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Patients Evaluated for Liver Transplant: Transplant List Denial and Subsequent Outcomes

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by

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Abstract

Background: The evaluation process for listing a patient on the liver transplant list is complicated and involves multiple consultations from various specialists, as well as extensive imaging and physiological studies. Although there are data on the outcomes of those listed, we know little about those that are denied listing. This research project will identify the reasons for liver transplant listing denial and predictors of death following denial for this challenging group of patients.

Methods: Data from all patients (n=1,500) evaluated for a liver transplant from 1997 to 2007 by the Department of Gastroenterology, Hepatology, and Nutrition located at Virginia Commonwealth University Health System's (VCUHS) Hume-Lee Transplant Program were reviewed to identify patients denied listing (n=350). Simple descriptive characteristics were generated and the reasons for denial were assessed. The Social Security Death Index was used to determine and/or confirm mortality and multiple logistic regression was conducted to determine the predictors of death following denial of transplant listing.

Results: The majority of the denied patients were white males and the mean age was 50.9, SE= 0.542). The primary liver disease diagnosis for those denied listing was Hepatitis C Virus (HCV) (33.6%). Study participants whose primary diagnosis was ethyl alcohol abuse or hepatocellular carcinoma had greater odds of dying after not being listed when compared to those diagnosed with HCV; however, these findings were not statistically significant. The majority of participants were denied listing for Hepatic-related (38.8%), psychosocial-related (21.7%), and cardiac-related (15.7%) reasons. Men were two times more likely to die after denial than women (OR= 2.18, CI= 1.03, 4.62). Patients with a MELD score less than 30 were less likely to die after being denied listing compared to those with MELD scores 31 to 40. The risk of dying after denial was not statistically different for patients who were denied listing for hepatic-related and cardiac-related reasons compared to subjects who were denied for cancer.

Conclusions: Our findings have clear implications for the future of transplant medicine and raise additional questions. The analysis shows men, those 51 years of age and older and patients with MELD scores between 31 and 40 are more likely to die after not being listed for transplant. We did not find significant evidence that those with particular primary liver disease diagnoses were more likely to die following denial for listing. Other studies taking into account the population of patients that are listed as well as those denied listing are necessary in order to understand the patho-physiological mechanisms so that patient-specific therapies may be developed if appropriate.

Background

Liver transplantation has been established as the effective treatment of choice for most patients with end-stage liver disease (ESLD) (Koffron et al., 2008). This has resulted in an increase in referrals for transplantation in an environment with a limited supply of donor organs (Selvaggi 2008; Brown et al., 2005; Merion et al., 2005; Talwalker et al., 2003; Yu et al., 2001,). Approximately 15,000-17,000 patients are on the waiting list to receive a liver transplant on a daily basis, but, annually, only one-third of those patients will have the opportunity to receive a transplant (Koffron et al., 2008; University of California San Francisco Medical Center, 2009).

Reasons for Liver Transplant

ESLD is caused, in the majority of cases, by chronic liver disease that is left untreated. Chronic liver disease has numerous etiologies including viruses (e.g., Hepatitis B, C, and D viruses), toxins (e.g. alcohol), metabolic disorders (e.g., fatty liver), immune diseases (e.g., autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis), and inherited disorders (e.g., hemochromatosis, alpha-1 antitrypsin deficiency, Wilson Disease (METDIS)) (Riley et al., 2001; Norman et al., 1998).

ESLD ultimately leads to a non-functioning liver, which results in the decreased development of necessary proteins to keep fluid in the bloodstream (Reddy et al., 2009). Serious problems such as liver cancer, kidney failure, and portal hypertensive bleeding are also by-products of ESLD (Heidelbaugh et al., 2006; Kress et al., 2000; Norman et al., 1998). Cirrhosis and viral hepatitis, both of which occur in a variety of forms, are chronic conditions that are responsible for the need for liver transplant in the majority of patients with ESLD (Norman et al., 1998).

Primary Causes of ESLD

Cirrhosis is a condition where the liver becomes inflamed, destroying its cells to the point where the liver eventually shrinks, and toughens as the soft (normal functioning) tissue is replaced by solidified tissue (scar tissue). The change in the ratio of normal functioning tissue impedes blood flow to the organ. Over time, nutrients, hormones, drugs and toxins cease to be effectively processed by the liver and the important production of proteins, such as albumin and coagulation factors, are decreased (Saftoiu et al., 2002; Norman et al., 1998; Said et al., 2004; Koffron et al., 2008; Heidelbaugh et al. 2006). In most clinical cases, this process occurs over a period of months to years; the fluctuation in time results in the differing causes of cirrhosis such as primary biliary and alcoholic cirrhosis being the concluding diagnosis (Transplant Experience, 2009; Norman et al., 1998). Primary biliary cirrhosis specifically destroys the bile ducts in the liver, impacting the process of breaking down of fats in the liver. Alcoholic cirrhosis, on the other hand, destroys the majority of the liver cells and does not necessarily target bile ducts. Alcoholic cirrhosis is caused by chronic, heavy drinking (i.e., more than two drinks per day for men and one drink per day for women (Centers for Disease Control and Prevention, 2009a; Transplant Experience, 2009). According to the National Institute of Diabetes, Digestive, and Kidney Disease (NIDDK), cirrhosis is currently considered to be the seventh leading cause of death in the United States (National Institute of Diabetes, Digestive, and Kidney Disease, 2009).

