

Liver Transplantation in Hepatocellular Carcinoma: Experiences from the Shiraz Transplant Center

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ABSTRACT

Background: Studies evaluating liver transplantation (LT) in hepatocellular carcinoma (HCC) in the Middle East have been scarce, mainly due to intricacy of this type of surgery.

Objective: In here we report our experiences with LT among patients with HCC cirrhosis.

Methods: All patients who underwent LT with primary diagnosis of HCC older than 18 years old, during 2004 to 2019, were initially included in our study.

Results: Overall, 124 patients entered our study, among which majority were males (86.3%). Mean (SD) age of patients was 53.1±10.6 years old. Most common underlying liver diseases were HBV (55.6%) and HCV infections (12.1%). Mean MELD score of patients was 18±5.5. Child-puge score of most patients was class B (50%). Mean (SD) duration of hospitalization was 12.1±3.5 days. Patients were followed for a median of 32 (9, 62) months. The most common causes of death were recurrence of HCC (47.7%) and sepsis (34.1%). Median (IQR) duration to recurrence and death were 18 (4, 34) months and 17.5 (5.7, 44.5) months, respectively. One-year survival (89%, 86.4%, and 63.2%, respectively) ($p=0.011$) and one year DFS (89%, 86.4%, and 57.9%, respectively) ($p=0.001$) was significant different between those who were selected based on the Milan, UCSF and extended criteria

Conclusion: Our study provides valuable experiences on LT and HCC from one of the largest LT center in the world. Accordingly, we found that the Milan criterion provides the best survival compared to the UCSF and our extended criteria for patient selection.

KEYWORDS: Liver transplantation; Hepatocellular carcinoma; Survival; Middle East; Iran

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common type of liver malignancy which accounts for 90% of all primary liver cancers [1]. The incidence of HCC has been rising over the past 20 years

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worldwide [2] and represents the third leading cause of death due to cancers worldwide [3].

Approximately 75% to 80% of all HCCs are associated with chronic viral infections including hepatitis B virus (HBV) and hepatitis C virus (HCV) [4] which eventually lead to cirrhosis. Alcohol induced injuries and genetic disorders such as hemochromatosis are other causes of HCC [5].

After the first liver transplantation (LT) was

performed for a patient with HCC in the nineteen-sixties [6], it has now become the modality of choice for the treatment of most end-stage liver diseases including HCC. By LT the underlying liver cirrhosis, HCC tumor and tumor margins are excised and liver function is restored [7]. In Europe, liver cancers are among the main indications for LT and their incidence has doubled in recent years; from 12% prior to 1997 to more than 24% [8].

Variable studies have reported on the outcomes of LT among patients with HCC in different regions of the world [9]. However, to date studies evaluating LT in HCC in the Middle East have been scarce and this is mainly due to the fact that only specialized centers are able to perform this type of surgery. In here we report our experiences with LT among patients with HCC cirrhosis.

MATERIALS AND METHODS

Study settings and design

This study was conducted in the Shiraz Transplant Center, Shiraz, Iran. The Shiraz Transplant Center is one of the largest transplantation centers in the world [10,11] in which about 600 liver transplantations are performed each year. The center is located in Abu Ali Sina Hospital, Shiraz Iran. To this date, data of 5000 plus patients with liver transplantations have been recorded in the center. For this study data were further extracted from Motahhari Clinic and the Faraparto Imaging Center, Shiraz, Iran.

For this study data of all patients who underwent LT with primary diagnosis of HCC according to imaging or histopathological evaluation, who were older than 18 years old, and had a liver transplantation from a deceased donor during 2004 to 2019, were initially included in our study. Any individual who had extrahepatic involvement of HCC, did not have cirrhosis, pediatric patients, and those who had salvage LT were excluded from the study.

In total, 253 patients entered the study, among which 22 cases were pediatric patients, 4 cases were salvage surgeries, 11 cases did not show

cirrhosis in their pathology reports, 22 cases had normal liver function and were not resectable due to the location of the tumor, 34 cases did not show HCC in their final pathology report and included other types of tumors, and 36 cases had regenerative tumors and were excluded from our current report.

