

Predictors of Recurrence of Hepatocellular Carcinoma after Living Donor Liver Transplantation

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related deaths worldwide. Liver transplantation has become the standard therapy for patient with early-stage HCC, as it addresses both the tumor and the underlying liver disease.

Aim: To investigate the risk factors of recurrence after living donor liver transplantation (LDLT) for HCC.

Methods: This retrospective study included 302 patients who underwent LDLT during the period between 2004 and 2021 for provisional diagnosis of HCC. Preoperative data included patient age, gender, BMI, comorbidities, previous surgeries, laboratory investigations and imaging. Operative data included approach, morphology of the tumor, tumor location, size, number, warm ischemia time, cold ischemia time, operation time, and intraoperative complications. Postoperative data included laboratory investigations, ICU stay, complications, survival, and the incidence of HCC recurrence.

Results: Postoperative complications occurred in 105 patients (34.7%). The commonest cause was due to respiratory complications (n=38, 12.5%) followed by vascular complications (n=23, 7.3%). Regarding predictors of early mortality, only patients with Child C score had a statistically significant correlation (p=0.026). Morbidity remains highly significant in both univariate and multivariate analysis and is a good predictor for early mortality (p≤0.001). Only 39 patients (15.5%) had recurrence. Pathological microvascular invasion was noted in 18 cases of the recurrence group and was statistically significant predictor for recurrence (p=0.001).

Conclusion: Microvascular invasion is a strong independent predictor of tumor recurrence after LDLT for HCC. Child-Pugh class C is a significant risk factor for early mortality. Also the rates of free survival from disease and rates of survival after recurrence among cases was higher after 1 year followed by 5 and 10 years.

Keyword: hepatocellular carcinoma, recurrence, early mortality, microvascular invasion, living donor liver transplantation

INTRODUCTION

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related deaths worldwide. The main etiological factor in Egypt is HCV infection (1). HCC ranks as the sixth and fourth common cancer in worldwide and Egypt, respectively (2). Its prevalence has been on the rise over the last 30 years, has been predicted to

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continue increasing. HCC is the most common cause of cancer-related morbidity and mortality in Egypt and is also the most common cancer in males (3).

Liver resection (LR) and liver transplantation (LT) are the main stay of curative treatment for HCC patients. For patients without cirrhosis, partial LR is the main surgical treatment for HCC. In patients with severely cirrhotic livers (Child-Pugh class B or C), transplantation is the optimal therapy for HCC as it simultaneously addresses the neoplasm and the underlying liver dysfunction (4).

Liver transplantation is now the standard therapy for patient with early-stage HCC (5). The Milan criteria set the standards for tumors that would benefit from LT. There is concern that the Milan criteria are too stringent and that minimal expansion in criteria has also been shown to be associated with good survival (6). Microvascular invasion (MVI) is the most important adverse prognostic factor for survival. Living donor liver transplantation (LDLT) has expanded donor options and has the advantage of lower waiting periods. Downstaging of tumors to prevent progression while waiting for an organ or for reduction in size to allow enrolment for transplantation has had variable success (7).

In Egypt, deceased donor liver transplant (DDLT) program is still awaited due to several legal limitations, making LDLT the only hope for patients with end stage liver disease (ESLD) with or without HCC. LDLT program was started in 2004 for the management of patients from a highly populated Delta region in the north side of Egypt (8). The main concern after liver transplantation is the risk of tumor recurrence and its impact on survival, it is estimated that the rate of recurrence occurred in 8-20 % (11) and usually occurred in the first 2 years (7 – 18 month) & 5 years survival reported to be 63 – 80 %. So, every effort must be made to decrease recurrence rate and improve the survival (5).

Aim of Work

The current study was designed to investigate the risk factors of recurrence after living donor liver transplantation for HCC.

PATIENTS AND METHODS

This retrospective study was held at Liver transplant unit, Gastrointestinal Surgical Center (GISC), Mansoura University, Egypt. The study included 302 patients who underwent LDLT in our center during the period between 2004 and 2021 for provisional diagnosis of

HCC. The data of these cases were retrieved from the online hospital management system (Ibn Sina Hospital management system) supported with paper documents from the medical archive. Data were collected in the period from May 2022 till May 2024. We excluded patients who were provisionally diagnosed with HCC and pathological examination of the explant showed absence of the tumor and patients with HCC who were not candidates for liver transplantation and underwent other lines of treatment.

Ethical Consideration

The study was approved by the local scientific committee and Institutional Review Board (IRB) of the faculty of medicine, Mansoura University (MD.22.02.605.R1). Patient confidentiality was preserved, and the collected data were used only for scientific purposes. All donors and recipients signed an informed written consent before performing the procedure after explaining the indications, and possible risks of the surgical procedure and after approvals from the Supreme Committee of Organ Transplantation, Ministry of Health, Egypt.

