Failure to Thrive and Short-term Survival of Liver Transplant Recipients with Tyrosinemia

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ABSTRACT

Background: Liver transplantation is the main treatment for tyrosinemia. The pre-operative conditions such as presence of failure to thrive (FTT) would affect the prognosis of transplant recipients.

Objective: To test whether the survival rate of liver transplant recipients with tyrosinemia was associated with pre-operative presence or absence of FTT.

Methods: In a historical cohort study, the survival rate of 42 liver transplant recipients with FTT was compared with that of 68 patients without FTT during 6 months of the transplantation. Kaplan-Meier survival analysis and Cox regression were used for data analysis.

Results: The recipients with and without FTT were matched for age, sex, baseline laboratory test results, and the frequency distribution of the underlying diseases. 35 (83%) of 42 recipients with FTT and 29 (43%) of 68 without FTT had rickets ($p<0.001$). Histopathological study of the resected livers revealed that 50% of those with FTT and 77% of recipients without FTT had hepatocellular carcinoma or hepatoblastoma ($p=0.015$). Recipients with FTT were followed for a median (IQR) of 62 (23–99) days; those without FTT, 31 (6–85) days. During the follow-up period, 9 (21%) of 42 recipients with FTT and 32 (47%) of 68 without FTT died. Recipients with FTT had a significantly ($p=0.013$) better survival. Presence of FTT in recipients was associated with a 65% reduction (HR 0.35, 95% CI 0.158–0.776) in the risk of death within 6 months of the transplantation.

Conclusion: Presence of FTT in patients with tyrosinemia undergoing liver transplantation, would significantly decrease the short-term mortality rate in transplant recipients.

KEYWORDS: Tyrosinemias; Liver transplantation; Survival analysis; Failure to thrive

INTRODUCTION

Tyrosinemia is an autosomal recessive metabolic disorder caused by a defect in the breakdown of tyrosine, a semi-essential amino acid [1]. The disease is categorized into three types. Type I or hepatorenal tyrosinemia, has the most clinical and pathological manifestations [2]. It can affect various organs including the liver (mainly involved), kidneys, and peripheral nerves [3]. Tyrosinemia can less commonly cause hypertrophy of the islets of Langerhans, hypoglycemia, diabetes mellitus, and in rare cases, hypertrophic cardiomyopathy [4]. The disease can usually be controlled with medication (nitisinone) and diet modification. However, providing an acceptable survival rate, liver transplantation is still the mainstay for the treatment of patients with tyrosinemia [5]. Numerous studies have so far been conducted on the treatment of the disease and the factors affecting the outcome of liver transplantation in the affected patients [4, 6-8].

Liver transplantation is a major surgery and the pre-operative condition of the recipient would seriously affect the survival of the patient. Presence of underlying diseases such as

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Table 1: Mean±SD (n) of demographic and baseline laboratory test results in the two studied groups.

Variables	Failure to thrive		P-value
	Yes	No	
Age, months	40.6±25.0 (42)	38.0±21.6 (68)	0.557
Female sex, %	45% (19/42)	52% (35/68)	0.525
AST, U/L	83.0±65.5 (42)	101.8±94.1 (68)	0.257
ALT, U/L	82.4±169.1 (42)	73.8±186.4 (68)	0.807
Total bilirubin, mg/dL	1.7±4.4 (42)	1.7±4.1 (68)	0.998
Direct bilirubin, mg/dL	3.4±7.1 (42)	3.7±7.8 (68)	0.800
PT, s	16.4±7.0 (42)	16.3±4.4 (68)	0.878
PTT, s	40.6±13.2 (32)	42.8±16.5 (57)	0.520
INR	1.5±1.1 (42)	1.5±0.7 (68)	0.780
WBC×10^3, per µL	8.23±3.99 (42)	6.91±2.99 (68)	0.052
Platelet×10^3, per µL	168±102 (42)	143±87 (68)	0.176
BUN, mg/dL	11.1±4.6 (40)	9.9±5.1 (68)	0.244
Creatinine, mg/dL	0.43±0.16 (40)	0.4±0.2 (68)	0.789
Albumin, g/dL	4.2±0.7 (42)	4.1±0.7 (68)	0.870
TG, mg/dL	102.5±47.6 (30)	113.2±47.4 (47)	0.339
Cholesterol, mg/dL	143.9±65.1 (30)	160.7±72.9 (49)	0.304
Hemoglobin, g/dL	11.7±2.2 (42)	11.2±2.0 (68)	0.164

AST: aspartate aminotransferase; ALT: alanine aminotransferase; PT: prothrombin time; PTT: partial thromboplastin time; INR: international normalized ratio; WBC: white blood cell count; BUN: blood urea nitrogen; TG: triglyceride .

failure to thrive (FTT), ascites, hypoalbuminemia, etc, would thus be of paramount importance in determining the prognosis and survival of transplant recipients [4, 5, 9]. FTT may have two opposing effects. It may be associated with a poor pre-operative general condition of the recipient and thus, would result in a poor outcome. On the other hand, FTT may be associated with malnourishment and depression of the recipient immune system, which would be associated with lower probability of transplant rejection, hence, a good prognosis. Given these two possible contradictory effects, we conducted this study to test whether the survival rate of liver transplant recipients with tyrosinemia was associated with pre-operative presence or absence of FTT.

