. Guided by strong recent evidence, Milan, University of California San Francisco and Hangzhou criteria are used in the majority centers, achieving excellent outcomes.
- This study based on a huge data set from mainland China compare post-transplant survival of recipients fulfilling Milan or Hangzhou criteria between SLT group and PLT group with propensity score matching analysis. The risk stratification system could assist for clinical decision guidance in SLT management, so as to achieve an improved long-term prognosis.

What is the implication, and what should change now?

- It implicated that well selected SLT recipients could achieve a comparable long-term prognosis as PLT recipients fulfilling current criteria.
- Given the current donor organ shortage, not all of HCC recipients need to be considered PLT right away. Radical hepatectomy could be performed firstly for some HCC patients. SLT could be considered based on the risk stratification system when tumor recurrence.

Methods

Patients and informed consent

This study retrospectively analyzed 23,476 liver transplants

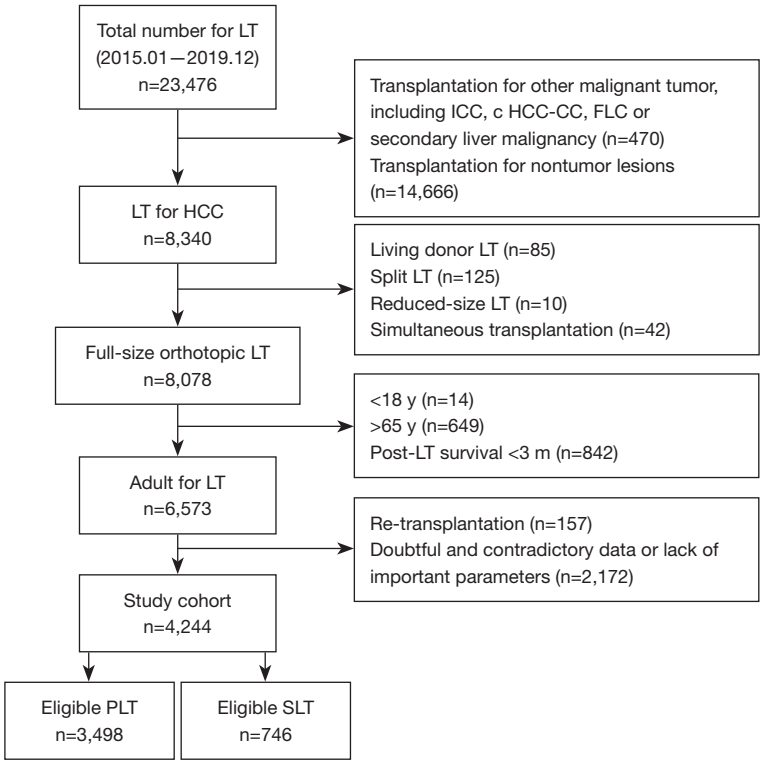


Figure 1 Flow chart for recipients enrollment. LT, liver transplantation; ICC, intrahepatic cholangiocarcinoma; HCC, hepatocellular carcinoma; c HCC-CC, combined hepatocellular carcinoma-cholangiocarcinoma; FLC, fibrolamellar hepatocellular carcinoma; PLT, primary liver transplantation; SLT, salvage liver transplantation.

performed from January 2015 to December 2019, and whose clinicopathological data were obtained from the CLTR. This was performed according to the Declaration of Helsinki (as revised in 2013) and approved by the CLTR (No. 20200039). Informed consent was obtained from all the patients for the use of their data for research purposes. The civilian organ donation is the sole source for organ transplant in China from January 2015 (6). All patients in this study did not receive liver grafts from prisoners. All patients with HCC scheduled for LT were evaluated preoperatively using ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET)-CT, bone scintigraphy, and colonoscopy to rule out extrahepatic disease which was unsuitable for LT. Preoperative loco-regional therapies, including radio frequency ablation (RFA), TACE and percutaneous ethanol injection, were performed to control or reduce the tumor lesion preoperatively. Moreover, the radiological information was acquired from the latest CT or MRI examination before LT. HCC recurrence was diagnosed based on the China Guidelines for Diagnosis and Treatment of Primary Liver Cancer in China.

Inclusion and exclusion criteria

The subject selection process is depicted in *Figure 1*. The excluded criteria were as follows: patients with concurrent other malignancies, or with pathologically-confirmed tumor types, including intrahepatic cholangiocarcinoma (ICC), combined HCC, fibrolamellar hepatocellular carcinoma (FLC) or secondary metastatic tumor; patients without histological confirmation of HCC for transplantation. Subsequently, a total of 8,340 patients were available for analysis. Additionally, patients who received a living donor LT, split LT, reduced-size LT or simultaneous transplantation were excluded, thereby obtaining 8,078 patients who underwent a full-size orthotopic LT. Next, pediatric patients (<18 years) or older patients (>65 years) and patients who died within 3 months after transplantation were excluded, thus, obtaining 6,573 patients suitable for analysis.

Finally, patients with incomplete follow-up, having doubtful or contradictory data and missing essential data for analysis or re-transplantation during follow-up time were excluded. Therefore, 4,244 patients were included in the study.

Baseline characteristics and postoperative follow-up

Patient's baseline clinical characteristics were collected along with demographic characteristics, including age, sex, body mass index (BMI), preoperative alpha fetoprotein (AFP) level; ABO blood matched or mismatched, hepatitis B virus (HBV) infection, Child-Pugh grade, model for end-stage liver disease (MELD), preoperative loco-regional therapy, largest tumor size, tumor number, satellite lesions, creatinine level, hypertension, diabetes and chronic pulmonary. Cold ischemia time, operative time, intensive care unit (ICU) stay time, operative bleeding and the use of glucocorticoids were also collected.

All the patients received regular follow-ups after discharge from the hospital. Any patients who failed to attend a follow-up appointment was contacted by a research nurse via phone. Liver function tests, serum tumor marker assays, abdominal ultrasound and CT, chest CT and bone scans were routinely performed every 6 months for the first 2 or 3 years and annually thereafter.

Statistical analyses

Continuous variables with a normal distribution are expressed as the mean ± standard deviation or median (interquartile range). Categorical variables are expressed as numbers (n) or proportions (%). The Student's *t*-test was used for comparison of continuous variables when applicable, otherwise, the Mann-Whitney *U* test was applied. Categorical variables were compared using χ^2 test or Fisher's exact test, as appropriate. Using the Kaplan-Meier method generated by the log-rank test, the DFS and OS rates were compared between SLT and PLT groups.

Landmark OS and DFS were calculated. Time-to-event endpoints (OS and DFS) were measured among the recipients event-free at the time point post randomization: 1 and 2 years. They were measured from the relevant time point to the time of the event of interest (DFS event or death) occurred (7). Recipients who did not experience the event of interest were censored at the date that they were last known to be alive. Survival rates were also evaluated using the Kaplan-Meier method and were compared using log-rank tests. Univariate and multivariate Cox proportional hazards models were performed to identify independent prognostic factors of OS and DFS in the SLT population and whole population respectively. In multivariate analysis, factors with $P \leq 0.2$ in univariate analysis were finally tested, and $P \leq 0.05$ in the Cox model was considered statistically significant.

Then, the results of the multivariate analysis served as the basis for the construction of the nomograms. The accuracy of the final OS and DFS models were evaluated by estimating the models' calibration, and the discrimination was measured using the concordance index (C-index) (8). The C-index is the probability that one event had a higher probability to happen according to the model in two selected group. A c-index of 0.5 indicated agreement by chance alone, and a c-index of 1 indicated perfect discrimination. Furthermore, SAS Version 9.4 software (SAS Institute Inc., Cary, NC, USA) was used to perform all statistical analyses.

