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Temporal Variations in Mortality after Liver Transplantation: Retrospective Investigation of Potential Risk Factors Using Propensity Score

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Abstract

Objective: We aim to detect over-time variations in mortality of liver transplant recipients stratified by the period of transplant. Since this is a retrospective investigation, bias reduction caused by possible confounding effects can be achieved by using propensity score weighting in a multivariate logistic regression model. **Methods:** Medical charts of all adult liver transplant recipients (n = 250) who were transplanted in three periods 2005-2009, 2010-2014 and 2015-2019 were retrospectively reviewed. The following recipient factors were analyzed: recipients and donors' ages, sex, renal impairment, body mass index (BMI), presence of bacterial or viral infections, MELD (Model for end-stage diseases). Multivariate logistic model adjusted by Propensity Scores (PS) was used to identify the effect of the risk factors on mortality, and death within five years, in the targeted time frame. Patient outcomes are recorded as; (patient status = 1 if dead, or patient status = 0 if alive). **Results:** Meld score, recipient age, and renal impairments were shown to be predictors of mortality in transplanted patients. Multivariate regression model was used to identify the significance of the specified risk factors, followed by pairwise comparisons between periods. Pairwise comparisons between periods using logistic regression weighted by the inverse propensity score, correcting for the possible confounding effect of measured covariates showed that the death rate is significantly reduced in subsequent periods as compared to the initial period. **Conclusions:** The clinical implications of these findings are the ability to stratify patients at high risk of posttransplant death by planning more intensive and accurate management for them.

Keywords

Liver Transplantation, Age, Body Mass Index, Renal Impairment, Inverse

Propensity Score Weighting

1. Introduction

Data on liver transplantation are globally available and to name but a few in [1] [2] [3]. Liver transplantation is still a complex and cost-intensive procedure [4] and the results are influenced by many interrelated factors. As liver transplantation has become a universally accepted treatment for end-stage liver disease, the number of patients accumulating on the waiting list has gradually outweighed the scarce resources of available organs. Fair allocation of donor livers to patients with end-stage liver disease remains a difficult task. In this study we addressed several questions, the first being whether there is a change in the rate of death among transplant recipients. Furthermore, we investigated the effect of several risk factors on patients' survival.

1.1. MELD Score

The first risk factor being investigated is model for end-stage liver disease (MELD) score [5]. The usually adopted policy stratifies the patients based on their risk of death while on the waiting list [6] [7]. The impact of the MELD score on post-operative mortality remains unclear. There are reports of reduced survival in groups with high MELD scores [8] [9] but also reports of no influence of MELD score on survival [10] [11].

The MELD score incorporates three simple laboratory parameters (serum creatinine and bilirubin, and INR for prothrombin time) and stratifies patients according to their disease severity in an objective and continuous ranking scale. Concordance statistics have demonstrated its high accuracy in stratifying patients according to their risk of dying in the short term (three months) [12].

1.2. Age

The second risk factor for mortality after liver transplant that we study in this paper is age.

Our second aim is to establish whether there is a relationship between the donor's age and patient and survival among liver transplant recipients and to determine the age at which this relationship emerges. A donor's age is one factor that determines the choice of a graft for transplant. However, the shortage of organs for a large number of waiting patients limits this decision. Thus, donors show a tendency toward older age, particularly in Europe compared with the United States [13]. Several factors may reduce the quality of grafts from older donors, including an increased degree of hepatic steatosis, a higher incidence of primary dysfunction or failure, a reduced functional capacity, and a greater extent of parenchymatous necrosis and fibrosis. [6] [7] [8] As a result, during the

last decade several studies reported a decline in the survival rates of patients who receive organs from donors older than 45, 50, or 60 years [13]. The aim of this study was to determine whether there is a relationship between donor age and recipient survival, and to establish a cut-off age.

