Balancing the Tightrope of Cardiac Allograft Rejection:
Equations or Experience?

Running title: Mehra; Prediction of cardiac allograft rejection

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Let’s face it. We love clinical prediction rules that forecast outcomes in cardiovascular medicine. Our clinical armamentarium is suffused with a variety of scores that seek to predict unique outcomes such as the Framingham risk score for future ischemic events, the CHADS score to ascertain the risk of neurological events in atrial fibrillation, or clinical decision rules to exclude acute coronary syndromes in patients presenting to the emergency department.

Generally, for a prediction rule to be successfully inserted into our clinical lexicon, it should be highly relevant, easy to employ and exercise sufficient discrimination between extremes to allow for deployment of decisional strategies. This frequently requires an artificial reductionism of the clinical outcome of interest into “yes” or “no” categorical variables. Often, such an over-simplification of an otherwise complex outcome variable can render it to be less informative.

In this issue of the journal, Kilic and colleagues sought to develop a clinical prediction rule for the risk stratification of propensity for cardiac allograft rejection. Using a relatively large and contemporary cohort of adult heart transplant recipients (1998-2008) drawn from the UNOS registry, these investigators meticulously correlated over 450 clinical variables per patient with the dichotomous primary outcome of cardiac transplant rejection treated at the clinician’s discretion by 1 year post transplant. After a laborious statistical process, they found 4 variables worthy of entry into a scoring system (range 0-13) that included age at transplant, recipient gender, recipient race and the number of donor-recipient HLA mismatches. This scoring system, that assigned numerical values to variables based on the magnitude of the odds ratio for the outcome, was able to provide a range of prediction for occurrence of treated rejections from
16.2% to 50.7% at the two extreme scores of 0 and 13, respectively. Not surprisingly, these authors found that while advanced age was protective, female gender, African American race and 5-6 donor-recipient HLA mismatches were associated with the greatest risk of rejection.

Clinical Experience in Risk Profiling

Using heuristics (experience-based techniques for problem solving), seasoned cardiac transplantation clinicians have long recognized these very variables to be necessary for post transplant risk stratification and the evident disparity in clinical outcomes among these distinct cohorts has led to performance of targeted intervention studies in these patient subsets in an effort to improve overall outcome. In 2002, we demonstrated that the combination of tacrolimus and mycophenolate mofetil was superior to one that employed cyclosporine as the calcineurin inhibitor in African American heart transplant recipients. This investigation found a significant reduction in hemodynamically compromising rejection and consequent enhanced survival. In a lower risk population (largely men of Caucasian descent) Baran and colleagues demonstrated that tailored monotherapy with tacrolimus is feasible and safe when compared with dual drug immunosuppression, and did not diminish outcomes significantly, thus suggesting that tailored therapy was possible in such populations. Therefore, the contention that one could employ a risk prediction rule to risk stratify heart transplant recipients and test tailored immunosuppression strategies is not a far-fetched one. In that sense, Kilic and colleagues have been rather astute in taking these known risk markers and “putting them together” in the form of this prediction rule algorithm. However, it would appear that the best discrimination achieved at the highest score category, is no more than a mere “coin flip” for a patient (50.7%). Why might this be so?

Era Effects in Transplant Recipient Management

The decade of 1998-2008 represented an era of intense activity characterized by several
fundamental shifts in our management of advanced heart failure and transplant patients. In 1998, evidence that mycophenolate mofetil was associated with a survival benefit on the heels of diminishing hemodynamically compromising rejection episodes, was greeted positively and led to it gradually supplanting azathioprine as the adjunctive immunosuppression of choice\(^7\). In tandem with this shift, tacrolimus became the more dominant calcineurin inhibitor for use instead of cyclosporine\(^8\). Investigations that studied different regimens of immunosuppression combinations suggested that the best risk-benefit ratio was achieved by the combination of tacrolimus and mycophenolate mofetil\(^9\). Although induction agents such as monoclonal antibodies supplanted the older polyclonal induction agent OKT3, evidence for a benefit was less well forthcoming\(^10,11\). Another important shift in the recipient characteristic was the slow but definite growth of mechanical circulatory support as a bridge to transplantation and recognition that the presence of this durable device resulted in distinct immunological perturbations in the host.

