

Airway molecular signatures in antibody-mediated lung transplant rejection

Mohanty RP, Calabrese DR, Moghbeli K, Iasella CJ, et al. *Am J Transplant*. 2026 Jul;26(7):1661-1672. | DOI: [10.1016/j.ajt.2026.02.002](https://doi.org/10.1016/j.ajt.2026.02.002)

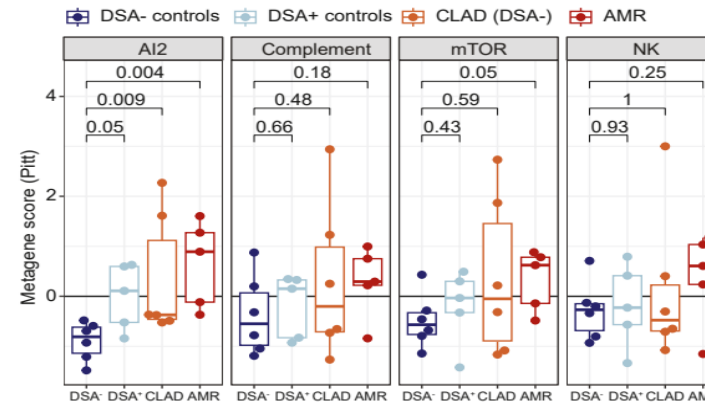
Study Highlights

Objective: This study analyzes airway inflammation gene signatures in AMR of the lung compared to matched controls.

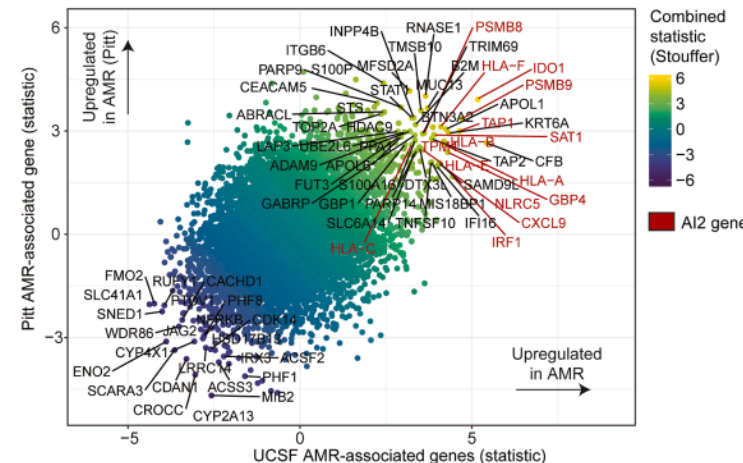
Methods: This two-center study of lung transplant recipients evaluated gene signatures of small airway brush RNA sequencing obtained from 16 AMR cases and 39 controls for four gene sets: airway inflammation 2 (AI2) score, complement, molecular target of rapamycin (mTOR), and natural killer (NK) cell response signature.

Results: AMR cases showed increased expression of the AI2 score, complement, and mTOR signaling pathways. AMR cases showed significantly elevated AI2 scores compared to controls ($P < .001$), with increasing AI2 scores associated with worse retransplant-free survival.

Conclusions: These data suggest that AMR cases were associated with transcriptional signatures more consistent with cellular rejection processes, as demonstrated in previous studies.



Metagene scores for pathways hypothesized to be associated with AMR were compared between AMR cases, donor specific antibody (DSA)- and DSA+ controls, and DSA- chronic lung allograft dysfunction (CLAD) samples.



Plotted pooled gene association scores for AMR. Both cohorts showed upregulation of similar genes in AMR.

Reviewer's Comments

- Lung transplant damage caused by AMR may occur via upregulation of complement, mTOR, or NK cell-mediated pathways, causing recognizable molecular signatures.
- The studied gene sets and results correspond with activation of the above pathways, as well as upregulation of genes associated with early chronic lung allograft dysfunction (AI2 score).
- The data suggest that AMR is associated with recognizable transcriptional pathways, which may provide future diagnostic and prognostic value.

Limitations

- Limited number and severity of AMR cases for the study.
- Different institutional definitions of AMR.
- Cases of severe AMR may not have been sampled due to clinical instability.
- AMR is thought to be injury involving alveolar capillary endothelium (not sampled on bronchial brushing).

