HOW MELD SCORES AFFECT THE SURVIVAL RATE OF LIVER TRANSPLANT RECIPIENTS

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Abstract:

In this paper, we attempt to model the effects of the Model for End-Stage Liver Disease (MELD) scores on the survival rates of liver transplant recipients. We attempt to determine the MELD scores that are optimal for patient survival one year after transplantation. The purpose of this model is to determine allocation of livers so that they will be utilized most effectively. To utilize the limited resource, it is best to provide a liver to a patient with a higher rate of survival after transplantation over someone with a smaller chance of survival. The national average MELD Score for patients on the liver transplant waiting list is 20. We examine our data to determine whether this value is optimal for saving the most lives with liver transplants, since most patients are on the transplant list for 12-36 months. Using our model, we determine that the optimal MELD score range for transplantation is between 21-30.

Introduction:

The MELD Score stands for Model for End-Stage Liver Disease, which was implemented in February 2002 to prioritize patients on the liver transplant waiting list. This score determines how urgently a patient needs a liver transplant within the next three months and is assigned based on laboratory test results. Three primary lab tests are used in determining a patient's MELD Score: bilirubin level, INR, and Creatinine. Bilirubin measures how efficiently the liver excretes bile. INR measures the liver's ability to make blood-clotting factors. Creatinine measures kidney function, and is included due to the fact that impaired kidney function is often associated with severe liver disease. MELD scores generally range from 6-40 and are divided into 4 categories. Patients with the most critical MELD scores, of 25 or greater, includes a score of 25 or greater, require laboratory tests every 7 days. Patients in the next score range, from 19 to 24, require laboratory tests every 30 days. Patients in the last two score ranges, 11 to 18 and less than 10, each require labs every 90 days or every year, respectively. However, MELD scores are not the only deciding factor when it comes to allocating liver transplants. There are a few special cases that automatically assign higher scores than the lab results initially indicate. These cases include: liver cancer, Hepatopulmonary Syndrome, which is abnormal changes in the lungs caused by high pressure in the liver, creating shortness of breath and low oxygen levels, and Familial Amyloidosis, which is a rare chronic disease that inflates body organs and causes life threatening organ damage ("MELD").

Literature Review:

Every year, undergraduate students from around the world are given the chance to participate in the Interdisciplinary Contest in Modeling (ICM). Through the ICM, students are asked to construct a mathematical model answering various questions prompted to them. They are then asked to present their results in a paper format. The papers are sent to COMAP for judging. Two top papers, claimed to be

Outstanding by the expert panel of judges, have the opportunity to be published in an issue of *The UMAP Journal.*

In 2007, a record total of 273 teams from five countries spent a weekend in February working on an applied modeling problem involving managing and promoting organ transplantation. Specifically, the students were given six tasks. Their first task was to build a generic model for the U.S. transplant network, and determine if the current system for organ transplantation is working effectively. Their second task was to investigate the transplantation policies used in a country other than the U.S., and write a report to Congress addressing their findings. Task three asked students to specifically focus on kidney transplantations and devise a procedure to maximize the number and quality of exchanges. In task four, they were asked to determine the optimal strategy for a patient to decide whether or not to take an offered kidney or even participate in a kidney exchange. Task five prompted the students to look into the ethics of organ transplantation. Finally, task six wanted the students to look at the situation for potential donor perspective and determine a model for their risks (Arney, 2007).

After submission and judging, it was determined that there were two outstanding papers. The first is entitled "Optimizing the Effectiveness of Organ Allocation." This paper was written by a group of students from Duke University in Durham, NC. The second paper is entitled "Analysis of Kidney Transplant System Using Markov Process Models." Three students from Princeton University in Princeton, NJ authored this document. Both appeared in the Summer 2007 edition of *The UMAP Journal*.

The paper written by the students at Duke University began by giving an overview on what they determined to be the key factors doctors use when determining capability in kidney transplants. The Duke students said that ABO blood type, Human Leukocyte Antigens, and Panel Reactive Antibody tests were the three most important factors to be considered. From there, the contestants modeled the generic U.S. transplant network as a rooted tree, growing downward. They then approximated the network's functioning as a discrete-time process, where each time step represented one day with four specific phases. In the end, the Duke University students determined that the policies of the Euro-transplant have the best groundwork for success and that the U.S. would benefit from the implementation of a list paired donation system (Arney, 2007).

