

Evaluation the Post-Transplant Survival in Hepatocellular Carcinoma Relative to the Cirrhosis and Alpha-Fetoprotein Levels in Patients with Liver Transplantation

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is the 4th leading cause of cancer-related deaths worldwide.

Objective: To assess the post-transplant survival factors in patients with hepatocellular carcinoma relative to the cirrhosis and alpha-fetoprotein levels in patients with liver transplantation in Abu-Ali Sina transplant hospital, Shiraz, 2010-2022.

Methods: In this retrospective study, demographic and clinical data affecting survival includes the underlying cause of cirrhosis and alpha-fetoprotein (AFP) levels were collected from all patients (n=207) who underwent transplantation with a definitive diagnosis of hepatocellular carcinoma. The 1, 2, 3, 4 and 5 years' survival rates and the median survival time were calculated. Kaplan-Meier method was used to determine the survival at different time intervals for determining the factors affecting survival.

Results: At the time of data collection, 145 (70%) patients were alive, 33 (15.9%) died from recurrence hepatocellular carcinoma and 29 (14%) had deaths from underlying diseases. 55.6% of patients who died from hepatic impairment had AFP less than 500 ng/dL and 8 patients (44.4%) had AFP more than 500 ng/dL and blood AFP level was significantly associated with mortality (P= 0.002). The prevalence of recurrence HCC death was also higher in people with AFP above 500 (29.6% vs. 9.17%). Survival in AFP <500 and AFP> 500 was almost the same until 40 months and after that survival time was significantly higher in individuals with AFP <500 (P= 0.076).

Conclusion: The present study showed that gender and the underlying causes of cirrhosis do not have a significant effect on determining the patient's survival rate and the only factor affecting was AFP which is a predictive and prognostic biomarker as a tumor antigen role in HCC.

KEYWORDS: Survival factors; Hepatocellular carcinoma; Cirrhosis; Alpha-fetoprotein; Liver transplantation

INTRODUCTION

Hepatocellular carcinoma (HCC) is a primary malignant liver tumor that typically develops in chronic liver

disease, especially in patients with cirrhosis or chronic infection with the hepatitis B virus (HBV). HCC is responsible for more than 90% of primary hepatic malignancies and considered as the 6th most commonly diagnosed malignant disease in the world [1] with about 841,000 new cases reported in 2018 [2, 3]. Liver transplantation (LT) is accepted to be the best curative option for HCC in patients with liver disease [4]. Selection of patients for

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Table 1: Demographic and clinical features of involved patients (n=207).

Variables	Number (%)
Sex	
Male	172 (83.1%)
Female	35 (16.9%)
AFP (ng/dL)	
<500	135 (83.3%)
>500	27 (16.7%)
Outcomes	
Alive	145 (70%)
HCC Recurrence	33 (15.9%)
Underlying causes	29 (14%)
Underlying causes of cirrhosis (overall)	
HBV	79 (49.4%)
HCV	16 (10.0%)
NASH	6 (1.0%)
Other	61 (38.1%)
Underlying causes of cirrhosis (stratified)	
Group A*	137 (66.2%)
Group B*	8 (3.9%)
Group C*	62 (30%)

AFP, alpha-fetoprotein; HBV, hepatitis-B virus; HCV, hepatitis-C virus; NASH, non-alcoholic steatohepatitis.

*Group A were the underlying causes leading to hepatitis such as HBV, HCV, alcoholic hepatitis, autoimmune hepatitis, and NASH.

*Group B consisted of biliary tract diseases (such as cholangiocarcinoma, PBC, PSC) or cryptogenic cirrhosis.

*Group C were metabolic diseases, tyrosinemia or HCC based on underlying causes other than diseases in group A or B.

LT adheres to the conventional Milan [5] and UCSF [6] criteria which yielded similar long-term outcomes. Dastyar et al., [7] study found that Milan criteria provides the best survival in comparing with UCSF for patient's selection. The incidence of HCC and the subsequent mortality rate are increasing in many parts of the world. In the United States, HCC mortality increased by 0.5% between 2014 and 2018 unlike other common solid organ tumors such as lung, breast, and prostate cancers in which mortality rates are declining. However, the increase rate of mortality seems to be slowing down compared to the previous period (i.e., 3.2% increase in mortality from 2009 to 2013) [8-10].