MATERIALS AND METHODS

In a historical cohort study, 110 patients with tyrosinemia who had undergone liver transplantation were studied. The patients were diagnosed with the disease and referred to Shiraz Organ Transplant Center, Avicenna Hospital, Shiraz University of Medical Sciences, Shiraz, southern Iran, between 2015 and 2020. The relevant study data were retrospectively retrieved from the hospital electronic archive. In addition to the initial clinical manifestations of studied patients, imaging data and histopathological tests were also considered in our analysis.

Patients who had incomplete information or did not give informed consent to participate in the study were excluded from the study. Patients' age and sex; pre-operative data including presence of hepatic disease, signs or symptoms of renal disease, rickets, and neurologic crises; clinical presentation, urinalysis, blood tests, kidney and liver function tests, pathology results, and computed tomography of the chest and abdomen; and the indication for liver transplantation were collected for each transplant recipient. Post-operative outcome

Table 2: Prevalence of the underlying diseases in recipients with and without FTT.

Underlying disease		Failure to thrive, n (%)		P-value
		Yes	No	
Hepatic failure	Yes	40 (95)	66 (97)	0.494
	No	2 (5)	2 (3)	
Renal tubulopathy	Yes	0 (0)	1 (2)	0.618
	No	42 (100)	67 (98)	
Cirrhosis	No	3 (7)	12 (18)	0.099
	Micronodular	39 (93)	56 (82)	
Portal hypertension	Yes	1 (2)	2 (3)	0.671
	No	41 (98)	65 (97)	
Ascites	Yes	5 (12)	7 (10)	0.331
	No	37 (88)	61 (90)	
Hypoalbuminemia	Yes	9 (21)	10 (15)	0.257
	No	33 (79)	58 (85)	
Seizure	Yes	7 (17)	10 (15)	0.492
	No	35 (83)	58 (85)	
Status	Acute	6 (14)	14 (21)	0.285
	Chronic	36 (86)	54 (79)	

(e.g., probable complications and the survival of the recipient) was assessed for each studied participant too.

The diagnosis of tyrosinemia in studied patients was made by genetic tests (fumarylacetoacetate hydrolase [FAH] gene mutation) and evaluation of plasma concentration of tyrosine and its metabolites. FTT was diagnosed using the US National Center for Health Statistics (NCHS) growth chart; FTT was considered in participants if they had a weight-for-age <5th percentile on the growth chart, a decrease in weight percentile of >2 major percentile lines on the growth chart, or <80th of median weight-for-height ratio [10].

Ethical Considerations

This study was conducted in accordance with the Declaration of Helsinki [11]. The study protocol was approved by Shiraz Organ Transplant Center, Avicenna Hospital Ethics Committee. Informed written consent was obtained from parents of each of the participants.

Statistical Analysis

SPSS® for Windows® ver 26 was used for data analysis. Student's t test for independent samples was used to compare means of two continuous variables. χ^2 test or Fisher's exact test (when necessary) was used to compare the frequency distribution of categorical variables. Kaplan-Meier survival analysis and log-rank (Mantel-Cox) test were used to study the association between presence of FTT and survival of liver transplant recipients. Cox regression analysis was used to calculate the hazard ratio (HR) after the model was adjusted for covariates with a $p<0.2$ in univariate analyses. Missing values were deleted from statistical analysis pair-wise. A p value <0.05 was considered statistically significant. All tests were two-tailed.

RESULTS

There were 42 (38.2%) recipients with FTT; 68 (61.8%), without FTT. The two groups were not significantly different in terms of frequency distributions of age and sex and the baseline laboratory test results (Table 1).

Table 3: Prevalence of post-operative histopathological findings in the resected livers in the recipients with and without FTT.

Histopathological findings	Failure to thrive, n (%)		P-value
	Yes	No	
Hepatocellular carcinoma	15 (36)	34 (50)	0.015
Hepatoblastoma	6 (14)	18 (27)	
Others	21 (50)	16 (24)	

Prevalence of the underlying diseases was also not significantly different between recipient with and without FTT (Table 2). There was no patient with hypertrophic cardiomyopathy or lymphovscular invasion. One of the recipients with FTT had lung metastasis.

Thirty-five (83%) of 42 recipients with FTT and 29 (43%) of 68 without FTT had rickets ($p<0.001$). There was a significant ($p=0.015$) association between the post-operative histopathological findings in the resected livers and FTT—50% of those with FTT and 77% of recipients without FTT had hepatocellular carcinoma or hepatoblastoma in the resected liver (Table 3).

