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TEMPORAL PREDICTION MODELS FOR MORTALITY RISK AMONG PATIENTS AWAITING LIVER TRANSPLANTATION

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Abstract

Liver allocation policy uses the Model for End-Stage Liver Disease (MELD) for patients with chronic liver disease to stratify potential recipients according to the risk of waitlist death. The MELD is a Cox proportional hazardous model that is composed of three statistically significant mortality predictors. It has been shown to be a good indicator of mortality risk at a single point in a patient's course. However, there is a need for accurately predicting the progression of End-Stage Liver Disease (ESLD). Previous studies either did not consider a heterogeneous patient population awaiting liver transplantation or did not address changes in mortality risk over time.

In a retrospective cohort study, we consider adult waitlist ESLD patients with multiple MELD score readings. We classify these patients via classification tree analysis. We identify a regression model for each patient class and then estimate the model parameters via traditional nonlinear regression and local regression for each patient. At the end, we construct a parameter estimator region for each patient class.

Keywords: MELD, mortality risk, classification tree analysis, local regression

1. Introduction

Mortality risk assessment for patients with End-Stage Liver Disease (ESLD) has been studied for more than four decades. Most of the research focuses on patient posttransplant survival and many of which study its relationship with organ quality [1,2]. This research, on the other hand, studies the dynamics of pretransplant survival and mortality risk.

Child and Turcotte [3] were among the first to describe a risk classification system for cirrhotic patients undergoing surgical procedures. Pugh's subsequent modification [4] provided a practical and predictive index on mortality. Child-Turcotte-Pugh (CTP) score has been used in the United States from 1997 to 2002 as one criterion to rank candidates awaiting liver transplantation [5]. However, the criticisms of CTP score on applying subjective criteria, such as hepatic encephalopathy and ascites, surfaced around 2000-01, given the grave imbalance between the suitable recipient candidates and available donors. Therefore, an objective and more accurate method was sought for ranking potential candidates according to waitlist mortality risk, which resulted in the development of the Model for End-Stage Liver Disease (MELD) by

Kamath et al. [6]. The MELD score has been implemented to replace the CTP score to determine the priorities of patients on the waitlist receiving donor liver offers, i.e., within the same pool of suitable recipient candidates, the patient with a higher MELD score is of higher priority to be offered with the donor liver [7].

The MELD uses a Cox proportional hazards regression model [8] and currently includes the following covariates (laboratory components) for each patient: the serum bilirubin level, the creatinine level, and the international normalized ratio for prothrombin time. The calculation is presented as: 0.957 × ln(serum creatinine) + 0.378 × ln(serum bilirubin) + 1.120 × ln(INR) + 0.643. Baseline calculation requires all three laboratory components within 14 days of placement on the waitlist. Subsequent MELD calculations are made whenever one or more laboratory components change. Scores are rounded to the nearest tenth and multiplied by 10. More details about the MELD, we refer to [7].

However, there are a number of concerns regarding the MELD in the current practice: 1) although promising, most of studies on the MELD rely on the determination of a single MELD score at a given time point on an individual patient's disease progression course and do not directly study a group of patients awaiting liver transplants; 2) the schedule of MELD score reassessment is somehow arbitrarily regulated at present. For patients with lower MELD scores, the reassessment is not too frequent thus may not be capable of capturing the elastic nature of liver disease progression; and 3) the MELD is a survivability predictor. However, there are competing reasons for a patient to be removed from the waitlist, such as receiving a transplant and health condition being improved.

In this paper, we will address the first two issues by classifying patients based on a wide variety of demographic and medical characteristics other than the three laboratory components. We then apply the same family of regression models for patients from the same patient class and construct the set of parameter estimator for the class. Te be specific, denote S to be the set of possible values of all demographic and medical characteristics used as predictors. Then $S(p)$ is a subset of S indicating which class patient p belongs to. Denote J to be the number of classes. Suppose a patient p belongs to class j, $j = 1,\ldots,J$. We identify a regression model associated with class j, to predict the magnitude and direction of change in MELD score. Suppose there are m MELD readings for a patient p. Denote M_i to be i^{th} MELD reading, $i = 1,\ldots,m$. Let $\Delta M_{i\text{-}1} = M_i - M_1$ or $\Delta M_i = M_i - M_1$, where M_1 is the initial MELD score and M_i is the i^{th} MELD score; let $\Delta t_{i\text{-}1} = t_i - t_1$ or $\Delta t_i = t_i - t_1$, where t_1 is the registration date and t_i is the time that the i^{th} reading takes place. Then the regression model of ΔM vs. Δt for patient p is

$$\Delta M = f_j(\Delta t), \quad \text{given that } p \text{ is a } j^{\text{th}} \text{ class patient.} \tag{1}$$

Knowing the regression model identified for class j, we obtain a vector of parameter estimates $\boldsymbol{b}(p)$ for patient p. Collecting $\boldsymbol{b}(p)$ for all patients p in class j, we construct a set of parameter estimators Bj.