Alpha-fetoprotein (AFP) and other tumor

markers indicates the recognition's increase which tumor biology dictates long-term outcome [11-13]. In HCC patients, the main determinant of long-term outcome after LT is tumor recurrence that is still believed recurrence leads to early death in most cases. Therefore, the management of post-transplant HCC recurrence remains very challenging for survival [14-16].

Since Shiraz is known as one of the centers for liver transplantation in Iran and hundreds of transplants are performed annually in the Abu-Ali Sina transplant hospital, therefore, we examine the patients who have undergone transplantation and their survival rate following transplant surgery based on the underlying causes of cancer. This study can help to improve the quality of surgery and find solutions to increase patient's survival by determining the survival rate of patients and comparing with other global findings.

MATERIALS AND METHODS

Study Population

This retrospective, cross-sectional study was conducted in all patients admitted to Abu-Ali Sina teaching hospital for liver transplantation due to the HCC from 2010 till the end of 2022. Our primary goal was assessing the survival rate of these patients based on the underlying causes of liver cirrhosis and the serum level of AFP. We included all patients who were qualified for receiving a new liver according to Milan Criteria. The criteria stated patients with one tumor equal or less than 5 centimeters or up to 3 lesions, each greater less than or equal to 3 cm without extrahepatic and major abdominal involvements were best fitted for receiving a new liver [5]. Moreover, patients with uncompleted medical records were excluded from the study.

Study Design

Patients' demographic and clinical data such as age, sex, the underlying cause of liver cirrhosis, and the serum level of AFP were collected from the patients' medical records. Due to the considerable diversity regarding the un-

Table 2: Outcomes' stratifications according to sex, serum level of AFP, and underlying diseases.

Variables		Outcomes			P-Value	Overall (%)
		Alive (%)	Death by HCC Recurrence			
			liver-related	Non-liver related		
Sex	Male	125(86.2%)	27(81.8%)	20(69.0%)	0.076	172(83.1%)
	Female	20(13.8%)	6(18.2%)	9(31.0%)		35(16.9%)
AFP (ng/dL)	<500	100(90.1%)	10(55.6%)	20(71.4%)	0.002	135(83.3%)
	>500	11(9.9%)	8(44.4%)	8(28.6%)		27(16.7%)
Underlying conditions	Group A*	95(65.5%)	27(81.8%)	15(51.7%)	0.024	137(66.2%)
	Group B*	4(2.7%)	0(0.00%)	4(13.8%)		8(3.9%)
	Group C*	46(31.7%)	6(18.2%)	10(34.5%)		62(30%)

AFP, alpha-fetoprotein

*Group A were the underlying causes leading to hepatitis such as HBV, HCV, alcoholic hepatitis, autoimmune hepatitis, and NASH.

*Group B consisted of biliary tract diseases (such as cholangiocarcinoma, PBC, PSC) or cryptogenic cirrhosis.

*Group C were metabolic diseases, tyrosinemia or HCC based on underlying causes other than diseases in group A or B.

derlying causes of cirrhosis, we have classified the causes within the three-following group includes group A consisted of all situations resulting in hepatitis. These were hepatitis B virus (HBV), hepatitis C virus (HCV), alcoholic hepatitis, autoimmune hepatitis, and non-alcoholic fatty steatohepatitis (NASH). Patients in group B had suffered from biliary tract diseases such as cholangiocarcinoma, primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC) or cryptogenic cirrhosis. Finally, group C had metabolic diseases tyrosinemia or HCC based on underlying causes other than diseases in group A or B.

Outcomes

The outcome was death due to HCC. In this study, the survival status of patients until 2022 was followed and questioned using the telephone. If there were deficiencies in the patients' medical records in terms of demographic characteristics, it was completed in the same telephone call.

Ethical Considerations

This study was conducted in accordance with the declaration of Helsinki and approved by the Institutional Review Board and Ethics Committee of Shiraz University of Medical Sciences (ethic code: IR.SUMS.MED.REC.1399.275). The gathered data did not consist of each patient's identifiers.