To explain some differences in the baseline patients demographics and tumor characteristics in the PLT and SLT groups that could impact outcomes, an analysis using a PSM was performed to match the population (9). The baseline characteristics of recipients which were not balanced in the two groups before PSM and the potential prognostic factors of LT recipients were included in our study [such as: age, sex, Child-Pugh, pre-operative TACE, pre-operative RFA, HBV, international normalized ratio (INR), BMI, MELD, tumor numbers, tumor maximum size, blood loss, cold ischemia time and ICU stay time]. The two groups were paired on a 1:1 ratio.

Results

Patient demographics and survivals

Of the 4,244 LTs performed to treat HCC, 3,498 patients underwent PLT (PLT group), and 746 patients underwent SLT for recurrence after LR (SLT group). Overall and PSM-matched patient demographics and tumor characteristics are listed in detail in *Table 1*. An imbalance in some variables between the PLT and SLT groups was observed (*Table 1*). The median BMI was 23.60 kg/m^2 (range, 21.80–25.63 kg/m^2) and 23.18 kg/m^2 (range, 21.26–24.80 kg/m^2) in the PLT and SLT groups, respectively ($P<0.001$). The PLT group had an impaired liver functional reserve before LT when compared with the SLT group (Child-Pugh A 18.87% *vs.* 27.35%, Child-Pugh C 46.46% *vs.* 40.88%, $P<0.001$). In the preoperative condition, the median AFP was 39.13 ng/mL (range, 5.58–525.60 ng/mL)

Table 1 Recipient and tumor characteristics between salvage liver transplantation and primary liver transplantation groups

Variables	Entire patients (n=4,244)			PSM		
	PLT (n=3,498)	SLT (n=746)	P value	PLT (n=728)	SLT (n=728)	P value
Median age, years	51.92 [45.92–57.00]	51.83 [45.00–57.17]	0.44	51.42 [44.54–56.17]	51.83 [45.0–57.21]	0.199
Sex						0.210
Male	3,144 (89.88)	672 (90.08)		640 (87.91)	655 (89.97)	
Female	354 (10.12)	74 (9.92)	0.869	88 (12.09)	73 (10.03)	
Median BMI, kg/m^2	23.60 [21.80–25.63]	23.18 [21.26–24.80]	<0.001	23.12 [21.39–24.91]	23.24 [21.27–24.82]	0.876
Child-Pugh						0.998
A	660 (18.87)	204 (27.35)		196 (26.92)	196 (26.92)	
B	1,213 (34.68)	237 (31.77)	<0.001	231 (31.73)	230 (31.59)	
C	1,625 (46.46)	305 (40.88)		301 (41.35)	302 (41.48)	
Objects in preoperative condition						
Median AFP, ng/mL	39.13 [5.58–525.60]	23 [4.04–242.00]	<0.001	36.05 [5.83–361.89]	23.0 [4.0–253.0]	0.880
TACE	1,072 (30.65)	372 (49.87)	<0.001	345 (47.39)	354 (48.63)	0.637
Yes						
RFA	468 (13.38)	193 (25.87)	<0.001	178 (24.45)	181 (24.86)	0.855
Yes						
Sorafenib	36 (1.03)	10 (1.34)	0.46	11 (1.51)	8 (1.10)	0.488
Yes						
HBV (+)	3,155 (90.19)	694 (93.03)	<0.001	673 (92.45)	676 (92.86)	0.763
Satellite tumor nodules	611 (17.47)	144 (19.30)	0.234	132 (18.13)	141 (19.37)	0.546
Present						
Median MELD	16 [10–33]	14 [8–35]	0.247	15.0 [9.0–33.0]	14.0 [8.0–35.0]	0.833
Median serum total bilirubin, mmol/L	55.05 [22–235]	43.95 [17–258]	0.406	45.0 [20.2–217.0]	43.95 [17.09–257.50]	0.576
Median creatinine, mmol/L	80 [63–134]	80.25 [65–151]	0.563	80.50 [62.0–125.0]	80.0 [64.65–148.82]	0.832
Median INR	1.44 [1.16–2.48]	1.30 [1.06–2.48]	0.129	1.40 [1.14–2.48]	1.30 [1.06–2.48]	0.709
Hypertension	376 (10.75)	80 (10.72)	0.984	77 (10.58)	78 (10.71)	0.932
Yes						
Diabetes	386 (11.03)	75 (10.05)	0.434	77 (10.58)	73 (10.03)	0.730
Yes						
Chronic pulmonary disease	40 (1.14)	6 (0.80)	0.417	10 (1.37)	6 (0.82)	0.315
Yes						
Blood type matching transplantation	341 (97.63)	738 (98.93)	0.026	724 (99.45)	720 (98.90)	0.246
Yes						

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Entire patients (n=4,244)			PSM		
	PLT (n=3,498)	SLT (n=746)	P value	PLT (n=728)	SLT (n=728)	P value
Objects in operative and postoperative condition						
Median blood loss, mL	1,000 [500–1,600]	1,000 [600–2,000]	0.005	1,000 [600, 2,000]	1,000 [600–2,000]	0.365
Median tumor maximum size, cm	4.0 [2.5–6.0]	3.0 [2.0–4.6]	0.558	3.80 [2.50–6.0]	3.0 [2.0–4.80]	0.850
Median number of tumors	1.0 [1.0–2.0]	2.0 [1.0–3.0]	0.728	2.0 [1.0–2.0]	2.0 [1.0–3.0]	0.792
Median operation time, hours	7.00 [5.75–8.14]	7.00 [5.65–8.50]	0.048	7.0 [5.79–8.0]	7.0 [5.66–8.50]	0.130
Median cold ischemia time, hours	6.33 [4.83–8.0]	7.00 [5.0–9.0]	0.001	6.38 [5.0–8.42]	7.00 [5.0–9.0]	0.174
ICU stay time, hours	72.0 [39.0–144.0]	90.0 [48.0–168.0]	0.001	84.0 [44.0–168.0]	89.0 [48.0–168.0]	0.682
Time in hospital after transplantation, days	21.0 [16.0–28.0]	21.0 [16.0–28.0]	0.361	22.0 [16.0–29.0]	21.0 [16.0–28.0]	0.795
Use glucocorticoid (yes)	2,875 (82.19)	585 (78.42)	0.016	564 (77.47)	575 (78.98)	0.485

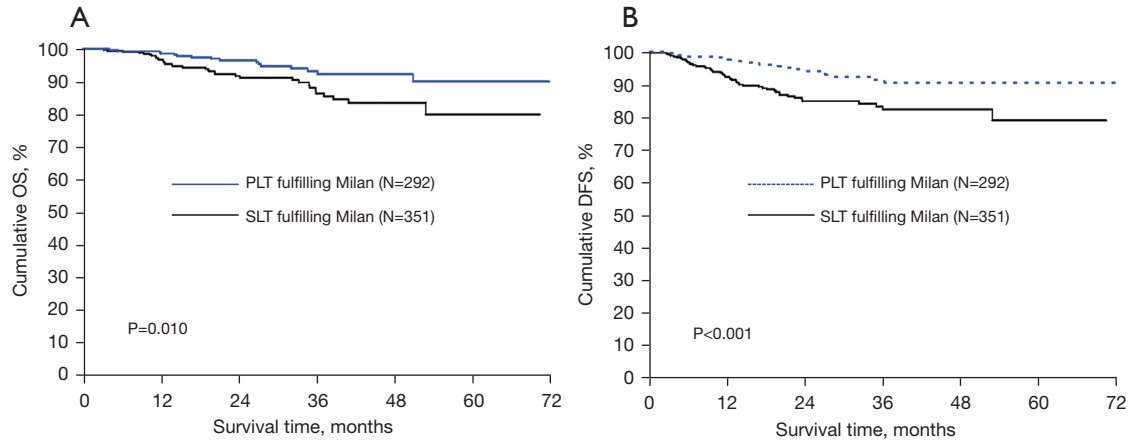
Data are presented as n (%) or median [IQR]. PSM, propensity score matching; PLT, primary liver transplantation; SLT, salvage liver transplantation; BMI, body mass index; AFP, alpha fetoprotein; TACE, transcatheter arterial chemoembolization; RFA, radio frequency ablation; HBV, hepatitis B virus; MELD, model for end-stage liver disease; INR, international normalized ratio; ICU, intensive care unit; IQR, interquartile range.

