Comparative cohort study between the outcome of living donor liver transplant in patients with hepatocellular carcinoma within and beyond Milan criteria

Ramy Nafady, Mostafa Abdo, Hatem S. Saber, Mahmoud Talaat, Mahmoud E. Alprawy, Amr A.A. Aal

Department of General Surgery, Faculty of Medicine, Ain Shams University, Cairo, Egypt

Correspondence to Ramy Nafady, MBBCh, MD, MRCS (Lon), Post code: 11311;
Tel: + (44) 7861369471;
e-mail: ramy.nafady@nhs.net

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Background
Liver transplantation has been accepted as an effective therapy for hepatocellular carcinoma (HCC). The Milan criteria is widely used across the world to select liver transplantation candidates in patients with HCC. However, the Milan criteria may be too strict because a substantial subset of patients who have HCC exceed the criteria, who would benefit from liver transplant, and may be unnecessarily excluded from the waiting list. In recent years, many extended criteria beyond the Milan criteria have been presented, which were proven to be able to yield similar outcomes compared with those patients meeting the Milan criteria. Because the simple use of the tumor's size and number was insufficient to indicate HCC biological features and to predict the risk of tumor recurrence, it was unrealistic to rely only on these two criteria to exclude a patient from transplant service.

Purpose
To fortify the principle of using University of California San Francisco criteria (UCSF) and 'up to seven' criteria for indicating patients with HCC for transplant and thus providing a wider inclusion scope for patients with HCC in transplant service, which would provide a potentially curative solution for previously excluded potentially curable patients.

Patients and methods
This is a retrospective comparative cohort study. Our study was performed in Egypt by comparing the outcome of patients with HCC transplanted from living donors within Milan criteria and those who are beyond Milan criteria, but within the University of California San Francisco criteria or up to seven criteria who responded to down-staging therapy and included back within Milan criteria in terms of recurrence rate and mortality and recurrence free. The study was performed in Air Force specialized hospitals and Nasser Institute in Cairo in the period from July 2015 to November 2021.

Results
The total study sample size was 70 patients. Overall, 72.9% (*n*=51) of them were transplanted in Air Force specialized hospitals, whereas 27.1% (*n*=19) in Nasser Institute. The study group was subdivided according to the listing criteria for transplant; 61.4% (*n*=43) were under the Milan criteria, whereas 38.6% (*n*=27) were listed under the University of California San Francisco criteria or 'up to seven' criteria (beyond Milan criteria group). The posttransplant HCC recurrence was detected in 4.7% (*n*=2) in the Milan criteria group, whereas in six (22.2%) patients of the beyond Milan criteria group (*P*=0). By comparing survival rates, the Milan criteria group's survival rates on 1-, 3-, 5-year follow-up were 90.6, 86, and 86%, respectively, whereas the rates were 92.5, 88.8, and 88.8% in the beyond Milan criteria group. The mean survival time in the Mila criteria group was 62.6 months compared with 65.28 months in the beyond Milan criteria group (*P*=0.6). The posttransplant recurrence free rates were 90.6, 83, and 83% in 1-, 3-, and 5-year follow-up in the Milan group, when analyzed in the beyond Milan criteria group, they were found to be 88.8, 77.7, and 74% in the same follow-up intervals, with *P* value of 0.566. This demonstrated comparable survival rates and recurrence-free rates between the two groups.

Conclusion
Efficient downstaging therapy has rendered the UCSF criteria and the 'up to seven' criteria more usable than before for including patients with HCC for the transplant service as they have been proven to have tumor recurrence rate, survival time, and tumor-free survival time comparable to the Milan criteria.

Hence, they provide the curative benefit of liver transplant for a wider scope of patients with HCC.

Keywords:
adult living donor liver transplant, hepatocellular carcinoma, liver transplantation, Milan criteria

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third most common cause of death from cancer. It is the most common primary tumor of the liver, accounting for 90% of all primary liver tumors. Mean survival is estimated to be 6–20 months without intervention. Over the last 30 years, the treatment of this cancer has changed greatly. Advances in surgical technique and immunosuppression regimens have made liver transplantation a feasible and potentially curative alternative for patients with HCC [1].

As HCC is recognized as a biologically aggressive tumor, the recurrence rate, which ranges from 9 to 16%, was the main challenging outcome to minimize, so all of the modalities to achieve that were applied to medical practice, including, most critically, the preoperative selection of transplant candidates within the preoperative predictors for HCC recurrence, including vascular invasion, degree of differentiation, tumor size, and number of nodules and satellites. This triggered the evolution of preoperative inclusion criteria for patients with HCC [2].