Living Donor Liver Transplantation Protocol for HCC

Preoperative evaluation of potential recipients included 4 phases. Phase I included Blood group typing, basic laboratory evaluation including tumor markers and virological evaluation, radiological evaluation including triphasic abdominal CT, portography, MRCP and anesthetic consultation. Phase II included detailed neuropsychiatric evaluation, autoimmune markers for suspected autoimmune hepatitis, MRCP and PET in cases of suspected metastasis. Phase III included endoscopic evaluation including upper and lower GIT endoscopy. Phase IV included routine consultations to excluded possible septic foci, and gynecological consultation for females in childbearing period. All the transplants were made using the right hemiliver graft.

The Recipient Procedure

Abdominal exploration was done via inverted-L shaped incision. After abdominal exploration, liver mobilization was done via dividing coronary, left, and right triangular ligaments. This was followed by division and suturing of the hepatocaval ligament. Retrohepatic veins emerging from the posterior liver surface and the IVC were sutured and ligated. Hilar

dissection was started till identification of portal vein branches, right and left hepatic arteries, and bile duct branches. This was followed by portal vein reconstruction, which was done between the graft right portal vein and the main portal vein of the recipient via continuous prolene 6/0 sutures. A growth factor was done for the posterior and anterior walls of the portal anastomosis to decrease the risk of anastomotic stenosis. The right hepatic vein of the graft was anastomosed to the right hepatic vein of the recipient while the distal end of the synthetic grafts from MHV tributaries were anastomosed to the IVC, LHV or MHV stump if present. Hepatic arterial reconstruction was then performed using interrupted 8/0 prolene sutures under surgical loupe magnification using posterior wall first technique with intra-operative doppler US done to check patency of the anastomoses. This was followed by bile duct reconstruction which was done via interrupted PDS 6/0 sutures. An occlusive cholangiogram was done to ensure patent biliary anastomosis with no leakage, stenosis or missed ducts. Three drains were inserted, one at the cut surface, one at the Morrison pouch, and one in the pelvis. That was followed by abdominal wound closure over subcutaneous drain.

Postoperative Management

Regarding immunosuppression, apart from the intra-venous (IV) bolus methylprednisolone given after perfusion, a steroid-free protocol was used in all cases. Regarding histopathological examination, the excised liver was sent to the GISC histopathology laboratory. All pathological examinations were done by two expert pathologists in liver pathology.

Postoperative Care

The recipients were transferred to LT intensive care unit (ICU) after the operation for close clinical, laboratory and radiological monitoring. Doppler ultrasound evaluation was performed routinely once daily during the first postoperative week, day after other during the second and third weeks and before hospital discharge. After discharge, doppler ultrasound was performed once weekly during the following 2 months. Any early postoperative complications were recorded (including bleeding, small for size syndrome, bile leakage, vascular thrombosis, etc.).

Follow-Up

Regular follow-up visits were arranged for all patients after the procedure. All patients were monitored clinically and by laboratory work-up including CBC, Liver functions, kidney functions, alpha fetoprotein level and evaluation for immunosuppressive medication. In case of recurrence, the recurrence was recorded, with time and the site of recurrence with further workup and management was planned after MDT meeting. Recurrent cases were managed with locoregional therapy if the recurrence was limited to the liver while systemic therapy and conservative therapy was conducted for cases with combined intra and extra hepatic recurrence.

Data Collection

Preoperative data included patient age, gender, BMI, smoking, comorbidities (diabetes mellitus or viral hepatitis), duration of symptoms, time on waiting list, previous surgeries or locoregional therapy, preoperative workup data including laboratory investigations including tumor marker and imaging investigations. Operative data included approach, morphology of the tumor, tumor location, size, number, presence of lymph nodes, warm ischemia time, cold ischemia time, operation time, blood loss, blood transfusion, venous reconstruction, arterial reconstruction, biliary reconstruction, and intraoperative complications. Postoperative data included post-operative laboratory investigations, post-operative complications, hospital stay, period of follow up, survival, and the incidence of HCC recurrence.

Statistical Analysis

Categorical data were expressed as numbers and percentages, whereas numerical data were expressed as mean and standard deviation or median and range when appropriate. Chi-square or Fischer Exact tests were used to compare categorical data, while Student t test or Mann-Whitney test were used for the continuous data. Survival analysis was conducted by Kaplan-Meier survival method and group comparison was done by Log-Rank method. Significant factors in univariate analysis were further targeted to multivariate analysis to determine potential predictive factors for OS and DFS. Predictive factors for recurrence were analyzed by binary logistic regression analysis. For all data types, a p value less than 0.05 was considered significant.