Primarily each patient was diagnosed based on spiral CT scans, MRI of the liver and clinical symptoms, after which definite diagnosis of HCC was based on postoperative pathological evaluation of explanted tumor.

Decision for LT for each patient was based on a multidisciplinary decision and was done according to the Milan criteria [12], university of California San Francisco (UCSF) criteria [13] or an extended criterion. Accordingly, patients were classified into three groups: those who met the Milan criteria, which included 87 patients (63%); those who were outside the Milan criteria but met the UCSF criteria, which included 23 patients (16.7%); and those who were outside the Milan and UCSF criteria (extended criteria), which included 28 patients (20.3%).

Generally, from 2014 onward, in cases where a patient was expected to be on the transplantation waiting list for more than 3 months, they were referred for locoregional therapy which included either transarterial chemoembolization (TACE) or radiofrequency ablation (RFA). Data on baseline characteristics (age and sex), underlying liver disease, social characteristics including use of cigarettes, use of waterpipe, family history of cancers, duration between surgery and diagnosis of HCC, lab data including preoperative alpha-feto protein (AFP) and CA19-9, MELD score and Child-Pugh scores prior to surgery, pathology data including histopathological grade of tumor, capsular invasion, microvascular invasion and extrahepatic invasion were recorded. Specific surgery-related data such as type of graft (living or deceased donor grafts), type of hepatectomy technique (standard or Piggyback), type of biliary anastomosis, cold ischemic time and warm ischemic time were registered for each patient.

Table 1: Baseline and clinical characteristics of patients with HCC that underwent liver transplantation.*

Variables		Statistics
Age - yrs		53.1 ± 10.6
Sex - no. (%)	Male	107 (86.3)
	Female	17 (13.7)
Cause of liver failure - no (%)	HCC alone	31 (25)
	HCC + HBV	69 (55.6)
	HCC + HCV	15 (12.1)
	HCC + other causes	10 (7.2)
Use of cigarette - no (%)	Yes	8 (6.5)
	No	116 (93.5)
Family history of cancer - no (%)	Yes	2 (1.6)
	No	120 (96.8)
Duration between diagnose of HCC to surgery - days		95.3 ± 35.2
Preoperative AFP level - ng/mL	Mean and SD	681.4 ± 2200.4
	Median and IQR	90 (15, 441)
AFP level - no (%)	<100	54 (50.5)
	100=500	30 (28)
	>500	23 (21.5)
Preoperative CA19-9 level - units/mL	Mean and SD	57.6 ± 77.3
	Median and IQR	21.0 (7.9, 100)
MELD score	Mean and SD	18.0 ± 5.5
MELD score - no (%)	<15	33 (26.6)
	15-29	87 (70.2)
	30-34	3 (2.4)
	≥35	1 (0.8)
Child-puge score - no (%)	A	40 (34.5)
	B	58 (50)
	C	18 (15.5)
Number of nodules - no (%)	1	100 (80.6)
	2	19 (15.3)
	3	3 (2.4)
	≥4	1 (0.8)
Size of largest nodule - cm	Mean and SD	5.0 ± 5.5
	Median and IQR	4 (3, 5.4)
Tumor size - cm	Mean and SD	4.0 ± 2.4
	Median and IQR	3.5 (2.5, 5)
Histology grade - no (%)	1	88 (74.6)
	2	23 (19.5)
	3	7 (5.9)
Capsular invasion - no (%)	Yes	8 (7.1)
	No	104 (92.9)
Microvascular invasion - no (%)	Yes	24 (19.4)
	No	90 (72.6)
Extrahepatic invasion - no (%)	Yes	3 (3.2)
	No	92 (96.8)
Duration of hospitalization - days		12.1 ± 3.5

HCC: hepatocellular carcinoma; HBV: hepatitis B virus; HCV: hepatitis C virus; AFP: alpha-feto protein; SD: standard deviation; IQR: interquartile range; MELD: model for end stage liver disease

*All plus-minus values are means and standard deviations unless stated otherwise.