The Milan criteria, introduced by Mazzaferro *et al.* [3], is the most used criteria worldwide and restricts transplantation in adults with HCC as follows: (a) single tumor diameter less than 5 cm; (b) not more than three foci of tumor, each one not exceeding 3 cm; (c) no microvascular invasion; and (d) no extrahepatic involvement. After Milan criteria was initially employed in liver transplantation for HCC, better outcomes of liver transplantation were observed. Small, single-center, European studies have suggested that the 5-year survival rate after liver transplantation for patients with HCC within the Milan criteria ranged from 71 to 75%.

Furthermore, some patients who are beyond Milan criteria may be candidates for liver transplant after having a downgrading therapy, including transarterial bland embolization/transarterial chemoembolization, yttrium-90/radiation therapy, and ablation (or combination) and may fulfill the Milan criteria, making them eligible candidates for liver transplant, but these candidate must not have any absolute contraindications for liver transplant and must follow another extended accepted criteria for liver transplant such as the University of California San Francisco criteria, which include allowing patients with a solitary tumor smaller than 6.5 cm, or patients having three or fewer nodules, with the largest lesion being smaller than 4.5 cm or having a total tumor diameter of less than 8.5 cm without vascular invasion [4].

Aim

The aim of this study was to compare the outcome of living donor liver transplant in patients with HCC within Milan criteria and those who are beyond Milan criteria but within the University of California San Francisco criteria or 'up to seven' criteria, whether transplanted within these criteria or received down-staging therapy and included back within the Milan criteria, in terms of recurrence rate, recurrence-free time, and mortality.

Patients and methods

(1) Type of study: a retrospective comparative cohort study was performed.
(2) Study setting: our study was performed in Egypt by following the results of 70 cases of HCC that received live donor liver transplant; 43 of them were included for transplant following the Milan criteria, whereas 23 were following the UCSF or 'up to seven criteria' in Air Force specialized hospitals and Nasser Institute in Cairo.
(3) Study period: it was performed from July 2015 to February 2021.
(4) The study population included 70 patients.

Inclusion criteria

The following were the inclusion criteria:

(1) Adult older than 18 years old.
(2) Patients eligible for liver transplantation.

(3) Patients diagnosed with HCC with radiological and/or pathological methods.
(4) Patients graded within Milan criteria.
(5) Patients beyond Milan criteria but within the University of California San Francisco criteria or 'up to seven' criteria.
(6) Patients with alpha-fetoprotein less than 400 IU at the time of transplant.
(7) Patients transplanted within the study period.

Exclusion criteria

The following were the exclusion criteria:

(1) Pediatric patients.
(2) Patients not eligible for liver transplantation.
(3) Patients graded beyond Milan criteria who did not respond to down-staging therapy.
(4) Patients graded beyond the University of California San Francisco criteria or 'up to seven criteria.'
(5) Patients with alpha-fetoprotein more than 400 IU at the time of transplant.

Sampling method: according to the inclusion and the exclusion criteria.

(1) Sample size: 70 patients.
(2) Ethical considerations: patients provided fully informed consent to participate. These informed consents in this retrospective study were verbal consents. Participant's confidentiality and data security were guaranteed. Participants had the right to withdraw from the research process at any time, and they also had the right to withdraw their data if they were identifiable and should be told when this would no longer be possible. They were informed of any expected benefits for the research participants and also any possible risk to them.
(3) Study tools:

Preoperative workup

Patients of transplant were subjected to the following:

(1) Full clinical assessment.
(2) Laboratory investigations: complete blood count, coagulation profile, liver function tests, kidney function tests, lipid profile, diabetes profile, serum electrolytes, viral markers and tumor markers, and laboratory tests for Bilharzias, autoimmune, and for metabolic liver dysfunction.
(3) Radiological investigations: triphasic pelvic-abdominal computed tomography (CT) with portovenography and arteriography, CT chest with contrast for all cases, PET-CT, and bone scan for selected cases.
(4) Endoscopy: upper gastrointestinal and colonoscopy.
(5) Medical consultations: cardiological, chest, psychological, ENT, and dental consultations.
(6) Calculation of MELD score and CHILD classification.

Postoperative workup for transplantation

The comparisons in outcomes between the two groups were in terms of HCC recurrence rate, recurrence-free time, and mortality. We used the following tools to assess the outcome.

Early workup (first 3 months):

(1) Follow-up laboratory investigations and Doppler ultrasound daily for 1 week, then every other day for 2 weeks, and then once weekly for 2 months.

Later (after 3 months):

(1) Follow up laboratory investigations and ultrasound every 2–4 weeks according to patient's demands.
(2) Follow-up tumor markers every 3 months and abdominal CT every 6 months (if clinically indicated).
(3) MRCP every 3–6 months according to clinically correlated need.
(4) Target follow-up and duration: 12 months.

Data management and analysis

The collected data were revised, coded, tabulated, and introduced to a PC using Statistical Package for the Social Sciences (SPSS 25.0, Armonk, NY: IBM Corp). Data were presented, and suitable analysis was done according to the type of data obtained for each parameter.

