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Original Article

Higher Transaminase Levels in the Postoperative Period After Orthotopic Heart Transplantation Are Associated With Worse Survival

Eniko Holndonner-Kirst, MD[*,†], Adam Nagy, MD[†], Nikoletta Rahel Czobor, MD[†,‡], Levente Fazekas, MD, PhD[§], Daniel Janos Lex, MD[†,¶], Balazs Sax, MD, PhD[§], Istvan Hartyanszky, MD, PhD[§], Bela Merkely, MD, PhD, DSc[§], Janos Gal, MD, PhD[*], Andrea Szekely, MD, PhD[*,1]

[*]*Department of Anaesthesiology and Intensive Therapy, Semmelweis University, Budapest, Hungary*
[†]*School of Doctoral Studies, Semmelweis University, Budapest, Hungary*
[‡]*Peterfy Sandor Street Hospital, Budapest, Hungary*
[§]*Heart and Vascular Center, Semmelweis University, Budapest, Hungary*
[¶]*Hungarian Defence Forces Military Hospital, Budapest, Hungary*

Objective: Preoperative liver function in heart failure patients is associated with extensive functional, structural, and hemodynamic abnormalities. The authors hypothesized that perioperative liver dysfunction is associated with worse 2-year survival after orthotopic heart transplantation.

Design: Retrospective study.

Setting: Single-center, university hospital.

Participants: The study comprised 209 consecutive patients undergoing heart transplantation.

Interventions: No interventions.

Measurements and Main Results: Hepatobiliary markers, hemodynamic parameters, echocardiographic parameters, the need for mechanical cardiac support, demographic parameters, and United Network for Organ Sharing and Model for End-Stage Liver Disease (MELD) scores were investigated. Fifty-five patients (26.3%) died, and the mean survival time was 3.61 years after transplantation. In multivariate Cox regression analysis, in addition to the preoperative modified MELD score, the 4th quartiles of the maximum aspartate transaminase (AST) and alanine transaminase levels on the 4th through 7th postoperative days were independently associated with mortality (odds ratio [OR] 2.46, 95% confidence interval [CI] 1.09-5.55; $p = 0.031$ and OR 2.41, 95% CI 1.13-5.18; $p = 0.024$, respectively). By expressing the transaminase values as the multiplier of the sex-specific top normal value, the maximum AST and alanine transaminase levels (OR 1.02, 95% CI 1.01-1.02; $p < 0.001$ and OR 1.02, 95% CI 1.01-1.03; $p = 0.001$, respectively) were linked to worse survival. Among the postdischarge parameters, the modified MELD score (OR 1.17, 95% CI 1.09-1.27; $p < 0.001$) and the AST level were associated with postdischarge mortality (OR 1.002, 95% CI 1.001-1.003; $p < 0.001$ as a continuous variable; OR 1.07, 95% CI 1.05-1.10; $p < 0.001$, expressed as the multiplier of the sex-specific normal value, respectively).

Conclusions: The severity of postoperative liver dysfunction negatively influences survival after heart transplantation, and liver function should be closely assessed in these patients.

[1]*Address reprint requests to* Andrea Székely, MD, PhD, DEAA, Department of Anesthesiology and Intensive Therapy, Semmelweis University, Üllői út 26, Budapest, H-1085, Hungary.

E-mail address: andi_szekely@yahoo.com (A. Szekely).

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END-STAGE HEART failure frequently is associated with reversible or irreversible organ dysfunction, with the kidney and liver being the most frequently affected organs. Pathophysiologically, hepatic dysfunction can be classified by consequences of low cardiac output and congestion.

As a consequence of low cardiac output, ischemic hepatic failure can be observed with centrilobular necrosis as represented by elevated transaminases (aspartate transaminase [AST] and alanine transaminase [ALT]) and bilirubin levels in the blood. Chronic congestive liver failure is characterized by cholestasis and high levels of serum alkaline phosphatase and gamma-glutamyl transferase.[1,2] The relationship between liver dysfunction, especially high transaminase levels, and mortality has only recently gained significant attention.[3] Although the exact pathomechanism is unknown, hypoxia and hypoperfusion play pivotal roles in this process, rather than congestion itself.