Statistical Analysis

Data were collected in the Statistical Package for Social Sciences Software (SPSS. Inc., Chicago, Ill., USA) version 20. Quantitative variables were described using the mean and standard deviation (SD); the qualitative ones were assessed with frequencies and percentages. Moreover, the Kaplan Meier survival estimator curve and the log-rank test were used to estimate one-, two-, three-, four- and five-years survival rates. In all comparative analyses, p-value equal to or less than 0.05 was considered statistically significant.

RESULTS

Overall, 207 patients were enrolled in this retrospective study with the mean age of 52 ± 14 years and ranged from 6-74 years old. Most of them were men (83.1%). At the time of data collecting, 145 patients were alive (70%), 33 cases (15.9%) and 29 patients (14%) died from HCC recurrence and underlying diseases, respectively (Table 1). The most common causes of cirrhosis were HBV (49.4%) and HCV (10%), respectively. One patient (0.65%) had HBV and alcohol consumption, and 2 patients (1.3%) had HBV and HCV co-infection. One hundred thirty-seven patients (66.2%) had HCC due to hepatitis-related factors (group A), and the prevalence of biliary (group B) and other diseases (group C) as the underlying causes of

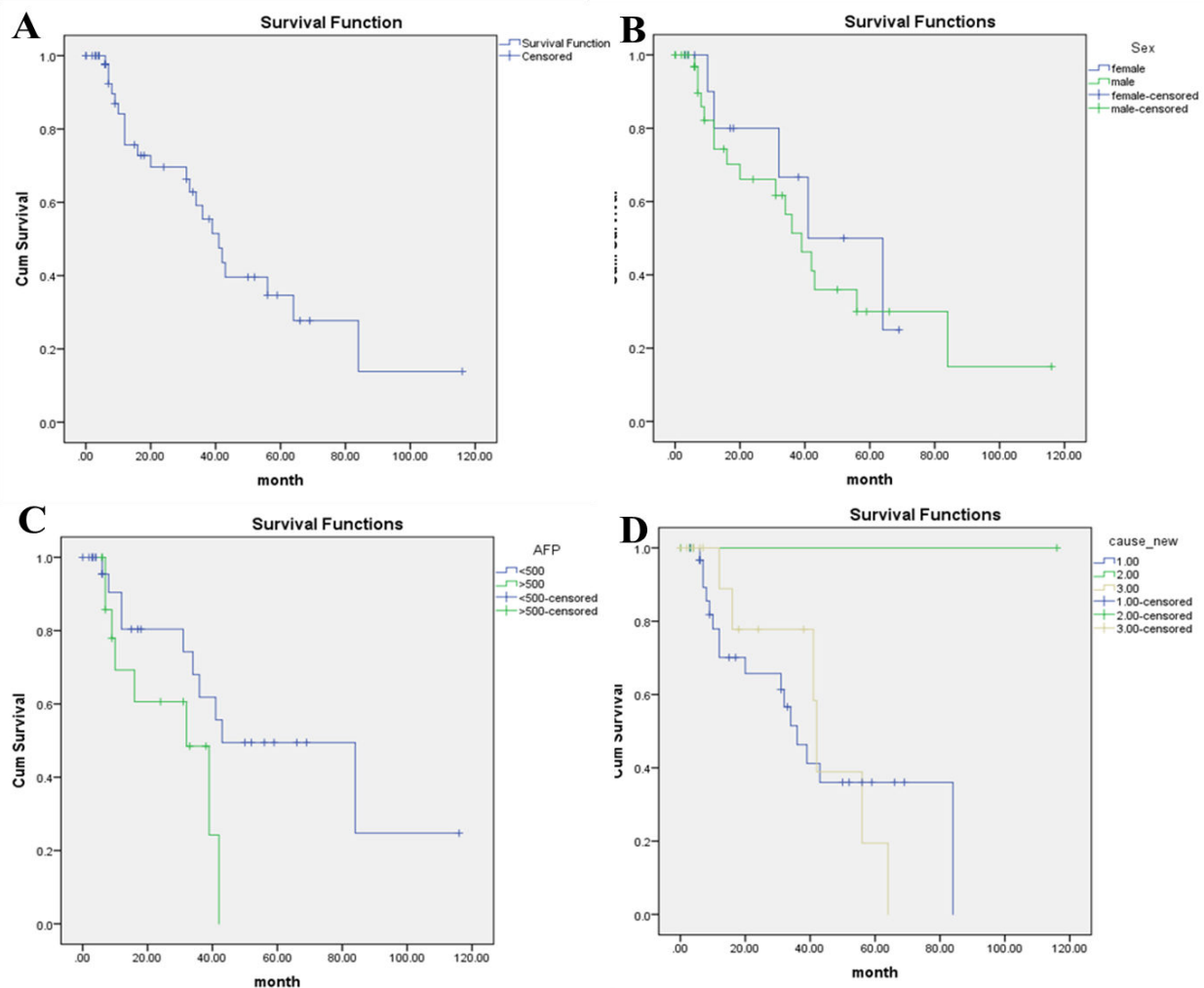


Figure 1: The Kaplan Meier Survival Curves. (A) showed the overall survival rate of the transplanted patients, (B) the differences between sex-related survival rates, (C) survival rates were evaluated according to the serum level of alpha-fetoprotein, and (D) we have shown the differences between the survival rates based on the underlying conditions.

HCC were equal to 8 (3.9%) and 62 patients (30%), respectively.

One hundred thirty-five patients (83.3%) had AFP blood levels below 500 ng. dl-1, and 27 patients (16.7%) had AFP levels above 500 ng/dL and AFP blood levels were not reported in 24 patients (Table 2). The overall mortality rate was higher among men than women, which was statistically significant ($P=0.076$). Moreover, there is a remarkable significant difference between the mortality rates were detected and the causes of liver cirrhosis ($P=0.024$). As we expected, AFP was significantly associated with mortality ($P=0.002$). The incidence of recurrence HCC death was

also higher in people with AFP above 500 (29.6%).