Descriptive statistics

(1) Mean, SD, and range for parametric numerical data, whereas median and interquartile range for nonparametric numerical data.
(2) Frequency and percentage for nonnumerical data.

Analytical statistics

(1) Student *t* test was used to assess the statistical significance of the difference between two study group means.
(2) Mann–Whitney test (*U* test) was used to assess the statistical significance of the difference of a nonparametric variable between two study groups.</LIST>

(3) χ^2 test was used to examine the relationship between two qualitative variables
(4) Fisher's exact test was used to examine the relationship between two qualitative variables when the expected count is less than 5 in more than 20% of cells.
(5) Kaplan–Meier survival analysis is a descriptive procedure for examining the distribution of time-to-event variables. Additionally, you can compare the distribution by levels of a factor variable or produce separate analyses by levels of a stratification variable.
(6) Log-rank test to compare time-to-event variables by levels of a factor variable.

Results

The total study sample size was 70 patients. Overall, 72.9% (*n*=51) were transplanted in Air Force specialized hospitals, whereas 27.1% (*n*=19) in Nasser Institute. However, they were all transplanted by the same surgical team. The sample's epidemiological analysis, including age, sex, mortality, and the primary hepatic pathology, is shown in Table 1.

Table 1 Statistical analysis of the study sample in terms of age, sex, and preoperative pathology and Child–Pugh class

Whole sample	Mean	SD
Age	57.86	7.87
	n (%)	
Center		
AFSH	51 (72.9)	
NIH	19 (27.1)	
Group		
Milan criteria	43 (61.4)	
UCSF or up to 7	27 (38.6)	
Death		
Alive	61 (87.1)	
Dead	9 (12.9)	
Sex		
Male	59 (84.3)	
Female	11 (15.7)	
HCV		
No	7 (10.0)	
Yes	63 (90.0)	
HCC		
No	0	
Yes	70 (100.0)	
PVT		
No	52 (74.3)	
Yes	18 (25.7)	
HBV		
No	58 (89.2)	
Yes	7 (10.8)	
Child Class		
A	21 (30.0)	
B	28 (40.0)	
C	21 (30.0)	

HCC, hepatocellular carcinoma; PVT, portal vein thrombus.

The study group was subdivided according to the listing criteria for transplant: 61.4% (*n*=43) were under the Milan criteria, whereas 38.6% (*n*=27) were listed by the University of California San Francisco criteria or 'up to seven' criteria (beyond Milan criteria group). The mean age was 56.37 and 60.22 years (*P*=0.045) in the Milan group and the beyond Milan group, respectively. HCV infection was the primary hepatic pathology, representing 86% (*n*=37) of the Milan group patients and 96.3% (*n*=26) in the other group (Table 2). Portal vein thrombus on initial imaging was detected in 18.6% (*n*=8) in the Milan criteria group and 37% (*n*=10) in the beyond Milan criteria group (*P*=0.086). Portal vein thrombus was presumed to be malignant radiologically in 2.3% (*n*=1) in the Milan group and 7.4% (*n*=2) in the beyond Milan criteria group (Table 3). The mean MELD score was 14.24 in the Milan criteria group compared with 13.3 in the beyond Milan criteria group (*P*=0.445) which was not found to be significant.

In comparing the pretransplant management of the primary hepatic pathology and HCC, 41.9% (*n*=18) achieved sustained viral response in the Milan criteria group, whereas 37% (*n*=10) did in the beyond Milan criteria group, which was not found to be a significant variable (*P*=0) (Table 3).

In the beyond Milan criteria group, only 66.7% (*n*=18) required downstaging therapy, whereas 33.3% (*n*=9) of them were transplanted directly. Bridging therapy was applied in 65.1% (*n*=28) in the Milan group and in 77.7% (*n*=21) in the beyond Milan group (*P*=0.202). This high number of bridging therapy in the beyond Milan group was because the downstaging therapy was considered as a bridging too till the patient was transplanted (Table 3).

Preoperative presumed malignant portal vein thrombus was detected in one (2.3%) patient and three (7.4%) patients in the Milan and beyond Milan groups, respectively, with *P* value of 0.55, which was also an insignificant variable statistically (Table 3).

The posttransplant HCC recurrence was detected in 4.7% (*n*=2) in the Milan criteria group and six (22.2%) patients in the beyond Milan criteria group (*P*=0.048), which was found to be a significant outcome variation (Table 4).