and 23.00 ng/mL (range, 4.04–242.00 ng/mL) in the PLT and SLT groups, respectively (P<0.001). Additionally, significant differences were observed between the two groups in terms of TACE, RFA and systemic chemotherapy (P<0.001). The HBV (+) rate was significantly higher in the SLT group (93.03%) than in the PLT group (90.19%) (P<0.001). Meanwhile, there was a difference between the two groups if the LT was blood type matched or not (P=0.026). In the operative condition, the median blood loss and operation time showed a significant difference between the two groups (P=0.005 and P=0.048, respectively). In the post-operative condition, the median ICU stay time was 72 hours (range, 39.0–144.0 hours) and 90 hours (range, 48.0–168.0 hours) in the PLT and SLT groups, respectively (P=0.001). Additionally, a difference was observed between the two groups whether glucocorticoid was used or not (P=0.016).

PSM analysis of the variants generated 728 matched recipients of the PLT group and SLT groups. No significant differences were found between the matched cases (*Table 1*). When compared the OS and DFS in the SLT and PLT groups after PSM, the 1-, 3- and 5-year OS between the two groups had no significant difference (92.17%, 74.10% and 68.81% *vs.* 92.42%, 78.74%, 69.80%; P=0.160; Figure S1A). No significant difference in DFS was also noted between the SLT group and PLT group (P=0.189; Figure S1B).

Landmark OS and DFS

The probabilities of surviving an additional 1-, 2- and 3-year given survival to 1 (N=630 in the PLT group, N=602 in the SLT group; after PSM) and 2 (N=381 in the PLT group, N=332 in the SLT group; after PSM) years were 92.06%, 85.20% and 82.08% in the PLT group *vs.* 88.56%, 80.39% and 76.31% in the SLT group, respectively (P=0.095, Figure S2A); 92.54%, 89.16% and 82.04% in the PLT group *vs.* 90.78%, 86.17% and 84.30% in the SLT group, respectively (P=0.611, Figure S2B). And the disease free survival an additional 1-, 2- and 3-year, given that DFS event was not experienced at 1 and 2 years were 93.12%, 86.55% and 81.06% in the PLT group *vs.* 87.21%, 81.81% and 78.83% in the SLT group, respectively (P=0.037, Figure S2C); 92.94%, 87.05% and 85.43% in the PLT group *vs.* 93.81%, 90.40% and 83.21% in the SLT group, respectively (P=0.623, Figure S2D). Indeed, the recipients who had given survival up to 1 year showed poor DFS in the SLT group compared with those in the PLT group.



Overall survival	1-year	3-year	5-year
PLT	98.61%	93.24%	90.05%
SLT	96.70%	86.38%	79.99%

Disease-free survival	1-year	3-year	5-year
PLT	97.57%	91.58%	90.65%
SLT	92.34%	82.44%	79.01%

Figure 2 Survival curves for recipients fulfilling Milan criteria in SLT and PLT groups. OS (A) and DFS (B) in recipients fulfilling Milan criteria after propensity score matching between SLT group (n=351) and PLT group (n=292). PLT, primary liver transplantation; SLT, salvage liver transplantation; OS, overall survival; DFS, disease free survival.

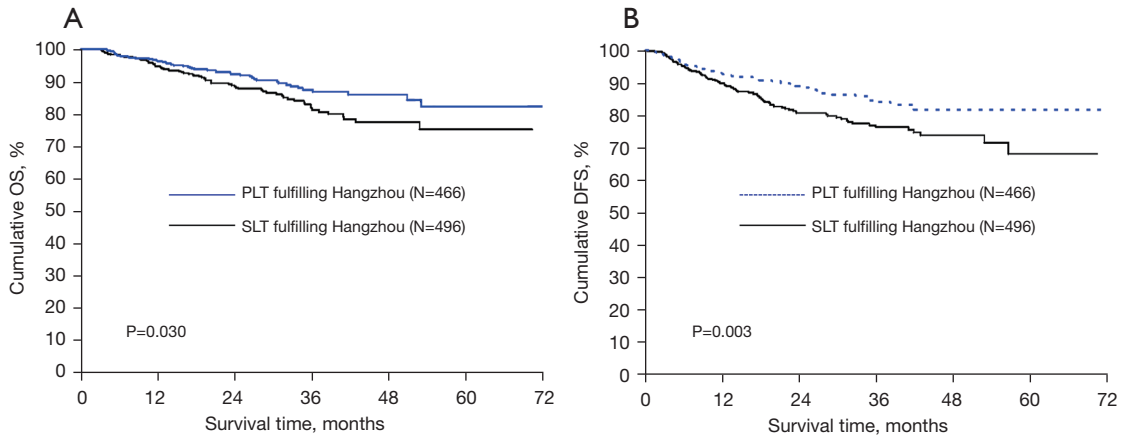
Comparison of survival between the SLT and PLT groups with Milan criteria or Hangzhou criteria

For recipients fulfilling the Milan criteria between the SLT group and PLT group before PSM, significant differences in OS and DFS were noted (P=0.027, P=0.002; Figure S3). Meanwhile, significant differences in OS and DFS were also noted between the recipients fulfilling the Hangzhou criteria in SLT group and PLT group before PSM (P=0.003, P<0.001; Figure S4).

After PSM, the 1-, 3- and 5-year OS of recipients fulfilling the Milan criteria between the SLT group and PLT group had significant difference (96.70%, 86.38%, and 79.99% *vs.* 98.61%, 93.24%, and 90.05%; P=0.01; *Figure 2A*). The 1-, 3- and 5-year DFS of recipients fulfilling the Milan criteria between the SLT group and PLT group also had significant difference (92.34%, 82.44% and 79.01% *vs.* 97.57%, 91.58%, 90.65%; P<0.001; *Figure 2B*). Meanwhile, the 1-, 3- and 5-year OS of recipients fulfilling the Hangzhou criteria between the SLT group and PLT group had significant difference (94.78%, 81.87% and 75.24% *vs.* 96.28%, 87.50% and 82.43%; P=0.03; *Figure 3A*). The 1-, 3- and 5-year DFS of recipients fulfilling the Hangzhou criteria between the SLT group and PLT group also had significant difference (89.89%, 76.34% and 68.13% *vs.* 92.82%, 84.71% and 81.70%; P=0.003; *Figure 3B*). The OS and DFS of the recipients exceeding Milan criteria or Hangzhou criteria in SLT group were comparable to those in PLT group (Figure S5).

