HEART FAILURE AND TRANSPLANTATION

Journal Watch

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REVIEWS:

Deo SV et al. "Model for end-stage liver disease excluding international normalized ratio (MELD-XI) score predicts heart transplant outcomes: Evidence from the registry of the united network for organ sharing." *J Heart Lung Transplant* 2015 Oct 9 [Epub ahead of print].

This article evaluates the prognostic importance of the Model for End-stage Liver Disease excluding international normalized ratio (MELD-XI) score after heart transplant. They query the United Network for Organ Sharing (UNOS) database (1994 to 2014).

The MELD score was initially implemented for listing priority of liver transplant recipients. MELD is calculated using baseline serum creatinine, serum bilirubin and international normalized ratio (INR). Since patients undergoing heart transplantation are often on oral warfarin therapy, the authors chose to calculate the MELD-XI score, which does not depend on the INR. This evaluation is important because the presence of hepatic or renal dysfunction might be reflection of many pathophysiological pathways, including significant right side failure but also HF-unrelated causes and have been shown to have prognostic implication after cardiac surgery, in particular after left ventricular assist device (LVAD) implantation. Furthermore, risk stratification in patients listed for cardiac transplantation is essential to optimize survival and organ allocation. The authors argued that despite the development of many scoring systems, their complexity might preclude their bedside applicability. The primary end-points studied were early (30-day) and late mortality. Secondary end-points were other post- operative outcomes.

The MELD-XI score was calculated using the creatinine and bilirubin values obtained before heart transplant from the transplant recipient registration (TRR) form according to the following formula: MELD-XI = 11.76 (ln creatinine) + 5.112 (ln total bilirubin) + 9.44. Patients with missing creatinine or bilirubin values were excluded from the analysis. In addition to analyzing MELD-XI score as a continuous variable, patients were also categorized into quartiles based on MELD-XI score (Q1: <7.02; Q2: 7.02 to10.67; Q3:10.67 to 14.43; Q4: >414.43).

The score could be calculated in 36 005 patients (90.6% of the UNOS database); most were male (75.9%), white (74.7%), and transplanted as Status 1A (34.2%). Their mean age at transplant was 52.27±11.99 years. Median MELD-XI score was 10.67 (interquartile range [IQR] 7.02 to 14.43). Patients with higher MELD-XI were slightly older and more likely to be male, black and have Status1A.They were also more acutely ill and more likely to have TAH, BiVAD, IABP, ECMO, ventilator and inotropes and infection before transplantation. Donors tended to be older and more likely male

Of the 36,005 patients transplanted during the twenty years of the study period, 1,966 (5.5%) patients died within 30 days of transplant. Early mortality increased from 3.7% in those with MELD- XI scores <5 to 28.0% in those with MELD-XI scores >30. Not surprisingly, high MELD-XI was also associated with increased morbidity such as infections, stroke, renal replacement therapy, rejection and prolonged hospitalization. Interestingly, MELD-XI score was also associated with late survival from infections and cerebrovascular disease, but except for graft failure, there was no difference in deaths from cardiovascular causes,pulmonary disease, hemorrhage or malignancy.

The authors concluded that:

1) Hepato-renal dysfunction, measured with MELD-XI score, predicts morbidity and mortality in patients undergoing orthotopic heart transplantation.
2) The etiology of hepato-renal dysfunction should be sought and treated before heart transplantation: A high MELD score should prompt a liver biopsy to identify the level of liver injury and rule-out the end-stage cirrhosis that precludes heart transplantation. Another approach would be to use transient hemodynamic support; patients with irreversible and severe hepaticorrenal dysfunction may qualify for dual-organ transplantation.
3) Interestingly, in the present study, the calculated MELD-XI score had prognostic implications in addition to serum creatinine and serum bilirubin, which comprised the actual score. This leads the authors to speculate that both renal and liver dysfunction have a compounding and additive adverse.

These findings are important. However it might be impossible clinically to optimize the hemodynamics and volemia in this very sick population, with more than one third of patients being listed as status IA and 60% on some circulatory support (inotropes or mechanical). Nevertheless, these data suggest that liver and kidney evaluation are crucial before cardiac transplantation and that the MELD-XI should be calculated for prognostic information.

Givens RC et al. "Outcomes of multiple listing for adult heart transplantation in the United States: Analysis of the OPTN Data from 2000-2013." *JACC Heart Fail* 2015 Oct 31 [Epub ahead of print].

