ORIGINAL ARTICLE

The effects of prognostic factors on transplant and mortality of patients with end-stage liver disease using Markov multistate model

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Background: Decompensated cirrhosis patients have a high risk of death which can be considerably reduced with liver transplantation (LT). This study aimed to simultaneously investigate the effect of some patients' characteristics on mortality among those with/without LT and also LT incident. **Materials and Methods:** In this historical cohort study, the information from 780 eligible patients aged 18 years or older was analyzed by the Markov multistate model; they had been listed between 2008 and 2014, needed a single organ for initial orthotopic LT, and followed at least for up to 5 years. **Results:** With a median survival time of 6 (5–8) years, there were 275 (35%) deaths. From 255 (33%) patients who had LT, 55 (21%) subsequently died. Factors associated with a higher risk of mortality and LT occurrence were included: higher model for end-stage liver disease (MELD) score (hazard ratio [HR] = 1.16, confidence interval [CI]: 1.09–1.24 and HR = 1.22, CI: 1.41–1.30) and ascites complication (HR = 2.34, CI: 1.74–3.16 and HR = 11.43, CI: 8.64–15.12). Older age (HR = 1.03, CI: 1.01–1.06), higher creatinine (HR = 6.87, CI: 1.45–32.56), and autoimmune disease versus hepatitis (HR = 2.53, CI: 1.12–5.73) were associated with increased risk of mortality after LT. **Conclusion:** The MELD and ascites are influential factors on waiting list mortality and occurrence of LT. Total life expectancy is not influenced by higher MELD.

Key words: Cirrhosis, life expectancy, model for end-stage liver disease, survival

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INTRODUCTION

Cirrhosis is the end stage of progressive liver fibrosis and decompensated liver cirrhosis (DLC) is characterized by the presence of variceal bleeding, ascites, and encephalopathy. DLC is associated with complex organ disorders and high short-term mortality, leading to substantial financial costs for the health-care system.[1-5]

DLC has emerged as a significant cause of global health burden and more than one million deaths per year worldwide.[6,7] In 2017, it accounted for approximately 4%, 5%, and 3% of all deaths in the United States, the European Region, and the Middle East, respectively.[8]

Regarding the burden of liver diseases in Iran, 1.7% of death was due to cirrhosis and other chronic liver diseases, lower than chronic kidney disease (2.2%).[8] Furthermore, among adults aged between 15 and 49 years who died in 2010, the leading causes of their deaths were gastrointestinal, liver cancers, and cirrhosis.[9] Finally, it is estimated in 2015 that a yearly number of deaths were hepatitis B virus (HBV) cirrhosis: 2500, nonalcoholic fatty liver disease: 3400, hepatitis C virus (HCV) cirrhosis: 1600, and cholestatic liver disease: 500.[10]

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After discovering immunosuppressant in 1983, orthotopic liver transplantation (LT) is introduced as an effective therapy; therefore, patients who have experienced LT are known to be at a substantially fewer risk of mortality even by up to 79%.[11-13] In Iran, the first LT was performed in Shiraz (1993)[14] and then in 2002 in Tehran Liver Transplant Center (TLTC). The details of TLTC have been published in a previous paper.[15]

In 2016, the establishment of the United Network for Organ Sharing (UNOS) in the United States showed that patients had been enrolled on the waiting list, and only 50% have undergone deceased donor LT due to limited resources of donor organs. According to the UNOS reports in 2019, it is notable that the liver (11.6%) was the most common demand organ after the kidney (86.7%).[16] The imbalance between demand for LT and deceased donation rates leads to a significant increase in mortality on the waiting list.

Since LT patients may benefit from this treatment, that is, they survive longer than nontransplant patients, the probability of death on the waiting list may be underestimated when LT status is not considered in the analysis, model 1. There are several methodological ways, some of which may lead to considerable biases or inefficiency in assessing the LT role in the survival of waiting list patients. Since the lead-time bias is obvious, comparing survival time distributions between LT and non-LT patients, model 2, is not an appropriate analysis.[17,18] In 1979 Jamieson reported this bias in the analysis of the Stanford heart transplant data.[19]

Survival analysis using the Cox proportional hazards model and its two generalizations allow LT to be considered a time-dependent covariate, models 3 and 4, or a competing outcome, models 5 and 6, and poses the following challenges: LT status is an internal time-dependent covariate that is effective on patient survival, and other factors also influence its occurrence. Therefore, the assumption of the Cox model is not met.[17,20] Furthermore, considering death as a competing risk for LT (or vice versa) is problematic because it violates the basic assumption of noninformative censoring.[21,22]

Studies analyzing mortality of cirrhosis patients on the waiting list do not currently consider the effect of LT on time to death and lead to a suboptimal one. Markov multistate model, model 7, can be used to address this problem.[23] In our study, the three-state model (illness-death model) was set based on clinical events, including end-stage liver disease (ESLD) as the initial state, LT as interim state, and death as the third state (absorbing state) [Figure 1].

