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Original Article

Outcomes of liver transplantation for hepatocellular carcinoma: Experiences from a Vietnamese center

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Backgrounds/Aims: Liver transplantation (LT) provides a favorable outcome for patients with hepatocellular carcinoma (HCC) and was launched in Vietnam in 2004. In this study, we evaluated the short-term and long-term outcomes of LT and its risk factors.
Methods: This retrospective study analyzed HCC patients who underwent LT at Viet Duc University hospital, Vietnam, from 01/2012–03/2022. The following data were gathered: demographics, virus infection, tumor characteristics, alpha-fetoprotein (AFP) level, Child-Pugh and MELD scores, selection criteria, type of LT, complications, 30-day mortality, and disease-free and overall survival (DFS and OS).
Results: Fifty four patients were included, the mean age was 55.39 ± 8.46 years. Nearly 90% had hepatitis B virus-related HCC. The median (interquartile range) AFP level was 16.2 (88.7) ng/mL. The average MELD score was 10.57 ± 5.95; the rate of Child-Pugh A and B were 70.4% and 18.5%, respectively. Nearly 40% of the patients were within Milan criteria, brain-dead donor was 83.3%. Hepatic and portal vein thrombosis occurred in 0% and 1.9%, respectively; hepatic artery thrombosis 1.9%, biliary leakage 5.6%, and postoperative hemorrhage 3.7%. Ninety-day mortality was 5.6%. Five-year DFS and OS were 79.3% and 81.4%, respectively. MELD score and Child-Pugh score were predictive factors for DFS and OS ($p < 0.05$). In multivariate analysis, Child-Pugh score was the only significant factor ($p < 0.05$).
Conclusions: In Vietnam, LT is an effective therapy for HCC with an acceptable complication rate, mortality rate, and good survival outcomes, and should be further encouraged.

Key Words: Liver transplantation; Survival; Carcinoma, hepatocellular; Vietnam

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common malignancy of the liver and the third leading cause of cancer-related deaths in the world. HCC mostly occurs in patients with chronic liver diseases such as hepatitis B virus (HBV) infection and hepatitis C virus (HCV) infection, or alcohol abuse [1,2]. Vietnam is among the countries with a high incidence of HCC with age-standardized incidence rates of HCC of 14 and 3.7 per 100,000 in males and females, respectively [3,4].

Liver transplantation (LT) is widely considered to be the most effective therapeutic option for certain patients with HCC [5]. HCC within the Milan criteria, published by Mazzaferro et al. [6] in 1996, is the most common indication for LT. As a result, the patients have a four-year overall survival (OS) of 75% and a better quality of life. Though many expanded criteria, such as University of California San Francisco (UCSF), Asan, Kyoto, and Tokyo have been introduced, the survival in LT within Milan criteria remains superior compared to other criteria [5,7]. The reported 3-year survival rate ranges from 76%–88% for

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within Milan criteria and 47%–73% for beyond Milan criteria and a 5-year survival rate of approximately 80% in big Asian centers [5,8]. Demand for LT continues to increase and spreads from developed countries to many developing countries, including Vietnam.

In Vietnam, LT was launched in 2004 and has been mostly conducted in specialized centers [9,10]. By the end of 2022, approximately 440 liver transplants, including 341 liver transplants from living donors and 99 transplants from brain-dead donors, had been performed in Vietnam. The first liver transplant for a patient with HCC was performed in December 2007 at Viet Duc University Hospital. Since then, the demand and number of liver transplants have been increasing yearly [11]. Thus, we evaluated the effectiveness of LT (short-term and long-term outcomes, and potential risk factors) for HCC in our institution.

MATERIALS AND METHODS

Patients

All patients were assigned and underwent liver transplant surgery for HCC (a pathologist confirmed HCC) at Viet Duc University Hospital from January 2012 to March 2022. Our study was approved by the Institutional Ethical Review Board (No. 02.2023.NCVĐ). The written informed consent was obtained from the recruited patients.

