Published in final edited form as:

J Heart Lung Transplant. 2012 June ; 31(6): 591–600. doi:10.1016/j.healun.2012.02.008.

Hepatic Dysfunction and Survival After Orthotopic Heart Transplantation: Application of the MELD Scoring System for Outcome Prediction

Aalap Chokshi, MD, Faisal H. Cheema, MD*, Kenneth J. Schaeffle, BS*, Jeffrey Jiang, BS*, Elias Collado, MD, Khurram Shahzad, MD, Tuba Khawaja, MD, Maryjane Farr, MD, Hiroo Takayama, MD*, Yoshifumi Naka, MD, PhD*, Donna Mancini, MD, and P. Christian Schulze, MD, PhD

Department of Medicine, Division of Cardiology, New York-Presbyterian Hospital/Columbia University Medical Center, New York, NY, USA

*Department of Surgery, Division of Cardiothoracic Surgery, New York, NY, USA

Abstract

BACKGROUND—The prevalence of heart failure (HF) is rising and the only corrective treatment is cardiac transplantation. Advanced HF is associated with congestive hepatopathy and progressive functional and ultrastructural changes of the liver. We hypothesized that hepatic dysfunction is associated with impaired clinical outcome after heart transplantation.

METHODS—Data of 617 adult patients (75% males, mean age of 53±12 years, mean BMI of 25±4 and mean ejection fraction of 19±9%) undergoing orthotopic heart transplantation (OHT) were analyzed retrospectively. Deviation from institutional normal ranges was used to define abnormal liver function. Standard model for end Stage liver disease (MELD) scores were calculated and a modified MELD score with albumin replacing INR (modMELD) was created to eliminate the confounding effects of anticoagulation.

RESULTS—Before OHT, AST, ALT and total bilirubin were elevated in 20%, 18% and 29% of the population, respectively. Total protein and albumin were decreased in 25 and 52% of the population, respectively. By 2 months post-transplantation, percentages of individuals with pathological values decreased significantly except ALT, total protein and albumin, all of which took longer to normalize. Individuals with a higher pre-transplantation MELD or modMELD score had worse outcome 30 days post-transplant and reduced long-term survival over a 10-year follow-up.

CONCLUSIONS—In this large, single-center retrospective study, we demonstrate dynamics of liver dysfunction after cardiac transplantation and that elevated MELD scores indicating impaired liver function are associated with poor clinical outcome following OHT. Therefore, preoperative liver dysfunction has a significant impact on survival of patients after cardiac transplantation.

© 2012 International Society for Heart and Lung Transplantation. Published by Elsevier Inc. All rights reserved.

Address for Correspondence: P. Christian Schulze, MD, PhD, Division of Cardiology, New York Presbyterian Hospital, Columbia University Medical Center, 622 W 168th Street, PH10-203, New York, NY 10032, U.S.A., Tel: 212-305-6916, Fax: 212-342-5355, pcs2121@columbia.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

DISCLOSURES

The authors have no conflicts of interest to disclose.

Keywords

Heart failure; Liver dysfunction; MELD; Heart transplantation; Outcomes

The number of patients with advanced heart failure (HF) is rising in the United States and worldwide with the gold standard for therapy being cardiac transplantation.¹ Organ shortage and clinical complications after cardiac transplantation make the appropriate donor and recipient selection essential for a successful outcome. HF is associated with congestive hepatopathy and cirrhosis due to increased venous pressure and reduced hepatic blood flow.² This results in impaired hepatic protein and lipid synthesis, marked by poor nutritional status and cachexia, and reduced detoxification of metabolites.

Prior studies have shown variability in serum hepatobiliary markers of patients with HF. The most consistent findings are elevated alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT). Markers of liver injury, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are elevated in 3–18% of the HF population. Multiple studies have shown a decrease in serum albumin or total protein in HF.

Abnormal liver function has been linked to increased short and long-term morbidity and mortality in patients undergoing both cardiac and non-cardiac surgeries.³ While a number of risk-scoring systems have been established to assess risks and performance measures for cardiac transplantation, these scores fail to adequately address liver abnormalities. Both the Child-Turcotte-Pugh (CTP) classification and the Model for End Stage Liver Disease (MELD) score have been used as prognostic tools prior to various cardiac and non-cardiac surgeries, mostly in a population of cirrhotic patients, but never in patients with cardiac hepatopathy undergoing cardiac transplantation. In chronic liver disease patients undergoing liver transplantation, 3 month post-operative mortality rate is 20% with a score of >20 and 71% with a score of >40.⁴

On the basis of a single center experience, we assessed the baseline serum levels of hepatic function tests and MELD scores, and followed the values for up to five years after cardiac transplantation. In this same cohort, we proposed and calculated a modified MELD score that by design excluded the effects of anticoagulation by substituting albumin for international normalized ratio (INR). Our analysis reveals that liver dysfunction is associated with higher rates of postoperative complications and impaired short- and long-term prognosis in patients undergoing orthotopic heart transplantation (OHT). Elevations in MELD and modified MELD scores reliably identify patients at higher risk for complications and reduced survival after OHT.