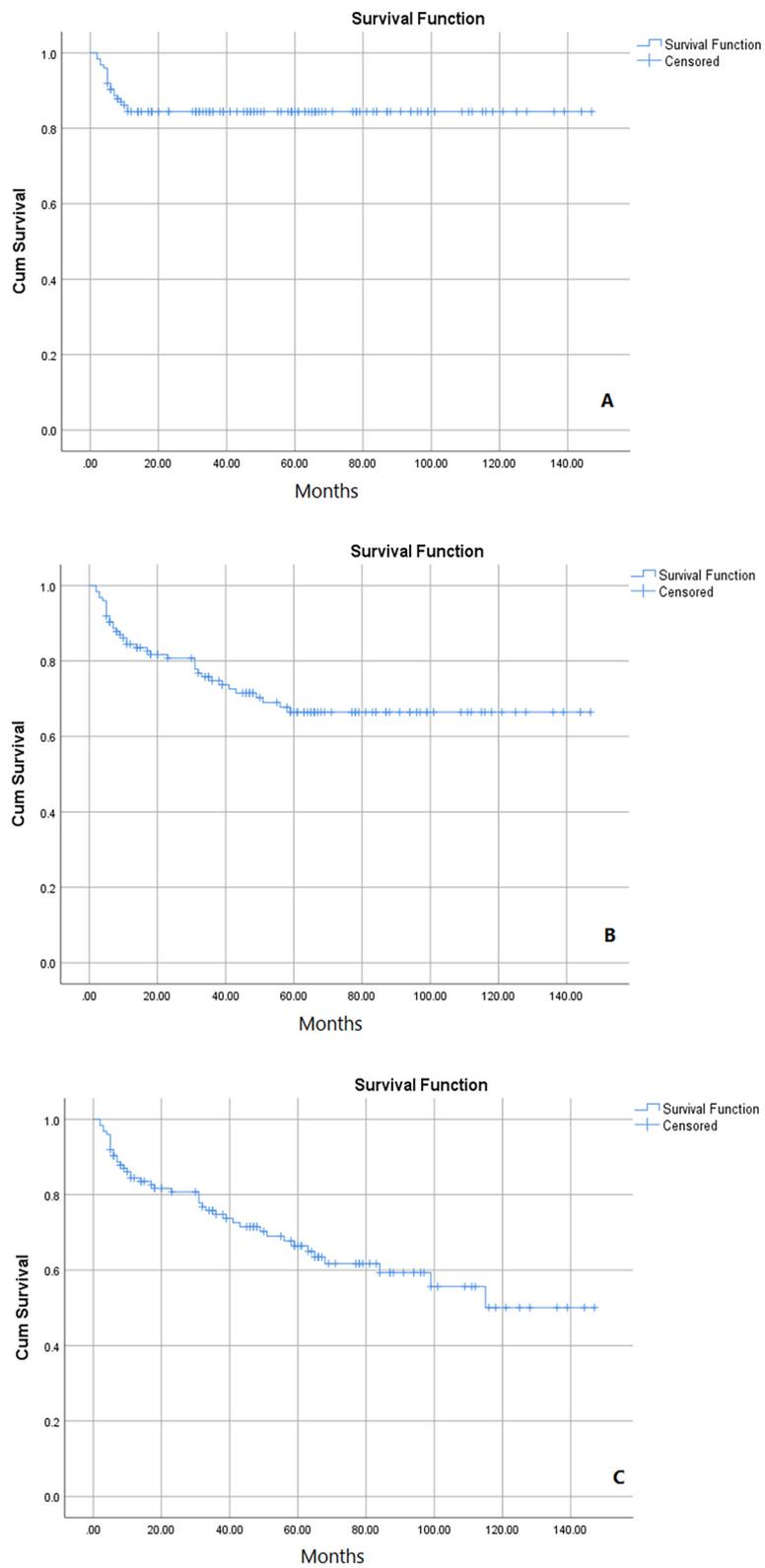


Figure 1: Survival plots of patients with HCC that underwent liver transplantation. (A) shows one-year survival, (B) shows five-year survival, and (C) shows ten-year survival.

Table 2: Treatment related characteristics and prognosis of patients with HCC that underwent liver transplantation.