Methods

We retrospectively collected data for the patients who underwent LT for HCC in our center. The data were divided into two groups: Within Milan and Out of Milan. We collected data for the baseline characteristics: age, sex, body mass index (kg/m^2), alcoholism, HBV infection, HCV infection; pretransplant treatment: history of transarterial chemoembolization, radiofrequency ablation, hepatectomy; clinical symptoms: jaundice, weight loss, ascites, Child-Pugh score, MELD score; laboratory results: hemoglobin, platelets, prothrombin time, liver enzymes (apartate aminotransferase [AST], alanine transaminase [ALT]), total bilirubin, albumin, alpha-fetoprotein (AFP). Imaging diagnosis (computed tomography/magnetic resonance imaging) included the number of tumors, tumor size, site; type of LT (living-donor [LDLT], deceased-donor [DDLT]), indications for LT: within Milan criteria or out of Milan criteria; reconstruction techniques used for the hepatic vein (HV) (classical, piggyback with common orifice of three HV, common orifice of middle hepatic vein [MHV] and left hepatic vein [LHV], common orifice of right hepatic vein [RHV] and MHV, enlarged orifice of RHV and modified piggyback with end-to-side cavocaval), warm ischemia time; Treatment outcomes: Early results: surgical complications including hemorrhage, hepatic artery (HA) stenosis/thrombosis, portal vein (PV) stenosis/thrombosis, biliary fistula, pleural effusion and management, Clavien-Dindo classification of surgical complications up to three months, length of hospital stay, 90-day mortality rate, long-term results: Disease-free survival (DFS), OS and its prognostic factors.

Surgical techniques

Step 1. The recipient hepatectomy: The bilateral subcostal incision with midline extension to the sternal xiphoid. Dissection of the hepatic pedicle: division of the common bile duct, right hepatic artery (RHA), and left hepatic artery. Dissection of the PV, exposed from the hilum of the liver and to the superior border of the pancreas. The posthepatic vena cava segment is conventionally preserved or excised with the liver if the tumor infiltrates the vena cava.

Step 2. Hepatic venous outflow, portal vein flow reconstruction: In general, for HV reconstruction, we used classical, piggyback, common orifice of three HV, enlarged RHV orifice, common orifice of the LHV and MHV, RHV with MHV reconstruction, and/or short HV. HV outflow reconstruction is carried out with 5/0 polypropylene sutures. For DDLT, we performed the classic technique with vena cava interposition, piggyback technique: end-to-end anastomosis between the suprahepatic vena cava of the donor's liver and the common orifice of the recipient's hepatic veins and modified piggyback technique: side-to-side or end-to-side veno-vena caval anastomosis. For LDLT using right liver graft: For liver graft without MHV, the RHV is anastomosed with the recipient's RHV after each orifice has been enlarged sufficiently, if V5 and V8 branches > 5 mm, they will be reconstructed with the cryopreserved iliac vein conduit from the brain dead donor. For the grafts with the MHV, the MHV will be reconstructed with the RHV in one orifice and then be anastomosed with the vena cava.

PV inflow reconstruction is carried out by end-to-end anastomosis of the recipient's PV with the grafted hepatic PV with 6/0 polypropylene sutures for conventional cases.

Liver reperfusion: releasing the portal clamp to allow blood and air to flow out through the lower end of the vena cava of the liver graft then releasing the hepatic venous outflow anastomosis clamp.

Step 3. Hepatic artery and biliary tract reconstruction. For DDLT, HA anastomosis is performed end-to-end using polypropylene suture 6/0–7/0 between the proper or common HA of the liver graft and the proper or common HA of the recipient to ensure that there is no twisting, folding, or tension, and the anastomosis is wide enough. For LDLT, the RHA of the liver graft is anastomosed with the recipient's RHA, interrupted or continuous suture with the 7/0–8/0 polypropylene. Bile duct anastomosis is performed end to end with a drainage tube.

Step 4. Check hemostasis and close the incision. Immunosuppression protocols: The standard combination of drugs including basiliximab (induction) on days 0 and 4, prednisolone + tacrolimus + mycophenolate mofetil (or mycophenolic acid). We reduce the dose of prednisolone from 500 mg first day to 20 mg after 7 days and usually stop after 3 months. The trough

concentration of tacrolimus was 8–10 ng/mL in the early stage of LT. After 1–3 months, mycophenolate mofetil (or mycophenolic acid) is changed to everolimus. Based on the patient's condition, the drug may vary.

