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Liver dysfunction as a predictor of outcomes in patients with advanced heart failure requiring ventricular assist device support: Use of the Model of End-stage Liver Disease (MELD) and MELD eXcluding INR (MELD-XI) scoring system

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BACKGROUND: Liver dysfunction increases post-surgical morbidity and mortality. The Model of End-stage Liver Disease (MELD) estimates liver function but can be inaccurate in patients receiving oral anti-coagulation. We evaluated the effect of liver dysfunction on outcomes after ventricular assist device (VAD) implantation and the dynamic changes in liver dysfunction that occur during VAD support.

METHODS: We retrospectively analyzed 255 patients (147 with pulsatile devices and 108 with continuous-flow devices) who received a long-term VAD between 2000 and 2010. Liver dysfunction was estimated by MELD and MELD-eXcluding INR (MELD-XI), with patients grouped by a score of ≥ 17 or < 17. Primary outcomes were on-VAD, after transplant, and overall survival.

RESULTS: MELD and MELD-XI correlated highly ($R \geq 0.901$, $p < 0.0001$) in patients not on oral anti-coagulation. Patients with MELD or MELD-XI < 17 had improved on-VAD and overall survival ($p < 0.05$) with a higher predictive power for MELD-XI. During VAD support, cholestasis initially worsened but eventually improved. Patients with pre-VAD liver dysfunction who survived to transplant had lower post-transplant survival ($p = 0.0193$). However, if MELD-XI normalized during VAD support, post-transplant survival improved and was similar to that of patients with low MELD-XI scores.

CONCLUSIONS: MELD-XI is a viable alternative for assessing liver dysfunction in heart failure patients on oral anti-coagulation. Liver dysfunction is associated with worse survival. However, if MELD-XI improves during VAD support, post-transplant survival is similar to those without prior liver dysfunction, suggesting an important prognostic role. We also found evidence of a transient cholestatic state after LVAD implantation that deserves further examination.

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Liver dysfunction due to end-stage heart failure (HF) is often referred to as cardiac or congestive hepatopathy.[1] The underlying pathophysiology is related to poor end-organ perfusion leading to ischemic parenchymal changes with hepatocellular necrosis, especially in cases of acute decompensation. Second, passive hepatic venous congestion develops in the setting of right heart dysfunction with increased right atrial pressures.[1,2] Cholestatic changes are the hallmark of chronic congestive hepatopathy, with serum

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bilirubin and alkaline phosphatase concentrations often elevated.[3] Although early stages are reversible, long-term congestive hepatopathy leads to irreversible damage to the liver parenchyma and cirrhosis with associated transaminitis.[4] The management is focused on treating the underlying cardiac abnormalities, and hepatic function has been shown to benefit from orthotopic heart transplantation (OHT), with normalization of liver function assays by 6 months after transplant.[5]

Although individual laboratory assays can provide some insight on a patient's liver function, the composite Model for End-Stage Liver Disease (MELD) is a more robust score of liver dysfunction. It was first developed to predict death in patients undergoing transjugular intrahepatic portosystemic shunt procedures[6,7] and has since been verified as a measure of liver dysfunction, providing an objective score based on a patient's creatinine, total bilirubin, and international normalized ratio (INR). In 2002, the United Network for Organ Sharing (UNOS) adopted this system for prioritizing liver transplant candidates based on disease severity.[8,9] Elevated MELD scores also predict post-operative death in cirrhotic patients undergoing major digestive, orthopedic, and cardiovascular operations.[10] For patients with a MELD score of < 8, 30-day mortality was 5.7% compared with $> 50\%$ for patients with MELD of > 20.

Left ventricular assist devices (LVADs) are increasingly used to treat patients with end-stage HF, leading to improvements in survival and quality of life as a bridge to transplant (BTT) or destination therapy (DT).[11] A recent study by Matthews et al[12] demonstrated that liver dysfunction (defined as a MELD > 17) before LVAD implantation predicts increased perioperative blood product use and 6-month survival. However, no study has analyzed the effect of dynamics in liver dysfunction on outcomes after LVAD insertion. LVAD support should lead to improvements in cardiac hepatopathy, yet no study has reported the specific factors associated with this potential relationship or its effect on survival. One reason has been the lack of a good measure of liver function in HF patients during LVAD support, which often requires oral anti-coagulation with warfarin. Because warfarin increases INR, which is a major component of the MELD score, MELD becomes an inaccurate gauge of liver dysfunction.

As an alternative to the traditional MELD system, the MELD-XI (MELD eXcluding INR) score was developed by Heuman et al.[13] It is calculated from creatinine and total bilirubin only. MELD-XI was validated in a population of $> 7{,}000$ patients with liver cirrhosis and highly correlated with MELD in patients not on oral anti-coagulation, with both scores predicting survival similarly. Given that INR is not used in its calculation, MELD-XI will remain accurate even if a patient receives oral anti-coagulation. Therefore, it is potentially a more effective method of estimating liver dysfunction in patients on LVAD support requiring concomitant oral anti-coagulation.

In this study, we aimed to validate the MELD-XI and MELD scoring systems in HF patients undergoing LVAD placement. We also followed serum markers of cholestasis, hepatic injury, and other relevant conditions during LVAD support and analyzed the role that changes in liver dysfunction assessed by MELD-XI may play in predicting survival after OHT.

Methods

Approval for this study was obtained from the Institutional Review Board at Columbia University Medical Center.

Patient selection

All patients who received a long-term VAD between January 1, 2000, and September 7, 2010, at Columbia University Medical Center were included. Given that 85% of these patients received a pulsatile or continuous-flow HeartMate (HM) or HeartMate II (HMII; Thoratec, Pleasanton, CA), we restricted our study cohort to those who received these devices. Sub-analysis was performed for patients who were supported by continuous-flow devices. The study excluded patients who were on temporary mechanical circulatory support before long-term VAD and those whose preoperative laboratory values were not available.

Data collection

Patient data were obtained from hospital medical records. Preoperative laboratory values were defined as the last set of results immediately before VAD implantation. Primary outcomes included overall survival, on-VAD survival, and survival after OHT in those who received an allograft. Post-operative laboratory values were assessed at 30 days, 3 months, and 6 months for those who had a VAD for at least that length of time and immediately before transplant if they underwent OHT. Post-operative right HF (RHF) was defined as requirement of nitric oxide inhalation > 48 hours, inotropic support > 14 days, and/or a right VAD (RVAD) after LVAD.

MELD and MELD-XI definition

We used the UNOS modification of the MELD score,[8] which uses the formula MELD $= 3.78 \times \text{Ln (bilirubin)} + 11.2 \times \text{Ln (INR)} + 9.57 \times \text{Ln (creatinine)} + 6.43$. Any variable with a value < 1 is assigned a value of 1 to avoid negative scores; thus, the minimum possible MELD score is 6.43. MELD-XI is defined by the formula MELD-XI $= 5.11 \times \text{Ln (bilirubin)} + 11.76 \times \text{Ln (creatinine)} + 9.44$.[13] Again, variables with values of < 1 were given the value of 1, with a minimum possible MELD-XI score of 9.44.[13] According to the MELD and MELD-XI score before VAD surgery, patients were dichotomized into those with values ≥ 17 and those with values < 17, as previously described.[12]

Statistical analysis

Statistical analyses were performed using Stata 11 software (StataCorp, College Station, TX). Statistical significance was determined based on a pre-established $\alpha = 0.05$. Associations between categoric data were tested using chi-square and Fisher's exact tests. Continuous data were com-