In addition, the model for end-stage liver disease (MELD) score in 2001 provides donor organs for listed recipients

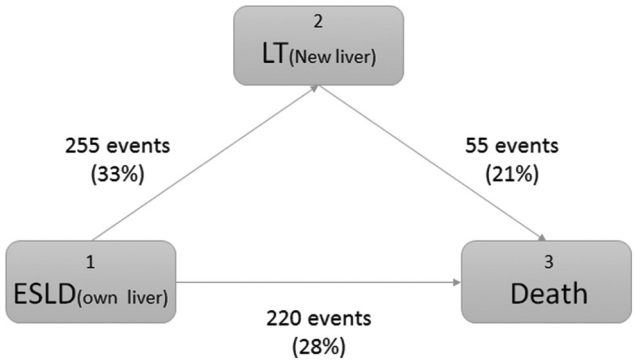

Figure 1: Progressive multistate model for a liver transplant on waiting list patients in Tehran Liver Transplantation Center (TLTC). Three possible states are considered: (1) ESLD: End-stage liver disease, (2) LT: Liver transplant, (3) death

with the highest estimated mortality before LT.[24] The MELD score's ability to predict recipient mortality after LT is still vague and controversial,[25,26] but the multistate model in our study can examine it.

The primary aim of this study is to investigate the impact of MELD score and other factors on mortality among ESLD patients with/without LT and also LT incident at once. Besides, the secondary purpose is estimating the life expectancy (LE), average number of years lived, with and without LT in different levels of MELD score.

MATERIALS AND METHODS

Participants, study design, and instruments

In this historical cohort study, patients with irreversible liver failure (confirmed by a hepatologist), regardless of the age and cause of the disease, were referred to TLTC (located at Imam Khomeini Hospital Complex in Tehran). Since the demand for liver transplant was high, but the number of deceased liver donors was low, some patients remained on the waiting list for a long time to receive a well-matched organ. During the follow-up, clinical events and other information were recorded in patient's files. Through the TLTC, 780 adult patients, aged 18 years or older, who were listed to transplant between March 2008, and March 2014, were identified. The main exclusion criteria were as follows: patient's reception in other centers, multi-organ transplantation, and re-transplantation [Figure 2].

The Ethics Committee of Tehran University of Medical Sciences approved this historical study (approval number: IR.TUMS.SPH.REC.1396.4825). The information of patients was de-identified prior to analysis.

Outcomes and variables

The beginning of follow-up corresponded to the date of waiting list registration. Information about vital status and date of death was obtained regularly through phone calls

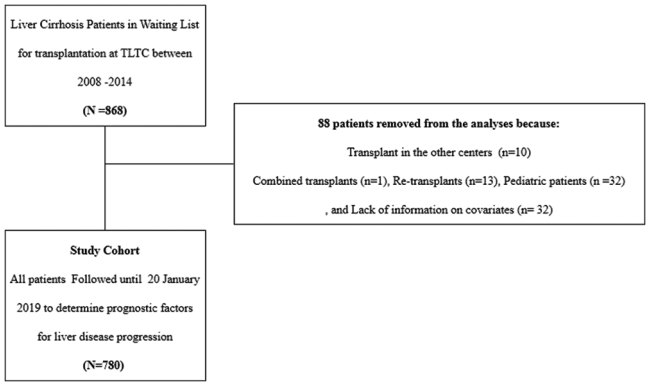

Figure 2: The flow diagram shows the patients in the study-defined cohort. TLTC: Tehran Liver Transplant Center

and medical records. Patients were censored at the time of loss to follow-up or at the end of the study in January 2019. In this study, time to transplantation and time to death with and without LT were considered as multistate outcomes. Transparently, observed transition times were as follows: time to LT (date of LT minus date of waiting list registration [start/origin time]), time to death (date of death minus origin time), and time to censoring (date of last visit/phone calls/January 2019 minus origin time). The censoring happened because of the study was finished and individuals do not experience the events or they were lost to follow-up during the study period.

The baseline characteristics in models were demographical (age and gender) and clinical (etiology/underlying diseases, ascites, creatinine, total bilirubin, international normalized ratio [INR], and MELD score) information.

Liver inactivity assessment

The liver inactivity of patients on the waiting list, in addition to a high MELD score which is currently the dominant criterion for liver allocation in this center, was also confirmed by the clinical judgment of transplant team members. This multidisciplinary committee included transplant surgeons, hepatologists, anesthesiologists, radiologists, pathologists, psychiatrists, infectious disease specialists, and liver transplant coordinators.

