Comparative Analysis of Hepatocellular Carcinoma Recurrence Rate in Living Donor Liver Transplant Patients: Milan Versus Up-To-Seven Criteria

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ABSTRACT

Background: Primary liver cancer is the most prevalent malignancies. Hepatocellular carcinoma (HCC) constitutes its predominant subtype. Various therapeutic modalities exist for HCC (surgical resection, radiofrequency ablation, transarterial chemoembolization, radioembolization, and liver transplantation (LT)). LT is one of the first-line treatment modalities, with the Milan criteria being accepted as the standard for transplantation. There is concern that the Milan criteria may be restrictive concerning tumor size.

Objective: This study aimed to assess recurrence rates of HCC after living donor liver transplantation (LDLT) among cases within Milan criteria or up-to-seven criteria to explore the potential for broadening the criteria without elevating recurrence rates. **Methods:** This retrospective comparative study was conducted at the Liver Transplantation Unit, Wadi El-Neel Hospital. The study involved 100 cases who underwent LDLT for HCC, based on either Milan criteria or up-to-seven criteria. The cohorts were divided into two groups: Group I (50 cases within Milan criteria) and group II (50 cases within up-to-seven criteria). All cases were subjected to post-operative monitoring for detection of recurrence.

Results: There was no significant difference in recurrence rates between cases within Milan criteria and up-to-seven criteria. The mean recurrence rate was 6% in Milan group compared to 14% in up-to-seven group.

Conclusion: The up-to-seven criteria are now more useful than before for including HCC cases in LT because they have tumor recurrence rates comparable to Milan criteria. Therefore, they provide a wider range of HCC cases to benefit from LT.

Keywords: Hepatocellular carcinoma, up-to-seven criteria, Milan criteria, HCC recurrence.

INTRODUCTION

Primary liver cancer continues to represent one of the most frequently diagnosed malignancies on a global scale, with significant implications for public health. Among the various histological subtypes, hepatocellular carcinoma (HCC) stands as the predominant form, accounting for approximately 75% of all diagnosed primary liver cancer cases. Management strategies for HCC have evolved significantly over recent decades, with liver transplantation (LT) and surgical resection now considered the principal curative options for selected patients [(1)]. The Milan criteria have been widely authorized and internationally adopted as a standard framework for selecting candidates with HCC for LT. These criteria are defined by the presence of a single tumor measuring ≤ 5 cm or up to three tumors, each with a maximum diameter of ≤ 3 cm, and no evidence of vascular invasion on imaging studies. Adherence to the Milan criteria has been shown to yield favorable post-transplantation survival outcomes, thereby establishing its central role in transplantation protocols. However, despite its success, concerns have been raised within the transplantation community that the Milan criteria may be restrictive, particularly in terms of tumor size limitations, potentially excluding a subset of patients who might otherwise benefit from LT [(2)].

Following the establishment of Milan criteria, numerous studies have thought to expand the selection parameters beyond the original limits of tumor number and size, without negatively impacting patient survival. Among the most commonly adopted expanded criteria are the up-to-seven criteria, which are defined by the sum of the size (in centimeters) of the largest tumor and the number of tumors equaling seven or less [(3)].

Despite precise patient selection for LT, based on established criteria such as Milan or up-to-seven, the risk of HCC recurrence post-transplantation remains a significant clinical challenge. Recurrence is associated with markedly poorer prognosis and reduced overall survival. Surveillance for post-transplant tumor recurrence involves a multimodal strategy, including the use of imaging modalities such as contrast-enhanced CT or MRI, serial monitoring of serum alpha fetoprotein levels, and histopathological confirmation via biopsy when non-invasive methods are inconclusive [(4)].

PATIENTS AND METHODS

This comparative retrospective study was carried out at the LT Unit of Wadi El-Neel Hospital with the primary objective of detecting HCC recurrence within five years following transplantation. The study involved a cohort of 100 cases who underwent LDLT according to either the Milan criteria or the up-to-seven criteria from 2002 to 2017.

Ethical approval:

Prior to data collection, the study protocol was presented to the Research Ethics Committee of the Faculty of Medicine, Helwan University, and ethical

Received: 02/01/2025
Accepted: 04/03/2025

approval was obtained. Additionally, approval was obtained from Wadi El-Neel Hospital LT Unit to retrospectively collect and analyze the data from their transplantation database.

Inclusion criteria: All adult cases aged 18 years or older who underwent LDLT for HCC and met either the Milan or up-to-seven criteria.