RESULTS

During the study period, a total of 302 patients with provisional diagnosis of HCC who underwent living donor liver transplantation were included. Of those, 41 patients with early mortality were excluded from the analysis of recurrence. Ten patients were provisionally diagnosed with HCC were found to be negative after pathological examination of the explant, none of those patients received bridging therapy, those patients were excluded from further analysis of recurrence. Among the included cases 2 patients were subjected for liver transplantation due to liver cell failure and were accidentally discovered to have HCC on pathological examination of the explant.

Table 1 shows that the median age of whole population was 53(32-67) years with male predominance (n=272, 90.1%) and 30 women (9.9%). Mean MELD score was 13.52±4.77. AFP median level was 12 (1-1283) ng/ml. The commonest presentation was jaundice (n=169, 56%), followed by lower limb edema (n=140, 46.4%), ascites (n=133, 44%), upper GIT bleeding (n=73, 24.2%), and hepatic encephalopathy (n=46, 15.2%). Among the study population, 131 patients (43.4%) underwent preoperative ablation, among which 73 patients (55.7%) underwent TACE as a bridging therapy, 17 (13%) underwent RFA, 11 (8.4%) underwent MWA and 30 patients (22.9%) underwent combined TACE and ablation. The median waiting time was 120 days. Regarding antiviral treatment, 88 patients (29.1%) received antiviral therapy.

Table 2 shows operative and postoperative data among the study population. Only 9 cases (3%) had portal vein thrombosis which may reflect proper pre-operative selection and underwent eversion of the thrombus. The mean time of the anhepatic phase was 53.6±20.53, cold ischemia mean time was 34.01±20.05 and warm ischemia mean time of 42.71±18.03. The mean operative time was 633.33±107.56. The mean graft-to-recipient weight ratio (GRWR) was 1.094±0.22. The mean time of hospital stay among the study cases was 30.88±17.88 and ICU stay was 7.43±6.56. Of the study population, 24 patients (7.9%) underwent re-operation, 8 of them due to pack removal and 16 due to internal hemorrhage. Postoperative morbidity occurred in 105 patients (34.7%). The commonest cause was due to respiratory complications followed by vascular.

Regarding predictors of early mortality among studied cases, table 3 shows that only patients with Child C score had a statistically significant correlation, P value 0.026. Table 4 shows logistic regression model

Table 1 - Patient demographics, baseline characteristics and pre-transplant treatment

	n = 302	%
Age (years)		
mean ±SD	52.09±6.46	
median (min-max)	53(32-67)	
Gender	n = 302	
male	272	90.1
female	30	9.9
Child-Pugh Score	n = 302	
A	121	40.1
B	133	44.0
C	48	15.9
MELD Score		
mean ±SD	13.52±4.77	
median (min-max)	13(6-13)	
AFP Level (ng/mL)		
median (min-max)	12(1-1283)	
Tumor Size (cm)		
mean ±SD	4.41±2.95	
median (min-max)	4(0.5-16)	
Case presentation	n = 302	
encephalopathy	46	15.2
jaundice	169	56.0
ascites	133	44.0
hematemesis & melena	73	24.2
edema lower limb	140	46.4
Preoperative ablation	n = 131	
TACE	73	55.7
RFA	17	13.0
MWA	11	8.4
Combined	30	22.9
Waiting time (day)		
median (min-max)	120 (30-1400)	
Anti-viral treatment	n = 88	
Interferon	20	22.7
DAAS	53	60.2
Mixed	15	17.0

TACE = trans arterial chemoembolization, MWA = microwave ablation, RFA = radiofrequency ablation, DAAS = direct acting anti hepatitis C virus drugs

to test the impact of child class, anhepatic phase time, warm ischemia time, cold ischemia time, blood loss, total operative time, re operation, acute cellular rejection and ICU stay on early mortality. Morbidity remains highly significant in both univariate and multivariate analysis with P value < 0.001* and is a good predictor for early mortality. Anhepatic phase duration and total operation time show marginal significance (p ~ 0.05).