Regarding survival rates, in the Milan criteria group, the 1-, 3-, and 5-year survival rates were 90.6, 86, and 86%, respectively, whereas they were 92.5, 88.8, and

Table 2 Statistical comparison between the Milan criteria group and beyond Milan group in terms of age, sex, mortality, preoperative pathology, and Child–Pugh class

	Milan criteria		UCSF or up to 7		Test of significance		
	Mean	SD	Mean	SD	value	*P* value	Significance
Age	56.37	7.98	60.22	7.20	t=–2.04	0.045	S
	n (%)		*n* (%)				
Death							
Alive	37 (86.0)		24 (88.9)		Fisher exact test	1.000	NS
Dead	6 (14.0)		3 (11.1)				
Sex							
Male	36 (83.7)		23 (85.2)		Fisher exact test	1.000	NS
Female	7 (16.3)		4 (14.8)				
HCV							
No	6 (14.0)		1 (3.7)		Fisher exact test	0.236	NS
Yes	37 (86.0)		26 (96.3)				
HCC							
No	0		0				
Yes	43 (100.0)		27 (100.0)				
PVT							
No	35 (81.4)		17 (63.0)		χ^2=2.95	0.086	NS
Yes	8 (18.6)		10 (37.0)				
HBV							
No	35 (89.7)		23 (88.5)		Fisher exact test	1.000	NS
Yes	4 (10.3)		3 (11.5)				
Child class							
A	12 (27.9)		9 (33.3)		χ^2=0.41	0.814	NS
B	17 (39.5)		11 (40.7)				
C	14 (32.6)		7 (25.9)				

HCC, hepatocellular carcinoma; PVT, portal vein thrombus.

88.8% in the beyond Milan group (*P*=0.511), with an insignificant difference between both groups (Table 4, Fig. 1). The mean survival time in the Milan group was 62.6 months compared with 65.28 months in the beyond Milan group (*P*=0.6). This demonstrated a comparable survival rate between the two groups (*P*=0.511) (Table 5).

The posttransplant recurrence-free rates were 90.6, 83, and 83% in 1-, 3-, and 5-year follow-up in the Milan group, whereas in the beyond Milan group were found to be 88.8, 77.7, and 74%, respectively, with *P* value of 0.566, which were found to be also a nonsignificant variation in the outcome (Table 4 and Fig. 2).

By correlating the post-HCC recurrence to the HCV viral status preoperatively, 14.3% (*n*=4) of those who achieved systemic viral response preoperatively had HCC recurrence compared with 9.5% (*n*=4) of those who were nonresponders (*P*=0.5), rendering the viral response a nonsignificant factor in HCC recurrence rate (Table 6).

In terms of correlation to tumor cellular viability, 12.1% of the patients who had viable tumor cells did have recurrence, whereas only 10.8% of those who had necrosed tumor cells developed recurrence (*P*=1), with an insignificant difference in the HCC recurrence rate (Table 6).

In the beyond Milan (UCSF or up to seven) group, downstaging therapy was used to regain patient eligibility to Milan criteria. The results showed that 83.3% (*n*=15) of those who received downstaging therapy did not have recurrence. In another way of expression, we can point it as that only 16.7% (*n*=3) of those who did not receive downstaging were reported to have posttransplant HCC recurrence. Therefore, by comparing the possibility of posttransplant recurrence between those who had down staging and those who did not receive it, it has been concluded that downstaging was not found a significant factor regarding the posttransplant recurrence rate (Table 7).

The serum level of alphafetoprotein has been compared preoperatively and postoperatively in patients with and without posttransplant HCC recurrence. The median preoperative serum level was 10 ng/ml in non-posttransplant HCC recurrence group compared with 59 ng/ml in posttransplant HCC recurrence group, with *P* value of 0.006, whereas the median postoperative serum level of alphafetoprotein was 2.47 and 247.3 ng/ml, respectively, with *P* value of 0 (Table 8).

Table 3 Statistical comparison between the Milan criteria group and Beyond Milan group in terms of preoperative tumor management, preoperative portal vein thrombus assessment, explant pathology, and postoperative immunosuppression