Indeed, by 2009, a third of all recipients undergoing transplantation were so bridged under support with a durable mechanical device\(^12\). Due to the limitations of registry based databases, Kilic and colleagues could not control for the evolving use of immunosuppressants, the presence or absence of inclusion of patients within the rigid frame work of clinical trials and targeted tailoring of immunosuppression by some centers for the elderly or recognized high risk groups.

**Changing Epidemiology of Cardiac Allograft Rejection**

Evidence has been forthcoming that the evolution of immunosuppression in the last decade has, in tandem, been associated with a changing epidemiology of rejection based outcomes during the recent decade from analyses embedded within the ISHLT registry\(^12\), which includes the UNOS database and also more broadly represents the state of transplantation across the globe. Among patients who underwent heart transplants between April 1994 and 2000, the need for
hospitalization for treatment of rejection within 1 and 5 years after transplant was 41% and 59%, respectively. In contradistinction, between 2001 and June 2009, hospitalization for rejection treatment decreased to 26% at 1 year and 44% within 5 years after transplant. This changing epidemiology raises some doubt about the performance of the proposed prediction rule in more contemporary cohorts characterized by an older recipient age, exposure to novel immunosuppressants and a greater bridging with mechanical circulatory support devices which may distinctly alter the immunological milieu but with acceptable rejection-based outcomes13,14.

Observations from Other Registry Analyses

In a separate registry study that consisted of 10,131 patients from 29 institutions in the Cardiac Transplant Research Database (n = 7,368, from 1990 to 2008) and 32 institutions in the Pediatric Heart Transplant Study (n = 2,763, from 1993 to 2008), George and colleagues15 estimated the probabilities of death due to rejection and infection with a parametric time-related model that was specifically adjusted for gender, ethnicity, date of transplant and age. These investigators discovered that death due to rejection at 5 years was highest among those transplanted at 10 to 30 years of age and lowest in those transplanted at >60 years of age. Death due to infection at 5 years was highest among patients >60 years of age. In this registry analysis, recipient risk markers for death for rejection were age, female gender, black race and transplant date. Importantly, modeling with respect to age at time of transplant showed an inverse relationship between infection and rejection death. Among patients transplanted at >60 years of age, there was a steep increase in infection-related deaths and a decrease in rejection deaths. Risk for rejection was highest among young adults 10 to 30 years of age at time of transplant, particularly for black females. Thus, the variables included by Kilic and colleagues appear to be those well characterized and confirmed in separate well-conducted registry-based analyses with evidence of
broad applicability. Even if the risk variables included in the scoring system to derive the prediction rule are robust, an even more important issue resides in the clinical relevance of the rejection-based outcome of primary interest.

**Diverse Phenotypes of Cardiac Allograft Rejection**

To denote rejection as a simplistic dichotomous variable is a fallacy that grossly limits the understanding of the diverse phenotype represented by this prognostically relevant end point.

Two distinct forms of cardiac allograft rejection are recognized including acute cellular rejection (ACR) and Antibody Mediated Rejection (AMR), which can sometimes co-exist.

Immunologically, ACR is typically a T-cell-mediated assault upon the donor allograft tissue and occurs most commonly early, within the first 6 months of transplantation with a declining incidence thereafter. The histopathology of cellular rejection is notable for lymphocytic infiltrates, which in mild cases of rejection are localized to the perivascular regions and in severe cases lymphocyte infiltration progresses diffusely into the cardiac interstitium. In late stages of severe ACR, multi-clonal cells like macrophages, neutrophils and eosinophils are observed with associated evidence of myocyte injury, intramyocardial hemorrhage, and myocyte necrosis. This form of rejection can remain clinically silent and histologically overt or progress to evidence of cardiac allograft failure. Thus, treatment and significance can be fairly diverse with the greatest variability in treatment threshold for asymptomatic forms of ACR. Some centers treat all such episodes, even those that are histologically graded as mild, while other centers have established non-treatment observational strategies with repeat endomyocardial biopsies in the setting of mild rejection, since there is recognition that a large majority of such episodes resolve spontaneously with longitudinal observation. This variability calls into question the notion of the informative significance of “any treated rejection” from multiple centers when more details
about the gravity of such episodes are unavailable. For instance, how did the center define “treatment” of rejection? Was it a simple up titration of the calcineurin inhibitor and anti-proliferative adjunctive agents? Was it augmentation in corticosteroids? Were the corticosteroids administered orally for a short duration or Intravenously in high doses? Was the patient hospitalized for such therapy or treated as an outpatient? Did the patient experience hemodynamic compromise of the cardiac allograft or was cardiac function preserved? Did the rejection episode resolve or was it persistent at milder grades? These issues cannot be answered adequately by the simplistic dichotomous outcome variable as studied by Kilic and colleagues and therefore clinical decision comfort around the construct of this prediction rule is weak at best.