Statistical analysis

The primary endpoint was DFS measured as the number of months from the operation until the disease recurrence, and OS (from the operation to the latest follow-up or death). Student's t-test for continuous variables, nonparametric test for the median parameter, and χ^2 test for categorical variables were used. DFS, OS, and survival probabilities were calculated by the Kaplan-Meier curves using the log-rank test. The Cox regression model was used for multivariate analysis. A two-tail p-value of ≤ 0.05 was considered statistically significant. The analyses were performed using SPSS 26.0 64-bit (IBM Corp).

Table 1. Baseline characteristics and laboratory results

Variable	Within Milan (n = 21)	Out of Milan (n = 33)	Total	p-value
Age (yr)	55.43 ± 9.02	55.36 ± 8.23	55.39 ± 8.46	
< 40	2 (9.5)	2 (6.1)	4 (7.4)	0.75
40–60	15 (71.4)	22 (66.7)	37 (68.5)	
> 60	4 (19.0)	9 (27.3)	13 (24.1)	
Sex				
Male	18 (85.7)	32 (97.0)	50 (92.6)	0.29
Female	3 (14.3)	1 (3.0)	4 (7.4)	
HBV infection (%)	19 (90.5)	29 (87.9)	48 (88.9)	> 0.99
HCV infection (%)	2 (9.5)	2 (6.1)	4 (7.4)	0.64
Alcohol abuse	3 (14.3)	5 (15.2)	8 (14.8)	> 0.99
Preoperative treatment				
TACE only	5 (23.8)	17 (51.5)	22 (40.7)	
RFA only	1 (4.8)	1 (3.0%)	2 (3.7)	0.14
TACE + RFA	7 (33.3)	10 (30.3%)	17 (31.5)	
Liver resection	6 (28.6)	8 (24.2%)	14 (25.9)	0.76
Hb (g/L)	128.8 ± 25.1	136.2 ± 19.5	133.3 ± 21.9	0.23
PLT (g/L)	113.3 ± 62.2	129.5 ± 56.0	123.2 ± 58.4	0.33
PT (%)	76.6 ± 20.6	80.4 ± 20.2	79.0 ± 20.3	0.51
AST (U/L)	54.7 ± 28.8	63.0 ± 43.2	59.8 ± 38.1	0.44
ALT (U/L)	46.5 ± 19.6	65.2 ± 41.8	57.9 ± 35.8	0.03*
Total bilirubin (umol/L)	29.2 ± 43.4	54.0 ± 118.2	44.3 ± 96.4	0.36
AFP (median [IQR]) (ng/mL)	14 (58.2)	31 (120.4)	16.2 (88.7)	0.06
Child-Pugh score				
A	13 (61.9)	25 (75.8)	38 (70.4)	0.56
B	5 (23.8)	5 (15.2)	10 (18.5)	
C	3 (14.3)	3 (9.1)	6 (11.1)	
MELD score	10.76 ± 4.61 (6–25)	10.45 ± 6.73 (6–38)	10.57 ± 5.95 (6–38)	0.86
Tumor parameters				
Number	1.10 ± 0.63	2.58 ± 1.20	2.00 ± 1.24	< 0.001
Size (mm)	21.76 ± 12.01	49.55 ± 21.26	38.74 ± 22.67	< 0.001
Site	(n = 21)[a]		(n = 54)	
Right	15 (71.4)	19 (57.6)	34 (63.0)	0.13
Left	2 (9.5)	5 (15.2)	7 (13.0)	
Both	2 (9.5)	9 (27.3)	11 (20.4)	
Cold ischemic time (min)			168.6 ± 78.2	

Values are presented as mean ± standard deviation, number (%), or mean ± standard deviation (range) unless otherwise indicated.
HBV, hepatitis B virus; HCV, hepatitis C virus; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; PLT, platelets; PT, prothrombin time; AST, apartate aminotransferase; ALT, alanine transaminase; AFP, alpha-fetoprotein; IQR, interquartile range.
[a]2 patients excluded due to recurrent after liver resection.
*p < 0.05.

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RESULTS

A total of 54 patients were selected. The mean age was 55.39 ± 8.46 years. Male:female ratio was 12.5:1. HBV infection was the main cause of HCC (88.9%), followed by alcohol abuse (14.8%) and HCV (7.4%). The main symptoms were jaundice (16.7%) and weight loss (16.7%). AFP level was 195.4 ± 471.9 ng/mL, there were no differences in Child-Pugh scores ($p = 0.56$) and MELD scores ($p = 0.86$) between the two groups (Table 1).

