**Retrospective Study on the Diagnostic Performance of MMDx, Histopathology, and Correlation of Cell-Free DNA with the Nebraska Medicine Rejection Risk Score in Heart Transplant Recipients**

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**Background:** Detecting heart transplant rejection remains challenging, with histopathology often missing biopsy-negative rejection cases. Newer diagnostic tools like MMDx and cell-free DNA (cfDNA) offer promise but require further evaluation. This study examines the agreement between MMDx and histopathology and develop a standardized approach using the Nebraska Medicine Rejection Score (NMRR) and assess its correlation with cfDNA levels.

**Methods:** The NMRR is a composite score based on five indicators: LVEF <50%, positive histopathology (>1R or C4D+), DSA, MMDx, and new-onset arrhythmia. Each component scores 1 point, except histopath (2 points). Kappa statistics assessed agreement between MMDx and histopathology, while Pearson correlation evaluated cfDNA’s relationship with NMRR and its components.

**Results:** Among 67 heart transplant patients (MMDx, n=67; histopathology, n=66), agreement between MMDx and histopathology was slight (kappa = 0.195, p = 0.1). cfDNA correlated significantly with NMRR (r = 0.383, p=0.001), particularly with MMDx (r = 0.546, p < 0.001), and moderately with histopathology (r = 0.300, p = 0.014), but not with DSA, LVEF, or arrhythmia (Table).

**Conclusion:** MMDx and histopathology show limited agreement, suggesting histopathology may miss rejection. cfDNA's correlation with NMRR, especially with MMDx, supports its potential in improving rejection detection.

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|  | | NMRR | MMDX | Histopath | DSA | LVEF<50% | new onset arrythmia |
| Cell-free DNA | Pearson Correlation | 0.383 | 0.546 | 0.300 | 0.145 | -0.159 | -0.061 | |
| Sig. (2-tailed) | 0.001 | 0.000 | 0.014 | 0.242 | 0.200 | 0.626 | |
| N | 67 | 67 | 66 | 67 | 67 | 67 | |