Original Article

Living donor liver transplantation for Barcelona clinic liver cancer (BCLC) intermediate-stage hepatocellular carcinoma

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Background: Barcelona clinic liver cancer (BCLC) stage B (intermediate stage) hepatocellular carcinoma (HCC) is highly heterogeneous; thus, identifying the most effective treatment for individual patients represents a significant clinical challenge. However, transarterial chemoembolization (TACE) is the only recommended treatment option. Therefore, we aimed to investigate the patient characteristics and outcomes of living donor liver transplantation (LDLT) for BCLC stage B HCC.

Methods: A total of 516 patients with BCLC stage B HCC who underwent LDLT (n=104) or did not undergo LDLT (non-LDLT; n=412) between 2004 to 2018 were analyzed by propensity score matching (PSM; 1:4) analysis. Factors influencing overall survival (OS) and recurrence were analyzed using Cox's proportional hazards models.

Results: Patients treated with LDLT achieved better OS than the non-LDLT group, including liver- and non-liver related survival (all P<0.001). Multivariate Cox regression analysis showed age >60 years (P=0.006), a neutrophil-lymphocyte ratio (NLR) >4 (P=0.016) and >3 locoregional therapies (LRT) before LDLT (P<0.001) were independent risk factors for HCC recurrence. In addition, age >60 years (P<0.001) and >3 LRT before LDLT (P=0.001) were independent risk factors for OS. Using a combination of age, NLR, and LRT before liver transplantation (LT), the patients can be divided into low-risk (none of risk), intermediate-risk (one of risk), and high risk (more than two of risk) groups. There were significant differences in the cumulative HCC recurrence (P<0.001) and mortality (P<0.001) rates among the three groups.

Conclusions: LDLT may represent a valuable therapeutic option for selected patients with BCLC stage B HCC.

Keywords: Living donor liver transplantation (LDLT); Barcelona clinic liver cancer stage B (BCLC stage B); intermediate stage; hepatocellular carcinoma (HCC)

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Introduction

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related deaths worldwide (1,2). Research in recent decades has shed light on the epidemiology, risk factors and molecular and genetic profiles of HCC, and this knowledge has contributed to the evolution of prevention, surveillance, early diagnosis and treatment strategies. Several staging systems have been developed to guide the management of HCC (3-7). The Barcelona clinic liver cancer (BCLC) classification, the most widely applied staging system to guide the management and predict the prognosis of patients with HCC, divides HCC into five stages based on tumor stage, cirrhosis stage and performance status (8). Intermediate-stage HCC, defined as BCLC B stage, includes a heterogenous group of patients, including patients with cirrhosis with a Child-Pugh score of A or B (score 5–9), tumor burden outside the Milan criteria (single tumor >5 cm or ≥4 tumors) and preserved performance status. Despite the varied clinical characteristics of intermediate-stage HCC, transarterial chemoembolization (TACE) is the only treatment modality recommended in the BCLC guidelines. Unfortunately, a significant proportion of patients with HCC present with intermediate stage disease, and curative treatment is frequently not possible (9). To date, evidence in support of therapeutic alternatives to TACE in BCLC B is scarce.

Liver transplantation (LT) is currently considered the optimal treatment for patients with HCC worldwide. LT can successfully treat HCC by removing both the tumor and underlying cirrhosis, which eliminates undetected intrahepatic metastases as well as the possibility of *de novo* HCC arising from underlying liver disease (10,11). In Asia, living donor LT (LDLT) has emerged as a solution to the shortage of organs from deceased donors to treat HCC. The number of deceased donor LT (DDLT) only increased slightly in Taiwan between 2006 to 2010, whereas the number of LDLT increased over 3-fold during the same period (11). The outcome of LT for early HCC is encouraging; however, little is known about the patient characteristics and outcomes of LDLT for intermediate-stage HCC. Thus, in this retrospective study, we assessed the impact of LDLT for intermediate-stage HCC on long-term recurrence and overall survival (OS). We present the following article in accordance with the STROBE reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-196/rc).

Methods

Patients

Clinical data were acquired with the approval and permission of the Institutional Review Board of Kaohsiung Chang Gung Memorial Hospital. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Institutional Review Board of Kaohsiung Chang Gung Memorial Hospital (IRB number: 201900065B0). The requirement for written informed consent was waived by the Institutional Review Board due to the retrospective design of the study and lack of relevant human or biological ethical issues.

The data were obtained from the Chang Gung Research Database (CGRD), which is derived from the largest private hospital system in Taiwan, Chang Gung Memorial Hospital (CGMH), and systematically updated annually to include new data generated at CGMH. The CGRD data is obtained from four medical institutes, Keelung, Linkou, Chiayi, and Kaohsiung CGMH, which are located in the northeast, northern, central, and southern regions of Taiwan, respectively. We retrospectively reviewed the CGRD database and retrieved data for patients with HCC treated between January 2004 to December 2018 (n=20,572). We excluded patients with BCLC stage 0 (n=1,460), BCLC stage A (n=4,960), BCLC stage C (n=5,168) and BCLC stage D (n=1,081). And patients with BCLC stage data (n=4,876) were also excluded. Finally, 3,027 patients with BCLC stage B were eligible for this study, of whom 106 received LT. After excluding two patients who received DDLT, a total of 104 patients with BCLC-B HCC who received LDLT and 2,921 patients receiving treatments other than LDLT (non-LDLT) were enrolled in this retrospective study (*Figure 1*).

