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Does the MELD Score Predict Mortality Before and After Liver Transplantation in Alberta?

by

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ABSTRACT

The growing demand for liver transplantation (LT) has resulted in a need to reevaluate our organ allocation system in Canada (CanWAIT), to ensure that the sickest patients will receive the next available organs. The purpose of this research was to validate the ability of the MELD score (Model for End-stage Liver Disease) to predict LT waiting list mortality in a cohort of Canadian patients. The MELD score's ability to predict 3-month and 1-year waiting list mortality was similar to the Child-Turcotte-Pugh (CTP) score and was significantly better than the CanWAIT status. The addition of hyponatremia did not improve the MELD. Despite increasing waiting time in recent years, MELD scores at time of LT are not increasing at the University of Alberta. MELD, CTP and CanWAIT status were all relatively poor predictors of survival following LT and MELD could not identify a point of futility for LT. Mechanical ventilation and renal function were more important predictors of survival following LT.

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I would like to thank my parents for their support and encouragement, especially during the last 18 years of my continuing post-secondary education. To my fiancée, Hilary I send my love. I could not have finished this project without her understanding and unconditional love.

This work is dedicated to the memory of my colleague and friend from the Mayo Clinic, Dr. David Brandhagen, who was taken from this world far too early. Godspeed my friend.

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LIST OF ABBREVIATIONS

ALF	Acute Liver Failure
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
CTP	Child-Turcotte-Pugh
ETOH	Ethanol (Alcohol)
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C
HR	Hazard Ratio
INR	International Normalized Ratio
LDLT	Live Donor Liver Transplant
LR	Likelihood Ratio
LT	Liver Transplantation
MELD	Model End-stage Liver Disease
OR	Odds Ratio
PBC	Primary Biliary Cirrhosis
ROC	Receiver Operating Characteristic
SBP	Spontaneous Bacterial Peritonitis
TIPS	Transjugular Intrahepatic Porto-systemic Shunt
UNOS	United Network of Organ Sharing
UofA	University of Alberta

I'm a peripheral visionary.

I see far into the future....

Just way off to one side.

Steven Wright, Comedian

1. INTRODUCTION

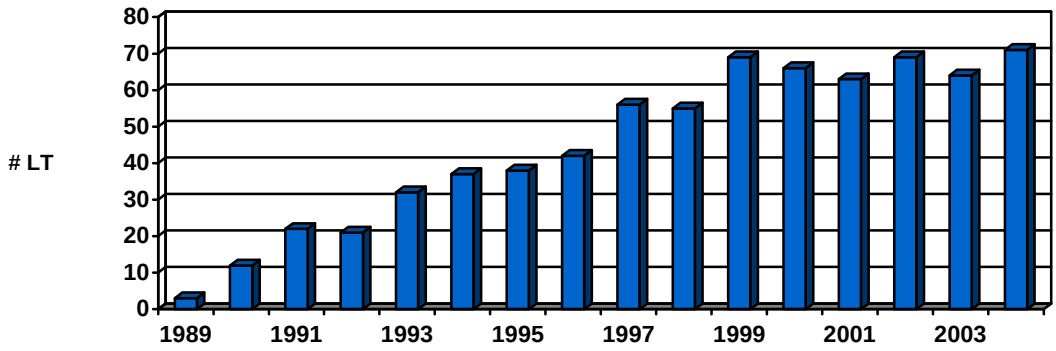
Waiting Time for Liver Transplantation

Liver transplantation (LT) is often the only life-extending option for patients with acute liver failure (ALF) and complications of chronic liver disease. In recent years the demand for LT has dramatically increased, largely due to the burden of chronic hepatitis C (HCV). In the USA, the number of patients awaiting LT has risen from 2,217 in 1992 to 18,505 in 2001 (1). However, the limited supply of cadaveric organs for transplantation has not increased to meet this growing demand. Over the same period of time, the number of cadaveric LT in the USA increased from 3,031 in 1992 to 4,665 in 2001 (1). Therefore, patients are waiting longer to receive their transplant. In the USA, the percentage of patients waiting longer than two years for LT increased from 13% in 1992 to nearly 40% in 2001 (1). This has lead to increasing rates of adult-to-adult live donor liver transplantation (LDLT); however, currently only 10% of LT preformed in the USA are from live donors and this percentage is not expected to grow higher than 15% (1).

The University of Alberta (UofA) began performing LT in 1989. Currently all patients from Alberta and Saskatchewan, as well as parts of Manitoba and British Columbia, who require LT will have their surgery in Edmonton. Between October 3, 1989 and December 31, 2004 a total of 722 LT were performed in 671 patients

at the UofA (Figure 1). This includes 108 LT into 91 pediatric patients and 34 LDLT, which were first performed at the UofA in 1998.

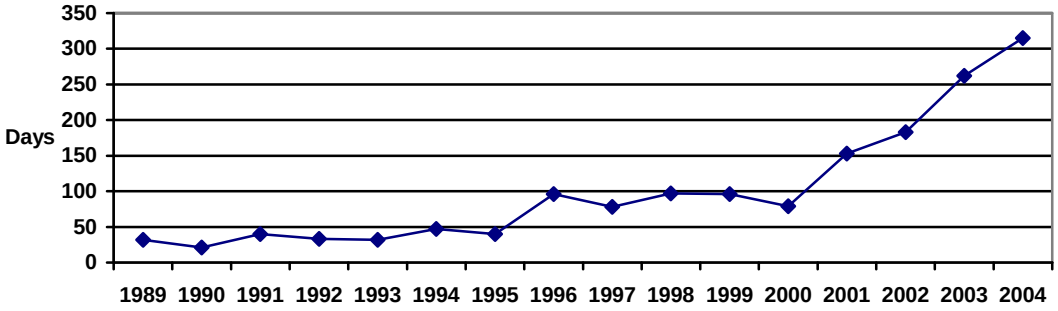
Figure 1. Number of LT per year at the UofA (1989-2004).



In the past, waiting lists in most Canadian transplant centers were short and mortality on the transplant waiting list was not a major problem. However, in recent years there has been an acute increase in the need for LT due the epidemic of HCV in this country. HCV has become the leading indication for transplantation in all Canadian centers. In 2003, 39% of adult LT performed at the UofA were done for HCV related liver disease (personal communication Dr. N. Kneteman). As donor rates have been relatively steady, the number of LT at the UofA has remained constant in the past 6 years (see Figure 1). The discrepancy between the need for LT and the availability of donor organs has resulted in significant increases in average waiting time for LT at the UofA (Figure 2). Over the past four years there has been a four-fold increase in waiting

time, from an average of 79 days in 2000 to 315 days in 2004 (personal communication Dr. Norman Kneteman). The problem is only expected to worsen, as it is estimated we will see a 106% increase in the prevalence of liver failure in Canada over the next decade due to HCV (2).

Figure 2. Average waiting time for LT at the UofA (excluding Status 3, 3F, 4 and 4F patients).



The increase in waiting time has resulted in more patients dying on LT waiting lists. In the USA, the total numbers of patients dying while awaiting LT increased from 519 in 1992 to 1,978 in 2001 (1). At the beginning of 2003 there were 59 adults on the LT waiting list at the UofA, and during that year there were 17 patients removed from the list because they had died or become too ill to undergo the surgery (personal communication Dr. Norman Kneteman). The dichotomy between supply and demand has led to a growing interest in the development of organ allocation systems for LT that ensure the greatest utility of this precious resource.

2. LITERATURE REVIEW

Organ Allocation in the USA

In 1998, the United Network of Organ Sharing (UNOS) adopted minimal listing criteria in the United States for patients to be placed on a LT waiting list (3). The Child-Turcotte-Pugh (CTP) classification was adopted to stratify severity of illness and need for transplantation. This index was initially developed to stratify operative risk of liver patients undergoing porto-systemic shunt surgery and has never been validated as a predictor of waiting list mortality (4). It is based on five variables (albumin, bilirubin, INR, encephalopathy and ascites) with each variable being given a score of 1-3 points depending on the magnitude of the liver dysfunction (Table 1). CTP scores therefore range from 5 to 15, and patients are broadly classified as having Child's A (5-6 points), Child's B (7-9 points), or Child's C (10-15 points) class cirrhosis.

Table 1. Child-Turcotte-Pugh (CTP) classification system

Variable	1 point	2 points	3 points
Ascites	None	Easily controlled	Poorly controlled
Encephalopathy	None	Grade 1 or 2	Grade 3 or 4
Albumin (g/L)	>35	28-35	<28
Bilirubin (µmol/L)	<17.1	17.1 - 34.2	> 34.2
INR	<1.7	1.7-2.3	>2.3

In the US, patients needed a CTP score of 7 points to be listed for LT and UNOS further stratified patients into four categories: Status 3 (CTP score 7-9), Status 2A (CTP score ≥10), Status 2B (CTP score ≥10, in the intensive care unit with an expected survival of < 7 days) and Status 1 (patients without chronic liver disease who developed acute fulminant liver failure) (3). Within blood groups, the next available organ would go to the patient with the highest status. With only 3 categories of disease severity for patients with chronic liver disease, there were many patients in each category who could potentially receive the next available organ. Ties were then broken by length of time on the waiting list. Under this system there was no guarantee that the sickest patient within each category would be the next to receive an organ.

The CTP classification system was criticized because the broad categories failed to prioritize patients for transplantation and therefore an emphasis was placed on waiting time. Under this system, patients were being listed earlier in the course of their liver disease so that they could accumulate waiting time before becoming too ill. This was reflected by a drop in LT waiting list death rates in the USA, falling from 270 (per 1000 patient years at risk) in 1992 to 115 in 2001 (1). The total numbers of patients dying while awaiting transplantation in the USA has steady increased over the past decade, but the actual death rates fell in recent years because of the increased number of relatively healthy patients that were placed on the waiting list (1). There is also other data that suggests waiting time is not a good predictor of mortality on the LT waiting list (5). Furthermore, two

components of the CTP score (severity of ascites and grade of encephalopathy) are subjectively assessed by physicians and therefore could be manipulated to increase the CTP score and a patient's transplant status. For these reasons, in 2000 the US Department of Health and Human Services adopted the Final Rule, which mandated the emphasis on waiting time be removed from the process of organ allocation in the United States and that an objective system be instituted to ensure that the sickest patients would be the next to undergo LT (6).

MELD Score and Liver Transplantation Waiting List Mortality

UNOS adopted the MELD scoring system as a means of liver allograft allocation in the USA in February 2002 (6). The MELD (Model of End-stage Liver Disease) was initially developed at the Mayo Clinic to estimate survival after the placement of TIPS (transjugular intrahepatic portosystemic shunts) (7). The MELD score provides an objective index of disease severity that is easily obtained from three laboratory values (serum creatinine, bilirubin and INR). It is calculated as follows:

$$MELD\ score = [0.957 \times \log_e(creatinine) + 0.378 \times \log_e(bilirubin) + 1.12 \times \log_e(INR) + 0.643] \times 10$$

with creatinine and bilirubin in mg/dL.

Kamath et al. subsequently validated the MELD in four other groups of patients with end-stage liver disease including 282 cirrhotic hospitalized patients, 491 outpatient cirrhotics, 326 primary biliary cirrhosis patients, and 1,179 historical patients diagnosed with cirrhosis at the Mayo Clinic (8). In all four groups, MELD

score was found to accurately predict 3-month and 1-year mortality using receiver operating characteristic (ROC) curve analysis (Table 2).

Table 2. ROC characteristics for MELD in predicting 3-month and 1-year mortality in 4 historical cohorts of patients (adapted from Reference 8). Values are expressed as area under ROC curve (95% confidence intervals).

	Hospitalized	Ambulatory Non-Cholestatic	Ambulatory PBC	Historical
N	283	491	326	1179
3-month mortality	0.87 (0.82-0.92)	0.80 (0.69-0.90)	0.87 (0.71-1.00)	0.78 (0.74-0.81)
1-year mortality	0.85 (0.80-0.90)	0.78 (0.70-0.85)	0.87 (0.80-0.93)	0.73 (0.69-0.76)

MELD has also been validated in a cohort of 129 European cirrhotic patients and was shown to be an excellent predictor of 6-month and 12-month survival in these patients (9). The 3-month mortality predicted by the MELD score has also been compared to actual waiting list mortality in 311 patients placed on the UNOS waiting list between November 1999 and June 2000 (10). The concordance for 3-month mortality was high (area under ROC curve = 0.82) (10). Subsequently, MELD has been validated in 3437 patients added to the LTwaiting list (UNOS Status 2A and 2B) in the USA between November 1999 and

December 2001 (11). In this study, 412 (12%) reached the primary endpoint of mortality within 3 months of listing, and the MELD score predicted mortality significantly better than the CTP score (area under ROC curve of 0.83 vs. 0.76; $p<0.001$) (11). The 3-month waiting list mortality in this study ranged from 1.9% for patients with a MELD <9 to a high of 71.3% for those with a MELD ≥ 40 (11). Higher MELD scores are associated with increased risk of mortality on the LT waiting list, with a MELD score of 30 representing a 3-month mortality risk of approximately 33% (11).

The MELD system was activated by UNOS on February 27, 2002. A preliminary assessment of MELD was performed on patients added to the list between February 28 and June 1, 2002 (1). Of patients with a MELD score >30, 38% received a LT within 30 days and 22% died while waiting for transplantation (1). Freeman published the experience with MELD after its first year as the new organ allocation system in the USA (12). He compared a 6-month period (February 27-August 30) in the years before and after the introduction of MELD. Under MELD there were fewer patients placed on the waiting list, fewer patients removed from the waiting list due to death or being too ill, and fewer live donor LT. Most importantly, the 90-day mortality after LT was the same for the MELD and the pre-MELD periods (12).

Because patients who are transplanted for hepatocellular carcinoma (HCC) often have less severe liver disease, UNOS assigned a MELD score of 24 to patients

with stage 1 HCC and a MELD score of 29 to patients with stage 2 HCC. Under the new allocation system there was a dramatic increase in the number of patients transplanted for HCC (21.5% vs. 8%) as these patients were artificially assigned higher MELD scores (1). The points awarded to HCC patients were therefore lowered to 20 and 24 points for stage 1 and stage 2 HCC patients, respectively. Subsequently, in April 2004 it was decided that only patients with stage 2 HCC would receive priority MELD points (13).

Recently, it has been suggested that the addition of serum sodium (Na) may improve the ability of MELD to predict LT wait list mortality (14). In this study, sodium levels and hyponatremia (Na <130) were significantly associated with 3-month wait list mortality using logistic regression. Furthermore, the addition of hyponatremia to MELD resulted in improved area under the ROC curve compared with MELD alone (0.905 vs. 0.894, p=0.006). Another study has confirmed that persistent ascites and hyponatremia (Na <135) were independent predictors of waiting list mortality in patients with lower MELD scores (≤ 20) but not in patients with higher MELD scores (15). UNOS is now studying the addition of hyponatremia to MELD prospectively, and it is apparent that the MELD allocation policy is under going a process of constant evolution (16).

Organ Allocation in Canada

Organ allocation in Canada is determined by the regional transplant centers using the CanWAIT algorithm (Table 3). Patients are grouped on waiting lists

according to blood group and body size. Of patients with chronic liver disease, those who are ventilated in the intensive care unit (ICU) have the highest priority for transplantation (status 4), followed by those in ICU not on a ventilator (status 3), those in the hospital (status 2) and finally patients awaiting transplantation at home (status 1). Patients with fulminant acute liver failure (ALF) receive a higher priority (status 3F or 4F), with organs being shared nationally for these very ill patients. Beginning in 2001, patients with large or rapidly progressing HCC were given priority over other patients at home (status 1T). In this system there are only five broad categories for patients with chronic liver disease. Therefore, as with the CTP categories previously used in the USA, the principal determinant of who is the next to receive a LT is the amount of time spent on the LT waiting list.

Table 3. CanWAIT liver allocation system (adapted from Reference 17).

CanWAIT Status	Definition
4F	ALF in ICU on ventilator
4	Chronic liver disease in ICU on ventilator
3F	ALF in ICU not requiring mechanical ventilation
3	Chronic liver disease in ICU for Grade 3 or 4 encephalopathy or renal dysfunction but not requiring ventilation
2	Chronic liver disease in hospital
1T	Chronic liver disease at home with HCC
1	Chronic liver disease at home
0	On hold for LT

With waiting time as the principle determinant of organ allocation in Canada, sicker patients who are referred late for LT may be disadvantaged. Therefore, it may be reasonable for Canadian transplant centers to adopt an objective scoring system, like the MELD score, to rank patients awaiting LT. In fact, a meeting of Canadian LT surgeons and hepatologists has been convened for October 2005 to discuss whether or not Canada should adopt the MELD score for liver allocation. However, the ability of the MELD score to predict LT waiting list mortality has not been validated in a population of Canadian patients and this must be done before MELD can be adopted in this country.

MELD Score and Survival after Liver Transplantation

Ideally, an organ allocation system would offer the next available organ to the patient with the most to gain. That would be someone with the greatest chance of dying without a transplant but also the best chance of surviving the surgery and returning to a good quality of life. Very ill patients have decreased survival after transplantation, and patients transplanted from the intensive care unit have higher death rates compared with patients called in for LT from home (1). There often comes a time at which a patient is so severely ill that their expected survival after transplantation is too low to warrant proceeding with the surgery. However, identifying this point of futility is very difficult.

Studies have shown that pre-transplant renal function is an important factor in predicting both early and late mortality after LT (18, 19). As creatinine is an

important component of the MELD, it stands to reason that the MELD score, calculated at time of LT, may also predict post-transplant mortality. A study of 404 adult patients undergoing LT at UCLA, found 1-year survival after transplant was worse in those with higher MELD scores (20). In this study, a MELD score of >36 carried a hazard ratio of 3.9 compared to a group with a MELD score <10 (20). Recent studies from a single centre in Texas have suggested the MELD score at time of transplant correlates with survival in the first two years after LT (21, 22). Specifically in a group of patients transplanted for HCV, patient and graft survival was lower at 3, 6, 12, and 24 months after transplant for those in the highest MELD strata (22). These studies suggest that MELD may not only identify the patients at highest risk of dying awaiting LT but may help us to identify patients who are too sick to undergo transplantation.

However, an examination of the largest LT database in the USA found the MELD score to be a relatively poor predictor of post-transplant outcomes (23). This study, which analyzed 2,565 patients from the UNOS database, demonstrated an increased risk of mortality and a longer hospital stay only in the patients with the highest quintile of MELD scores (MELD >24). A model that included recipient age, mechanical ventilation, dialysis and retransplantation was better at predicting post-transplant outcomes (23).

The only Canadian data regarding MELD comes from Dalhousie University (17). The authors of this study compared the ability of the MELD, CTP and CanWAIT

scores to predict 3-month mortality following LT in 228 LT recipients at the Atlantic Liver Transplant Program. The area under the ROC curve was similar for the CanWAIT (0.71), MELD (0.67) and CTP class (0.65). The authors concluded that MELD was not necessarily superior to the current CanWAIT system for predicting short-term outcomes after LT. In comparing the area under the ROC curves for the different scoring systems they concluded: “only the value for CanWAIT status exceeded 0.7, indicating that clinically it is the most useful” (17). However, they did not perform statistical testing to compare the area under the ROC curves for the three scoring systems. Given their relatively small sample size, the differences between ROC curves would not likely have been statistically significant if formal testing had been done. They also performed stepwise multivariate regression of 90-day survival with age, wait time, albumin, bilirubin, creatinine, MELD, CTP and CanWAIT status and found the CanWAIT status and age to be the best independent predictors of 90-day survival. However, this analysis can be criticized because it did not include mechanical ventilation, dialysis and retransplantation, which were previously shown to be important predictors of post-LT survival (23).

