Risk factors impacting mortality after living related liver transplantation for hepatocellular carcinoma: a retrospective cohort study

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Objective
Liver transplantation is an optimal form of radical therapy for selected patients with hepatocellular carcinoma (HCC). Yet, risk factors determining outcome after living donor liver transplantation (LDLT) are still lacking and need to be well identified to maximize recipient benefit and minimize donor risk.
Aim
The aim of this study was to retrospectively identify and analyze the factors impacting mortality in HCC patients after LDLT.
Patients and methods
This is a single-center retrospective analysis of data collected from 205 patients who underwent LDLT in the Department of Surgery, National Liver Institute, Menoufia University, between May 2004 and December 2013. Of these patients, 53 proved to have an HCC in the explanted liver. Preoperative data such as demographic criteria of the patients, liver status, tumor burden, and downstaging or bridging procedures, and all intraoperative and postoperative data were collected and compared against mortality outcome. Mortality was divided into three periods: hospital mortality, which occurred within 30 days after operation; early mortality, which occurred between 2 and 6 months postoperatively; and late mortality, which occurred 6 months after transplantation.
Results
The mean age of all patients was 48±6.1 years; 50 (94.3%) patients were male. During the follow-up period, 22 (41.5%) patients died. The majority of mortality cases (10; 18.9%) were in the perioperative period; six (11.3%) patients died in the early period and six (11.3%) in the late period. There was a statistically significant relation between mortality rate and cytomegalovirus immunoglobulin (CMV-IgG) negativity and TNM classification (IIIB). Concerning the operative data, there was a significant statistical relation between mortality and actual graft weight, actual graft/recipient weight ratio, and number of blood and plasma transfused units. Postoperatively, there was a significant statistical relation between mortality and the grade of tumor differentiation. In multivariate analysis, CMV-IgG negativity, TNM stage (stage III), actual graft weight, and number of blood transfusion units were independent predictors of mortality.
Conclusion
Several factors have an independent significant effect on post-liver transplantation mortality. CMV-IgG negativity, advanced tumor stage (IIIB), actual graft weight, volume of intraoperative blood transfusion, poor tumor grade of differentiation, and tumor recurrence have an influence on post-transplantation mortality. Because LDLT can be performed regardless of Child–Pugh classification, model of end-stage liver disease score, and portal hypertension, only tumor factors, graft volume, and technical complications should be considered when selecting HCC patients for LDLT.

Keywords:
hepatocellular carcinoma, living related liver transplantation, mortality

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Introduction

Liver transplantation (LT) is an optimal form of radical therapy for selected patients with hepatocellular carcinoma (HCC), as it treats both liver cirrhosis and provides the widest oncological safety margins of resected HCC [1]. Following the seminal paper of Mazzaferro *et al*. [2], highlighting the Milan criteria, which are considered the backbone of indications for LT in HCC patients, the 5-year survival increased to as

much as 75%, whereas recurrence rates decreased to less than 14%. These satisfactory results encouraged surgeons to further expand the criteria for suitability of HCC patients for LT – for example, the University of California, San Francisco (UCSF) criteria (single tumor ≤6.5 cm, or three or fewer nodules with the largest lesion ≤4.5 cm, and a total tumor diameter ≤8 cm, without vascular invasion) [3]. These expanding criteria also result in an overall survival and recurrence-free survival rate comparable to those following standard criteria [4–7].

Further, Living donor liver transplantation (LDLTx) is emerging as a compulsory treatment for HCC as it expands the donor pool and avoids the long waiting list for transplantation [1–3]. The results of living donor liver transplantation (LDLT) for HCC were comparable to those of deceased donor liver transplant (DDLT) as well as to those of LT for non-HCC end-stage liver disease. Nevertheless, the prognostic factors determining outcome after LDLT for HCC remain controversial, with several risk variables having been described by several authors on the basis of retrospective studies. However, single systemic factors like serum creatinine and tissue factors like tumor differentiation grade are well known to affect the HCC patient's outcome after LT [8,9].

Knowing the independent risk factors impacting the outcome of LDLT in HCC patients will facilitate proper selection of patients who will derive the maximum benefit and also avoid risks for volunteer donors. Therefore, the objectives of the present study were to retrospectively identify and analyze the factors impacting mortality in HCC patients after LDLT in our National Liver Institute.

Patients and methods

Patients

This is a single-center retrospective analysis of data collected from 205 patients who underwent LDLTx in the Department of Surgery, National Liver Institute, Menoufia University, between May 2004 and December 2013. The program of LDLT in our institute started in April 2003, and in May 2004 HCC patients started to be accepted as candidates for LDLTx. Among those 205 patients, 61 (29.7%) had undergone LDLT because of hepatic focal lesions, but only 53 (25.8%) were confirmed to have HCC based on histopathology of the explanted liver. Therefore, eight (3.9%) patients with negative pathological confirmation for HCC were excluded from our retrospective analysis.

Pretransplant data

Preoperative evaluation included the following:

(1) Patient status as determined by the patient's age, body build, performance status, and presence or absence of comorbidities such as diabetes mellitus (DM) or hypertension.
(2) Liver status as determined by the cause of cirrhosis, virology profile [cytomegalovirus (CMV), Epstein-Barr virus (EBV)], liver function tests, degree of portal hypertension, Child score, and model of end-stage liver disease (MELD) score.
(3) Tumor burden as described on computed tomography (CT) and MRI (tumor size, number, and vascular invasion), and on PET-CT to exclude extrahepatic metastases, and by serum α -fetoprotein (AFP) level as a surrogate for tumor biology.
(4) Evaluation of preoperative diagnostic biopsy and downstaging or bridging procedures. Preoperative tumor staging was based on different staging systems like the pTNM classification proposed by the American Union Committee on Cancer [10], the BCLC, the Milan criteria, and the UCSF expanding criteria, to facilitate patient categorization and comparison.