Exclusion criteria: Cases with extrahepatic tumors, presence of macrovascular invasion, individuals suffering from active, uncontrolled infection or sepsis post-transplantation, as well as those who were transplanted outside the boundaries defined by the Milan or up-to-seven criteria.

Grouping: The enrolled cases were categorized into two groups based on the transplantation criteria applied at the time of surgery. Group I included cases with HCC who underwent LDLT according to the Milan criteria, with a total of 50 cases. Group II included cases with HCC who underwent LDLT within the framework of the up-to-seven criteria and also included 50 cases.

HCC recurrence post transplantation was detected in accordance with the 2024 guidelines issued by the American Association for the Study of Liver Diseases (AASLD). A rigorous, multi-step diagnostic approach was employed to ensure the accurate identification of tumor recurrence. This included non-invasive imaging modalities such as contrast-enhanced CT and MRI, focusing on specific radiological features including tumor size, arterial phase hyperenhancement, delayed phase washout, and the capsule appearance. In addition to imaging findings, biomarker evaluation was conducted. However, serum AFP measurement alone was deemed insufficient for a definitive diagnosis of recurrence. In cases where imaging and biomarker data were inconclusive, pathological confirmation through biopsy was pursued. Biopsy not only served to confirm the recurrence but also provided valuable molecular and immunological information about the recurrent tumor, aiding in further therapeutic decision-making.

Follow up detection of recurrence: Post transplantation, all cases were enrolled in a structured follow-up program in the outpatient clinic to monitor their post-transplantation course and detect any early signs of recurrence. In the first six weeks post-LT, cases attended weekly. From six weeks to three months post-transplantation, follow-up appointments were scheduled every two weeks. Subsequently, cases were reviewed every four to six weeks for the next three to six months, then every two months from six months to one-year post-Liver Transplantation. Beyond the first year, follow-up intervals were extended to every three to six months depending on the clinical stability of each patient.

During each follow-up visit, cases underwent comprehensive clinical evaluation and laboratory investigations including CBC with differential count, a full hepatic function panel, serum magnesium levels, GGT, PT, PTT, AFP levels, and immunosuppressant drug level monitoring. Monthly AFP testing was mandated for all cases. Radiological surveillance included Triphasic CT scans, performed every three to six months or earlier if AFP levels increased by more than 15 ng/ml per month. In situations where AFP levels were rising but Triphasic CT findings remained normal, PET CT was ordered to explore the possibility of occult recurrence.

Sample size: All cases underwent living donor LT for HCC from year 2002 till 2017 fulfilling the inclusion and exclusion criteria were recruited in the study with minimum 50 cases for each group.

Cases were monitored for five years following the date of transplantation, ensuring that even those transplanted in 2017 had completed the five-year observation period by the expected date of the study in 2022.

Sample type: A convenient sampling method was employed, based on the availability of complete clinical and follow-up data and the natural flow of cases within the specified timeframe (2002–2017).

Statistical analysis

Data were entered into a computer and analyzed using IBM SPSS Statistics software, version 20.0 (Armonk, NY: IBM Corp). All collected data were subjected to comprehensive statistical analysis to ensure the reliability and accuracy of the study results. Qualitative variables were summarized using frequencies and percentages to describe the distribution of categorical data across the different study groups. The normality of distribution for quantitative variables was assessed by applying both the Kolmogorov-Smirnov and Shapiro-Wilk tests. These tests were used to determine whether the continuous data followed a normal distribution, which in turn dictated the choice of statistical tests applied for comparisons between groups. Quantitative data were expressed as mean and standard deviation (SD) for normally distributed variables, ensuring appropriate and consistent data presentation. The tests used were Chi-square test for categorical variables, to compare between different groups. Fisher's Exact for correction for chi-square when more than 20% of the cells have expected count less than 5. Student t-test, for normally distributed quantitative variables, to compare between two studied groups. Mann Whitney test for abnormally distributed quantitative variables, to compare between two studied groups. A two-tailed P value ≤ 0.05 was considered statistically significant.

RESULTS

There was significant difference between the two study groups regarding BMI. There was no significant difference between the two study groups regarding age, sex, weight and blood group. The mean BMI of the Milan group was 26.78 kg/m^2 and of up-to-seven group was 28.05 kg/m^2 (Table 1).

