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Redefining Cardiac Antibody-Mediated Rejection With Donor-Specific Antibodies and Graft Dysfunction

Goldberg JF, et al. Circulation Heart Failure 2024 Nov;17(12):e012438 | DOI: 10.1161/CIRCHEARTFAILURE.124.011592

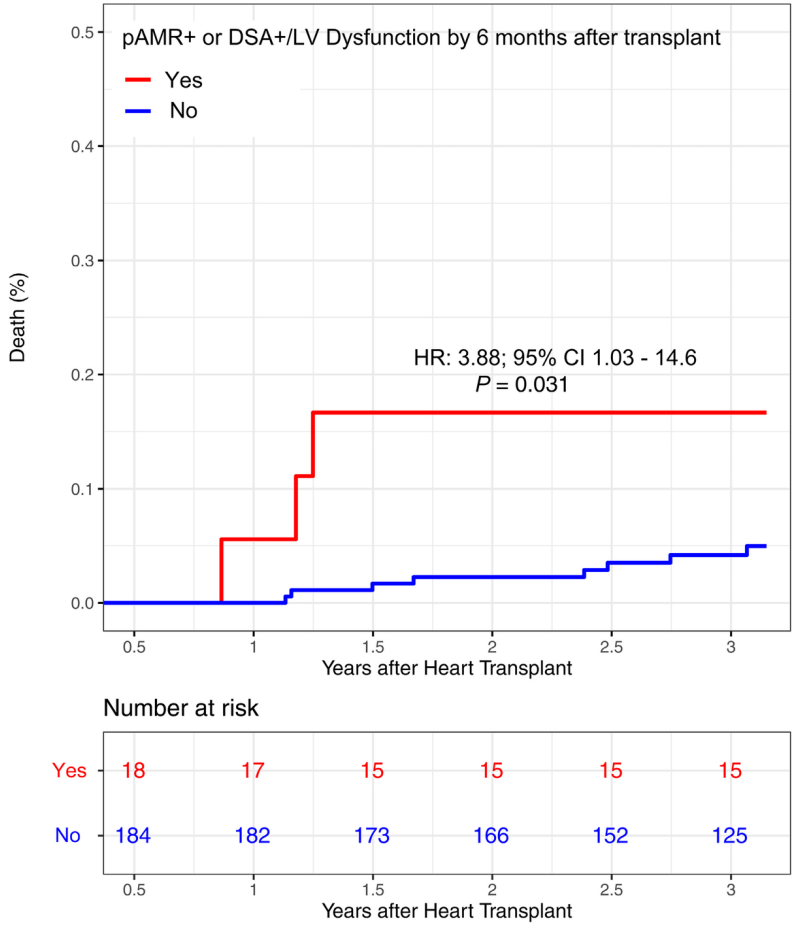
Study Highlights

Objective: To expand the definition of antibody-mediated rejection (AMR) to include cases with donor-specific antibodies (DSAs) and concurrent graft dysfunction.

Methods: Participants from this prospective, multicentre study underwent serial endomyocardial biopsy (EMB), echocardiogram, DSA, and donor derived cell-free DNA (dd-cfDNA) evaluations. Outcomes were defined as pAMR+ (pAMR≥1) or DSA+/left ventricle (LV) dysfunction (DSA presence + LVEF drop ≥10% to an LVEF≤50%). Cox regression evaluated the association between AMR categories and death or sustained (for 3 months) reduction of LVEF to <50%.

Results: 216 patients (29% women, 39% Black race, median age 55 [IQR, 47–62] years) had 1488 EMB, 2792 DSA, 1821 echocardiograms, and 1190 dd-cfDNA evaluations. 14 patients had isolated pAMR+ episodes and 8 patients had isolated DSA+/LV dysfunction episodes; 2 patients had pAMR+ and then subsequently DSA+/LV dysfunction with pAMR+. Median %dd-cfDNA was higher at diagnosis of pAMR+ (0.63% [IQR, 0.23–2.0]; P=0.0002), or DSA+/LV dysfunction (0.40% [IQR, 0.36–1.24]; P<0.0001), compared with patients without these outcomes (0.01% [IQR, 0.0001–0.10]). Both pAMR+ and DSA+/LV dysfunction were associated with death (n=18) or prolonged LV dysfunction (n=10): pAMR+ (hazard ratio (HR), 2.8 [95% CI, 1.03–7.4]; P=0.043); DSA+/LV dysfunction (HR, 26.2 [95% CI, 9.6–71.3]; P<0.001); composite of both definitions (HR, 6.5 [95% CI, 2.9–14.3]; P<0.001). Patients who developed pAMR+ or DSA+/LV dysfunction within the first 6 months of transplant were more likely to die within 3 years posttransplant (HR, 3.9 [95% CI, 1.03–14.6]; P=0.031).

Conclusions: Expanding the characterization of AMR to include patients with DSA and concurrent allograft dysfunction identified DSA+ patients at risk for death and prolonged LV dysfunction.



Legend: The Kaplan-Meier estimate of death by presence of composite outcome within 6 months post-transplant.

Reviewer's Comments

- Authors redefined AMR by incorporating DSAs and LV dysfunction, moving beyond traditional biopsy-based criteria.
- Elevated dd-cfDNA levels proved a robust non-invasive marker for graft injury, correlating with adverse outcomes and reinforced its predictive value for rejection, complementing current diagnostic practices.
- Future research should focus on mechanisms of DQ antibodies, long-term silent DSA outcomes, and advanced diagnostic tools like molecular diagnostics and AI-based pathology.