The referenced article by Givens, et al. examines the impact of the United States Network of Organ Sharing (UNOS) policy on multiple listing (ML). ML is a policy within the United States where patients maybe simultaneously listed at geographically distinct transplant centers. ML was introduced in 1987 to provide patients greater access to medical care and has been a source of periodic controversy over the past 28 years. ML is not an international standard. Eurotransplant (ET), an OPTN consortium of 8 countries within central Europe, prohibits simultaneous listing at 2 centers within or outside of the ET Zone. https://www.eurotransplant.org/cms/mediaobject.php?file=Chapter2_recipient14.pdf

The analysis is relevant because only some insurers cover the costs of ML, and state subsidized medical assistance, which covers the poorest and most needy patients, rarely covers out of state medical services. Furthermore, even if private insurance covers services at secondary centers, it does not cover costs associated with transportation and lodging incurred while living away from home and awaiting transplantation. The question raised then is whether ML allows wealthier and more privileged patients increased assess to organs.

The authors query the UNOS database for all patients listed for heart transplant between 2000-2013, and stratified them as to single listing (SL) and ML. They identify 679 patients (2.0 % of all listed patients) who were listed at multiple centers. In terms of baseline characteristics, ML patients had characteristics associated with a longer wait time (Blood Type O, Increased weight, lower UNOS priority at time of initial listing), and were

less likely to receive mechanical circulatory support. ML patients were more often Caucasian and male, have private insurance and a higher socioeconomic status, as determined by their ZIP Code.

The salient findings were that ML patients were much less likely to receive a transplant at their initial listing center (4.9 % vs. 70.0 %, $p < 0.0001$), but had a *higher* transplant rate overall (74.4 % vs. 70.0 %, $p = 0.0196$). Not surprisingly, 70.3 % ML patients registered at a secondary center with a lower median wait time than their primary center. Median wait times at ML secondary times were significantly lower than those at their primary centers (105 days [53-153] vs 151 days [114-201], $p < 0.0001$). Furthermore, ML patients had a lower crude waitlist mortality (8.1 % vs. 12.2 %, $p = 0.0011$).

The authors reach 4 primary conclusions:

1. Adult patients who pursue ML have baseline characteristics which predict longer wait times
2. ML provides enhanced access to transplant with a lower WL mortality
3. ML patients have higher incomes and are more likely to have private insurance
4. ML patients are not as critically ill through their wait time, and have less need for mechanical circulatory support.

Equitable access to organs is a critical tenant to transplant medicine. The public is keenly aware of this, and the referenced article received attention in the lay press, under the headline "…researchers detail how the wealthy game the system." https://www.washingtonpost.com/news/to-your-health/wp/2015/11/11/inequality-in-u-s-organ-transplants-researchers-detail-how-the-wealthy-game-the-system/

The authors contend that "*continued allowance of ML stands at odds with the ethical principles that govern human organ allocation and that it should be reconsidered at the national level*." The study is limited by its retrospective nature, and some of the necessary assumptions required for this type of analysis (utilizing ZIPcodes as surrogates for mortality), though the findings are provocative, and call for further investigation.

ADDITIONAL ARTICLES OF INTEREST:

Circulation-Heart Failure:

Christina Wu, Tomoko S. Kato, Ruiping Ji, Cynthia Zizola, Danielle L. Brunjes, Yue Deng, Hirokazu Akashi, Hilary F. Armstrong, Peter J. Kennel, Tiffany Thomas, Daniel E. Forman, Jennifer Hall, Aalap Chokshi, Matthew N. Bartels, Donna Mancini, David Seres, and P. Christian Schulze. **Supplementation of L-Alanyl-L-Glutamine and Fish Oil Improves Body Composition and Quality of Life in Patients With Chronic Heart Failure.** *Circ Heart Fail*. 2015;8:1077-1087, published online before print August 12 2015.

Caroline J. Coats, Khadija Rantell, Aleksandra Bartnik, Amour Patel, Bryan Mist, William J. McKenna, and Perry M. Elliott. **Cardiopulmonary Exercise Testing and Prognosis in Hypertrophic Cardiomyopathy.** *Circ Heart Fail*. 2015;8:1022-1031, published online before print September 15 2015.