Variables		Statistics
Patient selection criteria - no. (%)	Milan	82 (66.7)
	UCSF	22 (17.9)
	Extended	19 (15.4)
Locoregional therapy - no (%)	TACE	54 (43.5)
	RFA	19 (15.3)
	Both	2 (1.6)
	None	12.1 ± 3.5
Duration of hospitalization - days	Mean and SD	29 (23.4)
	Median and IQR	12 (10, 13.25)
Type of graft - no (%)	Diseased donor	124 (100)
Hepatectomy surgical technique - no (%)	Piggyback	76 (61.3)
	Standard	42 (33.9)
Biliary anastomosis - no (%)	Duct to duct	116 (93.5)
	Reux-en-Y	6 (4.8)
Cold ischemic time - hours		7.3 ± 2.7
Warm ischemic time - minutes		43.4 ± 8.5
Duration of follow-up - months	Mean and SD	41.0 ± 37.2
	Median and IQR	32.0 (9, 62)
Cause of death - no (%)	Recurrence of cancer	21 (47.7)
	Sepsis	15 (34.1)
	Other causes	6 (13.6)
	Unknown	2 (4.5)
Duration to recurrence - months	Mean and SD	26.5 ± 28.4
	Median and IQR	18 (4, 34)
Duration to death - months	Mean and SD	28.8 ± 28.3
	Median and IQR	17.5 (5.7, 44.5)
One-year survival - no (%)	Yes	105 (84.7)
	No	19 (15.3)
Five-year survival - no (%)	Yes	88 (71.0)
	No	36 (29.0)
Ten-year survival - no (%)	Yes	82 (66.1)
	No	42 (33.9)
One-year recurrence - no (%)	Yes	7 (5.6)
	No	117 (94.4)
Five-year recurrence - no (%)	Yes	15 (12.1)
	No	109 (87.9)
Ten-year recurrence - no (%)	Yes	18 (14.5)
	No	106 (85.5)
One-year disease free survival - no (%)	Yes	104 (83.9)
	No	20 (16.1)
Five-year disease free survival - no (%)	Yes	85 (68.5)
	No	39 (31.5)
Ten-year disease free survival - no (%)	Yes	77 (62.1)
	No	47 (37.9)

HCC: hepatocellular carcinoma; TACE: transarterial chemoembolization; RFA: radiofrequency ablation; SD: standard deviation; IQR: inter-quartile range.

*All plus-minus values are means and standard deviations unless stated otherwise.