Surgical procedures

In LDLT for HCC patients, procedures on recipients start before donor hepatectomy. Recipient hepatectomy was performed according to a standard technique. For ascites, aspiration and cytology were performed before beginning the operation. When lymph node enlargement was present, or in cases with suspicious metastatic disease, an intraoperative biopsy was performed. The operation was completed only in cases with negative biopsy results. We used the anterior approach for liver resection in recipients [11]. The anterior approach involves a 'no-touch' technique for resecting the liver tumor, decreasing the chance of tumor rupture and metastasis. Recipient hepatectomy was performed without the use of venovenous bypass or vena cava occlusion at any time. After liver removal, implantation started with right hepatic vein anastomosis. The inferior vena cava was incised longitudinally and caudally if the right hepatic vein was smaller than the liver graft. End-to-end portal vein anastomosis was created using 6-0 Prolene suture Ethicon Inc., a subsidiary of (Johnson and Johnson, produced in Cornelia, Georgia, USA). Hepatic artery anastomosis was performed using a microvascular technique with 9-0 nylon. Duct-to-duct anastomosis was performed using 5-0 polydioxanone Suture (PDS) with an internal stent.

The following intraoperative parameters were recorded: type and size of the graft, volume of blood and plasma

transfusion, cold and warm ischemia times, number and type of bile duct anastomoses, and operative time.

Post-transplant data

Immunosuppression regimens

We started an immunosuppressive regimen the day before transplantation or on the first postoperative day. Immunosuppression treatment included a regimen with a calcineurin inhibitor (CNI) such as tacrolimus (Prograf or FK) (Astellas Toyama Co., Ltd. 2-178 Kojin-machi, Toyama, 930-0809, Japan) (Astellas US Technologies, Inc. 1 Astellas Way, Northbrook, IL 60062) as part of a dual-drug or triple-drug regimen with prednisone and mycophenolate mofetil (Cellcept, Rakshit Pharmaceuticals Ltd, India). The aim of this combination is to decrease the dose and toxicity of each drug and for synergistic effect. Initially, Prograf blood levels should be between 10 and 15 ng/ml with reduction of the dose to obtain a blood level between 8 and 10 ng/ml in the first year after LT to prevent neurotoxicity. The usual immunosuppression protocol was modified in the event of toxicity from Prograf, or whenever recurrence was detected. In this case, a shift to another CNI such as cyclosporine (neural) or to mammalian target of rapamycin inhibitors such as sirolimus was made.

The following postoperative endpoints were reported:

(1) Pathological data of the explanted livers, including grade of tumor differentiation, capsule integrity, microvascular invasion, and the presence or absence of satellites.
(2) Recurrence of HCC: for early detection of cancer recurrence, AFP was checked monthly during the first year and then bimonthly thereafter. Abdomen CT, chest CT, and bone scintigraphy were routinely performed every 6 months during the first 2 years, and then annually. When tumor recurrence was suspected, MRI and/or PET-CT was performed.
(3) Patient mortality (timing and cause of death) was recorded. Postoperative mortality was recorded at three separate periods: intrahospital mortality or mortality within the first month after transplantation constituted data for the first period; early mortality seen within 2–6 months after transplantation constituted data for the second period; and late mortality occurring after the first 6 months from transplantation constituted data for the third period.

Statistical analysis

Numeric data were presented as mean, SD, or as median and range. Continuous variables (mean, SD, median, and range) were analyzed using an independent *t*-test or the χ^2-test or 2×2 Fisher's exact test. Multiple regression analyses were performed using Cox proportional hazards models for identification of factors independently associated with recurrence in 95% confidence interval. Univariate and multivariate analyses were performed to identify the independent risk factors impacting mortality after LDLT for HCC. Statistical analysis was performed using the statistical package for the social sciences (SPSS) software (version 21; SPSS Inc., Chicago, Illinois, USA). Statistical significance was accepted at *P* values less than 0.05.

Results

Patient and tumor characteristics

The mean age of all patients was 48±6.1 years (range: 36–60 years); 50 (94.3%) patients were male. The main cause of underlying liver disease was hepatitis C virus infection (98.1%), and only one patient had hepatitis B virus infection. Thirty-seven (69.8%) patients had one or more chronic comorbid illnesses, mostly DM. Almost half of the study group (25 patients) were of Child–Pugh class B, followed by 20 patients in Child class C and a minority (eight patients) in class A. The mean MELD score was 14.2±4.2. The mean AFP level was 323.9±947.9 ng/ml; 28 (52.8%) patients had a level below 20 ng/ml.

On the basis of imaging findings (CT, MRI, and PET-CT), the mean number of HCC focal lesions was reported to be 1.8±0.75 (range: 1–4); 17 (32.1%) patients had a single focal lesion. The mean diameter of HCC lesions was 4.42±2.43 cm (range: 0.8–11.5 cm). Of the 53 patients, 45 (84.9%) met the Milan criteria and eight (15.09%) met the UCSF criteria. Preoperative treatments were carried out in 19 (35.8%) patients. Patient characteristics are detailed in Tables 1 and 2. The operative and pathological criteria are presented in Tables 3 and 4.