Viral Hepatitis is characterized by inflammation of the liver due to either Hepatitis A, B, or C infection (Kemmer, et al., 2007). Hepatitis C (HCV) is the most commonly diagnosed chronic blood-borne infection in the United States, and the most

common reason people need liver transplants. Given data from population-based studies, it is estimated, that 40% of chronic liver disease caused by cirrhosis is due to HCV, which leads to approximately 8,000 to 10,000 deaths per year (Centers for Disease Control and Prevention, 2009a). The majority of HCV-infected individuals in the United States are between 30 to 49 years of age. The number of deaths due to HCV-related chronic liver disease is projected to increase over the next 10 to 20 years because infections of those 30 to 49 years of age will progress to decompensated cirrhosis and hepatocellular carcinoma (HCC) (Rasada, 2008; Norman et al., 1998). In addition, once cirrhosis develops, 1% to 4% of patients develop HCC annually, which increases the need for transplant (El-Serag 2002; Norman et al., 1998).

Organ Allocation

In the United States, the disparity between available livers and recipients in need of a transplant lead to a vigorous debate regarding the most effective way to allocate donor organs to patients among transplant centers, the Department of Health and Human Services (DHHS), the United Network for Organ Sharing (UNOS), and patient advocacy groups. In addition to the increasing shortage of donor organs, there is the issue of waiting-list mortality of potential transplant recipients. Due to these factors, in 1998, the DHHS issued a ruling in which the principles of organ allocation were defined to govern the operation of the Organ Procurement and Transplant Network (OPTN) (Organ Procurement and Transplant Network, 2009; Department of Health and Human Services, 2009). Guidelines were established to create an allocation policy intended to make the most effective use of organs by providing them to the most medically urgent patients ("sickest first") who might in turn be the most appropriate candidates for transplantation

given favorable chances of survival. Specifically, this ruling included the following guidelines: 1) organs should be allocated to transplant candidates in the order of medical emergency; 2) transplant waiting time should be minimized: and 3) attempts should be made to avoid futile transplants to promote sufficient use of scarce donor organs (Martin et al., 2007; Wiesner, 2004; Freeman et al., 2002; Freeman, 2004; Martin et al., 2007; Yoo et al., 2005; Department of Health and Human Services, 2009).

In response to this mandate to improve liver allocation, a new system was created to eliminate waiting time on the list and minimize the use of subjective variables for listing status assignment (Kamath et al., 2007; Freeman et al., 2002; Martin et al., 2007; Yoo et al., 2005). Specifically, in February 2002, UNOS implemented the Model for End Stage Liver Disease (MELD) scoring system to allocate liver grafts in a more systematic and objective manner (Kamath et al., 2007; United Network for Organ Sharing, 2009; Freeman, 2007; Talwalker et al., 2003). Prior to the implementation of MELD scoring, liver transplantation was done using subjective criteria and patients were assigned priority based on the time they had been on the transplant waiting list. Thus, patients placed on the list at an earlier point in time were at an advantage. This fact led physicians to start referring their patients to a liver transplant center at a very early stage, often before the patient required a liver transplant, which frequently caused waiting list "inflation" (Aranda-Michel et al., 2008; Kamath et al., 2007; Yoo et al., 2005).

Since its introduction in 2002, the MELD score now allows patients to be selected for transplantation from the waiting list based on their likelihood of death within three months using three laboratory ranges (i.e., total serum bilirubin concentration, international normalized ratio (INR), and serum creatinine concentration) (Selvaggi 2008;

Kamath et al., 2000; Kamath et al., 2001; Merion et al., 2003; Bambha et al., 2004). The MELD equation to calculate the severity score is: $9.6 \times \log_e$ (creatinine, mg/dl) + $3.8 \times \log_e$ (bilirubin, mg/dl) + $11.2 \times \log_e$ (INR) + 6.4 (Kamath et al., 2007; United Network for Organ Sharing, 2009). Patients are assigned a score in a continuous scale from 0 to 40, which equates to 3-month survival rates, such as 90% survival for a MELD score of 6 and 7% survival for a MELD score of 40 (Martin et al., 2007; Kamath et al., 2007; Desai et al., 2004). Approximately 75% of patients with scores of less than 11 who are listed remain alive without undergoing a liver transplant procedure with minimal change in their score at one year follow-up examinations (Kamath et al., 2007; United Network for Organ Sharing, 2009; Kamath et al., 2001; Aranda-Michel et al., 2008). Patients who have a MELD score of greater than 17 and proceed with transplantation have an increased survival benefit over those that are not able to receive transplantation as a form of therapy (Aranda-Michel et al., 2008; Merion et al., 2005; Kamath et al., 2007; Forman et al., 2001).

