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RISK FACTORS ASSOCIATED WITH DELISTING OF HEPATOCELLULAR CARCINOMA PATIENT'S CANDIDATES FOR LIVER TRANSPLANTATION

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Abstract

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide, with more than 1 million new cases diagnosed every year. Liver transplantation has been used as a curative treatment for patients with HCC.

Liver transplantation offers the best cure chance for unrespectable hepatocellular carcinoma (HCC), but the scarcity of cadaver liver grafts has seriously limited its role. With the recent advances in adult living donor liver transplantation (LDLT), there is potentially a drastic change in the role of liver transplantation. Recent Studies have demonstrated the theoretical survival benefit of LDLT over deceased donor liver transplantation (DDLT) which depends largely on the waiting time and drop-out rate. This study was conducted to analyze the different risk factors leading to delisting in liver transplant patients with hepatocellular carcinoma. Fifty patients presented to Ain Shams Specialized Hospitals from January 2017 to June 2018, with expected average hepatocellular carcinoma eligible for Adult Living Donor Liver transplantation (ALDLT) were studied. They were evaluated according to protocol of Ain Shams Center of Organ Transplantation (ASCOT). Inclusion criteria: 1-hepatocellular carcinoma with any underlying cause of cirrhosis. HCC is first diagnosed using spiral computed tomography of liver and sometimes Magnetic Resonance Imaging (MRI). 2- Patients within University of California San Francisco (UCSF) criteria (one tumor ≤6·5 cm, three nodules with largest ≤4·5cm, & total tumor diameter ≤8 cm). 3- Patients within these criteria underwent loco-regional therapy as bridging therapy including radiofrequency ablation, radio-embolization, trans-arterial chemoembolization, microwave ablation or liver resection to avoid delisting. 4- Patients beyond these criteria underwent loco-regional treatment as means of down staging to be within Milan or UCSF and candidates for ALDLT. Exclusion criteria: 1- metastatic HCC patients, 2- macrovascular invasion, & 3- poor general condition for surgery.

Key words: Transplantation, Priority, Hepatocellular carcinoma, Delisting.

Introduction

Hepatocellular carcinoma (HCC) is a major global health problem, being the sixth commonest cancer worldwide and the third cause of death (Forner *et al,* 2012). Also, cirrhosis due to HBV, HCV, alcoholic liver disease, nonalcoholic fatty liver disease and genetic diseases affecting the liver leading to liver failure and thus liver transplant (García-Criado and Castellon, 2018).

First orthotopic liver transplantation was in dogs (Moore *et al,* 1959). Then, Starzl *et al.* (1990) reported successful used tacrolimus in patients underwent liver transplantation, who had rejection despite receiving conventional immuno-suppressive treatment. In the interim, liver transplantation becomes the standard therapy for end-stage liver complications management (Rahimi and Trotter, 2015). With the growing number of patients in bad need of liver transplantation, there was need of adopting new and modifying existing allocation policies that prioritize these patients. The policy should ensure fair allocation reproducible and strongly predictive of best pre- and post-transplant outcomes while taking into consideration the natural history of potential recipients liver disease and its complications (Schilsky and Moini, 2016).

The patients with fulminant hepatic failure were afforded the highest priority, known as

status 1, and then those with other liver diseases were ordered below them on waiting list. This approach replaced the older system that prioritized patients based on a combination of medical urgency and accumulated wait time. Since the change to the system, adult patients were prioritized based on their Model for End-Stage Liver Disease (MELD) scores (Wang *et al*, 20130).

This score was most validated for cirrhosis patients as predicted the risk of death without transplantation while on the waiting list. Scores range from 6 to 40 maximally (Kulik, 2015). The so-called expanded criteria of the University of San Francisco, California were proposed (Yao *et al,* 2005) that set the limit for LT to a single lesion ≤ 6.5cm in diameter or 2-3 lesions each ≤4.5cm with a maximum diameter ≤ 8cm, to have similar survival after LT to that of the MC. Criteria were criticized as only 24% of patients did not meet the MC, and a retrospective study based on the histologic data. Mauricio *et al.* (2011) found that a total tumor diameter > 7 cm resulted in an increase in the percentage of recurrence and proposed a new MC (= up-to-seven), using seven as the sum of the size of the largest tumor (cm) and the number, which yielded 5-year overall survival of 71.2%. Many au-thors validated these criteria (Chiao *et al,* 2013).