Clinical and biochemical measurements

Ascites was detected by sensitive imaging studies such as ultrasonography and physical examination. The cause of death among deceased liver donors were included as: anoxia, cerebrovascular accident, head trauma, central nervous system tumor, and other causes. Liver disease classification was based on the most common type, i.e., HCV, HBV, autoimmune disease (AID), and so on. The biochemical measurements including serum creatinine, total bilirubin, and INR were collected from medical record of patients. These laboratory values were included since they constituted the MELD score and were also used to allocate patients on the transplant list.

The MELD equation, used to calculate the severity score, was:[27]

$$Meld = 9.6 \times \ln(creatinin\,[\text{mg/ dl}]) + 11.2 \times \ln(\text{INR}) + 3.8 \times \ln(bilirubin\,[mg\,/\,dl]) + 6.43$$

According to the UNOS modifications, to avoid a negative score in the above equation, laboratory values below one were rounded to 1, and maximum serum creatinine was considered 4 mg/dl.[28] We adopted three categories for liver disease classification that their definitions were similar to Roberts *et al.*'s study.[29] Details about surgical procedures and related factors in TLTC were reported in the previous paper.[30]

Statistical analysis

Categorical variables were described as frequencies (percentages) and continuous as mean ± standard deviation (SD). The normality assumption was not met for continuous variables using Kolmogorov–Smirnov test. The association between baseline characteristics of the study population and patient's status at the end of follow-up was assessed using Chi-square and Mann–Whitney tests. The reverse Kaplan–Meier method was applied to estimate the median survival time. Assuming missing completely at random or missing at random mechanism, baseline variables that had <10% missing values were imputed by Bayesian models and through the Markov chain Monte Carlo method. Hence, the observed data of other variables were used to predict the missing values in a variable by regression models. In this study, linear regression models were used for continuous variables and logistic models were used for qualitative variables. In total, 78 (11%) patients had missing data on at least one of desired variables at the time of registration and the range of missing value percentages was between 0% and 8%.

To correctly estimate the effect of desired variables, especially meld score, on hazard of death pre- and post-LT, eight models were run in our study; only the results of model 1: without considering LT status in the analyses and model 7: using the multi-state model, will be shown in the main text; and the results of other models, including model 2: LT status as a grouped variable, models 3 and 4: LT status as a time-dependent variable with and without interaction effects, models 5 and 6: utilizing competing risks methods, and model 8 that consider time to first event (LT or death) as an outcome, have been shown in Appendix.

First, univariate and multiple Cox proportional hazard modes without considering LT intervention were used

to estimate overall hazard ratio (HR). All variables that were significant in the univariate models or those clinically important were entered into multiple models. The proportional hazards assumptions underlying Cox regression were assessed using independence between the scaled Schoenfeld residuals and time.

Then, using multistate model, three transition intensities described the progression of the ESLD: (1) the intensity of developing LT (λ_{12}), (2) the intensity of LT-free death (λ_{13}), and (3) the intensity of death after the LT (λ_{23}) [Figure 1]. The model is as:

$$\lambda_{i,gh}(t) = \lambda_{0gh}(t)\exp(X^{T}_{gh,i}\gamma_{gh}),\ g = 1,2 \quad h = 2,3$$

Where $\lambda_{i,gh}(t)$ indicates the transition intensity from state g to state h for the ith individual at time t. λ_{0gh} is the baseline hazard for this transition and γ_{gh} corresponds to transition-specific covariate ($X^{T}_{gh,i}$) coefficient vectors.

The goodness of fit for the multistate model was assessed by comparison between observed and expected prevalence. In R 4.0.4 software, the msm,[31] ELECT,[32] and R2OpenBUGS[33] packages were used to obtain HRs, LE, and missing data imputation, respectively. The statistical significance level was set at 0.05.

RESULTS

Descriptive findings

According to Figure 2, after eliminating transplant patients in the other centers: 10 (1%), combined transplants: 1 (0.1%), re-transplants: 13 (1.5%), pediatric patients: 32 (4%), and lack of information on eligible covariates: 32 (4%), 780 ESLD patients with mean age 43 ± 13 years were analyzed, of whom 448 were male (57%), and 248 (32%) had ascites. The mean ± SD of MELD scores was 16 ± 6 that 49%, 32%, 17%, and 2% of the patients had MELD scores <15, 15–20, 20–30, and >30, respectively. The most common cause of LT was (AID, 37%), (HBV/HCV, 30%), and other liver diseases (33%). The characteristics of patients are described in Table 1.

There were 275 (35%) deaths, with an overall median survival time of 6 (5–8) years. Two hundred and fifty-five (33%) patients experienced LT, of whom 55 (21%) subsequently died. As shown in Table 2, survival probabilities of ESLD patients, without considering LT, were 92%, 79%, and 68% at 1, 3, and 5 years, respectively.