The second paper, "Analysis of Kidney Transplant System Using Markov Process Models," took a slightly different approach. In this paper, the Princeton University students used Markov processes to develop a mathematical model for the U.S. kidney transplant system. Their goal was to analyze the effect of certain parameters on transplant waitlist size, and to investigate the effects of policy changes on the model's behavior. Their results showed that waitlist size is increasing due to the

flood of new transplant candidates and insufficient deceased donor and living donor transplants available. Much like the preceding paper, this paper also suggests kidney-paired exchanges along with generic *n*-cycle kidney exchanges (Arney, 2007).

The summer 2007 issue of *The UMAP Journal* provided our group with inspiration for our own project. From the 2007 ICM, we got the idea to incorporate organ transplantation and donation into the topic for our research paper. We decided to replicate these models similarly for liver transplantation.

Another journal article, consisting of local data and written by researchers from the University of Pittsburgh, proved to be a useful tool for our project. This journal article titled, "A Clinically Based Discrete-Event Simulation of End-Stage Liver Disease and the Organ Allocation Process," is centered on the medical issue of liver transplantation. Unfortunately, the demand for livers is substantially greater than the supply of donor livers. In this article, the topic of optimal donor liver allocation is discussed and a corresponding model is created using Discrete-Event Simulation.

The data for this model came from the United Network for Organ Sharing (UNOS) as well as the University of Pittsburgh Medical Center (UPMC). From UNOS, the researchers used 17,044 patient records who had received transplants. Additionally, they used 1,997 patient records from UPMC. The data was used for various aspects of the model (Shechter, 2005).

The liver allocation model built in this journal article was a discrete event, Monte Carlo micro-simulation, written in C programming language. The model consists of 5 main modules: the patient generator, organ generator, pre-transplant natural history, matching algorithm, and post-transplant survival. These are discussed in great detail in the journal article and will be briefly explained below.

The first module, the patient generator, deals with the initial patient data by adding patients to the waiting list, assigning the patients various clinical and demographic attributes, and initializing "patient-specific variables." The organ generator module handles donor liver data by registering the arrival of the donated livers, determining the individual status of the respective donated livers, and generating the characteristics of the liver that will be used in the donor-recipient matching process. The pre-transplant natural history module models how the disease will advance in the patient between the time they are placed on the waiting list to the time they either receive a transplant or die before a transplant is available. The matching algorithm module uses variables in the model to determine a candidate's position on the waiting list at a given time. The post-transplant survival module models the probability of patient death and organ rejection or loss to assist in the estimation of survival probability distributions. In addition to the five main modules, quality of

life (of patients waiting for liver transplant) is another factor that is considered in the model (Shechter, 2005).

Before they were able to compare results from different allocation policies, the researchers needed to consider the possibility of random variation between simulation systems that could cause the results to be partially invalid. In order to eliminate this possibility, the researchers used standard variance-reduction techniques. They conducted a "warm-up period" across policies, starting with 1992 as the beginning of the simulation and using the same baseline matching process for testing the individual alternative policies. This assured that any differences observed between the policies were independent of patient type differences prior to 1992. In addition, the model went through several stages of validation before it was complete and before results could be obtained.

After running the data and creating various comparison charts and tables, the researchers were able to draw some conclusions from the model. The calculated results from the baseline model closely approximated the UNOS data, allowing researchers to conclude that the model can be used to approximate different aspects relating to liver allocation. Consequently, it follows that the model can be used to test different allocation policies and predict on some level the effectiveness of an allocation policy (Shechter, 2005).

Due to the severity of end-stage liver disease and the unfortunate gap between the supply and demand of donor livers, any advancement toward a solution to the liver allocation optimization problem is a step in the right direction. This journal article introduced a discrete-event simulation model, which can be used to compare different allocation policies, in an effort to determine the most efficient policy. Since our project is based on a comparison of MELD scores and survival rates, this article was helpful in proposing the idea of using a discrete event simulation to model our data.