Despite the usefulness of the MELD scoring system, many individuals involved in transplant medicine are working to improve its accuracy and use as a tool in objective liver allocation. Improvement may be achieved by the addition of lab values to the equation (e.g., serum sodium), and by evaluating the prevalence of disease factors across populations with ESLD (e.g., hyponatremia) (Said et al., 2004; Freeman et al., 2002; Northup et al., 2000; Martin et al., 2007; Yoo et al.,2005).

<u>Public Health Implications</u>

ESLD is not only a leading cause of mortality in the United States, but it has detrimental direct costs (e.g., medical costs that affect private insurance and put pressure

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on programs such as Medicaid and Medicare) and indirect costs such as those from disability (Kaplan et al., 2004). Further, these costs affect people in their most productive phase of life (Kaplan et al., 2004). The direct and indirect costs of ESLD have contributed the widening gap between the need and availability of livers. This gap has resulted in an increase waitlist time for transplantation, and because of this there has been an increase in mortality for those on the waiting list (Yu et al., 2001; Merion et al., 2005; United Network for Organ Sharing, 2009). Due to this gap there has been a reassessment within the transplant medicine specialty of the selection and listing criteria for transplantation, as well as an alteration in the current standard of organ allocation and distribution (Merion et al., 2005; Yu et al., 2001; United Network for Organ Sharing, 2009; Kamath et al., 2001; Santori et al., 2005; Organ Procurement and Transplantation Network, 2009). The answer to closing the widening gap in donor availability, for those on the waitlist, lies in using evaluation systems that most accurately and equitably select the right recipient for the limited supply of available donors. Finding this solution is of consequential importance for the public's health.

<u>**Gaps in the Literature**</u>

Many patients who are evaluated for liver transplant are deemed ineligible for medical (such as cardiac abnormalities that interfere with surgical procedures) and psychosocial (such as alcoholism and mental illnesses that will not allow the patient to comply with medications) conditions that make them poor liver transplant candidates (United Network for Organ Sharing, 2009). The ineligibility is determined by a very complicated evaluation process that involves multiple consultations from various specialists, as well as extensive imaging and physiological studies. In transplant medicine

literature there is a wealth of data concerning the outcomes of those listed for transplantation; however, very little data exists on those who are denied listing. If more data were available it would allow for the prediction of crude and attributable mortality in patients denied liver transplantation, before or after the implementation of the MELD scoring system (Kress et al., 2000; Aranda-Michel et al., 2008; Freeman et al., 2002, Freeman et al., 2004).

To date, the only study currently found in the literature involves a cohort of patients admitted to the Intensive Care Unit (ICU) at the University of Chicago Hospital who were denied liver transplantation listing after evaluation (Kress et al., 2000). The researchers found patients denied listing had substantially higher mortality rates than those who were placed on the transplant list within the hospital's ICU during the study period. This study was performed before the implementation of the MELD scoring system. As of this writing there are no definitive epidemiological or clinical studies that look exclusively at a patient population that was evaluated and ultimately denied liver transplantation after the implementation of the MELD scoring system. Thus, within transplant medicine literature, there is considerable need to evaluate outcomes for those evaluated and denied listing so patient outcomes can be accurately predicted by type of diagnoses and reason for denial of listing.

Objectives

This research project will identify clinical outcome predictors for this challenging group of patients paying particular attention to those patients who have been disqualified from liver transplant listing within the Virginia Commonwealth University Health System (VCUHS). The specific aims of this research project are to: 1) define the reasons

for denial to the liver transplant list at VCUHS given demographics; 2) determine if the number patients being turned down has increased since the implementation of new transplant protocols (MELD-based system) within the VCUHS in February 2002; 3) determine the outcomes of those patients denied listing (all cause mortality from time of denial); and 4) determine independent predictors of mortality for those denied listing.

This study will evaluate the demographics used to assess a candidate's ability to be listed for a transplant, which will ultimately allow physicians at the VCUHS to better understand the determinants of their evaluation protocols and whether they are successful at correctly choosing patients who should not be listed, specifically since the implementation of the MELD-based system. It is also suggested that further exploration of patients denied listing could facilitate a greater number of successfully transplanted patients (Kress et al., 2000).

Methods

Study Population

The setting for this study is the Department of Gastroenterology, Hepatology, and Nutrition at Virginia Commonwealth University Health System's (VCUHS) Hume-Lee Transplant Program. Our study population includes patients who underwent evaluation for liver transplants from 1997 to 2007. A total of 1,500 patients were evaluated. Overall, we excluded 1,150 patients because they did not meet the inclusion criteria. Specifically, 1,117 were excluded because they were listed for transplant, seven were excluded due to their age and/or there were no records found for them in the VCUHS medical records system, 23 were excluded because a decision was still pending on their

listing eligibility. Our final sample was 350 patients, which was 23% of the initial
population over the ten year period.