Recipient selection

The detailed decision-making process for primary

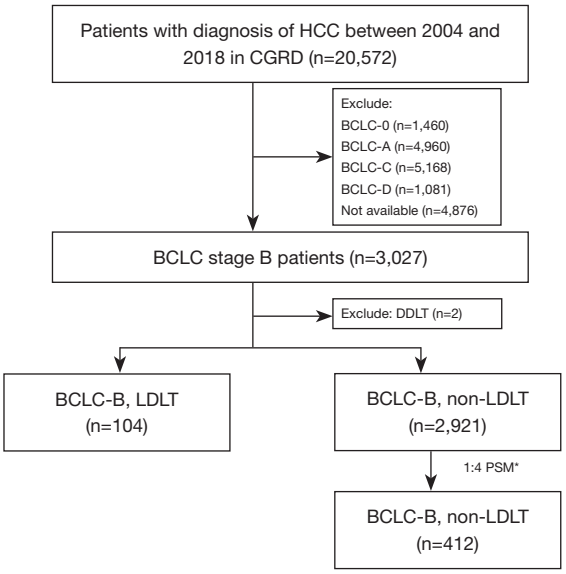

Figure 1 Schematic flowchart of the enrolment process. *, PSM analysis was based on the following variables: age, sex, body mass index, diabetes mellitus, viral hepatitis, AST, ALT, total bilirubin, albumin, INR, NLR, Child-Pugh score, MELD score, ALBI score, and AFP. HCC, hepatocellular carcinoma; CGRD, Chang Gung Research Database; BCLC, Barcelona clinic liver cancer; DDLT, deceased donor liver transplantation; LDLT, living donor liver transplantation; PSM, propensity score matching; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; NLR, neutrophil-lymphocyte ratio; MELD, model for end-stage liver disease; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein.

resection, locoregional therapy (LRT), or LDLT has been previously described (10). Acceptance for LDLT required the candidate to fit the University of California San Francisco (UCSF) criteria, in accordance with Taiwan National Health Insurance Policy. Acceptance for LDLT required the candidate to fit the UCSF criteria (a solitary tumor ≤6.5 cm in diameter, or two or three tumors each with a diameter ≤4.5 cm and a total tumor diameter ≤8 cm), in accordance with Taiwan National Health Insurance Policy. Routine pretransplant evaluation for HCC included abdominal ultrasound, liver computed tomography (CT), liver magnetic resonance imaging (MRI), bone scan, chest CT, and brain MRI. Patients with tumors beyond the UCSF criteria at initial presentation were downstaged.

Tumor downstaging

Patients with tumors beyond the UCSF criteria at initial presentation but no signs of metastatic disease or vascular invasion as indicated by CT of the chest, abdomen, and pelvis were downstaged using LRT, including TA(C)E, radiofrequency ablation (RFA), and/or percutaneous ethanol injection (PEI). The result of LRT was evaluated 4 weeks after the procedure by CT. MRI or gadoxetic acid (primovist) MRI were used to assess small equivocal tumors. Patients who met the UCSF criteria after LRT were scheduled for transplantation as soon as possible.

Post-LDLT management

The post-LDLT management protocol has been described in detail previously (10). Basiliximab (Simulect; Novartis Pharma AG, Basel, Switzerland) was intravenously administered (20 mg) twice, 6 h after portal vein reperfusion and on post-LDLT day 4. Steroid therapy (methylprednisolone 500 mg) followed by 20 mg/day, was tapered down and withdrawn after 3 months if no acute cellular rejection occurred. Tacrolimus (Prograf; Fujisawa, Ireland) was administered at 5 to 10 ng/mL during the 1st week after LDLT. Mycophenolate mofetil (CellCept; Roche, Puerto Rico) was continuously administered at 0.5 to 1 mg/day. No adjuvant therapy was given to prevent recurrence. All rejections were biopsy-proven and managed with either increased immunosuppression or intravenous pulse methylprednisolone (10 mg/kg/body weight). Steroid pulse therapy was avoided whenever possible, particularly in patients with HCV. During follow-up, the dosage of immunosuppressants was intentionally minimized if liver function was normal or stable. The backbone immunosuppressants were a combination of tacrolimus and sirolimus in most recipients. All patients were followed-up by the same team of transplant surgeons after discharge, initially twice a week every month and then once every 2 to 3 months. Liver ultrasonography, blood biochemistry, and serum levels of immunosuppressive agents were determined according to the study protocol.

Study design

In the first part of this study, we compared the survival

benefits of LDLT with non-LDLT treatments for patients with intermediate-stage HCC. In the second part of this study, we analyzed the impact of LDLT for intermediate-stage HCC on long-term recurrence and OS.

Comparison of the survival outcomes for LDLT and non-LDLT in intermediate-stage HCC

Based on the fixed 104 cases in this study, according to the consideration of epidemiological study design on optimal ratio of case and controls (12,13), therefore, we applied 1:4 ratio of PSM to identify a LDLT group (n=104) and non-LDLT group (n=412) with comparable baseline characteristics, including age, sex, body mass index, diabetes mellitus, viral hepatitis, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, albumin, international normalized ratio (INR), neutrophil-to-lymphocyte ratio (NLR), Child-Pugh score, model for end-stage liver disease (MELD) score, albumin-bilirubin (ALBI) score, and alpha-fetoprotein (AFP). NCSS 10 Statistical Software (NCSS LLC, Kaysville, UT, USA) was employed for PSM using a caliper width 0.2-fold of the standard deviation of the propensity score between the two groups. The standardized mean difference (SMD) was used to evaluate the balance of the covariates after PSM. OS, defined as the interval between the date of HCC diagnosis and death or date of last follow-up, liver-related death or non-liver related death was compared between patients with and without LDLT.