Research Rationale

In recent years, waiting times for LT have dramatically lengthened, resulting in an increased chance of dying while awaiting an organ. The current organ allocation system in Canada (CanWAIT) ranks patients with chronic liver disease according to location (intensive care unit, hospital ward or home) with ties in these broad

categories being broken by time on the waiting list. With the heavy reliance upon waiting time, this system does not guarantee that the sickest patients will be the next to undergo LT. In 2002, the United States adopted the MELD score as an objective means of allocating organs to the patients with the greatest need, thereby de-emphasizing waiting list time (6). The MELD score (based on bilirubin, creatinine and INR) was first used to predict survival after TIPS and was later validated as a predictor of mortality in patients awaiting LT in the USA (7-11). The MELD score's ability to predict waiting list mortality needs to be validated in a cohort of Canadian patients before it can be adopted as an organ allocation system in Canada. Studies examining the ability of the MELD score to predict post-LT mortality have yielded discrepant results (17, 20-23); therefore, further study is warranted to examine the ability of MELD to predict early post-LT mortality.

Design Considerations

This historical cohort study is designed to evaluate the prognostic ability of the MELD score. The MELD score has been adopted by the USA as a means of improving the equity of LT. This "sickest first" policy attempts to ensure that the patients with the greatest chance of dying will be the next to receive LT. Death on the LT waiting list is the clinically important outcome that MELD is predicting.

In general, prognostic or diagnostic tests are evaluated by determining their sensitivity, specificity, positive predictive value and negative predictive value (25).

The accuracy of the MELD score to correctly predict risk of death on the transplant waiting list was examined by calculating the area under the receiver operating characteristic (ROC) curve. The area under the ROC curve (equivalent to concordance or c-statistic) has become the most frequently performed statistical analysis in the validation studies of the MELD score (8-11). The ROC curve is a plot of sensitivity vs. 1-specificity and the area under the ROC curve provides a measure of the overall accuracy of a diagnostic test or prognostic model (26). The ROC curve is a combined measure of a model's positive and negative predictive powers. The area under a ROC curve ranges from 0-1, with 1 representing perfect discrimination and 0.5 being due to chance alone. For example, if you were to compare the risk of death in two patients awaiting LT, the area under the ROC curve would be 1.0 if the patient with the higher MELD score always died first (8). A diagnostic or prognostic test is generally accepted as clinically useful when the area under the ROC is ≥ 0.7 and a ROC area of 0.8-0.9 indicates an excellent ability to predict an outcome. In the validation studies of MELD the area under the ROC for MELD has generally ranged between 0.78-0.87 (10, 11). This indicates that at a given MELD score the model will correctly predict which patient is going to live and which is going die 78-87% of the time (24).

Alternatively, the validity of MELD as a prognostic test for survival can be examined by comparing mortality rates in different strata of MELD scores. If MELD accurately stratifies patients according to mortality risk, the highest strata

of MELD scores should have the highest mortality rates. The original study which validated the MELD score in four different population of chronic liver patients, examined survival within the following strata of MELD scores [≤9, 10-19, 20-29, 30-39, ≥40] (8). Onanca et al (20) also compared post-LT mortality in three MELD strata [<15, 15-25, >25]. The present analysis will therefore also examine survival before and after liver transplantation by different MELD strata, CTP classes and CanWAIT status.

3. OBJECTIVE

The primary purpose of this research was to validate the ability of the MELD score to predict mortality in a cohort of Canadian patients awaiting LT and to determine if MELD was superior to the CTP score and CanWAIT status in predicting waiting list mortality.

4. RESEARCH QUESTIONS

Primary Research Question

1. Is the MELD score at time of listing better than the CTP score and CanWAIT status at predicting 3-month and 1-year mortality on the LT waiting list?

Secondary Research Questions

1. As waiting times have lengthened in more recent years, have the MELD scores of patients transplanted between July 01, 2000 – December 31, 2002 increased compared to those transplanted between January 01, 1998 – June 30, 2000?
2. Does the addition of hyponatremia to the MELD score improve its ability to predict wait list mortality?
3. Is the MELD score at time of transplantation better than the CTP score and CanWAIT status at predicting 3-month and 1-year mortality after LT?
4. At the time of LT, is there a MELD score that can predict a low success rate of the LT (a 1-year survival of <50%)?
5. Are other variables better predictors of post-LT survival than MELD?

5. RESEARCH HYPOTHESES

1. When compared with the CTP score and the CanWAIT status, the MELD score (at time of listing) will more accurately predict the 3-month and 1-year mortality on the transplant wait list for patients listed for LT at the UofA.
2. Increasing waiting times in recent years will result in higher MELD scores for patients transplanted between July 01, 2000 – December 31, 2002 compared to those transplanted between January 01, 1998 – June 30, 2000.
3. Addition of hyponatremia will improve the ability of the MELD score to predict wait list mortality.
4. When compared with the CTP score and the CanWAIT status, the MELD score (at time of LT) will more accurately predict the 3-month and 1-year mortality after transplantation for patients who underwent LT at the UofA.
5. A MELD score will be identified which predicts a one-year post-LT survival of <50%.
6. Other variables, such as mechanical ventilation or renal function, will be identified through multivariate analysis as predictors of decreased post-LT survival.

6. METHODS

Study Design and Population

The ability of the MELD score to predict LT wait list mortality and early post-transplant mortality was examined in two historical cohorts of patients at the UofA, from whom data had been collected prospectively into an electronic chart (OTTR) and a LT research database. As not all patients listed will survive long enough to undergo LT, for the purpose of this analysis two cohorts of patients at the UofA were examined: 1) those placed on the LT waiting list between January 1, 1998 and December 31, 2002 *(Wait List Analysis)* and 2) those who received LT between January 1, 1998 and December 31, 2002 *(Post-LT Analysis).*

Inclusion Criteria

- Adult patients (>18 years old) who were listed for or had cadaveric LT at the UofA between January 1, 1998 and December 31, 2002

Exclusion Criteria

- Pediatric patients (<18 years old)
- Previous solid organ (including liver) or bone marrow transplant
- Patients who received simultaneous small bowel or renal transplants
- Patients who received a transplant from a live donor (LDLT)
- Patients who voluntarily removed themselves from the list because they no longer wanted LT

- Patients who were removed from the list because they recovered liver function (too well to need LT)
- Patients who were delisted for active substance abuse or medical issues discovered during the transplant evaluation (prior to activation)
- Patients without complete laboratory data to calculate the MELD (creatinine, bilirubin and INR) at time of transplantation or within 3 months of the listing date for LT

Note: This study did include patients who were listed with fulminant acute liver failure (ALF = status 3F or 4F), although these patients receive preferential status and in the USA are not ranked by the MELD score. The analysis was therefore completed both with and without ALF patients.

Operational Definitions

The primary outcome variable in this study is mortality. Mortality was defined differently in the Wait List and Post-LT analyses.

Wait List Analysis: Mortality = death or delisting for being too ill

Post-LT Analysis: Mortality = death

Study Location and Access to Research Setting

This research project was performed in Calgary, with data being provided by the UofA Liver Transplant Program in Edmonton. As the director of the Southern

Alberta Liver Transplant Clinic (SALTC), I am responsible for the care of approximately 160 patients who were transplanted in Edmonton. Clinical and laboratory information on LT patients is maintained in an electronic chart (OTTR) from the time patients are listed for LT. The OTTR electronic chart is located both in Calgary and Edmonton, and these clinical databases are connected electronically. Data on patients who receive LT is also stored in a separate research database in Edmonton. Dr. Norman Kneteman (Director of Transplantation) and Dr. Vince Bain (Medical Director of Liver Transplantation) granted me access to the Edmonton Liver Transplant Research Database that is maintained and operated by the LT research coordinator, Glenda Meeberg.

Data Collection

Data within the research and OTTR clinical databases was extracted and recorded in an Excel spreadsheet. The data was then imported into STATA 8.0 (STATA Corp., College Station, TX) for all analysis. The data was checked for missing and implausible values. Summary statistics for the continuous data and proportions for categorical data were calculated for descriptive purposes.

Data Elements

Survival on the LT wait list was calculated from the time of listing until patients were transplanted or until they were removed from the list because of death or because they had become too ill (delisting). The OTTR database was used to obtain the laboratory data (bilirubin, creatinine and INR) needed to calculate the

MELD score (within three month of listing date). Additionally, albumin, aspartate aminotransferase (AST), alkaline phosphatase (ALP) and sodium (Na) levels were collected. Patient demographics (age, sex and home city) as well as liver disease diagnosis, blood group, comorbidity (diabetes, infection) and complications of chronic liver disease (ascites, spontaneous bacterial peritonitis, variceal bleeding, encephalopathy, renal dysfunction and need for portosystemic shunting) were collected from the research database and electronic chart.

The laboratory data (as above) for post-LT analysis was collected immediately prior to the surgery. Other data collected at the time of transplant included: age, sex, home city, liver disease diagnosis, mechanical ventilation, dialysis, waiting time and location at time of call for LT (home, hospital or ICU).

Statistical Analysis

All statistical tests were performed using STATA 8.0 software. Tests of significance were two-sided with an alpha value of 0.05.

Calculation of the MELD Score

The MELD score was calculated as per the original model developed at the Mayo clinic (2). The formula for calculating MELD (MELDMAYO) is as follows:

$[0.957 \times \log_e(\text{creatinine}) + 0.378 \log_e(\text{bilirubin}) + 1.12 \log_e(\text{INR}) + 0.643] \times 10.$

Creatinine and bilirubin were converted from µmol/L to mg/dL (conversion factor 17.1 for bilirubin and 88.4 for creatinine). The MELD score was also calculated

as per UNOS guidelines (MELDUNOS), with the following exceptions: no extra points were awarded for hepatocellular carcinoma (HCC), and the score was not capped at 40. When calculating the MELD score, UNOS takes values of creatinine, bilirubin and INR that are <1 and increases them to 1.0 to avoid negative MELD scores. Creatinine values of >4 mg/dL are decreased to 4.0, and patients on dialysis with a creatinine <4 mg/dL have the value increased to 4. Not capping the MELD score allowed for examination of the full range of MELD scores to determine if higher MELD scores are positively correlated with an increased risk of mortality in our population. As some of our tumour patients were given preferential status (status 1T) beginning in 2001, separate analysis of waiting list mortality was performed both including and excluding hepatocellular carcinoma patients.

Wait List Analysis

Primary Research Question

To answer the primary research question, logistic regression was used to examine the ability of MELD, CTP and CanWAIT status to predict 3-month and 1-year mortality on the LT waiting list. The primary outcome was mortality, a dichotomous variable defined as death or delisting for being too ill. Predictor variables included the CanWAIT status, CTP score and MELD score as continuous variables. The models were compared using a chi-squared test for the equality of the area under the ROC curves calculated by STATA using a non-parametric algorithm suggested by DeLong et al (27).

The ability of the MELD score to predict one-year wait list survival was also examined using standard survival analysis techniques. Survival was calculated from the time of listing on the LT waiting list until death or removal from list (too ill). Patients were censored at the time of LT or at 365 days. Kaplan Meier curves were created for patients within five strata of MELD scores [≤9, 10-19, 20-29, 30-39, ≥40] and three MELD strata [<15, 15-25, >25] as well for the three CTP classes and the different CanWAIT categories. Differences in survival curves were compared using the log-rank test. These categories were also used as independent variables in a Cox proportional hazards model, in which time to death or delisting was the dependent variable. The hazard ratios for the different MELD strata were compared using the lowest MELD strata as the reference group. CTP classes B and C were compared to CTP class A patients and comparisons among CanWAIT categories used Status 0 patients as the reference group.

Secondary Research Questions

Median waiting times for LT were calculated for each year of the study period and were compared using the Kruskal-Wallis rank test. The median waiting time for the first half of the study period (January 01, 1998 – June 30, 2000) was compared to the second half of the study period (July 01, 2000 – December 31, 2002) using a two-sample Wilcoxon rank-sum (Mann-Whitney) test. Summary statistics for MELD scores at time of transplant were calculated for each one-year

interval of the study period and were compared using the Kruskal-Wallis rank test. The median MELD scores for the first (January 01, 1998 – June 30, 2000) and second (July 01, 2000 – December 31, 2002) halves of the study period were compared using a two-sample Wilcoxon rank-sum (Mann-Whitney) test.

To examine whether hyponatremia could improve the ability of the MELD score to predict wait list mortality, multivariate logistic regression and Cox proportional hazards models with and without hyponatremia were compared using the likelihood ratio (LR) test.

Post-LT Analysis

Secondary Research Questions

Logistic regression was used to examine the ability of MELD, CTP and CanWAIT status to predict 3-month and 1-year mortality after LT. The areas under the ROC curves were compared for the MELD score, CTP score and CanWAIT status. Patient survival was estimated using Kaplan-Meier method and survival between MELD strata, CPT classes and CanWAIT categories was compared using the log-rank test. These categories were also used as independent variables in a Cox proportional hazards model, in which time to death or delisting was the dependent variable. Hazard ratios for the different categories were calculated with comparison to a reference group (lowest MELD strata, CTP class A or CanWAIT status 1).

To examine if there was a MELD score that could predict a low success rate of the LT (a 1-year survival of <50%) mortality rates were compared for patients within five strata [≤9, 10-19, 20-29, 30-39, ≥40]. Mortality rates for patients with MELD scores <30 and those ≥30 were compared with a Fisher's exact test.

To determine if other variables are better predictors of post-LT survival than MELD, univariate and multivariate Cox proportional hazards regression models for 1-year post-LT survival were examined.

Sample Size Considerations

The wait list analysis examined 320 patients listed for transplantation at the UofA, of which 49 patients were removed from the waiting list because of death or for becoming too ill. This provides a similar sample size to the initial study performed to validate the MELD (8), in which four groups of chronic liver patients were used with sample sizes of 282 hospitalized cirrhotics, 491 outpatient cirrhotics, 326 PBC outpatients and 1,179 historical cirrhotics. Subsequently, MELD has also been validated using 311 patients added to the UNOS waiting list (10) and in 129 European patients (9).

The post-LT analysis examined 250 patients who received a LT at the UofA, of which 32 patients died within the first year after transplantation. This is similar to previously published studies that have looked at the MELD score's ability to

predict post-transplant survival, which had sample sizes ranging from 228 to 669 subjects (17, 20, 21).

Ethical Considerations

Prior to initiating this project the Research Ethics Boards in both Calgary and Edmonton reviewed and approved this protocol (see APPENDIX A). The analysis for this project involved a retrospective review of an existing electronic chart and research database. Data was stored, analyzed and presented in an anonymous manner. There was no need to contact patients or their families directly for additional information. As many subjects were deceased, individual consent would have been impossible to gain. Therefore, the Research Ethics Boards in Calgary and Edmonton waived the requirement for individual consent.

7. RESULTS

WAIT LIST ANALYSIS

Subjects

A total of 354 adults met inclusion criteria and were listed for LT at the UofA between January 01, 1998 and December 31, 2002. Of these patients, a total of 34 subjects were excluded from this analysis. Seventeen subjects were delisted for being too well or because they no longer wanted to proceed with LT. Eight patients were delisted for active substance abuse (most commonly ongoing alcohol consumption). Four patients were removed because of significant comorbidity discovered during the LT evaluation, including non-hepatocellular carcinoma in 2 subjects, unstable cardiovascular disease in one subject, and an uncontrolled seizure disorder in one subject. One subject was made inactive for many months with osteomyelitis and lung infections and had not undergone LT at the time of analysis. One subject was excluded because there were insufficient laboratory results within 3 months of listing to calculate a MELD score. Therefore, the final analysis was performed on 320 subjects. The mean age (±SD) of subjects listed was 50.2±10.0 with a median age of 50.3 years (range 20.8 to 70.3). More males were listed than females (67.5% vs. 32.5%). The most common indications for LT were alcoholic liver disease (33.4%) and HCV (32.8%). Fifteen subjects (4.7%) had acute liver failure (ALF). The numbers of subjects added to the LT waiting list each year is shown in Table 4. More patients were added to the waiting list during the later years.

Table 4. Number of subjects added to the LT waiting list by year.

Listing Year	Number of Subjects	Percentage
1998	55	17.19%
1999	50	15.63%
2000	70	21.88%
2001	73	22.81%
2002	72	22.50%
Total	**320**	**100.00%**

The home addresses of subjects were as follows: city of Edmonton (23.4%), city of Calgary (22.2%), other Alberta city or town (32.2%) and other province (22.2%). Table 5 summarizes the distribution of patients according to their Health Region.

Table 5. Distribution of subjects listed for LT by Health Region.

Health Region	Number of Subjects	Percentage
R1 - Chinook	10	3.13%
R2 - Palliser	4	1.25%
R3 - Calgary	**80**	**25.00%**
R4 - David Thompson	25	7.18%
R5 - East Central	6	1.88%
R6 – Capital (Edmonton)	**91**	**28.44%**
R7 - Aspen	17	5.31%
R8 - Peace County	13	3.75%
R9 - Northern Central	4	1.25%
R0 - Out of Province	**71**	**22.19%**
TOTAL	**320**	**100.00%**

Table 6 shows the CanWAIT status at the time of listing for 320 subjects. The majority of patients were listed as Status 1 (waiting at home for LT); however, nearly one-third of patients were listed as Status 0 (pending further investigations before being activated).

Table 6. Distribution of CanWAIT status at the time of listing for LT.

CanWAIT Status	Number of Subjects	Frequency
0	105	32.81%
1	146	45.63%
1T	9	2.81%
2	43	13.44%
3	4	1.25%
3F	1	0.31%
4	4	1.25%
4F	8	2.50%
TOTAL	**320**	**100.00%**

Continuous Variables

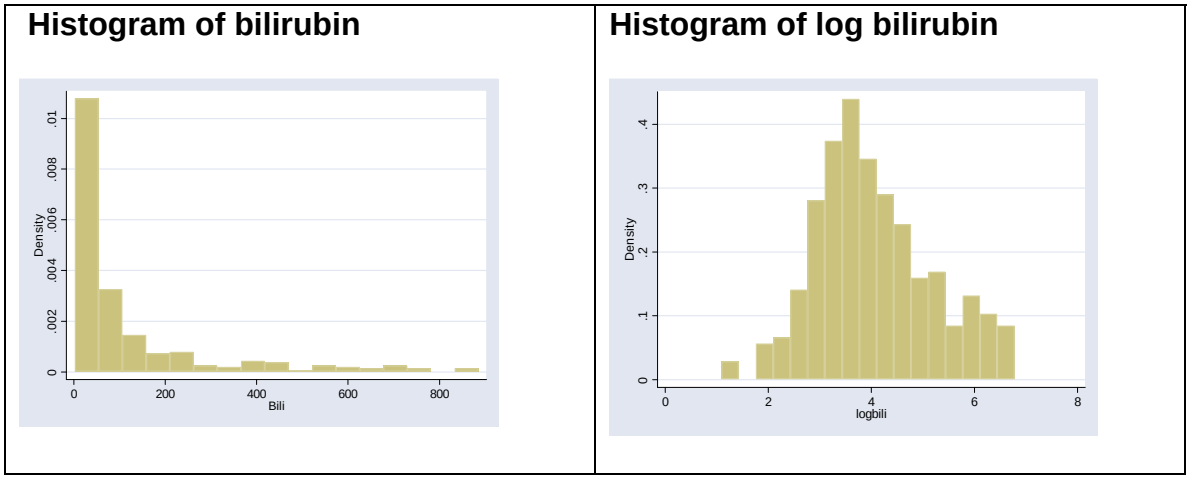
Data was collected on the bilirubin, INR, creatinine, albumin, AST, ALP and sodium at the time of listing for LT, and summary statistics for these continuous variables are shown in Table 7. The albumin and sodium levels were normally distributed. Log transformations were performed on the non-normally distributed variables (bilirubin, INR, creatinine, AST and ALP) before further analysis. The

distribution of the variables used to calculate MELD before and after the log transformations are summarized in the histograms of Figure 3.

