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Hepatic dysfunction and survival after orthotopic heart transplantation: Application of the MELD scoring system for outcome prediction

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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% men, mean age 53 ± 12 years, mean BMI 25 ± 4, mean ejection fraction 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 anti-coagulation.

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 pathologic values decreased significantly, except for 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 demonstrated the dynamics of liver dysfunction after cardiac transplantation and that elevated MELD scores indicating impaired liver function are associated with poor clinical outcome after OHT. Thus, pre-operative liver dysfunction has a significant impact on survival of patients after cardiac transplantation.

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The number of patients with advanced heart failure (HF) is rising in the USA 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.

Studies have shown variability in serum hepatobiliary markers of patients with HF. The most consistent findings

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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% to 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 surgery.[3] Although a number of 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 types of cardiac and non-cardiac surgery, mostly for cirrhosis patients, but never in patients with cardiac hepatopathy undergoing cardiac transplantation. In chronic liver disease patients undergoing liver transplantation, the 3-month post-operative mortality rate is 20% for those with a score of >20 and 71% for those 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 5 years after cardiac transplantation. In this same cohort, we proposed and calculated a modified MELD score that by design excluded the effects of anti-coagulation by substituting albumin for international normalized ratio (INR). Our analysis reveals that liver dysfunction was associated with higher rates of post-operative complications and impaired short- and long-term prognosis in patients undergoing orthotopic heart transplantation (OHT). Elevations in MELD and modified MELD scores could reliably identify patients at higher risk for complications and reduced survival after OHT.

Methods

Patient cohort

Information was collected retrospectively on 780 adults undergoing orthotopic heart transplantation (OHT) at the Columbia University Medical Center/New York–Presbyterian Hospital between November 1998 and November 2008. We excluded patients with incomplete laboratory data sets ($n = 106$); patients undergoing cardiac retransplantations ($n = 42$); 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 for analysis.

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

Data collection

Pre-operative data were collected by electronic chart review for the most recent laboratory analysis before cardiac transplantation. Post-operative data were collected at 2, 6 and 12 months, and also at 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 were recorded for age, gender, 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. Post-operative complications occurring within 30 days of transplant were also recorded, which 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

Pathologic 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/liter, 41 U/liter 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/liter and 58 U/liter, respectively.

MELD score

The standard MELD score was calculated by using the formula established by Kamath et al: $1.12 \times (\ln \text{INR}) + 0.378 \times (\ln \text{Tbil}) + 0.957 \times (\ln \text{Cr}) + 0.643$.[3] If the INR, Tbil (total bilirubin) or Cr (creatinine) was <1, their values were assumed to be 1 so that the score did not become negative. The raw score was multiplied by 10 and rounded to the nearest integer. To exclude the impact of oral anti-coagulation 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 between reduced albumin levels and 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 g/dl − serum albumin), was positive, 1 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 was >4.1, then the modified MELD score was calculated as follows: $1.12 \times (\ln 1) + 0.378 \times (\ln \text{Tbil}) + 0.957 \times (\ln \text{Cr}) + 0.643$. If serum albumin was <4.1, then the modified MELD score was calculated as: $1.12 \times (\ln [1 + (4.1 - \text{albumin})]) + 0.378 \times (\ln \text{Tbil}) + 0.957 \times (\ln \text{Cr}) + 0.643$. As with the standard MELD score, these raw scores were multiplied by 10 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 ($p < 0.001$).