Mortality

The mean length of hospital stay was 22.5±14.5 days, with a range of 0–80 days. The mean follow-up period was 21±21.4 months, with a range of 0–72 months. During the follow-up period, 22 (41.5%) patients died. Ten (18.9%) patients died very early during their hospital stay. Of them, four (7.5%) patients died because of hepatic causes: one patient experienced graft failure after hepatic artery thrombosis (HAT); the second patient had graft failure following portal vein thrombosis (PVT); the third patient had a small-for-size graft; and the fourth patient had early graft dysfunction. Two (3.8%) patients died from sepsis,

Table 1 shows the demographic and characteristic of recipients

Category	Frequency	Percentage
Recipient age		
• Mean ± SD	48.8 ± 6.1	
• Range	36–60	
Recipient gender		
• Male	50	94.3%
• Female	3	5.7%
Diabetes Mellitus		
- Negative	30	56.6%
- Positive	23	43.4%
Hypertension		
- Negative	48	90.6%
- Positive	5	6.4%
Cardiac disease		
- Negative	40	75.5%
- Positive	13	24.5%
Renal disease		
- Negative	49	92.5%
- Positive	4	7.5%
Performance status		
• 0	39	73.6%
• 1	10	18.9%
• 2	4	7.5%
Hepatitis Virus infection		
• HBV	15	1.9%
• HCV	2	98.1%
Cytomegalo virus infection (CMV IgG)		
• Negative	15	28.3%
• Positive	38	71.7%
Portal hypertension		
- Positive	53	100%
Ascites		
- Negative	10	18.9%
- Positive	43	81.1%
Spontaneous bacterial peritonitis (SBP)		
- Negative	52	98.1%
- Positive	1	1.9%
Oesophageal varices		
- Negative	18	34%
- Positive	35	66%
Encephalopathy		
- Negative	45	84.9%
- Positive	8	15.1%

Table 2 Assessment and staging system of the patients and the disease

Category	Frequency	Percentage
CHILD score		
•A	8	15.1%
•B	25	47.2%
•C	20	37.7%
MELD score		
•Mean ± SD	14.2 ± 4.7	
•Range	7–34	
Okuda staging		
-I	4	7.5%
-II	40	75.5%
-III	9	17%
CLIP scoring system		
•0	2	3.8%
•1	13	24.5%
•2 (Early)	15	28.3%
•3	18	34%
•4–6 (Advanced)	5	9.4%
BCLC staging system		
•A 2	1	1.9%
•A 4	11	20.7%
•B	12	22.6%
•C	7	13.2%
•D	22	41.5%
TNM staging system(radiological)		
•T1 No Mo (I)	15	28.3%
•T2 No Mo (II)	19	35.8%
•T3 No Mo (III A)	6	11.3%
•T3 N1 Mo (III B)	11	20.8%
•T4 N1 Mo (IV A)	1	1.9%
•T4 No M1 (IV B)	1	

which resulted from CMV infection in one patient and chest infection in another. Three (5.7%) patients died from multiorgan failure resulting from hypovolemic shock following massive hemorrhage; in one patient intraoperative severe bleeding was the cause, a second patient died from hepatic artery injury during percutaneous insertion of a pigtail catheter for the drainage of postoperative biloma, and the third patient from a spontaneous postoperative intra-abdominal bleeding of undetermined cause. The last case (3.8%) of intrahospital mortality was heart failure.

Six (11.3%) patients died in the early postoperative period (2–6 months): two cases after graft failure, one due to PVT and the second due to HAT; two cases from intra-abdominal abscess (abdominal infection) due to biliary leak; the fifth patient from pulmonary embolism; and the last one from intracerebral bleeding of undetermined cause.

The remaining six (11.3%) patients died in the very late period (>6 months). Tumor recurrence was the cause of death in four (7.5%) patients. Of these patients with tumor recurrence, two had intrahepatic and extrahepatic recurrence and died from intra-abdominal bleeding following resection of these recurrent tumors, and the other two patients had extrahepatic recurrence in the bone and lung. Two (3.8%) other patients died from medical complications: heart failure in one patient and renal impairment in another.

Table 3 shows operative data

Category	Frequency	Percentage
Type of the graft		
•Right lobe	45	84.9%
•Right lobe + MHV	4	7.5%
•Right posterior sector	1	1.9%
•Left lobe + MHV	3	5.7%
Actual graft weight (gm)		
•Mean ± SD	847.7 ± 163.8	
•Range	450–1216	
Actual GRWR		
•Mean ± SD	1.0464 ± 0.16661	
•Range	0.65–1.6	
Calculated graft weight (gm)		
•Mean ± SD	848.9 ± 154.5	
•Range	450–1200	
Calculated GRWR		
•Mean ± SD	1.01 ± 0.16661	
•Range	0.68–1.6	
Cold ischemia time (minute)		
•Mean ± SD	60.5 ± 23.99511	
•Range	20–120	
Warm ischemia time (minute)		
•Mean ± SD	53.00 ± 15.5511	
•Range	30–95	
Operative time (Hours)		
•Mean ± SD	13.713 ± 4.624	
•Range	8–23	
Blood transfusion(Units)		
•Mean ± SD	5.6038 ± 6.2859	
•Range	0–28	
Plasma transfusion(Units)		
•Mean ± SD	8.4200 ± 10.4570	
•Range	0–30	