Identification of risk factors for LDLT for intermediate-stage HCC

A total of 104 patients with intermediate-stage HCC who underwent adult LDLT were enrolled in this study. The associations between various clinicopathological factors, including HCC stage (BCLC stage, UCSF criteria, up-to-7 criteria, and Kinki criteria), serum albumin, serum AFP, Child-Pugh class, MELD score, etiology of HCC, NLR and the ALBI grade before LDLT and recurrence-free survival (RFS) and OS were evaluated; follow-up ended on May 31th, 2020.

Definitions

All diagnoses of HCC were confirmed by contrast-enhanced multiphase CT or MRI, in accordance with the criteria of the practice guidelines of the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Disease (AASLD) (14,15). The UCSF criteria define HCC using the following criteria: a solitary tumor of ≤6.5 cm or ≤3 nodules with a largest lesion of ≤4.5 cm and a total tumor diameter of ≤8 cm (16). The up-to-7 criteria define HCC using a cut-off of seven for the sum of the diameter of the largest tumor (in cm) and the number of tumors (17). The Kinki criteria classify BCLC B stage as B1 (Child-Pugh score 5–7 and within up-to-7), B2 (Child-Pugh score 5–7 and beyond up-to-7) and B3 (Child-Pugh score 8 or 9 and any tumor status) (18). The NLR was calculated by dividing the absolute neutrophil count by the lymphocyte count. The ALBI score was calculated using the formula ($-0.085 \times$ albumin in g/L) + ($0.66 \times \log_{10}$ bilirubin in μmol/L) (11). ALBI was stratified into three grades: grade I, ≤–2.60; grade II, –2.60 to ≤–1.39; and grade III, >–1.39, as previously reported (19).

Statistical analysis

Continuous variables were summarized as means ± standard deviations or medians and interquartile ranges (IQRs), while categorical variables were summarized as frequencies and relative percentages. Receiver operating characteristic (ROC) analysis was used determine the optimal cut-off values for NLR and the number of pre-LT LRT. Comparisons of categorical data between groups were performed using the Chi-square test (or Fisher's exact test, if appropriate) and the distributions of continuous variables were analyzed using the Student's *t*-test (or the Mann-Whitney U-test, as appropriate). For the PSM analysis, OS was compared between the LDLT group and non-LDLT group using the Kaplan-Meier method and log-rank test. In the LDLT group, Kaplan-Meier survival curves were constructed for each variable to estimate cumulative RFS and OS. Factors that were significant in the univariate analysis ($P<0.05$) or close to significant ($P<0.1$) were included in the multivariate analysis using a Cox forward stepwise variable selection process of estimated OS and RFS.

To reduce selection bias and the effects of potential confounders, PSM was conducted based on age, gender, body mass index, diabetes, etiology of HCC, MELD score, NLR and serum AFP to account for the non-random assignment of patients to the LDLT and non-LDLT groups. Differences between these groups were balanced by 1:4 PSM analysis.

All statistical analyses were performed using SPSS 23.0

Table 1 Clinicopathological features of the propensity score matched patients with BCLC-B HCC treated with and without LDLT

Characteristic	LDLT (n=104)	Non-LDLT (n=412)	P value
Age, years (mean ± SD)	54.2±7.5	54.4±8.1	0.782
Male, n (%)	84 (80.8)	343 (83.3)	0.549
Body mass index, kg/m^2	25.6±4.5	25.1±4.4	0.272
Diabetes mellitus, n (%)	32 (30.8)	108 (26.2)	0.350
Etiology, n (%)			0.353
HBV infection	63 (60.6)	233 (56.6)	
HCV infection	26 (25.0)	90 (21.8)	
HBV + HCV infection	6 (5.8)	26 (6.3)	
Alcoholism	21 (20.2)	125 (30.4)	
AST (>40 U/L), n (%)	74 (71.8)	290 (70.4)	0.772
ALT (>40 U/L), n (%)	61 (58.8)	245 (59.5)	0.880
Total bilirubin (mg/dL), (mean ± SD)	1.2±0.9	1.3±1.1	0.230
Albumin (g/dL), (mean ± SD)	3.7±0.6	3.8±0.6	0.152
INR (mean ± SD)	1.2±0.2	1.2±0.2	0.284
Tumor size >5.0 cm$^{\#}$, n (%)	13 (12.5)	56 (13.6)	0.751
Child-Pugh score (mean ± SD)	5.9±1.1	5.6±1.0	0.234
MELD score (mean ± SD)	9.9±3.0	9.9±3.2	0.914
NLR (mean ± SD)	3.2±4.4	2.8±2.4	0.374
ALBI score (mean ± SD)	–2.3±0.6	–2.4±0.6	0.252
AFP (>20 ng/L), n (%)	48 (46.2)	216 (52.8)	0.225

Data are expressed as mean ± standard deviation or median and interquartile ranges or numbers (percentages). $^{\#}$, diameter of the largest tumor nodule. BCLC, Barcelona clinic liver cancer classification; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; SD, standard deviation; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; MELD, model for end-stage liver disease; NLR, neutrophil-to-lymphocyte ratio; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein.

software (Chicago, IL, USA) and R software (V.3.4.4, https://www.R-project.org/). A two-sided P value <0.05 was considered significant.