1.3. Renal Impairment

The third risk factor is chronic renal dysfunction which has also been shown to have a significant association with cardiovascular events in retrospective analyses [14] [15] [16] [17]. One study of data from the Organ Procurement and Transplant Network (OPTN) assessed risk factors for cardiovascular mortality in 5057 patients undergoing liver transplant for nonalcoholic steatohepatitis and found moderate or severe kidney disease (estimated GFR [eGFR] < 60 mL/min/1.73 m^2) to incur a 1.8-fold increase in risk ($p < 0.001$) [14]. A single-center retrospective analysis of 202 primary liver transplants has reported a doubling of the risk for both cardiovascular events and cardiovascular mortality in patients with eGFR < 60 mL/min/1.73 m^2 [18].

1.4. Infections (Bacterial, Viral, and Fungal)

Virtually any bacteria can cause disease after liver transplantation [19] [20] [21] [22]. Risk factors for resistant bacterial pathogens are prior antibiotic One of the most common bacterial infections found to manifest itself early after liver transplantation, is surgical site infection, which has been estimated to occur in about 10% of patients. Intra-abdominal infections account for 27% - 47% of early bacterial infections after liver transplantation [23]. Intraabdominal abscesses, peritonitis, and cholangitis commonly present during the first few weeks after liver transplant as fever, leukocytosis, and abdominal pain, although clinically asymptomatic cases which are mainly manifested with elevated liver enzymes are not uncommon.

Liver recipients are somewhat unique among transplant recipients because they are commonly chronically infected with hepatitis B or C viruses, often with an accelerated clinical course [24]. Respiratory and gastrointestinal viruses may occur throughout the post-liver transplant period, with seasonal variations for some viruses such as influenza and parainfluenza [25] [26] [27].

Although various fungal species infect liver transplant recipients, by far the most common are the *Candida* species followed by the *Aspergillus* species. *Cryptococcus neoformans* occurs much less commonly in the form of meningitis, lung disease and cellulitis [28] [29] [30].

1.5. Patient BMI

The fifth risk factor we studied is patients' body mass index (BMI). In the general population, a high BMI is associated with the development of cardiovascular diseases, diabetes, musculoskeletal disorders and cancer, resulting in increased morbidity and mortality [31] [32].

2. Methods of Analysis

Data analyses are done using the SAS software version 9.4. Among the 250 transplant recipients, 17/55 died within the first five years, 16/75 died in the subsequent five years, 16/120 died in the third five years. We used the Cochran-Armitage chi-square test for trend and found that the rate of death varied significantly among the three periods with p-value = 0.010. Descriptive statistics of variables measured on the continuous scale are summarized in Table 1. MELD score was significantly higher among the dead recipients (p-value = 0.0001). Donor's BMI was not significantly different (p-value = 0.253). Dead donors had mean age (30.64 years) which was significantly larger than the mean age of the survivors (32.5 years) with a p-value = 0.0001. Donors BMI was slightly higher among the survivors (mean = 23.84) as compared to the dead recipients (mean = 22.8), but the difference was marginally significant (p-value = 0.044).

We used the chi-square test to compare categorical variables in the two groups of transplant recipients. There was no significant difference in the death rate in males (30/154) when compared to females (20/96), the p-value = 0.795. The death rate in the infected recipients (whether viral or bacterial infection) was higher (24/66) as compared to the infection-free recipients (26/184) with p-value = 0.0001. Similarly, we found that the death rate of patients with renal impairment (14/19) was significantly higher than the rate of death in patients with no renal impairment (36/231) with p-value = 0.0001.

Several studies [8] [9] attempted to find a cut-off for MELD that will dis

The ROC area = 0.716 with 95% confidence interval (0.63 - 0.802) p-value = 0.0001.

Optimal cut-offs point for MELD is (24.5) giving sensitivity = 0.44 and specificity = 0.833.

The ROC area = 0.727 with 95% confidence interval (0.646 - 0.807) p-value = 0.0001.