Univariate and multivariate analysis of OS and DFS in the SLT group

Univariate and multivariate analysis were applied to determine the risk factors affecting OS in the SLT group. According to the univariate analysis, factors in the preoperative condition associated with OS included AFP >400 ng/mL (P<0.0001), tumor maximum size >8 cm (P=0.031), tumor number >3 (P<0.0001), total tumor diameter >8 cm (P=0.002) and preoperative TACE (P=0.009). The complete univariate analyzes were shown in *Table 2*. According to cox regression model, factors in the preoperative condition associated with OS included AFP >400 ng/mL (P<0.0001), tumor maximum size >8 cm (P=0.031), total tumor diameter >8 cm (P=0.002) and preoperative TACE (P=0.036) (*Table 2*). Determinant DFS factors in univariate analysis are shown in Table S1. On including the variables in the preoperative condition, AFP >400 ng/mL (P<0.0001), tumor maximum size >8 cm (P=0.008), tumor number >3 (P=0.011), total tumor diameter >8 cm (P=0.012), preoperative TACE (P=0.009) and sorafenib use (P=0.002) were found to be poor



Overall survival	1-year	3-year	5-year
PLT	96.28%	87.50%	82.43%
SLT	94.78%	81.87%	75.24%

Disease-free survival	1-year	3-year	5-year
PLT	92.82%	84.71%	81.70%
SLT	89.89%	76.34%	68.13%

Figure 3 Survival curves for recipients fulfilling Hangzhou criteria in SLT and PLT groups. OS (A) and DFS (B) in recipients fulfilling Hangzhou criteria after propensity score matching between SLT group (n=496) and PLT group (n=466). PLT, primary liver transplantation; SLT, salvage liver transplantation; OS, overall survival; DFS, disease free survival.

prognostic factors for DFS (Table S1).

Nomograms to estimate the predicted probability of 3-year OS and DFS

The results of multivariable analysis were used to create a nomogram to estimate the predicted probability of 3-year OS (*Figure 4A*). The nomogram is a graphic depiction of the model wherein points are assigned based on the rank order of the effect estimated. Factors assigned the highest number of points included preoperative AFP and tumor total diameters. As shown in *Figure 4B*, the calibration plot for the OS model was plotted between the predicted probability of 3-year OS and the observed data. The modeled 3-year estimates of OS closely approximated those of observed estimates, but deviated relatively among individuals with poor survival. Model discrimination was evaluated using the C-index, which quantifies the level of concordance between the predicted and observed OS. The C-index for the final OS model was 0.70 [95% confidence interval (CI): 0.65–0.75].

In the SLT group, there was no difference in the OS between the recipients fulfilling the Hangzhou criteria and Milan criteria (P=0.091; Figure S6). Factors independently associated with DFS in multivariable analysis were applied to construct a nomogram to estimate the predicted probability of 3-year DFS (Figure S7A). Meanwhile, the nomogram was a graphic depiction of the model, in which points were assigned based on the rank order of the effect estimated. Figure S7B shows the calibration plot for the DFS model wherein the predicted probability of 3-year DFS was plotted against the observed data. The C-index for the final DFS model was 0.69 (95% CI: 0.65–0.73).

Furthermore, based on the nomograms and median risk score, we conducted SLT risk stratification system to further classify SLT recipients into low- (< median) and high- (> median) risk groups. The 1-, 3- and 5-year OS of recipients between low-risk SLT group and high-risk group had significant difference (95.34%, 84.26%, and 77.20% *vs.* 85.38%, 54.87%, and 51.23%; P<0.001; *Figure 4C*). The DFS of the two groups mentioned above had similar results (P<0.001; Figure S7C). Moreover, OS (P=0.107, *Figure 4D*) and DFS (P=0.055, Figure S7D) were not statistically significant between the recipients in the low-risk group who underwent SLT and the recipients in PLT fulfilling the Hangzhou criteria.

Discussion

This study indicated that no statistically significant difference was observed in OS between SLT group and PLT group before (P=0.143) or after (P=0.189) PSM. These results indicated that the two surgical modalities had similar prognoses in the non-screened setting. Additionally,

Table 2 Univariate and multivariate analysis of overall survival for salvage liver transplantation group

Objects in preoperative condition	Entire patients (n=746)			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
AFP (ng/mL)	2.799 (2.012–3.894)	<0.0001	2.205 (1.507–3.098)	<0.0001
≤400				
>400				
Tumor maximum size (cm)	3.463 (2.250–5.330)	<0.0001	1.766 (1.054–2.961)	0.031
≤8				
>8				
Tumor number	2.217 (1.581–3.109)	<0.0001	1.375 (0.921–2.054)	0.119
≤3				
>3				
Total tumor diameter (cm)	3.324 (2.387–4.628)	<0.0001	2.034 (1.299–3.185)	0.002
≤8				
>8				
MELD score	0.790 (0.565–1.103)	0.167		
≤15				
>15				
HBV (+)	1.276 (0.671–2.426)	0.457		
Preoperative TACE	1.546 (1.114–2.147)	0.009	1.458 (1.025–2.076)	0.036
Sorafenib	1.680 (0.535–5.275)	0.375		
RFA	0.761 (0.518–1.116)	0.162		
Child-Pugh A	1.134 (0.804–1.598)	0.474		

The variables (tumor maximum size, tumor number and total tumor diameter) used in above analysis were the post-operative pathological data of tumor to make the analysis more accurate. However, such variables could be obtained from imaging date before liver transplantation. HR, hazard ratio; CI, confidence interval; AFP, alpha fetoprotein; MELD, model for end-stage liver disease; HBV, hepatitis B virus; TACE, transcatheter arterial chemoembolization; RFA, radio frequency ablation.

a cohort study also reported that the vascular and biliary complications rates of in-hospital mortality and OS were similar in the recipients undergoing salvage living donor liver transplantation (LDLT) and primary LDLT (10). In addition, Guo *et al.* found that SLT was a viable treatment with similar outcomes for 5-year OS (P=0.345) and 5-year recurrence-free survival (P=0.263). Meanwhile, OS from the point of primary resection over 10 years period also showed no significant difference between the two groups (11). Thus, the outcomes of SLT were quite similar to that of PLT in the total population, except for technical difficulties in some SLT recipients from a surgical oncology standpoint (12). Notably, the median MELD score was 14/16 in SLT and PLT groups respectively, which was a little higher when compared with western population. But based on the Chinese population, Ling *et al.* (13) reported that mean MELD score was approximately 19 in a cohort of 125 LT recipients. Another recent study on extended criteria donor also reported mean MELD score in Chinese LT recipients up to 16 (14). LT indication was different in China, with a higher proportion of high-MELD recipients.

Meanwhile, the probabilities of surviving additional 1-, 2- and 3-year given survival to 1 or 2 years were investigated. The probabilities of disease free surviving additional 1-, 2-