MATERIALS AND METHODS

Patient Cohort

Information was collected retrospectively on 780 adults undergoing orthotopic heart transplantation (OHT) at Columbia University Medical Center/New York Presbyterian Hospital between November 1998 and November 2008. We excluded patients with incomplete laboratory datasets (n=106), patients undergoing cardiac re-transplantations (n=42) and individuals with elevations in hepatobiliary markers secondary to known hepatitis, hepatic tumors, hepatic trauma, bile duct diseases, bone diseases or bone neoplasias (n=15) leaving a total of 617 patients in the analysis.

The study protocol was approved by the local institutional review board and complied with the Health Insurance Portability and Accountability Act regulations and the ethical guidelines outlined by the 1975 Declaration of Helsinki.

Data Collection

Pre-operative data was collected by electronic chart review for the most recent laboratory analysis before cardiac transplantation. Post-operative data was collected at 2, 6 and 12 months, as well as 2, 3, 4 and 5 years post-transplant from electronic medical records based on the original transplant date. The mean time between laboratory value collection and transplantation was 12.3 ± 19 days for creatinine, 14.3 ± 16.6 days for hepatobiliary markers and 11.9 ± 17.3 days for coagulation panels.

Data on age, sex, race, body mass index (BMI), left ventricular ejection fraction, etiology of heart failure, pre-transplant medications, prior ventricular assist device (VAD) implant, comorbidities, and clinical outcome were recorded. Post-operative complications occurring within 30 days of transplant were recorded. This included respiratory failure, renal insufficiency (increase in creatinine $>30\%$ baseline), bleeding, wound infections, ventricular assist device placement, cerebrovascular accident and in-hospital death. Survival data were collected using the Social Security Death Index (SSDI) at an end observation date of March 1, 2010. If no death was recorded, the patient was recorded to be alive at the time of follow-up.

Hepatopathy

Pathological or abnormal hepatobiliary values were defined as those that fell outside the institutional normal ranges. The upper limits of normal used for AST, ALT, and total bilirubin were 38 U/L, 41 U/L and 1.3 mg/dL, respectively. The lower limits of normal used for total protein and total albumin were 6.7 and 4.1 g/dL, respectively. The upper limits of normal for ALP and GGT were 96 U/L and 58 U/L, respectively.

MELD Score

The standard MELD score was calculated by using the formula published by Kamath et al.: $1.12 * (\ln \text{INR}) + 0.378 * (\ln \text{T. bili}) + 0.957 * (\ln \text{Creat.}) + 0.643$ (3). If the INR, total bilirubin, or creatinine was less than 1, their values were assumed to be 1 so that the score did not become negative. The raw score was multiplied by ten and rounded to the nearest integer. In order to exclude the impact of oral anticoagulation and its impact on INR, we used a modified MELD score replacing INR with albumin levels to substitute impaired production of coagulation factors (as reflected by INR) with albumin, another secretory protein produced by the liver. This was further justified by a strong association of reduced albumin levels with impaired survival in our patient cohort. The modified MELD score (modMELD) was identical to the standard score except for substitution of the INR component with albumin. In place of INR, a conditional value was used based on the difference between the serum albumin and normal albumin (4.1 g/dL). If this difference, $(4.1 \text{ g/dL} - \text{serum albumin})$, was positive, one was added to the absolute value of the difference before substitution for the INR component. If the difference was negative, the number 1 was used in place of the INR component. Therefore, if serum albumin >4.1 , the modified MELD score was calculated as follows: $1.12 * (\ln 1) + 0.378 * (\ln \text{T. bili}) + 0.957 * (\ln \text{Creat.}) + 0.643$. If serum albumin <4.1 , then the modified MELD score was calculated as: $1.12 * (\ln [1 + (4.1 - \text{albumin})]) + 0.378 * (\ln \text{T. bili}) + 0.957 * (\ln \text{Creat.}) + 0.643$. As with the standard MELD score, these raw scores were multiplied by ten and rounded to the nearest integer. This modified MELD score correlated with the standard MELD score with individuals at the extremes of MELD scores having better correlations ($p < 0.001$).

Surgical Procedures and Immunosuppression

All patients in this cohort underwent OHT using the bicaval technique. Heart transplant recipients received standard immunosuppressant therapy with cyclosporine, mycophenolate mofetil, and prednisone. Pre-operatively, patients received 4 mg/kg of azathioprine and intraoperatively 500 mg of solumedrol. Post-operatively, patients received 125 mg solumedrol every 8 hours for three doses. Mycophenolate mofetil was started at a dose of 1,500 mg twice daily. High-dose oral prednisone was started at 100 mg daily and tapered to 30 mg daily by 2 weeks. Since 1998, induction therapy using interleukin-2 receptor antagonists has been administered on eligible patients 24 hours after cardiac transplantation.⁵ All patients, except those with active infections or undergoing re-transplantation received induction therapy.