In the end of the study, 335 (43%) ESLD patients were still in state 1; hence, time to transplant and time to death were censored for them. On the other hand, 200 (78%) transplanted patients were in state 2, and time to death after LT was censored for them [Figure 1].

Effects of prognostic factors on mortality using Cox model

In the univariate analysis – which does not consider LT intervention [Table 1], the unadjusted effects of all prognostic variables, except INR, were found to be significant factors on the patients' survival. According to multiple Cox regression model results, i.e., model 1, there were significant effects on mortality, including aging (HR: 1.03, confidence interval [CI]: 1.02–1.05), ascites complication (HR: 1.40, CI: 1.08–1.82), and high MELD

Table 1: Baseline characteristics of the study population stratified by patient's status at the end of follow-up, Tehran Liver Transplant Center, 2008-2019

Variables	Mean±SD or *n* (%)					*P**	Overall++	Overall+++
	All (*n*=780)	Survival status					Crude HR (95% CI)	Adjusted HR (95% CI)
		Alive		Died				
		In waiting list (*n*=305; 39%)	After LT (*n*=200; 26%)	In waiting list (*n*=220; 28%)	After LT (*n*=55; 7%)			
Age (year)	43±13	41±13	40±12	47±12	43±13	<0.001	1.04 (1.02-1.04)	1.03 (1.02-1.05)
Sex (male)	448 (57%)	160 (53%)	113 (57%)	144 (65%)	31 (56%)	0.010	1.45 (1.13-1.85)	1.11 (0.86-1.44)
Diseases								
HCV/HBV (reference)	237 (30%)	86 (28%)	49 (25%)	93 (42%)	9 (16%)	0.010	-	-
AID	287 (37%)	107 (35%)	86 (43%)	68 (31%)	26 (47%)		0.67 (0.51-0.89)	0.97 (0.72-1.32)
Other*	256 (33%)	112 (37%)	65 (33%)	59 (27%)	20 (36%)		0.64 (0.48-0.86)	0.83 (0.61-1.13)
Ascites (yes)	248 (32%)	0 (0%)	136 (68%)	70 (32%)	42 (76%)	<0.001	1.69 (1.33-2.15)	1.40 (1.08-1.82)
Creatinine (mg/dL)	1.08±0.25	1.06±0.16	1.06±0.16	1.13±0.40	1.08±0.20	0.002	2.21 (1.64-2.98)	1.27 (0.86-1.89)
Total bilirubin (mg/dL)	4.05±5.63	2.89±5.05	5.16±5.38	4.50±6.17	4.62±6.23	0.005	1.02 (1.01-1.04)	0.99 (0.96-1.01)
INR	1.64±0.76	1.44±0.41	1.84±0.91	1.66±0.70	1.97±1.34	0.049	1.09 (0.99-1.21)	0.83 (0.66-1.03)
MELD score	16±6	13±5	18±5	16±6	18±6	<0.001	1.05 (1.03-1.07)	1.07 (1.025-1.12)

*Primary biliary cirrhosis, primary sclerosing cholangitis, hepatocellular carcinoma, metabolic liver disease, and others; **P*-value(s) calculated based on Mann-Whitney and Chi-square tests; ++Univariate Cox proportional hazard mode without considering LT intervention; +++Multiple Cox proportional hazard mode without considering LT intervention (the including variables in this model are age, sex, disease, ascites, and laboratory tests); The significant level was considered at 5%. CI=Confidence interval; AID=Autoimmune and cryptogenic disease; HCV=Hepatitis C virus; HBV=Hepatitis B virus; INR=International normalized ratio; MELD=Model of end-stage liver disease; HR=Hazard ratio; LT=Liver transplantation

score (HR: 1.07, CI: 1.03–1.12). The hazard of death was 0.97 (CI: 0.72–1.32) fold among patients with AID compared with hepatitis ones. Furthermore, patients with higher creatinine levels had a higher mortality rate (HR = 1.27, CI: 0.86–1.89), but these are not statistically significant in this model [Table 1]. To see the impact of adjusting for LT, we considered it as a fixed-in-time variable and also as a time-dependent variable in models 2 and 3, respectively, and its interactions with other factors considered in model 4, results shown in Appendix Tables 1a and 2a. Finally, in models 5 and 6, we use the conventional approach of "competing risks", but because of informative censoring results, not valid and related results were reported in Appendix Table 3a.