Table (1): Comparison between Milan group and up-to-seven one regarding demographic data

Variables	Milan Criteria (N= 50)	Up-to-seven Criteria (N= 50)	P
Age (years)			
Mean (SD)	53.24 (7.66)	53.86 (6.57)	^{t}p=0.665
Sex N (%)			
Male	45 (90.0%)	49 (98.0%)	^{FE}p=0.204
Female	5 (10.0%)	1 (2.0%)	
Weight (kilograms)			
Mean (SD)	78.26 (11.84)	82.46 (12.45)	^{t}p=0.117
BMI (kg/m2)			
Mean (SD)	26.78 (3.09)	28.05 (3.36)	^{U}p=0.033*
Blood group N (%)			
A	19 (38.0%)	18 (36.0%)	^{FET}p=0.480
B	12 (24.0%)	13 (26.0%)	
AB	2 (4.0%)	6 (12.0%)	
O	17 (34.0%)	13 (26.0%)	

t: Student t-test, **U:** Mann Whitney test, **FET:** Fisher Exact test, **p:** p value for comparing between the studied groups, ***:** Statistically significant at $p \leq 0.05$

There was significant difference between the two study groups regarding tapping. There was no significant difference between the two study groups regarding comorbidity (diabetes mellitus and hypertension), ascites and spontaneous bacterial peritonitis. The percentage of Milan cases underwent tapping was 54% and of up-to-seven cases was 34% (Table 2).

Table (2): Comparison between Milan group and up-to-seven one regarding medical history

Variables	Milan Criteria (N= 50)	Up-to-seven Criteria (N= 50)	□□p value
Comorbidity			
DM N (%)	24 (48.0%)	21 (42.0%)	0.546
HTN N (%)	4 (8.0%)	7 (14.0%)	0.338
Ascites N (%)			
Yes	32 (64.0%)	29 (58.0%)	0.539
No	18 (36.0%)	21 (42.0%)	
Tapping N (%)			
Positive	27 (54.0%)	17 (34.0%)	0.044*
Negative	23 (46.0%)	33 (66.0%)	
SBP N (%)			
Positive	9 (18.0%)	8 (16.0%)	0.790
Negative	41 (82.0%)	42 (84.0%)	

□**2:** Chi square test**, p:** p value for comparing between the studied groups, ***:** Statistically significant at $p \leq 0.05$

There was no significant difference between the two study groups regarding Child score, MELD score, AFP and portal vein thrombosis (Table 3).

Table (3): Comparison between Milan group and up-to-seven one regarding clinical data

	Variables	Milan Criteria	Up-to-seven Criteria (N= 50)	P value
Child-Pugh score: N (%)	A	4 (8.0%)	7 (14.0%)	□□p=0.476
	B	24 (48.0%)	19 (38.0%)	
	C	22 (44.0%)	24 (48.0%)	
MELD score	Mean (SD)	16.48 (4.83)	15.74 (4.78)	^{U}p=0.338
AFP	Mean (SD)	117.15 (320.44)	205.40 (525.73)	^{U}p=0.767
Portal vein N (%)	Patent	46 (92.0%)	42 (84.0%)	□□p=0.218
	Thrombosed	4 (8.0%)	8 (16.0%)	

□**2:** Chi square test, **U:** Mann Whitney test, **p:** p value for comparing between the studied groups, ***:** Statistically significant at $p \leq 0.05$

There was significant difference between the two study groups regarding bridging and downstaging therapies. The percentage of Milan cases underwent bridging therapies was 52% and of up-to-seven criteria cases was 14%. The percentage of Milan cases underwent downstaging therapies was 0% and of up-to-seven cases was 50% (Table 4).

Table (4): Comparison between Milan group and up-to-seven one regarding bridging and downstaging

Variables	Milan Criteria N= 50	Up-to-seven Criteria N= 50	□□p value
Cases underwent bridging therapies N (%)	26 (52.0%)	7 (14.0%)	<0.001*
Cases underwent downstaging therapies N (%)	0 (0.0%)	25 (50.0%)	< 0.001*

□**2:** Chi square test, **p:** p value for comparing between the studied groups, ***:** Statistically significant at p ≤ 0.05

There was no significant difference between the two study groups regarding 5-year recurrence and survival. The percentage of 5-year recurrence rate in Milan patients was (6%) and in up-to-seven patients was (14%). The mean survival (months) of the Milan patients was (79.22) and of up-to-seven patients was (79.85).

Table (5): Comparison between Milan group and up-to-seven one regarding recurrence and survival

Variables	Milan Criteria N= 50	Up-to-seven Criteria N= 50	P value
5 year recurrence rate			
N (%)	3 (6.0%)	7 (14.0%)	□□P=0.182
Survival (months)			
Mean ± SD	79.22 ± 56.50	79.85 ± 38.27	UP=0.769

□**2:** Chi square test, **U:** Mann Whitney test**, p:** p value for comparing between the studied groups,
***:** Statistically significant at p ≤ 0.05

DISCUSSION

The potential for expanding transplantation criteria in cases with HCC holds significant clinical importance, particularly given the rising global incidence of the disease.