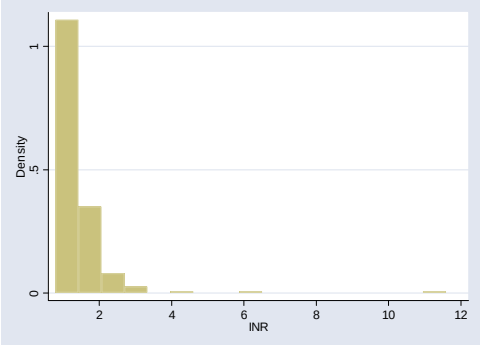
Table 7. Summary statistics for continuous variables at time of listing.

Variable	Mean	Std Dev	Median	Low	High
Bilirubin (µmol/L)	115.8	164.5	47	3	886
INR	1.4	0.8	1.3	0.8	6.2
Creatinine (µmol/L)	103.2	89.0	81	22	911
Albumin (g/L)	29.8	6.6	30	14	51
AST (U/L)	161.4	556.7	78	12	9100
ALP (U/L)	235.4	236.4	165.5	29	1980
Sodium (mmol/L)	135.8	5.3	136	120	154

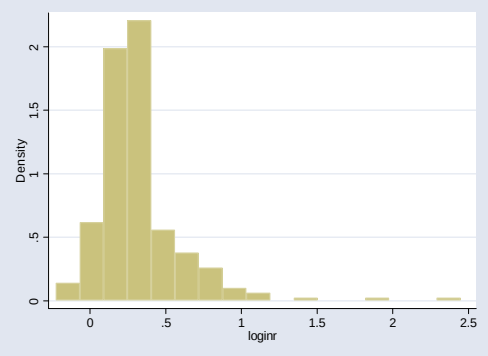
Figure 3. Histograms of bilirubin, INR and creatinine before and after log transformations.



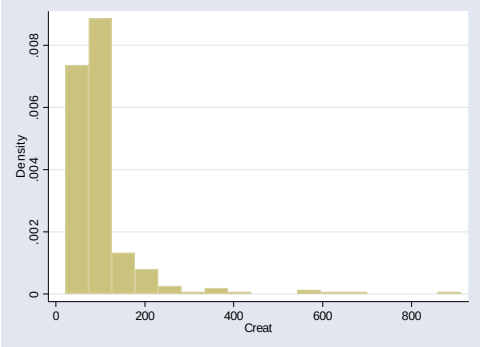
Histogram of INR



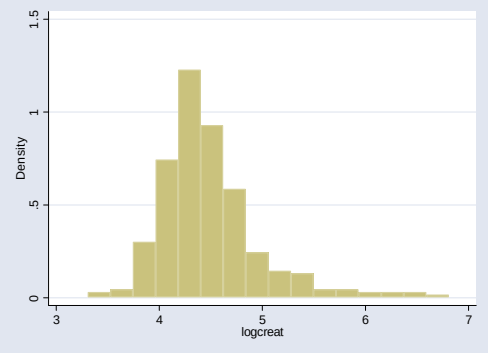
Histogram of log INR



Histogram of creatinine



Histogram of log creatinine



Categorical Variables

Data was collected on the following categorical variables: complications of cirrhosis, comorbidities, the need for dialysis and porto-venous shunting prior to LT. The frequency of these variables is summarized in Table 8. Ascites was the most common complication of cirrhosis and was present in 75.6% of subjects at time of listing for LT. The ascites was complicated by spontaneous bacterial peritonitis (SBP) in 4.7% of subjects. Varices were present in 59.1% of subjects but bleeding varices were seen in only 45.9%. Portosystemic encephalopathy (PSE) was seen in nearly one-half of subjects at listing (48.4%). Thirteen

subjects (4.1%) were on dialysis at the time of listing. Porto-venous shunting had been performed in 17 subjects, and in all but one patient this was done with TIPS. A total of 60 subjects had diabetes at the time of listing, but 42 subjects (13.1%) were controlled with diet alone and only 18 subjects (5.6%) were on therapy for diabetes at time of listing for LT.

Table 8. Frequency of categorical variables at listing.

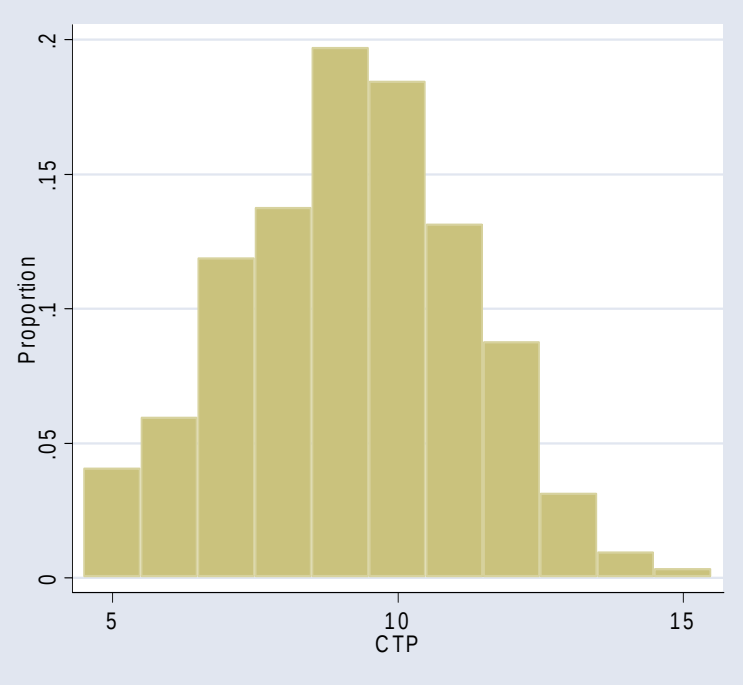
Variable	n	Frequency
Ascites	242	75.6%
Encephalopathy	155	48.4%
Bleeding Varices	147	45.9%
SBP	15	4.7%
Dialysis	22	4.1%
Infection	74	23.1%
Diabetes	60	18.8%

Calculated Variables

Child-Turcotte-Pugh (CTP) Score

The mean (±SD) CTP score was 9.18 ± 2.03, with a median score of 9 (range 5 to 15). The distribution of CTP scores at time of listing is illustrated in Figure 4. Ten percent of subjects were CTP class A at listing (CTP score 5 or 6). CTP class B cirrhosis (CTP score 7-9) accounted for 45.3% of subjects and 44.7% had CTP class C cirrhosis (CTP score 10-15) at the time of listing for LT.

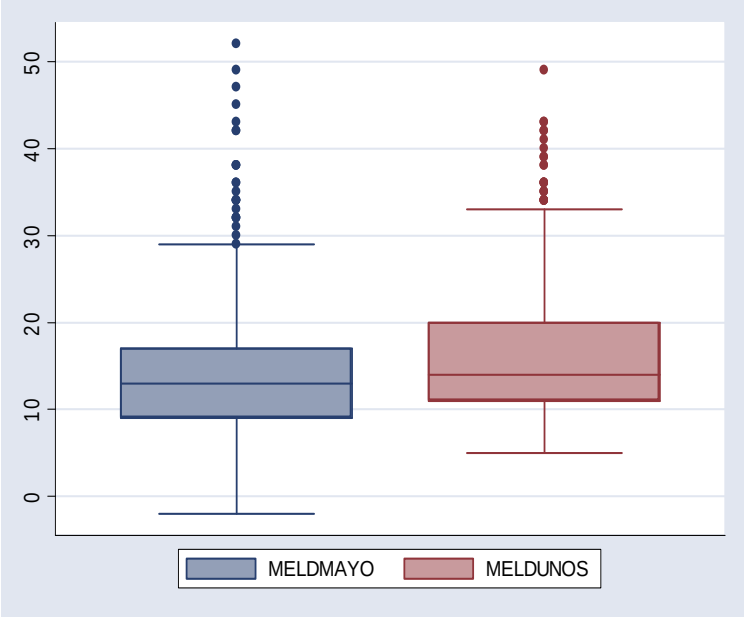
Figure 4. Histogram of CTP scores at listing.



MELD Score

The MELD score was calculated as per the original Mayo model (MELDMAYO) and as per UNOS guidelines (MELDUNOS) (Figure 5). The MELDUNOS scores ranged from 5 to 49; there are no negative MELD scores because the individual components of MELD are rounded up to a value of 1.0 if they are less than 1.0 (log of a number between 0 and 1 will give a negative value). The MELD scores were positively skewed with a median score of 13 (range -2 to 52) for MELDMAYO and 14 (range 5 to 49) for MELDUNOS. Because the scores are similar and MELDMAYO is unadjusted, throughout the remainder of the paper the MELDMAYO will be used as the MELD score.

Figure 5. Boxplots comparing MELD scores at time of listing calculated as per the Mayo model (MELDMAYO) and UNOS (MELDUNOS).



Wait List Mortality

Primary Research Question: Is the MELD score at time of listing better than the CTP score and CanWAIT status at predicting 3-month and 1-year mortality on the LT waiting list?

The main outcome variable in the Wait List analysis was mortality (defined as death or delisting) while awaiting LT. Of the 320 subjects, 271 patients (84.69%) successfully underwent LT. A total of 49 patients (15.31%) were removed from the waiting list because of death or delisting for being too ill (Table 9). Thirty-one removals occurred within 3 months of listing and 47 of the 49 removals occurred within one year of listing. Seven patients were removed from the list because

their hepatocellular carcinoma progressed beyond the accepted criteria for LT (13). Nine patients had become too ill for LT and were removed from the list shortly before their deaths. Four patients went to the operating room for transplantation but did not receive an allograft. One of these patients was found to have disseminated cholangiocarcinoma and one patient was found to have an adenocarcinoma mass at the porta hepatitis at laparotomy. One LT was abandoned because of significant pulmonary hypertension discovered in the operating room and one patient developed cardiac instability before the LT could be completed.

Table 9. Reasons for removal from the LT waiting list.

Reason for Removal	Number of subjects
Death	29
Delisted for hepatocellular carcinoma progression	7
Delisted for being too ill	9
Aborted surgery	4
Total	**49**

The mortality rates on the waiting list by MELD categories, CTP class and CanWAIT categories are shown in Table 10. The mortality rates ranged from 7.6% for MELD scores ≤9 to 46.7% for MELD scores 30-39. Within the CTP class, the highest mortality rates (25.2%) were seen in class C (CTP score 10-15). Although the numbers were very small, patients with chronic liver disease on a ventilator (status 4) had the highest mortality rate within the CanWAIT system.

Table 10. Overall Wait List mortality by MELD Strata, CTP class and CanWAIT categories.

MELD	≤9	10-19	20-29	30-39	≥40
Deaths	7	22	11	7	2
Total (n)	92	160	46	15	7
Mortality	7.6%	13.8%	23.9%	46.7%	28.6%

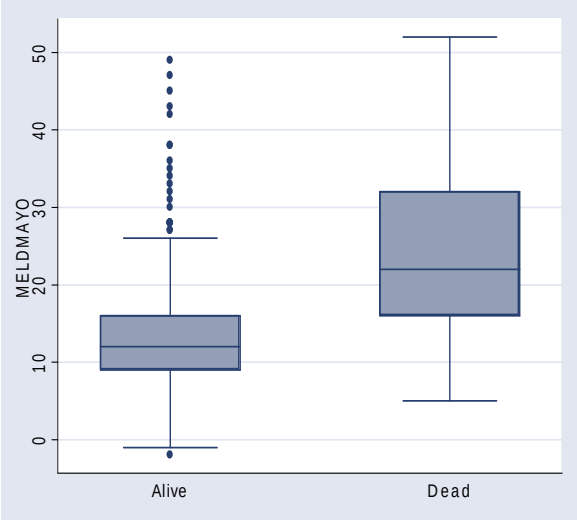
CTP Class	A	B	C
Deaths	3	10	36
Total (n)	32	145	143
Mortality	9.4%	6.9%	25.2%

CANWAIT	0	1	1T	2	3	3F	4	4F
Deaths	15	20	2	7	1	0	2	2
Total (n)	105	146	9	43	4	1	4	8
Mortality	14.3%	13.7%	22.2%	16.3%	25%	0%	50%	25%

3-Month Wait List Mortality

The median MELD score in subjects who died within the first 3 months of listing was 22 (range 5 to 52) compared to a median MELD score of 12 (range -2 to 49) for those surviving (Mann-Whitney test, p<0.0005) (Figure 6).

Figure 6. Boxplots of MELD score for patient who did and did not survive 3 months on LT waiting list (Mann-Whitney test, p<0.0005).



From logistic regression, the estimated odds ratios (95% CI) per unit change in MELD, CTP and CanWAIT status for the prediction of 3-month mortality are summarized in Table 11. The more clinically meaningful OR for a 10 unit change in MELD score is also presented (MELD/10). Interaction terms for age and sex were not significant indicating there was no evidence of effect modification by age or gender. There was also no evidence of confounding by age or sex. Therefore, the crude odds ratios are reported.

Table 11. Estimated OR (95% CI) per unit change in MELD, CTP and CanWAIT for 3-month wait list mortality.

	Odds Ratio	95% Confidence Interval		p value
MELD	1.1	1.06	1.14	<0.0005
***MELD/10**	2.59	1.81	3.71	<0.0005
CTP	1.65	1.33	2.06	<0.0005
CanWAIT	1.31	1.08	1.60	0.006

* MELD/10 represents the OR per 10 unit change in the MELD score

The three ROC curves for 3-month waiting list mortality are shown in Figure 7, and the estimated area under ROC curves and 95% confidence intervals for the MELD, CTP and CanWAIT status are shown in Table 12.

Figure 7. ROC curves for MELD, CTP and CanWAIT scores for 3-month waiting list mortality.

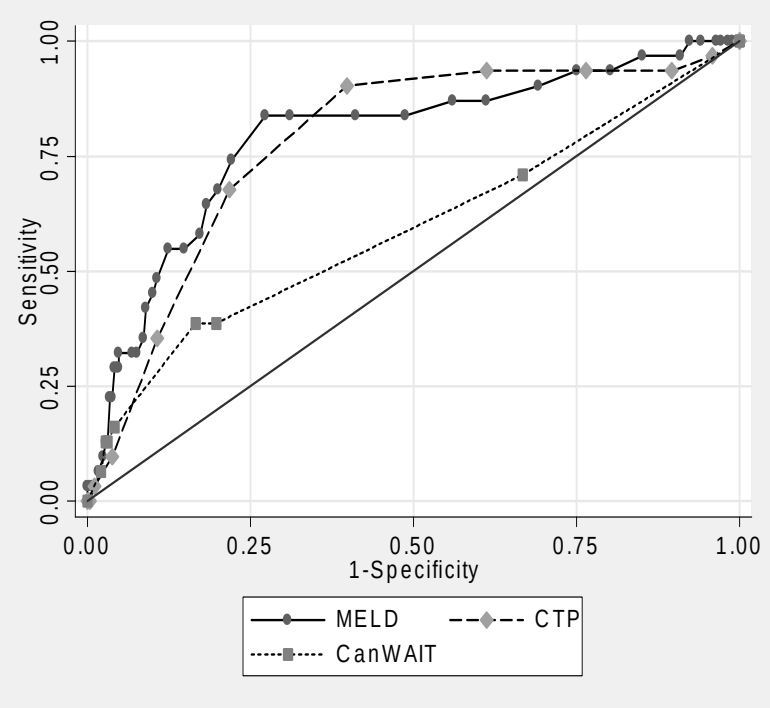


Table 12. Estimated area under ROC curve (95% CI) for the MELD, CTP and CanWAIT for prediction of 3-month waiting list mortality.

	Area under ROC	95% Confidence Interval	
MELD	0.79	0.70	0.88
CTP	0.78	0.69	0.86
CanWAIT status	0.59	0.48	0.71

The area under the ROC curves was similar for the MELD and CTP scores (p=0.8043). The ROC area for the CanWAIT status was only 0.59 and was significantly lower than the area under the ROC curve for both the MELD (p=0.0005) and CTP scores (p=0.0015).

1-Year Wait List Mortality

The median MELD score in subjects who died within the first year of listing was 17 (range 2 to 52) compared to a median MELD score of 12 (range –2 to 49) for those surviving (Mann-Whitney test, p<0.0005) (Figure 8). From logistic regression, the estimated crude odds ratios (95% CI) per unit change in MELD, CTP and CanWAIT status for prediction of 1-year wait list mortality are summarized in Table 13. Crude odds ratios are presented, as there was no evidence of effect modification or confounding by age or gender. The three ROC curves are shown in Figure 9, and the estimated area under ROC curves and 95% confidence intervals for the MELD, CTP and CanWAIT status for prediction of mortality within 1-year of listing are shown in Table 14.

Figure 8. Boxplots of MELD score of patients who did and did not survive 1 year on LT waiting list (Mann-Whitney test, p<0.0005).

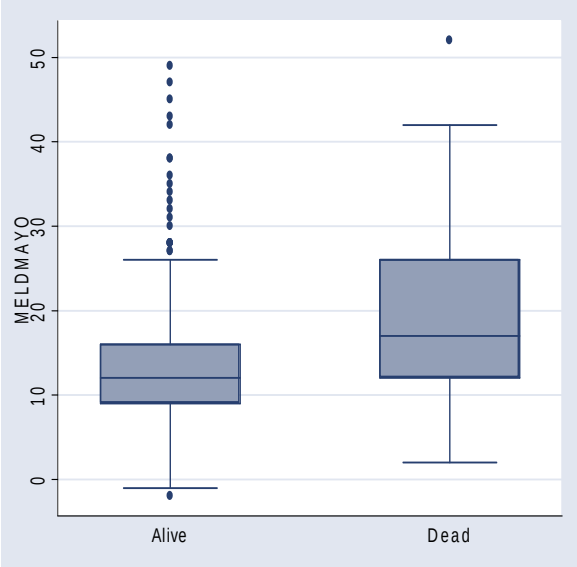


Table 13. Estimated OR (95% CI) per unit change in MELD, CTP and CanWAIT for 1-year wait list mortality.

	Odds Ratio	95% Confidence Interval		p value
MELD	1.07	1.04	1.10	<0.0005
MELD/10	1.97	1.44	2.68	<0.0005
CTP	1.41	1.19	1.68	<0.0005
CanWAIT	1.17	0.97	1.40	0.092

* MELD/10 represents the OR per 10 unit change in the MELD score

Figure 9. ROC curves for MELD, CTP and CanWAIT scores for 1-year waiting list mortality.

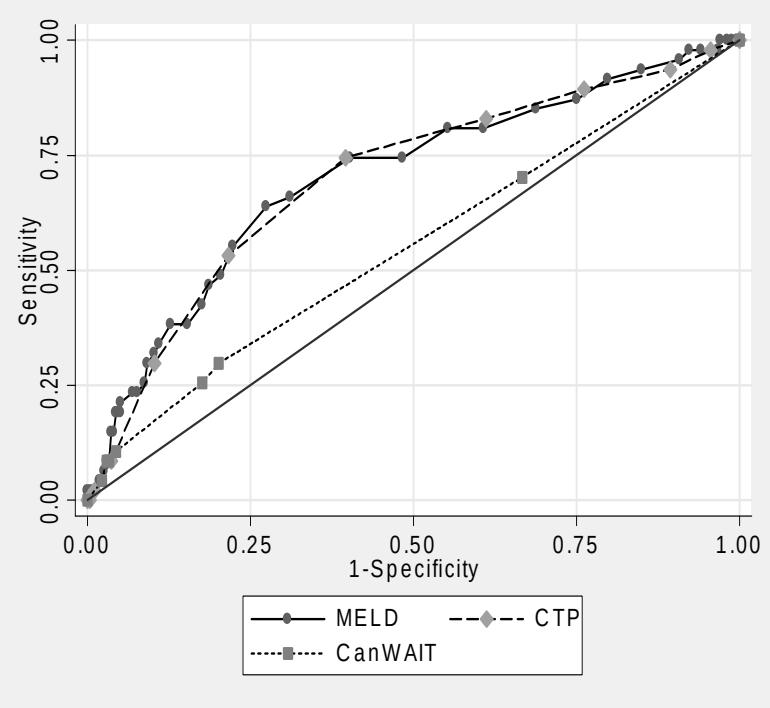


Table 14. Estimated area under ROC curve (95% CI) for the MELD, CTP and CanWAIT for prediction of 1-year waiting list mortality.