Table 4 shows post-operative pathology data

Category	Frequency	Percentage
Number of focal lesion		
• Mean ± SD	1.5 ± 0.77	
• Range	1–4	
• Single	28	52.8%
• Multiple	25	47.2%
Site of focal lesion		
• Right lobe	21	39.6%
• Left lobe	10	18.9%
• Bilobar	22	41.5%
Size of largest focal lesions diameter		
•Mean ± SD	2.65 ± 1.21	
Size of total focal lesions diameter		
•Mean ± SD	4.01 ± 2.38	
Pathological ablation of HCC		
Number of preoperative ablative therapy	19	
• Well ablated	4	21%
• Not well ablated	15	79%
Presence of capsule		
• Present	10	18.9%
• Absent	43	81.1%
Focal lesion differentiation		
• Well differentiated	19	35.8%
• Moderate differentiated	34	64.2%
Focal lesion grading		
• Grade I	12	22.6%
• Grade II	23	43.4%
• Grade III	6	11.3%
• Grade I & II	3	5.7%
• Grade II & III	9	17%
Microvascular invasion		
Present	12	22.6%
Absent	41	77.4%
Macrovascular invasion		
Present	2	3.8%
Absent	51	96.2%
Zero biopsy		
Normal	35	66%
Minimal ischemic changes, mild periportal fibrosis	6	11.3%
Mild ischemic changes	9	17%
Moderate ischemic changes	1	1.9%
Mild/moderate perfusion injury	1	1.9%
Focal reperfusion/ preservation injury	1	1.9%

Patient demographics, tumor characteristics, operative events, and pathological findings were compared between the patients who survived and the patients who died in the different post-transplant periods. The results of the univariate analysis are shown in Tables 5–8. According to preoperative data, age, sex, cause of disease, Child–Pugh score (which was sensitive at a score of 6.5 on the receiver operating characteristic curve) (Fig. 1), and MELD scores showed no statistically significant difference. In contrast, there was a statistically significant relation between mortality and cytomegalovirus immunoglobulin (CMV-IgG) negativity and TNM classification (IIIB).

With regard to operative data, there was a significant statistical relation between mortality and actual graft weight, actual graft/recipient weight ratio (GRWR), and blood and plasma transfusion units. Pathologically, there was a significant statistical relation between mortality and the grade of tumor differentiation. By contrast, tumor size, tumor number, Milan and UCSF criteria, presence or absence of tumor capsule, and microvascular or macrovascular invasion showed no statistically significant relation with mortality.

To identify the risk factors related to mortality, a multivariate analysis of the factors that had shown a statistically significant relation in univariate analysis was performed. It was found that CMV-IgG negativity, advanced TNM stage (stage III), actual graft weight, and number of blood transfusion units

Table 5 shows univariate analysis of recipient pre-operative data

	Groups Died (N=22) No/%	Survived (N=31) No/%	p-Value align="center"
Recipient gender			
-Male	19/86.4	31/100	0.06
-Female	3/13.6		
Recipient blood group			
-A	6/27.3	9/29.0	0.6
-B	3/13.6	8/25.8	
-AB	1/4.5	1/3.2	
-O	12/54.6	13/42.0	
Blood groups:			
-Compatible	8/36.4	8/25.8	0.41
-Identical	14/63.6	23/74.2	
Recipient comorbidity:			
-Absent	7/31.8	9/29	0.83
-Present	15/68.2	22/71	
Performance status:			
-0	17/77.3	22/71.0	0.69
-1	3/13.6	7/22.5	
-2	2/9.1	2/6.5	
HCV:			
-Negative	0	1/3.2	1
-Positive	22/100	30/97.8	
CMV IgG:			
-Negative	15/68.2	0	0.0000001
-Positive	7/31.8	31/100	
Child score:			
-Child A	3/13.6	5/16	0.66
-Child B	12/54.6	13/42	
-Child C	7/ 31.8	13/42	
Milan criteria:			
-Within	16/73	19/61.3	0.39
-Beyond	6/27	12/38.7	
UCSF:			
-Within	18/81.8	25/80.6	1
-Beyond	4/18.2	6/19.4	
Okuda:			
-I	2/9.1	2/6.5	0.43
-II	18/81.8	22/71	
-III	2/9.1	7/22.5	
CLIP:			
-0	0	2/6.5	0.5
-1	4/18.2	9/29	
-2 early	6/27	9/29	
-3	10/45.2	8/25.8	
-4 advanced	2/9.1	2/6.5	
-6	0	1/3.2	
BCLC:			
-A4	2/9.1	9/29	0.23
-A2	1/4.5	0	
-B	4/18.2	8/25.8	
-C	4/18.2	3/9.7	
-D	11/50	11/35.5	
TNM:			
-T1 N0 M0 (I)	3/13.6	12/38.7	0.00001
-T2 N0 M0 (II)	2/9.2	17/54.8	

(*Continued*)

Table 5 (*Continued*)

	Groups Died (N=22) No/%	Survived (N=31) No/%	p-Value align="center"
-T3 N0 M0 (III A)	4/18.2	2/6.5	
-T3 N1 M0 (III B)	11/50	0	
-T4 N1 M0 (IV A)	1/4.5	0	
-T4 N0 M1 (IV B)	1/4.5	0	
MELD score			
Mean ± SD	15.2 ± 5.6	13 ± .4	>0.05