AST and ALT were 59.8 ± 38.1 and 57.9 ± 35.8 U/L, respectively. Total bilirubin was 44.3 ± 96.4 umol/L, there was no statistical difference among the two groups ($p = 0.36$). Most of the tumors were in the right lobe (63.0%). There was a significant difference in the number of tumors (1.10 ± 0.63 vs. 2.58 ± 1.20, $p < 0.001$) and tumor size (21.76 ± 12.01 vs. 49.55 ± 21.26 mm, $p < 0.001$) between the within Milan and out of Milan groups (Table 1).

DDLT was performed in 83.3% of cases. We used the right graft for LDLT and reconstructed the HV using RHV (55.6%) and RHV with MHV reconstruction (44.4%). The mean warm ischemic time was 61.09 ± 30.42 minutes. The most frequent complication was pleural effusion (44.4%), and vascular complication included HA thrombosis/stenosis (1.9%) and PV thrombosis (1.9%). Bile leakage was seen in 5.6% of cases, 2 patients (3.7%) had graft rejection, 1 patient was medically treated and the other one died. The 90-day mortality rate was 5.6% (Table 2).

The mean follow-up time was 51.2 ± 38.1 months, mean DFS and OS were 101.8 ± 6.8 and 103.3 ± 6.4 months. The 1-, 3-, and 5-year DFS of the within Milan group was 90.0%; and OS was 90.5%, respectively. For the out of Milan group, the DFS was 80.4%, 73.1%, and 73.1%; and OS was 73.2%, 69.7%, and 69.7%, respectively. In univariate analysis, there was a statistically significant difference in both DFS and OS between the Child-Pugh classification and MELD score (cut-off = 15) ($p < 0.05$) (Fig. 1). In multivariate analysis, the Child-Pugh score was the sole significant factor of DFS and OS (Table 3).

DISCUSSION

Our study showed that the main cause of HCC was HBV. Nearly 40% of the HCC cases were within Milan criteria, while 61.1% of the HCC cases were out of Milan criteria. DDLT was the main type of surgery. Pleural effusion was the most common complication; grade 3–4 complications were 40.8%. Ninety-day mortality was 5.6%, 5-year survival rate reached 81.4%.

Vietnam is among the countries with a high proportion of HBV infection, ranging from 5.7%–24.7% with an age-standardized incidence rate of HCC of 14 and 3.7 per 100,000 for males and females, respectively [3,4]. However, the estimated number of patients receiving the antiviral drugs is thought to be very low because of the unawareness and costly treatment. Consequently, there is a high number of patients with HBV-induced HCC in Vietnam, leading to a high national burden.

In total, over 100 LTs have been performed in our center since 2007 and approximately 80% are brain-death donors. In this study, most of the donors (83.3%) were also brain-death donors. The figure is different from other transplant centers in Vietnam [9]. This is partly because, currently, in the Northern area, our hospital is the largest and the most specialized center

Table 2. The postoperative outcomes

Variable	DDLT (n = 45)	LDLT (n = 9)	Total
Complications			
Hemorrhage	2 (4.4)	0 (0)	2 (3.7)
HA thrombosis/stenosis	1 (2.2)	0 (0)	1 (1.9)
PV thrombosis	1 (2.2)	0 (0)	1 (1.9)
HV thrombosis	0	0	0
Bile leakage	1 (2.2)	2 (22.2)	3 (5.6)
Bile duct stenosis	1 (2.2)	0	1 (1.9)
Need-to-drain pleural effusion	20 (44.4)	4 (44.4)	24 (44.4)
Graft rejection	2 (4.4)	0 (0)	2 (3.7)
Clavien-Dindo classification			
1	0	0	0
2	1 (2.2)	0	1 (1.9)
3	16 (35.6)	5 (55.6)	21 (38.9)
4	1 (2.2)	0	1 (1.9)
5	2 (4.4)	1 (11.1)	3 (5.6)
90-day mortality	2 (4.4)	1 (11.1)	3 (5.6)

Values are presented as number (%).
DDLT, deceased-donor liver transplantation; LDLT, living-donor liver transplantation; HA, hepatic artery; PV, portal vein; HV, hepatic vein.