	Milan criteria [*n* (%)]	UCSF or up to 7 *n* (%)]	Test of significance		
			Value	*P* value	Significance
HCV outcome					
Nonresponder/no treatment	25 (58.1)	17 (63.0)	χ^2=0.16	0.688	NS
SVR	18 (41.9)	10 (37.0)			
Down staging					
No	43 (100)	9 (33.3)	22.774	<0.002	S
Yes	0	18 (66.7)			
Bridging					
No	15 (34.8)	6 (22.3)	0.189	0.663	NS
Yes	28 (65.1)	21 (77.7)			
Tumor viability					
Viable	22 (51.2)	11 (40.7)	χ^2=0.72	0.395	NS
Necrosed	21 (48.8)	16 (59.3)			
Type of immunosuppression					
No FK or neoral	0	2 (7.4)	Fisher exact test	0.154	NS
FK	41 (95.3)	23 (85.2)			
Neoral	2 (4.7)	2 (7.4)			
MMF					
No	34 (79.1)	22 (81.5)	χ^2=0.06	0.806	NS
Yes	9 (20.9)	5 (18.5)			
Everolimus					
No	23 (53.5)	16 (59.3)	0.224	0.636	NS
Yes	20 (46.5)	11 (40.7)			
Heat ablation					
No	28 (65.1)	20 (74.1)	0.618	0.432	NS
Yes	15 (34.9)	7 (25.9)			
TACE					
No	22 (51.2)	5 (18.5)	7.46	0.006	S
Yes	21 (48.8)	22 (81.5)			
Nexavar					
No	42 (97.7)	24 (88.9)	Fisher exact test	0.291	NS
Yes	1 (2.3)	3 (11.1)			
PVT radiological type					
No	35 (81.4)	17 (63.0)	Fisher exact test	0.179	NS
Benign	7 (16.3)	8 (29.6)			
Malignant	1 (2.3)	2 (7.4)			
PVT explant thrombus type					
No	35 (81.4)	17 (63.0)	2.95	0.086	NS
Benign	8 (18.6)	10 (37.0)			
Malignant	0	0			

PVT, portal vein thrombus.

Discussion

Being a curative intentional treatment, liver transplant effectiveness for HCC can be assessed upon multiple factors, but the most important is the rate of HCC recurrence in the transplanted liver. In our study, we focused on the initial inclusion criteria for the candidates for the live donor liver transplant as being a single influencing factor in defining the possibility of HCC recurrence in posttransplant setting.

The current accepted Milan criteria for transplantation originally demonstrated 4-year survival and recurrence-free rates of 75 and 83%, respectively [3]. These results have been validated by numerous subsequent studies showing equivalent or superior survival advantages [5,6]. UCSF criteria have been used as an extended form of the Milan criteria and found to have comparable survival and recurrence-free rates in many centers [7].

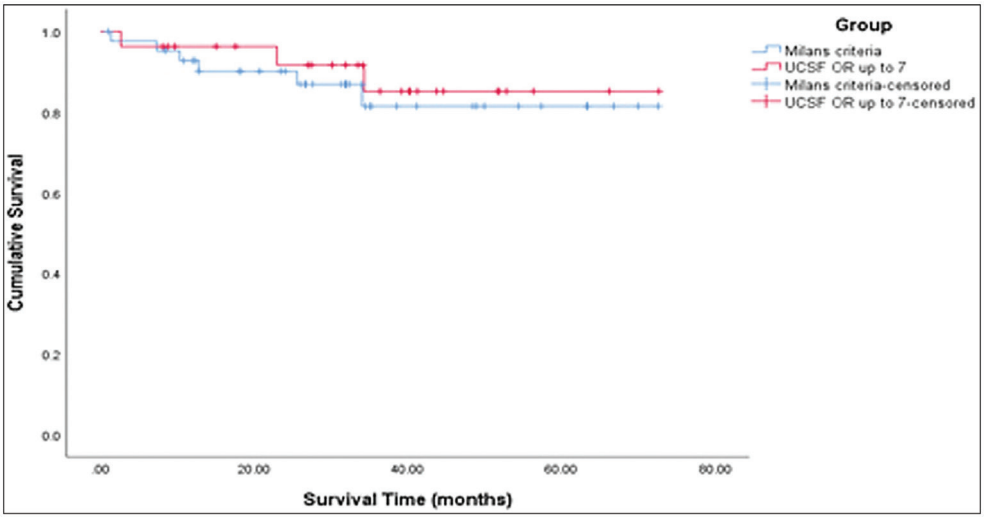
As a standard care, the Milan criteria have been used as primary criteria for selecting patients for living donor liver transplant in the selected centers in our study. However, the delayed presentation and absent nominated surveillance program for HCC lead to presentation of many patients who are borderline or just beyond the Milan criteria. This has driven us to considering other criteria to include such patients for

Table 4 Statistical comparison between the Milan criteria group and beyond Milan group in terms of posttransplant hepatocellular carcinoma recurrence, survival interval, recurrence free rate

	Milan criteria [*n* (%)]	UCSF or up to 7 [*n* (%)]	Test of significance		
			Value	*P* value	Significance
Post-LTx HCC recurrence					
No	41 (95.3)	21 (77.8)	Fisher exact test	0.048	S
Yes	2 (4.7)	6 (22.2)			
Survival rates					
1 year	39 (90.6)	25 (92.5)	χ^2=0.43	0.511	NS
3 years	37 (86)	24 (88.8)			
5 years	37 (86)	24 (88.8)			
Recurrence free rate					
1 year	39 (90.6)	24 (88.8)	χ^2=0.33	0.566	NS
3 years	36 (83)	21 (77.7)			
5 years	36 (83)	20 (74)			

HCC, hepatocellular carcinoma.

