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ISHLT pathology antibody mediated rejection score correlates with increased risk of cardiovascular mortality: A retrospective validation analysis

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BACKGROUND: Antibody-mediated rejection (AMR) in cardiac transplant recipients is a serious form of rejection with adverse patient outcomes. The International Society of Heart and Lung Transplantation (ISHLT) has published a consensus schema for the pathologic diagnosis of various grades of antibody-mediated rejection (pathology antibody-mediated rejection [pAMR]). We sought to determine whether the ISHLT pAMR grading schema correlates with patient outcomes.
METHODS: Using our database, which contains a semi-quantitative scoring of all pathologic descriptors of pAMR, we retrospectively used these descriptors to convert the previous AMR categories to the current ISHLT pAMR categories. Cox proportional hazard models were fit with cardiovascular (CV) death or retransplant as the outcome. The pAMR value was included as a categorical variable, and cellular rejection (CR) values were included in a separate model.
RESULTS: There were 13,812 biopsies from 1,014 patients analyzed. The pAMR grades of pAMR1h, pAMR1i, and pAMR2 conferred comparable increased risk for CV mortality. Significantly increased risk of CV mortality was conferred by biopsies graded as severe AMR (pAMR3).
CONCLUSIONS: The new ISHLT pAMR grading schema identifies patients at increased risk of CV mortality, consistent with risks published from several programs before 2011. The current schema is validated by this analysis in a large biopsy database. Because pAMR1h, pAMR1i, and pAMR2 have similar CV risks associated with them, the threshold for a positive diagnosis of pAMR should be re-evaluated in future iterations of the ISHLT schema.
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Antibody-mediated rejection (AMR) of cardiac allografts was first defined in the late 1980s and 1990s.[1–5] In 2003, a National Institutes of Health consensus conference aimed

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to standardize the definition of AMR across the different solid-organ allograft types.[6] Additional consensus documents focusing on cardiac AMR diagnosis were sponsored by the International Society of Heart and Lung Transplantation (ISHLT) in 2005–2006 and 2011–2013.[7–11] A 2011 ISHLT guideline for diagnosis of AMR represented a major shift from the previous 2005 guideline by proposing to move from a combination of clinical and pathologic diagnostic findings to a purely pathologic diagnosis of AMR (pathology antibody-mediated rejection [pAMR]). In this new schema, the salient parameters considered in AMR diagnosis are clearly defined. The grades are defined as histopathologic AMR alone (pAMR1h) immunopathologic AMR alone (pAMR1i), pathologic AMR (pAMR2), and severe pathologic AMR (pAMR3).[11] There have been no large, multicenter studies describing the relationship of this new ISHLT schema to clinical outcome. We used our transplant database containing all the descriptors needed to assign pAMR grading to answer this question.

Methods

Study population

This study was approved by the Institutional Review Board and Privacy Boards of Intermountain Healthcare for publication of the data. The requirement for specific informed consent for this study was waived on the basis of minimal privacy risk. The study population comprised patients transplanted within the Utah Transplantation Affiliated Hospitals (U.T.A.H.) between 1986 and 2014 ($N = 1,224$). The participating hospitals are LDS Hospital and Intermountain Medical Center, the Primary Children's Hospital, the George E. Wahlen Salt Lake City Department of Veterans Affairs Medical Center, and the University of Utah Health Sciences Center. All patients who underwent transplantation during the study period for whom pathology and clinical parameters were available were included in the study. Induction and maintenance immunosuppression were standardized across the U.T.A.H. institutions but varied with time based on programmatic changes. The mean follow-up time for the patients in our study was 3.74 years (SD 4.47 years).

Endomyocardial biopsy procedure and database

The protocol for frequency of biopsy surveillance is described elsewhere.[12,13] Examination for AMR by immunofluorescence (IF) was extended beyond the first 12 weeks in patients with early AMR and done when AMR was suspected on clinical grounds. All biopsy data obtained since the inception of the U.T.A.H. program in 1985 have been recorded in a single database, with histologic and IF findings recorded separately. By protocol, endomyocardial biopsies were prospectively described using a semi-quantitative scale documenting individual histologic and IF findings, although the program was informal rather than routine until 1987, when routine surveillance as described was instituted; the George E. Wahlen Salt Lake City Department of Veterans Affairs Medical Center and the University of Utah Health Sciences Center shortly afterward followed suit. The Primary Children's Hospital performed their first transplant in 1989 when the surveillance protocol was well established, but the biopsy frequency for pediatric patients is different than that for adults.[2,12–15]

IF features defining pAMR include the detection and distribution of C3d for the entire data set. C4d was added a routine marker after 1999. To account for this difference in marker status, the data were analyzed in 2 cohorts, before and after 1999. Table 1 shows how the data collected in the U.T.A.H. program were used to generate pAMR grades for this study. When data contained insufficient information to generate a pAMR grade, the biopsy was excluded from analysis. Queries were constructed by M.E.H.H., who also reviewed the entire biopsy record on each patient. After 2011, pAMR grades were prospectively assigned based on the 2011 ISHLT schema.

Cardiovascular mortality

Patient demographics and clinical information including survival were collected in the U.T.A.H. database. Mortality was classified as a cardiovascular (CV) death if it resulted from sudden death, acute myocardial infarction, heart failure, or progressive allograft dysfunction, criteria consistent with the criteria used for reporting to the United Network for Organ Sharing and the Cardiac Transplant Research Database.[3,14] The final determination of the cause of death was made by the cardiologist caring for the patient at the time of death.

Statistical analysis

Most cardiac allograft recipients undergo rejection episodes of different types and severity over their lifetime, interspersed with periods of immunologic quiescence. Also, it is unclear whether a current negative biopsy result mitigates the immediate or long-term impact of a preceding rejection on the allograft or whether the cumulative consequences of repeated rejections over time are more important than that of a single rejection. We designed an approach to data analysis that partially accounts for these concerns. The data were analyzed using a Cox proportional hazards model regression with time-varying covariates, similar to our previous approach.[15,16] The covariates used pAMR grades from the most recent biopsy in estimating the hazard ratios (HRs). We sought the individual, combined, and cumulative impact of pAMR grades on clinical outcome. The main outcome of interest was CV mortality. The individual pAMR grades all were entered into a single model with pAMR0 as the baseline and the coefficients corresponding to the comparisons of the higher most recent pAMR grades to baseline (pAMR1i or pAMR1h vs pAMR0, pAMR2 vs pAMR0, pAMR3 vs pAMR0). One model also included an indication of cellular rejection (CR) (CR, ISHLT 1R, 2R, 3R) to analyze whether mixed rejection differed from AMR; this model was compared with the model with only pAMR grades using a likelihood ratio test. Figure 1 shows the Cox proportional hazard model for CR, pAMR alone, and CR + pAMR.

Additional models were fit that compared pAMR grades at or above a given cutoff with all values below that cutoff (e.g., all biopsies with scores of pAMR1i, pAMR1h, or above were compared with pAMR0 scores). A separate model compared pAMR2 and above with pAMR0, pAMR1i, and pAMR1h. These models used time-varying covariates representing only the most recent grade. The analysis was done using 2 cohorts, split chronologically after 1999 when C4d became a standard reagent for complement detection. Another set of models also used the cutoff principle, but rather than looking at the most recent biopsy, they used the cumulative number of biopsies at or above the cutoff.

The R statistical program and its survival package were used for the analysis. Cox proportional hazards models were used to