	Area under ROC	95% Confidence Interval	
MELD	0.70	0.62	0.79
CTP	0.70	0.62	0.78
CanWAIT status	0.55	0.46	0.64

The area under the ROC curve was similar for the MELD and CTP scores (p=0.948). The ROC area for the CanWAIT status was only 0.55 and was significantly lower than the area under the ROC curve for both MELD (p=0.0025) and CTP scores (p=0.006).

Removal of ALF and Status 1T Patients

As MELD score is not used for patients with fulminant acute liver failure (ALF), it was decided *a priori* to repeat the analysis without these patients. Also, the Status 1T priority for HCC patients was introduced in the middle of the study period (2001). Therefore, these patients were removed from the repeat analysis. During the study period there were 15 patients with ALF and there were 9 patients who were listed as Status 1T for LT. Another 4 patients were listed as status 0 but were activated as Status 1T on the waiting list. Excluding these patients left 292 patients with chronic liver disease without HCC for repeat analysis. Table 15 summarizes the ROC curves for this cohort of patients.

Table 15. Estimated area under ROC curve (95% CI) and for the MELD, CTP and CanWAIT status for prediction of 3-month and 1-year waiting list mortality excluding Status 1T, 3F and 4F patients (n=292).

	3-month Mortality	1-year Mortality
MELD	0.78 (0.67,0.88)	0.70 (0.60, 0.79)
CTP	0.77 (0.67,0.87)	0.70 (0.61, 0.80)
CanWAIT status	0.54 (0.42,0.69)	0.51 (0.42, 0.60)

The areas under the ROC curves were not statistically different for MELD and CTP for predicting 3-month (p=0.8756) or 1-year (p=0.9279) waiting list mortality. MELD was significantly better than CanWAIT status at predicting mortality on the waiting list at 3-months (p=0.0005) and 1-year (p=0.0005). Similarly, CTP was also significantly better than CanWAIT at predicting 3-month (p=0.001) and 1-year (p=0.0009) waiting list mortality.

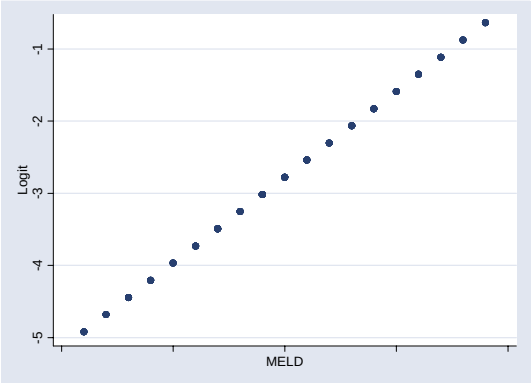
Testing the Assumptions of Logistic Regression

One of the most important assumptions of logistic regression is that the logits (log odds) are linear functions of the X variable. This can be examined by graphing the logits vs. the MELD score for prediction of 3-month mortality (Figure 10). To determine if outliers are influencing the data, the predicted and actual probabilities of death at 3 months can be examined. For the purpose of this analysis, MELD scores were grouped into 19 categories of at least 10 patients.

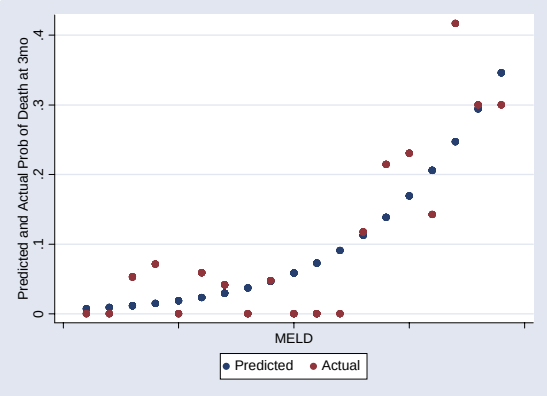
Although there are outliers, a plot of the Pearson's standardized residuals against the predicted mortality shows that no residuals fall outside the range of z ± 2.

Figure 10. Testing the assumptions of logistic regression.

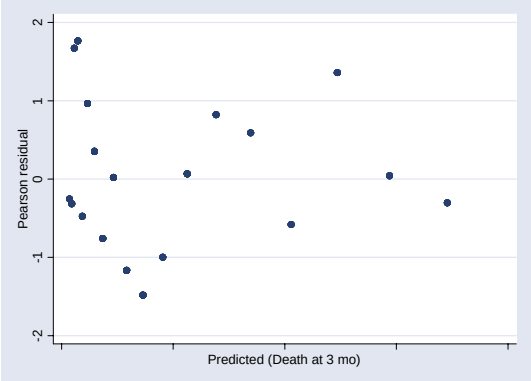
Logits vs. MELD score



Actual vs. Predicted 3mo Mortality



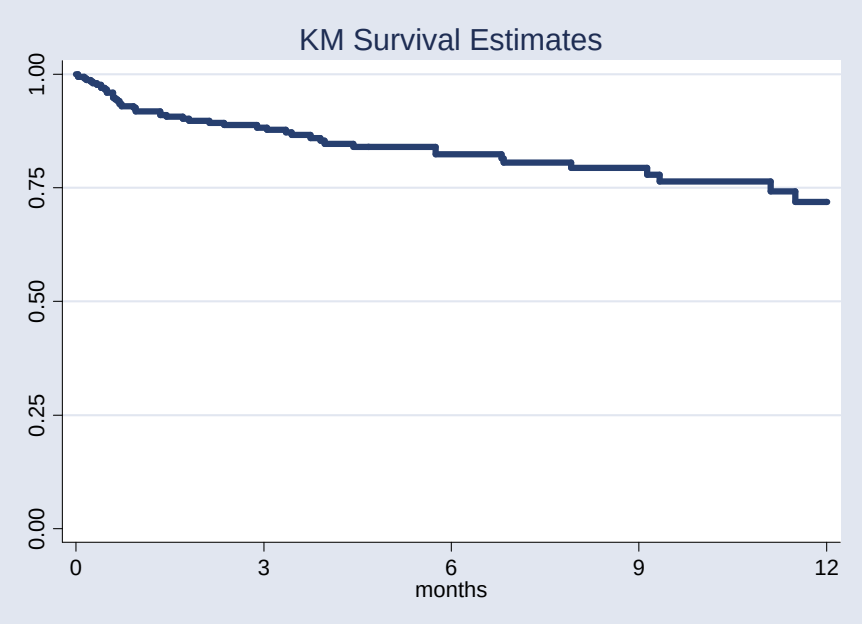
Standardized Residual vs. Predicted



Survival Analysis

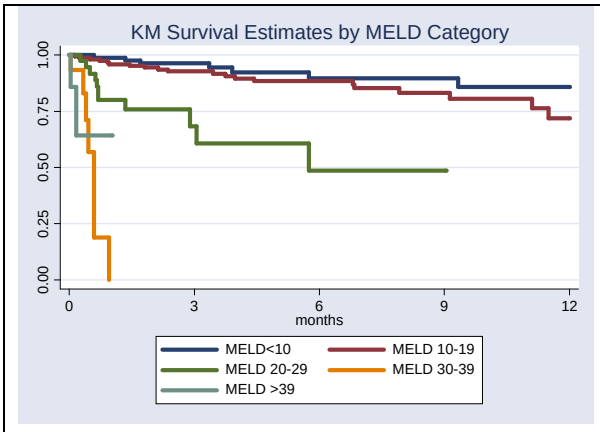
One-year waiting list survival was analyzed using Kaplan Meier (KM) estimates of the survival function and Cox proportional hazards models. Mortality was defined as removal from the list due to death or delisting for being too unwell. Survival was censored at the time of LT. Figure 11 shows the KM survival curve for patients on the LT waiting list. The 1-year estimated survival for patients added to the LT waiting list at the UofA between January 1998 and December 2002 was nearly 75%.

Figure 11. KM survival estimates on the LT waiting list.

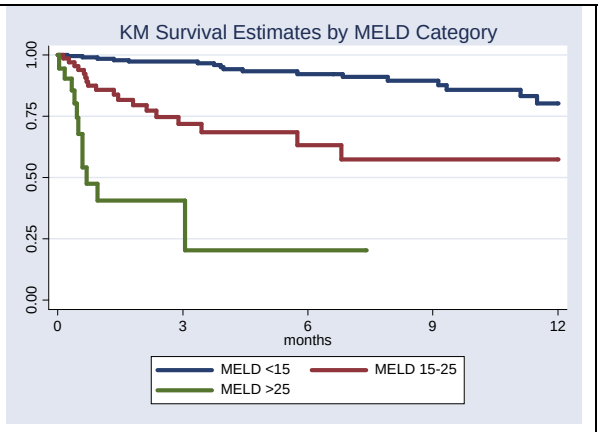


To further examine the ability of the MELD score to predict waiting list survival, KM survival estimates were compared between different strata of MELD scores [<10, 10-19, 20-29, 30-39, ≥40] and [15, 15-25, >25] (Figure 12). The log rank test for equality of survivor functions testing the null hypothesis of no difference between groups (trend test) was significant (p<0.0005) in both examples. Similarly, the KM survival estimates were compared between CTP classes and the different CanWAIT categories (Figure 13). Once again, the log rank test for equality of survivor functions was significant (p<0.0005) in both cases.

Figure 12. KM survival estimates of 1-year waiting list survival for different strata of MELD scores.

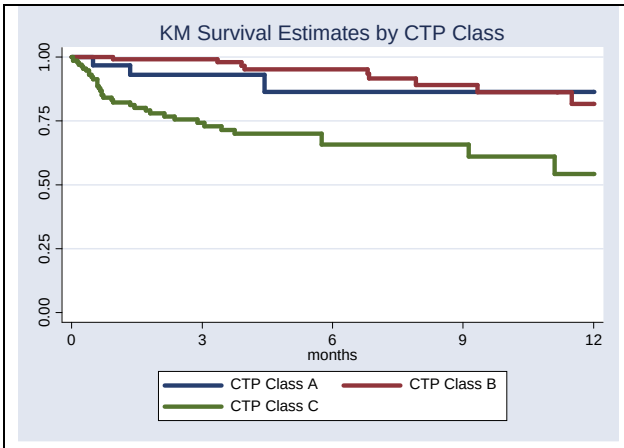


Log rank, p<0.0005

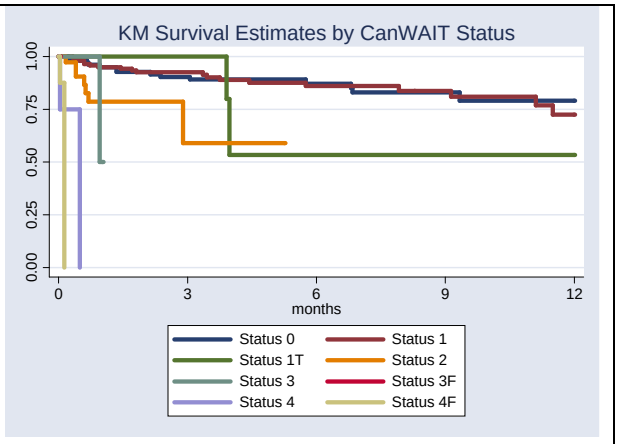


Log rank, p<0.0005

Figure 13. KM survival estimates of 1-year waiting list survival for the different CTP classes and CanWAIT categories.



Log rank, p<0.0005



Log rank, p<0.0005

Cox Proportional Hazards Model

The hazard ratios (95% CI) per unit change in MELD, CTP and CanWAIT status for 1-year waiting list mortality calculated with Cox proportional hazard models is shown in Table 16. The HR (95% CI) for the different MELD strata, CTP classes and CanWAIT categories (for patients with chronic liver disease) are shown in Table 17, using the lowest MELD strata, CTP Class A and CanWAIT status 0 as the reference groups. The assumptions of the proportional hazards model were examined using "log-log" plots (Figure 14). When the curves of the "log-log" plots are parallel the proportional hazards assumption is not violated.

Table 16. Estimated HR (95% CI) per unit change in MELD, CTP and CanWAIT for 1-year wait list mortality.

	Hazard Ratio	95% Confidence Interval		p value
MELD	1.14	1.10	1.17	<0.0005
MELD/10	3.60	2.70	4.79	<0.0005
CTP	1.66	1.39	1.99	<0.0005
CanWAIT	2.04	1.62	2.57	<0.0005

* MELD/10 represents the OR per 10 unit change in the MELD score

Table 17. Cox proportional hazards models for 1-year wait list mortality for different MELD strata, CTP classes and CanWAIT categories.

5 MELD Strata	n	Hazard Ratio	95% Confidence Interval		p value
<10	92	-	-	-	-
10-19	160	1.74	0.74	4.12	0.207
20-29	46	8.48	3.17	22.64	<0.0005
30-39	15	82.02	24.28	277.08	<0.0005
≥40	7	54.88	10.35	290.95	<0.0005

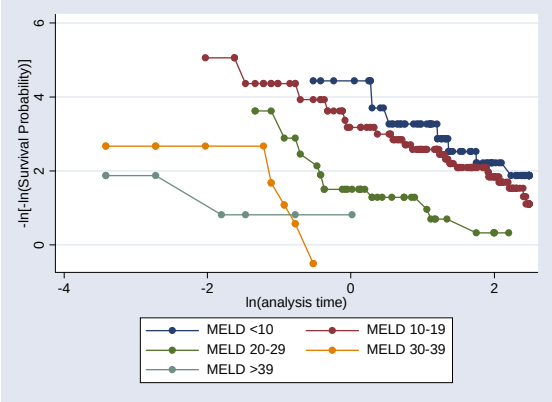
3 MELD Strata	n	Hazard Ratio	95% Confidence Interval		p value
<15	215	-	-	-	-
15-25	69	5.30	2.70	10.40	<0.0005
>25	36	26.62	11.85	59.75	<0.0005

CTP Classes	n	Hazard Ratio	95% Confidence Interval		p value
Class A	32	-	-	-	-
Class B	145	0.66	0.18	2.45	0.539
Class C	143	3.84	1.18	12.52	0.026

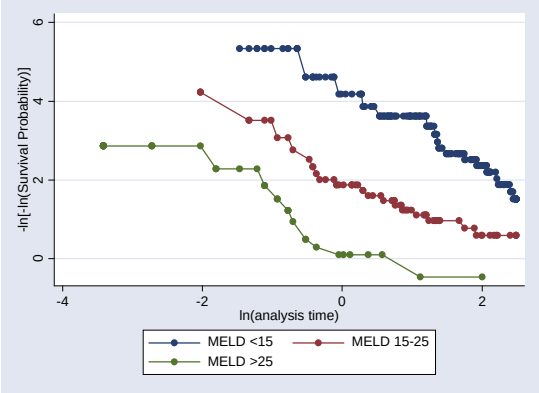
CanWAIT Status	n	Hazard Ratio	95% Confidence Interval		p value
0	105	-	-	-	-
1	146	1.03	0.51	2.05	0.941
2	43	4.67	1.78	12.24	0.002
3	4	8.69	1.09	69.12	0.041
4	4	95.31	18.32	495.77	<0.005

Figure 14. Log-log plots testing Cox proportional hazard assumptions for models with MELD strata, CTP class and CanWAIT status.

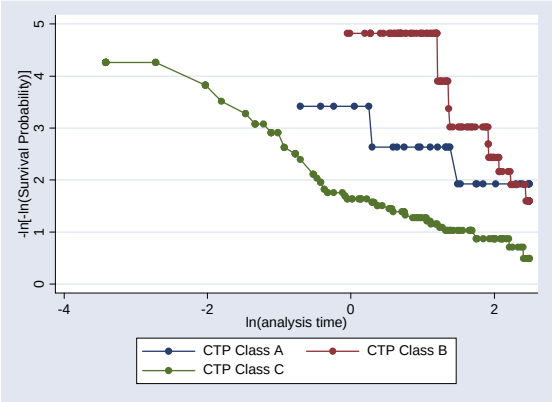
Log-log plot for 5 MELD Strata



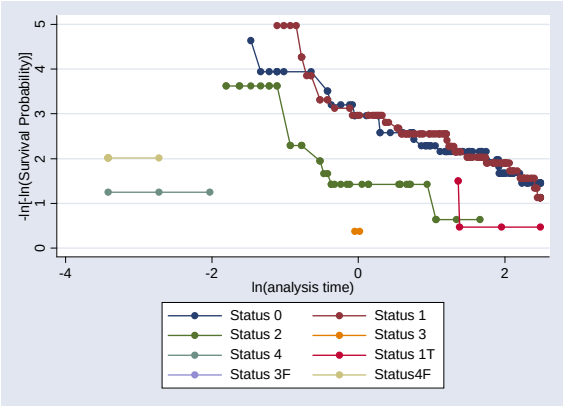
Log-log plot for 3 MELD Strata



Log-log plot for CTP class



Log-log plot for CanWAIT status

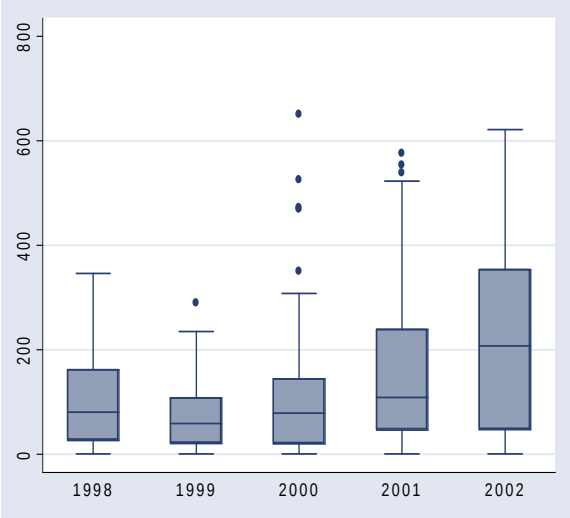
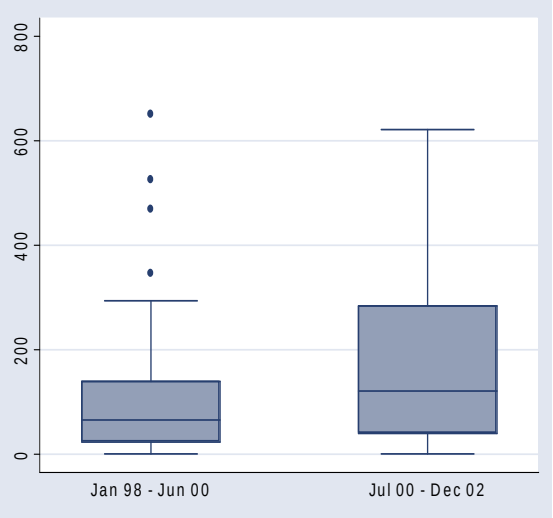


Changes in Waiting Time and MELD

Secondary Research Question: As waiting times have lengthened in more recent years, have the MELD scores of patients transplanted between July 01, 2000 – December 31, 2002 increased compared to those transplanted between January 01, 1998 – June 30, 2000?

The median waiting time for LT increased from 81 days (range 1 to 346 days) in 1998 to 208 days (range 1 to 622 days) in 2002 (Figure 15). The difference in waiting times between listing years was significant (Kruskal-Wallis test, p=0.0001). The median waiting time for LT nearly doubled from 65.5 days (range 1 to 651) in the first half of the study period (January 01, 1999 – June 30, 2000) to 121.5 days (range 1 to 622) in the second half of the study period (July 01, 2000 – December 31, 2002) (Figure 15). This difference was significant using a two-sample Wilcoxon rank-sum (Mann-Whitney) test (p<0.0005).