Emergence and Recognition of Antibody Mediated Rejection

The recent recognition and standardization of AMR represents culmination of an evolving concept of a distinct form of rejection that was not adequately characterized in the cohort studied from 1998-2008\textsuperscript{18}. This form of rejection is immunologically described as a non-cellular, antibody driven phenomenon that was debated for years and only recently officially recognized with equal pathological rigor as ACR. Only recently has the transplant pathology community developed a standardized nomenclature for this entity due to the recognition that this phenotype of rejection is being recognized more often in current patient cohorts while potent novel immunosuppression has achieved a reduction in the incidence of significant ACR\textsuperscript{19}. AMR is a form of rejection associated with cardiac allograft arteriolar vasculitis and a pattern of immunopathologic findings of immunoglobulin deposition and complement fixation on immunofluorescence, along with histopathological findings of endothelial swelling and interstitial edema on routine light microscopy. AMR is associated with decreased cardiac
allograft survival compared to ACR and seminally characterized by the emergence of donor specific antibodies in the peripheral circulation that are thought to bind to the allograft, thereby propagating the reaction of AMR. Commonly, this phenotype leads to acute allograft dysfunction and increases the risk for cardiac allograft vasculopathy, even when the phenomenon is initially restricted to the histology of the allograft without overt signs of cardiac dysfunction\textsuperscript{20, 21}. The reported incidence of “non-cellular” rejection or AMR has been variable depending on clinical and histopathology criteria employed, with an estimated incidence of 8 -20\%\textsuperscript{22}. Strikingly, treatment paradigms for AMR are still not clearly established and outcomes remain poor, especially for AMR associated with allograft dysfunction\textsuperscript{23}. Of the variables identified in the Kilic study, African American race and female gender have been associated with an increased propensity for AMR, especially in the setting of a positive donor-specific cross match and elevated circulating donor directed antibodies\textsuperscript{22}. Moreover, heightened antibody expression and subsequent propensity to AMR is uniquely associated with the increasing application of mechanical circulatory devices\textsuperscript{24, 25}. It may well be that prediction rules developed predominantly using ACR end points may need to be reworked for application in AMR to refine the predictive value and make such rules clinically meaningful.

**Potential Clinical Applications of Prediction Rules**

Even then, what might the potential applications of such rejection-based prediction rules be in cardiac transplantation? While 1 year outcomes in cardiac transplantation have seen improvements in survival to >90\%, 10-year survival has not improved in tandem with these early advances\textsuperscript{26}. We now recognize that early events in the post transplantation period, particularly rejection, continue to exact a late toll leading to selective attrition of survival by the development of cardiac allograft vasculopathy, renal dysfunction, and malignancy\textsuperscript{26}. Prediction rules may
allow discrimination, albeit crude, to develop target populations that are at risk of poor late survival and this cohort may be most amenable to active study surrounding therapeutic targets that concentrate on reducing metabolic complications, tailoring of immunosuppression to avoid over immunosuppression and its sequelae such as renal failure and malignancy. As genomic, transcriptomic and protein-based predictive biomarkers become available, it would be ideal to identify the bio-signatures that mechanismically serve as the underpinnings that identify and predict risk of adverse immunological outcomes, allowing a much better refinement of predictive risk scores that eliminate the classical individual heterogeneity of outcome risk. It may well be that a combined biomarker-clinical phenotype risk prediction model may provide greater clinical decision support.

In summary, algorithmic prediction rules are important guides to more rational thinking but not designed to replace heuristics. As B.F. Skinner said eloquently “The real problem is not whether machines think but whether men do”.

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