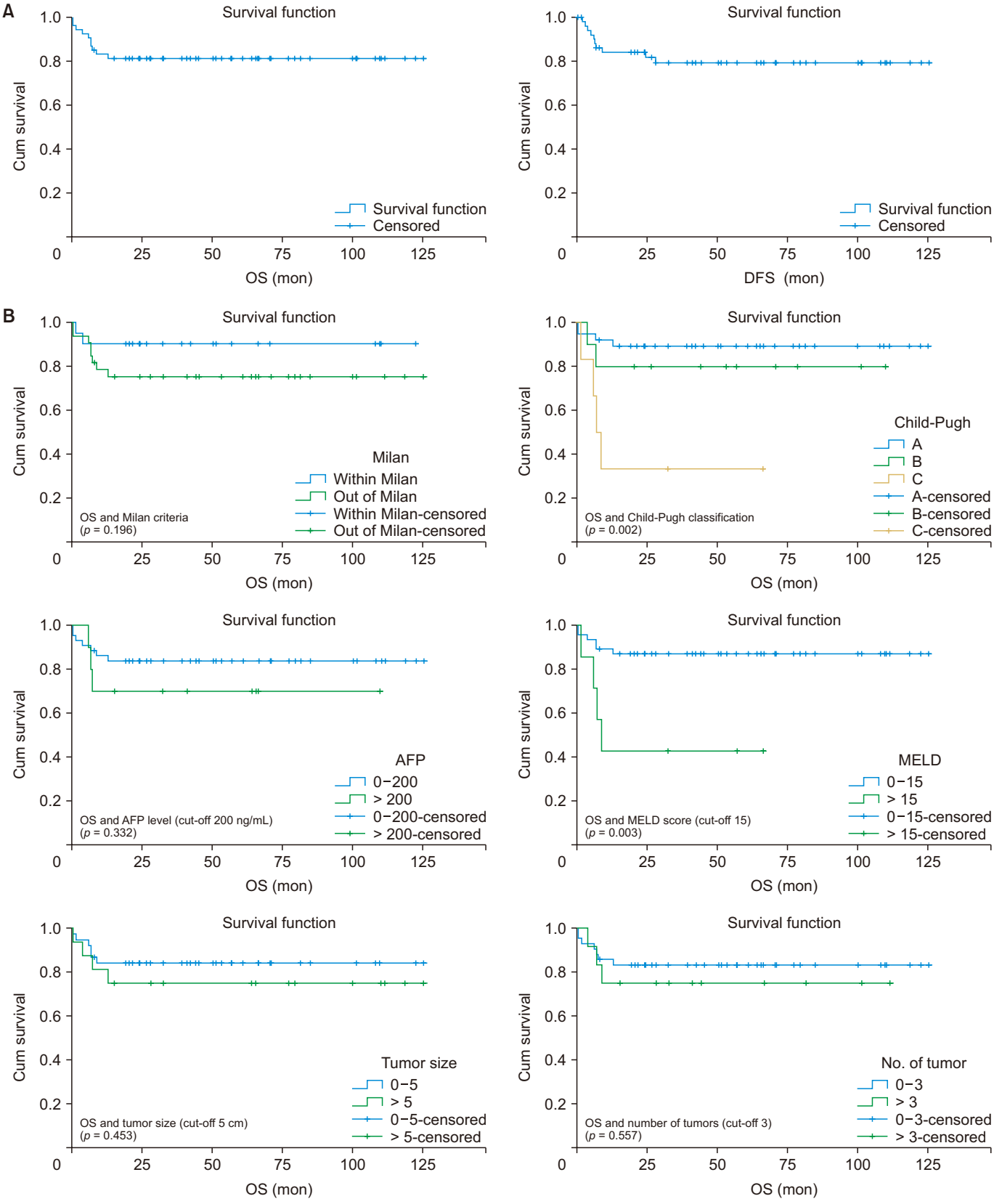

Fig. 1. (A) Overall survival (OS) and disease-free survival (DFS). (B) OS and the associated factors. (C) DFS and the associated factors.