Results

LDLT vs. non-LDLT for BCLC-B HCC

The 1:4 PSM analysis resulted in a total of 516 patients (104 patients in the LDLT group and 412 patients in the non-LDLT group), with no significant differences in terms of any clinical covariates, including age, gender, diabetes, albumin, Child-Pugh score, MELD score, ALBI score, NLR and serum AFP (*Table 1*).

During the follow-up period, a total of 245 patients died; 18 and 227 in the LDLT and non-LTLT groups, respectively (P<0.001). In the LDLT group, 18 patients died, 16 (88.9%) of liver-related causes and the other two (11.1%) of non-liver-related causes. In the non-LDLT group, 194 (85.5%) liver-related deaths and 33 (14.5%) non-liver related death occurred. Detailed data on all-cause mortality among patients with and without LDLT are shown in *Table 2*. Among the 16 liver-related deaths in the LDLT group, 3 deaths were due to local HCC recurrence; 5 were due to distal HCC metastasis; 6 were due to multi-organ failure after LT, and the other 2 were due to biliary tract infection. Among the 194 liver-related deaths in the non-LDLT group, 178 were due to local HCC recurrence, 8 were due to distal HCC metastasis,

Table 2 Causes of mortality among patients who underwent LDLT and did not undergo LDLT

Causes of mortality	LDLT (n=104)	Non-LDLT (n=412)	P value
All-cause mortality, n (%)	18 (17.3)	227 (55.1)	<0.001
Liver-related mortality	16 (88.9)	194 (85.5)	<0.001
HCC local recurrence	3 (18.7)	178 (91.8)	
HCC distal metastasis	5 (31.3)	8 (4.1)	
MOF after LT	6 (37.5)	–	
Biliary tract infection	2 (12.5)	–	
CHB with AE	–	8 (4.1)	
Non-liver-related mortality	2 (11.1)	33 (14.5)	0.002
Other malignancy	2 (100.0)	3 (9.1)	
Sepsis	–	20 (60.6)	
Undetermined	–	10 (30.3)	

LDLT, living donor liver transplantation; HCC, hepatocellular carcinoma, MOF, multiple organ failure; LT, liver transplantation; CHB, chronic hepatitis B; AE, acute exacerbation.

and 8 were due to acute chronic liver failure (liver-related deaths in the LDLT groups *vs.* the non-LDLT group; P<0.001). In contrast, the two non-liver-related deaths in the LDLT group were both due to other malignancies. However, among the 33 non-liver-related deaths in the non-LDLT group, 3 were due to other malignancies; 20 were due to sepsis, and the other 10 were due to undetermined causes (non-liver-related deaths in the LDLT group *vs.* the non-LDLT group; P=0.002).

As shown in *Figure 2*, the non-LDLT group had significantly higher rates of overall mortality and liver or non-liver-related death compared to the LDLT group (all P<0.001). In the multivariate Cox proportional hazard model, LDLT was associated with a significantly lower risk of death than non-LDLT (data not shown).

Factors associated with OS and RFS after LDLT in BCLC-B HCC

The main clinicopathological characteristics of the 104 patients with BCLC stage B HCC who underwent LDLT are shown in *Table 3*. The median follow-up time was 65 months. The majority of patients were male (80.8%) and the mean age at LDLT was 55.6 years. Most tumors were classified as Child-Pugh A (n=73, 70.2%). The mean NLR was 5.6±19.9. No cases were within the Milan criteria when HCC was diagnosed, while 49% and 51% of cases were within the UCSF and up-to-7 criteria, respectively. The median time from HCC diagnosis to LDLT was 9.1 months (IQR, 4.1–22.5 months).

During the median follow-up duration of 65 months, 12 patients (11.5%) developed recurrent HCC and 18 (17.3%) died. The 1-, 3-, and 5-year recurrence rates were 4%, 12%, and 13.5%, respectively, and the 1-, 3-, and 5-year OS rates were 92.3%, 89.2%, and 84.1%, respectively.

Ninety-four patients (90.4%) had received LRT pre-LDLT; 18 cases had undergone tumor resection, 84 cases had received TA(C)E, and 35 cases received RFA (*Figure 3A*). Kaplan-Meier analysis showed that >3 LRT before LT was associated with higher HCC recurrence (P=0.0004, *Figure 3B*) and poor OS (P=0.044, *Figure 3C*).

In stepwise Cox proportional hazard analysis, older age [>60 years; hazard ratio (HR) =4.303; 95% CI: 1.194–15.504; P=0.006], NLR >4 (HR =4.371; 95% CI: 1.324–14.435; P=0.016) and >3 LRT before LT (HR =11.509; 95% CI: 3.008–44.037; P<0.001) were independent risk factors for HCC recurrence (*Table 4*). The multivariate Cox proportional hazards model for OS revealed that older age (>60 years; HR =9.061; 95% CI: 2.736–30.008; P<0.001), and >3 LRT before LT (HR =6.964; 95% CI: 2.105–23.041; P=0.001) were independent risk factors associated with overall mortality (*Table 5*).