Table 1. Summary statistics of the transplanted patients stratified by patient status.

Patient Status		MELD	BMI	Donor age	Donor BMI
0	Mean	19.02	26.68	25.93	23.84
	N	200	200	200	200
	Std. Deviation	5.567	4.808	5.491	3.246
1	Mean	24.82	27.68	30.64	22.80
	N	50	50	50	50
	Std. Deviation	7.951	7.875	5.934	3.295
Total	Mean	20.18	26.88	26.87	23.63
	N	250	250	250	250
	Std. Deviation	6.527	5.553	5.882	3.276

The optimal cut-off point for donor's age at donation was 32.5 years giving sensitivity = 0.45 and specificity = 0.834.

Our second objective is to model the joint effect of the selected risk factors on patients' survival using a multivariate logistic regression model.

3. Multivariate Analysis

Figure 1 and Figure 2 show the ROC curves for MELD and donor's age, respectively and the related information on such areas under the curves and the significance of the departure of each area from the 50% null point. We shall utilize the Propensity Score (PS) method to build a multivariate regression model that links the outcome of interest (mortality) to all the measured risk factors. The PS method involves calculating the conditional probability (propensity) of being in a specific period given a set of covariates, weighting the data based on these propensity scores, and then analyzing the outcome (mortality) using the weighted data. The fundamental objective of using the PS is to bring an observational or a retrospective investigation closer to the randomized prospective study design. The method of weighting we used in this paper is "weighting by the inverse PS". It was proposed by Imbens [33] and further discussed by Hirano and Imbens [34]. It was shown that weighing based on the inverse of the PS produces unbiased estimates of the group effect. This method has nice mathematical properties as was demonstrated in [35].

In Table 2 we present the results of the maximum likelihood estimation of the

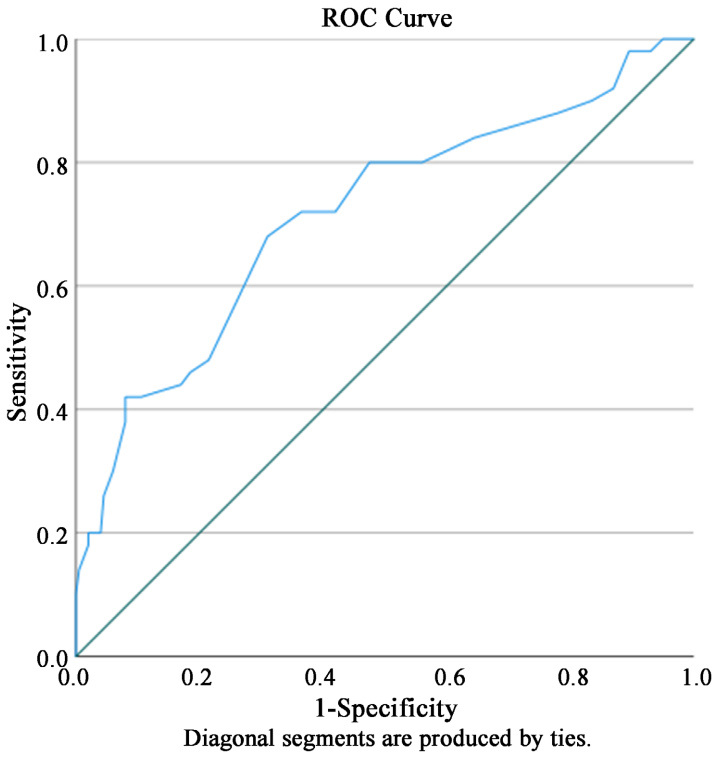

Figure 1. The ROC curve is used to identify the optimal cut-off MELD that discriminates dead from alive transplant recipients.