Statistical Analysis

Continuous variables are presented as mean $\pm$ standard deviation and categorical data as percentages and frequency distributions. Continuous variables were compared using independent samples students' t-tests and categorical variables were compared using chi-square tests with post-hoc Fisher's Exact Test. Kaplan-Meier curves between groups were analyzed with Mantel-Cox log rank test. Univariate Cox-hazards regression was conducted for all hepatobiliary variables. A multivariate proportionate hazards model was created by stepwise reduction of hepatobiliary factors with a significance cut-off point of 0.05. The final multivariate model satisfied proportionality assumptions for Cox-hazards regression. For all analyses, a p-value of less than 0.05 was considered to be statistically significant. Data was analyzed using standard statistical software, SPSS version 18 (SPSS Inc., Chicago, IL), GraphPad Prism (GraphPad Software, San Diego, CA) and Stata 10 (StataCorp LP, College Station, TX).

RESULTS

Patient Characteristics

Pre-transplant baseline clinical characteristics for all patients analyzed in the study are shown in Table 1. Baseline characteristics and pre-OHT medications for all patients were further stratified according to MELD score (Table 2) and modified MELD score subgroups (Table 3). Significant baseline differences existed in age, gender, VAD prior to surgery and renal failure between the different MELD categories. In both MELD categorizations, there are significant differences in the use of ACE-inhibitors and β -blockers, but only in the standard MELD categorizations is the use of coumadin, diuretics and aldosterone antagonists significantly different. Post-operative complications are listed in Table 4 for the standard MELD scores and in Table 5 for the modified MELD scores. In both MELD categorizations, higher scores are associated with increased frequency of reoperation for bleeding and in-hospital death, but only in the modified categorization is respiratory failure and renal failure increased in the higher risk category.

Response of Hepatobiliary Markers after OHT

The percentage of heart failure patients who had pathological levels of AST, ALT, and total bilirubin was 20%, 18% and 29%, respectively. The percentage of patients who had pathological levels of total protein and albumin was 25% and 52%, respectively. The percentage of patients who had pathological levels of ALP and GGT was 38% and 68%, respectively. Within two months after cardiac transplantation, the percentage of the cohort with a pathological serum level of any hepatobiliary markers decreased significantly except for ALT, total protein and albumin. In addition, elevated hepatobiliary markers pre-

transplantation corrected within two months except for total protein and GGT, which take slightly longer to reach the normal range (Supplemental Figures 1–6).

Changes in MELD and Modified MELD Scores after OHT

The percentage of patients in the standard MELD score > 20 group and standard MELD score 14–20 group decreases two months after transplantation and stabilizes over one year while the percentage of patients in the lowest standard MELD score group (<14) slightly increases (Figure 1A). The average standard MELD score in the group > 20 falls ten points within two months post-transplantation (Figure 1B). In the modified MELD score stratification, the percentage of individuals with a score > 20 is stable out to one year; more dramatic change is seen in the decreased percentage of individuals in the modified MELD 14–20 group and increased percentage of individuals in the modified MELD <14 group over one year (Figure 2A). Similar changes are seen in the average modified MELD scores within two months and subsequent stabilization over one year (Figure 2B).

Survival Analysis

A univariate analysis for survival was performed to assess the likelihood of hepatobiliary markers being prognostic indicators of mortality. Serum albumin, AST, total bilirubin, total protein and alkaline phosphatase were individually correlated with increased mortality (Table 6 and Supplemental Figures 8–10). Multivariate analysis revealed that only albumin and creatinine, both essential parts of the modified MELD score, were independently associated with survival after cardiac transplantation (Table 7). Both increased pre-transplantation standard and modified MELD scores were associated with poor short- and long-term survival (Figures 3 and 4). One-year survival was 91.4% in patients with MELD score <14 compared to 85.5% in patients with MELD >20 and 91.9% in patients with modified MELD score <14 compared to 75% in patients with a modified MELD score >20. 5-year survival was 83.2% in patients with a MELD score <14 and only 70.1% in patients with MELD score >20. Patients with a modified MELD score <14 had a 5-year survival of 82.2% compared to 55.1% in patients with a modified MELD score >20.

DISCUSSION

This single-center, retrospective analysis on patients undergoing OHT demonstrates that a significant proportion of patients with advanced heart failure have elevated hepatobiliary serum markers and that these laboratory markers improve after OHT. Both elevated MELD scores and elevated modified MELD scores improved after OHT. Elevated scores pre-OHT are associated with worse morbidity and mortality after OHT indicating that pre-transplant liver dysfunction plays an important role for the long-term survival of patients undergoing OHT.

Advanced heart failure is a state of multi-organ dysfunction secondary to impaired cardiac function. Hepatic congestion and liver dysfunction can develop in response to chronically increased central venous pressure. A characteristic progressive deposition of collagen and formation of fibrous septa in the sinusoids is caused by a stromal reaction to congestion, hypoxia, and hepatocellular necrosis.⁶ Further, disruption of the hepatic zona occludens leads to fistulas between liver sinusoids and the bile canaliculi.⁷ Liver function abnormalities are most commonly seen in HF patients with a cardiac index of less than 1.5 L/min/m^{2.6} and the magnitude of liver function abnormalities is related to the hemodynamic severity of heart failure.² Chronic cardiac hepatopathy has consistently shown no significant deviations from physiological levels of transaminases in several small studies. Our findings on the percentages of individuals with elevations of AST, ALT and total bilirubin are consistent with other studies.^{8–11} Compared to other smaller studies, our

cohort had a higher proportion with decreased serum total protein and albumin which might be related to more advanced heart failure in our population. In the CHARM study, in which 18% of its population had reduced albumin, only 2.6% of all patients had Stage IV congestive HF.⁹

We here show that in the majority of patients, pathological hepatobiliary markers normalize after cardiac transplantation. This confirms the results of a small previous study that showed improvement in hepatobiliary markers within 3 months after cardiac transplantation.⁸ In the current study, a significant improvement in average hepatobiliary values for AST, ALT, total bilirubin, albumin and ALP is detectable from abnormal levels within two months and remains in the normal range over five years of follow-up.