As the HCC patient is listed and waiting for a transplant, there is a distinct possibility that the patient disease will progress such that an OLT is no longer a reasonable treatment option. Prolonged time on waiting list affects post-transplant survival of hepatocellular carcinoma patients. But, it was not known which patients were at higher risk for early dropout from the list, as several delisting causes were tumor progression, non-compliance, death or unavailable donor (Salvalaggio *et al,* 2015).

The study aimed to analyze the different risk factors leading to delisting in liver transplantation to patients with hepatocellular carcinoma at Ain Shams Specialized Hospital for liver transplantation.

Subjects and Methods

This study was a retrospective cohort study carried out between January 2017 and June 2018. Forty-eight HCC patients were listed for LDLT at Ain Shams Center for Organ Transplantation (ASCOT). The study protocol was approved by the Medical Ethics Committee of Ain Shams University.

Patients were divided in to 3 groups: GI: 29 delisted due to any cause including death, GII: 12 received LDLT during the study period, and GIII: 7 still on the waiting list at the study end.

Inclusion criteria: a- Hepatocellular carcinoma with any underlying cause of cirrhosis was included. HCC was diagnosed using spiral computed tomography (CT) of liver and sometimes MRI was indicated, b- Patients within Milan criteria, University of California San Francisco (UCSF) criteria or Up to 7 criteria, c- Patients within these criteria, and had loco-regional therapy as bridging therapy including radiofrequency ablation, radio-embolization, trans-arterial chemo-embolization, microwave ablation or liver resection to avoid delisting, & d-Patients beyond these criteria had loco-regional treatment as means of down staging to be within Milan or UCSF and so candidates for ALDLT.

Exclusion criteria: a- Metastatic HCC patients were excluded. Chest CT and bone scan were done, b- Macrovascular invasion was also an exclusion criterion detected by CT or MRI, and c- Poor general condition or presence of co-morbidities for surgery.

Donors criteria included: 1- Living donors usually close family members or spouses; unrelated living donors were not accepted according to center's rules and regulations, 2- ABO blood type compatibility, 3- Ages between 18-37years, & 4- Without previous significant abdominal surgery or medical problems.

Complete history taking: Name, sex, weight (actual weight ± interstitial fluid, as ascites or lower limb edema), and body mass index (BMI).

Laboratory investigations: CBC, Kidney function tests and electrolytes {Blood urea nitrogen (BUN), serum creatinine, sodium (Na), potassium (K)}, Liver function tests (AST, ALT, ALP, GGT), Total protein, Albumin, Total bilirubin (T. Bil.), Direct bilirubin (D. Bil.), Prothrombin time (PT), International normalization Ratio (INR), Partial thromboplastin time (PTT), CRP (C-reactive protein), Lipid profile (cholesterol, triglycerides, HDL, LDL).

Child Pugh Score & MELD score or model for end-stage liver disease: Equals = 3.78 ×log [serum bilirubin (mg/dL)] + 11.2× log [INR] + 9.57×log [serum creatinine (mg/dL)] + 6.43

Serological tests: HAV, HBV, HCV, Cytomegalovirus (CMV), Epstein Barr virus (EBV), Herpes Simplex virus (HSV), and HIV.

Tumour markers: Alpha fetoprotein (AFP), Carcinoembryonic antigen (CEA), Cancer antigen 19-9 (CA 19-9), antigen 125 (CA 125), & antigen 15-3 (CA 15-3), Prostate specific antigen (PSA).

Recipients underwent imaging: Chest X-ray, Abdominal ultrasound with special comment on portal vein patency and compressibility, triphasic CT scan and petrography, MRI abdomen if CT scan was not done as in renal impairment, CT chest with contrast and bone scan to exclude metastases.

Endoscopy: Upper gastrointestinal endoscopy for esophageal varices with reference to grading (small, medium, or large with small varices as minimally elevated veins above esophageal mucosal surface, medium varices defined as tortuous veins occupied < 1/3 esophageal lumen, & large varices occupied > 1/3 esophageal lumen), and colonoscopy with rectal biopsy for malignancies and living schistosomiasis ova.