<u>Data Collection and Abstraction</u>

The dataset used for this study includes patient information (65 data fields)
collected during the transplant evaluation process; which was entered in a Department
database (PATS). The database contained information collected by physicians and staff
during the patient's evaluation visit. Data missing in the database for the final study
sample (n=350) was abstracted from the patients' medical records if the data were
variables typically found in medical records. Both the paper version kept within the
Department and the hospital's electronic medical record system (i.e., CERNER, as well
as the hospital's dictation system) were used.

The variables of interest were those considered to be associated with evaluation to
transplant listing such as demographic information (i.e., gender, age, race and ethnicity)
disease etiology, laboratory values (i.e. MELD scores, creatinine and sodium), reasons
for transplant listing denial, and alcohol use. Additional variables, for example,
employment status, insurance/method of payment, etc. were of interest; however, they
were not included due to high prevalence of missing data (>60% missing in most cases).

Mortality measures were determined from the study database, medical records,
and the Social Security Death Index (SSDI). The SSDI was accessed in 2008 to
determine mortality status for those with missing data in the study database, and to
confirm mortality status for those who had mortality status listed in the study database.

Data Coding

From the 65 available data fields within the PATS database, ten variables were selected for inclusion in the analyses. Specifically, all demographic information was retained (i.e. gender, age at evaluation, race/ethnicity), as well as serum creatinine, serum sodium, primary liver diagnosis (PLD), reasons for transplant listing denial, MELD scores, evaluation date, and mortality status.

The variables were collapsed for the purpose of analysis. Race was grouped into four categories (i.e. white, Black/African-American, Hispanic Latino, other) given the distribution of each group within the PATS database. Primary liver diagnosis was collapsed into nine groups (i.e., ethyl alcohol abuse (EtOH), hepatocellular carcinoma (HCC), cryptogenic (CCX), HCV, adenomatous hyperplastic nodules (AHN), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), METDIS (Wilson's Disease), and other. Reason for denial of transplant listing was categorized into ten groups (i.e., cancer-related, cardiac-related, financial-related, psychosocial-related, pulmonary-related, neurology-related, renal-related, gastro-intestinal-related (GI), hepatic-related, and other). Lab values for creatinine and sodium were each grouped in three categories (i.e., below normal, normal, above normal). MELD scores were collapsed into four groups (i.e. 0-9, 10-20, 21-30, and 31-40). In some of the variable categories (i.e. race/ethnicity, age, MELD, primary liver diagnosis, all lab values, and reasons for denial) there was missing data for the patients. The main outcome variable was death, which was coded dichotomously for each patient (i.e. yes, no) as determined by the medical records and SSDI. It should be noted that for the purposes of the logistic regression (explained in the statistical analysis section), variables were collapsed further

given the fact that some categories had very few subjects. All recoding decisions were based on what is known conceptually or on biological plausibility to ensure the model with the best possible fit.

Statistical Analysis

The data were analyzed using SAS software (version 9.1; SAS Institute Inc, Cary NC). Descriptive characteristics were generated for the study population. Frequencies were calculated to determine the number and percent of patients denied transplant listing annually from 1997 to 2007, which included years prior to and after the implementation of MELD scoring. Frequencies were also generated to determine the reasons for denial of transplant listing as well as the number of patients who died after being denied liver transplant. Lastly, multiple logistic regression was conducted to determine independent predictors of mortality for the cohort of patients denied listing. Specifically, odds ratios and 95% confidence intervals were calculated and a p-value < 0.05 was considered statistically significant. As mentioned in the data coding section, not all variables were included as originally coded in the logistic regression. Specifically, serum creatinine was not used in the model. Also, due to small numbers of those with PSC and PBS, these two primary liver diagnoses were added to the "Other" category. Further, again due to small sample sizes, the reasons for denial were collapsed differently so that the following categories were assessed: hepatic-related, psychosocial-related, financial-related, cardiac-related, and cancer-related and other. An analysis for effect modification (i.e. interaction) using ANOVA was not performed.

Results

Table 1 shows the demographic characteristics of patients who were evaluated and listed on the transplant list during the study period. Age was missing for the majority of patients who were listed. Approximately 40% were 35 to 50 years of age (n= 442). The majority were men (70.8%, n= 767) and non-Hispanic whites (62.2%, n=695).