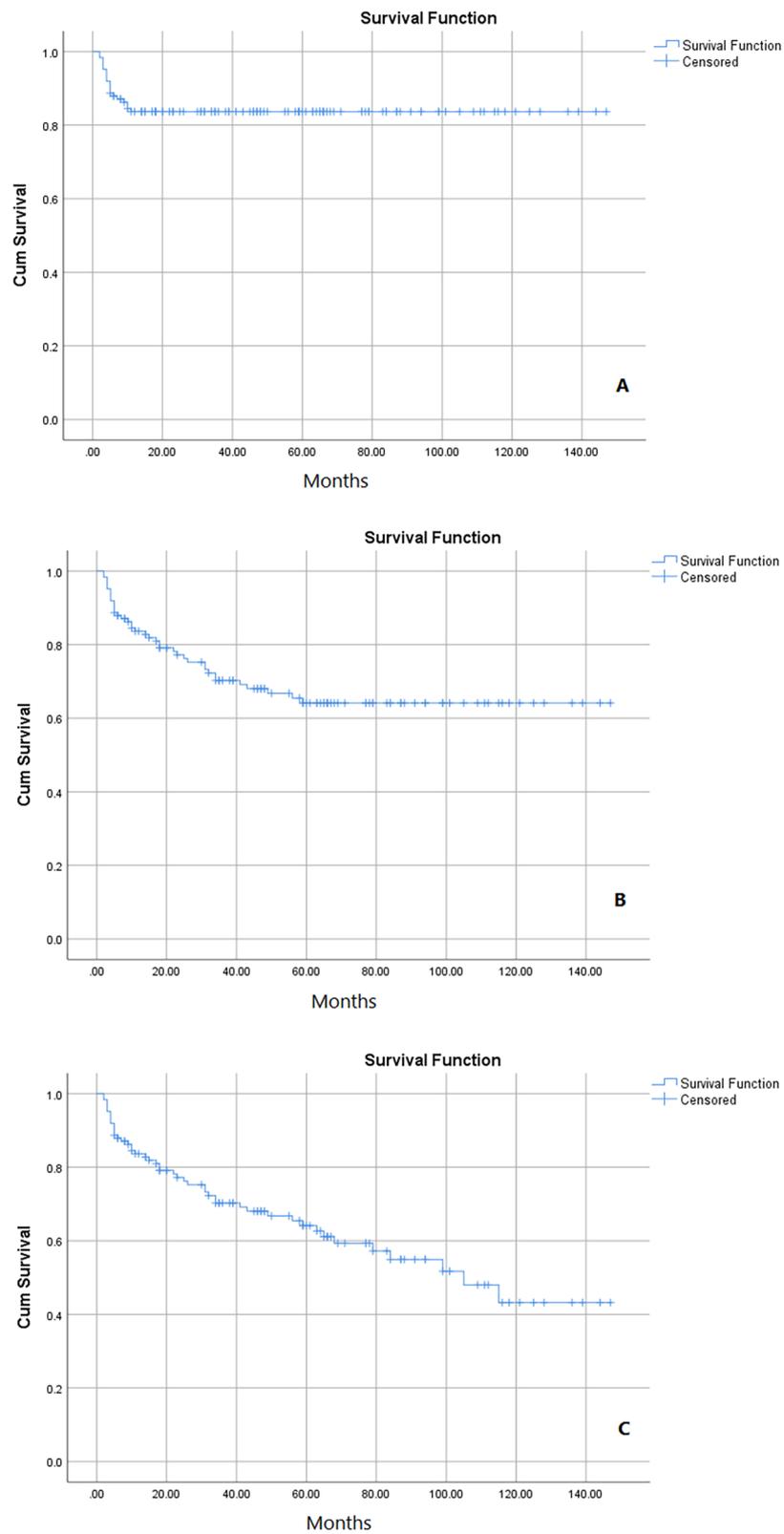


Figure 2: Disease-free survival plots of patients with HCC that underwent liver transplantation. (A) shows one-DFS survival, (B) shows five-year DFS, and (C) shows ten-year DFS.

Moreover, duration of hospitalization, cause of death, duration to death and recurrence were recorded for each patient. We should mention that in our institution after 2016, MELD-Na+ was used.

Follow-up

After liver transplantation patients were followed in a standard manner by a multidisciplinary transplantation team. Generally, up to three years after transplantation each three months a liver CT scan is requested and AFP is checked for each patient. If any patient develops symptoms including pulmonary and/or neurological symptoms and musculoskeletal pain or a rise in AFP is seen, imaging studies including CT scan, MRI, bone scans are done and if needed a biopsy is taken from that patient. After this period, patients are followed similar to other patients who undergo LT.

Ethical consideration

The study protocol was approved by the Institutional Review Board of Shiraz University of Medical Sciences. No patient personal data were released to the public and secrecy of data was maintained throughout the study.

Statistical Analysis

Data was analyzed using the statistical package for social sciences software (SPSS Inc., Chicago, Illinois, USA), for windows, version 26. Survival and disease free survival (DFS) were analyzed using the Kaplan-Meier function. The Log Rank test was used to compare survival between groups.

DFS was considered from time of treatment to event which was either death or recurrence. Quantitative variables with normal distribution are reported as means and standard deviations (SD) and those without a normal distribution are reported as medians and interquartile range (IQR). Qualitative variables are reported as frequency and percentage. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 124 patients with HCC who underwent LT entered our study, among which majority were males (86.3%). Mean (SD) age of patients was 53.1 ± 10.6 years old. Most common underlying liver diseases were hepatitis B virus (HBV) (55.6%) and hepatitis C virus (HCV) infections (12.1%). Regarding social characteristics, overall, 6.5% of patients used cigarettes. Mean duration between diagnosis of HCC and transplantation was 95.3 ± 35.2 days. Baseline and clinical characteristics of patients have been reported in Table 1.