Given that the liver allocation policy in the U.S. is targeted towards providing donated livers to patients with the greatest risk for waitlist mortality, analysis of updated MELD scores and mortality risk during the patients' entire waiting courses is an important step in the evaluation of the MELD as a basis for liver allocation. To the best of our knowledge, Merion et al. [9] are the only people that consider the dynamics presented within the MELD. The authors use ΔM as a prognostic factor and conclude that serial MELD scores can predict waitlist mortality significantly better than a single baseline MELD score. However, the authors did not study the heterogeneity of the patient population and the prediction window is short (30 and 90 days). In addition, like most of the previous work, the studied patient population is small. We in this paper analyze a large amount, up-to-date data, to develop prediction models for longer periods of time. Our data were acquired from the data repository of the United Network for Organ Sharing (UNOS), the organization that operates the unified transplant network in the U.S.

2. Methodology

In this section, we first discuss the classification of patients by building a classification tree based on patient waitlist *registration* information. We then describe the local regression method for each patient subpopulation associated with each leaf node on the classification tree, based on patient waitlist *follow-up* information. At the end of this section, we describe our study design, data collection, and data exclusion.

2.1. Classification Tree Analysis

To deal with a heterogeneous population with various prognoses and registration times, we believe the courses of mortality risk dynamics are different from patient to patient. However, developing a regression model based on the waitlist follow-up data for each patient does not provide much prediction power. Furthermore, there are only a handful number of MELD score readings for most of the patients.

Generally speaking, traditional statistical methods are cumbersome to use, or of limited utility, in classifying patients into clinically important categories. There are a number of reasons for these difficulties: 1) there are generally many possible predictor variables which make the task of variable selection difficult; 2) predictor variables are rarely nicely distributed; 3) complex interaction or patterns may exist in the data [10]. All three difficulties exist in our research. Therefore, we apply classification and regression tree (CART) analysis, which was originated from the work by Fisher [11] (see also *Discriminant Function Analysis* and *General Discriminant Analysis*).

CART analysis is a form of binary recursive partitioning of the subjects [12]. Classification and regression trees are developed for predicting categorical predictor variables (class, group membership, etc.) and continuous dependent variables, respectively. There are a number of CART methods for analyzing classification-type problems and to compute predicted classifications, either from simple continuous predictors, from categorical predictors, or both. The main advantage of the tree methods is that it is nonparametric and nonlinear. The final results of using them can be summarized in a series of (usually few) logical if-then conditions (leaf nodes). In addition, CART has a sophisticated method for dealing with missing variables, which is the case in both patient registration and follow-up data sets.

In our case, we build classification trees and attempt to predict the class of each patient's MELD score progression course. Within each class (each patient population subgroup), we assume that all patients' MELD scores would change with the same magnitude and direction with respect to time. In our case, predictors are 38 medical and demographic characteristics obtained when patients register for waiting lists (not including the three initial lab values that are used to calculate the initial MELD score). They are 35 categorical predictors such as geographic location and blood type of the patient; and 3 continuous predictors: weight, height, and body mass index of the patient.

2.2. Local Regression

Once patients are classified into population subgroups, we collect the follow-up data of all patients from the same classification tree node. For every node, our preliminary regression analysis with smoothing for the corresponding population subgroup indicates that the mortality risk dynamics is clearly nonlinear but does not offer more guidance in terms of the family of nonlinear models. We therefore first test a number of simple polynomial functions: quadratic and cubic. In each node, we develop a nonlinear regression model for each patient and record the parameter estimates. We construct a parameter estimation region, a multidimensional object that contains all parameter estimates for patients from the same tree node. Hence for any hypothetical patient, we can classify her based on the classifiers determined by the classification tree analysis, and then draw a combination of parameter estimates (a point within the object).

We then apply the *loess* method, a nonparametric method for estimating local regression surfaces pioneered by Cleveland [13]. The method allows greater flexibility than traditional modeling tools because one can use it for situations in which one does not know a suitable parametric form of the regression surface. Furthermore, the method is suitable when there are outliers in the data and a robust fitting method is necessary.

In our research we use the LOESS procedure provided in SAS/STAT® software for performing local regression. The main features of the procedure include 1) fits nonparametric models; 2) supports the use of multidimensional predictors; 3) supports both direct and interpolated fitting using kd trees; and 4) computes confidence limits for predictions; and 5) performs iterative reweighting to provide robust fitting when there are outliers in the data.