To enable further informative clinical analysis, the patients were further categorized into three risk groups according to the combination of three factors, low-risk

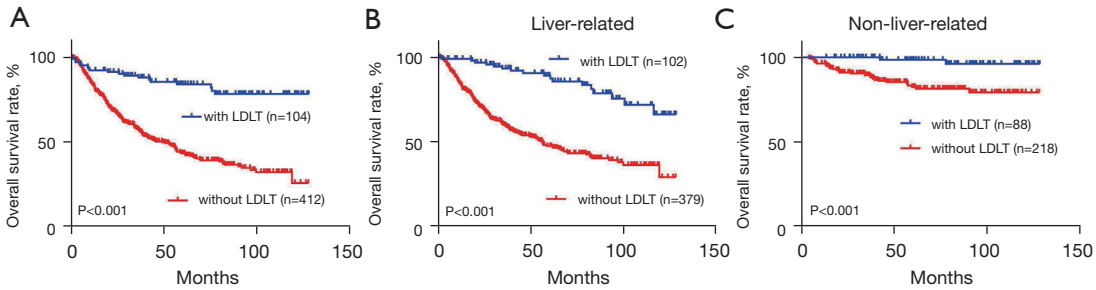

Figure 2 Kaplan-Meier survival curves for patients with BCLC stage B who underwent LDLT or non-LDLT. (A) OS (P<0.001); (B) liver-related survival (P<0.001); (C) non-liver related survival (P<0.001; log-rank test). LDLT, living donor liver transplantation; BCLC, Barcelona clinic liver cancer; OS, overall survival.

Table 3 Baseline clinicopathological features of the 104 patients with BCLC-B HCC who underwent LDLT

Characteristic	Value
Age, years [median (IQR); mean ± SD]	56 (52–61); 55.6±7.2
Male, n (%)	84 (80.8)
HCC at diagnosis	
Within UCSF, n [%]	51 [49]
Within up-to-7, n [%]	53 [51]
Kinki criteria (B1/B2/B3)	45/47/12
Child-Pugh (A/B/C)	73/22/9
MELD score, (mean ± SD)	10.3±4.4
NLR (mean ± SD)	5.6±19.9
ALBI grade (I/II/III)	26/61/17
AFP (ng/L), (mean ± SD)	50±132
Histological grade (I/II/III), n	18/52/12
Microvascular invasion, n [%]	14 [14]
LRT before LT, n (%)	94 (90.4)
Resection, n	18
TA(C)E, n	84
RFA, n	35
Time to LDLT [months; median (IQR)]	9.1 (4.1–22.5)

Data are expressed as mean ± standard deviation or medians and interquartile ranges or numbers (percentages). BCLC, Barcelona clinic liver cancer classification; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; IQR, interquartile range; SD, standard deviation; UCSF, University California of San Francisco; MELD, model for end-stage liver disease; NLR, neutrophil-to-lymphocyte ratio; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; LRT, locoregional therapy; LT, liver transplantation; TA(C)E, transarterial (chemo)embolization; RFA, radiofrequency ablation.

group (defined as age ≤60 years, NLR ≤4 and ≤3 LRT before LT), intermediate-risk group (defined as one of three risk factors), and high-risk group (defined as more than two of three risks). The low-, intermediate-, and high-risk groups contained 45 (43.3%), 45 (43.3%), and 14 patients (13.4%), respectively. One (2.2%), 5 (11.1%) and 6 patients (42.9%) developed HCC recurrence in the low-, intermediate-, and high-risk groups, respectively, and 3 (6.7%), 7 (15.6%), and 8 patients (57.1%) died in the low-, intermediate-, and high-risk groups, respectively, during follow-up. There were significant differences in the cumulative HCC recurrence (P<0.001, *Figure 4A*) and mortality (P<0.001, *Figure 4B*) rates among the three groups.

The relationships between the NLR and the clinicopathological features of the patients are summarized in *Table 6*. Patients with a NLR >4 had lower platelet counts (P=0.033), lower hemoglobin (P=0.012), lower serum albumin (P=0.006), higher serum AST (P=0.022) and a higher MELD score (P=0.026) compared to patients with a NLR ≤4. However, no associations were observed between any other characteristics, such as age, gender, hepatitis, serum total bilirubin, AST, creatinine, AFP levels, presence of diabetes mellitus, Child-Pugh class, ALBI grade, tumor number and size, and the UCSF and the up-to-7 criteria.

Discussion

To the best of our knowledge, this is the first study to compare the outcomes of patients with BCLC-B HCC who received LDLT and patients who did not receive LDLT and evaluate the risk factors for patients with BCLC-B HCC after LDLT. PSM analysis revealed that patients receiving LDLT achieved better OS compared to patients who did

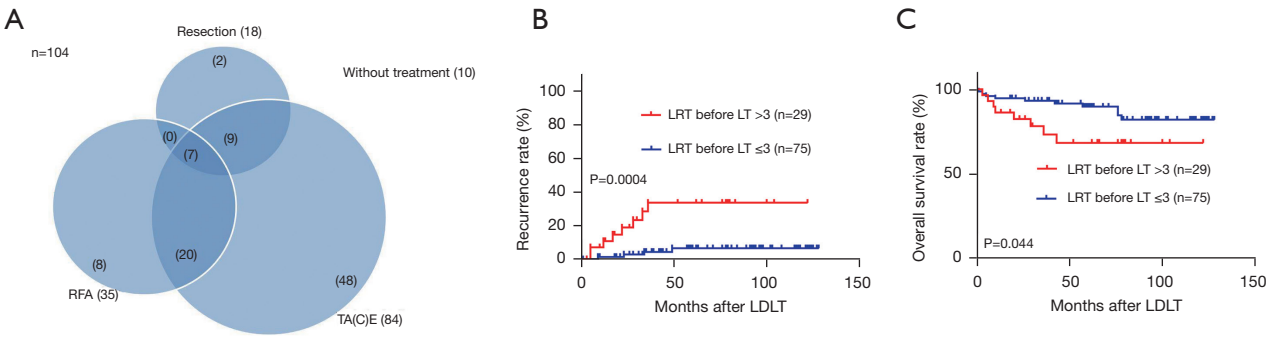

Figure 3 Higher number of pre-transplant local regional therapy worsens the survival after liver transplantation. (A) Pretreatment for the BCLC-B HCC patients who underwent LDLT. Recurrence-free (B) and OS (C) rates after LDLT for patients with BCLC-B HCC stratified by HCC treatment before LDLT. RFA, radiofrequency ablation; TA(C)E, transarterial (chemo)embolization; LRT, locoregional therapy; LT, liver transplantation; LDLT, living donor liver transplantation; BCLC, Barcelona clinic liver cancer; HCC, hepatocellular carcinoma; OS, overall survival.