Candidacy for liver transplantation and urgency on the waiting list can be described by Model for End-Stage Liver Disease (MELD) scores (original and their modifications).[4] In the last few years, these scores have been introduced successfully in the risk stratification of the heart failure patients waiting for cardiac surgery and heart transplantation (HTX).[5–8] Postoperative acute liver failure is a life-threatening complication after transplantation, and the therapeutic strategies are relatively limited.

Due to the differences observed between the results of the authors' institution and those of the International Society for Lung and Heart Transplantation registry, the authors aimed to assess the contributing patient-specific factors on adverse outcomes.[9] To achieve this, the predictive values of different MELD scores and hepatobiliary markers in the perioperative period of patients undergoing orthotopic heart transplantation (OHTX) relative to short- and medium-term outcomes were assessed.

Methods

After Institutional Review Board approval (TUKEB 54/2016) was received, the data of patients who underwent OHTX between January 2012 and October 2016 were analyzed. For the retrospective analysis, a single-center database from the Heart and Vascular Center, Semmelweis University in Budapest, Hungary, was used. Preoperative data and laboratory markers were retrieved from electronic records. The authors recorded and analyzed the last preoperative and the 1st, 2nd, 3rd, and 4th through 7th postoperative day maximum bilirubin and transaminase values. After discharge, the same laboratory markers were recorded, and the pretransplantation and postdischarge MELD scores were calculated. In the authors' institution, the upper normal limits of AST are 32 U/L and 40 U/L in females and males, respectively. ALT upper limits are 33 U/L and 41 U/L in females and males, respectively.

The following data were analyzed: age; sex; body mass index; latest hemodynamic measurements, including cardiac output and pulmonary vascular resistance; echocardiographic measurements during the 1st, 2nd, and 3rd postoperative days; etiology of heart failure; prior mechanical cardiac support; and coexisting diseases. In addition, the virus serology results, preoperative amiodarone, steroid use, and drug and alcohol abuse in the patient's history were examined. The perioperative course and postoperative complications during OHTX hospitalization were recorded, including respiratory failure (mechanical ventilation longer than 72 h), renal failure requiring hemodialysis, bleeding, the number of blood products required during hospitalization, infections, primary graft failure, ventricular assist device placement, cerebrovascular accident, and in-hospital death.

Liver enzyme levels were expressed as raw values (U/L) and as the multiplier of the sex-specific top-normal level.

The standard MELD score was calculated using the following formula: $1.12 \times (\ln \text{INR}) + 0.378 \times (\ln \text{T bili}) + 0.957 \times (\ln \text{Creat}) + 0.643$,[4] where INR is international normalized ratio, T bili is total bilirubin, and Creat is creatinine. If the INR, T bili, or Creat score was less than 1, then the value was assumed to be 1 so that the score did not become negative.[10] The modified MELD score (modMELD) was identical to the standard score except for substitution of the INR component with albumin to evaluate the synthetic activity of the liver regardless of anticoagulation. In place of INR, a conditional value was used based on the difference between 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, for serum albumin > 4.1, the modMELD score was calculated as follows: $1.12 \times \ln 1 + 0.378 \times \ln \text{T bili} + 0.957 \times \ln \text{Creat} + 0.643$. For serum albumin < 4.1, the modMELD score was calculated as follows: $1.12 \times \ln [1 + (4.1 - \text{albumin})] + 0.378 \times \ln \text{T bili} + 0.957 \times \ln \text{Creat} + 0.643$. As with the standard MELD score, these raw scores were multiplied by 10 and rounded to the nearest integer.[11]

The revised MELD score including serum sodium level (MELD-NA) (NMELD) scores were calculated as $\text{MELD Na} = \text{MELD} - \text{Na} - 0.025 \times \text{MELD} \times (140 - \text{Na}) + 140$.[12]

To calculate MELD excluding INR (MELD-XI) without considering synthetic liver activity, the following formula was used: $5.1 \times \ln \text{T bili} + 11.76 \times \ln \text{Creat} + 9.44$. Here, if T bili or Creat was less than 1, then the value was assumed to be 1 so that the score did not become negative.[13]

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