Electrocardiography (ECG): Dobutamine stress echocardiography and pulmonary function test (PFT): Graft recipient weight ratio (GRWR) or graft volume/recipient weight: A minimal graft-recipient weight ratio (0.8% to 1% was suggested without taking recipient's disease into graft-recipient weight ratio.

Statistical analysis: Data were analyzed, using the mean, standard deviation, student (unpaired) t- test, and Chi-square linear correlation coefficient, by SPSS V17. Unpaired Student T-test compared between 2 groups in quantitative data. Chi-square hypothesis the row and column variables were independent, without strength or direction relationship. Fisher's exact test & Yates' corrected chi-square computed for 2x2 tables. Linear correlation co-efficient correlated between two quantitative variables in a group. $P > 0.05$: non-significant (NS), $P < 0.05$: significant (S), & $P < 0.01$: highly significant (HS)

Results

HCC patients (48) were listed for LDLT at Ain Shams Center for Organ Transplantation (ASCOT) at Ain Shams Specialized Hospital till liver transplantation. The details were given in tables (1, 2, 3, 4, 5 & 6) and figures (1 & 2).

Table 1: Comparison between groups regarding MELD.

MELD	Delisted or not		
	Delisted	Transplanted	Pending
Range	10-30	8-26	7-21
Mean ±SD	15.724±5.189	15.000±5.063	12.714±4.751

MELD score = non-significant difference (P value 0.381).

Table 2: Comparison between groups in regards to number of tumours.

Tumors number	Delisted or not							
	Delisted		Transplanted		Pending		Total	
	No.	%	No.	%	No.	%	No.	%
One	15	51.72	6	50.00	5	71.43	26	54.17
Two	9	31.03	3	25.00	1	14.29	13	27.08
Three	2	6.90	3	25.00	1	14.29	6	12.50
Four	3	10.34	0	0.00	0	0.00	3	6.25
Total	29	100.00	12	100.00	7	100.00	48	100.00

A single tumor (54.17%), two tumors (27.08%), 3 tumors (12.5%), & 4 tumors (6.25%), without significant difference

Table 3: Comparison between tumor progression patients delisted regarding number of LDTs.

Liver directed therapies	Delisted or not							
	Tumor progression		Transplanted		Pending		Total	
	No.	%	No.	%	No.	%	No.	%
No	1	12.50	5	41.67	3	42.86	9	33.33
One	1	12.50	6	50.00	0	0.00	7	25.93
Two	3	37.50	1	8.33	3	42.86	7	25.93
Three	2	25.00	0	0.00	0	0.00	2	7.41
Four	1	12.50	0	0.00	1	14.29	2	7.41

Significant 0.05 by comparing delisted patients due to tumor progression regarding number of LDTs.

Table 4: Comparison between groups as to LDT response in terms of lesion ablation/embolization

LDT response in lesion ablation/ embolization	Delisted or not							
	Delisted		Transplanted		Pending		Total	
	No.	%	No.	%	No.	%	No.	%
Not well ablated/ embolized lesions	15	71.43	5	71.43	2	50.00	22	68.75
Well ablated/embolized lesions	6	28.57	2	28.57	2	50.00	10	31.25
Total	21	100.00	7	100.00	4	100.00	32	100.00

Patients (68.75%) not well ablated/embolized lesions, (31.25%) well ablated/embolized lesions, without significant.

Table 5: Comparison between tumor progression in delisted patients and others regarding LDT response.

LDT response in terms of mRECIST criteria	Delisted or not							
	Delisted by tumor progression		Transplanted		Pending		Total	
	No.	%	No.	%	No.	%	No.	%
Partial response	1	14.29	2	28.57	1	25.00	4	22.22
Stable disease	2	28.57	3	42.86	1	25.00	6	33.33
Progressive disease	4	57.14	0	0.00	0	0.00	4	22.22
Complete response	0	0.00	2	28.57	2	50.00	4	22.22

No significant difference

Table 6: Causes of delisting of all the delisted candidates.

Cause of delisting	Patient No.	%
No donor	15	51.72
Tumor progression	8	27.59
Died	3	10.34
Non-compliant	3	10.34
Total	29	100.00

51.72% not delisted no donor, 27.59% delisted as tumor progressed, 10.34% death, &10.34% delisted without compliant.