Table 2 shows the risk factors for denial of listing. The majority of those denied transplant listing were non-Hispanic whites (65.1%, n= 228), males (67.7%, n= 237), and 51 years and older (53.7%, n= 188). The mean age was 50.90, (SE= 2.72). The primary liver diagnoses for those denied listing were HCV (33.4%, n= 117), and ethyl alcohol abuse (12.9%, n= 45); however, the "Other" category, which included diseases such as CCX, METDIS, AHN, PBC, and PSC made up 32.9% of the sample (n= 115). The majority of those denied listing (47.7%, n= 167) had MELD scores between 31 and 40, 10.8% (n= 38) had scores between 10 and 20 and 21.7% (n= 76) had missing MELD scores. Approximately 41.7% (n= 146) had elevated creatinine lab and 42% (n= 147) had normal values. On the other hand, only 26.0% (n= 91) had sodium levels that were below normal and 62.8% (n= 220) had normal values. The majority of participants were denied listing for hepatic-related reasons (38.9%, n= 136) followed by psychosocial-related reasons (21.7%, n= 21.7) and cardiac-related reasons (15.7%, n= 55).

Table 3 shows the odds ratios and 95% confidence intervals for the odds of death after being denied liver transplant listing from the multiple logistic regression analyses. After adjustment, males had a two-fold increased risk of death when denied listing compared to females (OR=2.18, 95% CI=1.03, 4.62). In general, whites who were denied listing were more likely to die compared to other races; however, these findings

were not statistically significant. Study participants who were 51 years of age and older were almost four times more likely to die after denial of listing compared to those who were in the 18 to 34 age range (OR=3.91, 95% CI=1.05, 14.48). Neither the primary liver disease nor the reasons for denial of listing were statistically associated with risk of death after listing denial. After multivariate adjustment, those with MELD scores less than 31 were approximately 67% to 79% less likely to die compared to those with MELD scores between 31 and 40 (MELD scores 0-9: OR=0.209, 95% CI=0.075, 0.583; MELD scores 10-20: OR=0.184, 95% CI=0.065, 0.520; MELD scores 21-30: OR=0.334, 95% CI=0.119, 0.940). Sodium lab values were not associated with death after denial of liver transplant listing.

Figure 1 shows the percentage and number of subjects denied listing by year throughout the study period (1997-2007). The lowest number of patients denied listing occurred in 1999 (n=9), which represents 8.4% of those evaluated for transplant in that calendar year. The highest absolute number of patients denied listing occurred in 2002 (n=62), the first year the MELD score was implemented; however, this represents 26.1% of those evaluated for potential listing. The highest annual percent of patients denied listing throughout the study occurred in 2004 (n=39; 45.8%).

Discussion

To our knowledge this is the first study to look specifically at patients denied listing to the liver transplant list in a non-emergency hospital setting after the implementation of the MELD scoring system. Overall, we found 23.9% of patients evaluated for liver transplant, who met our eligibility criteria were denied listing over the ten year study period. The majority of those denied listing were males (67.7%). On

average, a larger percentage of patients were denied liver transplant listing in the years following the MELD score implementation compared to the years prior to its implementation (Figure 1). After listing denial, men were more likely to die compared to women and those 51 years of age and older were more likely to die than those 18 to 34 years of age. Further, those with higher MELD scores (31-40) were more likely to die compared to those with lower MELD scores.

The majority of denied patients were male (67.7%), which was expected given the majority of patients evaluated for liver transplant at VCUHS were male (70.8%). This could be the result of riskier behaviors (i.e. alcohol and drug abuse, not seeing a physician on a regular basis, etc.) that males engage in more often than females (Centers for Disease Control and Prevention, 2009b). In addition, the majority of patients denied listing were white (65.1%), which is most likely due to the majority of patients being evaluated for liver transplant at VCUHS were white (63%). A few reasons could explain why whites were evaluated more often then all other racial/ethnic groups. For example, historically, whites tend to have better access to care compared to historically underserved racial/ethnic minorities. Also, in our case, the Richmond metropolitan area is surrounded by several counties that are predominantly white (U.S. Census Bureau, 2009a; U.S. Census Bureau, 2009b; U.S. Census Bureau, 2009c; U.S. Census Bureau, 2009d). Patients denied listing were predominantly older (51 years and older) compared to those who were evaluated and listed (35 to 50 years) (53.7% versus 34.2), which is consistent with information in previously published literature (Kress et al., 2000). This is most likely because older patients traditionally do not fare as well after transplantation or during the transplant procedure itself (Norman et al., 1998).

The most prevalent primary liver disease diagnosis for patients denied listing during the study period was the Hepatitis C Virus (33.4%), which was expected given Hepatitis C is the most likely cause of end-stage liver disease (Aranda-Michel et al., 2008). Alcohol abuse (12.9%) was the second highest specific primary liver disease for those denied. These two primary liver diseases made up 46% of those denied listing. Thus, almost half of the patients denied could have potentially avoided the need for transplant had they practiced healthier lifestyle behaviors to limit their risk. Extrapolation of these findings would equate to the possible prevention of approximately 162 deaths in a population such as the one in this study had healthier behaviors been observed.