Regarding clinical characteristics, mean MELD score of patients was 18 ± 5.5 . Majority of patients had a MELD score of between 15 and 29 (70.2%) and <15 (26.6%). Child-pugh score of most patients was class B (50%). With regard to tumor characteristics, median (IQR) tumor size was 3.5 cm (2.5, 5) and the median (IQR) largest detected nodule in CT scan imaging was 4cm (3, 5.4). Majority of patients had grade one tumors (74.6%) in histopathological evaluations. Almost one fifth (19.4%) of tumors were associated with microvascular invasion.

With regard to treatment specifics, TACE alone was the most common locoregional therapy used (43.5%) followed by percutaneous RFA alone (15.3). Mean (SD) duration of hospitalization was 12.1 ± 3.5 days, moreover all transplantations were done using diseased donor grafts. Mean warm ischemic time and cold ischemic time were 43.4 ± 8.5 minutes and 7.3 ± 2.7 hours, respectively.

Patients were followed for a median of 32 (9, 62) months. The most common causes of death in this population were recurrence of HCC (47.7%) followed by sepsis (34.1%). Median (IQR) duration to recurrence and death were 18 (4, 34) months and 17.5 (5.7, 44.5) months, respectively. The one-year, five-year and ten-year survival in our series was 84.7%, 71% and 66.1%, respectively (Fig 1). The one-year, five-year and ten-year recurrence rate in our series was 5.6%, 12.1% and 14.5%, respectively.