Discussion

As the HCC patient is listed and waiting for a transplant, there is a distinct possibility that the patient's disease will progress such that an OLT is no longer a reasonable treatment option. Prolonged time on the waiting list affects post-transplant survival of patients with hepatocellular carcinoma (HCC). However, it is not yet known which patients will be at higher risk for early dropout from the list. Several causes of delisting include tumour progression, non-compliance, death or lack of available donor (Salvalaggio *et al,* 2015). Approximately 10% of children on the liver transplant wait-list in the United States die every year (Hsu *et al,* 2017).

Regarding the condition of the liver disease including the MELD score; it was more or less in the same range for all the 3 groups with range between 6-40 without significant difference. This disagreed with Salvalaggio *et al.* (2016) who found higher MELD score was in the delisted group. This difference might be attributed to the fact that in living donor liver transplantation allowed shorter time and the procedure was based on donor availability and MELD score. But, in their patients the waiting list the severity of liver disease forced better patients wait longer.

Concerning the number of focal lesions, in this study, 54.17% of candidates had unicentric tumors while 45.83% had multicentric tumors (2,3 or 4), but without difference among the 3 groups. This agreed with Maddala *et al.* (2004) who found that 74% of patients had unicentric tumors of which 87.5% received liver transplantation, but 25.9% had multicentric tumors of which 78.57% recei-

ved liver transplantation. This showed that tumor's number didn't significantly affect the probability of delisting.

In the present study, 33.33% of patients didn't receive any LDT, but 66.67% received the LDTs (1, 2, 3 or more) without significant difference among the three groups This agreed with Vitale *et al.* (2009) who reported that 87% of patients received LDT, which was not necessarily mean less risk of delisting, compared only the patients delisted due to tumor progression with the transplanted patients. This can further reinforce the concept that LDT as a not urgent chances of liver transplantation.

In the present study, when looking closely at the LDT importance, both LDT type and response didn't significantly affect the delisting chance. Moreover, even when comparing those delisted due to tumor progression only with the rest of the study the difference was still non-significant. This disagreed with Salvalaggio *et al.* (2015) who found a significant difference as where poor response to LDT didn't predict higher dropout rates. The discrepancy may be attributed to the limitation of using triphasic CT and m-RECIST criteria in judging the response to the LDT.

In the present study, 25% of patients were transplanted, 60.42% were delisted, and 14.58% on the waiting list. Maddala *et al.* (2004) reported that 67% of patients were transplanted while 33% were delisted. Vitale *et al.* (2009) reported that 85.18% of the patients were transplanted while 14.81% were delisted. Salvalaggio *et al* (2016) reported that 70.3% of patients were transplanted, 18.35% were delisted and 11.3% remained on the waiting list. This great difference in number of transplanted and delisted patients was attributed to the fact that 51.72% of the present studied patients were delisted due to unavailability of related donor.

In Ain-Shams Ain Shams Specialized Hospital only relative donors were allowed to donate, as no organ allocation systems. Generally speaking, in Egypt deceased donor liver transplantation is illegal and limited to the living relative donors (Abdeldayem *et al*, 2008).

Looking further on the causes of delisting we see that of the 60.42% delisted, 51.72% had no suitable donor, 27.59% had tumour progression, 10.34% died and 10.34% were non-compliant. This agreed with Llovet *et al.* (2004), as 25% of patients were delisted due to tumor progression and Yao *et al.* (2005) reported that it was only 15% both due to tumor progression and death.

In the present study, fifteen patients who had no suitable donors, five donors were accidentally discovered HCV positive, 3 donors were non-compliant, three donors ABO incompatible while four patients had a small graft size seen in volumetric. Eight patients were delisted due to tumor progression seen in the form of distant metastasis (3 patients), malignant vascular invasion (3 patients), rising alpha-fetoprotein (2 patients). 3 patients died due to liver decompensation where 1 dies due to fatal hematemesis, 1 due to myocardial infarction, and 1 due to cerebrovascular stroke. The 3 non-compliant patients refused to do the necessary workup and follow up needed prior to transplantation.

In the present study, tumor characteristics; size or volume and vascular invasion didn't vary significantly among the three groups. This didn't go with Salvalaggio *et al.* (2016) where larger tumors showed more chances of delisting. This could be further emphasized that tumor size and vascular invasion separately cannot judge well tumor aggressiveness.