In patients with heart failure, the predictive value of abnormal liver function tests has been evaluated before. In the heart failure cohort of the CHARM study, a univariate analysis for survival showed that a decrease in albumin levels and elevations in total bilirubin and ALP predicted mortality.⁹ Further, elevations in total and direct bilirubin have been associated with increased cardiovascular hospitalization and mortality^{9, 12}; hyperbilirubinemia coincident with cardiac decompensations predicts long-term prognosis in chronic heart failure.¹² In a small study by Dichtl et al. no correlation was found between pre-transplant liver function markers and survival.⁸ In contrast, van Deursen et al. showed that AST, GGT and ALP were significant predictors of all-cause mortality.² In our analysis, we replicate the predictive value of albumin, total protein and alkaline phosphatase, but not the other hepatobiliary values.

No study has systematically evaluated the risk during cardiac transplantation using parameters of liver dysfunction in patients that have cardiac hepatopathy. Composite scoring systems such as MELD or Child-Turcotte-Pugh scores have been developed to prognosticate the outcome of patients with chronic liver disease and evaluate patients for liver transplantation. The Child-Pugh score, based on the presence of ascites and encephalopathy, serum albumin, total bilirubin, and prothrombin time, is inferior to the MELD score and was not used in our current study due to a lower prognostic value.¹³ In addition, the clinical presentation of ascites and encephalopathy is rather rare and common oral anticoagulation in patients with heart failure affects coagulation values. The standard MELD score is based on serum levels of creatinine, total bilirubin and INR. It has been established to eliminate the subjective assessment of patients with liver dysfunction and has been shown to better predict clinical outcome than the Child-Pugh score. In addition to using the standard MELD score in this study, a modified MELD score utilizing serum albumin as a substitute for INR measurements was used for analysis because of the confounding effects of oral anticoagulation. The substitution of INR with albumin was based on the fact that both are indicators of secretory liver function and that changes in serum albumin were associated with impaired outcome in our analysis. This novel score is superior to the standard MELD score due to the lack of an interaction with oral anticoagulation. Comparison of predictive power of the two scores revealed higher receiver operating characteristic (ROC) values for the modified MELD score compared to the standard MELD score and the individual factors for prediction of survival following OHT.

Subgroup analysis revealed that patients with MELD scores >20 are older and have more comorbidities with a lower average ejection fraction and body mass index. They are less likely to have received a ventricular assist device (VAD) prior to OHT. The presence of renal failure is inherent to the calculation of the MELD score since creatinine is one of its components. Similar findings are present when the cohort is stratified by modified MELD score. Higher rate of postoperative complications in the higher MELD score group include reoperation for bleeding and in-hospital death. Bleeding complications could have been

driven by increased anti-coagulation in this group. However, when INR is eliminated from the calculation, those with an elevated modified MELD score have a similar rate of bleeding complications. This indicates additional impairments of hemostasis in this group of patients. Using both scoring systems, poor post-OHT outcome and reduced survival is associated with elevated composite score values. Although the cause of death was not collected in this dataset, the modified MELD score analysis reveals that respiratory and renal dysfunction was significantly different across different score groups. We speculate that this difference may have contributed to the increased short-term mortality post-transplantation.

Abnormal liver function and cirrhosis have been linked to poor outcome of patients undergoing both cardiac and non-cardiac surgeries. In a large cohort of non-cardiac cirrhotic patients undergoing non-transplant surgical procedures, Northup et al. used the MELD score to show that there is a direct correlation between MELD score and postoperative mortality.¹⁴ Ailawadi et al. found that a standard MELD score > 15 in a group of 168 cirrhotic patients undergoing non-transplant cardiac surgeries led to a significantly higher post-operative mortality.¹⁵ Filsoufi et al. have found that Child-Pugh scoring is superior to MELD scoring because of a significant correlation between Child-Pugh score, mortality and post-operative complications; they further concluded that a cut-off value of seven is also predictive of worse outcome where no cut-off can be decided upon for the MELD scoring. However, Suman et al. found that hepatic decompensation and mortality are significantly related when using either the Child-Pugh or MELD scoring system in cirrhotic patients undergoing cardiac surgery.¹⁶

In a small retrospective study by Hsu et al., 12 cirrhotic patients underwent cardiac transplantation and only 50% survived at discharge.¹⁷ They concluded that liver cirrhosis is still a relative contraindication to heart transplantation and the long-term outcome is uncertain, but transplantation in this population can still be considered with careful selection.¹⁷ Given the current limitations of donor organ availability, recipient status and factors including liver dysfunction should be carefully evaluated in high risk patients with the goal of optimal organ utilization. Our study demonstrates increased short and long-term mortality in patients post-OHT with both standard and modified MELD scores >20. Liver dysfunction prior to transplantation leads to nutritional compromise, increased susceptibility to infections as a result of altered immune function and impaired hemostasis which altogether might explain the worse prognosis of patients with elevated MELD scores.