Figure 1



Kaplan–Meier curve demonstrating survival analysis for the Milan criteria group and beyond Milan group.

Table 5 Mean survival time of Milan criteria group and beyond Milan group

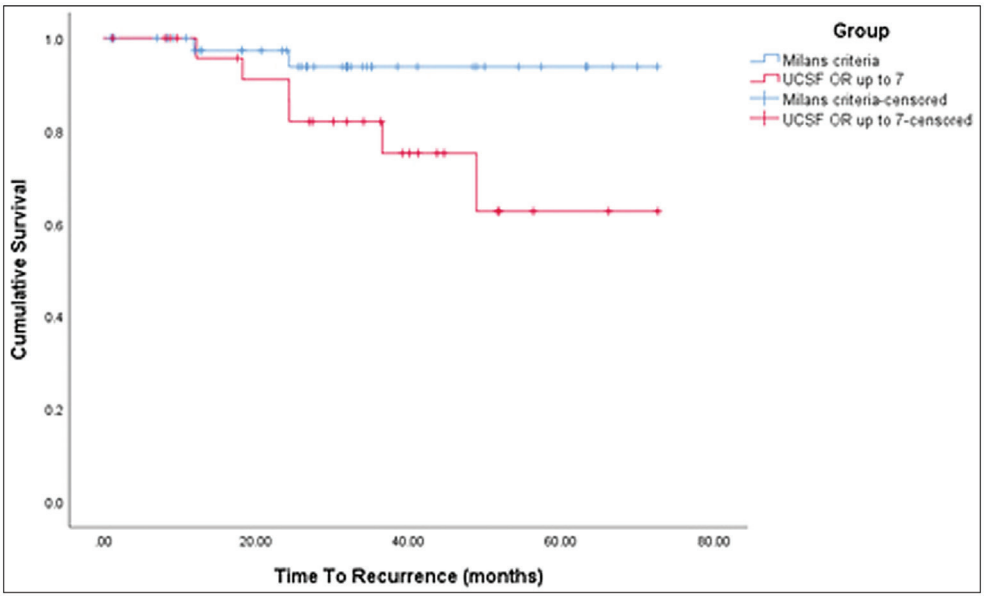
	Mean survival (95% CI)	Log rank test		
		χ^2	*P* value	Significance
Milan criteria	62.6 (55.23–69.98)	0.25	0.616	NS
UCSF or up to 7	65.28 (57.47–73.09)			
Overall	63.7 (58.28–69.13)			

the transplant program so they can benefit from the curative potentiality of liver transplant.

Our study was conducted in two of the high-volume centers of liver transplant in Egypt with the same surgical team to omit the variability of preoperative planning, operative practice, and postoperative management from being an influencing factor in the outcome. A total of 70 patients were included in our study according to the listing criteria for transplant: 61.4% (*n*=43) were under the Milan criteria, whereas 38.6% (*n*=27) were listed by the University of California San Francisco criteria or 'up to seven' criteria (beyond Milan criteria group). Our main point of analysis was the posttransplant HCC recurrence, which was detected in two (4.7%) patients in the Milan criteria group and six (22.2%) patients in the beyond Milan criteria group, with *P* value of 0.048. It was found to be a significant outcome, which could favor Milan criteria as selection criteria.

However, while comparing the survival rate, the first-year survival rate was 90.6% in the Milan group and 92.5% in the beyond Milan group, which are almost near rates and were found insignificant variation in the outcome (Table 4). In the long-term follow-up, 86

Figure 2



Kaplan–Meier curve demonstrating HCC recurrence-free interval analysis for the Milan criteria group and beyond Milan group. HCC, hepatocellular carcinoma.

Table 6 Statistical correlation of the posttransplant hepatocellular carcinoma recurrence to hepatitis C status, down-staging therapy and the hepatocellular carcinoma viability in the whole study sample

Whole sample	No post-LTx HCC recurrence [*n* (%)]	Post-LTx HCC recurrence [*n* (%)]	Fisher exact test	
			P value	Significance
HCV				
No	7 (100.0)	0	1.000	NS
Yes	55 (87.3)	8 (12.7)		
HCV outcome				
Nonresponder/no treatment	38 (90.5)	4 (9.5)	0.705	NS
SVR	24 (85.7)	4 (14.3)		
Down staging				
No	46 (93.9)	3 (6.1)	0.047	S
Yes	16 (76.2)	5 (23.8)		
HCC status				
Viable	29 (87.9)	4 (12.1)	1.000	NS
Necrosed	33 (89.2)	4 (10.8)		

HCC, hepatocellular carcinoma.

and 88.8% were the survival rates of the Milan group and the beyond Milan group, respectively, at 3 years of follow-up assessment, with the same recorded rates after 5 years of follow-up. This shows an almost near long-term survival rates, which is already the intended ultimate goal of liver transplant.