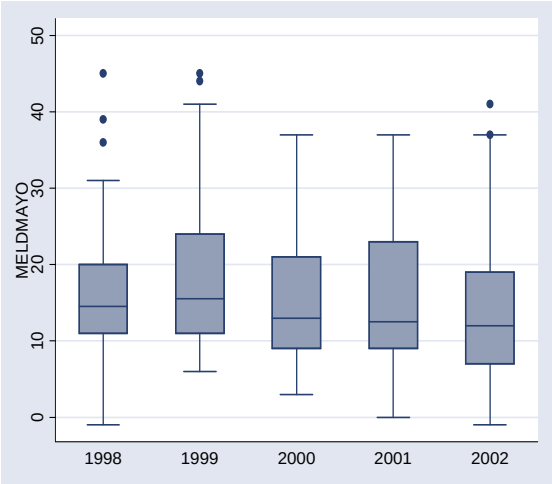
Figure 15. Waiting time for LT (days) by year of listing and study period.

Waiting time by year listing	Waiting time for LT by study period
	
Kruskal-Wallis test, p=0.0001	Mann-Whitney test, p<0.0005

Despite the increase in waiting time in later years, the median MELD score at the time of LT (Figure 16) did not vary significantly between the years of the study period (Kruskal-Wallis test, p=0.1147). The median MELD score for patients transplanted in the first half of the study period was 15 (range -1 to 45) compared to the second half of the study period when the median MELD was only 11.5 (range -1 to 41) (Figure 16). The median MELD at time of LT was significantly lower in the second half of the study period (Mann-Whitney rank sum test, p=0.0036).

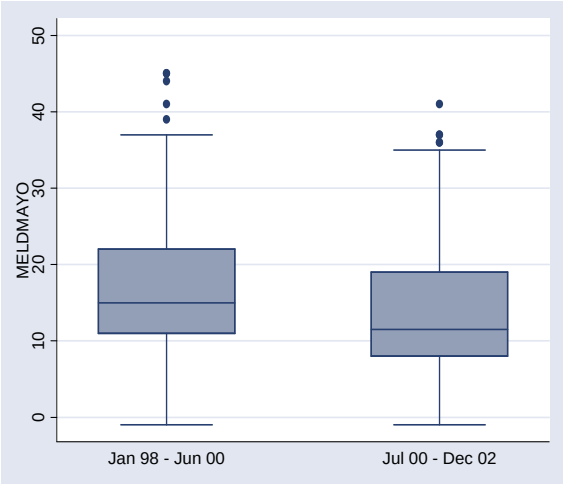
Figure 16. MELD score at LT by year of LT and study period.

MELD at time LT by year of LT



Kruskal-Wallis test, p=0.1147

MELD at time of LT by study period



Mann-Whitney test, p=0.0036

Table 18 illustrates the number of removals (for death or being too ill) from the LT waiting list by year. The median MELD score for patients removed from the list was 17 (range 2 to 52) compared to those who successfully had a liver transplant where the median MELD was only 12 (range -2 to 49) at time of listing. This difference was statistically significant (Mann Whitney test, $p<0.0005$).

Table 18. Median (range) MELD score at listing by year of listing for subjects undergoing LT compared to those removed from the list.

Listing Year	1998	1999	2000	2001	2002
Number of successful LT	50	48	58	57	58
Median MELD (range)	14 (1, 38)	13 (3, 49)	12 (-2, 38)	12 (-1, 35)	11 (0, 47)
Number of removals from list	5	2	12	16	14
Median MELD (range)	19 (15, 38)	22.5 (16, 29)	13 (2, 36)	18 (8, 42)	14 (7, 52)

Can Hyponatremia Improve the MELD?

Secondary Research Question: Does the addition of hyponatremia to the MELD score improve its ability to predict wait list mortality?

Using univariate logistic regression, hyponatremia (defined as serum sodium < 130 mmol/L) was not significantly associated with 3-month mortality OR=1.99 (95% CI: 0.76, 5.22) or 1-year mortality OR=1.72 (95% CI: 0.73, 4.03). Logistic regression models including MELD and hyponatremia were not statistically better than the simpler models with MELD alone (3 month mortality: LR test, p=0.9095; 1-year mortality LR test, p=0.8067). Using Cox proportional hazards analysis, hyponatremia (Na<130) was associated with an increased risk of 1-year mortality HR=2.41 (95% CI: 1.11, 5.21; p=0.026). However, the hazard ratio for MELD was unchanged by the addition of hyponatremia to the model (LR test, p=0.622).

POST-LT ANALYSIS

Subjects

A total of 250 adult cadaveric LT were performed between January 1, 1998 and December 31, 2002 at the UofA. This excluded patients who had previously received solid-organ transplants and those receiving repeat transplants, LDLT, and combined organ transplants. The numbers of LT per year was relatively stable throughout the study period (Table 19).

Table 19. Number of subjects transplanted by year.

Listing Year	Number of Subjects	Percentage
1998	44	17.6%
1999	54	21.6%
2000	51	20.4%
2001	50	20.0%
2002	51	20.4%
Total	**250**	**100.0%**

The mean age (± SD) of subjects at LT was 50.5±10.2 years with a median age of 50.4 years (range 18.1 to 74.3). More males were transplanted than females (64.4% vs. 35.6%). More subjects with blood group O (45.6%) and blood group A (39.6%) had LT compared to those with blood group B (10.4%) and blood group AB (4.4%). Of the 250 subjects receiving LT, 26.0% were from the city of Edmonton, 20.8% were from the city of Calgary, 34.4% were from another city or

town in Alberta and 18.8% were from out of province. The most common indications for liver transplantation were hepatitis C (HCV) and alcoholic liver disease (ETOH). A total of 80 subjects were antibody positive for HCV (32%) and 78 subjects had a history of excessive ETOH consumption (31.2%). The distribution of subjects by the primary diagnosis is shown in Table 20. Of the 42 patients transplanted with tumours, 40 were hepatocellular carcinoma, one was a cholangiocarcinoma and one was an epithelioid hemangioendothelioma.

Table 20. Distribution of primary diagnosis at time of LT.

Primary Diagnosis*	Number of Subjects	Percentage
Acute Liver Failure (ALF)	10	4.0%
Alcohol (ETOH)	37	14.8%
Viral Hepatitis (VIRAL)	70	28.0%
Cholestatic Liver Disease (CHOL)	53	21.2%
Other Hepatocellular Disease (OTHER)	38	15.2%
Primary Liver Cancer (TUMOUR)	42	16.8%
Total	**250**	**100.0%**

* In subjects with multiple diagnoses, the primary diagnosis was designated by assigning priority as follows: TUMOUR or ALF > VIRAL > ETOH > OTHER.

Table 21 shows the CANWAIT status at the time of LT for the 250 subjects. The majority of patients were transplanted from home (Status 1); however, more than one-quarter of patients were transplanted as Status 2 (as hospitalized inpatients).

Ten percent of patients with chronic liver disease were transplanted while in the ICU (Status 3 and 4) and 3.6% of patients were transplanted for ALF (Status 3F and 4F). The preferential status for patients with hepatocellular carcinoma (Status 1T) was introduced in 2001.

Table 21. Distribution of CanWAIT status at the time of LT by year of LT.

CanWAIT	1998	1999	2000	2001	2002	Total	Frequency
1	31	29	28	27	24	139	55.6%
2	8	15	19	14	9	65	26.0%
3	1	2	2	0	1	6	2.4%
4	3	7	2	5	2	19	7.6%
1T	0	0	0	2	10	12	4.8%
3F	0	0	0	0	2	2	0.8%
4F	1	1	0	2	3	7	2.8%
Total	**44**	**54**	**51**	**50**	**51**	**250**	**100.0%**

Continuous Variables

Data was collected on bilirubin, INR, creatinine, albumin, AST, ALP and sodium at the time of LT and summary statistics for these continuous variables are shown in Table 21. The albumin and sodium levels were normally distributed. Log transformations were performed on the non-normally distributed variables (bilirubin, INR, creatinine, AST and ALP) before further analysis.

Table 22. Summary statistics for continuous variables at time of LT.

Variable	Mean	Std Dev	Median	Low	High
Bilirubin (µmol/L)	137.5	202.4	50.5	3	1129
INR	1.5	0.8	1.3	0.9	10.2
Creatinine (µmol/L)	107.2	69.3	90.5	28	515
Albumin (g/L)	30.9	6.9	30	13	51
AST (U/L)	154.2	349.9	78.5	11	4560
ALP (U/L)	227.9	243.8	160	29	2143
Sodium (mmol/L)	136.1	5.4	136	120	151

Categorical Variables

Data was collected on the following categorical variables: prior complications of cirrhosis, comorbidities, location at the time of transplant (home, hospital or ICU) and the need for dialysis or mechanical ventilation at the time of LT. The frequency of these variables is summarized in Table 23. Ascites was the most common complication of cirrhosis and was present in 72.8% of subjects prior to LT. The ascites was previously complicated by SBP in only 1.6% of transplanted subjects. Varices were present in 54% of subjects but bleeding varices were seen in only 42%. Encephalopathy was seen in nearly one-half of subjects (48%). A total of 47 subjects had diabetes at the time of LT, but 34 subjects (13.6%) were controlled with diet alone and only 13 subjects (5.2%) were on therapy for diabetes at time of LT. The majority of subjects were transplanted from home (60.4%), but 26% were transplanted from a hospital ward bed and

13.6% were transplanted from the ICU. At the time of LT, 10.4% of subjects were on mechanical ventilation and 4.4% were on dialysis.

Table 23. Frequency of categorical variables at time of LT.

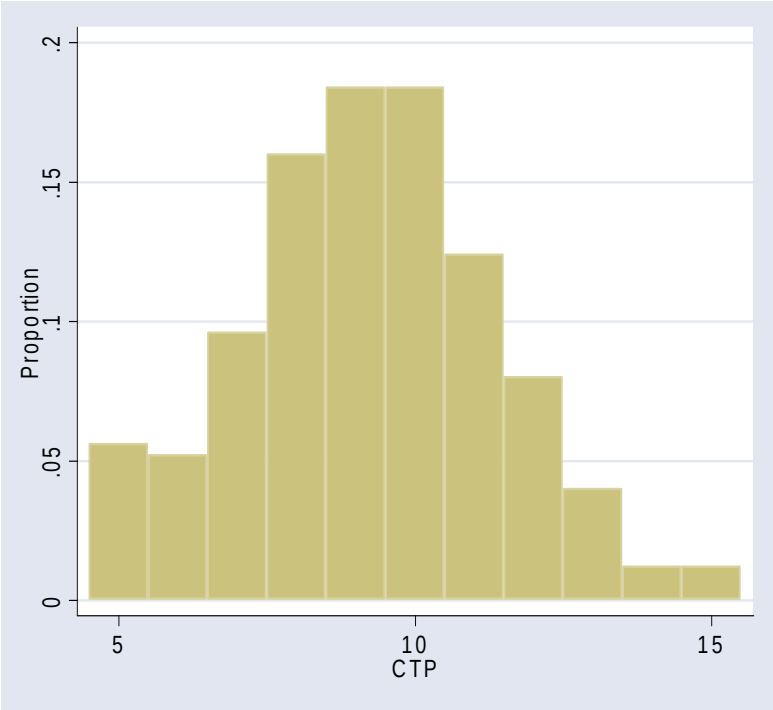
Variable	n	Frequency
Ascites	182	72.8%
Encephalopathy	120	48.0%
Bleeding Varices	105	42.0%
SBP	4	1.6%
Infection	47	18.8%
Diabetes	47	18.8%
Location – Home	151	60.4%
Location – Hospital	65	26.0%
Location – ICU	34	13.6%
Mechanical Ventilation	26	10.4%
Dialysis	11	4.4%

Calculated Variables

Child Turcotte Pugh (CTP) Score

The mean (±SD) CTP score was 9.23 ± 2.16, with a median score of 9 (range 5 to 15). The distribution of CTP scores at time of LT is illustrated in Figure 17. Eleven percent of subjects were CTP class A at LT (CTP score 5 or 6). CTP class B cirrhosis (CTP score 7-9) accounted for 44% of subjects and 45% had CTP class C cirrhosis (CTP score 10-15) at the time LT.

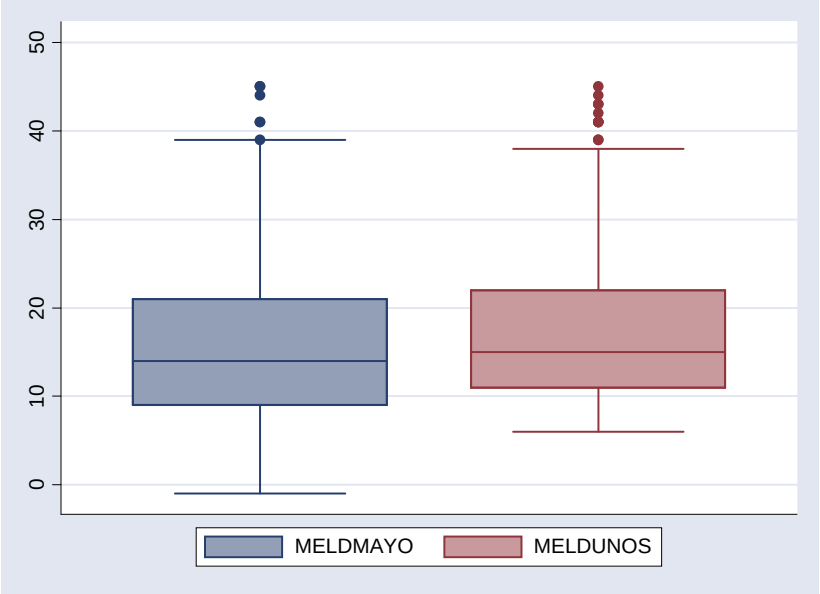
Figure 17. Histogram of CTP score at time of LT.



MELD Score

Figure 18 compares the distribution of the MELD score calculated as per the Mayo model and as per UNOS. The MELDMAYO scores ranged from -1 to 45 and the MELDUNOS scores ranged from 5 to 49. The median MELD score was 15 for MELDMAYO and 14 for MELDUNOS at the time of LT. As the two scores are similar and MELDMAYO is unadjusted, throughout the remainder of the post-LT analysis the MELDMAYO will be used as the calculated MELD score.

Figure 18. Boxplots comparing MELD scores at time of LT calculated as per the Mayo model (MELDMAYO) and UNOS (MELDUNOS).



The median MELD score at time of LT did not vary significantly between blood groups (Kruskal-Wallis test, p=0.2209) or location or home address (Edmonton, Calgary, other Alberta town, or other province) (Kruskal-Wallis test, p=0.1623) (Figure 19). There was a significant difference between the median MELD scores according to CanWAIT status (Kruskal-Wallis test, p=0.0001) with patients transplanted for fulminant acute liver failure (Status 3F and 4F) and those patients in the ICU (Status 3 and 4) having the highest median MELD scores (Figure 20). Patients with Status 1T had the lowest median MELD scores. There were significant differences in median MELD score according to location at time of LT (home, hospital or ICU) (Kruskal-Wallis test, p=0.0001) (Figure 19).

Figure 19. Boxplots of MELD by blood group and home address at LT.

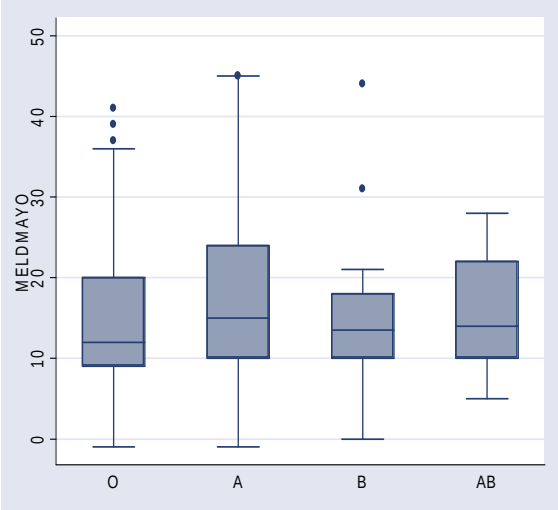
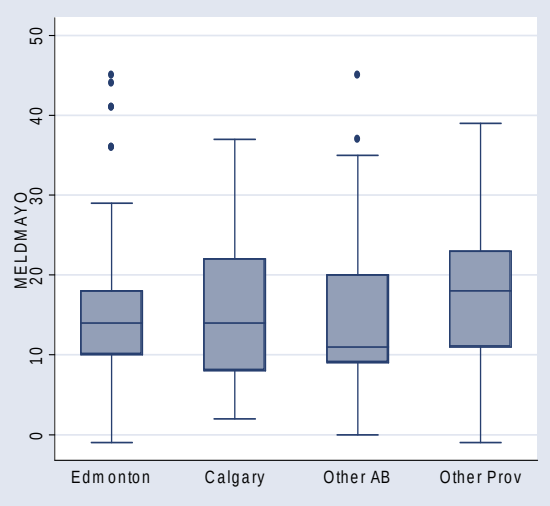
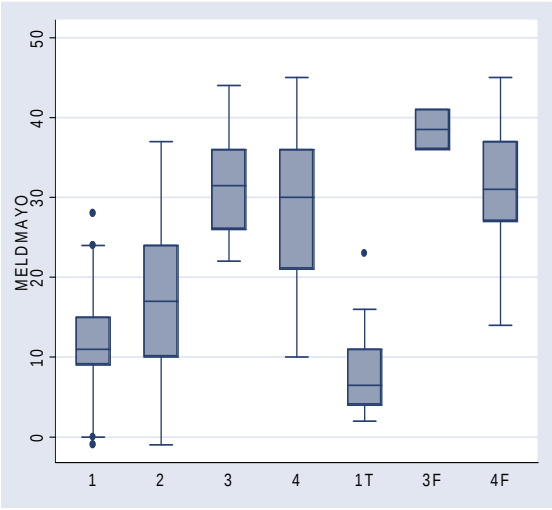
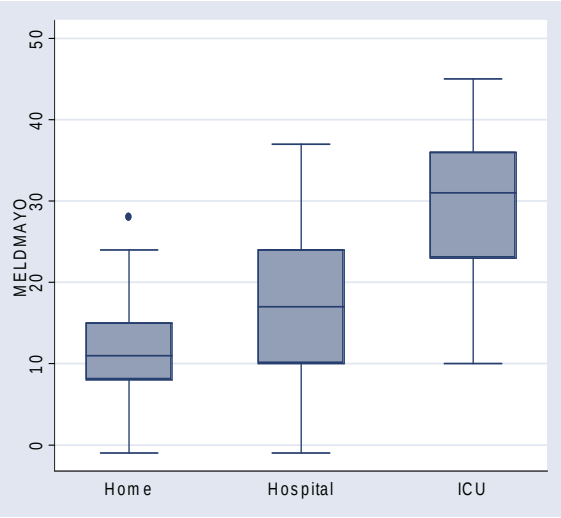
MELD by blood group	MELD by home address
	
Kruskal-Wallis test, p=0.2209	Kruskal-Wallis test, p=0.1623

Figure 20. Boxplots of MELD by CanWAIT status and location at LT.

MELD by CanWAIT status	MELD by location
	
Kruskal-Wallis test, p=0.0001	Kruskal-Wallis test, p=0.0001

Post-LT Mortality

Secondary Research Question: Is the MELD score at time of transplantation better than the CTP score and CanWAIT status at predicting 3-month and 1-year mortality after liver transplantation?

3-Month Post-LT Mortality

The median MELD score in subjects who died within the first 3 months of LT was 21 (range 7 to 45) compared to a median MELD score of 13 (range -1 to 45) for those surviving (Mann-Whitney test, p=0.019) (Figure 21). From logistic regression, the estimated OR (95% CI) per unit change in MELD, CTP and CanWAIT status are shown in Table 24. The OR per 10-unit change in MELD is also shown (MELD/10) as this is clinically more meaningful. The crude odds ratios are shown as there was no evidence of effect modification or confounding by age or gender. The three ROC curves are shown in Figure 22, and the estimated area under ROC curves and 95%CI for the MELD, CTP and CanWAIT status for the prediction of mortality within 3-month of listing are shown in Table 25.

Figure 21. Boxplots of MELD score in patient who did and did not survive 3 months after LT (Mann-Whitney test, p=0.019).