Table 6 shows univariate analysis of recipient operative data, pathology, hospital stay and survival

	Groups	Mean	Std. Deviation	p-value
AFP (ng/dl)	Died	380.669	921.729	>0.05
	Alive	260.524	991.450	
Actual_graft_weight	Died	802.8	180.3	<0.05
	Alive	898	129.1	
Actual_GRWR	Died	0.99	0.18	<0.05
	Alive	1.10	0.13	
Cold_ischemia_time/ minutes	Died	63.9	24.1	>0.05
	Alive	56.1	23.6	
Warm_ischemia_time/ minutes	Died	51.3	13.5	>0.05
	Alive	55.2	17.8	
Operative_time/h	Died	15.2	2.5	>0.05
	Alive	12.1	5.8	
Blood_transfusion_unit	Died	8.0	7.5	<0.01
	Alive	2.8	2.9	
Plasma_transfusion_unit	Died	11.8	12.5	<0.05
	Alive	4.1	4.3	
Pathology No of focal lesions	Died	1.6	0.9	>0.05
	Alive	1.4	0.6	
Pathology of focal lesion largest diameter	Died	2.7	1.3	>0.05
	Alive	2.6	1.0	
Pathology of focal lesions total diameter	Died	4.2	2.7	>0.05
	Alive	3.8	2.1	
Hospital stay (days)	Died	22.5	16.4	>0.05
	Alive	22.4	12.3	
Survival/days after LT	Died	265.6	528.6	>0.05
	Alive	32.5	18.4	

were independent predictors and had a significant influence on mortality (Table 9).

Discussion

HCC is a disease with peculiar characteristics because it commonly appears along with liver cirrhosis and is heterogenous; therefore, a wide range of therapeutic options are available. Some of these modalities are curative, such as resection, transplantation, and radiofrequency ablation (RFA), and other modalities are palliative, such as transarterial chemoembolization (TACE). LT is particularly important as it cures both the cirrhotic liver as well as the HCC lesions. In countries in which there is no deceased organ donation or a shortage of deceased organs, LDLT can be the mainstay of therapy [12].

However, there is concern that LDLT has disadvantages in terms of endangering a healthy donor's life and probability for HCC recurrence, compared with DDLT. Therefore, precise selection criteria for LDLT are likely applied more widely than DDLT criteria [13–15]. Yet, LDLT candidates have no opportunity to be screened for aggressive tumor biology [16]. Furthermore, graft volume has an important impact on LDLT outcome in general because of being relatively small-sized grafts that are subject to an additional mechanical injury at the start of reperfusion, as well as a rapid rate of graft regeneration accelerating tumor growth [17–19]. Therefore, the risk factors impacting the outcome, particularly mortality, need to be more precisely identified to minimize risk to the donor and maximize the recipient's benefits.

In the present study, the risk factors impacting mortality after LDLT in 53 patients with HCC were retrospectively analyzed and statistically identified. Out of these transplanted patients, 22 (41.5%) died at three different post-transplantation times because of various causes. The majority (18.9%; 10 cases) of deaths were reported in the very early perioperative period, whereas equal mortality rates were detected in both the early (6 months) and late (beyond 6 months) periods after LT. With regard to the cause of death, the most frequent causes were hepatic in nature, accounting for 45.5% of cases, whereas tumor recurrence was responsible for 7.5% and occurred in the very late post-transplant period.

This trimodal pattern of post-transplantation mortality distribution has been described in two previous studies.

Table 7 shows univariate analysis of recipient type of graft and pathological criteria

	groups Died (N = 22) No /%	Survived (N = 31) No /%	
Type of graft:			
-Right lobe	19/86.5	26/83.9	0.58
-Right lobe and MHV	1/4.5	3/9.6	
-Right posterior sector	1/4.5	0	
-Left lobe and MHV	1/4.5	2/6.5	
Pathology FLs capsulation:			
-Absent	18/81.8	25/80.6	1
-Present	4/18.2	6/19.4	
Pathology FLs differentiation:			
-Well	3/13.6	16/58.1	0.004
-Moderate	19/86.4	15/41.9	
PathologyFL grade:			
-Grade I	3/13.6	9/29	0.01
-Grade II	8/36.5	15/48.4	
-Grade III	6/22.7	0	
-Grade I and II	0	3/9.7	
-Grade II and III	5/22.7	4/12.9	
Micro vascular invasion:			
-No	16/72.7	25/80.6	0.52
-Yes	6/27.3	6/19.4	
Macro vascular invasion:			
-No	20/90.9	31/100	0.17
-Yes	2/9.1	0	
Zero biopsy:			
-Normal	13/59.2	22/64.0	0.24
-Minimal ischemic changes, mild periportal fibrosis	1/4.5	5/20.0	
-Mild ischemic changes	5/22.8	4/16.0	
-Moderate ischemic changes	1/4.5	0	
-Mild or moderate perfusion injury	1/4.5	0	
-Focal reperfusion preservation injury	1/4.5	0	