Despite significant improvement in liver function post-OHT, a small group of patients shows no improvement in hepatobiliary markers or MELD scores. For these patients, hepatobiliary dysfunction appears irreversible. One might speculate that these patients had more profound cirrhotic hepatic changes and it remains to be elucidated whether a potential intervention exists that might have an impact on the post-OHT outcome in these patients. Factors predicting the irreversibility of hepatic dysfunction remain to be identified but might include histologic parameters on liver biopsies and a detailed analysis of right ventricular function and hemodynamics through echocardiography, invasive right heart catheterization and hepatic wedge pressure analysis prior to OHT.

Conclusion

While limited to a single center, our study is advantageous to other studies based on the long observational period (>10 years) and the number of patients involved (>600). The complete dataset on this large study cohort is unique and the close follow-up allows an exact assessment of the dynamics and significance of the baseline abnormalities of liver function and its course postcardiac transplantation. Most patients normalize their hepatobiliary function parameters within a relatively short period after OHT. More important to physicians and surgeons, both standard and modified MELD scores provide simple, yet

valuable and efficient prognostic tools for evaluating patients for cardiac transplantation. Early recognition of hepatic dysfunction may warrant more intensive treatment of heart failure with a goal to define the cause of abnormal liver function parameters and potentially correct hepatic dysfunction prior to transplantation.

Limitations

This study was limited by being a retrospective analysis that has its inherent biases. Several potential confounders such as medication, duration of heart failure, differences in operative characteristics could have falsely elevated or reduced the actual hepatobiliary values.¹⁷ In fact, it is known that cardiopulmonary bypass leads to the release of vasoactive substances and cytotoxic chemicals that affect vascular integrity, fluid balance and coagulopathy; other consequential problems are hypothermia, hemodilution and hypoperfusion.¹⁹ The current analysis is limited to laboratory parameters for the characterization of liver and renal dysfunction and their impact on survival after OHT. Analysis of invasive preoperative assessments and echocardiographic evaluations of patients before and after transplantation would be beneficial for a further characterization of this patient cohort and the impact of cardiac factors on hepatic dysfunction. Immunosuppressive medication as required after cardiac transplantation has a negative impact on hepatobiliary function. While a significant improvement of MELD scores occurs early after cardiac transplantation, we cannot exclude that a number of laboratory abnormalities after transplantation are related to immunosuppressive medication. Only limited data are available on long-term causes of death. Further, our analysis does not include data on the frequency of acute and chronic cellular and antibody-mediated rejection, transplant coronary artery disease or opportunistic infections following cardiac transplantation.

Laboratory values closest to the time of hospitalization prior to transplantation were collected unless the patient was urgent as per documentation. In terms of cut-off values for being considered pathologic, institutional limits of normal were used. However, no distinction was made for females, who on average usually have lower limits of normal for AST, ALT, ALP and GGT.²⁰ These values can still be considered appropriate given the male predominance in the cohort studied. A lack of access to all hemodynamic measures, liver imaging or histology prevented the full confirmation of initial diagnosis and subsequent improvement.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the Irving Institute for Clinical and Translational Research of Columbia University (UL1 RR 024156) and grants from the NHLBI to Dr. Schulze (K23 HL095742-01 and P30 HL101272-01). Aalap Chokshi was supported by the Doris Duke Medical Foundation.

ABBREVIATIONS

ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
BMI	Body mass index
CTP	Child-Turcotte-Pugh

GGT	Gamma-glutamyl transferase
HF	Heart failure
INR	International normalized ratio
MELD	Model for End Stage Liver Disease
ModMELD	Modified MELD
OHT	Orthotopic heart transplantation
StdMELD	Standard MELD
VAD	Ventricular assist device