One more critical outcome was analyzed, which is the posttransplant recurrence free rates. As shown in the results, the first-year recurrence-free rates were 90.6% in the Milan group and 88.8% in the beyond Milan group; on the 3-year follow-up, they were 83–77.7%, respectively; and on the 5-year follow-up, the rates were 83 and 74% for Milan group and beyond Milan group, respectively. There were no significant differences in the recurrence-free rate upon the regular follow-up of the two groups by regular alpha-fetoproteins, ultrasound, and CT scan in case of high suspicion. This is a ground breaking point, fortifying the use of the University of California San Francisco criteria or 'up to seven' criteria in deemed patients.

The posttransplant HCC recurrence was also correlated with other variables. Each was analyzed individually to assess its effect on the HCC recurrence rate. The first was the preoperative viral status; 14.3% (n=4) of those who achieved systemic viral response preoperatively had HCC recurrence compared with 9.5% (n=4) of those who were nonresponders (P=0.5), rendering the viral response a statistically nonsignificant factor in HCC recurrence rate. However, keeping in mind that the total number of those who responded

Table 7 Statistical correlation of the posttransplant hepatocellular carcinoma recurrence to hepatitis C status, down-staging therapy and the hepatocellular carcinoma viability in beyond Milan criteria sample

UCSF or up to 7	No post-LTx HCC recurrence [*n* (%)]	Post-LTx HCC recurrence [*n* (%)]	Fisher exact test	
			P value	Significance
HCV				
No	1 (100.0)	0	1.000	NS
Yes	20 (76.9)	6 (23.1)		
HCV outcome				
Nonresponder/no treatment	15 (88.2)	2 (11.8)	0.153	NS
SVR	6 (60.0)	4 (40.0)		
Down staging				
No	9 (75.0)	3 (25.0)	1.000	NS
Yes	15 (83.3)	3 (16.7)		
HCC status				
Viable	7 (63.6)	4 (36.4)	0.187	NS
Necrosed	14 (87.5)	2 (12.5)		

HCC, hepatocellular carcinoma.

Table 8 Statistical analysis of preoperative and postoperative serum level of alphafeto protein in patients with and without posttransplant hepatocellular carcinoma recurrence

Whole sample	No post-LTx HCC recurrence		Post-LTx HCC recurrence		Mann–Whitney test		
	Median	IQR	Median	IQR	*Z*	*P* value	Significance
Preoperative serum alphafeto protein	10.00	4.1–33.7	59.00	30.5–129.5	–2.727	0.006	S
Postoperative serum alphafeto protein	2.47	1.6–4	247.30	17.75–3950.5	–4.225	.0.000	S

HCC, hepatocellular carcinoma; IQR, interquartile range.

preoperatively (*n*=28) was less than the total number of nonresponders (*n*=38), this would favor preoperative viral treatment for patients with HCC before being listed for transplant unless they are indicated for short target time transplant.

Another individual factor was the tumor cellular viability, which did not show up as a significant contributor in the HCC recurrence process, and this has been demonstrated in the results where all of the patients (100%) who had viable tumor cells did not have recurrence, whereas 90.5% (*n*=19) did not have recurrence with necrosed tumor cells (*P*=0.233).

Preoperative assumption of malignant portal vein thrombosis based on radiological finding was found in three patients in the whole study, which was found on the explant pathology as benign. However, two of these patients developed a posttransplant HCC recurrence, which should raise the importance of better assessment of preoperative assumed malignant portal vein thrombus.

Nowadays, additional preoperative tumor parameters can help to refine the graft allocation process and help predict the posttransplant tumor recurrence. One of these parameters is the serum level of alphafetoprotein, which was found in our study to be a significant preoperative predictor of post-HCC recurrence when compared with patients with and without posttransplant recurrence, with *P* value of 0.006. The postoperative serial serum alphafetoprotein was also found as a statistically significant detector of HCC recurrence when compared with patients with and without HCC recurrence in posttransplant settings.

There remains one more question: does down-staging therapy have a significant effect on the HCC recurrence rate? Downstaging therapy was used to regain patient eligibility to Milan criteria in patients belonging to beyond Milan group. The results showed that 80% (*n*=12) of those who received downstaging therapy did not have recurrence; in other words, we can state that only 25% (*n*=3) of those who did not receive down-staging were reported to have posttransplant HCC recurrence (Table 6). This supports the idea of transplanting the patient directly within the University of California San Francisco or 'up to seven' criteria without an urgent need to downstaging if the patient is ready for transplant or needs to be transplanted readily.