Data:
The data that we have gathered to assist in creating our model is obtained from the Scientific Registry of Transplant Recipients (SRTR). Data is provided for all of the liver transplant centers within the United States that conducted transplants in 2011. We took a subset of this data and used data from the tri-state area of New York, Pennsylvania, and Ohio. For each of the transplant centers, the location of the hospital, the number of transplant candidates and the number of transplants conducted is supplied. Additionally, the survival rate percentage of the transplant recipient after one year is provided. From this statistic, we calculated the number of survivors and deaths at each hospital. The data also provides the percentage of patients within each MELD score range and blood type. The ranges of MELD scores are 6-10, 11-14, 15-20, 21-30, and 31-40. From these percentages and the number of transplant patients, we calculated the number of people in each category and use

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these to determine the optimal MELD scores for survival after transplantation. A condensed version of our data is provided on the next page.
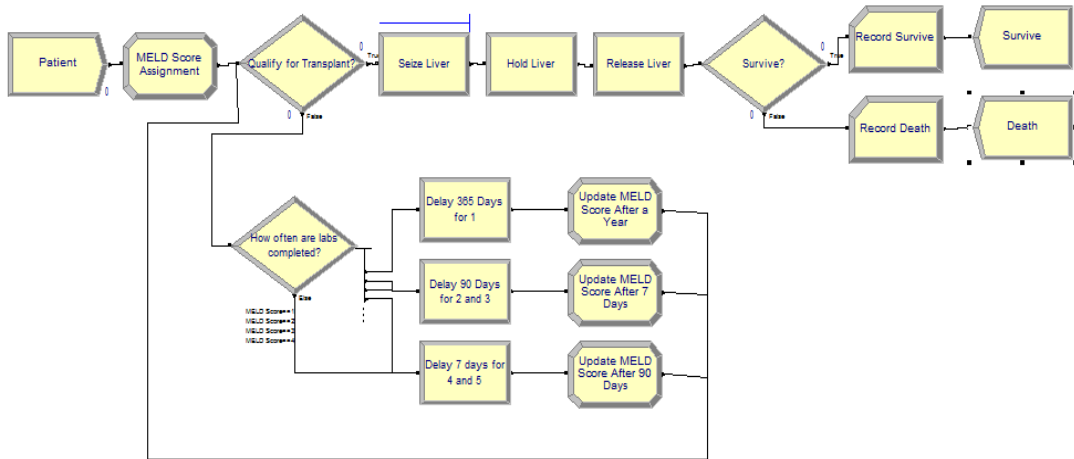

Figure 1: Screenshot of Model in Arena

Model:

Although this paper focuses only on the affects MELD scores have on the survival rates of liver transplant recipients, there are several other factors that must also be taken into account. A patient's match with a donor also depends on blood type, body size, and the geographic distance between the donor and recipient. We assume that these factors are optimal for transplantation in our model. Additionally, we assume 10 patients are added to the waiting list and 3 livers are available for transplant each day in the entire tri state area, but not for each hospital. Also, the data we have chosen to analyze only provides us with whether or not the transplant recipient survived for a year after transplantation; therefore, our projections cannot be extended to how long they will live beyond a year. The goal of our simulation is to maximize the number of people surviving at least one year after transplantation (SRTR).

In our model, the dependent variable is the survival rate of patients. Based on the data we collected, we hypothesized that if we allocate transplants to patients with a MELD score in the range of 21-30, then we will observe the highest survival rate. We used Arena simulation software to create our discrete event model and test our hypothesis.

In Arena, we first began buy using the create module to represent the number of patients, or entities, entering the waiting list. We set this value to represent the fact that an average of ten patients arrive each day. From there, each patient is randomly assigned a MELD score in the assign module. The MELD score was arbitrarily given

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to the entering patient as an attribute, based on our data and a determined discrete probability distribution. Then, using the decide module, it is determined, based upon a patient's MELD, score whether or not they will receive a transplant. In order to test our hypothesis, we will be changing the MELD score that permits transplantation for each separate simulation. Therefore, MELD Score is the independent variable. If a patient qualifies for transplant, whether or not they actually receive the transplant is based upon the number of available livers in the model. This is represented in a seize module, where we allow for three livers to enter our system each day.