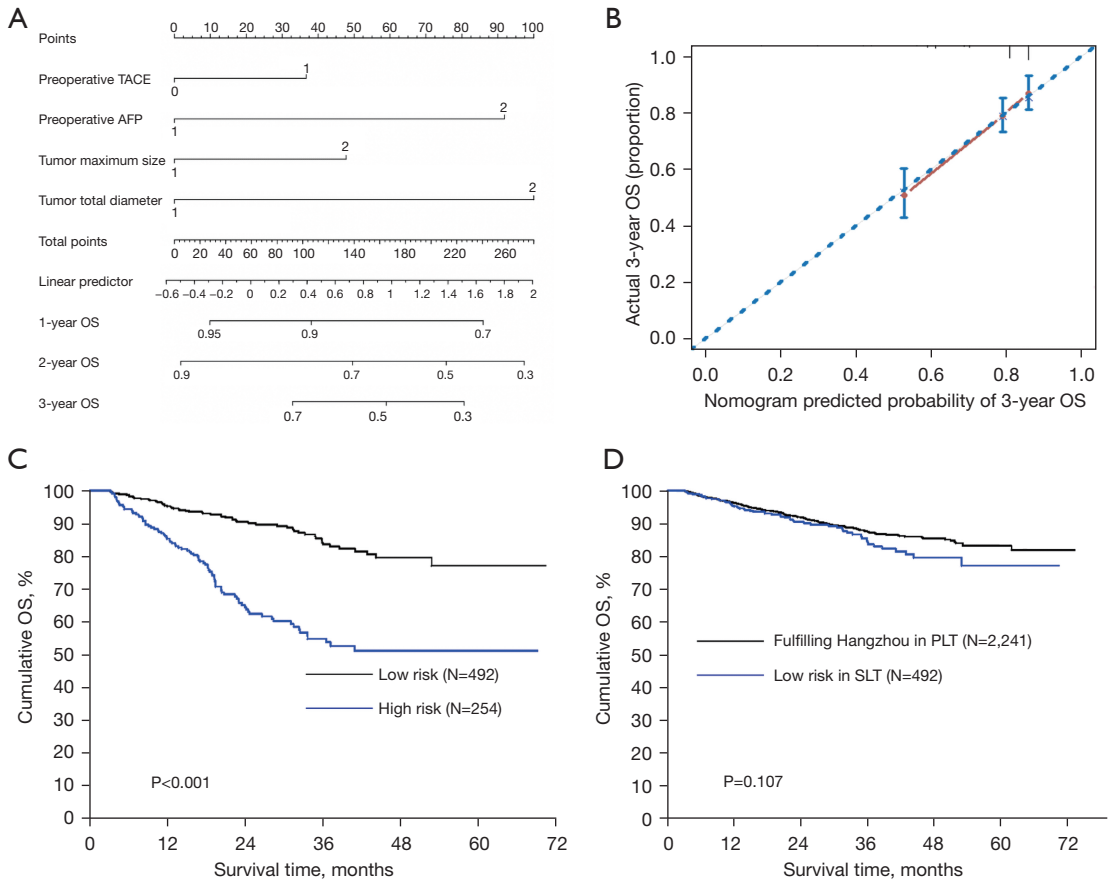


Figure 4 Nomograms to classify recipients in SLT group. The nomogram for the prediction of 3-year OS (A); to use the nomogram, draw a line straight upward from the location on corresponding axis to the top line labeled "points". Sum the points for all predictors then draw a line straight downward from the axis labeled "Total Points" to find the 3-year OS of recipients in SLT group. The calibration curves of nomogram for the prediction of 3-year OS (B) in the internal validation. The OS of low-risk and high-risk recipients was compared in SLT group (C). The OS of recipients in low-risk SLT group *vs*. recipients fulfilling Hangzhou criteria in PLT group (D). TACE, transarterial chemoembolization; AFP, alpha fetoprotein; OS, overall survival; PLT, primary liver transplantation; SLT, salvage liver transplantation.

and 3-year, given that DFS event was not experienced at 1 year was better in the PLT group than in the SLT group. Therefore, the criteria that used survival time were not solely applicable to the selection of SLT recipients in China. There was certainly room for SLT recipients to research of selection criteria further. And our study was based on the huge data set from mainland China to compare the survival of SLT and PLT recipients after PSM. In the recent 10 years, such a large sample study with PSM was not reported.

The 1-, 3- and 5-year OS and DFS of recipients fulfilling the Milan criteria in SLT group were significantly reduced when compared with those in PLT group (OS, P=0.01; DFS, P<0.001). The same conclusion was also drawn for recipients fulfilling the Hangzhou criteria. Given this, these criteria were not appropriately applied to the selection of SLT recipients. Previously, similar conclusions have been reported, which indicated that the selection criteria for SLT have not been well-established and that the Milan criteria were not suitable for selecting recipients undergoing LT for recurrent HCC after LR (15). Lee *et al.* (16) reported that the extent and timing of HCC recurrence after LR played important roles in the outcomes of SLT. Another study suggested that the residual tumor burden after the treatment of recurrent HCC played a more vital role in post-transplant tumor recurrence than the timing of tumor recurrence after LR (17). Thus, these studies indicated that there is a lack of data on the selection of suitable

SLT recipients. And we found that the OS and DFS of recipients was worse in SLT group than in PLT group. It is well-known that LR is widely used in HCC recipients at early stages and provides an opportunity to control tumor progression. However, it has been previously suggested that surgical stress will promote HCC cell entry into the circulation (18). Ren *et al.* (19) demonstrated that platelet TLR4-ERK5 axis implicates surgery-driven distant metastasis with a murine model of localized surgical stress. Recent clinical study has also reported that hepatectomy is associated with increased circulating tumor cells (CTCs) counts, which is an independent risk factor for recurrence after LT (20). Furthermore, a previous single cell transcriptome study indicated that the existence of active crosstalk between relapse HCC and immune cells in HCC, which will compromise antitumor function and promote tumor cell migration (21). In addition, the SLT recipients tend to have poor hepatic function and sarcopenia as a result of liver cirrhosis. And the sarcopenia has been reported to reduce recipients survival and be associated with high risk of postoperative complications (22,23). In addition, sarcopenia was showed to be associated with tumor recurrence and metastasis in a multicenter, large sample clinical study (24). Therefore, the above mechanisms may cause the relatively poor survival for LT recipients with a recurrent HCC after resection.

Consequently, a reliable model for the filtering of SLT recipients was needed. To these effect, multivariate analysis in the SLT group was performed based on the results of the univariate analysis. Preoperative TACE, AFP >400 ng/mL, tumor maximum size >8 cm and total tumor diameter >8 cm were found to be independent risk factors affecting OS in the SLT group. As for the factors affecting DFS, they were preoperative TACE, AFP >400 ng/mL, tumor maximum size >8 cm, tumor number >3, total tumor diameter >8 cm and preoperative sorafenib administration. Indeed, for the use of SLT in cirrhotic patients with HCC, an intention-to-treat analysis reported that the pre-resection predictors of a SLT strategy included the absence of TACE (25). Several studies reported that preoperative TACE up-regulated the expression of vascular endothelial growth factor protein (26), which is associated with metastasis and recurrence (27). Meanwhile, TACE causes hypoxia and HIF-1α expression in HCC cells, which are associated with poor outcomes (28). However, the adverse effects of preoperative TACE and sorafenib require further studies in the future. Moreover, it is well-known that tumor size and tumor biology are important factors associated with recipients OS and DFS (29,30). Notably, compared with Hangzhou criteria and Milan criteria, the results of our multivariate analysis take into account more pre-transplant treatments.

The nomograms were plotted based on the results of the multivariate analysis. In order to make the nomograms more accurate for SLT recipients selection, the variables (tumor maximum size and tumor number) used in nomograms were the post-operative pathological data of the tumor (31). However, the variables (tumor maximum size and tumor number) could be obtained from imaging date before LT. So that our model could be used to select recipients in SLT group before LT. Based on the median risk score, the SLT group was classified into the low-risk (< median) and high-risk (> median) groups. And in SLT group, no statistical difference was observed in the OS between the recipients fulfilling Hangzhou criteria and Milan criteria. Other studies also reported that the OS of recipients fulfilling the Hangzhou criteria was similar to those fulfilling the Milan criteria (29,32,33). To confirm the validity of models, we found OS and DFS were not statistically significant between the low-risk SLT group and PLT recipients fulfilling the Hangzhou criteria. So that, the internally validated nomograms in this study established the selection criteria for selecting appropriate recipients to undergo SLT.

Our results were pertinent and sensible from at least two perspectives. Firstly, this study based on a huge data set from mainland China compared post-transplant survival of recipients fulfilling Milan or Hangzhou criteria between SLT group and PLT group with PSM analysis. So that, these criteria were not appropriately applied to the selection of SLT recipients in China. Secondly, nomograms were plotted based on the results of the multivariate analysis to classify the SLT group into low-risk and high-risk groups. The low-risk group had a better outcome than the high-risk group, meanwhile, similar OS and DFS were observed in the recipients fulfilling Hangzhou criteria when compared with the recipients in the low-risk group. Thus, the nomogram can be used to improve the selection of SLT recipients.