Recipients with FTT were followed for a median (interquartile range [IQR]) of 62 (23–99) days; those without FTT, 31 (6–85) days. During the follow-up period, 9 (21%) of 42 recipients with FTT and 32 (47%) of 68 without FTT died. Recipients with FTT had a significantly ($p=0.013$) higher cumulative survival (Fig. 1). Cox regression analysis revealed that after adjusting for pre-operative hemoglobin concentration, white blood cell count, platelet count, and presence of cirrhosis, the variables with a $p<0.2$ in univariate analyses, presence of FTT in recipients was associated with a 65% reduction (HR 0.35, 95% CI 0.158–0.776) in the risk of death within six months post-transplantation (Table 4).

DISCUSSION

Survival rate of liver transplant recipients with FTT was significantly higher than the rate in those without FTT. Those with FTT were not significantly different from recipients without FTT in terms of age and sex, baseline laboratory test results, and the prevalence of the underlying diseases. Therefore, the two study groups could be considered matched. The prevalence of rickets in those with FTT, however, was almost twice that in recipients without FTT. This might be attributed to the presence of hypophosphatemic rickets due to FTT [12]. The frequency distribution of the histopathological findings in the resected livers was also different in the two studied groups—about half of the recipients with FTT did not have any findings in favor of hepatocellular carcinoma or hepatoblastoma in the resected livers (Table 3). Although it is not possible to make any causal inference based on this observation, this association might be a clue for better understanding of the underlying process, an important topic to be elucidated in future research studies.

Table 4: Results of Cox regression analysis.

Variables	Adj HR* (95% CI)	P-value
Failure to thrive	0.350 (0.158–0.776)	0.010
Cirrhosis	1.502 (0.525–4.299)	0.449
Hemoglobin	0.981 (0.824–1.167)	0.826
Platelet count	1.000 (1.000–1.000)	0.032
White blood cell count	1.000 (1.000–1.000)	0.858

*Adj HR: adjusted hazard ratio; CI: confidence interval

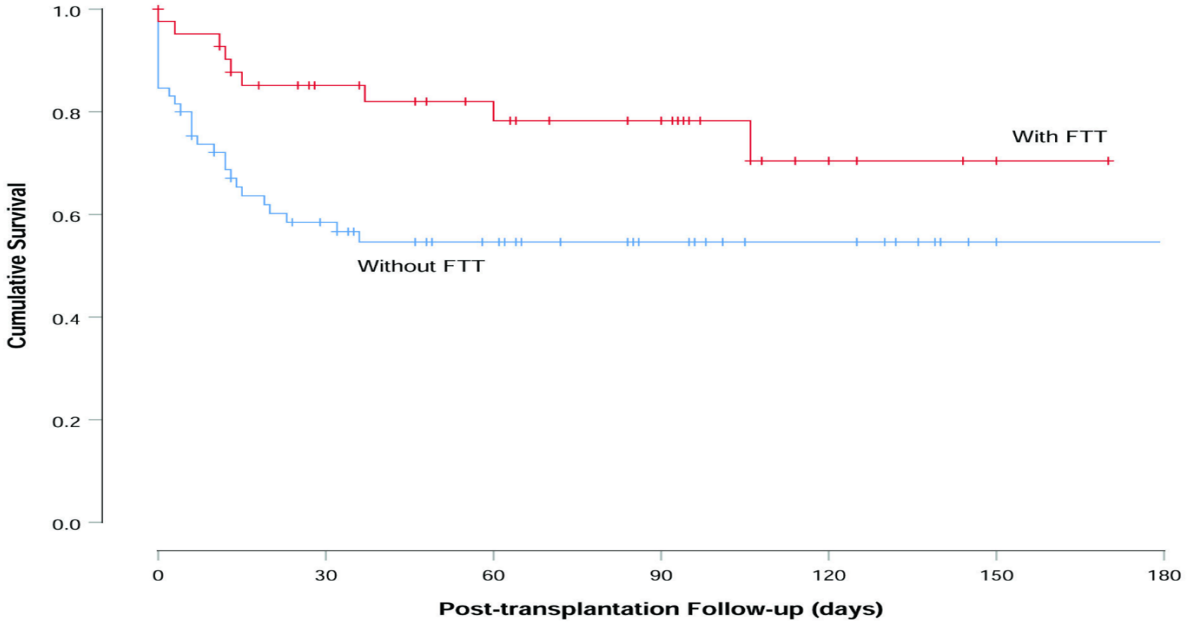

Figure 1: Kaplan-Meier survival curves for recipients with and without failure to thrive (FTT). Small vertical tick-marks indicate right-censored cases.

Although diet modification is recommended as the first line of treatment for tyrosinemia, due to the restrictions in consumption of foods containing the amino acids phenylalanine and tyrosine, the mainstay of the treatment is still liver transplantation. Diet modification, although helpful, does not prevent the progression of the disease.

One of the limitations of our study was the small sample size of the current study. However, given that our center is among the largest transplant centers in the world [13], collecting a sufficiently large sample from a single center would be unlikely and conducting a multi-center study on a large population with a widespread genetic distribution is suggested.

In conclusion, presence of FTT in patients with tyrosinemia undergoing liver transplantation, would decrease the recipient mortality rate by 65% within six months post-transplantation.

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CONFLICT OF INTEREST: None declared.

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