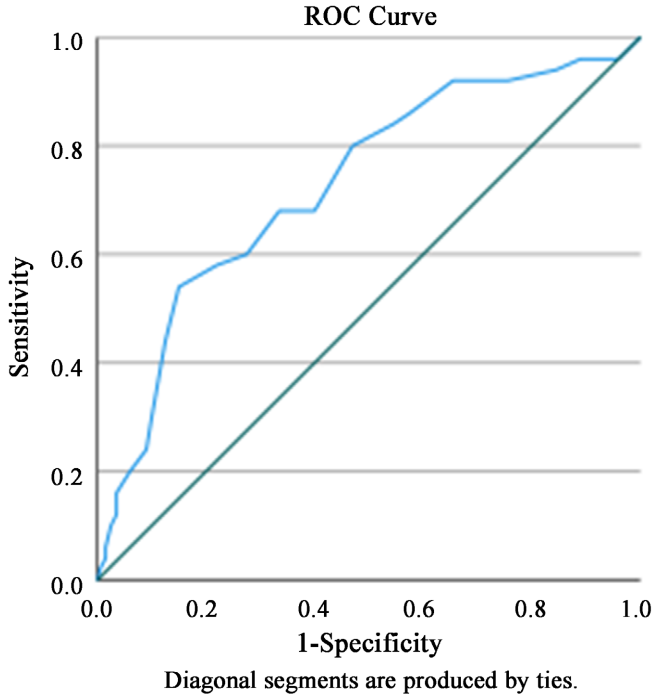

Figure 2. ROC analysis for donor's age at donation.

Table 2. The maximum likelihood analysis of logistic regression.

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept		1	9.3468	2.7973	11.1651	0.0008
Age		1	0.00871	0.0176	0.2436	0.6216
Sex	1	1	0.1582	0.2272	0.4845	0.4864
MELD		1	−0.1528	0.0385	15.7735	<0.0001
BMI		1	−0.0946	0.0423	4.9973	0.0254
period		1	−0.2306	0.2590	0.7932	0.3731
Donors Age		1	−0.2052	0.0399	26.4858	<0.0001
Donor BMI		1	0.1154	0.0686	2.8294	0.0926
infection	0	1	0.4200	0.2307	3.3138	0.0687
Renal impairment	0	1	1.0220	0.3513	8.4617	0.0036

logistic regression model. As can be seen, MELD, patient's BMI, donor's age, and renal impairment have joint significant effects and are considered potential risk factors for death within five years from liver transplantation.

From Table 3, we conclude that when period 1 is the reference period the odds of death during that period are significantly higher than the odds of death in the subsequent two periods. One can then conclude that the quality of patients' care has improved in the second and third periods relative to the first period.

Table 3. Pairwise comparison of odds of death between periods.

Odds Ratio Estimates: Pairwise comparison			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
period 2 vs 1	1.954	1.562	2.445
period 3 vs 1	3.293	2.612	4.153

4. Discussion

It is well known that there is a global shortage of organs that can be used for transplant in patients with liver diseases. It is therefore very important to identify patients who benefit most from a liver transplantation and to detect risk factors associated with poor outcomes (mortality). The main findings of this study were that donor's age, patient's BMI, MELD, renal impairment are relevant for prediction of long-term patient survival. The association between infection and donor's BMI was not significant in the multivariate logistic regression model. This finding contrasts with numerous previous studies that demonstrated a significantly decreased survival in recipients of older donations. Based on our work, strict recommendations for the acceptance or refusal of potential liver donors cannot be made. Moreover, we conclude that careful donor organ and recipient selection can lead to excellent results. One of the major strengths of this paper is the multivariate modeling and the use of propensity score weights which leads to bias reduction in the estimations of covariate effects.

5. Conclusions

The main limitation of this study is the retrospective data collection. More studies involving larger samples are necessary to confirm the results obtained. In conclusion, knowing the factors that can determine a specific cause of early death in the post-transplant liver transplantation will allow us to stratify more accurately those patients at high risk of death.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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