Despite the advantages, this study has some limitations. This study is a retrospective analysis of observational data over a long period of time, which is mostly associated with the quality of data available in CLTR database. With lack of the survival data from initial LR to SLT, an intention-to-treat analysis could not be performed. In this regarding, prospective, multicenter, randomized clinical study remains

to be conducted to provide a higher level of clinical evidence for SLT recipient selection and therapeutic strategy.

Conclusions

This study demonstrated that the OS and DFS of recipients fulfilling the Milan criteria or Hangzhou criteria showed a significant reduction in the SLT group compared to PLT group. A novel nomogram was plotted by using the independent risk factors from multivariate analysis. SLT risk stratification system based on this nomogram could further classify SLT recipients into low- and high-risk groups. And low-risk SLT group showed comparable OS and DFS to PLT group fulfilling Hangzhou criteria. In this regarding, the nomogram-based risk stratification system could assist for clinical decision guidance in SLT management, so as to achieve an improved long-term prognosis.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-22-304/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-22-304/coif). Q.X. serves as an unpaid editorial board member of *Hepatobiliary Surgery and Nutrition*. The other authors have no conflicts of interest to declare.

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. This study was performed according to the Declaration of Helsinki (as revised in 2013) and approved by the CLTR (No. 20200039). Informed consent was obtained from all the patients for the use of their data for research purposes. No organs from executed prisoners were used.

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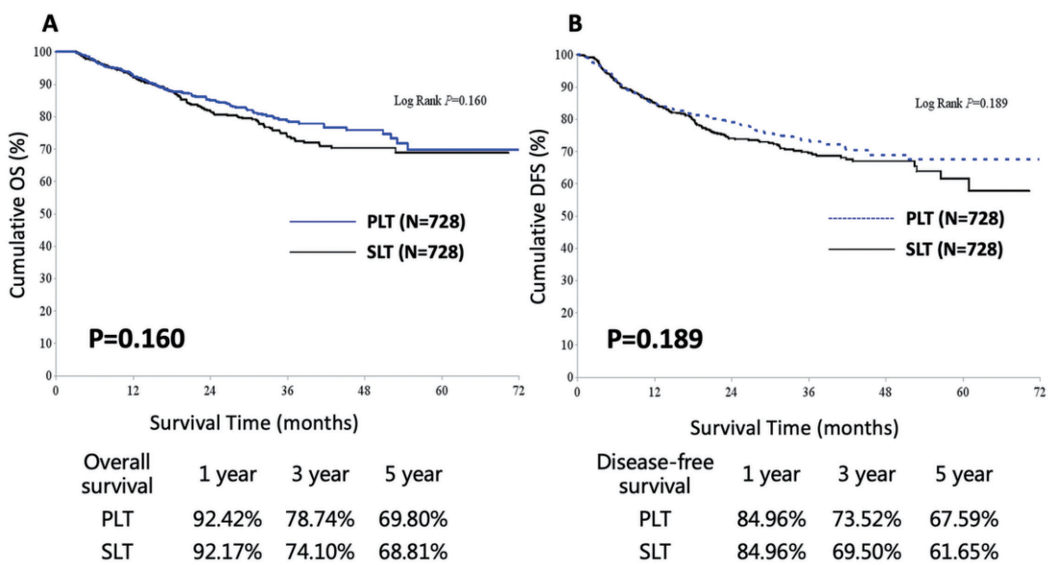
Supplementary

Table S1 Univariate and multivariate analysis of disease-free survival for salvage liver transplantation strategy

Variable	Entire patients (n=746)			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Objects in preoperative condition				
AFP (ng/mL)	2.555 (1.911-3.415)	<0.0001	2.198 (1.635-2.955)	<0.0001
≤400				
>400				
Tumor maximum size (cm)	2.763 (2.062-3.703)	<0.0001	1.703 (1.148-2.525)	0.008
≤8				
>8				
Tumor number	2.190 (1.633-2.937)	<0.0001	1.566 (1.108-2.212)	0.011
≤3				
>3				
Total tumor diameter (cm)	2.929 (1.974-4.346)	<0.0001	1.833 (1.144-2.935)	0.012
≤8				
>8				
MELD score	0.909 (0.686-1.206)	0.508		
≤15				
>15				
HBV (+)	1.583 (0.861-2.911)	0.140		
Preoperative TACE	1.658 (1.248-2.203)	0.001	1.461 (1.096-1.947)	0.009
Sorafenib	2.714 (1.203-6.122)	0.016	3.592 (1.572-8.208)	0.002
RFA	0.962 (0.702-1.317)	0.807		
Child-Pugh A	1.141 (0.846-1.539)	0.387		

The variables (tumor maximum size, tumor number and total tumor diameter) used in above analysis were the post-operative pathological data of tumor to make the analysis more accurate. However, such variables could be obtained from imaging date before liver transplantation. SLT: salvage liver transplantation; HR: hazard ratio; HBV: hepatitis B virus; AFP: alpha fetoprotein; MELD: model for end-stage liver disease; TACE: transcatheter arterial chemoembolization; RFA: radio frequency ablation.



Overall survival	1 year	3 year	5 year
PLT	92.42%	78.74%	69.80%
SLT	92.17%	74.10%	68.81%

Disease-free survival	1 year	3 year	5 year
PLT	84.96%	73.52%	67.59%
SLT	84.96%	69.50%	61.65%

Figure S1 Survival curves for recipients in SLT and PLT groups. OS (A) and DFS (B) between SLT and PLT groups after propensity score matching. SLT, salvage liver transplantation; PLT, primary liver transplantation; OS, overall survival; DFS, disease free survival.

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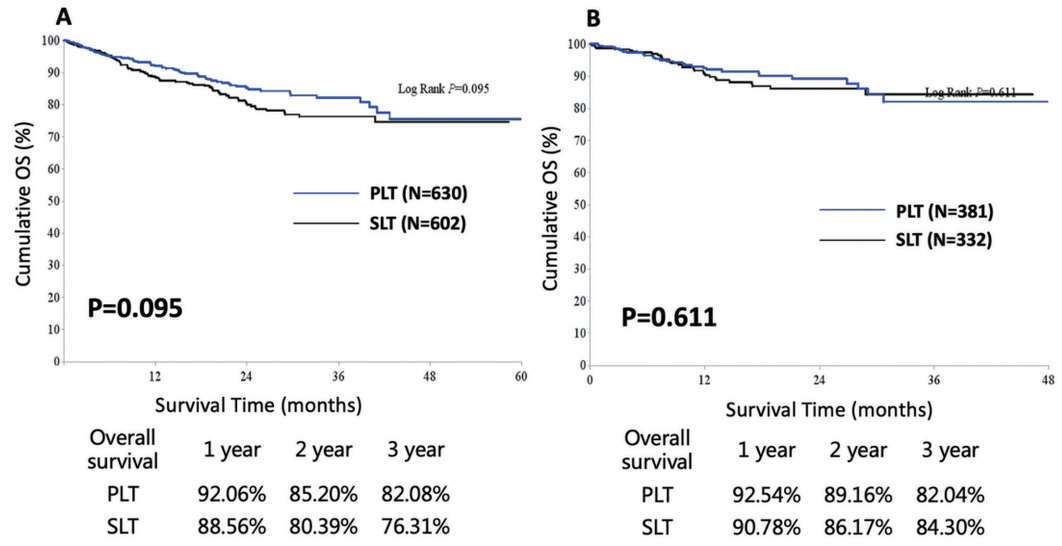
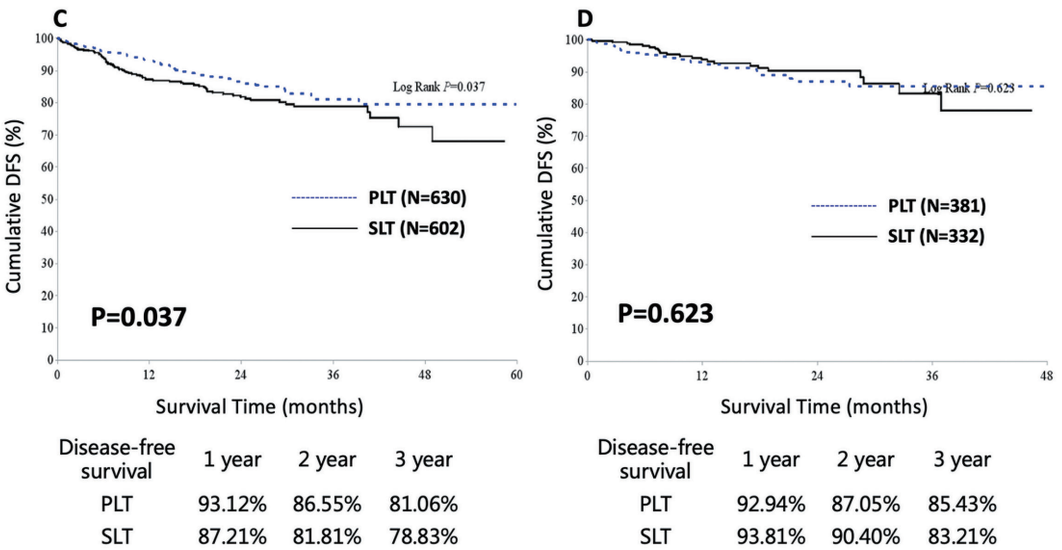