Table 4 Factors associated with recurrence in patients with BCLC-B HCC after LDLT

Variable	Comparison	Univariate		Multivariate	
		HR (95% CI)	P value	HR (95% CI)	P value
Age (years)	>60 *vs.* ≤60	2.141 (0.679–6.751)	0.194	4.303 (1.194–15.504)	0.006
Sex	Male *vs.* female	1.247 (0.273–5.700)	0.776	–	–
UCSF criteria	Beyond *vs.* within	1.484 (0.469–4.671)	0.504	–	–
Up-to-7 criteria	Beyond *vs.* within	1.701 (0.538–5.376)	0.366	–	–
AFP, peak (ng/L)	>200 *vs.* ≤200	1.767 (0.532–5.871)	0.353	–	–
AFP, pre-LT (ng/L)	>200 *vs.* ≤200	2.229 (0.287–17.297)	0.443	–	–
Child-Pugh	C/B *vs.* A	1.132 (0.341–3.760)	0.840	–	–
MELD	>10 *vs.* ≤10	0.727 (0.219–2.416)	0.603	–	–
ALBI grade	II/III *vs.* I	1.690 (0.370–7.715)	0.498	–	–
NLR	>4 *vs.* ≤4	4.600 (1.456–14.532)	0.009	4.371 (1.324–14.435)	0.016
Histological grade	II + III *vs.* I	4.480 (0.665–9.244)	0.176	–	–
miV invasion	Present *vs.* absent	1.981 (0.536–7.324)	0.305	–	–
LRT before LT, n	>3 *vs.* ≤3	6.633 (1.989–22.113)	0.002	11.509 (3.008–44.037)	<0.001

BCLC, Barcelona clinic liver cancer classification; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; HR, hazard ratio; UCSF, University California of San Francisco; AFP, alpha-fetoprotein; LT, liver transplantation; MELD, model for end-stage liver disease; ALBI, albumin-bilirubin; NLR, neutrophil-to-lymphocyte ratio; miV, microvascular; LRT, locoregional therapy.

not receive LDLT. Furthermore, older age, high NLR and a higher number of LRT for HCC before LDLT were identified as independent risk factors for tumor recurrence. Moreover, older age and higher number of LRT before LT were independent risk factors for OS after LDLT. Thus, this study indicates LDLT could represent a valuable therapeutic option for selected patients with BCLC-B HCC.

TACE is recommended as the first-line therapy for intermediate-stage (BCLC-B) HCC. However, BCLC-B comprises a highly heterogeneous cohort of patients in terms of either liver function (Child-Pugh score 5–9) and single large nodule or multinodular HCC without

Table 5 Factors associated with mortality in patients with BCLC-B HCC after LDLT

Variable	Comparison	Univariate		Multivariate	
		HR (95% CI)	P value	HR (95% CI)	P value
Age (years)	>60 *vs.* ≤60	3.722 (1.464–9.461)	0.006	9.061 (2.736–30.008)	<0.001
Sex	Male *vs.* female	0.911 (0.299–2.771)	0.870	–	–
UCSF criteria	Beyond *vs.* within	1.484 (0.469–4.671)	0.504	–	–
Up-up-7 criteria	Beyond *vs.* within	1.701 (0.538–5.376)	0.366	–	–
AFP, peak (ng/L)	>200 *vs.* ≤200	1.663 (0.624–4.435)	0.309	–	–
AFP, pre-LT (ng/L)	>200 *vs.* ≤200	2.547 (0.583–11.134)	0.214	–	–
Child-Pugh	C/B *vs.* A	1.529 (0.350–6.670)	0.572	–	–
MELD	>10 *vs.* ≤10	0.938 (0.363–2.422)	0.895	–	–
ALBI grade	II/III *vs.* I	1.171 (0.385–3.560)	0.781	–	–
NLR	>4 *vs.* ≤4	2.981 (1.117–7.957)	0.029	–	–
Histological grade	II + III *vs.* I	2.474 (0.793–7.718)	0.119	–	–
miV invasion	Present *vs.* absent	0.690 (0.158–3.008)	0.662	–	–
LRT before LT, n	>3 *vs.* ≤3	2.514 (0.989–6.392)	0.053	6.964 (2.105–23.041)	0.001

BCLC, Barcelona clinic liver cancer classification; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; HR, hazard ratio; UCSF, University California of San Francisco; AFP, alpha-fetoprotein; LT, liver transplantation; MELD, model for end-stage liver disease; ALBI, albumin-bilirubin; NLR, neutrophil-to-lymphocyte ratio; miV, microvascular; LRT, locoregional therapy.