For each patient, assume that for $i = 1$ to n, the i^{th} MELD reading and the corresponding time point t_i are related by $\Delta M_i = g(t_i) + \varepsilon_i$, where g is the regression function and ε_i is a random error. The idea of local regression is that near $x = x_0$, the regression function $g(x)$ can be locally approximated by the value of a function in some specified parametric class. Such a local approximation is obtained by fitting a regression surface to the data points within a chosen neighborhood of the point x_0. Note that g is dependent upon the patient class.

2.3. Study Design, Data Collection, and Data Exclusion

We in our study included all adult liver transplant candidates who were placed on the United Network for Organ Sharing (UNOS) waitlist prior to June 15th, 2006, the time the request was placed to UNOS for data acquisition from their institutional database. We acquired two datasets: transplant information and candidate waitlist history. In the original datasets, there are records for 30,906 patients. We queried the transplant candidate dataset to acquire a data set consisting of 38 predictors related to transplant candidate registration. We conducted our classification tree analysis in R® and regression analyses in SAS/STAT® software.

From the registration dataset, we excluded the patients who died before the implement of the MELD. Patients who had MELD score greater than 50, body mass index less than 10 or greater than 200, height less than 50 cm, weight less than 20 kg, were also excluded. We then conducted a classification tree analysis. For each tree node, we merged the two datasets with the keyword waitlist ID. We then deleted patients with fewer than 5 MELD readings. After data exclusion, we had 50,263 MELD records for 6438 patients. At the end, we calculated ΔM and Δt.

3. Results

Table 1: Basic demographic characteristics of waitlist patients at registration

Variable	Value
Age (yr)	
18 – 34	373 (2.1%)
35 - 49	1983 (11.2%)
50 – 64	3924 (22.1%)
>= 65	625 (3.5%)
Missing	10851 (61.1%)
Gender	
F	6305 (35.5%)
M	11451 (64.5%)
Race	
White	12872 (72.5%)
Black	1279 (7.2%)
Hispanic	2741 (15.4%)
Asian	664 (3.7%)
Other	200 (1.1%)

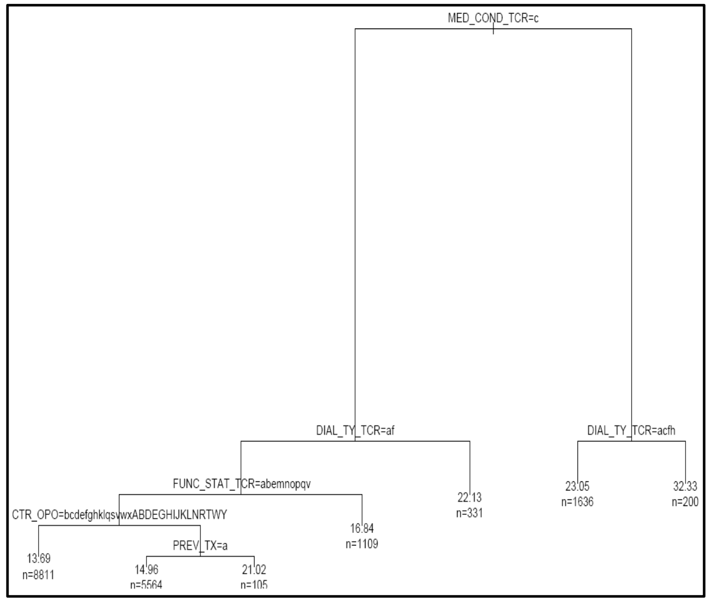


Figure 1: Classification Tree

Figure 1 shows that patient diagnosis at the registration is a strong predictor in the classification. It is followed by whether the patient is on dialysis or not and his/her functional status at the registration. Table 2 reports the number of patients in each class. Node 1 has the most patients. It only contains patients from a certain subset of OPOs. Figure 2 plots all ΔM vs. Δt data from Node 1.