If a patient does not qualify for a transplant, he/she will be sent through a loop in the model that re-evaluates his/her MELD score. So, a patient who enters the loop is first passed through a decide module where their initial MELD score is considered so that their delay between test times can be determined. If the patient is in 21-30 or 31-40 range they are delayed for seven days and then a value of .0001 is added to their score. If the patient is in the 11-14 or 15-20 range they are delayed for ninety days and then a value of .001 is added to their score. If the patient is in the 6-10 range they are delayed for 365 days and then a value of .01 is added to their score.

This re-evaluation simply entails an additional increase in the current MELD score to represent the worsening of the liver condition as time has passed while the patient remains on the waiting list. Then, the patient is put back into the appropriate MELD score range category, and the process is repeated. Three livers are available in the tri-state area per day, which is represented in the seize module. After the livers are seized, they are delayed one day and then released to the patient in a release module. The purpose for this one-day delay is to ensure that there are exactly three livers available each day, and that the supply of the livers is not replenished before the day is over.

Finally, it is then decided whether or not the patient survives the transplant or not. This is based on the data we collected. The numbers of people that do and do not survive are recorded in record modules and then the model is completed using dispose modules. The results are then given. Figure 1 shows the model created in Arena.

Results:
We ran our simulation five times; once for every category of MELD Score. Each trial of our simulation ran for five years, or 1,825 days. This let 18,250 people enter our system for each trial. We determined that when transplants were given to patients with a MELD Score that was in the 21-30 range, their chance of survival was the highest.

When we chose to give transplants to patients in the 21-30 range, a total of 1,825 patients actually received a transplant. 1,585 of these patients were recorded to

survive after one year, while 240 of these patients did not survive. This gave us an 86.9% survival rate, which was the highest survival rate of our five trials. During our simulation for this range, our reports showed us that the average MELD Score of the patients in our system, throughout the five years, was 3.5709. This means that the average score was in the 15-20 range. The number of MELD Scores updated through the loop in the 6-10 range was 2,218; in the 11-14 and 15-20 range were 5,006; and in the 31-40 range was 1,586,972. The report produced from Arena is shown in Figure 2.

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Unnamed Project — Replications: 1

Replication 1	Start Time:	0.00	Stop Time:	1,825.00	Time Units: Days

Tally

Expression	Average	Half Width	Minimum	Maximum
Record MELD SCORE	3.5907	(Correlated)	1.0000	6.0260

Counter

Count	Value
Record Death	240.00
Record getting updated 1	2,773.00
Record getting updated 2	2,235.00
Record getting updated 3	3,034.00
Record getting updated 4	0
Record getting updated 5	1,599,834.00
Record Number Updated 1	2,218.00
Record Number Updated 2 and 3	5,006.00
Record Number Updated 4 and 5	1,586,972.00
Record Released	1,825.00
Record Seized	1,826.00
Record Survive	1,585.00

Figure 2: Screenshot of Arena Output

Conclusion:

For our project, we created an Arena Discrete-Event simulation model to determine an optimal liver allocation system based on a transplant patient's MELD Score. This model assigns MELD scores to patients based upon a probability distribution of

MELD Scores. The model then allocates available donor livers to patients with MELD Scores of our choosing. After transplantation, the model decides the patient's survival outcome after one year and records the outcome. By running this simulation 5 different times, each time allocating livers to a different MELD Score level, we are able to compare the simulation results and determine a possible optimal strategy.

From the analysis of our results, we conclude that patients with MELD scores in the 21-30 range have the greatest chance of survival. This means, of all the patients waiting on the transplant list, it is optimal to transplant when their MELD score is between 21 and 30. Before this point, transplantation is not quite as necessary. After this point, the patient's chance of survival is not as high and decreases as the MELD score increases. By using these standards for transplantation, not only does it save the lives of patients, but it optimizes the use of the donated livers by giving them to patients with higher rates of survival after transplantation.

Further Research:
To expand on this project, data for the entire country could be used to obtain a more accurate model. Due to time constraints, we only obtained data from the tri-state area of New York, Ohio and Pennsylvania. Additionally, we only considered the MELD score ranges provided in our data. It is possible to alter these ranges in order to find an even more efficient range of MELD score for transplantation. In our model we also only considered permitting one range for transplantation at one time, this could be altered to include multiple ranges to be eligible for transplantation.

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