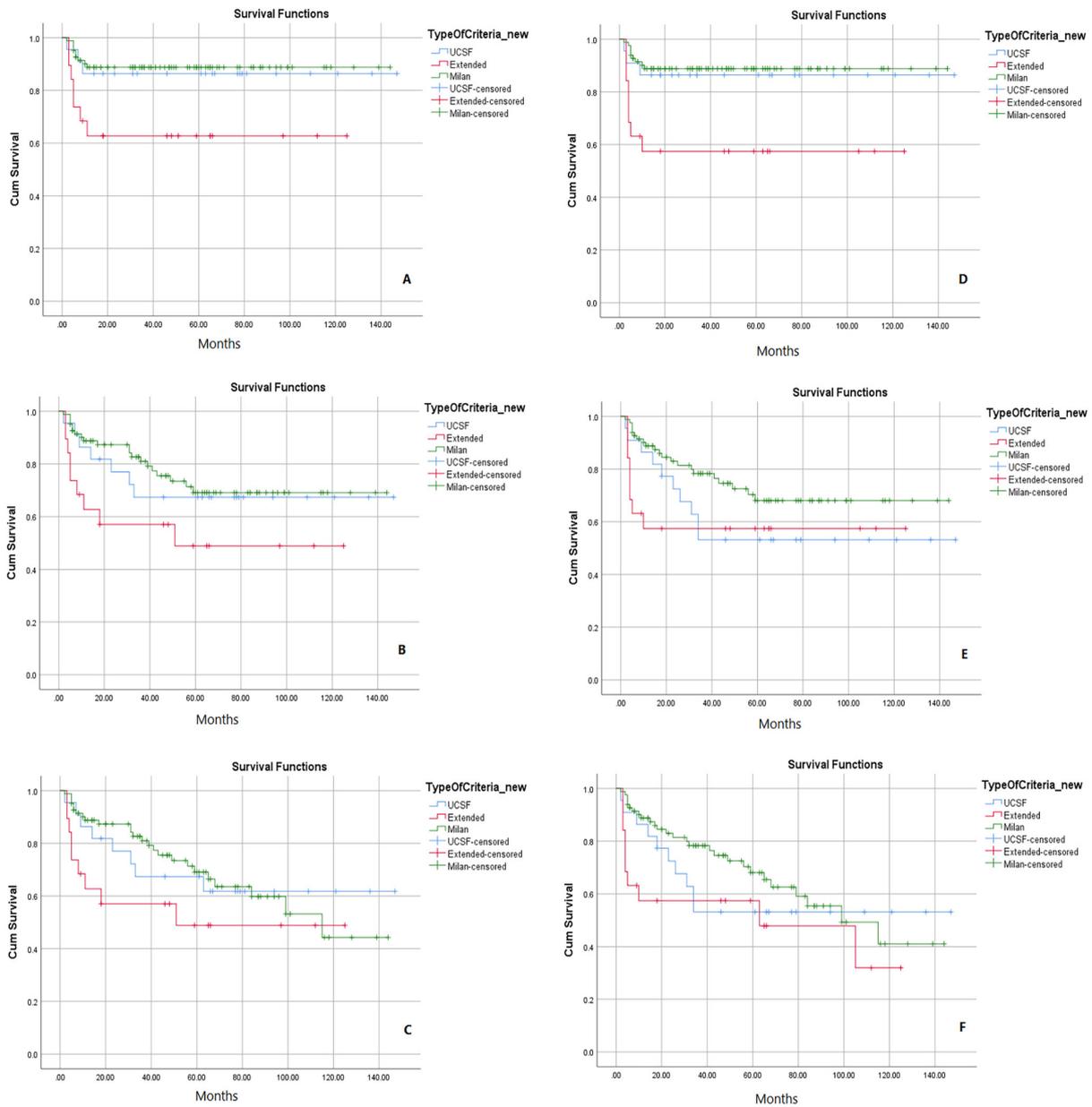


Figure 3: This figure shows survival and DFS of patients with HCC that underwent liver transplantation according to different patient selection criteria as Milan, UCSF and an extended criteria. (A, B, and C) show one-year survival, five-year survival, and ten-year survival, respectively and (D, E, and F) one-year DFS, five-year DFS, and ten-year survival, respectively.

One-year, five-year and ten-year DFS was 83.9%, 68.5% and 62.1%, respectively (Table 2) (Fig 2).

We further compared the Milan criteria, the UCSF, and the extended criteria with regard to survival. The one-year survival (89%, 86.4%, and 63.2%, respectively) was significant different between those who were selected based

on the Milan, UCSF and extended criteria, respectively according to the Logrank test ($p = 0.011$), however with regard to five-year (75.6%, 68.2%, and 52.6, respectively) and ten year survival (69.5%, 63.6% and 52.6%, respectively) the three groups were not significantly different (Fig 3).

One-year DFS was also higher among those

selected according to the Milan criteria (89%) and the UCSF criteria (86.4%) compared to those selected according to the extended criteria (57.9%) ($p=0.001$) (Fig 3). Five year (74.4%, 54.5%, and 57.9%) and ten year DFS (67.1%, 54.5%, and 47.4%) was not significantly different between patients selected based on the Milan, UCSF and extended criteria.

DISCUSSION

In here we reported our experiences with liver transplantation among patients with HCC. To the best of the authors' knowledge this is among the largest series on HCC/cirrhosis and LT in the Middle East.

Reports on HCC and LT are variable with regard to patient selection and patient outcomes in literature. In one study during an 11-year period [14], Müller, *et al*, reported on a series of 43 patients diagnosed with HCC with cirrhosis from Germany. In this study similar to our experience, all their patients underwent deceased donor transplantations. Similarly, majority of their patients were males (85%) and the median age was 57.8 years old. In their report, the most common underlying diseases associated with HCC were hepatitis C (43.2%) and alcoholic hepatitis (27.9%). A total of 72% of their patients had bridging treatment using TACE and RFA (44.1% had TACE alone, 11.6% had RFA alone and 16.2% had both). During a median follow-up of 59 months (ranging from 0 to 138 months), they reported recurrence in 10.4% of patients (median time to recurrence was 20 months which was similar to that of our report). One-year survival in their series was 70.4%. Overall, we had higher recurrence rates among our patients (14.5% vs. 10.4%), although one year survival was better among our patients (84.7% vs. 70.4%).

In a large series of patients with HCC and LT from Turkey [15], authors reported their experiences with 165 cases. Mean age of their patients was 57.7 ± 7.3 years (ranging from 31 to 72 years old) and majority of their patients were males. In their series 84% of patient had living donor transplantations. With regard

to transplantation specifics, patients' mean MELD score was 12.3 ± 4.8 and AFP levels was 271.8ng/ml at time of transplantation. In their report 37.5% of patients had lymphovascular invasion. They followed their patient for a mean of 27.8 ± 20 months (24% of their patients were lost to follow-up). In this series the recurrence rate was 14% and one-year, three-year and five-year survival was 85%, 71% and 64%, respectively. Their patient survival rates were very similar to that of our series (one-year survival of 84.7% vs. 84.2% and five-year survival of 64% vs. 71%), although we had higher mean AFP (271.8 vs. 681.4 ng/ml) and MELD score (12.3 vs. 18.0) prior to transplantations which may be showing a worse clinical condition at time of transplantation.