REFERENCES

1. Neubauer S. The failing heart--an engine out of fuel. *N Engl J Med*. 2007; 356:1140–1151. [PubMed: 17360992]
2. van Deursen VM, Damman K, Hillege HL, van Beek AP, van Veldhuisen DJ, Voors AA. Abnormal liver function in relation to hemodynamic profile in heart failure patients. *J Card Fail*. 2010; 16:84–90. [PubMed: 20123323]
3. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology*. 2001; 33:464–470. [PubMed: 11172350]
4. Wiesner R, Edwards E, Freeman R, et al. United Network for Organ Sharing Liver Disease Severity Score Committee. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology*. 2003; 124:91–96. [PubMed: 12512033]
5. Uriel N, Vainrib A, Jorde UP, et al. Mediastinal radiation and adverse outcomes after heart transplantation. *J Heart Lung Transplant*. 2010; 29:378–381. [PubMed: 19804988]
6. Naschitz JE, Slobodin G, Lewis RJ, Zuckerman E, Yeshurun D. Heart diseases affecting the liver and liver diseases affecting the heart. *Am Heart J*. 2000; 140:111–120. [PubMed: 10874271]
7. Cogger VC, Fraser R, Le Couteur DG. Liver dysfunction and heart failure. *Am J Cardiol*. 2003; 91:1399. [PubMed: 12767448]
8. Dichtl W, Vogel W, Dunst KM, et al. Cardiac hepatopathy before and after heart transplantation. *Transpl Int*. 2005; 18:697–702. [PubMed: 15910296]
9. Allen LA FG, Pocock S, McMurray JJ, et al. CHARM Investigators. Liver function abnormalities and outcome in patients with chronic heart failure: data from the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program. *Eur J Heart Fail*. 2009; 11:170–177. [PubMed: 19168515]
10. Lau GT, Tan HC, Kritharides L. Type of liver dysfunction in heart failure and its relation to the severity of tricuspid regurgitation. *Am J Cardiol*. 2002; 90:1405–1409. [PubMed: 12480058]
11. Kubo SH, Walter BA, John DH, Clark M, Cody RJ. Liver function abnormalities in chronic heart failure. Influence of systemic hemodynamics. *Arch Intern Med*. 1987; 147:1227–1230. [PubMed: 3606280]
12. Shinagawa H, Inomata T, Koitabashi T, et al. Prognostic significance of increased serum bilirubin levels coincident with cardiac decompensation in chronic heart failure. *Circ J*. 2008; 72:364–369. [PubMed: 18296830]
13. Nishi H, Takahashi T, Ichikawa H, Matsumiya G, Matsuda H, Sawa Y. Prediction of postoperative hepatic dysfunction after cardiac surgery in patients with chronic congestive heart failure. *Gen Thorac Cardiovasc Surg*. 2009; 57:357–362. [PubMed: 19597925]
14. Northup PG, Wanamaker RC, Lee VD, Adams RB, Berg CL. Model for End-Stage Liver Disease (MELD) predicts nontransplant surgical mortality in patients with cirrhosis. *Ann Surg*. 2005; 242:244–251. [PubMed: 16041215]
15. Ailawadi G, Lapar DJ, Swenson BR, et al. Model for end-stage liver disease predicts mortality for tricuspid valve surgery. *Ann Thorac Surg*. 2009; 87:1460–1467. [PubMed: 19379885]

16. Suman A, Barnes DS, Zein NN, Levinthal GN, Connor JT, Carey WD. Predicting outcome after cardiac surgery in patients with cirrhosis: a comparison of Child-Pugh and MELD scores. *Clin Gastroenterol Hepatol*. 2004; 2:719–723. [PubMed: 15290666]
17. Hsu RB, Chang CI, Lin FY, et al. Heart transplantation in patients with liver cirrhosis. *Eur J Cardiothorac Surg*. 2008; 34:307–312. [PubMed: 18539042]
18. Ziser A, Plevak DJ. Morbidity and mortality in cirrhotic patients undergoing anesthesia and surgery. *Curr Opin Anaesthesiol*. 2001; 14:707–711. [PubMed: 17019169]
19. Hayashida N, Aoyagi S. Cardiac operations in cirrhotic patients. *Ann Thorac Cardiovasc Surg*. 2004; 10:140–147. [PubMed: 15312008]
20. Vasconcelos LA, de Almeida EA, Bachur LF. Clinical evaluation and hepatic laboratory assessment in individuals with congestive heart failure. *Arq Bras Cardiol*. 2007; 88:590–595. [PubMed: 17589636]

Figure 1.

Normalization of Standard MELD Scores Post-Transplant. (A) The percentage of patients in the intermediate and elevated Standard MELD score groups decreases after cardiac transplantation at various time-points (n_1). (B) The course of mean Standard MELD scores (mean $\pm$ SD) of each Standard MELD score group is followed after cardiac transplantation.

Figure 2.

Normalization of Modified MELD Scores Post-Transplant. (A) The percentage of patients in the intermediate and elevated Modified MELD score groups decreases after cardiac transplantation at various time-points (n_1). (B) The course of mean Modified MELD scores (mean $\pm$ SD) of each Modified MELD score group is followed after cardiac transplantation.

Figure 3.

Actuarial Survival for heart transplant patients by pre-transplantation Standard (Std) MELD score over a 10 year follow-up post-cardiac transplantation.

Figure 4.

Actuarial Survival for heart transplant patients by pre-transplantation Modified (Mod) MELD score over a 10 year follow-up post-cardiac transplantation.