In the present study, the number of focal lesions was 54.17% of patients with unicentric tumors while 45.83% had multicentric tumors (2, 3, or 4), but without significant difference among the three groups. This agreed with Maddala *et al.* (2004) where 74% of patients had unicentric tumors of which 87.5% received liver transplantation, while 25.9% had multicentric tumors of which 78.57% received liver transplantation. This also showed that tumor number didn't significantly affect the probability of delisting.

Conclusion

The high rate of chronic liver diseases increased Egyptian patients' number suffering from end stage liver disease necessitated liver transplantation. Ages, tumor classification and the use of liver directed therapies were independent predictors of delisting HCC patients' candidates for liver transplantation.

References

Abdeldayem, HM, Salama, I, Soliman, S, Gameel, K, *et al*, 2008: Patients seeking liver transplant turn to China: Outcomes of 15 Egyptian patients went to China for deceased-donor liver transplant. Exp. Clin. Transplant. 6, 3:194-8.

Chiao, H, Yang, CE, Frenette, CT, 2013: Review on liver transplant for hepatocellular carcinoma. Transplant. Cancer Res. 2, 6:472-81.

Forner, A, Llovet, JM, Bruix, J, *et al,* 2012: Hepatocellular carcinoma. Lancet 379:1245.

García-Criado, A, Castellón, D, 2018: Presentation of the series: Cirrhosis of the liver and its complications. Radiologia 60, 1:73. doi: 10.1016 /j.rx.2017.10.003

Hsu, EK, Shaffer, ML, Gao, L, Sonnenday, C, Volk, ML, *et al,* 2017: Analysis of liver offers to pediatric candidates on the transplant wait list. Gastroenterology153, 4:988-95.

Kulik, L, 2015: Criteria for liver transplantation in hepatocellular carcinoma. Clin. Liver Dis. 6: 100-2.

Llovet, JM, Fuster, J, Bruix, J, 2004: The Barcelona approach: diagnosis, staging, and treatment of hepatocellular carcinoma. Liver Transplant. 10, 2:S115-20.

Maddala, YK, Stadheim, L, Andrews, J, *et al,* 2004: Dropout rates of patients with hepato-cellular cancer listed for liver transplantation: Outcome with chemoembolization. Liver Transplant. 10:449-55.

Moore, FD, Smith, LL, Burnap, TK, Dallenbach, FD, Dammin, GJ, *et al,* 1959: One-stage homo-transplantation of the liver following total hepatectomy in dogs. Transplant. Bull. 6, 1:103-7.

Rahimi, RS, Trotter, JF, 2015: Liver transplantation for hepatocellular carcinoma: Outcomes and treatment options for recurrence: Quarterly Hellenic Society of Gastroenterology. Ann. Gastroenterol. 28, 3:323-30.

Salvalaggio, PR, Felga, G, Axelrod, DA, *et al,* 2015: List and liver transplant survival according to waiting time in patients with hepatocellular carcinoma. Amer. J. Transplant. 15:668-77.

Salvalaggio, PR, Felga, G, Guardia BD, *et al,* 2016: Time of dropout from the liver transplant list in patients with hepatocellular carcinoma: Clinical behavior according to tumor characteristics and severity of liver disease. Transplant. Proceed. 48, 7:2319-22

Schilsky, ML, Moini, M, 2016: Advances in liver transplantation allocation systems. World J. Gastroenterol. 22, 10:2922-30.

Vitale, A, Boccagni, P, Brolese, A, *et al,* 2009: Progression of hepatocellular carcinoma before liver transplantation: Dropout or liver transplantation. Transplant. Proceed. 41, 4:1264-7

Wang, J, Li, J, Howard, PK, 2013: A system model of work flow in the patient room of hospital emergency department. Hlth. Care Manag. Sci. 16, 4:341-51.

Yao, F, Kinkhabwala, M, La Berge, J, *et al,* 2005: The impact of pre-operative loco-regional therapy on outcome after liver transplantation for hepatocellular carcinoma. Am. J. Transplant. 5:795-80.

Explanation of figures

Fig. 1: Comparison between tumor progression patients in delisted group with the others classified before and after intervention.
Fig. 2: Comparison between groups regarding number of tumors.