Table 5 shows that the mean follow up period for the studied cases was 89 (5-217) months. Only 39 patients had recurrence. Among the recurrence group the median time to recurrence was 74.5 months. Of those, 8 patients suffered from intrahepatic recurrence, 8 patients had extrahepatic recurrence while 23 patients had both intrahepatic and extrahepatic recurrence. The commonest pattern of recurrence was multifocal systemic recurrence in 27 patients involving multiple organs, followed by isolated lung recurrence in

Table 2 - Operative, postoperative data and postoperative morbidity among studied cases

	n	%
Operative data		
Patent portal vein	293	97.0
Portal thrombus eversion	9	3
Anhepatic phase (minutes)	53.6±20.53 (18-142)	
Cold ischemia time (minutes)	34.01±20.05 7-175	
Warm ischemia time (minutes)	42.71±18.03 20-137	
Operative time (minutes)	633.33±107.56 243-1200	
Blood loss (ml)	7055.84±5478.02 250-20000	
Postoperative data		
Hospital stay (day)	30.88±17.88	
ICU stay (day)	7.43±6.56	
Reoperation incidence	24	7.9
Reoperation		
Pack removal	8	33.3
Internal hemorrhage	16	66.7
Postoperative morbidity		
Morbidity	105 (34.7%)	
Respiratory complications	38 (12.5%)	
Pneumonia	11 (3.6%)	
Pleural effusion	23 (7.6%)	
ARDS	4 (1.3%)	
Renal complications	14 (4.6%)	
Collection	14 (4.6%)	
Vascular complications	23 (7.3%)	
Biliary complications	46 (15.2%)	
Primary non-function	8 (2.6%)	
Acute cellular rejection	20 (6.6%)	
Early mortality	41 (13.6%)	

ARDS = adult respiratory distress syndrome, ICU = intensive care unit

7 patients, then isolated bone recurrence in 3 patients and isolated left supra renal gland recurrence in 1 patient. Patients who had solitary liver recurrence 3 of them underwent TACE, 1 patient had radiofrequency ablation, 1 patient had combined TACE and microwave ablation and 3 of them were managed conservatively. Patients with extrahepatic recurrence were managed mainly by Sorafenib (59.1%) as a part of management of their systemic recurrence. Only 1 patient had surgical excision of isolated rib recurrence, and 1 patient had left adrenalectomy for isolated left suprarenal recurrence.

Recurrence was studied after exclusion of cases of early mortality. Among the studied variables, pathological microvascular invasion was noted in 18 cases of the recurrence group and was statistically significant predictor for recurrence with P value of 0.001. There was an insignificant difference observed among patients with and without recurrence regarding age, gender, AFP level, tumor size, bridging therapy, Milan criteria, USCF criteria, MELD score and tumor grade (table 6). The rates of disease-free survival were highest after the first year while was least after 10 years with rates 98% for the first year, 86.8 after the third year, 87.3% after 5 years and 82.65 after 10 years (table 7).

Kaplan-Miére curve showing disease free survival of studied cases (fig. 1).

Kaplan-Miére curve showing impact of recurrence on survival of studied cases P <0.001.

Log Rank test was done and it showed a highly sig-

Table 3 - Predictors of early mortality among studied cases

	total number n = 302	early mortality n = 41	no early mortality n = 261	Test of significance
Age (years)	302	1.02±0.16	1.11±0.32	t =1.73 p=0.085
Gender				
male	272	40(14.7)	232(85.3)	$\chi^2 = 2.98$
female	30	1(3.3)	29(96.7)	p = 0.096
Encephalopathy	46	8(17.4)	38(82.6)	$\chi^2 = 0.673$ p = 0.412
Jaundice	169	21(12.4)	148(87.6)	$\chi^2 = 0.433$ p = 0.511
Ascites	133	20(15)	113(85)	$\chi^2 = 0.433$ p = 0.511
Hepatomegaly	73	14(19.2)	59(80.8)	$\chi^2 = 2.53$ p = 0.112
Oedema	140	21(15)	119(85)	$\chi^2 = 0.451$ p = 0.502
Associated medical conditions	16	2(12.5)	14(87.5)	$\chi^2 = 0.017$ p = 0.897

Table 3 - Cont'd

	total number n = 302	early mortality n = 41	no early mortality n = 261	Test of significance
Associated surgical conditions	46	4(8.7)	42(91.3)	$\chi^2 = 1.10$ p = 0.294
Child-Pugh Score				
A	120	11(9.2)	109(90.8)	$\chi^2 = 9.30$
B	133	21(15.8)	112(84.2)	p = 0.026*
C	48	8(16.7)	40(83.3)	
CMV Ig G	178	23(12.9)	155(87.1)	$\chi^2 = 0.158$ p = 0.691
Cold ischemia time	302	32(15-150)	30(7-175)	Z = 0.779 p = 0.436
Platelet count	302	69(4-300)	55(10-321)	Z = 1.53 p = 0.126
Neutrophil \ lymphocytic count ratio	302	2.22(0.92-5)	2(0.64-36.36)	Z = 1.76 p = 0.08
BMI	302	29.41(21.39-40.26)	28.68(14.27-133.14)	Z = 0.823 p = 0.410
Time to Transplant (days)	302	40(25-120)	37(20-137)	Z=1.33 p = 0.184
MELD Score	302	13(1-27)	13(6-31)	Z = 0.196 p = 0.845
AFP Level (ng/mL)	302	15(1.4-1283)	11.4(1-1283)	Z = 0.483 p = 0.629