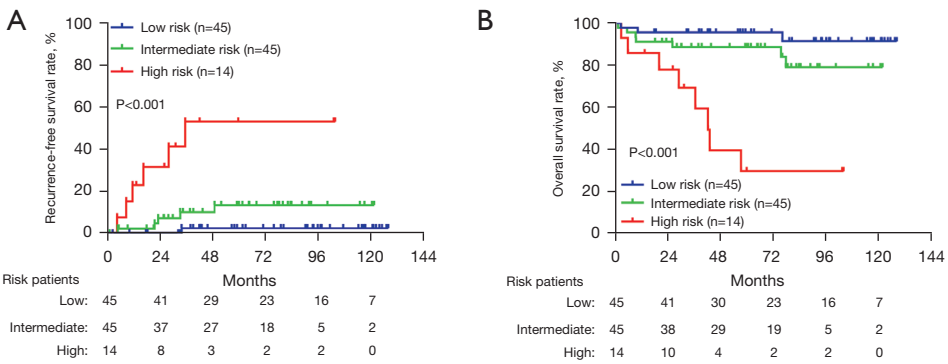

Figure 4 Recurrence (A) and OS (B) rates after LDLT for patients with BCLC-B HCC stratified as the high-risk, intermediate-risk, and low-risk groups based on age, NLR and HCC treatment before transplantation. OS, overall survival; LDLT, living donor liver transplantation; BCLC, Barcelona clinic liver cancer; HCC, hepatocellular carcinoma; NLR, neutrophil lymphocyte ratio.

vascular invasion or distant metastasis (20). In general, tumors beyond the Milan criteria (single tumor >5 cm or ≥4 nodules) are classified as BCLC-B HCC. Therefore, not all patients with intermediate stage HCC are good candidates for TACE alone, particularly patients with a large tumor bulk, multinodular spread or impaired liver function; complete TACE treatment cannot be achieved in these so-called TACE unsuitable cases. Hence, several studies have suggested that patients achieving significant downstaging after TACE or combined treatments may be considered for radical treatment, such as hepatic resection or even LT (21). This flexible approach to the treatment of BCLC B HCC is now considered in most guidelines (7,22,23); however, the characteristics and outcomes

Table 6 Comparison of the clinical and pathological characteristics of patients with NLR >4 and NLR ≤4 before LDLT

Characteristic	NLR >4 (n=16)	NLR ≤4 (n=88)	P value
Age (years)	55.2±9.1	55.7±6.9	0.805
Sex, male	12 (75.0)	72 (81.8)	0.524
CHB/CHC/B+C/NBNC	14/2/0/0	49/24/6/9	0.104
Diabetes mellitus	7 (43.8)	25 (28.4)	0.221
Hemoglobin (g/dL)	10.5±1.7	12.1±2.4	0.012
Platelet (1,000/μL)	62.1±36.9	90.8±50.7	0.033
AST (U/L)	81.3±75.0	52.8±37.3	0.022
ALT (U/L)	61.8±74.9	44.2±40.3	0.373
Total bilirubin (mg/dL)	1.7±1.0	1.3±1.1	0.182
Albumin (g/dL)	3.1±0.6	3.5±0.6	0.006
Creatinine (mg/dL)	0.9±0.4	0.8±0.3	0.207
AFP (>200 ng/mL), n (%)	2 (12.5)	3 (3.4)	0.114
Child-Pugh A/B/C	10/3/3	63/19/6	0.295
MELD score	12.6±4.3	9.9±4.3	0.026
ALBI grade (I/II/III)	6/7/3	32/43/11	0.796
Multiple tumors, n (%)	13 (81.3)	62 (70.5)	0.795
Tumor size max. (cm)	3.7±2.1	3.9±2.1	0.705
UCSF criteria met, n (%)	9 (56.3)	42 (47.7)	0.530
Up-up-7 criteria met, n (%)	9 (56.3)	44 (50.0)	0.646

Data are expressed as mean ± standard deviation or medians and interquartile ranges or numbers (percentages). NLR, neutrophil-to-lymphocyte ratio; LDLT, living donor liver transplantation; CHB, chronic hepatitis B; CHC, chronic hepatitis C; NBNC, no HBV or HCV infection; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP, alpha-fetoprotein; MELD, model for end-stage liver disease; ALBI, albumin-bilirubin; UCSF, University California of San Francisco.

of LDLT for intermediate-stage HCC are not well characterized. In our cohort of patients with BCLC-B HCC receiving LDLT, the 1, 3-, and 5-year OS rates were 92.3%, 89.2%, and 84.1%, respectively, significantly better than the corresponding rates of 84.1%, 57.7%, and 43.3% for the non-LDLT group. According to previous studies, the 3-year OS rate for intermediate-stage HCC patients receiving TACE ranges from 10% to 40% (24,25). Thus, the survival outcomes after LDLT for intermediate-stage HCC appear highly favorable.

It is worth noting that a higher number of LRT before LT (≥4) was identified as an independent risk factor for post-LT recurrence and mortality. In our cohort, most patients (>90%) received LRT to reduce the tumor burden from outside the pre-established limits to within the UCSF criteria (so-called downstaging). However, two factors may possibly explain why some patients receive more LRT before LDLT. Firstly, a larger tumor burden, including a larger tumor, higher number of tumors and rapid tumor recurrence, may make it more difficult to achieve downstaging. Secondly, patients may have been on the waiting list, but no suitable living donors were available for LT; thus, additional LRT may have been required to maintain potential LT recipients within the UCSF criteria. In addition, ten patients underwent LDLT without receiving any LRT before LT; however, no significant differences in RFS or OS were noted between these ten patients and those who received LRT. Thus, these results indicate intensive monitoring of the tumor response after each LRT and early referral for LT to reduce the waiting time to transplantation may lead to better outcomes in patients with BCLC-B HCC. These suggestions are also

compatible with our observation that a longer time from HCC diagnosis to receiving LDLT was an independent risk factor for OS.