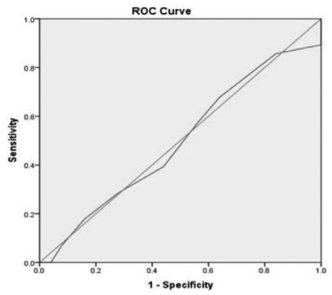
In the first early study, by Lama *et al.* [20], in which the mortality rate was 29%, two patients died intraoperatively, 13 (10%) died in the early period, and 77 (61%) died in the late period, 6 months after LT. In that study, the most common causes of perioperative death were complications related to the operation (medical or surgical) and cellular rejection. During the early mortality period, ductopenic rejection was the main cause of mortality, whereas late mortality cases were due to recurrence of viral infection and or tumor regrowth [20]. In the second relatively recent study, by Watt *et al.* [21], the probability of death exhibited a trimodal pattern, with the greatest risk (11%) during the first 6 months after transplant, decreasing to 2.5–5% between 6 months and 8 years after LT. In the latter study, a total of 327 patients died over 12.6 years of follow-up (median: 10 years). Of them, 78 (23.9%) died of hepatic causes, 207 (63.3%) of nonhepatic causes, and 42 (12.8%) of unknown cause [21].

On statistical analysis and comparison of demographic and preoperative patient characteristics, we reported that age, sex, cirrhosis etiology, Child–Pugh scores, and MELD scores were statistically nonsignificant as risk factors for mortality. In contrast, CMV-IgG seronegativity was proven to be a significant risk factor and independent predictor of mortality in patients undergoing transplantation in both univariate and multivariate analysis. In a review study by Razonable [22], the author reported that CMV is an independent predictor of mortality after LT, either directly by CMV syndrome or indirectly by increasing the predisposition to acute and chronic allograft rejection, accelerating hepatitis C recurrence, and by reducing overall patient and allograft survival. The most common predisposing factors to CMV infection are lack of effective immunity (seronegative recipients) and use of immunosuppressive agents (especially high-dose steroids and cyclosporine). However, CMV infection can be overcome by the use of antiviral prophylaxis (preemptive therapy) in high-risk patients – namely, seronegative recipients

Table 8 shows univariate analysis of recipient various causes of death

	Groups Died (N= 22) No/%	Survived (N= 31) No /%	P-value align="center" align="center"
Acute rejection:			
-No	18/81.8	22/7	0.37
-Yes	4/18.2	19/29	
Recurrent disease:			
-No	18/77.3	31/100	0.02
-Yes	4/22.7	0	
Graft cause:			
-No	16/72.7	31/100	0.0003
-Yes	6/27.3	0	
Renal cause:			
-No	18/81.8	31/100	0.02
-Yes	4/18.2	0	
Cardiac cause:			
-No	19/86.4	31/100	0.06
-Yes	3/13.6	0	
Pulmonary cause:			
-No	21/95.5	31/100	0.42
-Yes	1/4.5	0	
Sepsis cause:			
-No	18/81.8	31/100	0.02
-Yes	4/18.2	0	

Figure 1



Child score cut level	Sensitivity	Specificity	AUC	p- value	95% Confidence Interval	
					Lower Bound	Upper Bound
6.5	85.7	16.0	0.495	0.950	0.338	0.652

Shows ROC curve for Child score.

Table 9 shows Multivariate analysis of dependent predictors of mortality

Studied variables	B constant = 0.28 R = 0.54 B	p-value
CMV IgG	5.833	<0.05
TNM	7.686	<0.01
Actual graft weight	5.120	<0.05
Actual GRWR	3.208	>0.05
Blood transfusion unit	5.135	<0.05
Plasma transfusion unit	3.213	>0.05
Pathology FLs differentiation	0.933	>0.05
Pathology FLs grade	0.734	>0.05
Hepatic cause	2.864	>0.05
Sepsis cause	1.750	>0.05

– and when high-dose immunosuppression is needed [22].

The Child–Pugh score, which was primarily used to predict intraoperative mortality during LT, was statistically nonsignificant in the present analysis in relation to post-transplant mortality. By receiver operating characteristic curve analysis, the Child score was only sensitive (85.7%) at a cut-off point of 6.5. (85% is the sensitivity of the screening test not the patient percent). This means that high Child scores might have an effect on post-transplantation mortality, although the relation is statistically nonsignificant. Similarly, Jo *et al.* [23] reported that the accuracy rates of pretransplant Child–Pugh classification in predicting postoperative mortality were low.

In the same context, MELD score was a nonsignificant risk factor for post-transplant mortality in patients with HCC in the present study. This finding was confirmed in two other previous studies: Hayashi *et al.* [24] reported that preoperative MELD score had no predictive value in 1-year post-transplant outcome and Wai *et al.* [25] reported that a high MELD score had no impact on post-transplant survival among cirrhotic patients undergoing LDLT.

Conversely, several other studies reported that a preoperative high MELD score was a significant risk factor for mortality after LT [26–29].

AFP level was considered a surrogate indicator of tumor biology by many authors and therefore has been implicated in some staging systems of tumor assessment. Duvoux *et al.* [30] reported that pretransplant serum AFP correlated with vascular invasion and tumor differentiation and was independently predictive of tumor recurrence and poorer outcome after LT. In contrast, this marker was not found to be a predictor of post-transplant mortality in our study. Some authors have reported that an AFP level before LT of more than 200 or more than 1000 ng/ml affected tumor recurrence. In the study by Zhou *et al.* [31], a stratification correlation of AFP and post-LT outcome was described. The authors concluded that a prognostic value for AFP was detected at higher levels (≥400 ng/ml). At this level, patients tend to have a large tumor, bilobar involvement, PVT, and a lower survival rate [31]. However, the negative correlation of AFP level with the mortality rate in our study might be explained by the fact that an AFP level less than 1000 ng/ml was a crucial criterion in the selection of patients for LDLT in our series.