The analysis of the MELD scoring system for patients denied listing was consistent with the intended purpose of MELD. Specifically, MELD scores are meant to differentiate lower risk/higher benefit candidates for liver transplantation. Almost 48% of those denied listing had MELD scores between 31 and 40. Further, in the multiple regression analysis, it was apparent that those with lower MELD scores were less likely to die following listing denial compared to those with MELD scores greater than 31, which was expected. Interestingly, 21.7% of patients denied listing had missing MELD score information. Thus, the decision to deny listing for these patients did not include deliberations pertaining to their MELD score by the transplant committee. For these patients, the decision to deny listing could have been based on medical and/or psychological co-morbidities, which would make survival following transplant less likely. That said, the MELD scoring system is designed to efficiently determine the best candidates for transplant using scientifically sound objective variables. As such, with the

high percentage of those denied listing not having a record of their MELD score it would seem that the transplant evaluation process measures may not be fully implemented. Therefore, VCUHS needs to address this issue and strive to determine MELD scores for 100% of patients to facilitate the most successful transplant committee decisions.

Hepatic-related reasons were the most prevalent reason (38.9%) for patients being denied listing at VCUHS, which is consistent with what was predicted given the leading causes of ESLD and the primary liver diagnoses of patients in this study population. Psychosocial reasons were the second most prevalent reason for being denied listing (21.7%). In theory, if effective preventative care and mental health services were accessed within VCUHS or if they were provided for by the state and federal governments, this subset of the population denied listing would decrease. Financial reasons did not appear to be an important factor in the committee's decision for listing denial given financial issues were the reason of denial for less than 7% of the population. However, given that everyone should be entitled to adequate healthcare, even this relatively low percent of denial due to financial reasons is problematic. Specifically, no patients should have been denied solely due to financial concerns.

After multivariate adjustment, the only variables that were associated with mortality risk were gender, age, and MELD score. These significant findings are understandable. Older individuals are more likely to die after denial. As stated earlier, there is evidence that males partake in riskier behaviors, such as drinking which could possibly be the reasoning for the significant association with mortality (Centers for Disease Control and Prevention, 2009a). We also have evidence that the MELD score is accomplishing its intended goal – to successfully predict survival.

Some of the multivariate logistic regression results were surprising. For example, we had predicted that specific disease etiologies and certain primary liver diagnoses would have been statistically significant factors in patient mortality. There are many possibilities why disease etiology and reasons for denial were not significant correlates of mortality in our model. The small sample size for many categories of the aforementioned variables could have affected our ability to detect a statistically meaningful association. While data were missing, the actual numbers of missing data were very low for the variables of interest. Although not statistically significantly related to mortality, knowing the frequency of various primary liver diseases and reasons for denial for those denied listing could potentially enable clinicians at VCUHS to better understand the percentage of patients who have certain disease etiologies or social circumstances that keep them from being listed. In which case this may prompt VCUHS to allocate a greater amount of resources for tools such as earlier screening to detect more treatable cancers and cardiac disorders, earlier referral for patients with hepatic conditions, better support programs for patients with psycho-social issues like addictions, and higher quality health education for patients with an emphasis on preventative measures such as diet and exercise, and stress reducing techniques. If these types of preventive measures were implemented VCUHS could possibly help more patients become candidates of liver transplantation.

From Figure 1 it is clear that a higher percent of patients were denied listing each year following the 2002 implementation of the MELD scoring system than before its use at VCUHS. This suggests that the MELD scoring system changed organ allocation practices. However, more studies should be conducted to determine whether the MELD

scoring system at VCUHS is successfully allocating livers to those who would most likely be able to survive transplantation.

Due to the fact that very little information exists on this patient population the strengths of the study are in the innovativeness of the study and the implications it has for future research on the subject, but there were are limitations as well. The study sample is representative of patients presented to the transplant committee at VCUHS and not of the general United States population, which makes the comparison with existing data or the generalizability of the results difficult. However, the VCUHS is a major referral center with a high volume of transplant patients in Virginia (a state with only one other transplant hospital). Also, there were other potential risk factors/confounders such as employment history, lifestyle risk factors (i.e. smoking and drug abuse), transplant history, and transplant type (i.e. initial), and as mentioned earlier disease etiologies (i.e. PBC), and lab values (i.e. creatinine); but, due to missing data (>60% missing) these variables were not included in the multiple logistic regression model. Also the majority of the information included in the database was collected during interviews with subjects so under-reporting or over-reporting of variables could spuriously affect the results. For example, it is possible that due to social stigmatization of alcohol and drug abuse as well as certain disease etiologies some individuals may have deliberately omitted this information from their self-report.) The data for all patients were collected using a standard data collection tool (i.e. PATS and medical records). Further, VCUHS cannot control referrals for transplant evaluation. For example, referrals are made for transplant evaluation from providers outside the VCUHS (e.g. cardiologists in private practice). These numerous patients who were denied listing were not actually captured in the