In the present study, 100 cases who underwent LT for HCC according to either Milan or the up-to-seven criteria were included. The cases were divided into two groups: The Milan group (50 cases) and the up-to-seven group (50 cases).

We compared both groups regarding demographic data, medical history, clinical data, bridging and downstaging and 5-year recurrence and survival.

We noticed that BMI was significantly higher in the up-to-seven group than in the Milan one, p value = 0.033. The mean BMI of the Milan group was 26.78 kg/m^2 and of the up-to-seven group was 28.05 kg/m^2. The two study groups were comparable with respect to age, sex, weight, and blood group. Similarly, **Di Martino *et al.*** [5] in their study evaluating the extension of LT criteria beyond the Milan criteria for HCC cases, also reported that gender and age were comparable between their groups.

We noticed that the number of Milan cases underwent tapping was significantly higher than up-to-seven cases (p value = 0.044). The two study groups were comparable regarding comorbidities (diabetes mellitus and hypertension), ascites, and spontaneous bacterial peritonitis. The percentage of Milan cases underwent tapping was 54% and of up-to-seven cases was 34%. The two study groups were comparable in terms of Child score, MELD score, AFP levels, and the presence of portal vein thrombosis. In agreement with our results, **Lei *et al.*** [6] conducted a study to evaluate whether the up-to-seven criteria should be adopted as an inclusion standard for LT in cases with HCC. They found that pre-transplantation liver function, assessed by MELD score and Child score, was comparable among the study groups, with no significant differences observed.

Di Martino *et al.* [5] conducted a study involving 54 cirrhotic cases with HCC who underwent LT based on the up-to-seven criteria as the upper limit for transplantation eligibility. Their outcomes were compared to those of a similar cohort of 47 cases transplanted according to the Milan criteria during the period from 2006 to 2012. The Child-Pugh and MELD scores were found to be comparable between the two groups. Similar to our observations, **Lei *et al.*** [6] reported in their study that there was no significant difference in the AFP level among the groups (P > 0.05).

We noticed that bridging therapies were significantly more elevated in Milan cases than in up-to-seven cases (p value = 0.001), while downstaging therapies were significantly more elevated in up-to-seven cases than in Milan cases (p value = 0.001). The percentage of Milan cases underwent bridging therapies was 52% and of up-to-seven cases was 14%. The percentage of Milan cases underwent downstaging therapies was 0% and of up-to-seven cases was 50%. **Di Martino *et al.*** [5] noted a recent rise in the number of

interventional procedures performed, reflected by a significantly higher proportion of bridged or down staged cases in the up-to-seven group.

In the present study, no significant difference was observed between the two groups regarding the five-year recurrence rate. Specifically, the five-year recurrence rate was 6% in the Milan group and 14% in the up-to-seven group.

Consistent with our findings, **Di Martino *et al.*** [5] also reported no significant difference in recurrence rates, with five-year HCC recurrence rate was 7.2% in the up-to-seven group and 8.5% in the Milan group. In agreement with our results, **Gugenheim *et al.*** [7] who aimed to detect recurrence after LT for HCC according to up-to-seven criteria. They found that cases within the Milan criteria had a lower recurrence rate (9.4%) compared to those within the Up-to-seven criteria (15.8%) (p value = 0.0290).

Nafady *et al.* [8] conducted a comparative retrospective cohort study and similarly found that HCC recurrence rates were higher in cases within the up-to-seven criteria or the University of California San Francisco criteria (22.2%) compared to those within the Milan criteria (4.7%) (p value = 0).

Also, **D'Amico *et al.*** [9] who investigated recurrence after LT in cases exceeding the up-to-seven criteria, reported recurrence rates of 14% for cases within the up-to-seven criteria and 11% for those within the Milan criteria. Another study by **Morgul *et al.*** [10] evaluated the potential for expanding transplantation limits beyond the Milan criteria and found that HCC recurrence rates were comparable between the up-to-seven group (4.7%) and the Milan group (5.4%).

RECOMMENDATION

There was no significant difference between Milan criteria and up-to-seven criteria regarding 5 year recurrence rate, so we recommend expanding the transplantation criteria in HCC cases.

CONCLUSION

Up-to-seven criteria are now more useful than they were previously for including cases with HCC in the transplantation service because it has been established that they have tumor recurrence rates comparable to the Milan criteria. Therefore, they provided a wider range of HCC cases who got benefit from the curative advantage of liver transplantation.

Financial support and sponsorship: Nil.
Conflict of Interest: Nil.

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