Out of 207 patients, just the data of 98 patients were completed for a survival interpretation. Among all deaths (98 cases), 33 patients (33.7%) died due to recurrence HCC, and the other 65 individuals (66.3%) from underlying diseases. The survival rate varied from 0.01 -116 month (median= 41 month). The one-, two-, three-, four-, and five-years survival rates were 80%, 70%, 61%, 41%, and 36%, respectively (Fig 1A). According to the Kaplan Meier survival estimator curve and log-rank test, no statistically significant difference was observed between the two genders ($P=0.34$) (Fig 1B). In Fig 1C,

we have evaluated the survival rate regarding the serum level of AFP (cut-off value= 500 ng/dL). It has shown that the survival rate was the same between these two groups until 40 months' post-transplantation, although the survival rate was higher in patients with AFP< 500 ng/dL thereafter. Moreover, the log-rank test has shown that this difference was relatively significant ($P=0.08$). Finally, we have estimated the survival rates based on the underlying causes of liver cirrhosis (Fig 1D). Of note, all of 4 patients in group B were alive at the time of writing this manuscript. According to the Kaplan-Meier survival estimator curve, the survival rate was higher in group A than in group C until 60 months, after which the survival rate was contrariwise. Although according to the Wilcoxon test, it was statistically significant ($P=0.036$).

Because age is a quantitative variable, Cox regression was utilized to determine the association between age and the survival rate. The results revealed that there is any significant correlation between the mentioned parameters ($P=0.595$).

For modeling the effective factors on the survival rate of liver transplantation, the variables which had a P-value less than 0.2 ($P<0.2$) in univariate analysis are included in this model. Therefore, the survival rate of liver transplantation Alongside age, gender, and the cause of liver cirrhosis are involved in this model, whose results demonstrated that just the serum level of AFP was relatively significant ($P=0.0257$, HR=3.2), and the mortality rate in the patients who had AFP blood levels above 500 ng/dL partially was 3.2 times more than patients who had AFP blood levels below 500 ng/dL.

DISCUSSION

The present study evaluated the survival rate and associating factors among liver-transplant patients in Abu-ali Sina transplant hospital. The study is a paramount importance; as Shiraz is a head center for liver transplantation surgery in Iran. Unlike other solid tumors,

both the incidence and mortality rate of HCC are increasing within the last years.