MELD = Model for end stage liver disease, AFP = Alfa fetoprotein

Table 4 - Study of multiple variables to predict early mortality

Variable	Univariate analysis Odds ratio (P value)	Multivariate analysis Odds ratio (P value)
CP Class B	1.500 (p=0.350)	0.501 (p=0.339)
CP Class C	1.800 (p=0.340)	0.596 (p=0.373)
Anhepatic Phase Time	0.020 (p=0.070)	0.016 (p=0.075)
Cold Ischemia Time	0.015 (p=0.200)	0.012 (p=0.227)
Warm Ischemia Time	0.005 (p=0.800)	0.003 (p=0.823)
Blood Loss	0.000 (p=0.400)	0.000 (p=0.374)
Operative Time	0.003 (p=0.060)	0.003 (p=0.064)
ICU Stay		0.069 (p=0.045*)
Re-operation	0.550 (p=0.400)	0.501 (p=0.414)
ACR		-1.465 (p=0.092)
Morbidity	16.4 (p<0.001*)	14 (p<0.001*)

nificant impact of recurrence on over all mortality of the study group with P value <0.001* (fig. 2).

DISCUSSION

Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer and the third most common cause of cancer-related death. Its incidence is increasing worldwide, ranging between 3-9% annually because of the dissemination of hepatitis virus infection (1). HCC occurs in 80%-90% of patients with underlying cirrhosis. Among patients with cirrhosis who had hepatitis B virus (HBV) or hepatitis C virus (HCV)

Table 5 - Recurrence outcomes

	n = 251	%
Recurrence rate	39	15.5
Time to recurrence (months)		
Mean±SD	78.63±51.28	
Median (min-max)	74.5(2-217)	
Location of recurrence	n = 39	
Intrahepatic (%)	8	20.5
Extrahepatic (%)	8	20.5
Both (%)	23	59
Treatment of liver recurrence (n=15)		
RFA	1	6.7
TACE	3	20.0
Conservative	5	33.3
Sorafenib	5	33.3
TACE+MWA	1	6.7
Treatment of extrahepatic recurrence (n=22)		
Radiotherapy	9	40.9
Sorafenib	13	59.1

RFA = radiofrequency ablation, TACE = trans arterial chemo embolization, MWA = microwave ablation

infection, the incidence of HCC was 88% or 93%, respectively (9).

In Egypt, about 7.2 % of chronic liver disease patients due to hepatitis C virus develop HCC (1). Males are more commonly affected by HCC with male: female ratio of 5:1. Liver transplantation now becomes the standard therapy for patient with early-stage HCC (10). Liver transplantation, which offers the theoretical advantage of removing both the tumor and the organ

Table 6 - Predictors of recurrence among studied cases

	total number n = 251	No recurrence n = 212	Recurrence n = 39	Test of significance
Age (years)	251	51.88±6.59	51.95±6.01	t = 0.06 p = 0.9
Gender				
male	222	189(95.8)	33(14.2)	$\chi^2 = 0.845$
female	29	23(79.3)	6(20.7)	p = 0.357
Encephalopathy	38	32(84.2)	6(15.8)	$\chi^2 = 0.025$ p = 0.874
Jaundice	148	126(85.1)	22(14.9)	$\chi^2 = 0.002$ p = 0.968
Ascites	113	95(84.1)	18(15.9)	$\chi^2 = 0.153$ p = 0.696
Hepatomegaly	59	50(84.7)	9(15.3)	$\chi^2 = 0.004$ p = 0.950
Oedema	119	100(84.0)	19(16.0)	$\chi^2 = 0.180$ p = 0.671
Antibodies	249	220(84.9)	39(15.1)	$\chi^2 = 0.354$ p = 0.552
Child-Pugh Score				
A	109	97(89)	12(11)	$\chi^2 = 2.28$
B	102	92(82.1)	20(17.9)	p = 0.320
C	40	33(82.5)	7(17.5)	
CMV IgG	155	127(81.9)	28(18.1)	$\chi^2 = 2.93$ p = 0.087
HbsAg	10	8(80)	2(20)	$\chi^2 = 0.209$ p = 0.647
Previous bridging surgery				
No	246	221(86.3)	35(13.7)	FET = 0.103
Localized resection	5	4(80)	1(20)	p = 0.558
Milan Vs UCSF criteria				
Within Milan	165	148(85.5)	25(14.5)	$\chi^2 = 0.908$
UCSF	31	25(83.3)	5(16.7)	p = 0.823
Beyond UCSF	55	47(85.5)	8(14.5)	
Milan pathological				
Within Milan	167	139(81.8)	31(18.2)	$\chi^2 = 5.75$
Within UCSF	48	46(95.8)	2(4.2)	p = 0.056
Beyond UCSF	37	31(83.8)	6(16.2)	
Pathological microvascular invasion	50	32(64)	18(36)	$\chi^2 = 20.58$ p = 0.001*
Capsular invasion	4	3(75)	1(25)	$\chi^2 = 0.296$ p = 0.487
Tumor grade				
I	195	167(85.6)	28(14.4)	$\chi^2 = 2.82$
II	51	39(81.2)	9(18.8)	p = 0.243
III	5	3(60)	2(40)	
Single	131	113(83.7)	22(16.3)	$\chi^2 = 0.222$
Multiple	120	103(85.8)	17(14.2)	p = 0.637
PET scan suspected activity	159	130(81.8)	29(18.2)	$\chi^2 = 3.37$ p = 0.07
Diabetes	39	34(87.2)	5(12.8)	$\chi^2 = 0.162$ p = 0.687
Previous bridging Surgery	5	4(80)	1(20)	FET = 0.1003 p = 0.558
Cold ischemia time	251	30(7-175)	30(10-80)	Z = 0.643 p = 0.521
Platelet count	251	55.5(10-321)	50(19-270)	Z = 0.789 p = 0.430
Neutrophil \ lymphocytic count ratio	251	2(0.64-36.36)	1.83(0.8-5.6)	Z = 0.235 p = 0.814
BMI	251	28.68 (17.87-133.14)	28.09 (14.27-38.63)	Z=0.769 P=0.442