Overall survival	1 year	2 year	3 year
PLT	92.06%	85.20%	82.08%
SLT	88.56%	80.39%	76.31%

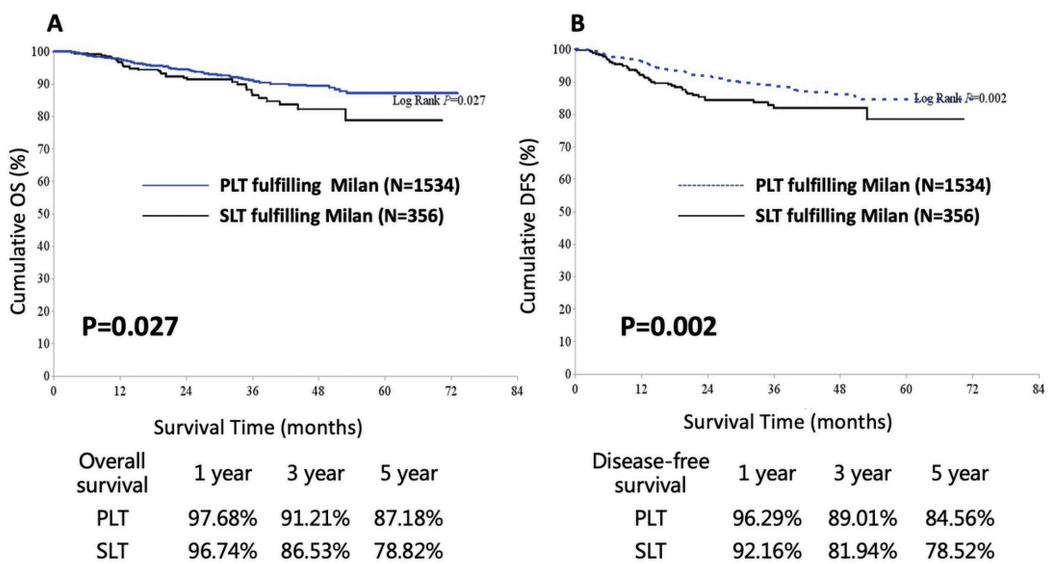
Overall survival	1 year	2 year	3 year
PLT	92.54%	89.16%	82.04%
SLT	90.78%	86.17%	84.30%



Disease-free survival	1 year	2 year	3 year
PLT	93.12%	86.55%	81.06%
SLT	87.21%	81.81%	78.83%

Disease-free survival	1 year	2 year	3 year
PLT	92.94%	87.05%	85.43%
SLT	93.81%	90.40%	83.21%

Figure S2 Landmark OS and DFS between the SLT and DLT groups after propensity score matching; The probabilities of surviving an additional 1-, 2- and 3-year given survival to 1 (A) and 2 (B) years; The disease free survival an additional 1-, 2- and 3-year, given that DFS event was not experienced at 1 (C) and 2 (D) years. SLT, salvage liver transplantation; PLT, primary liver transplantation; OS, overall survival; DFS, disease free survival.



Overall survival	1 year	3 year	5 year
PLT	97.68%	91.21%	87.18%
SLT	96.74%	86.53%	78.82%

Disease-free survival	1 year	3 year	5 year
PLT	96.29%	89.01%	84.56%
SLT	92.16%	81.94%	78.52%

Figure 3 Survival curves for recipients in SLT and PLT groups. OS (A) and DFS (B) in recipients fulfilling Milan criteria before propensity score matching between SLT and PLT groups. SLT, salvage liver transplantation; PLT, primary liver transplantation; OS, overall survival; DFS, disease free survival.

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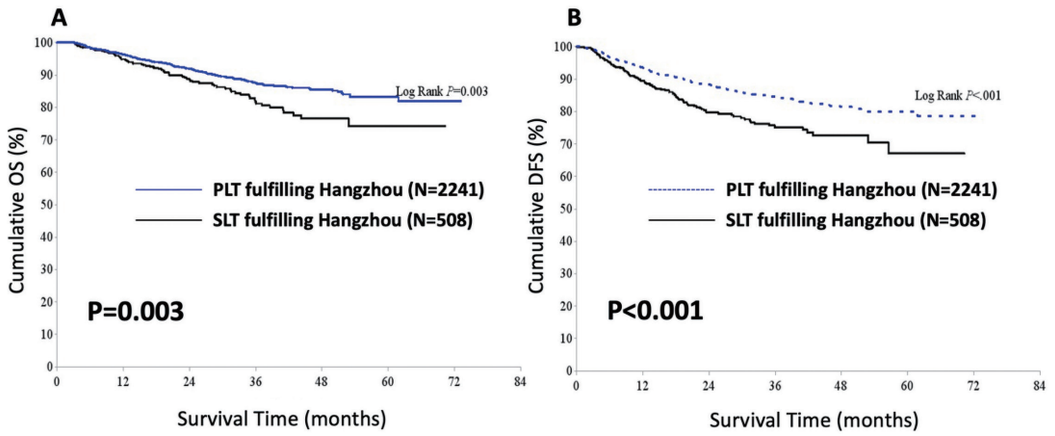
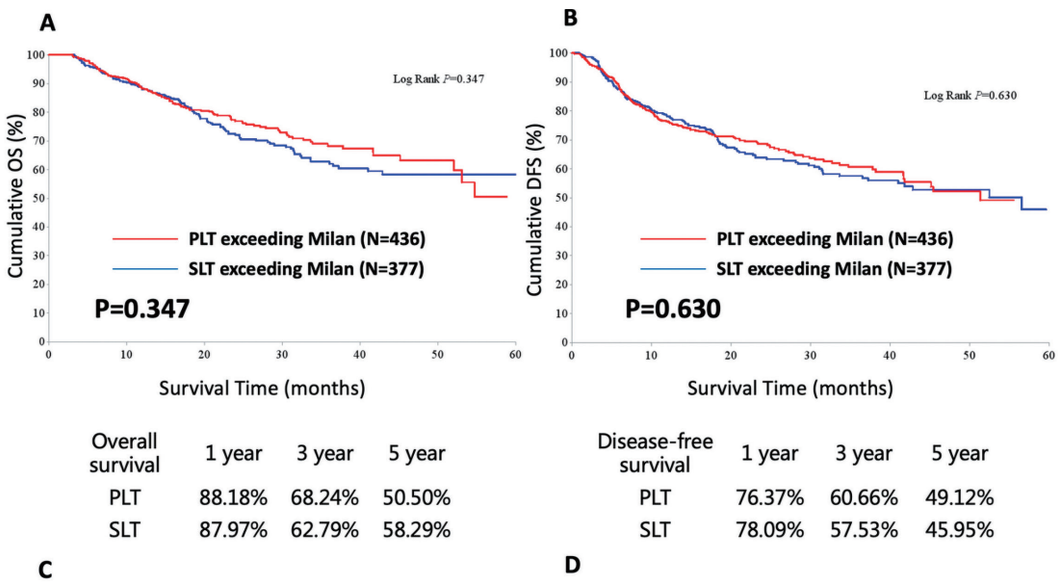