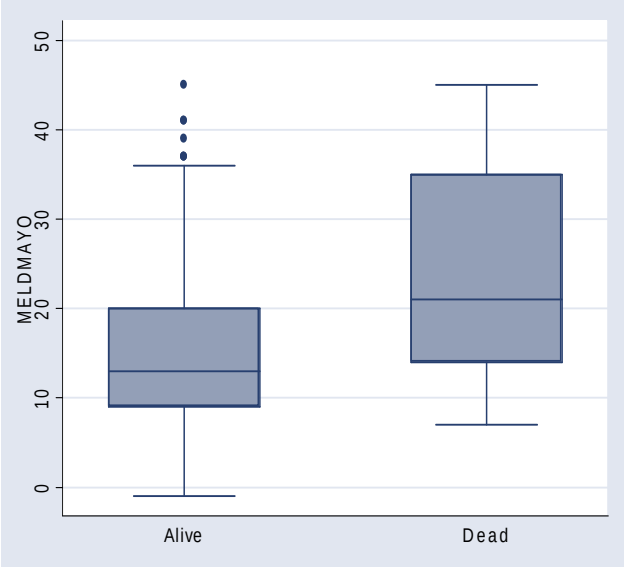


Table 24. Estimated OR (95% CI) per unit change in MELD, CTP and CanWAIT for 3-month post-LT mortality.

	Odds Ratio	95% Confidence Interval		p value
MELD	1.07	1.02	1.12	0.004
MELD/10	2.01	1.25	3.24	0.004
CTP	1.33	1.04	1.71	0.024
CanWAIT	1.47	1.15	1.88	0.002

* MELD/10 represents the OR per 10 unit change in the MELD score

Figure 22. ROC curves for MELD, CTP and CanWAIT scores for 3-month post-LT mortality.

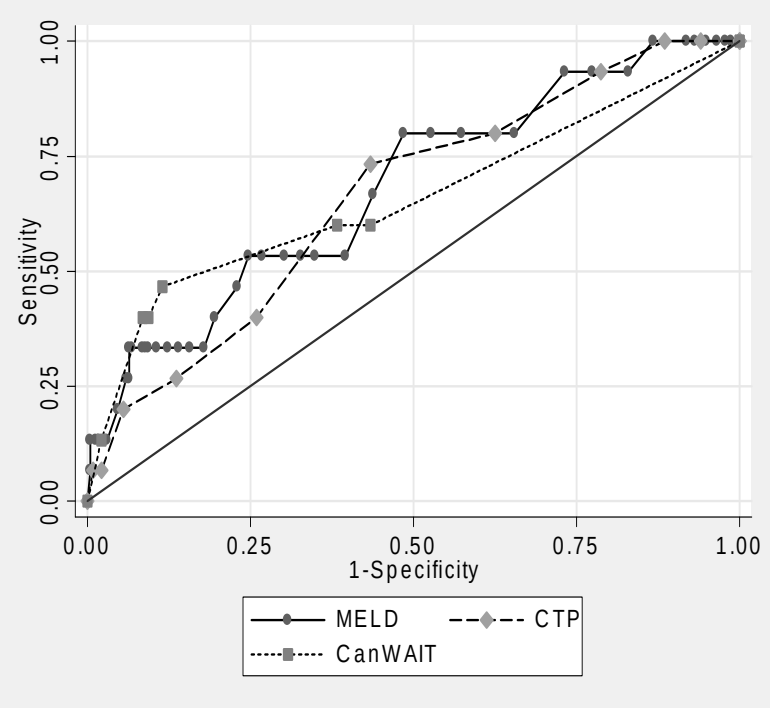


Table 25. Estimated area under ROC curve (95% CI) for the MELD, CTP and CanWAIT for prediction of 3-month post-LT mortality.

	Area under ROC	95% Confidence Interval	
MELD	0.68	0.54	0.82
CTP	0.66	0.52	0.80
CanWAIT status	0.66	0.49	0.82

The areas under the ROC curve were not significantly different for the MELD, CTP, and CanWAIT status (p=0.8798).

1-Year Post-LT Mortality

The median MELD score in subjects who died within the first year post LT was 16 (range 3 to 45) compared to a median MELD score of 13 (range -1 to 45) for those surviving (Mann-Whitney test, p=0.0761) (Figure 23). From logistic regression, the estimated crude OR (95% CI) per unit change in the MELD, CTP and CanWAIT status are shown in Table 26. The three ROC curves are shown in Figure 24, and the estimated area under ROC curves and 95% CI for the MELD, CTP and CanWAIT status for the prediction of mortality within 1-year of LT are shown in Table 27.

Figure 23. Boxplots of MELD score in patient who did and did not survive 1 year after LT (Mann-Whitney test, p=0.0761).

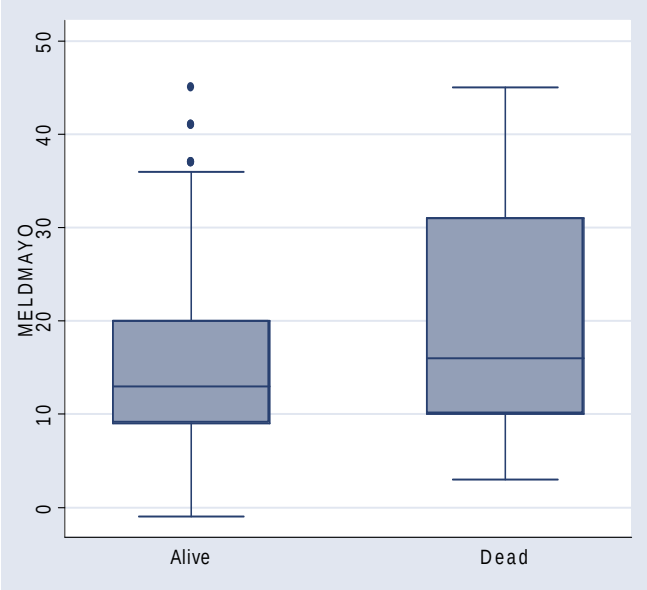


Table 26. Estimated OR (95% CI) per unit change in the MELD, CTP and CanWAIT for 1-year post-LT mortality.

	Odds Ratio	95% Confidence Interval		p value
MELD	1.05	1.01	1.09	0.011
MELD/10	1.59	1.11	2.27	0.011
CTP	1.15	0.96	1.36	0.124
CanWAIT	1.31	1.09	1.59	0.005

* MELD/10 represents the OR per 10 unit change in the MELD score

Figure 24. ROC curves for MELD, CTP and CanWAIT scores for 1-year post-LT mortality.

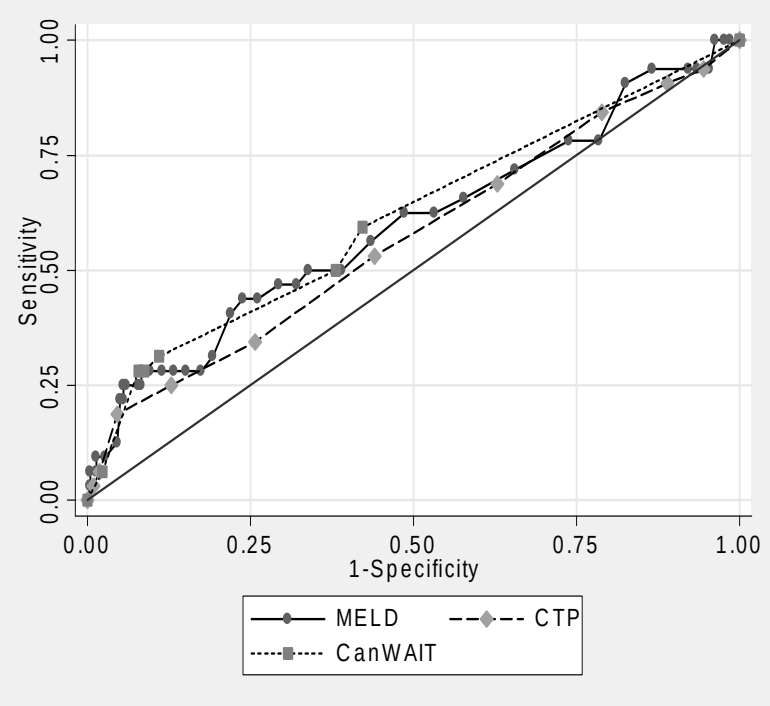


Table 27. Estimated area under ROC curve (95% CI) for the MELD, CTP and CanWAIT for prediction of 1-year post-LT mortality.

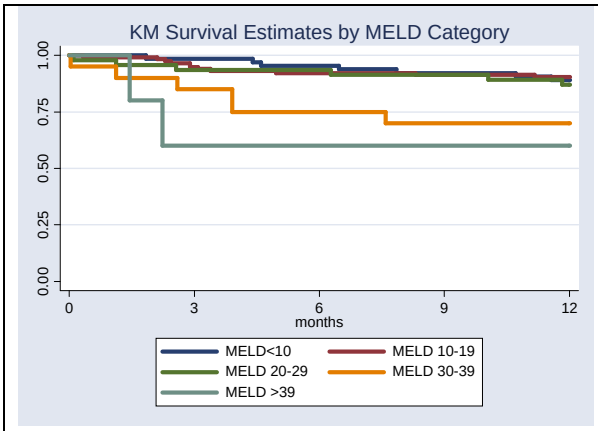
	Area under ROC	95% Confidence Interval	
MELD	0.60	0.48	0.71
CTP	0.57	0.46	0.68
CanWAIT status	0.61	0.51	0.72

The areas under the ROC curve were not significantly different for the MELD, CTP, and CanWAIT status (p=0.7126).

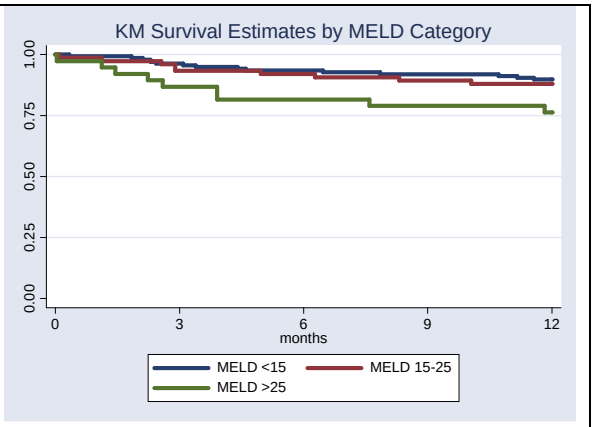
Survival Analysis

Survival analysis was also performed using Kaplan Meier (KM) estimates and Cox proportional hazard models. One-year survival was 87.2% and the 7-year estimated survival by KM methods for patients following LT at the UofA was greater than 75%. To further examine the ability of the MELD score to predict post-LT survival, KM survival estimates were compared between different strata of MELD scores and CTP classes (Figure 25). Similarly, the KM survival estimates are compared between different CanWAIT categories, location at LT and need for mechanical ventilation (Figure 26).

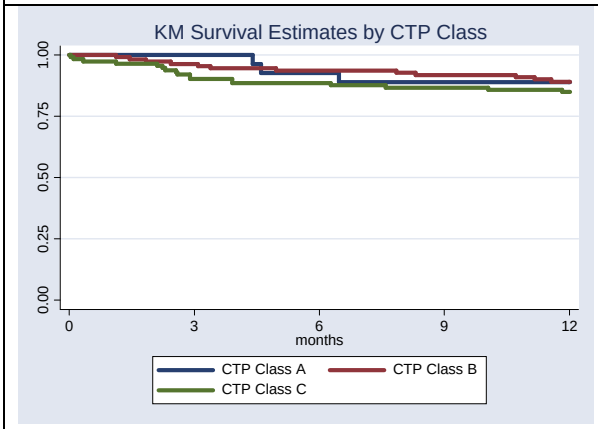
Figure 25. KM survival estimates of 1-year post-LT survival for different strata of MELD scores and CTP classes.



Log rank, p=0.0139

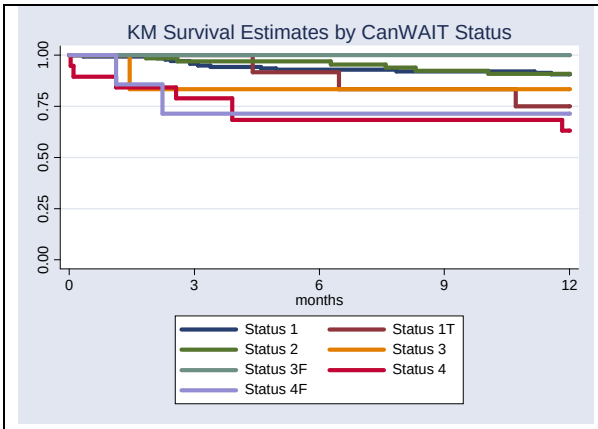


Log rank, p=0.0677

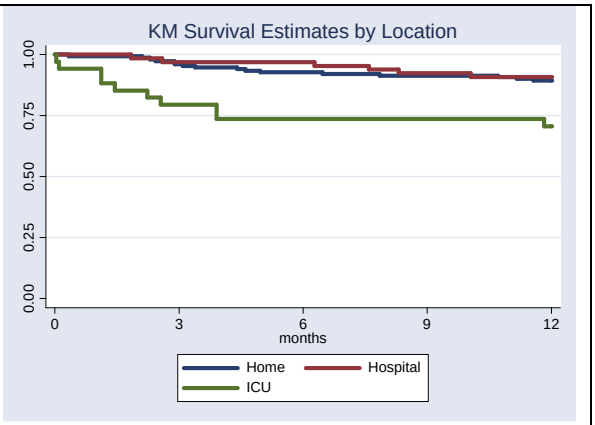


Log rank, p=0.5885

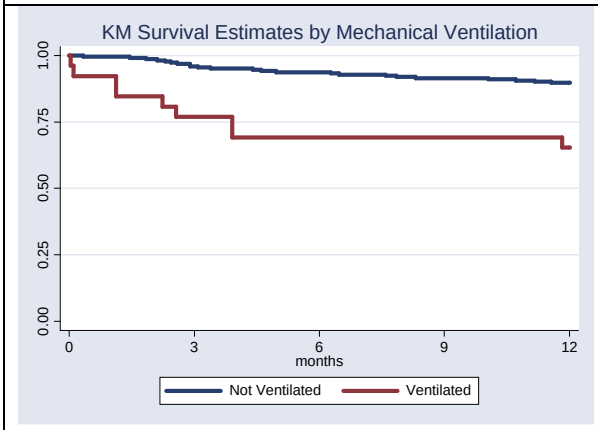
Figure 26. KM survival estimates for of 1-year post-LT survival for the different CanWAIT categories, location at LT and ventilation status.



Log rank, p=0.005



Log rank, p=0.0025



Log rank, p=0.0001

Cox Proportional Hazards Model

The hazard ratio (95% CI) per one unit change in MELD, CTP and CanWAIT status for 1-year post-LT survival calculated with Cox proportional hazard models is shown in Table 28. The HR (95% CI) for the different MELD strata, CTP classes and CanWAIT categories, using the lowest MELD strata, CTP Class A and CanWAIT status 1 as the reference groups is shown in Table 29. The assumptions of the proportional hazards model were examined using "log-log" plots (Figure 27).

Table 28. Estimated HR (95% CI) per unit change in MELD, CTP and CanWAIT for 1-year post-LT mortality.

	Hazard Ratio	**95% Confidence Interval**		**p value**
MELD	1.04	1.01	1.08	0.006
MELD/10	1.56	1.14	2.18	0.006
CTP	1.14	0.97	1.34	0.108
CanWAIT	1.30	1.10	1.54	0.002

* MELD/10 represents the OR per 10 unit change in the MELD score

Table 29. Cox proportional hazard models for 1-year post-LT mortality for different MELD strata, CTP classes and CanWAIT categories.

5 MELD Strata	n	Hazard Ratio	95% Confidence Interval		p value
<10	64	-	-	-	-
10-19	115	0.89	0.35	2.29	0.809
20-29	46	1.23	0.41	3.66	0.711
30-39	20	3.22	1.08	9.58	0.036
≥40	5	5.15	1.07	24.81	0.041

3 MELD Strata	n	Hazard Ratio	95% Confidence Interval		p value
<15	137	-	-	-	-
15-25	75	1.19	0.52	2.75	0.682
>25	38	2.55	1.10	5.90	0.028

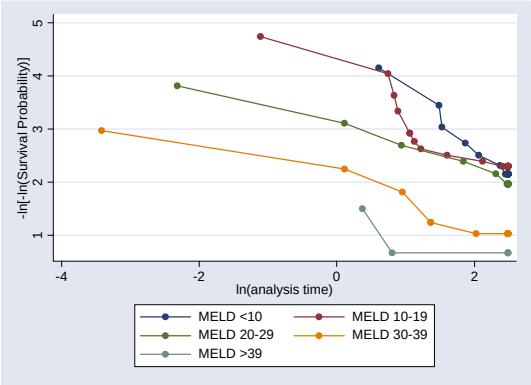
CTP Classes	n	Hazard Ratio	95% Confidence Interval		p value
Class A	27	-	-	-	-
Class B	110	0.99	0.28	3.51	0.988
Class C	113	1.43	0.42	4.87	0.571

CanWAIT Status	n	Hazard Ratio	95% Confidence Interval		p value
1	139	-	-	-	-
1T	12	2.73	0.78	9.57	0.117
2	65	0.98	0.37	2.57	0.962
3	6	1.98	0.26	15.10	0.512
3F	2	*			
4	19	4.86	1.94	12.18	0.001
4F	7	3.78	0.85	16.76	0.08

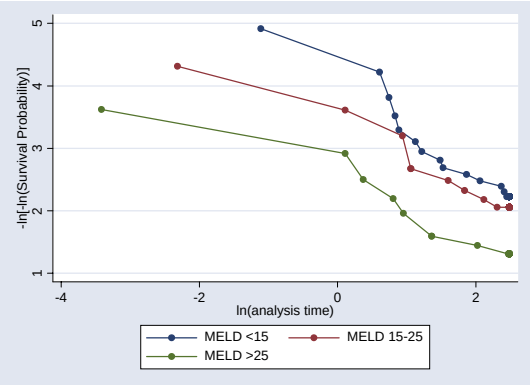
* Both Status 3F patients survived past one year (100% survival)

Figure 27. Log-log plots testing Cox proportional hazard assumptions for models with MELD strata, CTP class and CanWAIT status.

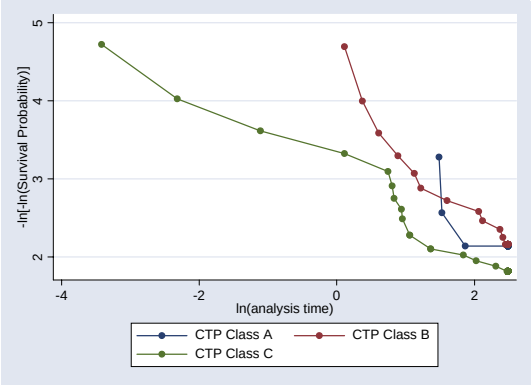
Log-log plot for 5 MELD Strata



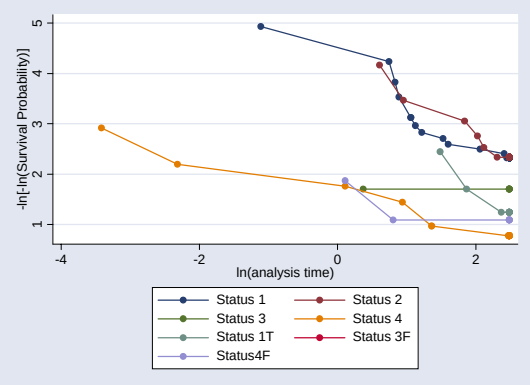
Log-log plot for 3 MELD Strata



Log-log plot for CTP class



Log-log plot for CanWAIT status



Can MELD Identify a Point of Futility?

Secondary Research Question: At the time of LT, is there a MELD score that can predict a low success rate of the LT (a 1-year survival of <50%)?