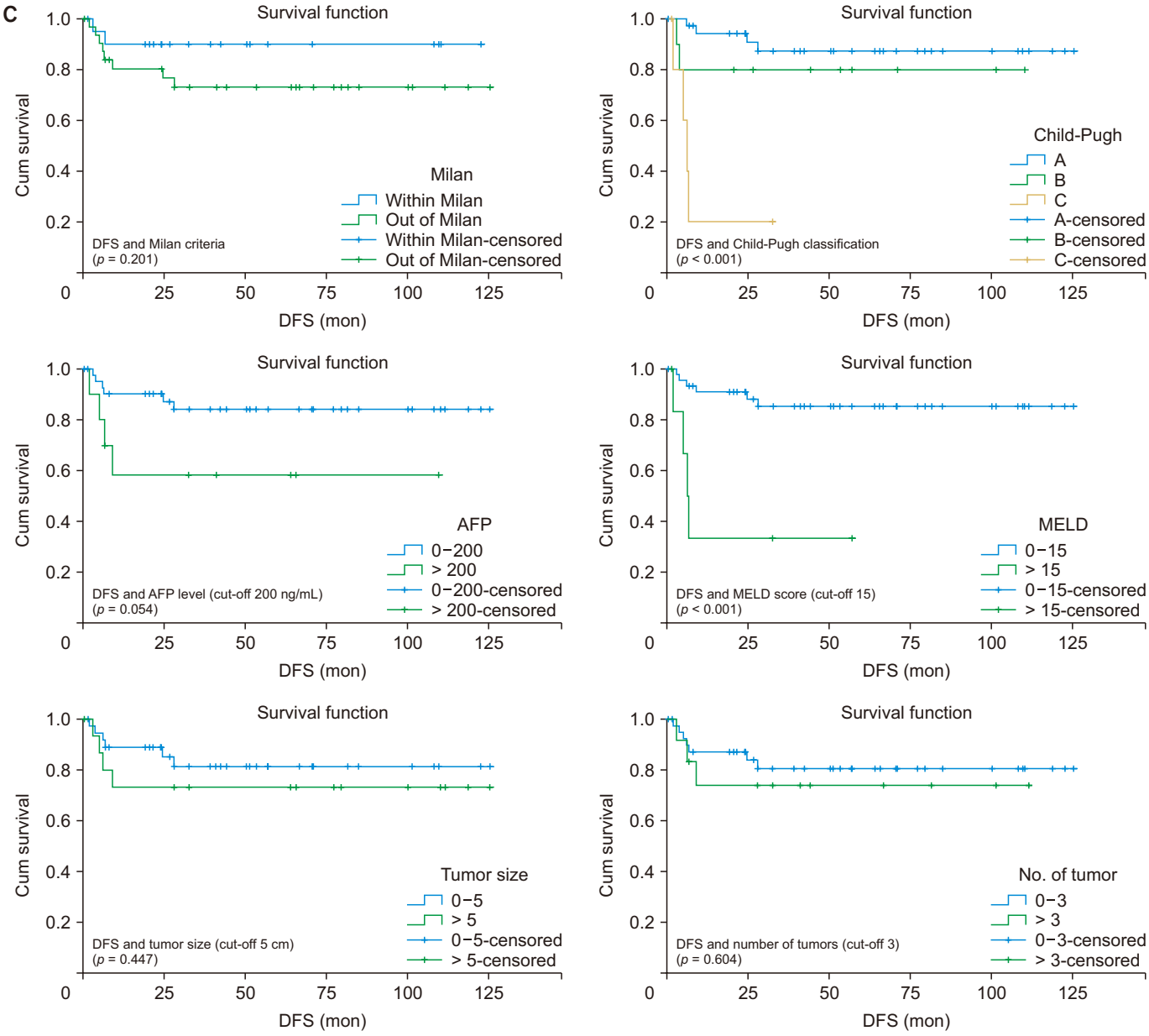

Fig. 1. Continued.