Concerning the tumor staging systems and treatment guidelines, it was found that systems such as the Okuda, cancer of the liver Italian program (CLIP), and Barcelona clinic liver cancer staging (BCLC) were not statistically significant as predictors of post-LT mortality, whereas advanced TNM stage III was found to be independently correlated with post-LT mortality. Similar to the present study results, Vauthey *et al.* [32] reported that TNM staging was a good predictor of mortality in patients undergoing LT for HCC. On the other hand, Nanashima *et al.* [33] and Zhang *et al.* [34] reported that the CLIP score was a better staging system in predicting overall survival compared with BCLC and TNM. However, on reviewing the HCC staging systems, we found that there is no ideal system that accurately predicts the outcome of treatment. Nevertheless, the BCLC system is considered to represent a good treatment algorithm and has a high prognostic value compared with other staging systems [35,36]. This controversy arose from the fact that staging systems are based on radiological findings that they were found not to have a good correlationwith the pathological tumor criteria [37].

In most transplant centers, the Milan and UCSF criteria constitute the backbone for selection of HCC patients for LDLT. Both the Milan and UCSF criteria adequately reflect recurrence. In 2012, the European Association for the Study of the Liver published clinical practice guidelines stating that the Milan selection criteria constitute an independent set of prognostic factors after LT for HCC patients. Accordingly, the perioperative, 1-year, and 5-year mortality rates are expected to be 3%, less than or equal to 10%, and less than or equal to 30%, respectively, which in turn were similar to those for LT in benign non-HCC patients [38]. Nonetheless, in the current study, these two criteria had no direct impact on patient mortality. This might be collectively attributed to our restricted indications based on Milan criteria and low serum AFP level and low MELD score.

However, there is considerable debate surrounding the criteria for selection of HCC patients for LT, between the restrictive ones based on the Milan criteria (1996) and the extension criteria based on UCSF (2001). Yet, Duffy *et al.* [39] and Chen *et al.* [40] reported that patients falling under the Milan and UCSF criteria had the same survival curves on pretransplant imaging and pathologic staging, but patients with values exceeding those laid down in the UCSF criteria had significantly worse survival rates. In contrast, in a recent analysis by Mazzaferro *et al.* [41], the authors reported that patients with tumor stage beyond that specified in the Milan criteria had a higher risk for recurrence and a low survival rate compared with patients falling within the Milan criteria. On the other hand, Zhang *et al.* [34] reported that both Milan and UCSF criteria were limited for predicting post-LT outcomes, a result similar to ours in the present analysis. Therefore, many centers have center-based criteria for selection of patients who do not fall within the Milan criteria.

Downstaging and bridging procedures are frequently used to decrease tumor burden and bridge time until donor assessment and preparation. At the same time, response to pretransplant procedures is considered by many authors as an indicator of tumor biology [42]. In our study, 19 (35.8%) patients had undergone bridging treatment, which showed no direct effect on post-transplant mortality. According to Maluf *et al.* [43], bridging therapy was safe and effective in reducing HCC progression in patients on the waiting list for LT. However, the authors reported that patients who had undergone a bridging procedure had the same tumor-free survival (30±12 months) as patients who had not undergone bridging treatment [43]. Conversely, Bartlett and Heaton [42] reported that

preoperative RFA reduced the dropout rate from the waiting list, with no evidence for tumor recurrence after transplant. In contrast, the effect of preoperative TACE on long-term survival, on the expansion of selection criteria, or on the reduction of dropout rates on the waiting list was controversial [42]. The current practice guidelines from the European Association for the Study of the Liver, published in 2012, state that bridging therapy, using RFA or TACE as a second option, is safe and effective in patients who are candidates for LT, if the waiting time exceeds 6 months [38].

In the present analysis, the graft type had no impact on postoperative mortality but there was significant statistical relation between mortality in HCC patients and actual graft weight and actual GRWR. Actual graft weight was also an independent predictor of mortality. Similarly, Soejima *et al.* [44] reported that the outcome from LDLT after left lobe graft was the same as that after right lobe graft; hence, graft type had no impact on post-transplant mortality. Although the small-for-size graft syndrome has been reported more frequently in left lobe grafts, it did not necessarily lead to graft loss [44]. Also, in the study by Chen *et al.* [45], LDLT of small grafts (low actual graft weight and actual GRWR) was not a significant risk factor impacting graft and patient survival. In fact, many reports confirmed that small-for-size grafts (<1% of recipient body weight) are associated with lower graft survival, probably through enhanced parenchymal cell injury and reduced metabolic and synthetic capacity [46]. Consequently, Alves *et al.* [26] and Xu *et al.* [47] concluded that GRWR less than 0.8 are associated with higher probability for graft failure after LDLT. Recently, Cauley *et al.* [29] reported that HCC patients receiving a living donor or deceased donor partial graft had an increased risk for mortality compared with deceased donor whole-graft recipients.

With regard to intraoperative events and their impact on mortality, the total operative time and both warm and cold ischemia times were not correlated to postoperative mortality in our study. Conversely, Totsuka *et al.* [48] reported that both warm and cold ischemia times were independent risk factors affecting graft outcome and patient survival in the early postoperative period after LT. On the other hand, intraoperative blood and plasma transfusion units were shown to have a significant correlation with mortality in our series. Moreover, transfused blood units were one of the independent predictors of postoperative mortality. To date, various groups have reported that the volume of intraoperative blood loss and blood transfusion are predictors of postoperative mortality [49–52].