Overall, in this cohort of patients the 1-year survival following LT was 87.2%. Table 30 summarizes the survival rates per MELD category. Survival was lower in patients with MELD scores ≥ 30 (68% vs. 89.3%, p=0.0068, Fischer's exact test). Using a Cox proportional hazards model, there was a significant increase in mortality risk in patients with MELD scores ≥ 30 (HR=3.58; 95% CI 1.16, 7.99; p=0.02) compared to those with a MELD score <30. However, even in the highest MELD strata the survival was 60%. Therefore, a futility point (defined as a 1-year survival <50%) could not be identified for a particular MELD score in this cohort of patients.

Table 30. Survival rates for first post-LT year by MELD strata.

MELD	**≤ 9**	**10-19**	**20-29**	**30-39**	**≥ 40**	**Total**
Alive	57	104	40	14	3	218
Dead	7	11	6	6	2	32
Survival	89.1%	90.4%	87.0%	70.0%	60.0%	87.2%

Mechanical ventilation at the time of transplant was associated with very poor survival after LT. The actual 1-year survival for patients with chronic liver disease who were transplanted on a ventilator (status 4, n=19) was only 63.1%.

Predicting Survival Post-LT

Secondary Research Question: Are there better predictors of post-LT survival than MELD?

As an exploratory analysis, each possible predictor variable was included as the independent variable one at a time in a Cox proportional hazards model for 1-year post-LT survival. Age, when used as a continuous (p=0.157) or dichotomous variable (age>60, p=0.585), was not significantly associated with survival. Gender (p=0.585), home city (p=0.183), year of LT (p=0.247), blood group (p=0.208), waiting time (p=0.307), diagnosis (p=0.093), tumour at LT (p=0.455), sodium (p=0.628), hyponatremia (Na<130, p=0.346), log AST (p=0.743), log ALP (p=0.933), varices (p=0.533), diabetes (p=0.784), infection (p=0.071) and dialysis (p=0.558) were not significantly associated with survival in the first year after LT. The results for the components of the MELD, CTP and CanWAIT system are shown in Table 31.

Table 31. Univariate analyses for 1-year post-LT survival

Variable	Hazard Ratio	95% Confidence Interval		p value
MELD	**1.05**	**1.01**	**1.08**	**0.006**
Log Creatinine	**2.90**	**1.58**	**5.31**	**0.001**
Log INR	2.16	0.99	4.73	0.053
Log Bilirubin	1.11	0.84	1.46	0.467
CTP class	1.29	0.75	2.23	0.362
Albumin	**0.95**	**0.90**	**0.997**	**0.041**
Hypoalbuminemia	**2.00**	**1.00**	**4.01**	**0.05**
Encephalopathy	1.25	0.63	2.51	0.523
Ascites	0.79	0.37	1.66	0.530
CanWAIT status	**1.31**	**1.10**	**1.57**	**0.002**
ALF	1.79	0.43	7.49	0.426
Location	**1.73**	**1.12**	**2.66**	**0.013**
Ventilation	**4.16**	**1.92**	**9.00**	**<0.0005**

MELD and CanWAIT status, but not CTP class, were significant predictors of 1-year post-LT survival. The only component of the CTP score to be a significant predictor of survival was serum albumin, when used either as a continuous or dichotomous variable (hypoalbuminemia = albumin <28 g/L; cutoff for 3 points on the CTP scale). Of the components of the MELD score, only the log creatinine was a significant predictor of survival, with the log INR being of borderline significance. Similarly, a closer examination of the components of the CanWAIT status (consisting of location, mechanical ventilation and diagnosis of ALF) it is

apparent that mechanical ventilation is the most important predictor of survival in the first year following LT.

A multivariate model was therefore constructed with mechanical ventilation, log creatinine, albumin and appropriate interaction terms to examine effect modification. More complex models were tested against simpler models using the LR test. The final model and the estimates of the coefficients are summarized below:

$$\text{Log } h(t) = h_0(t) + \beta_1(v) + \beta_2(c) + \beta_3(a) + \beta_4(ac)$$

v=ventilator, c=log creatinine, a=albumin, ac=albumin*log creatinine

$$\text{Log } h(t) = h_0(t) + 1.161(V) + 3.652(C) + 0.436\,(A) - 0.100\,(AC)$$

$$h(t) = h_0(t) \exp [1.161(V) + 3.652(C) + 0.436\,(A) - 0.100\,(AC)]$$

Tests of the proportional hazards assumption (STATA: *stphtest*) for the covariates and the global test of the model (p=0.5489) were not significant indicating that the proportional hazards assumption has not been violated. A simpler model without the interaction term (albumin x log creatinine) was significantly different from the model with the interaction term (LR test, p=0.0234). In the final model, the hazard ratio for mechanical ventilation was 3.19 (95%CI, 1.37-7.43, p=0.007). As there is evidence of albumin being an effect modifier of log creatinine (interaction term significant, p=0.028), the hazard ratio for log creatinine will vary depending on the level of albumin. For example, the equations for different levels of albumin for non-ventilated patients are shown below:

Log $h(t) = h_0(t) + \beta_1(v) + \beta_2(c) + \beta_3(a) + \beta_4(ac)$

$h(t) = h_0(t) \exp[\beta_2(c) + \beta_3(a) + \beta_4(ac)]$

For non-ventilated patients V=0 and a=A, the equation simplifies to:

$h(t) = h_0(t) \exp[\beta_3 A + (\beta_2 + \beta_4 A) C]$

Solving for the exponent :

For an albumin of 20 g/L (A=20)

$= 20\beta_3 + (\beta_2 + 20\beta_4) C$

$= 20(0.436) + [3.652 – (20) 0.100] C = 10.372 C$

For an albumin of 30 g/L (A=30)

$= 30\beta_3 + \beta_1 v + (\beta_2 + 30\beta_4) C$

$= 30(0.436) + [3.652 – (30) 0.100] C = 13.732 C$

For an albumin of 40 g/L (A=40)

$= 40\beta_3 + \beta_1 v + (\beta_2 + 40\beta_4) C$

$= 40(0.436) + [3.652 – (40) 0.100] C = 17.092 C$

Comparing non-ventilated patients with albumin of 30g/L and 20g/L the hazard ratio for log creatinine is $e^{13.732C} / e^{10.372C} = 1.32$, but comparing patients with an albumin of 40g/L and 30g/L the hazard ratio is $e^{17.092C} / e^{13.732C} = 1.24$. Despite the same 10-point rate of change in the albumin, the hazard ratios for the log creatinine in the two examples varies based on the albumin level because of the interaction between the variables.

8. DISCUSSION

Review of Findings

The median MELD scores were significantly higher in patients who died while awaiting LT compared to those surviving 3-months or 1-year. Logistic regression was used to examine waiting list mortality as a binary outcome (alive vs. death or delisting). For 3-month mortality, the odds ratio for a change of 10 MELD points was 2.59, indicating that for each successive 10 point increase in the MELD score the odds of mortality were 2.59 times higher. The odds ratio for the CTP score was 1.65, indicating 65% greater odds of dying for each one point increase in CTP score. The odds ratio of 1.31 for the CanWAIT indicates that the odds of mortality are 1.31 times between subjects in successive CanWAIT categories (for example a Status 3 patient vs. a status 2 patient). The overall accuracy and predictive ability of the logistic regression models for MELD, CTP and CanWAIT were examined by plotting ROC curves. The area under the ROC curves for MELD, CTP and CanWAIT scores for prediction of 3-month and 1-year waiting list mortality in this cohort of patients with chronic liver disease at the UofA (excluding ALF patients) are summarized in Table 32. Status 1T patients are also excluded as this preferential status for tumour patients was introduced in the middle of the study period. For comparison the area under the ROC curves for prediction of post-LT mortality are also shown in Table 32.

Table 32. Summary of area under ROC curves (95%CI) for MELD, CTP and CanWAIT scores for predicting 3-month and 1-year mortality before and after LT. Wait list analysis excludes Status 1T, 3F and 4F patients.

	Wait List Mortality		Post LT Mortality	
	3-month	**1-year**	**3-month**	**1-year**
MELD	0.78 (0.67, 0.88)	0.70 (0.60, 0.79)	0.68 (0.54, 0.82)	0.60 (0.48, 0.71)
CTP	0.77 (0.67, 0.87)	0.70 (0.61, 0.80)	0.66 (0.52, 0.80)	0.57 (0.46, 0.68)
CanWAIT	0.54 (0.42, 0.67)	0.51 (0.42, 0.60)	0.63 (0.47, 0.79)	0.63 (0.52, 0.73)

The MELD score was significantly better at predicting waiting list mortality than the current CanWAIT system. The area under the ROC for 3-month mortality approached 0.80 indicating that it is a good prognostic test for predicting short-term mortality on the UofA LT waiting list. The area under the ROC curve for the MELD scores was similar to the area under the ROC curves found in other validation studies, in which ROC areas ranged from 0.78 to 0.87 for the prediction of 3-month mortality (8, 11). In contrast, the area under the ROC curve for the CanWAIT algorithm was no better than chance alone at predicting waiting list mortality (95% confidence intervals included 0.5). The ability of the MELD score to predict longer term mortality at the UofA was decreased, but the area under the ROC curve of 0.7 indicates that the MELD is still a useful test for predicting 1-year waiting list mortality. Once again, the MELD was significantly

better than the current CanWAIT allocation system at predicting 1-year waiting list mortality at the UofA. Unlike the large validation study in the USA (11), in which MELD was shown to be significantly better than the CTP score (ROC area of 0.83 vs. 0.76; $p<0.001$), the present study found the MELD and the CTP scores to have nearly identical prognostic abilities for waiting list mortality.

The inclusion or exclusion of ALF patients did not dramatically change the area under the ROC curves. In fact, there is some emerging evidence that the MELD score may be a useful predictor of survival in patients with fulminant liver failure (28, 29).

Survival of patients awaiting LT by the different MELD strata was examined graphically by Kaplan Meier plots and by comparing hazard ratios for mortality to a reference group. When broken down into 5 MELD strata, it is apparent that patients with MELD scores of 10-19 had similar survival to those with MELD <10 (95%CI for HR includes 1.0). Decreased waiting list survival and significant hazard ratios were only seen in the higher strata (MELD 20-29, 30-39, ≥40). To examine if the Cox proportional hazard assumption had been violated the log-log plots were examined. For the most part the lines of the log-log plot are parallel; however, they did cross for the two highest MELD strata. However, there were only a small number of patients in the higher MELD strata (accounting for the large confidence interval of the hazard ratios) and the *stphtest* was not significant ($p=0.6468$) indicating that the Cox proportional hazards assumption was not

violated. Comparing mortality in the 3 MELD strata, using MELD <15 as the reference strata, the hazard ratios for MELD 15-25 was 5.3 (95%CI, 2.7-10.4) and for MELD >25 was 26.6 (95%CI, 11.9-59.8).

The Kaplan Meier curves for CTP class A and B patients overlapped, and only CTP class C patients had a significant hazard ratio of 3.8 (95%CI 1.18-12.5) when compared to Child's class A subjects. CanWAIT status 0 patients (reference group) had a KM survival curve that overlapped with the Status 1 patients (HR=1.0, 95%CI, 0.51-2.05). The hazard ratio for status 2 patients was 4.67 (95%CI, 1.8-12.2). The hazard ratios for mortality for Status 3 and 4 patients were significant despite having only small numbers of patients in these groups (4 in each group).

Waiting times for LT at the UofA are on the rise. There was a significant increase in the median waiting time for LT for patients listed in the second half of the study period. I had hypothesized that this would result in sicker patients, with higher MELD scores being transplanted in the latter years of the study period. In fact the opposite was true, and the median MELD score of patients at the time of LT was lower in patients transplanted in the later half of the study period. There appears to have been a selective removal of the sickest patients from the transplant list. More patients were removed from the list in the latter years of the study period and the median MELD score of patients who died or were delisted was significantly higher than those who ultimately went on to have a successful LT.

The longer waiting times may have played a role in patients becoming sicker while awaiting LT, and this may have lead to more patients being removed from the list for being too ill in the latter years of the study period.

Recently, it has been suggested that hyponatremia, as a surrogate marker for refractory ascites, may improve the MELD score's prognostic ability (14, 15). However, in the present study the addition of hyponatremia to both logistic regression and Cox proportional hazards models failed to improve the ability of the MELD to predict waiting list mortality.

The ability of the MELD score to predict post-LT mortality was examined in an identical manner to the Wait List analysis. Following LT the MELD, CTP and CanWAIT status were all relatively poor predictors of 3-month and 1-year mortality, indicated by area under the ROC curves that were <0.70 (see Table 30). We found no statistical difference in the area under the ROC curves for the MELD, CTP and CanWAIT status. The study from Dalhousie University also examined the area under the ROC curve for the prediction of 3-month post-LT mortality and found similar results (CanWAIT = 0.71, MELD = 0.67, CTP class= 0.65) (17). In the study of the UNOS database (n=2,565) the area under the ROC curve for the MELD score to predict 3-month post-LT mortality was only 0.54 (23).

Survival analysis was also used to examine the ability of MELD to predict post-LT mortality. Examining the KM curves for the 5 strata of MELD scores found only the patients in the two highest MELD strata to have significantly decreased survival. Using the group with a MELD score <10 as the reference group, patients with MELD scores of 30-39 had a hazard ratio of 3.2 (95%CI, 1.1-9.6) and MELD ≥40 had a hazard ratio of 5.15 (95%CI, 1.1-24.8). When examining the 3 MELD strata, only patients with MELD >25 (reference group MELD <15) had a significant risk of 1-year mortality (HR= 2.55, 95%CI, 1.1-5.9). Although the curves cross for the log-log plots of MELD <15 and MELD 15-25 strata, the *stphtest* was not significant (p=0.3919) indicating that the Cox proportional hazards assumption was not violated in this analysis. The present study confirms the findings of the study from UCLA, in which only the highest strata of MELD scores were significantly associated with 1-year patient survival (MELD >36 vs. MELD <10, HR= 3.9, 95%CI, 1.55-10.27) (20).

To examine if other factors may be better predictors of post-LT mortality, each possible predictor variable was included one at a time as the independent variable in a Cox proportional hazards model for 1-year post-LT survival. Of the components of MELD, only the creatinine was found to be significantly associated with survival. This was also seen in the examination of the UNOS database, in which creatinine was significant, but INR and total bilirubin were not (23). Of the five components of the CTP class, only hypoalbuminemia was significantly associated with decreased survival. Although, the hazard ratio for

the CanWAIT status was significant, it is the presence of mechanical ventilation that is the most significant predictor of mortality on univariate analysis. Once again, this confirms the findings of the large UNOS database study, in which a Cox proportional hazards analysis using forward and backward selection found four independent variables (age, mechanical ventilation, hemodialysis, and retransplantation) to be associated with post-LT mortality (23). Patients with retransplantation were not included in our study and age was not a significant predictor of mortality on univariate analysis when examined as a continuous variable or a dichotomous variable (cutoff of age 60). There were only a small number of patients on dialysis at the time of LT and dialysis was not associated with mortality in our study. However, renal dysfunction (as measured by serum creatinine) was a significant predictor of mortality. Hypoalbuminemia was included in the multivariate analysis because it can reflect both liver dysfunction and nutritional status, and it was significantly associated with mortality on univariate analysis.

A model examining ventilation, renal dysfunction (log creatinine) and hypoalbuminemia demonstrated that mechanical ventilation was an important predictor of 1-year post-LT survival (HR=3.19, 95%CI 1.37-7.43, p=0.007), even when controlling for renal dysfunction and albumin level. There was evidence of effect modification between hypoalbuminemia and log creatinine, with the interaction term being significant (p=0.028).

Adopting a “sickest first” policy, as is the case with the MELD allocation policy in the USA, does not take into account the outcomes of these patients after LT. In the USA, there have been discussions about adopting policy to remove patients from LT waiting lists automatically once the MELD reaches a certain threshold (30). There is, however, no consensus on how to define futility and there is little evidence that MELD alone can predict this. In the present study, futility was defined as a 50% survival at 1 year, and survival was above this threshold even in the highest MELD categories. Others have suggested that 50% survival at 5 years may be a more appropriate end point for measuring futility (30). At the UofA, 5-year survival was above 50% for patients even in the highest MELD strata and for those patients transplanted on a ventilator (data not shown). The present study therefore could not identify a futility point, even when extending the definition out to five years.

Threats to Validity and Limitations of the Study

The validity of a study’s results can often be threatened by bias. Bias within an epidemiologic study can be defined as any systematic error in the design, conduct or analysis of a study which interferes with the correct estimate of exposure and outcome (31). Selection bias may be introduced if there were differences in the selection of cases (those who died awaiting LT) and controls (those who survived to LT). In the waiting list analysis, bias may have been introduced because we excluded patients who recovered liver function or who no

longer wanted LT. These patients were excluded because they ultimately did not have a chance of being transplanted and the final outcome of these patients (death or survival) was unknown. If these excluded patients had high MELD scores at the time of listing and they ultimately survived, they may have increased the median MELD score of the group surviving compared with those who died. This may have decreased the prognostic ability of the MELD.

One limitation of the study was in the collection of the data to calculate the CTP score at the time of listing. The CTP score at the time of transplantation had been recorded in the UofA LT research database. However, the CTP score at the time of listing had to be calculated from lab data and clinical information located in the electronic chart. The two subjective variables in the CTP score were estimated by reviewing clinic notes before the time of listing. Encephalopathy was graded as present (2 points) if it was mentioned as a complication of cirrhosis or if the patient was on lactulose, and was graded as severe (3 points) if the patient required hospitalization for management of encephalopathy. Ascites was graded as easy to control (2 points) if it was detected clinically or on ultrasound, or if the patient required diuretics, and was graded as severe (3 points) if the patient required repeat large volume paracentesis or TIPS to control the ascites. However, this should have only introduced non-differential misclassification bias, as the information was collected in the same manner regardless of the outcome of the subjects (death, delisting or successful LT). This type of bias tends to move the estimated OR towards 1.0 (31).

Another limitation was the inclusion of Status 0 patients in the Wait List Analysis. Although Status 0 patients cannot receive a LT until they are activated, it was important to include these potential LT recipients to capture all patients who died or were delisted for being too ill (15 out of 49 removals from the list were in Status 0 patients). The Status 0 group included patients who were later transplanted as Status 1 (n=57), Status 1T (n=4), Status 2 (n=22), Status 4 (n=6) and Status 4F (n=1).

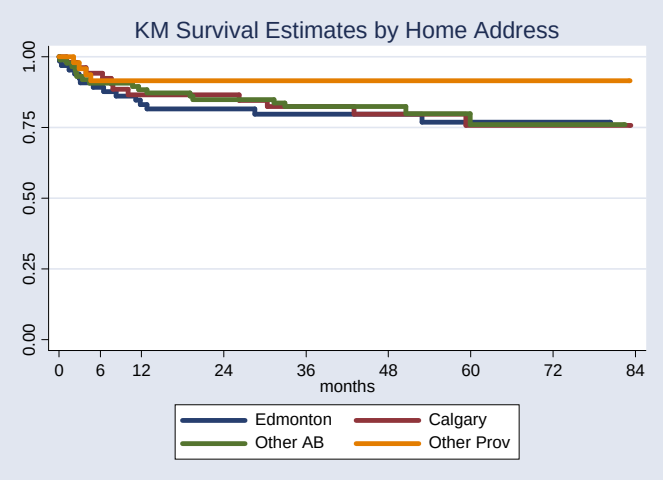
Selection bias may have also influenced the results of the post-LT analysis. It was apparent from this study that patients who were removed from the waiting list had much higher MELD scores than those who successfully underwent LT. At the UofA, 50% of patients were transplanted with a MELD score of below 15, indicating that it is a relatively healthy cohort of patients. The ability of the MELD to predict post-LT survival will be reduced if the sickest patients with the highest MELD scores are not allowed to undergo LT. This practice of physicians removing patients deemed “too ill” to undergo LT has been recognized as a potential source of selection bias in other studies examining post-LT outcomes (30).