Table 1**Baseline Demographics**

Cohort Size	617
Age (yrs) *	52.88 ± 11.99
Gender (n, %)	
Male	464 (75.2)
Female	153 (24.8)
Race (n,%)	
White	395 (64.02)
Black	93 (15.07)
Hispanic	42 (6.81)
Other	87 (14.1)
BMI (kg/m ²) *	25.15 ± 4.54
LVEF (%) *	18.5 ± 9.19
Indication for Transplant (n, %)	
Ischemic Cardiomyopathy	222 (36.22)
Dilated Cardiomyopathy	269 (43.15)
Hypertrophic Cardiomyopathy	17 (2.77)
Other [†]	105 (17.86)
VAD prior to surgery (n, %)	185 (29.98)
Smoking (n, %)	207 (33.55)
Diabetes (n, %)	165 (26.74)
Hypertension (n, %)	208 (36.17)
CAD (n, %)	267 (43.27)
Prior CVA (n, %)	71 (11.51)
Renal Failure (n, %)	76 (12.5)

* Represented as Mean ± SD

BMI = Body Mass Index, LVEF = Left Ventricular Ejection Fraction, VAD = Ventricular Assist Device, CAD = Coronary Artery Disease, CVA = Cerebrovascular Accident

[†] Congenital heart diseases, infiltrative diseases, myocarditis, valvular cardiomyopathy, postpartum cardiomyopathy, cardiac tumor

Table 2**Baseline Demographics by Standard MELD Score**

	Std. MELD < 14	Std. MELD 14 – 20	MELD > 20	<i>p-value</i>
Cohort Size	314	233	70	Total: 617
Age (yrs)	50.1 ± 12.43	54.46 ± 11.09	56.15 ± 11.59	<0.001
Gender (n,%)				
Male	222 (71)	183 (79)	59 (84)	0.019
Female	92 (29)	50 (21)	11 (16)	
BMI (kg/m ²)	25.48 ± 4.84	25.67 ± 4.49	24.38 ± 5.49	0.783
LVEF (%)	18.84 ± 9.24	18.24 ± 9.26	17.92 ± 8.77	0.733
VAD prior to surgery (n,%)	117 (37)	52 (22)	16 (23)	<0.001
Smoking (n, %)	113 (36)	71 (30)	23 (33)	0.399
Diabetes (n, %)	84 (27)	66 (28)	16 (21)	0.521
Hypertension (n, %)	114 (36)	85 (36)	28 (40)	0.840
CAD (n, %)	139 (44)	100 (43)	28 (40)	0.802
Prior CVA (n, %)	43 (14)	20 (9)	8 (11)	0.181
Renal Dysfunction (n, %)	28 (9)	32 (14)	16 (23)	0.004
β-Blockers	152 (48.56)	138 (59.22)	35 (50.00)	0.042
ACE-Is	143 (45.69)	87 (37.34)	22 (31.43)	0.034
ARBs	20 (6.39)	24 (10.30)	10 (14.29)	0.062
Spironolactone/Eplerenone	93 (29.71)	103 (44.20)	22 (31.43)	0.002
Digoxin	115 (36.74)	100 (42.92)	33 (47.14)	0.159
Diuretics	188 (60.06)	175 (75.11)	53 (75.71)	<0.001
Anti-platelets	130 (41.53)	84 (36.05)	22 (31.43)	0.194
Statins	84 (26.84)	55 (23.61)	20 (28.57)	0.594
Coumadin	91 (29.07)	147 (63.09)	55 (78.57)	<0.001
Amiodarone	92 (29.39)	73 (31.33)	70 (40.00)	0.224
Insulin	19 (6.07)	21 (9.01)	3 (4.29)	0.264
Oral antidiabetic agents	21 (6.71)	22 (9.44)	8 (11.43)	0.31
Inotropes	82 (26.20)	77 (33.05)	24 (34.29)	0.150
Vasodilators	28 (8.95)	17 (7.30)	4 (5.71)	0.595

* Represented as Mean ± SD

BMI = Body Mass Index, LVEF =Left Ventricular Ejection Fraction, VAD = Ventricular Assist Device, CAD = Coronary Artery Disease, CVA = Cerebrovascular Accident, ACE-I = Angiotensin converting enzyme inhibitor, ARBs = Angiotensin receptor blockers

Table 3

Baseline Demographics by Modified MELD Score

	Mod. MELD < 14	Mod. MELD 14 – 20	Mod. MELD > 20	<i>p-value</i>
Cohort Size	383	210	24	Total: 617
Age (yrs)	51.59 ± 12.48	55.18 ± 11.053	53.26 ± 8.57	0.002
Gender (n,%)				
Male	267 (70)	176 (84)	21 (87)	<0.001
Female	122 (30)	34 (16)	3 (13)	
BMI (kg/m ²)	25.53 ± 4.52	25.64 ± 5.25	24.74 ± 4.59	0.715
LVEF (%)	18.5 ± 8.64	18.63 ± 10.3	16.82 ± 5.6	0.819
VAD prior to surgery (n,%)	109 (28)	69 (33)	7 (29)	0.535
Smoking (n, %)	122 (32)	78 (37)	7 (29)	0.385
Diabetes (n, %)	100 (26)	59 (28)	6 (25)	0.856
Hypertension (n, %)	139 (36)	81 (39)	7 (29)	0.595
CAD (n, %)	154 (40)	102 (49)	11 (46)	0.141
Prior CVA (n, %)	48 (13)	23 (11)	0 (0)	0.168
Renal Dysfunction (n, %)	29 (8)	35 (17)	12 (52)	<0.001
β-Blockers	222 (58.12)	93 (44.29)	10 (41.67)	0.003
ACE-Is	173 (45.29)	74 (35.24)	5 (20.83)	0.007
ARBs	35 (9.16)	18 (8.57)	1 (4.17)	0.698
Spironolactone/Eplerenone	131 (34.29)	77 (36.67)	10 (41.67)	0.682
Digoxin	155 (40.58)	86 (40.95)	7 (29.17)	0.526
Diuretics	259 (67.80)	143 (68.10)	24 (58.33)	0.616
Anti-platelets	155 (40.58)	73 (34.76)	8 (33.33)	0.333
Statins	107 (28.01)	49 (23.33)	3 (12.50)	0.145
Coumadin	185 (48.43)	97 (46.19)	11 (45.83)	0.860
Amiodarone	111 (29.06)	77 (36.67)	5 (20.83)	0.085
Insulin	24 (6.28)	17 (8.10)	2 (8.33)	0.756
Oral antidiabetic agents	33 (8.64)	16 (7.62)	2 (8.33)	0.911
Inotropes	111 (29.06)	65 (30.95)	7 (29.17)	0.888
Vasodilators	35 (9.16)	13 (6.19)	1 (4.17)	0.346