Table 3. Multivariate analysis for DFS and OS

Variable	DFS		OS	
	Exp (B)	*p*-value	Exp (B)	*p*-value
AFP	2.421	0.261	0.971	0.972
Child-Pugh	4.040	0.001*	3.541	0.003
Age	1.314	0.698	1.002	0.997
Milan	6.346	0.062	2.913	0.176
Sex	2.244	0.534	0.000	0.985

DFS, disease-free survival; OS, overall survival; AFP, alpha-fetoprotein.
*$p < 0.05$.

for brain injury patients (approximately 2–5 brain-death cases/day). However, due to cultural perspectives, organ donation after brain death remains low in Vietnam [12]. Furthermore, the primary drawbacks of brain-death donor were donor scarcity, failing to satisfy the high demand, as well as the quick factor, which caused many patients to drop out of the waiting list due to long waiting times [8].

We mainly used Milan criteria and UCSF criteria to select the patients to undergo LT and could get a 5-year OS of 81.4%. In our study, the selection criteria were based on preoperative imaging, and though downstaging was applied, we still counted all of the necrotic tumors as viable tumors to classify whether the patients were within Milan or not. Interestingly, the data suggested that the Child-Pugh score was the significant factor in both DFS and OS, but not the selection criteria. In the within Milan group, the tumor burden was not big, but the rate of decompensated liver function and severe complications was higher than in the out of Milan group. Two out of 21 patients died within three months because of complications/infection after LT, which might have led to the lower survival outcomes of this group. The survival might not reflect the role of Milan criteria, the prognosis for DFS was nearly statistically significant ($p = 0.06$). In our study, CTP and MELD were significantly correlated. Lee et al.'s research study [13] (2019) showed that if HCC patients have a high MELD score (> 20), the presence of tumors does not impact survival. Since a consensus about LT for HCC based on Child-Pugh grade C/high MELD score is yet to be established, we suggest that Child-Pugh classification could be a prognostic factor in patients with HCC. This evidence could somehow show that liver function is still an important factor in LT and should be focused on.

To increase the chance of LT, our center also tried to manage the patient by downstaging method (RFA, TACE, liver resection). The patient follow-up was every one to three months using an MRI/CT scan and tumor marker, and was considered a successful LT candidate if the tumor size decreased and the AFP level was below 400 ng/mL. A minimum waiting time of three months from successful downstaging was applied. We still have 42.6% of patients who were out of Milan and UCSF criteria. Based on the Metroticket 2.0 model, 21.7% of them have a prognostic survival rate of below 50% [14]. These patients were in the advanced stage, and all of the other treatments could partially control the tumor progression. LT was chosen as the last option. Meanwhile, some patients acknowledged the role of LT right after they were diagnosed with HCC and determined to have LT soon. The complications rate was 48.1%, similar to Pham et al.'s study (2022) [9]. Twenty eight patients (51.9%) had no complications, this was higher than Daugaard et al.'s study (7.9%) [15] and Pham et al.'s study [9]. Percentage of vascular complications in our study was 5.6%, similar to the study of Khalaf (7%–13%) [16]. Biliary complications occured in 7.4% of the patients, similar to Nemes et al.'s systematic review (2015) [17], which showed that 8.5% of the patients had biliary leakage and 14.7% had biliary stricture. Ninety-day mortality was 5.6%. One patient died due to uncontrolled hemorrhage, one patient due to fungal-related HA thrombosis, and one patient because of bile leakage.

More than half of the patients who underwent LT had HCC. Though the demand is increasing and we are one of the leading LT teams in Vietnam, we perform only 15–25 liver transplants per year. This volume is classified as low volume center and we aim to raise it up [18]. There are several obstacles to be pointed out, including cultural perspective in DDLT, donor safety in LDLT, and financial issues. We try to do policy advocacy and prioritize the living donor as the main source for LT and we expected that more patients could benefit from LDLT in our center and Vietnam, in general [9,10].

To the best of our knowledge, this is the first worldwide publication about LT for HCC with the longest follow-up in Vietnam. We are aware that LT is still a new and challenging operation in Vietnam. Though it is a retrospective study with a limited study population, we believe that it is valuable data that could be a useful tool for policymaking and a milestone for our country.

In conclusion, LT is a promising treatment option for patients with HCC in developing countries, including Vietnam. LDLT increases the donor pool to meet the increasing demand for transplantation in Vietnam.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Conceptualization: KVN, TDN. Data curation: DHD, TDN. Methodology: KVN, DHD. Visualization: PHT, TH. Writing - original draft: KVN, DHD, TDN. Writing - review & editing: DTL, NQN.

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