American Journal of Transplantation:

Loupy A, Toquet C, Rouvier P, Beuscart T, Bories MC, Varnous S, Guillemain R, Pattier S, Suberbielle C, Leprince P, Lefaucheur C, Jouven X, Bruneval P, Duong Van Huyen JP. **Late Failing Heart Allografts: Pathology of Cardiac Allograft Vasculopathy and Association With Antibody-Mediated Rejection.** Am J Transplant. 2015 Nov 20. doi: 10.1111/ajt.13529. [Epub ahead of print]

Journal of Cardiac Failure:

Lim HS, Zaphiriou A. **Sodium Nitroprusside in Patients with Mixed Pulmonary Hypertension and Left Heart Disease: Hemodynamic Predictors of Response and Prognostic Implications.** J Card Fail. 2015 Nov 4. pii: S1071-9164(15)01171-9. doi: 10.1016/j.cardfail.2015.10.018. [Epub ahead of print]

International Heart Journal:

Nitta D, Kinugawa K, Imamura T, Hatano M, Ono M, Nakamura F, Kurokawa M, Komuro I. **How Should We Treat Early Post-Transplant Lymphoproliferative Disease After Heart Transplantation?** Int Heart J. 2015 Nov 6. [Epub ahead of print]

International Journal of Cardiology:

Watanabe T, Seguchi O, Nishimura K, Fujita T, Murata Y, Yanase M, Sato T, Sunami H, Nakajima S, Hisamatsu E, Sato T, Kuroda K, Hieda M, Wada K, Hata H, Ishibashi-Ueda H, Miyamoto Y, Fukushima N, Kobayashi J, Nakatani T. **Suppressive effects of conversion from mycophenolate mofetil to everolimus for the development of cardiac allograft vasculopathy in maintenance of heart transplant recipients.** Int J Cardiol 2015 Oct 23;;203:307-314

Journal of the American College of Cardiology:

Jerry D. Estep, Randall C. Starling, MPH, Douglas A. Horstmanshof, Carmelo A. Milano, Craig H. Selzman, Keyur B. Shah, Matthias Loebe, Nader Moazami, James W. Long, Josef Stehlik, Vigneshwar Kasirajan, Donald C. Haas, John B. O'Connell, Andrew J. Boyle, David J. Farrar, and Joseph G. Rogers. **Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management**

in Ambulatory Heart Failure Patients: Results From the ROADMAP Study. J Am Coll Cardiol. 2015 Oct 20;66(16):1747-61. doi: 10.1016/j.jacc.2015.07.075.

Journal of Heart and Lung Transplantation:

Deo SV, Al-Kindi SG, Altarabsheh SE, Hang D, Kumar S, Ginwalla MB, ElAmm CA, Sareyyupoglu B, Medalion B, Oliveira GH, Park SJ. **Model for end-stage liver disease excluding international normalized ratio (MELD-XI) score predictsheart transplant outcomes: Evidence from the registry of the united network for organ sharing.** J Heart Lung Transplant 2015 Oct 9

Kfoury AG, Miller DV, Snow GL, Afshar K, Stehlik J, Drakos SG, Budge D, Fang JC, Revelo MP, Alharethi RA, Gilbert EM, Caine WT, McKellar S, Molina KM, Hammond ME. **Mixed cellular and antibody-mediated rejection in heart transplantation: In-depth pathologic and clinical observations.** J Heart Lung Transplant. 2015 Oct 23. pii: S1053-2498(15)01477-1. doi: 10.1016/j.healun.2015.10.016. [Epub ahead of print]

BMC Cardiovascular Disorders:

Crespo-Leiro MG, Stypmann J, Schulz U, Zuckermann A, Mohacsi P, Bara C, Ross H, Parameshwar J, Zakliczyński M, Fiocchi R, Hoefer D, Deng M, Leprince P, Hiller D, Eubank L, Deljkich E, Yee JP, Vanhaecke J. **Performance of gene-expression profiling test score variability to predict future clinical events inheart transplant recipients.** BMC Cardiovasc Disord 2015 Oct 9;15:120

Expert Review of Cardiovascular Therapy:

Chang DH, Kobashigawa JA. **Current diagnostic and treatment strategies for cardiac allograft vasculopathy.** Expert Rev Cardiovasc Ther. 2015 Oct;13(10):1147-54. doi: 10.1586/14779072.2015.1087312.