* Represented as Mean ± SD

BMI = Body Mass Index, LVEF = Left Ventricular Ejection Fraction, VAD = Ventricular Assist Device, CAD = Coronary Artery Disease, CVA = Cerebrovascular Accident, ACE-I = Angiotensin converting enzyme inhibitor, ARBs = Angiotensin receptor blockers

Table 4

Postoperative Complications by Standard MELD Score

	Std. MELD < 14	Std. MELD 14 – 20	Std. MELD > 20	<i>p-value</i>
Cohort Size	314	233	70	Total: 617
VT (n, %)	17 (6)	14 (6)	3 (4)	0.844
VF (n, %)	7 (2)	3 (1)	2 (3)	0.616
AF (n, %)	25 (9)	29 (13)	8 (12)	0.251
VAD (n, %)	6 (2)	11 (5)	3 (4)	0.161
Respiratory Failure (n, %)	13 (4)	19 (8)	5 (7)	0.135
Renal Insufficiency (n, %)	21 (7)	23 (10)	8 (11)	0.263
Renal Failure (n, %)	31 (10)	31 (13)	13 (19)	0.105
Reoperation for Bleeding (n, %)	26 (8)	28 (12)	17 (24)	0.001
Wound Infection (n, %)	21 (7)	12 (5)	6 (9)	0.548
Stroke (n, %)	5 (2)	4 (2)	1 (1)	0.985
In-hospital Death (n, %)	10 (3)	23 (10)	11 (16)	<0.001

VT = Ventricular Tachycardia, VF = Ventricular Fibrillation, AF = Atrial Fibrillation, VAD = Ventricular Assist Device

Table 5

Postoperative Complications by Modified MELD Score

	Mod. MELD < 14	Mod. MELD 14 – 20	Mod. MELD > 20	<i>p-value</i>
Cohort Size	383	210	24	Total: 617
VT (n, %)	19 (5)	14 (7)	1 (4)	0.756
VF (n, %)	7 (2)	5 (3)	0 (0)	0.735
AF (n, %)	35 (10)	26 (13)	1 (4)	0.320
VAD (n, %)	11 (3)	7 (3)	2 (9)	0.388
Respiratory Failure (n, %)	16 (4)	15 (7)	6 (25)	<0.001
Renal Insufficiency (n, %)	25 (7)	25 (12)	2 (8)	0.043
Renal Failure (n, %)	35 (9)	31 (15)	9 (38)	<0.001
Reoperation for Bleeding (n, %)	38 (10)	27 (13)	6 (25)	<0.06
Wound Infection (n, %)	18 (5)	19 (9)	2 (8)	0.134
Stroke (n, %)	5 (1)	5 (2)	0 (0)	0.497
In-hospital Death (n, %)	18 (5)	21 (10)	5 (21)	0.001

VT = Ventricular Tachycardia, VF = Ventricular Fibrillation, AF = Atrial Fibrillation, VAD = Ventricular Assist Device

Table 6

Univariate Analysis of Survival of Patients After Cardiac Transplantation.

	Hazard Ratio	p-value	95% confidence interval
AST (U/L)	1.01	0.025	1.00–1.01
ALT(U/L)	1.00	0.485	0.99–1.00
Total Bilirubin (mg/dl)	1.20	0.006	1.05–1.37
Total Protein (g/dL)	0.83	0.037	0.69–0.99
Albumin (g/dL)	0.72	0.009	0.56–0.92
ALP (U/L)	1.002	0.005	1.00–1.01
GGT (U/L)	1.00	0.585	0.99–1.00
Creatinine (mg/dL)	1.16	0.123	0.96–1.4
MELD	1.03	0.04	1.00–1.06
modMELD	1.07	<0.001	1.04–1.11

Table 7

Multivariate Analysis of Survival of Patients After Cardiac Transplantation.

	Hazard Ratio	<i>p</i>-value	95 % Confidence Interval
Albumin (g/dL)	0.63	0.003	0.46–0.86
Creatinine (mg/dL)	1.36	0.014	1.06–1.75