

Editorial

Predicting Primary Nonfunction of Liver Transplants With Laboratory Values: Can It Be Done?

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Determination of primary nonfunction (PNF) of a liver transplant can be one of the most difficult assessments in transplantation. PNF can initially manifest in a variety of ways both dramatic and subtle, and no one parameter is sufficient for diagnosis (1,2). The determination of PNF informs the decision to relist for a second liver transplant. Once relisted, one or more additional confirmations are subsequently necessary in the context of deciding whether to retransplant as donors become available. In addition, a retransplant operation is not without risk, especially in the setting of the existing or impending multiorgan system failure that can be associated with PNF. On the other hand, an incorrect decision to not retransplant can lead to profoundly adverse short- and long-term outcomes. For these reasons, the need for accurate real-time prediction of PNF is critically important, to ensure appropriate use of organs but most importantly to make the best choices for a critically ill transplant recipient.

Existing criteria are helpful but have limitations in their ability to identify PNF, and the determination remains heavily dependent on clinical judgment. By logistical necessity, many operational definitions of PNF align with those established for urgent liver allocation. Both United Kingdom (UK) and United States (US) criteria incorporate aspartate aminotransferase (AST), international normalized ratio (INR), and acidosis/lactate, but with different thresholds and algorithms (3,4). However, because of the imperfect predictive power of these criteria, there are numerous examples of recipients meeting criteria who are not clinically judged to have PNF and who uneventfully recover, and unfortunately others who do not meet criteria who are judged to have sufficient dysfunction to warrant retransplantation. In the United States, the latter can be accomplished through the high Mayo End-Stage Liver Disease scores often found in these patients, but ideally these recipients would have the more

expanded access to donor livers associated with 1A status.

In this issue of AJT, Al-Freah et al have developed a model of PNF using lab-based parameters that improves upon existing methods (5). The formula includes only biochemical parameters, and utilizes data over 7 days—albumin at transplant, day-1 AST, day-1 lactate, day-3 bilirubin, day-3 INR, and day-7 AST were identified as independent factors associated with PNF. The model was able to predict PNF as defined by death or retransplant within 2 weeks with significantly superior performance over current criteria in the United Kingdom and United States (model AUROC of 0.912 vs. UK PNF criteria of 0.669 and US criteria of 0.774). The model was also able to predict PNF at 3 days, albeit with less accuracy, and thus can be also used early after transplant. By expanding the timeframe for defining PNF to 2 weeks after transplant, the authors have built in potential utility in borderline cases that may have less urgency, but are no less important to evaluate. With substantially improved performance in predicting PNF, this easy-to-use model has the potential to have an important impact in the management of early graft dysfunction.

There are several noteworthy methodological features. One is the decision to eliminate modifiable variables such as renal function or renal replacement therapy. While more sound in the derivation of the model by eliminating practice variations that might introduce bias, from an application perspective it leaves out a potentially important predictor that could influence recipient outcomes. It is somewhat reassuring that including creatinine and renal replacement did not appreciably alter model performance, and was not predictive of outcome. Second is the exclusion of hepatic artery thrombosis (HAT) from the cohort, under the rationale that HAT is sufficient to consider retransplantation by itself. This leaves out an important population whose outcomes are variable enough that they could benefit from a predictive tool for subsequent PNF.

The most important caveat in assessing the potential impact of this work is the lack of a perfect endpoint, or “gold standard,” for defining PNF. Although death is clearly defined, retransplantation is determined by clinical practice; thus the model is influenced by selection biases

and could be simply reaffirming current UK clinical practices. It is important to note that in this study, these practices were guided by existing UK relisting criteria and are at least likely to be internally consistent. Nevertheless, this unavoidable limitation only highlights the need for external validation through multicenter investigations in other allocation systems and countries before broad application can be recommended.

Regardless of the predictive ability of a lab-based model, determinations of PNF will still require consideration of other less quantifiable factors and reasoned and experienced clinical judgment. However, this effort represents a possible adjunct to such judgment, and a potentially significant step forward in the difficult and high-stakes process of determining PNF.

Disclosure

The author of this manuscript has no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

References

1. Johnson SR, Alexopoulos S, Curry M, Hanto DW. Primary non-function (PNF) in the MELD Era: An SRTR database analysis. *Am J Transplant* 2007; 7: 1003–1009.
2. Olthoff KM, Kulik L, Samstein B, et al. Validation of a current definition of early allograft dysfunction in liver transplant recipients and analysis of risk factors. *Liver Transpl* 2010; 16: 943–949.
3. NHS ODT. NHS Blood and Transplant Liver Advisory Group. Liver transplantation: Selection criteria and recipient registration. [cited 2017 Feb 21]. Available from: http://www.odt.nhs.uk/pdf/liver_selection_policy.pdf.
4. Organ Procurement and Transplantation Network. Policies: Allocation of livers and liver-intestines. [cited 2017 Feb 21]. Available from: https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf#nameddest=Policy_09.
5. Al-Freah M, McPhail M, Dionigi E, et al. Improving the diagnostic criteria for primary liver graft non-function in adults utilizing standard and transportable laboratory parameters. An outcome based analysis. *Am J Transplant* 2017; doi: 10.1111/ajt.14230.