Effects of prognostic factors on occurrence of LT, mortality with and without LT using Markov multistate model

According to multistate analysis, the probability of remaining in ESLD state – without LT and mortality events – was 82%, 65%, and 38% after 1, 3, and 5 years, respectively. In turn, the probability of waiting list mortality was 8%, 22%, and 33% at 1, 3, and 5 years, respectively. The transition probability of ESLD to LT after 1, 3, and 5 years was 10%, 22%, and 29%, respectively. The rest of the transition probabilities are presented in Table 2.

The effects of each prognostic factor on death hazard with and without LT and the hazard of LT incident have been investigated by Markov multistate model. Therefore, factors significantly associated with the incidence of LT were as follows: higher MELD score (HR = 1.22, CI: 1.14–1.30), ascites complication (HR = 11.43, CI: 8.64–15.12), less creatinine (HR = 0.34, CI: 0.17–0.68), and fewer INR (HR = 0.55, CI: 0.38–0.81).

Although ascites complication (HR = 2.34, CI: 1.74–3.16) and higher MELD score (HR = 1.16, CI: 1.09–1.24) significantly affect waiting list mortality, these factors did not affect post-LT survival [Table 2].

The factor associated with a higher risk of mortality with and without LT was older age (HR = 1.03, CI: 1.01–1.06 and HR = 1.03, CI: 1.02–1.04). Mortality risk after LT among AID patients was higher than hepatic ones (HR = 2.53, CI: 1.12-5.73), and higher creatinine increased this risk (HR = 6.87, CI: 1.45–32.56).

Figure 3 shows the LEs, among 40 older adults with AID and ascites based on MELD categories. The LEs with LT were higher than without LT, but total LEs for MELD 20–30 and MELD ≥30 are low. LE for a patient with MELD (20–30) was about 15 and 1 year with and without LT, respectively.

Table 2: Estimated crude transition probabilities with and without considering liver transplantation intervention at 1, 3, and 5 years; Tehran Liver Transplant Center, 2008-2019

From	To	Crude transition probabilities without considering LT in Cox model			Crude transition probabilities with considering LT in multistate model		
		1st year	3rd year	5th year	1st year	3rd year	5th year
ESLD	ESLD	0.92	0.79	0.68	0.82	0.56	0.38
ESLD	Death	0.08	0.21	0.32	0.08	0.22	0.33
ESLD	LT	-	-	-	0.10	0.22	0.29
LT	LT	-	-	-	0.95	0.86	0.77
LT	Death	-	-	-	0.05	0.14	0.23

ESLD=End stage liver disease; LT=Liver transplant

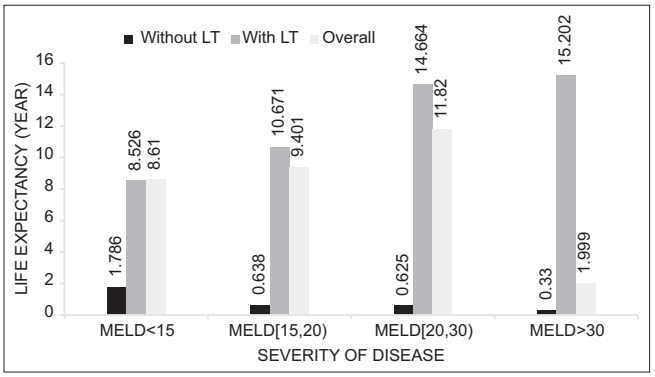

Figure 3: Life expectancy with and without LT at age 40 years for males with a history of ascites in different severity of liver dysfunction. LE: life expectancy

DISCUSSION

In this study, we found that the post-LT survival rate (79%) was higher than pre-LT one (72%). Therefore, LT is an important event in the evolution of ESLD. It is essential to determine what factors may prioritize the patient to LT and how its occurrence may affect other events as a prognostic factor. Little attention has been paid to this important question in previous studies, but in our study, Markov multistate model allows considering LT as an intermediate event between baseline prognostic factors and the ultimate event of death.

As shown in Table 2, the probability of death in the waiting list was underestimated when LT status was not considered in the analysis. These biases increased over time since patients, who underwent LT, had proper survival. In Markov multistate model, we found that post-LT survival probabilities were 95%, 86%, and 77% at 1, 3, and 5 years, respectively, and higher than pre-LT survival probabilities (86%, 56%, and 38%) [Table 2]. The survival probabilities in the study were estimated to be higher than previous works,[34,35] which indicates the importance of complication management.