Overall survival	1 year	3 year	5 year
PLT	96.35%	87.55%	83.20%
SLT	94.90%	81.70%	74.26%

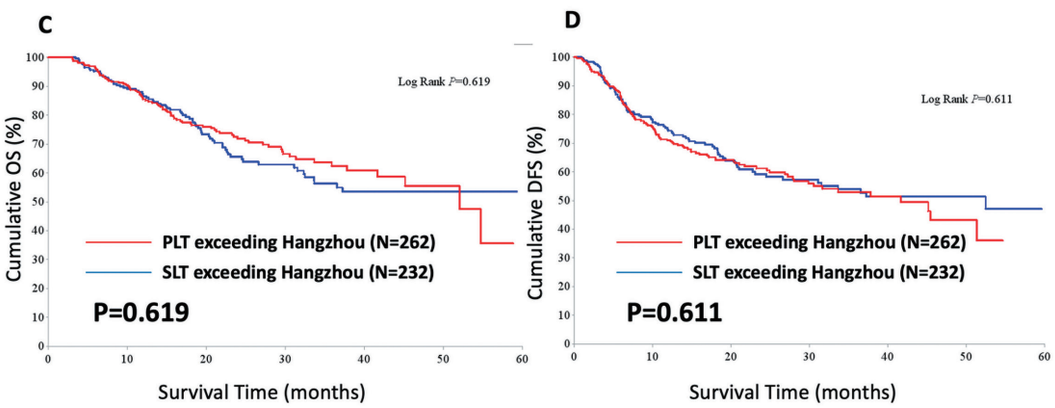
Disease-free survival	1 year	3 year	5 year
PLT	93.55%	84.51%	79.98%
SLT	84.96%	73.52%	67.59%

Figure S4 Survival curves for recipients in SLT and PLT groups. OS (A) and DFS (B) in recipients fulfilling Hangzhou criteria before propensity score matching between SLT and PLT groups. SLT, salvage liver transplantation; PLT, primary liver transplantation; OS, overall survival; DFS, disease free survival.



Overall survival	1 year	3 year	5 year
PLT	88.18%	68.24%	50.50%
SLT	87.97%	62.79%	58.29%

Disease-free survival	1 year	3 year	5 year
PLT	76.37%	60.66%	49.12%
SLT	78.09%	57.53%	45.95%



Overall survival	1 year	3 year	5 year
PLT	85.50%	62.42%	35.62%
SLT	86.56%	56.26%	53.55%

Disease-free survival	1 year	3 year	5 year
PLT	70.91%	52.95%	36.01%
SLT	74.35%	53.97%	47.02%

Figure S5 Survival curves for recipients in SLT and PLT groups. OS (A) and DFS (B) in recipients exceeding Milan criteria before propensity score matching between SLT and PLT groups; OS (C) and DFS (D) in recipients exceeding Hangzhou criteria before propensity score matching between SLT and PLT groups. SLT, salvage liver transplantation; PLT, primary liver transplantation; OS, overall survival; DFS, disease free survival.

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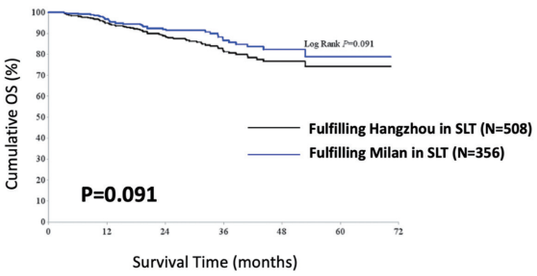

Figure S6 Comparison of survival outcomes between the patients within the Milan and Hangzhou criteria in salvage liver transplantation group.

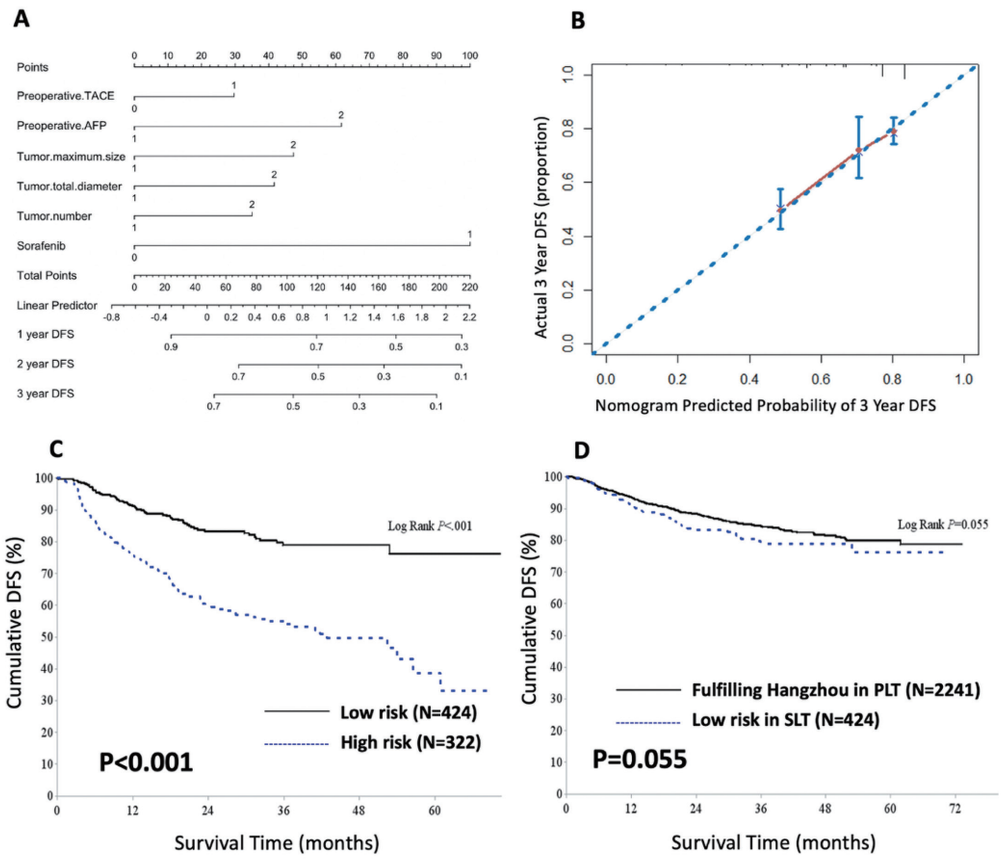

Figure S7 Nomograms to classify recipients in SLT group. The nomogram for the prediction of 3-year DFS (A). The calibration curves of the nomogram for the prediction of 3-year DFS (B) in the internal validation. The DFS of low-risk and high-risk patients was compared (C). The DFS of recipients in low-risk SLT group vs recipients fulfilling Hangzhou criteria in PLT group (D). SLT, salvage liver transplantation; PLT, primary liver transplantation; DFS, disease free survival.

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