Table 2: Classification Tree Node Summary

Node	1	2	3	4	5	6	7
# of Pat.	8811	1496	2102	1684	2213	2305	3233

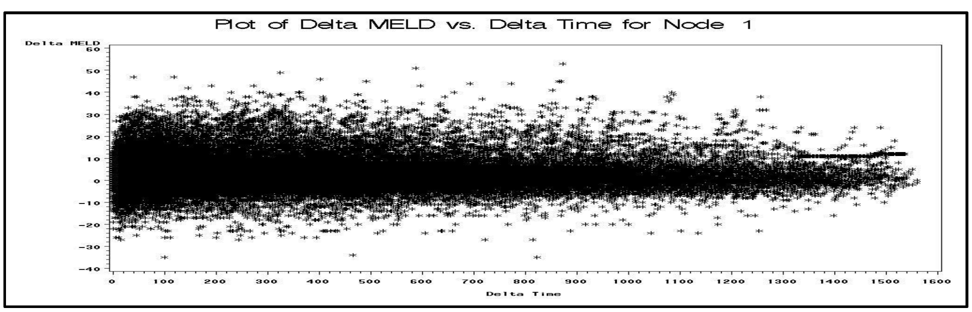
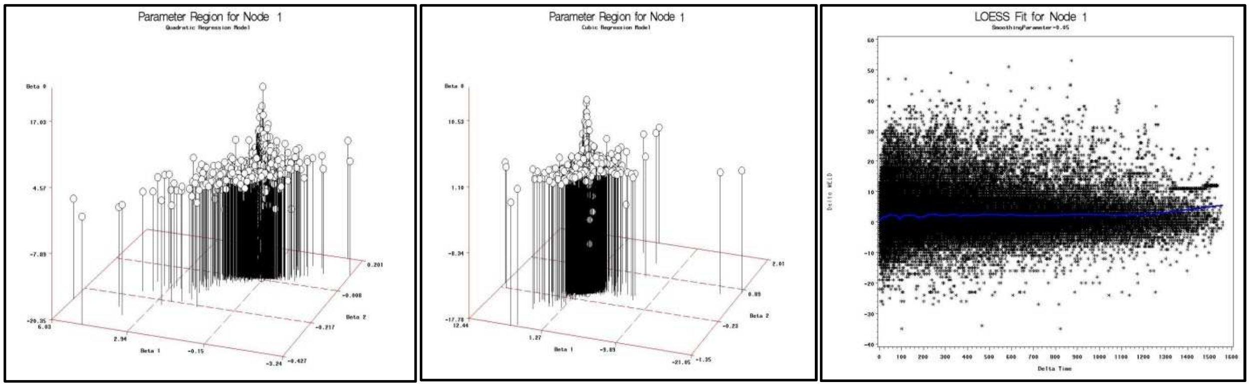


Figure 2: Data Plot for Node 1

For each tree node, we first regressed all patients' MELD readings with the application of smoothing. We then identified a regression model and estimate the parameters for each patient within the class. We applied both traditional nonlinear regression (quadratic and cubic) and local regression (loess method). Figures 3a and 3b show the regions of parameter estimators for Node 1 in the cases where the region models are quadratic and cubic, respecitvely. Figures 3c shows the Loess fit with smoothing parameter = 0.05 for patients in Node 1.



(a) (b) (c)

Figure 3: Regression analysis results

4. Conclusions and Future Research

In this paper, we present our first attempt in developing temporal prediction models for ESLD patients' mortality risks. In the future we will validate the models and explore more accurate models with higher predicting power.

References:

1. Adam, R. et al., 1995, "Deleterious Effect of Extended Cold Ischemia Time on the Posttransplant outcome of Aged Livers," Transplantation Proceedings, 27(1): 1181-1183.
2. Marino, I.R., et al., 1997, "Preoperative Assessment of Risk in Liver Transplant: A Multivariate Analysis in 2376 Cases of the UW era," Trans. Proc., 29(1-2), 454-455.
3. Child, C.G. III, and Turcotte, J.G., 1964, "Surgery and Portal Hypertension." In: Child C. G. III (ed), The Liver and Portal Hypertension, 49-64. Saunders, Philadelphia.
4. Pugh, R.N.H., et al., 1973, "Trasection of the Oesophagus for Bleeding Oesophageal Varices," British Journal of Surgery, 60, 646-649.
5. IOM, 1999, Organ Procurement and Transplantation, NAP, Washington, D.C.
6. Kamath, P.S., et al., 2001, "A Model to Predict Survival in Patients with End-Stage Liver Disease," Hepatology, 33, 464-470.
7. United Network for Organ Sharing. Policy 3.6. Allocation of Livers. Available at http://www.unos.org/PoliciesandBylaws2/policies/pdfs/policy_8.pdf.
8. Cox, D.R., 1972, "Regression Model and Life Tables (with Discussion)," Journal of the Royal Statistics Society – Series B, 34, 187-220.
9. Merion, R.M., et al., 2003, "Longitudinal Assessment of Mortality Risk among Candidates for Liver Transplantation," Liver Transplantation, 9(1), 12-18.
10. Lewis, R.J., 1999. "An Introduction to Classification and Regression Tree (CART) Analysis," Presented at the 2000 Annual Meeting of the Society for Academic Emergency Medicine, San Francisco, CA.
11. Fisher, R.A., 1936, "Heterogeneity of Linkage Data for Friedreich's Ataxia and the Spontaneous Antigens," Annals of Eugenics, 7, 17-21.
12. Breiman, L., et al., 1984, Classification and Regression Trees, Wadsworth International, Belmont, CA.
13. Cleveland, W.S, 1979, "Robust Locally-Weighted Regression and Smoothing Scatterplots," Journal of American Statistical Association, 74, 829-836.