Table 3: Hazard ratios by the results of the multistate model for the association of liver transplant incident, mortality among those with and without liver transplant with patients' characteristics, donor, and surgical factors, Tehran Liver Transplant Center, 2008-2019

HR (95% CI)	LT incident	*P*	Mortality among those without LT	*P*	Mortality among those with LT	*P*
Age (year)	1.00 (0.99-1.01)	0.855	1.03 (1.02-1.04)	<0.001	1.03 (1.007-1.06)	0.024
Sex (male)	0.89 (0.69-1.16)	0.386	1.10 (0.82-1.47)	0.533	0.88 (0.48-1.60)	0.690
Diseases						
HCV/HBV (reference)	-		-		-	
AID	1.32 (0.92-1.88)	0.128	0.76 (0.54-1.07)	0.116	2.53 (1.12-5.73)	0.026
Other*	1.31 (0.92-1.86)	0.133	0.65 (0.46-0.92)	0.015	2.27 (1.01-5.11)	0.047
Ascites (yes)	11.43 (8.64-15.12)	<0.0001	2.34 (1.74-3.16)	<0.0001	1.45 (0.76-2.75)	0.260
Creatinine (mg/dL)	0.34 (0.17-0.68)	0.002	0.71 (0.44-1.15)	0.163	6.87 (1.45-32.56)	0.015
Total bilirubin (mg/dL)	0.97 (0.94-1.001)	0.053	0.98 (0.95-1.007)	0.122	0.997 (0.92-1.08)	0.947
INR	0.55 (0.38-0.81)	0.002	0.61 (0.37-0.99)	0.048	1.13 (0.81-1.59)	0.487
MELD score	1.22 (1.14-1.30)	<0.0001	1.16 (1.09-1.24)	<0.0001	0.96 (0.86-1.07)	0.473

*Primary biliary cirrhosis, primary sclerosing cholangitis, hepatocellular carcinoma, metabolic liver disease, and others. The significant level was considered at 5%.
CI=Confidence interval; AID=Autoimmune and cryptogenic disease; HCV=Hepatitis C virus; HBV=Hepatitis B virus; INR=International normalized ratio; MELD=Model of end-stage liver disease; CIT: Cold ischemic time; HR=Hazard ratio; LT=Liver transplantation

In this center, 33% of the waiting list patients managed to receive donated liver and according to results of Markov multistate model, the probability of underwent transplant for each patient was estimated about 30% at the 5th year; it was similar to other single centers with scarce deceased donor organ.[36]

Based on our knowledge, this is the first study, analyzing the prognostic performance of MELD score on pre- and post-LT survival simultaneously. Although the MELD score is associated with overall survival without considering LT (HR = 1.07), according to multistate model results, high MELD score increased the risk of mortality only before transplant (about 16%) and did not have a significant effect on post-LT survival. Some study confirm these findings.[25,37,38] It may happen due to the MELD index introduced to reduce waiting list mortality, not to predict post-LT survival. Alternatively, other distinct analyses showed that patients with a higher MELD score tended to experience worse/better post-LT survival.[11,39-42] Finally, the occurrence of LT among patients with high MELD score was increased about 22%.

A study by Heuman *et al*. demonstrated that in patients with MELD score above 21, the only independent predictor for death in waiting list was MELD, but if the MELD score was lower than 21, ascites was the only predictors;[43] also in other studies, ascites was related to pretransplant mortality.[44] Similarly, in our study, ascites was an influential factor in overall mortality. Although this factor increased the incidence of LT (HR = 11.43), pre (HR = 2.34), and post (HR = 1.45) LT mortality, it was not statistically significant factor on the mortality after LT. It seems that adding ascites factor into the new risk model might refine and improve the accuracy of the MELD index.

In our center, the primary underlying diseases were autoimmune-cryptogenic followed by hepatitis cirrhosis vice versa; according to a study in Iran, in 2018, the leading causes for LT were hepatitis B-related cirrhosis, followed by cryptogenic and primary sclerosing cholangitis.[45] Howbeit, in this study, the etiology of liver disease was not a significant factor for transplant and mortality before LT, but patients with autoimmune cryptogenic cirrhosis (HR= 2.53) had poorer survival after LT, compared to those with hepatitis [Table 3]. This is in line with another study which showed post liver transplant survival was strongly related to underlying disease.[15,46,47] Furthermore, a disease-specific analysis of LT survival, which encompasses both pre- and posttransplant events, showed an increased survival rate after LT among HCV + patients with >30 MELD increased and a decrease in patients with MELD 9-29, compared with HCV – patients.[48] In other work, HCV was also correlated with the survival rate before LT.[49]

Sharma *et al*. believe that the weight of creatinine in the MELD formula is overestimated, because people with creatinine levels less than 1 are not indistinguishable, and high bilirubin in cirrhotic patients can interfere with creatinine measurement.[50] Therefore, our research found that patients with lower creatinine and INR levels were more likely to transplant.

In the following, the post-LT mortality rate of patients with high creatinine levels was higher than those with lower values [Table 3]. It may happen due to immunosuppressive drug use after transplantation – although it prevents transplant rejection – that further damage kidney function. Hence, renal dysfunction is a common complication after LT that depends on various factors before, during, and after surgery.