Tumor characteristics have been demonstrated to have a significant prognostic impact on post-transplantation tumor recurrence and hence on patient survival. In our study, the grade of tumor differentiation had a significant correlation with mortality. Yet, there was no definite correlation between vascular invasion and outcome. Similar results confirmed our findings concerning the positive correlation between tumor differentiation and post-transplant mortality [53–55]. In addition, other tumor criteria have been shown to impact the postoperative outcome, such as vascular invasion, nodal involvement, tumor size more than 5 cm, bilobar HCC, and multifocality [3,56]. In fact, de Carlis *et al.* [57] reported that vascular invasion and tumor grade are seemingly more important than the number and size of lesions. Unfortunately, vascular invasion cannot be reliably diagnosed before transplantation in most cases, even with preoperative tumor biopsy [58].

Postoperative complications – namely, graft failure, sepsis, and renal complications – were shown to be predictors of postoperative mortality in the present study. However, postoperative cardiac and pulmonary complications did not show significant correlation with mortality. Watt *et al.* [21] reported that the most common cause of post-transplant death was liver-related etiology, which accounted for one-third of mortalities. Among these hepatic-related factors, HAT and PVT were the most common vascular complications after LT, which were strictly associated with high morbidity and mortality during the immediate postoperative period, reaching 53 and 33%, respectively [47,59]. In the same context, post-transplant septicemia is a well-known risk factor for multiorgan failure and thus an important cause of death in the early post-transplantation period, being responsible for approximately 44.4% of post-LT deaths [21,47].

Tumor recurrence, in our report, was shown to be a dependent predictor of mortality. Xu *et al.* [47] reported that recurrent HCC was the second most common cause of mortality and was seen in 22% of mortality cases in their series. Therefore, factors affecting tumor recurrence – radiological factors like tumor size and number, or biological factors like serum AFP level – become a hot topic of research. The disadvantage of LDLT in terms of increased tumor recurrence compared with DDLT can be attributed to many factors, including a shorter waiting time, which

does not allow a tumor to exhibit its aggressiveness, and the surgical process for LDLT [19,60,61]. Conversely, other authors claim that LDLT is a compulsory treatment strategy for HCC before tumor progression, as at least 20–30% of candidates in a long waiting list drop out before receiving LT because of tumor progression [62,63].Acute renal injury (ARI) is a serious complication after LT. Several studies have demonstrated an association between ARI and increased mortality after DDLT [64–66], revealing an eight-fold increase in mortality risk [67]. Although ARI-associated mortality after Orthotopic liver transplantation (OLT) has been reported to be as high as 45.1–67%, patients with ARI can have a good prognosis with a recovery rate of 97% [68,69]. Previous studies have demonstrated that preoperative renal injury [66,70–72], recipient age, male sex, hepatitis C virus, preoperative hypertension, diabetes [73], red blood cell transfusion [74], use of vasopressors, overexposure to CNIs [75–77], and hypoalbuminemia [78] are risk factors for postoperative ARI, which can be a cause of post-transplant mortality.

By using the RIFLE criteria (Risk, Injury, Failure, Loss, and End-stage Kidney), Utsumi *et al.* [79] have reported a 60% incidence for ARI. However, depending on the definition used for ARI, the occurrence of post-LT ARI has been reported by Bilbao *et al.* [70] and Velidedeoglu *et al.* [80] as 51.5% with serum creatinine more than 1.5 mg/dl and as 39.2% with serum creatinine more than 2 mg/dl. In their multivariate analysis of risk factors for ARI, preoperative DM, MELD more than or equal to 20, small-for-size graft (GRWR$<$0.7%), blood loss/body weight more than 55 ml/kg, and overexposure to CNI were found to be associated with severe ARI [71,80]. However, ARI after adult LDLT may occur because of persistent portal hypertension and a hyperdynamic state in patients with a small-for-size graft [71]. Recent treatment strategies for Small for size syndrome (SFSS), such as portosystemic shunt, splenectomy, and splenic artery ligation or embolization, could improve prognosis [81–87]. Other authors [76,88] suggested that ARI-associated risk factors could be mitigated through intentional care management, by strict therapeutic drug monitoring for CNI, and by accepting only donor livers with sufficient graft volume (i.e. Graft weight/recipient body weight (GW/RBW) $>$0.7% in high-risk recipients with MELD more than 20 and/or DM). The immunosuppressive regimen should be modified with mycophenolate mofetil or with any other agent for lowering the CNI dose [77,88].

Conclusion

LDLT is a safe and optimal treatment strategy for HCC, particularly after strict selection criteria and improved procedures. Nevertheless, risk factors impacting post-transplant mortality need to be better identified. In the present study, several factors have significant independent effects on mortality. CMV-IgG negativity, advanced tumor stage (IIIB), actual graft weight, volume of intraoperative blood transfusion, poor tumor grade of differentiation, and tumor recurrence have an influence on post-transplantation mortality. Because LDLT can be performed regardless of Child–Pugh score, MELD score, or portal hypertension, only tumor factors, graft volume, and technical complications should be considered as criteria for selecting HCC patients for LDLT.

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Conflicts of interest

There are no conflicts of interest.

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