Using logistic regression and ROC curve analysis to compare the predictive ability of the MELD, CTP and CanWAIT system is based on the assumption that the logits are linear functions of the X variable. This appears to hold true for the

MELD (Figure 10). However, the difference between CTP points or CanWAIT status are ordinal and analysis which views them as interval data should be viewed with caution. For example, using logistic regression it is assumed that the log of odds for mortality is the same between a Status 1 and Status 2 patient as it is between a Status 3 and Status 4 patient. The KM curves for the different strata suggest that this is not the case.

Finally, one concern in survival analysis is the loss of patients to follow-up. This may be a concern for UofA program, in that 74% of patients are from outside the city of Edmonton and 18.8% were from another province. As patients are usually monitored very closely during the first post-LT year, this is less of a concern when examining early post-LT mortality. However, the long-term survival curves suggest that loss to follow up may be a problem with patients from outside Alberta (Figure 28).

Figure 28. Long-term KM survival estimates by home address.



Implications of the Findings

In October 2005, Canadian LT hepatologists and surgeons will be meeting in Montreal to discuss one fundamental question: *Should Canada adopt the MELD as a means of organ allocation in this country?* The present study has confirmed the ability of the MELD scoring system to predict short-term waiting list mortality in a cohort of Canadian patients (area under the ROC curve of 0.78) and has shown MELD to be superior to the current CanWAIT system in predicting death while awaiting LT. It is therefore reasonable to suggest adopting MELD as an organ allocation policy in Canada.

A recent report from Australia suggests that MELD would significantly alter organ allocation in their country (32). The Australian system is similar to the Canadian system, in that the 6 transplant centers in Australia and New Zealand share organs for urgent patients, but then organs are allocated by each centre based on clinical judgment. They concluded that organ allocation under MELD would be better at prioritizing patients who would ultimately die without LT (32).

Should other variables added to the MELD in the listing score? Other variables such as variceal bleeding, ascites, encephalopathy and albumin do predict mortality, but previous research has shown that they add little to the MELD, and there is a consensus in the USA not to add subjective variables back to the MELD score (30). It is also recognized that some factors such as age, race and gender may be “off limits” for incorporation into organ allocation policy purely for

political reasons (30). However, in the present study there was no evidence for age and gender causing effect modification or confounding on the relationship between MELD and mortality. Based on the data from Argentina, which suggests hyponatremia improves the predictive ability of MELD (14), UNOS has decided to collect data prospectively using sodium with the MELD (30). Our data does not support this decision, and others have recently suggested that serum sodium adds little to the prognostic value of MELD (33).

MELD organ allocation system considers only justice (transplanting the next sickest patient with the high risk of dying) but not overall utility (the greatest good for all). There is increasing interest in the concept of “transplant benefit” defined as “the number of years gained by transplantation compared to waiting on the list” (30). To support this concept you must have predictors of both waiting list and post-LT mortality. Our study confirmed that sicker patients are more likely to be removed from the waiting list and that selection bias is therefore introduced into the examination of post-LT outcomes. Despite this, our data suggests that MELD can predict post-LT survival although with less accuracy compared to on the waiting list. Patients with the highest MELD scores not only have the highest risk of dying awaiting transplantation but also have lower survival after LT. Our study confirmed that renal function and mechanical ventilation are more important predictors of mortality after LT and these factors therefore need to be considered in models examining transplant benefit. How to deal with this problem is unclear. Perhaps we should temporarily or permanently delist patients with

chronic liver disease who end up ventilated or with significant renal dysfunction, or alternatively they could receive negative MELD points which would move other patients with better post-LT prognosis ahead of them on the LT waiting list.

An important finding in our multivariate analysis of post-LT mortality was the significant interaction between albumin and creatinine. To my knowledge, all previous studies examining MELD appear to have used simple additive models without interaction terms. The recent summary report of a US conference held to examine evolving concepts of liver allocation in the era of MELD recommended: “posttransplant outcome analyses should consider possible interactions between predictor factors and MELD and PELD scores” (30). Simple additive models may not be enough, although more complex models including interaction terms will bring increased complexity to a predictive scoring system.

It has been suggested that a MELD score of 15 is where patients obtain a survival benefit from LT (34). In a cohort of nearly 13,000 patients, Merion and colleagues determined that the risk of dying in the first post-LT year was higher then the risk of patients dying on the waiting list for patients with MELD scores 6-11 (HR=3.64) and MELD scores 12-14 (HR=2.35) (34). This has led UNOS to consider a minimal MELD criterion for listing (MELD ≥10) and resulted in adoption of the “Share 15 Policy”, in which organs must be offered to patients within the region with MELD scores ≥15 before transplanting patients locally with lower MELD scores (30). At the UofA, patients with MELD scores <20 had

similar 1-year survival on the waiting list (89.3%) and after LT (89.9%) and the 1-year mortality was significantly higher on the waiting list compared to after LT only when the MELD score was ≥20 (29.4% vs. 19.7%). In July 2005, the UofA began a trial period of MELD for organ allocation. A hybrid system between MELD and CanWAIT was eventually adopted in which patients at home with MELD scores ≥20 were moved to the top of the Status 1 list. The results of our study suggest that transplant benefit at the UofA is gained at a MELD ≥20 and support the continuation of this policy for the time being.

Finally, are there alternatives to MELD? Unlike the study by Wiesner et al (11), MELD was not superior to the CTP score in our study. Others have examined the UNOS database, and when UNOS Status 3 patients (at home with a CTP score 7-9) were added to the analysis the area under the ROC curve for the CTP and MELD scores were nearly identical for the prediction of 3-month waiting list mortality (0.793 vs. 0.789) (35). The CTP system has been criticized because of its subjective quantification of ascites and encephalopathy, and for the capping of laboratory values (for example, patients with a bilirubin of 35 and 700 µmol/L get the same points). However, the CTP classification system does have the advantage of familiarity to most hepatologists and simplicity as it can be calculated at the bedside without log transformations. Some authors have suggested that the original Child's classification should be reassessed and validated prospectively, along with addition of additional markers such as renal function and creation of a CTP class D category to capture sicker patients (36).

In conclusion, as the MELD score is superior to the current CanWAIT system at predicting waiting list mortality at the UofA, this study supports the adoption of MELD as an organ allocation system in Canada. However, other factors such as mechanical ventilation and renal function are more important predictors of post-LT survival and these factors may need to be incorporated into an organ allocation policy that considers overall utility and transplant benefit.

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APPENDIX A

UNIVERSITY OF CALGARY

Faculty of Graduate Studies

APPOINTMENT OF SUPERVISOR AND/OR SUPERVISORY COMMITTEE

Name of Student: Kelly Burak UCID # 955643

Department/Faculty/Program Department of Community Health Sciences Degree MSc

Supervisor *(must be appointed by second annual registration)*

This represents: ☒π Appointment of Supervisor
☐π Change of Supervisor *(attach explanatory memo)*
☐π Appointment of Co-Supervisor

Current ☐ Interim Advisor or ☒ Supervisor and/or ☐ Co-Supervisor: Dr. Robert Hilsden

Recommended Supervisor: _____
Recommended Co-Supervisor (if applicable): _____

Supervisory Committee *(Doctoral students, and Master's students as necessary; print or type names)*
The Supervisory Committee should be established as soon as possible after the appointment of the Supervisor. This section should also be completed when replacing a member of the Supervisory Committee who is on leave.

	Committee Member's Complete Name	If U.of Calgary faculty member, list Department. If not, list University & Department or other affiliation
(1)	Dr. Mark Swain	Medicine
(2)	Dr. Gordon Fick	Community Health Sciences
(3)	Dr. Winnie Wong	University of Alberta, Department of Medicine
(4)		
(5)		

This information is collected under the Freedom of Information and Protection of Privacy Act to appoint a supervisor and/or a supervisory committee. The information will form part of the student and supervisory record. Questions may be directed to the Administrator, Faculty of Graduate Studies (403) 220-5417.

I am aware of these arrangements.	Kelly Burak *Signature of Student*	Date Jan 26/04
I agree to these arrangements.	*Signature of Interim Advisor or Current Supervisor*	Date Jan 26/04
I agree to these arrangements.	*Signature(s) of Proposed Supervisor/Co-Supervisor*	Date
Recommended by:	Reg Hamm *Signature of Department Head*	Date Feb 2 '04.
	Faculty of Graduate Studies	Date

UNIVERSITY OF CALGARY

MEMO

FACULTY OF MEDICINE

Department of Community Health Sciences

To: Dr. R.S. Sauve, Graduate Program Coordinator
Department of Community Health Sciences

Date: February 2, 2004

From: Dr. Robert Hilsden
Department of Community Health Sciences

Re: **Approval Of Proposal**

Name of Student: **Kelly Burak**
Degree Program: MSc
Title of Thesis Proposal: "Does the MELD Score Predict Mortality Before and After Liver Transplantation at the University of Alberta?"

We, the undersigned, have approved the attached proposal from a scientific perspective, and are forwarding it for ethical review. We acknowledge that if alterations to this proposal are made, we will submit another approval form. This project does not involve the handling of animals.

Dr. Robert Hilsden, Supervisor — Date: Apr 12/04

Dr. Gordon Fick, Community Health Sciences
Member of Supervisory Committee — Date: May 20, 2004

Dr. Mark Swain, Gastrointestinal Sciences
Member of Supervisory Committee — Date: March 24/04

Dr. Winnie Wong, Department of Medicine
University of Alberta
Member of Supervisory Committee — Date: 25/3/04.

cc: Kelly Burak
Dr. Robert Hilsden
Dr. Tom Noseworthy, Head, Department of Community Health Sciences

Foothills Medical Centre
1403 29 Street NW
Calgary, Alberta, Canada T2N 2T9
website www.calgaryhealthregion.ca

calgary health region
Foothills Medical Centre

30 June 2004

Dr. Robert Hilsden
Department of Medicine
Foothills Medical Centre

Dear Dr. Hilsden:

Re: #17829 – Does the MELD Score Predict Mortality Before and After Liver Transplantation in Alberta?

Thank you for submitting an application regarding the above project for review by the Adult Research Committee of the Calgary Health Region (CHR). This will confirm that the committee has granted institutional approval for this project, and that the CHR has granted approval under Sections 53 and 54 of the Health Information Act. **This approval is contingent on approval by the Conjoint Health Research Ethics Board.**

It is understood from your submission that your study will be entirely funded through external sources and that the CHR will be reimbursed for all research costs associated with this project. To facilitate a smooth startup of your project, please notify affected departments in the Region well in advance of your intent to initiate this study.

Please accept the committee's best wishes for success in your research.

Yours sincerely,

Elizabeth MacKay, MD
Acting Chair, Adult Research Committee

cc: Dr. K Burak, Dr. J. Conly, Conjoint Health Research Ethics Board

FACULTY OF MEDICINE | UNIVERSITY OF CALGARY

2004-06-29

OFFICE OF MEDICAL BIOETHICS

Room 93, Heritage Medical Research Bldg
3330 Hospital Drive NW
Calgary, AB, Canada T2N 4N1

Telephone: (403) 220-7990
Fax: (403) 283-8524
Email: omb@ucalgary.ca

Dr. R. Hilsden
Department of Medicine
HSC-1703
University of Calgary
Calgary, Alberta

Dear Dr. Hilsden:

RE: Does the MELD Score Predict Mortality Before and After Liver Transplantation in Alberta?

Grant-ID: 17829

The above-noted thesis proposal (dated March 21, 2004) has been submitted for Committee review and found to be ethically acceptable.

Please note that this approval is subject to the following conditions:

(1) consent for access to personal identified health information in retrospective chart review is not required on grounds considered under Section X of the Health Information Act,

(2) a copy of the informed consent form must have been given to each research subject, if required for this study;

(3) a Progress Report must be submitted by 2005-06-29, containing the following information:
   - i) the number of subjects recruited;
   - ii) a description of any protocol modification;
   - iii) any unusual and/or severe complications, adverse events or unanticipated problems involving risks to subjects or others, withdrawal of subjects from the research, or complaints about the research;
   - iv) a summary of any recent literature, finding, or other relevant information, especially information about risks associated with the research;
   - v) a copy of the current informed consent form;
   - vi) the expected date of termination of this project.

(4) a Final Report must be submitted at the termination of the project.

Please note that you have been named as a principal collaborator on this study because students are not permitted to serve as principal investigators. Please accept the Board's best wishes for success in your research.

Yours sincerely,

Christopher J. Doig, MD, MSc, FRCPC

Chair, Conjoint Health Research Ethics Board

CJD/am

c.c. Adult Research Committee Dr. J. Conly (information) Research Services K. Burak (Research Coordinator)
Office of Information & Privacy Commissioner

Health Research Ethics Board

2J2.27 Walter Mackenzie Centre
University of Alberta, Edmonton, Alberta T6G 2R7
p.780.492.9724
p.780.492.0459
p.780.492.0839
f.780.492.7303
ethics@med.ualberta.ca

August 17, 2004

Our file #5453

Dr. Winnie Wong
GILDR Group
205 College Plaza

Dear Dr. Wong:

Re: Does the MELD score predict mortality before and after liver transplantation in Alberta?

Thank you for submitting the above study to the Research Ethics Board. Dr. Morrish has reviewed your application to conduct this retrospective data review and has approved it on behalf of the committee. Your approval form is enclosed. We assume that Dr. Burak has applied to the University of Calgary Conjoint REB for approval at that site.

In order to comply with the Health Information Act, a copy of the approval form is being sent to the Office of the Information and Privacy Commissioner. .

Next year, a few weeks prior to the expiration of your approval, a Progress Report will be sent to you for completion. If there have been no major changes in the protocol, your approval will be renewed for another year. All protocols may be subject to re-evaluation after three years.

For studies where investigators must obtain informed consent, signed copies of the consent form must be retained, and be available on request. They should be kept for the duration of the project and for a full calendar year following its completion.

Approval by the Health Research Ethics Board does not encompass authorization to access the patients, staff or resources of Capital Health or other local health care institutions for the purposes of research. Enquiries regarding Capital Health administrative approval, and operational approval for areas impacted by research, should be directed to the Capital Health Regional Research Administration office, #1800 College Plaza, phone 407-1372.

Yours sincerely,

Judith Abbott

Judith R. Abbott (Ms.)
Administrative Coordinator
Health Research Ethics Board (Biomedical Panel)

/ja
enc.

Health Research Ethics Board

2J2.27 Walter Mackenzie Centre
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ETHICS APPROVAL FORM

Date: **August 2004**

Name(s) of Principal Investigator(s): **Dr. Winnie Wong**

Department: **Medicine**

Title: **Does the MELD score predict mortality before and after liver transplantation in Alberta?**

The Health Research Ethics Board (Biomedical Panel) has reviewed the protocol involved in this project which has been found to be acceptable within the limitations of human experimentation.

Specific Comments:

The Research Ethics Board assessed all matters required by section 50(1)(a) of the Health Information Act. The REB Panel determined that the research described in the ethics application is a retrospective chart review for which subject consent for access to personally identifiable health information would not be reasonable, feasible or practical. Subject consent therefore is not required for access to the personally identifiable health information described in the ethics application.

D. W. Morrish, M.D.
Chairman, Health Research Ethics Board
Biomedical Panel

This approval is valid for one year

Issue #5453

NOV 2 6 2004

The Northern Alberta clinical trials and research centre

November 22, 2004

Dr. Kelly Burak
Medicine, University of Calgary
RmG128 Health Sciences Centre
3350 Hospital Drive NW
Calgary AB. T2N 4N1

RE: Research Project: Does the MELD Score Predict Mortality Before and After Liver Transplantation in Alberta?

Dear Dr. Burak,

Please retain the attached administrative approval for the referenced study for your records. Thank you for your cooperation and patience with providing this office with the required information prior to granting you administrative approval.

Also attached is a Health Information Act (HIA) agreement, please sign and date and return the original to me.

Good Luck with your study, if you require further assistance from this office please contact me at 407-6041.

Sincerely,

S. Maharaj

Shanie Maharaj
Research Administration

Capital Health

Regional Research Administration
Clinical Trials Centre
1800 College Plaza
8215 - 112 Street
Edmonton, AB T6G 2C8
Phone (780) 407-1372

NOTICE OF ADMINISTRATIVE APPROVAL FOR PROPOSED RESEARCH

Site: **UAH**

Project Title: Does the MELD Score Predict Mortality Before and After Liver Transplantation in Alberta?

Project Number: W-2368

Investigator Name: Wong, Winnie Dr.

Department: Medicine

Division: Gastroenterology

Supporting Documents:

Ethics Appoval Date: 17-Aug-04 **Ethics File #:** 5453

Study Protocol

Sponsor: No Costs

CRO:

Type of Funds:

Overhead rate: 0%

Legacy Account: **Oracle Account:**

Contract Finalized Date:

Project Approved: 22-Nov-04 **Comment:** This is a thesis project by Dr. Kelly Burak

Kathy Brodeur-Robb
Regional Research Administration

K. Brodeur Robb

Copies to: Finance and Administration

Monday, November 22, 2004

The Northern Alberta clinical trials and research centre

November 22, 2004

TO: Dr. Kelly Burak

FROM: Kathy Brodeur-Robb
Manager, Regional Research and Administration

RE: Agreement By Researchers In Compliance With Health Information Act (HIA) Pursuant To Section 54(1)]

To be in compliance with Section 54(1) to the Health Information Act (HIA), for access to patients records held by a custodian (Capital Health), all researchers are being asked to sign the attached agreement.

Section 54(1) states: "If the custodian decides to disclose health information to a researcher, the researcher must enter into an agreement with the custodian".

This agreement only needs to be signed once and will be applied to all research you are conducting within Capital Health. The original will be kept in the Capital Health Regional Research Administration Office, 1800 College Plaza, with a copy of each administrative approval for the studies that will be covered by this agreement.

Regards,

K. Brodeur-Robb

Kathy Brodeur-Robb
Manager, Regional Research and Administration

A joint venture of
Capital Health and
the University of Alberta

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8215-112 Street
Edmonton, Alberta
T6G 2C8

P. 780.407.8007
F. 780.407.8021

Capital Health

AGREEMENT BY RESEARCHER IN COMPLIANCE WITH HEALTH INFORMATION ACT (Pursuant to Section 54(1))

I, Dr. Kelly Burak, am conducting research approved by the University of Alberta Health Research Ethics Board (the "Board"), a research ethics committee as defined in the Health Information Act and its Regulations (collectively the "Act"). I will be using or will have disclosed to me by Capital Health, health information as this term is defined in the Act. In accordance with Section 54(1) of the Act, I hereby agree as follows:

1) To comply with:
   i. the Act;
   ii. any conditions imposed by Capital Health or the Board relating to the use, protection, disclosure, return or disposal of the health information as set forth in Schedule A or as established from time to time; and
   iii. any requirement imposed by Capital Health or the Board to provide safeguards against the identification, direct or indirect, of an individual who is the subject of the health information.

2) To use the health information only for the purpose of conducting the proposed research as approved by the Board.

3) Not to publish the health information in a form that could reasonably enable the identity of an individual who is the subject of the information to be readily ascertained.

4) Not to make any attempt to contact an individual who is the subject of the health information to obtain additional health information other than that contemplated in the Board approved project, unless the individual has provided Capital Health with consent.

5) To allow representatives from Capital Health to access or to inspect my research premises to confirm that I am complying with the enactments, conditions, and requirements referred to in paragraph 1.

6) To be liable for the actions of my employees, agents, consultants or other persons for whom I am in law responsible respecting the collection, use or disclosure of the health information and for ensuring compliance with the Act by these persons.

If I contravene or fail to meet the terms and conditions of this agreement, this agreement will be terminated. This agreement shall apply to any and all research I conduct now or in the future which has been submitted to, and received approval from the Board. This agreement shall continue in full force until such time as I notify Capital Health in writing that I no longer wish to be bound by its terms and conditions.

Kelly Burak
Signature

Nov 25, 2004
Date