According to many studies,[51-54] including our results in the multistate analysis, age was identified as a risk factor that affects mortality before and after transplantation [Table 3].

This may be due to biological status; therefore, diagnosing and transplanting at a younger age is essential in improving patient survival.

In general, female liver recipients had a more extended LE,[35] but in our study, the multistate model adjusted to common clinical risk factors for mortality. We calculate LE with and without LT among 44-year-old male patients with a history of ascites in different severity of liver dysfunction. Results showed that the LE of patients waiting list with any disease severity, if transplanted, will increase significantly, and it can be hypothesized that their LE after transplantation is like other healthy people in the population.

Limitations

This work is an observational-retrospective study and prone to some biases[55] because we did not access information about other risk factors mentioned in previous studies.

CONCLUSION

The multistate model gives new insights into ESLD progression and takes into consideration the role of LT intervention. More than one-third of patients with cirrhosis have been transplanted in TLTC. MELD score and ascites are most strongly associated with the hazard of death without LT. High MELD does not guarantee increasing total LE, and individuals with MELD <15 can expect greater longevity after transplant.

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Conflicts of interest

Dr. Mohssen Nassiri-Toosi is the chief of Liver Transplantation Research Center. The other authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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APPENDIX

A. To correctly estimate the effect of desired variables, especially meld score, on hazard of death pre and post LT, eight models were run in our study.

The results of model 1: Without considering LT status in the analyses and model 7: Using the multi-state model, were shown in the main text.

Results of other models including model 2: LT status as a grouped variable, models 3 and 4: LT status as a time-dependent variable with and without interaction effects, respectively, have been shown in [Table 1a] and [Table 2a].

Whereas LT is a highly significant protective factor for death, its effect has lead time bias in model 2. Therefore, adjusting for LT in time-varying LT model may provide valid estimates of the impact of ascites (HR = 2.26, CI: 1.71–2.98) and MELD score (HR = 1.11, CI: 1.06–1.16) on mortality. Furthermore, the risk of death among transplant patients 71% decreased (HR = 0.29, CI: 0.21–0.40) [Table 1a].

The tests of the interactions with LT, model 4, yielded statistically significant for some factors particularly MELD score [Table 2a].

Models 5 and 6: Utilizing competing risk methods and model 8 that consider time to first event (LT or death) as an outcome have been shown in [Table 3a].

APPENDICES

Table 1a: Multiple Cox model analyses for all-cause mortality

Variable	HR (95% CI)	
	With LT as a grouping variable (model 2)	With LT as a time-dependent variable (model 3)
LT (yes)	0.109 (0.077-0.156)	0.288 (0.2049-0.4036)
Age (year)	1.027 (1.016-1.039)	1.031 (1.02-1.043)
Sex (male)	1.098 (0.8485-1.42)	1.097 (0.847-1.421)
Diseases		
HCV/HBV (reference)	-	-
AID	1.093 (0.802-1.49)	0.962 (0.707-1.309)
Other*	0.901 (0.661-1.228)	0.826 (0.608-1.122)
Ascites (yes)	4.809 (3.559-6.498)	2.258 (1.713-2.976)
Creatinine (mg/dL)	0.797 (0.526-1.206)	0.951 (0.6319-1.43)
Total bilirubin (mg/dL)	0.983 (0.957-1.009)	0.983 (0.958-1.008)
INR	0.757 (0.573-1.001)	0.768 (0.5996-0.983)
MELD score	1.112 (1.059-1.169)	1.11 (1.06-1.163)

*Primary biliary cirrhosis, primary sclerosing cholangitis, hepatocellular carcinoma, metabolic liver disease, and others. HR=Hazard ratio; LT=Liver transplantation; CI=Confidence interval; AID=Autoimmune and cryptogenic disease; HCV=Hepatitis C virus; HBV=Hepatitis B virus; INR=International normalized ratio; MELD=Model of end-stage liver disease

Table 2a: Changes in the effects of baseline prognostic factors after liver transplantation; interactions of them with time-varying liver transplantation in Cox model, (model 4)