One of the most important factors for patient prognosis in the settings of LT for HCC remains to be patient selection. Since the introduction and implementation of the Milan criteria (single tumor ≤ 5 cm in size or maximum 3 tumors with diameter ≤ 3 cm, and no macrovascular invasion), survival rates of LT due to HCC have improved significantly (5 year overall survival of 70%) [16]. There are several reports evaluating LT in HCC patients beyond Milan criteria using different criteria and have reported acceptable survival and recurrence rates. These include the UCSF criteria (single tumor ≤ 6.5 cm or up to three tumors with the largest ≤ 4.5 cm), the "up to seven" criteria (sum of number of nodules and tumor maximum size without microvascular invasion), Toso criteria (AFP ≤ 400 ng/ml and tumor volume ≤ 115 cm³) and the Hangzhou University criteria (tumor diameter ≤ 8 cm or tumor diameter > 8 cm with histological grade one or two and AFP ≤ 400 ng/mL) [17].

In a recently published report Victor, *et al*, [18] reported on their experience with 220 patients who underwent LT for HCC during 2008 up to 2017 in the Houston Methodist Hospital, Texas, USA. Majority of their patients were males (72.3%) and median age of their patients was 61 years. Most common underlying disease was hepatitis C virus infection, and median MELD score was 13. The most common preoperative treatment used among

their patients was TACE (80.4%). They did not find any difference in one-year (92%, 100%, and 97%), three-year (87%, 88%, and 87%) and five-year survival (81%, 88% and 80%) between the those who were operated based on the Milan criteria, outside the Milan and inside the UCSF and those operated outside the UCSF criteria. This was unlike our results as we found that those who had been chosen for LT according to the extended criterion had the lowest survival compared to the Milan and UCSF criterion, furthermore in our report the Milan criterion resulted in higher survival compared to the UCSF criteria as well.

Beside the latter study, other reports have rendered similar results to that of our series including the study by Zheng, *et al*, [19], in which they studied LT for HCC among a total of 195 patients diagnosed with HCC. The overall 5-year tumor-free survival rate in their report was 34.6%. In patients within the Milan criteria, the 5-year tumor-free survival rate was 69.7%. These rates were much lower in patients who exceeded the Milan criteria in their report (10.6%).

One interesting point and difference between our series and that of other regions in the world, is that the most common underlying liver disease in our population is HBV, unlike other regions of the world in which HCV infections are predominant. This is perhaps due to the high rates of HBV infections among Iranians which eventually cause cirrhosis compared to other regions of the world.

Among the reasons why our overall survival rates were low could be attributed to the fact that 15.4% of our patients were operated outside both Milan and UCSF criteria. When categorized according to selection criteria, survival rate of this group of patients was much lower compared to those inside the Milan and UCSF criteria.

One of the main concerns with patients who undergo LT for HCC is recurrence of the cancer. Studies have reported variable recurrence rates and most recurrences occur during the first two years after transplantation [20]. As

in our report, despite our frequent postoperative screening schedule, the most common cause of death among patients was recurrence of primary HCC.

Considering that those who were operated using our extended criteria had much lower survival compared to the other groups, and further considering existing shortage in organs, this indicates that perhaps using living donor grafts in these specific patients is beneficial. This will further decrease the average waiting time and will provide other patients who have been chosen according to the Milan or UCSF criteria with better grafts for transplantations.

This study had some limitations. Our criteria for patient selection was different at different time intervals and we used three different criteria including the Milan criteria, the UCSF criteria and the extended criteria, although majority of patients were selected according to the Milan criteria in our study. Due to the nature of the disease, number of patients with HCC that underwent LT in our center, similar to other reports from the world, are limited.

Our study provides valuable experiences on LT and HCC from one of the largest LT center in the world. Accordingly, we found that the Milan criterion provides the best survival compared to the UCSF and our extended criteria for patient selection.

CONFLICTS OF INTEREST: None to be declare.

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