transplant database because they were denied by other providers before ever being considered for transplant by the committee. In addition, although the transplant committee membership at VCUHS never changed throughout the study timeline, we cannot control for subjective decisions made by committee members concerning individual patients. Further, the SSDI was used to assess mortality status for those with missing data and confirm status for those with information within the study database and medical records. However, errors could exist due to the fact that it has been suggested that the SSDI is sensitive for certain populations such as males and Caucasians, but, it could be inaccurate for females or other race/ethnic populations (Schisterman et al., 2004) Thus, our main dependent variable could be biased. In addition, we did not assess one- or five-year survival. We merely assessed whether patients had died. Thus, those who were denied, for example, in 1999 would be more likely to have died by the time we assessed mortality compared to those who were denied in 2007. Lastly, assessment for effect modification (i.e. interaction) was not conducted, which is an important, significant limitation. Without assessing for interaction, we are unable to determine whether the dependent variable (i.e. mortality) is affected non-additively by one or more variables. If effect modification exists, the analyses should have been stratified by the variable(s) that were significant and the particular item(s) should not have been modeled as a confounder. In other words, if effect modification is present, the analyses do not appropriately or adequately represent the data when stratification is not done.

Conclusions

Our study results suggest there are still many clinically important questions that remain unanswered concerning patients who are denied listing for liver transplantation.

This study found the percent of patients denied listing for liver transplant after the implementation of MELD scores was higher than prior to the use of this objective criteria. The results of this study demonstrated gender, age, and MELD score were significant predictors of mortality among patients denied liver transplant. While HVC and hepatic-related reasons were the most common primary liver disease diagnoses and reason for denial, respectively, neither was associated with mortality following denial. Future work should be done to overcome the limitations of this study. Work focusing on creating patient-specific therapies that could result in a lower percentage of individuals being denied for psychosocial and medical reasons would be useful. These patient-specific therapies could include better mental health and preventative care for patients with some of the most prevalent primary liver diagnoses and reasons for denial. Further research concerning the one- and five-year survival after denial of listing for evaluated patients would be of interest. Also a study comparing patients who were evaluated and listed for transplant to patients who were evaluated and denied would be of great value so that transplant medicine specialists may be able to further understand the patho-physiological mechanisms brought into play and to anticipate the outcomes of these patients accurately.

Table 1. Demographics of Patients Evaluated for Liver Transplant and Added to Transplant List (N=1117)

| Variable	Number of Patients	Percent
Female	327	29.2
Age		
18-34 years old	104	9.3
35-50 years old	442	39.5
51 + years old	383	34.2
Missing	188	53.7
Race		
White	695	62.2
Black/African-American	159	14.2
Hispanic/Latino	62	5.5
Other	49	4.3
Missing	152	13.6

Table 2. Demographics and Potential Risk Factors of Patients Evaluated for Liver Transplantation and Denied Listing (N=350)

Variable	Number of Patients	Percent
Gender		
Female	113	32.3
Age		
18-34 years old	21	6.0
35-50 years old	126	36.0
51 + years old	188	53.7
Missing	15	4.3
Race		
White	228	65.1
Black/African-American	72	20.6
Hispanic/Latino	14	4.0
Other	10	2.9
Missing	26	7.4
Primary Liver Diagnosis		
Hepatitis C Virus	117	33.4
Alcohol Abuse	45	12.9
Hepatocellular Carcinoma	18	5.1
Cryptogenic	17	4.8
METDIS (Wilson's Disease)	16	4.6
Adenomatous Hyperplastic Nodules	8	2.3
Primary Biliary Cirrhosis	7	2.0
Primary Sclerosing Cholangitis	5	1.4
Other	115	32.9
Missing	2	0.06
MELD Score		
0-9	33	9.4
10-20	38	10.8
21-30	36	10.2
31-40	167	47.7
Missing	76	21.7
Creatinine Lab Value		
Below Normal	2	0.06
Normal	147	42.0
Above Normal	146	41.7
Missing	55	15.7
Sodium Lab Value		
Below Normal	91	26.0
Normal	220	62.8
Above Normal	7	2.0
Missing	32	9.1

Table 2 continued. Demographics and Potential Risk Factors of Patients Evaluated for Liver Transplantation and Denied Listing (N=350)

Variable	Number of Patients	Percent
Reason for Denial of Listing		
Hepatic-related	136	38.9
Psychosocial-related	76	21.7
Cardiac-related	55	15.7
Cancer-related	22	6.2
Financial-related	20	5.7
Pulmonary-related	11	3.1
Neurology-related	8	2.3
Renal-related	6	1.7
Gastrointestinal-related	1	.02
Other	11	3.1
Missing	4	1.1

Table 3. Predictors of Death Following Liver Transplant Listing Denial (n=350)