In 2011, a retrospective review was performed of prospectively collected data. Between 1998 and 2009, 56 of 356 OLTs were performed in patients with HCC. Based on pathological examination of liver explants, patients were retrospectively categorized into three groups: Milan+ (*n*=34), Milan–/UCSF+ (*n*=7), and UCSF– (*n*=14). Recurrence rates were 5.8, 14.3, and 40% in the Milan+, Milan–/UCSF+, and UCSF– groups, respectively. When OS rates were calculated

according to the criteria used, the 1-, 3-, and 5-year OS rates for the Milan+ group were 91.2, 87.7, and 87.7%, respectively. The rates of disease-free survival at 1, 3, and 5 years after Orthotopic Liver Transplant (OLT) were 91.2, 87.7, and 87.7%, respectively. Therefore, the results given come in line with our study results, which suggest comparable long-term survival and recurrence-free rates for Milan criteria and beyond Milan criteria [8].

The United Network of Organ Sharing (UNOS) database was searched for patients who had undergone OLT for HCC from 2002 to 2007, and 1972 patients (Milan criteria, *n*=1913, and UCSF criteria, *n*=59) were identified. Patients were stratified by pretransplant criteria (Milan vs. UCSF), and clinical and pathologic factors and overall survival were compared. There were no differences in age, sex, diabetes mellitus, BMI, and hepatitis B or C status between the two groups. Overall survival was similar between the Milan and UCSF cohorts (1-, 2-, 3-, and 4-year survival rates: 88, 81, 76, and 72% vs. 91, 80, 68, and 51%, respectively, *P*=0.21). Although the number of patients within UCSF criteria was small, the results nevertheless suggest that patients with HCC may have equivalent survival when transplanted under Milan and UCSF criteria. This supports the outcome of our study of comparable survival rates between the two groups [9].

In the University of Sao Paulo in Brazil, a systematic review and meta-analysis was performed, in which scientific articles from five databases (PubMed, Lilacs, Embase, Central, and Cinahl) were analyzed. The studies included in the review consisted of liver transplantation in patients with HCC in different subgroups according to donor type (deceased or living), population (eastern or western), tumor evaluation (radiological or pathological), and adopted the Milan or UCSF criteria for the indication of the procedure. There was no significant difference between the Milan and UCSF criteria in the overall survival rates at 1, 3, and 5 years, and the overall estimated values were found to be 1.03 (0.90, 1.17) at 1 year, 1.06 (0.96, 1.16) at 3 years, and 1.04 (0.96, 1.12) at 5 years. Regarding the analysis of the data, no significant difference was observed in any of the subgroups with a follow-up of 1, 3, or 5 years [4].

Compared with the Milan criteria, Valencia, the university of California San Francisco, University Clinic of Navarra, and Hangzhou criteria provided an expansion of 12.4, 16.3, 19.6, and 51.5%, respectively, in a review for 6012 patients of HCC from the China Liver Transplant Registry. There was an excellent efficiency in recurrence prediction for the expanded criteria compared with the Milan criteria in patients exceeding Milan but fulfilling the Hangzhou criteria (*N*=1352), which support the idea of safe and effective expansion of the Milan criteria [10].

Over a 5-year period, the UCSF criteria were used as selection guidelines for OLT in 168 patients in California university hospitals, San Francisco, including 38 patients exceeding Milan but meeting UCSF criteria (T3A). The 1- and 5-year recurrence-free rates were 95.9 and 90.9%, and the respective survival rates without recurrence were 92.1 and 80.7%. Patients with preoperative T1/T2 HCC had 1- and 5-year recurrence-free rates of 95.7 and 90.1%, respectively, versus 96.9 and 93.6%, respectively, for preoperative T3A stage (*P*=0.58). Under-staging was observed in 20% of T2 and 29% of T3A HCC (*P*=0.26). When explant tumor exceeded UCSF criteria (15%), the 1- and 5-year recurrence-free rates were 80.4 and 59.5%, versus 98.6 and 96.7%, respectively, for those within UCSF criteria (*P*<0.0001). This shows the ability of the UCSF criteria to discriminate prognosis after OLT and to serve as selection criteria for OLT, with a similar risk of tumor recurrence and under-staging when compared with the Milan criteria [11].

Conclusion

Milan criteria is a safe method for selecting HCC patients for liver transplant but expanding the selection criteria beyond it to be within USCF or even within 'up to seven' criteria has yielded a wider scope for including patients who could benefit from liver donor liver transplant.

Furthermore, efficient downstaging therapy has rendered the UCSF criteria and the 'up to seven' criteria more usable than before for including patients with HCC for the transplant service, but even if patients have to be transplanted directly on criterion beyond Milan, it would be feasible as they have been proven to have tumor recurrence rate, survival time, and tumor-free survival time comparable to the Milan criteria. Hence, these criteria provide the curative benefit of liver transplant for a wider scope of patients with HCC.

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Conflicts of interest

There are no conflicts of interest.

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