Table 6 - Cont'd

	total number n = 251	No recurrence n = 212	Recurrence n = 39	Test of significance
Time to Transplant (days)	251	120(30-1400)	120(60-460)	Z = 0.557 p = 0.578
MELD Score	251	13(6-31)	13(6-21)	Z = 0.626 p = 0.531
AFP Level (ng/mL)	251	11(1-1036)	13(1.4-1283)	Z = 1.54 p = 0.124
Total Tumor Size (cm)	251	4(0.5-16)	4(1-13)	Z = 296 p = 0.768
Viable Tumor size (cm)	251	4.1(0-16)	4.4(1-13)	Z = .879 p = 0.38

MELD = model for end stage liver disease, AFP = alfa fetoprotein, CMV = cytomegaly virus, Hb s ag = hepatitis B surface antigen, UCSF = University of California San Francisco.

t: Student t test χ^2 = Chi-Square test, FET: Fisher exact test, z: Mann Whitney U test, *statistically Significant

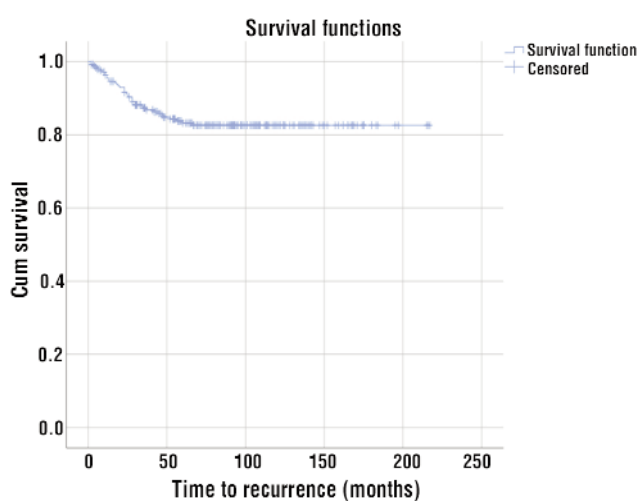


Figure 1

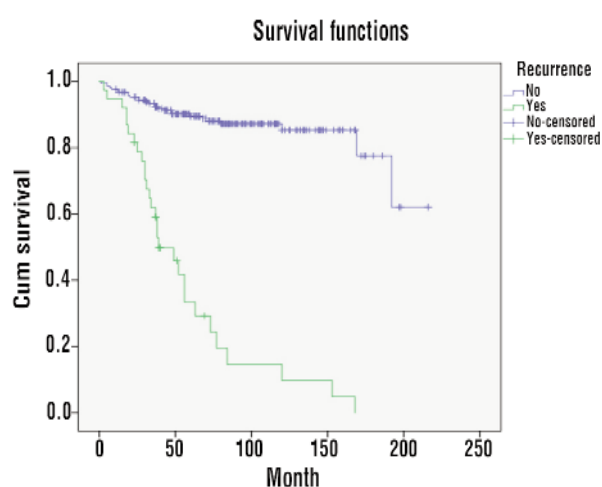


Figure 2

that are at risk of developing future malignancy, is an established therapy for HCC in patients with liver cirrhosis (11). Living donor LT (LDLT) has been established as an alternative and effective treatment for HCC, especially in Egypt, countries in the Americas and Europe are still distressed by long waiting times for deceased donor liver transplantation (DDLT) (4). The risk of tumor recurrence that occurs in approximately 6-20% of patients is another concern accompanied by the use of LT for HCC, which represents not only the loss of the donor organ but is also associated with a poor prognosis (12).