Limitations

- Limited number of rejection cases (<10%) reduces statistical power, particularly for subgroup analyses.
- Less than 2 years of follow-up may underestimate long-term impacts of DSA positivity and late AMR complications like cardiac allograft vasculopathy (CAV).
- Differences in treatment and induction protocols across centers introduce heterogeneity, potentially affecting outcome comparisons.

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Severe early graft dysfunction post-heart transplantation

Hoong SL, et al. *JHLT* 2025 Feb;44(2):161-170. | DOI: 10.1016/j.healun.2024.09.002

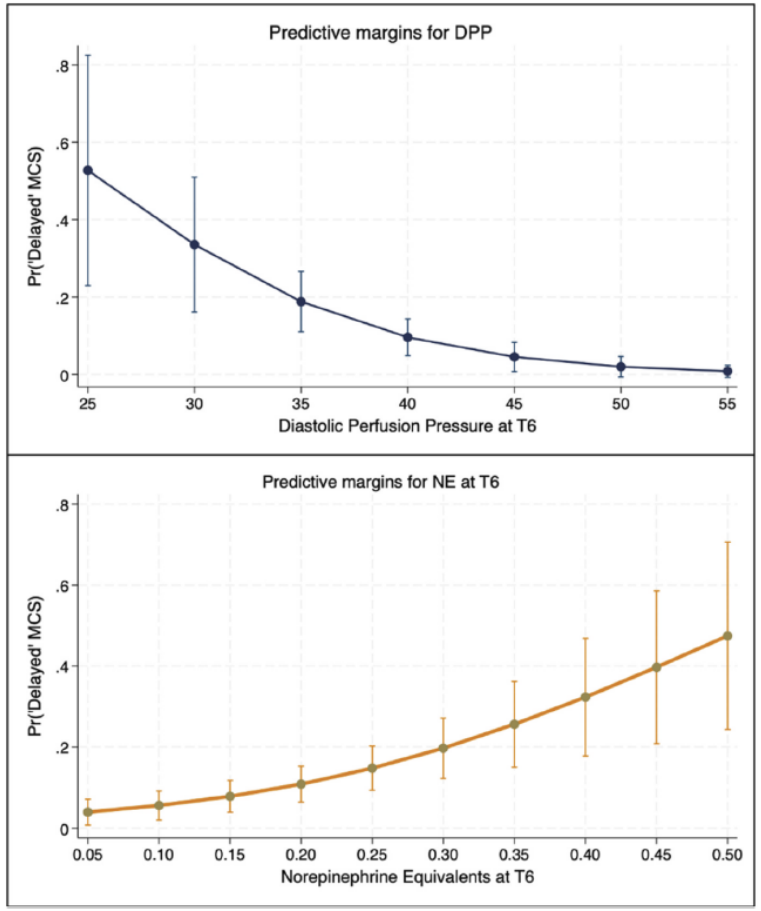
Study Highlights

Objective: To characterize clinical patterns of severe (primary) graft failure (use of mechanical circulatory support [MCS] as "immediate" intra-operative vs "delayed" following admission into ICU, and to describe their associated hemodynamic parameters.

Methods: Prospective study at 2 centres that included patients with a heart transplant (HT) between 2019 and 2022. Patients were divided into "no post-HT use of MCS", "immediate graft failure", and "delayed graft failure". Groups of immediate and delayed graft failure were compared.

Results: A total of 216 patients were included with 67 (31%) developing severe graft failure and thus requiring MCS. Overall, 1-year survival was 90%. Patients with immediate graft failure had longer warm ischemic time and longer cardiopulmonary bypass time likely due to more resternotomy and adult congenital heart disease as the aetiology. Mortality at 1 year was 34.9% in immediate graft failure and 8.0% in delayed graft failure ($p<0.001$). Predictors of delayed graft failure were diastolic perfusion pressure (diastolic pressure – central venous pressure) and norepinephrine equivalents at 6 hours after admission into the ICU. A greater proportion of patients in delayed graft failure were treated with milrinone and at higher doses.

Conclusions: Severe (primary) graft failure is characterized by 2 different clinical trajectories. Immediate severe graft failure was related to traditional risk factors such warm ischemic time whereas delayed graft failure was associated to measures suggesting vasoplegia as the aetiology.



Legend Probability of developing delayed graft failure based on diastolic blood pressure (DPP) at the top and norepinephrine equivalents at the bottom, both at 6 hours after admission into the ICU

Reviewer's Comments

- The proportion of patients experiencing severe graft failure and thus requiring MCS was greater than what's reported in the literature, likely suggesting a high-risk cohort.
- The differences in hemodynamic parameters between patients with no severe graft failure and delayed graft failure were small at admission to the ICU, but it was the trajectory over the first 6 hours what discriminated patients who developed graft failure.

Limitations

- The number of patients developing severe graft failure was relatively small.
- Intra-operative hemodynamic data was not available for analysis.
- Post heart-transplant management, including the decision to proceed with MCS was not standardized
- It is not clear if changes in hemodynamic parameters from hr0 to hr6 after admission in the ICU were included as predictors of delayed graft support
- Causes of death were not described.