Beyond Donor-Specific Antibodies: Molecular Characterization of Antibody-Mediated Rejection Using Tissue-Based Transcriptomics in Heart Transplantation

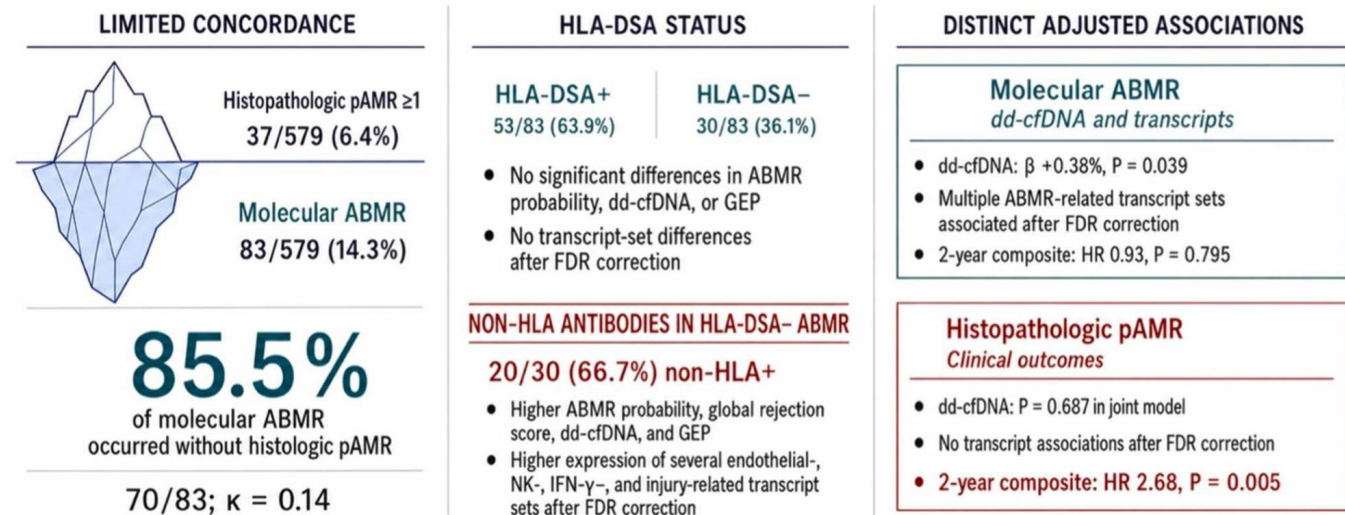
Valledor AF, Baranowska J, Hertz A, Moeller CM, et al. *JHLT* 31 Aug 2026. | DOI: [10.1016/j.healun.2026.08.015](https://doi.org/10.1016/j.healun.2026.08.015)

Study Highlights

- This study aimed to characterize Molecular Microscope Diagnostic System (MMDx)-defined antibody mediated rejection (AMR) according to donor specific antibody (DSA) status and to determine its association with outcomes.
- 579 consecutive for-cause cardiac transplant biopsies with paired MMDx and histopathological analyses were included.
- 83 (14.3%) biopsies showed MMDx-defined molecular AMR, of which 30 occurred in the absence of detectable HLA-DSA.
- DSA-negative and positive groups showed no significant difference in AMR probability, donor-derived cell free DNA (dd-cfDNA) levels, gene expression profiles (GEP) or transcriptomic profiles.
- Non-HLA antibodies were detected in 66.7% of HLA-negative molecular AMR cases and were associated with greater molecular rejection activity and dd-cfDNA levels.
- There was low concordance between molecular and histopathological AMR ($\kappa=0.14$).
- Whilst molecular AMR was associated with dd-cfDNA and transcriptomic activation, only histopathological AMR was significantly associated with clinical endpoints (2-year composite of death, re-transplantation, graft dysfunction, and subsequent rejection).

Molecular ABMR and Histopathologic pAMR: Limited Concordance and Distinct Associations

579 for-cause heart transplant biopsies with molecular and histopathologic assessment



Reviewer's Comments

- This study provides evidence that molecular diagnostics captures early, tissue-based parameters of immune-mediated allograft injury that are not detected by histology alone in a relatively large cohort of for-cause cardiac transplant biopsies.
- The findings support a conceptual framework in which AMR may manifest as a continuum of intragraft molecular activation, dd-cfDNA release, histomorphological damage and allograft dysfunction, where molecular, serological and pathological assessments provide different diagnostic and prognostic information.
- The clinical significance of MMDx-defined AMR remains unclear given the lack of association with outcomes. Future prospective studies are needed to assess if early molecular AMR detection improves longer term outcomes in for-cause and surveillance biopsy cohorts.

Limitations

- The study included for-cause endomyocardial biopsies only, which may impact translation of findings to routine surveillance cohorts with lower pre-test rejection risk.
- This was a single center study and histological grading of AMR is influenced by center and pathologist, which may limit the external validity of the conclusions.
- Quantification of circulating DSA, non-HLA antibodies, dd-cfDNA, and GEP was not standardized or available across the entire study cohort.
- Follow-up was variable and possibly insufficient to assess progression to cardiac allograft vasculopathy.