The Milan criteria (MC) have significantly improved the outcome of LT for HCC and have become the gold standard to achieve a favorable outcome after LT for HCC (13). Tumor recurrence is a major concern in LT for HCC, which represents a loss of the donor organ and is also associated with a poor prognosis (14). This retrospective study was conducted at Mansoura liver

transplant program, Mansoura University in period from 2004 to 2021. The study included 302 patients who underwent living donor liver transplantation for provisional diagnosis of HCC. This study was designed to identify risk factors of recurrence after living donor liver transplantation for HCC.

The present study revealed that according to demographic data in the studied group, the mean age of studied patients was 53 with range 32-67, 90.1% of patients were male and 9.9% were female. The

Table 7 - Disease free survival

Disease free survival	%
1 YEAR	98%
3 Years	86.8%
5 Years	87.3%
10 years	82.6%

majority of patients 95.4% had liver disease due to HCC on top of cirrhosis, 44% of patients had Child-Pugh Score. The mean MELD score of studied patients was 13.52 and the mean tumor size of studied patients was 4.41 cm with SD of 2.95. Our findings in agreement with Fathi et al., (5) who aimed to evaluate our center experience of living-donor liver transplantation (LDLT) in hepatocellular carcinoma (HCC) patients regarding recipients' mortality and morbidity and study the various prognostic factor affecting tumor recurrence and its impact on patients' survival. The study included 252 patients with 230 males (91.3%) and 22 females (8.7%). The mean age was 52 ± 6 years (range: 32 - 65). All patients had underlying liver cirrhosis with hepatitis C virus in 241 patients (95.6%), hepatitis B virus in 6 patients (2.4%), both in 4 patients (1.6%), and cryptogenic cirrhosis in one patient (0.4%). Most of the patients belong to child B (43%) and C (35%) cirrhosis. MELD score ranged from 6-27 with mean 14 and the mean tumor size was 4.8.

As well, our results are in concordance with Kang et al., (15) who aimed to predict the recurrence of hepatocellular carcinoma after primary living donor liver transplantation. A total of 49 patients (40 men and 9 women; mean age 54 years) were enrolled in this study. The mean MELD score was 10.3 ± 4.1 , the mean Child-Pugh score was 6.3 ± 1.8 and the of mean tumor size was 4.5.

Also, our findings are in line with Devillers et al., (16) who aimed to compare HCC recurrence-free survival. 121 patients were included in this study. They found that 93 (76.9%) were males and 28 (22.1%) were females (8.7%). The mean age was 60.7 (53.4-66.1) years. Most patients 118 (97.5%) had liver disease due to HCC on top of cirrhosis. The mean MELD score was 12.2 (9.3-16.2).

Our findings in agreement with Galal et al., (17) who aimed to assess pre-transplantation α -fetoprotein (AFP) level as a predictor for HCC recurrence after living donor liver transplantation (LDLT). Data of 75 patients with HCC who underwent LDLT were analyzed. They reported that mean WBCs was 5.12 ± 2.62 , mean hemoglobin was 11.05 ± 1.87 , mean platelets count was 70.85 ± 38.11 , mean serum albumin was 2.62 ± 0.57 , mean serum bilirubin was 2.9 (1.6-4.8), mean serum alanine transaminase (ALT) was 44 (28-83), mean serum Aspartate transferase (AST) was 68 (47-114), mean serum international normalized ratio 1.62 ± 0.43 , and mean serum creatinine (mg/dl) was 0.95 ± 0.36 .

In our study we reported that the median waiting time of studied patients was 4 months. Among 131 patients the majority of them 55.7% had TACE ablation

type, only 8.4% of them had MWA ablation type, 135 had RFA and the remaining 22.9% had combined TACE and ablation. This came in accordance with Fathi et al., (5) who revealed that among 252 patients, the majority of them (59%) had TACE ablation type. As well, our results in concordance with Devillers et al., (16) who found that the median of waiting time was 7.7 (3.7-11.1) months. Over a quarter (26.4%) received loco-regional therapy TACE or TARE as downstaging before transplantation.