The recurrence of post-transplant HCC is seen in 10-20% of the patients and has remained stable over the years. Repeated efforts have done to refine the selection criteria for transplantation to get the best outcome [17]. Another study demonstrated a mean recurrence rate of 16% and the mean time for HCC recurrence was 13 months (range 2-132 months). Post-transplant HCC is the key determinant for survival. It will manage patients with recurrence continue to be a challenge because none of the treatment options guarantee long term survival [18].

Based on our findings, one-year survival rate was 80%, and constantly decreased to 36% after five years postoperatively. Similar studies conducted by Loho et al., [19] during 1998-1999 and 2013-2014. The authors were failed to show any significant survival rates' improvements between these time periods. The one-year survival rates were 24.1% and 29.4% between 1998-1999 and 2013-2014. We hypothesized that the higher survival rate in our specialized center might be primarily due to early diagnosis of HCC. Because in both studies, demographic features and the HCC-leading causes were relatively similar. The median survival time in our study was similar to a study from Japan (47.2 months) and higher than the median survival rate in the USA and Spain (18.6 and 24 months, respectively) [20, 21].

AFP levels play an important role in liver cancer prognosis, diagnosis, recurrence and treatment response. AFP level is used as an indicator for monitoring recurrence in patients with HCC [22, 23]. We tried to analyze the AFP levels change respondent to treatment in the patients of our study. AFP was high (>500 ng/dL) in 27 patients and in 135 patients (80.1%) was below the 500 ng/dL. Patients who had high AFP levels was those who had recurrence and patients with decreasing response to treatment had a longer survival. Other studies showed that 60-70% of patients with liver cancer especially hepatocellular carcinoma

(HCC) have elevated of AFP levels which are lower in HCC [24, 25]. To diagnose the liver cancer, AFP has sensitivity in clinical practice [26] and some studies [26, 27] showed that higher AFP levels result in worse overall survival which its effects on HCC prognosis is not clear. In the present study, the mortality rate regarding the serum level of AFP was equal between the two groups up to 40 months post-operatively; however, the survival rate was higher in the group whose serum AFP level was less than 500 than the other group after this time interval. Overall, a high serum level of AFP (more than 500 ng. dl-1) increased the mortality rate 3.2 times. Our finding re-emphasized the importance of AFP as a higher serum level and it was associated with more invasive HCC which was constantly reported in several previous studies [28, 29].

In the present study, most common underlying liver diseases were HBV (49.4%) and HCV (10%) infections. Muller et al., [30] study reported that the majority of their patients was men (85%) and the most common underlying diseases with HCC was HCV (43.2%) which has conflict with our study. Golabi et al., [31] showed that the mortality risk in patients with HCC was 1.11 and 0.94, respectively, due to non-alcoholic fatty liver disease (NAFLD) and HBV vs. HCV, and the underlying factor could influence the patients' outcomes. This finding was contrary to our study. We have concluded that none of the underlying diseases related to cirrhosis could affect mortality and the survival rate. This discrepancy may result from our low sample size which led us to compare the underlying causes as three "groups" rather than a "single" cause of liver cirrhosis.

In the present study, there was only 6 patients with NAFLD-induced HCC. Moreover, HBV and HCV were among the most common causes of cirrhosis which is similar to the other studies but unlike in western societies only one case of alcoholic liver disease was reported [32]. Younossi et al., [33] study also showed that the survival rate of patients with NAFLD was lower than others.

The present study showed that gender and the

underlying cause of cirrhosis did not significantly affect patients' survival rate. AFP is a predictive and prognostic biomarker and has a role of tumor antigen in HCC.

The present study had several potential limitations. The first one was our small sample size. Several patients could not be reached because their phone numbers and/or addresses were changed. Therefore, we were not able to contact these patients. Another limitation of the study was the lack of an appropriate scoring system such as CLIP, CUPI, etc. Finally, the retrospective designation may skew our analysis. Therefore, we suggest that it is better to conduct further prospective studies with higher sample sizes. Then, the physicians could determine the HCCs' survival rate and their associating factors. Moreover, it seems that a proper registry system should be set up in Abu-Ali Sina transplant hospital as the main transplant center in Iran, therefore, the patients' information can be accessed more easily and precisely.

CONFLICT OF INTEREST: None declared.

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