In contrast to the LDLT group, the non-LDLT group had relatively more complex LRT, including resection (n=1,026, 48.9%), TA(C)E (n=1,502, 51.4%), RFA (n=251, 8.6%), sorafenib treatment (n=24, 0.8%), best supportive care (BSC) (n=36, 1.2%), and other factors (i.e., systemic chemotherapy, hepatic artery infusion chemotherapy, or external beam radiation therapy; n=81, 2.8%). These observations are reasonable and compatible with our prior study (26). Even though the treatment choices differed between the two groups, TA(C)E currently remains the main treatment of choice for BCLC stage B HCC.

The NLR, which reflects the potential balance between neutrophil-associated pro-tumor inflammation and lymphocyte-dependent anti-tumor immune function, has previously been shown to have predictive value in HCC (27). A meta-analysis of patients with HCC concluded that a high NLR predicted poor RFS (HR =1.45, P=0.001) and OS (HR =1.54, P<0.001) (28). However, in our previous study by Huang *et al.*, NLR only predicted poor OS, but not RFS, which might be explained by the heterogeneity of the HCC population (29). In the present study, a high NLR was associated with a higher rate of recurrence after LDLT for HCC (HR =4.37; 95% CI: 1.32–14.44; P=0.016). This finding is consistent with previous studies, which reported an elevated NLR pre-LT was associated with a significantly increased risk of recurrence in patients undergoing LT for HCC (30,31). Similar to those studies, we used a cut-off value of 4 for the NLR. In this study, receiver operating characteristic (ROC) analysis demonstrated that the sensitivity and specificity were highest when the NLR was 4.153 (data not shown). The underlying mechanisms by which the NLR affects tumor recurrence remain unclear, though some studies have proposed that patients with a high NLR have higher serum and peritumoral levels of IL-17, which correlates with peritumoral CD163 (30). In the present study, we found that patients with a NLR >4 had lower platelet counts (P=0.033), lower hemoglobin (P=0.012), lower serum albumin (P=0.006) higher serum AST (P=0.022) and a higher MELD score (P=0.026) compared to patients with a NLR ≤4 (*Table 4*). It remains unclear whether these differences are associated with peritumoral IL-17. Additional molecular and clinical investigations are necessary to fully elucidate the pro-carcinogenic effects of a high NLR in this specific patient population.

In addition to the NLR, the ALBI grade—a novel evaluation method—has exhibited impressive ability to predict the prognosis of patients with HCC (32). ALBI grade was previously shown to predict RFS and OS for patients with HCC receiving LT (33). However, no significant predictive value of ALBI was noted in the present study. This conflicting result may be associated with the different methods of LT; all recipients were DDLT in the study by Kornberg *et al.* (33), but all were LDLT in the present study. The characteristics of LDLT and DDLT recipients are quite different. A recent study compared adult patients who received LDLT (n=245) and DDLT (n=592) between 2009–2019 at the University of Pittsburgh Medical Center (34). Most baseline characteristics, including the proportion of males, retransplants, MELD score and donor age, were significantly different between the LDLT and DDLT groups. Thus, further studies are necessary to compare the predictive value of pre-LT ALBI grade in patients undergoing LDLT or DDLT.

Finally, based on the significant factors identified in our multivariate analysis of recurrence after LT (*Table 3*), we stratified the patients into high- and low-risk groups by age, NLR and LRT before LT. Using this simple classification, one could determine the prognosis of a patient on presentation, which is important for clinicians when devising individual patient's management plans. Currently, there is no predictive model for the outcomes of patients with HCC after LT, especially the BCLC stage B group. Thus, our novel model may provide further insight for clinicians to identify high-risk patients who should be treated using alternative modalities, such as immunotherapy or targeted therapy, as well as low-risk patients who should be referred early for LT once down-staged to the UCSF criteria. However, further research is required to validate the prognostic value of this model in BCLC stage B.

This study has some limitations. First, as the study population had BCLC stage B and more than half of patients received TA(C)E as their first treatment, the original pathological characteristics of HCC could not be obtained for either the LDLT or non-LDLT groups. In addition, the definite tumor number was also unavailable. This scarcity of information might lead to an unbalanced tumor background between two groups, even though PSM was performed. In the future, analysis of a larger cohort with more comprehensive tumor pathologic data, including information on histological grade, vascular

invasion, capsule invasion, and satellite nodules, is required to validate our results. Secondly, this was a retrospective analysis, which may lead to some degree of missing data and patient selection bias, such as in patients either ineligible or unwilling for LDLT, is certain to occur. Third, more than half of the patients in our cohort had HBV infection as the etiology of HCC, whereas chronic HCV infection is the major cause for the development of HCC in Western countries and Japan (35).

Conclusions

In conclusion, LDLT may represent a valuable therapeutic option for selected patients with BCLC intermediate-stage HCC; further prospective studies are warranted to validate this suggestion.

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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-21-196/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-196/coif). CLC serve 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Institutional Review Board of Kaohsiung Chang Gung Memorial Hospital (IRB number: 201900065B0). The requirement for written informed consent was waived by the Institutional Review Board due to the retrospective design of the study and absence of relevant human or biological ethical issues.

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