In our study we reported that the recurrence time was 74.5. Among the recurrence group (39 patients), the majority of them 56.4% subjected to extrahepatic recurrence. Majority of patients managed conservatively as treatment for intrahepatic recurrence, 33.3% of them take sorafenib while only 6.7% of them take RFA or TACE as a treatment. This came in accordance with Kim et al., (18) who aimed to elucidate based on clinicoradiologic features the patterns of and prognostic factors for recurrence of hepatocellular carcinoma after liver transplantation. The subjects were 119 patients with unresectable hepatocellular carcinoma who underwent liver transplantation. They found that time to development of recurrence ranged from 0.8 to 41.5 months after liver transplantation. Recurrence was found in 16 (13.4%) of 119 patients and was most frequent in the liver, with no specific pattern.

As well, our results in concordance with Kang et al., (15) who reported that HCC recurred in 16 patients (32.7%) after 18.6 ± 14.6 months (5-54 months) of LDLT; 5 patients experienced recurrence within 12 months of LDLT, 7 patients between 12-24 months, and 4 patients between 24-60 months. Seven patients had extrahepatic recurrence, with the most common sites being lung (4 patients), bones (3 patients), peritoneum (1 patient), adrenal gland (1 patient), and regional lymph node (1 patient).

In our study we reported that there was statistically insignificant difference observed between patients with and without incidence of recurrence regarding age, gender, etiology of liver disease, Child-Pugh Score, MELD Score, AFP Level, tumor size, Milan US/CSF criteria, Milan pathological, tumor grade, cold ischemia time, platelet count, neutrophil/lymphocytic count ratio, single vs multiple tumors, BMI, diabetes, time to transplant, anti-viral treatment while there was highly statistically significant difference observed between patients with and without incidence of recurrence regarding pathological microvascular invasion.

Our results in concordance with Kang et al., (15) who reported that there was no statistically significant difference between recurrence and non-recurrence

groups as regard age, gender, etiology of liver disease, Child-Pugh Score, MELD Score, AFP Level, tumor size, Milan criteria, tumor grade and cold ischemia time. While there was statistically significant difference observed between recurrence and non-recurrence groups as regards microvascular invasion.

As well, our results in concordance with Devillers et al., (16) who found that there was no statistically significant difference observed between recurrence and non-recurrence groups as regard age, gender, etiology of liver disease, MELD Score and tumor grade. While there was statistically significant difference observed between recurrence and non-recurrence groups as regard Microvascular invasion. This study in contrast with our results in AFP as there were statistically significant differences between patients with recurrent HCC and those who had no recurrence regarding AFP.

Similarly, our findings in agreement with Fathi et al., (5) who revealed that there was statistically significant difference observed between recurrence and non-recurrence groups as regard micro-vascular invasion as it is associated with high incidence of tumor recurrence 33 % compared to 9.7 % in patient without micro-vascular invasion. While this study in contrast with our results in alpha feto-protein, Milan pathological (within Milan, within UCSF), tumor grade and single vs multiple tumors as there were statistically significant differences between patients with recurrent HCC and those who had no recurrence regarding alpha fetoprotein, Milan pathological (within Milan, within UCSF), tumor grade and single vs multiple tumors.

As well, our results in concordance with Kang et al., (15) demonstrated that there was no statistically significant difference between the recurrence and non-recurrence groups as regard age, gender and etiology of liver disease. There was statistically significant difference observed between recurrence and non-recurrence groups as regards vascular invasion. This study is in contrast with our results in AFP, tumor size, tumor number and T-stage as there were statistically significant differences between patients with recurrent HCC and those who had no recurrence regarding AFP, tumor size, tumor number and T-stage.

Also, Choi et al., (19) reported that there was no statistically significant difference between the recurrence and non-recurrence groups as regard age, gender etiology of liver disease, Child-Pugh Score, MELD Score, AFP Level, tumor size, and tumor number while there was statistically significant difference observed between patients with and without incidence of recurrence regarding pathological microvascular invasion.

In our study we revealed that rates of free survival from disease in patients was higher after 1 year followed by 5 and 10 years 98%, 87.3% and 82.6% respectively. Our results in concordance with Fathi et al., (5) who revealed that the 1-, 3-, and 5-year disease-free survival rate was 93%, 85%, and 78%, respectively. As well, our results in concordance with Harimoto et al., (20) who found that HCC recurred in 28 patients (14.7%) with disease-free survival (DFS rates 1, 3 and 5 years after LDLT of 92.7, 85.9 and 85.1%, respectively.

CONCLUSION

We conclude that pathological microvascular invasion is the most important independent predictor of recurrence after LDLT for HCC. Child-Pugh class C significantly increases early mortality. Long-term disease-free survival remains favorable, with most recurrences occurring late. These findings can inform patient selection and post-transplant surveillance strategies.

Conflict of Interest

All authors have no conflicts of interest that are directly relevant to the content of this review.

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