Variable	Total N	Death N (%)	Adjusted Odds Ratio	95% CI
Gender				
Female	113	76 (67.3)	Referent	--
Male	237	190 (80.2)	2.183	(1.030, 4.624)
Race				
White	228	176 (77.2)	Referent	--
Black/African-American	72	54 (75.0)	0.725	(0.311, 1.686)
Hispanic/Latino	14	9 (64.3)	0.358	(0.063, 2.042)
Other	10	7 (70.0)	0.220	(0.041, 1.190)
Patient's Age (years)				
18-34	21	11 (52.4)	Referent	--
35-50	126	91 (72.2)	1.484	(0.387, 5.683)
51+	188	164 (81.9)	3.917	(1.059, 14.487)
Primary Liver Disease				
HCV	117	89 (76.1)	Referent	--
Alcohol	45	33 (73.3)	1.186	(0.387, 3.627)
CCX	17	9 (52.9)	0.503	(0.104, 2.425)
HCC	18	16 (88.9)	2.545	(0.423, 15.319)
AHN	8	4 (50.0)	1.294	(0.165, 10.136)
METDIS	16	10 (62.5)	1.560	(0.303, 8.020)
Other	127	103 (81.1)	2.415	(1.017, 5.737)
MELD SCORE				
0-9	33	21 (63.6)	0.209	(0.075, 0.583)
10-20	38	26 (68.4)	0.184	(0.065, 0.520)
21-30	36	26 (72.2)	0.334	(0.119, 0.940)
31-40	167	143 (85.6)	Referent	--
Reason For Denial of Listing				
Cancer-related	22	19 (86.4)	Referent	--
Cardiac-related	55	46 (83.6)	0.449	(0.040, 5.060)
Financial-related	21	14 (66.7)	0.175	(0.014, 2.220)
Psychosocial-related	76	55 (72.4)	0.258	(0.025, 2.681)
Hepatic-related	136	99 (72.8)	0.172	(0.018, 1.658)
Other	39	32 (82.1)	0.344	(0.028, 4.277)
Sodium Lab Value				
Below Normal	91	75 (82.4)	1.347	(0.577, 3.143)
Normal	220	163 (74.1)	Referent	--
Above Normal	7	6 (85.7)	1.569	(0.127, 19.438)

Figure 1. Percent of Patients Evaluated and Denied Transplant Listing: 1997-2007
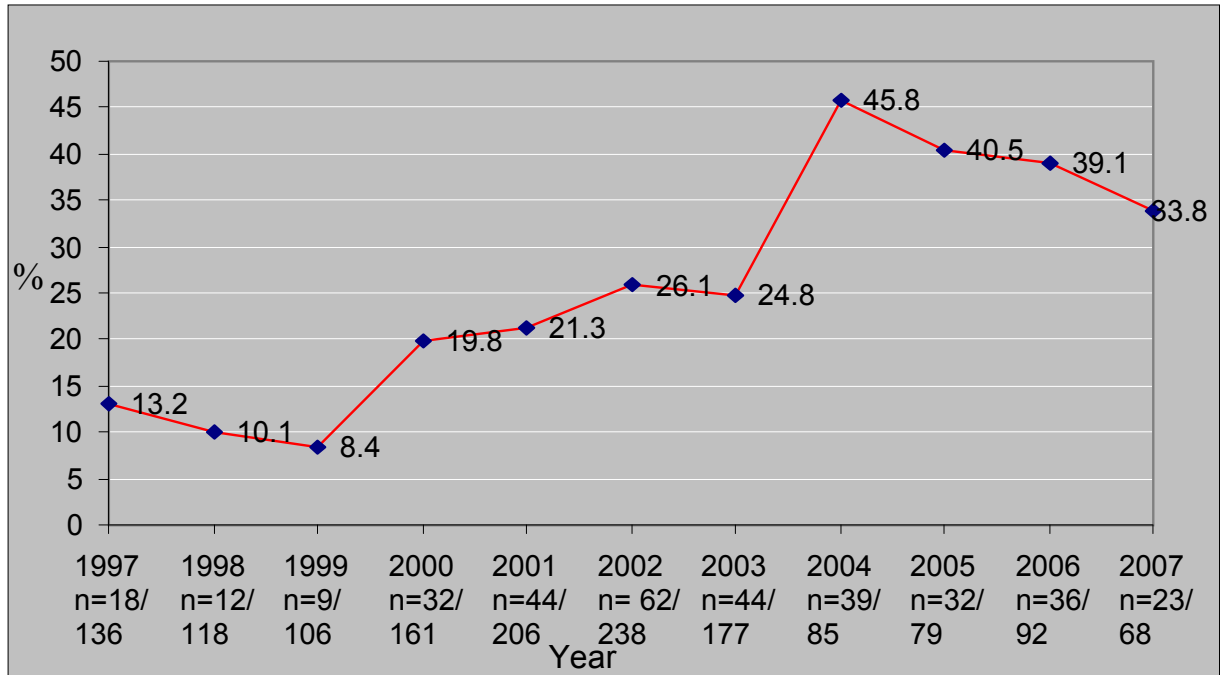
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