Acute cellular rejection after heart transplantation: validation of HEARTBiT, a transcriptomic biomarker

Shannon CP, Assadian S, Rajasekaran A, Yang C, et al. *European Heart Journal* 29 Sep 2026. ehag751. | DOI: [10.1093/eurheartj/ehag751](https://doi.org/10.1093/eurheartj/ehag751)

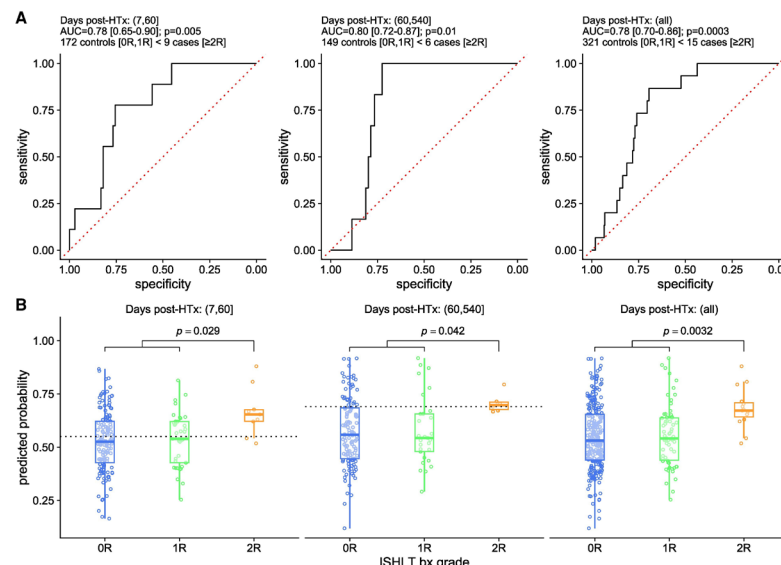
Study Highlights

Objective: This study aims to prospectively validate HEARTBiT, a blood transcriptomic biomarker used to detect moderate-to-severe ACR (ISHLT grade $\geq 2R$) within the first 60 days post-transplant, when the risk for ACR is highest.

Methods: A prospective, multicenter diagnostic accuracy study evaluated a nine-gene expression signature associated with cellular rejection, generating a HEARTBiT score from 0 (low concern) to 1 (high concern). The study analyzed 336 paired blood samples and endomyocardial biopsies (EMB) from 117 participants, using consensus grading by pathologists as the reference standard. The primary outcome was detection of $\geq 2R$ ACR. An exploratory longitudinal analysis assessed whether changes in HEARTBiT preceded histology-detected rejection.

Results: Overall AUC was 0.78 (95% CI 0.70–0.86); 0.78 at ≤ 60 days and 0.80 beyond 60 days. At ≤ 60 days (using prespecified threshold of >0.54): sensitivity 88.9%, specificity 55.8%, NPV 99.3%, PPV 6.8%. Beyond 60 days (with the same threshold): 100% sensitivity and 49.0% specificity.

Conclusions: These data suggest a low HEARTBiT score can identify patients at low risk of moderate-severe ACR and potentially avoid an invasive biopsy. The exploratory finding that HEARTBiT may rise before biopsy-detected rejection raises the possibility that serial testing could identify patients at increasing risk before biopsy becomes positive.



- A) ROC curves showing diagnostic accuracy of HEARTBiT for moderate-to-severe acute cellular rejection (ISHLT $\geq 2R$) and ability to distinguish from grade 0R/1R according to time after transplant.
- B) Distribution of HEARTBiT predicted probabilities according to biopsy rejection grade, demonstrating higher HEARTBiT values among patients with $\geq 2R$ rejection. The prespecified decision threshold of 0.54 and exploratory threshold of 0.68 are shown.

Reviewer's Comments

- The high negative predictive performance of HEARTBiT suggests that the assay could potentially reduce the frequency of surveillance EMBs.
- It is important to note that this biomarker is a rule-out test, not a stand-alone diagnostic marker. With a PPV of 6.8%, a high score does not establish ACR and would require biopsy assessment.
- Although HEARTBiT is described as a T-cell biomarker, several genes in the panel are associated with neutrophil, mast-cell or acute-phase transcripts. Thus, non-ACR inflammation or infection could pose as possible confounders that require further exploration.

Limitations

- Several authors are named on the HEARTBiT patent.
- Among the 336 visits, only 15 visits (4.5%) demonstrated $\geq 2R$ ACR. The high NPV of 99.3% is a product of the low prevalence. If the test is applied in a higher prevalence setting, the rule-out performance would likely be worse.
- All participants were adults, so the findings cannot be extrapolated to pediatric heart transplant recipients.
- Although biopsies underwent centralized expert review, histology remains an imperfect reference standard. The exploratory longitudinal analysis also relied on locally graded biopsies rather than centralized consensus review.