Variable	HR (95% CI)		
	Before LT+	After LT+	Interaction with LT
Age (year)	1.029 (1.016-1.042)	1.032 (1.007-1.058)	1.003 (0.9753-1.031)
Sex (male)	1.103 (0.8229-1.478)	0.8768 (0.4811-1.598)	0.7975 (0.409-1.555)
Diseases			
HCV/HBV (reference)	-	-	-
AID	0.7763 (0.548-1.1)	2.54 (1.122-5.748)	3.348 (1.379-8.132)
Other*	0.6559 (0.4649-0.9254)	2.28 (1.013-5.131)	3.51 (1.454-8.469)
Ascites (yes)	2.552 (1.896-3.435)	1.457 (0.7674-2.768)	0.6213 (0.3064-1.26)
Creatinine (mg/dL)	0.6883 (0.426-1.112)	6.835 (1.439-32.47)	9.643 (1.889-49.23)
Total bilirubin (mg/dL)	0.9763 (0.9473-1.006)	0.997 (0.9178-1.083)	1.02 (0.9343-1.114)
INR	0.5875 (0.3567-0.9676)	1.13 (0.8055-1.585)	1.878 (1.031-3.418)
MELD score	1.167 (1.091-1.248)	0.9572 (0.859-1.067)	0.8236 (0.7254-0.9352)

*Primary biliary cirrhosis, primary sclerosing cholangitis, hepatocellular carcinoma, metabolic liver disease, and others. +Stratified model based on time-varying LT (*P*-value of likelihood ratio test to compare model 4 and model 3 was <0.001). HR=Hazard ratio; LT=Liver transplantation; CI=Confidence interval; AID=Autoimmune and cryptogenic disease; HCV=Hepatitis C virus; HBV=Hepatitis B virus; INR=International normalized ratio; MELD=Model of end-stage liver disease

Table 3a: Comparison of the Cox model-based estimates of the effects of prognostic factors on two competing events: Liver transplantation versus death-without-liver transplantation

Variable	HR (95% CI)		
	Outcome=LT or death (Model 8)	Outcome=LT (censoring on death) (Model 5)	Outcome=LT-free death (censoring on LT) (Model 6)
Age (year)	1.012 (1.004-1.02)	1.002 (0.9911-1.012)	1.029 (1.0165-1.042)
Sex (male)	0.9928 (0.818-1.205)	0.8945 (0.6886-1.162)	1.0995 (0.8204-1.473)
Diseases			
HCV/HBV (reference)	-	-	-
AID	0.9781 (0.7672-1.247)	1.3258 (0.9292-1.892)	0.7584 (0.5361-1.073)
Other*	0.888 (0.699-1.128)	1.3150 (0.9257-1.868)	0.6494 (0.4605-0.916)
Ascites (yes)	5.483 (4.537-6.627)	11.393 (8.613-15.070)	2.346 (1.743-3.158)
Creatinine (mg/dL)	0.534 (0.3654-0.7802)	0.3384 (0.1675-0.6839)	0.7089 (0.4387-1.1455)
Total bilirubin (mg/dL)	0.9751 (0.9541-0.9966)	0.9689 (0.9373-1.002)	0.9772 (0.9483-1.007)
INR	0.5913 (0.4411-0.7927)	0.5587 (0.3825-0.8159)	0.6016 (0.3670-0.9864)
MELD score	1.185 (1.134-1.239)	1.215 (1.141-1.293)	1.162 (1.088-1.242)

*Primary biliary cirrhosis, primary sclerosing cholangitis, hepatocellular carcinoma, metabolic liver disease, and others. HR=Hazard ratio; LT=Liver transplantation; CI=Confidence interval; AID=Autoimmune and cryptogenic disease; HCV=Hepatitis C virus; HBV=Hepatitis B virus; INR=International normalized ratio; MELD=Model of end-stage liver disease

B. The goodness of fit test results for final multistate model are shown below:

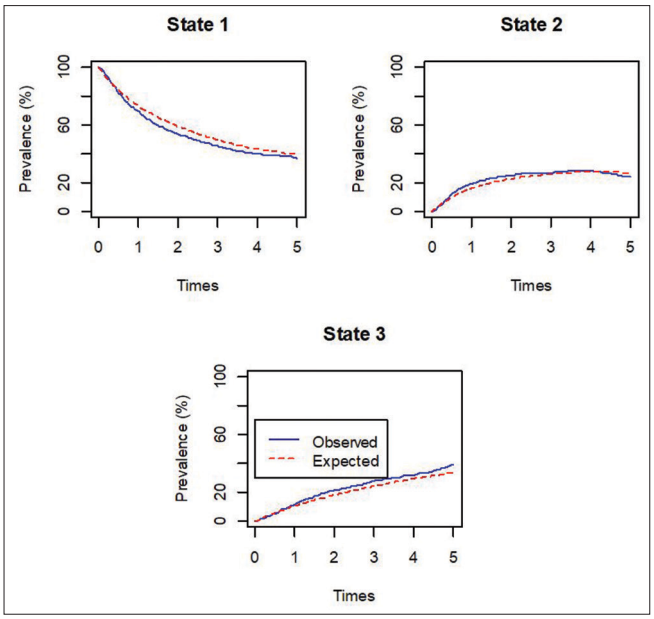

Figure 1: Observed and expected prevalence plots; the goodness of fit assessment of Markov multistate models