

Supplemental Digital Content

Table S1. Bootstrapped AUROC and diagnostic accuracy measures for acute rejection (AR, acute cellular rejection (ACR) + antibody-mediated rejection (AMR)) vs stable and combined (AR + chronic lung allograft dysfunction/neutrophilic-responsive allograft dysfunction (CLAD/NRAD) + allograft infection (INFXN)) vs the stable cohort (dd-cfDNA fraction thresholds of 0.50%-1.25%).

a) AR vs stable (AUROC: 0.91 (95% CI:0.83, 0.98))

	0.50%	0.75%	1.00%	1.25%
Sensitivity	94.73% (86.35-100.00%)	90.63% (78.70-100.00%)	89.06% (76.17-100.00%)	85.13% (70.24-100.00%)
Specificity	52.67% (39.98-65.36%)	75.85% (64.98-86.72%)	82.86% (73.29-92.44%)	88.76% (80.73-96.78%)
PPV	29.38% (23.52-35.24%)	43.83% (32.28-55.37%)	51.93% (37.52-66.34%)	61.15% (43.69-78.61%)
NPV	97.96% (94.75-100.00%)	97.50% (94.37-100.00%)	97.33% (94.25-100.00%)	96.63% (93.36-99.90%)

b) Combined vs stable. (AUROC 0.76 (95% CI: 0.66-0.85))

	0.50%	0.75%	1.00%	1.25%
Sensitivity	77.39% (65.49-89.30%)	65.52% (51.99-79.05%)	59.92% (45.96-73.87%)	53.22% (39.01-67.43%)
Specificity	54.44% (41.15-67.74%)	76.43% (65.12-87.75%)	83.87% (74.06-93.68%)	89.78% (81.71-97.84%)
PPV	26.10% (19.74-32.46%)	36.63% (24.49-48.76%)	43.57% (27.56-59.58%)	51.97% (31.18-72.76%)
NPV	92.05% (87.81-96.30%)	91.43% (88.14-94.71%)	90.96% (87.94-93.98%)	90.23% (87.43-93.02%)

Table S2. Bootstrapped diagnostic accuracy measures for ACR vs the stable cohort, AMR vs the stable cohort and combined rejection (AR+ chronic lung allograft dysfunction/neutrophilic-responsive allograft dysfunction (CLAD/NRAD)) vs the stable cohort (dd-cfDNA fraction threshold $\geq 1.0\%$).

	ACR vs Stable	AMR vs Stable	Combined Rejection vs Stable
AUROC	0.87 (0.76-0.98)	0.96 (0.92-1.00)	0.79 (95% CI:0.69-0.89)
Sensitivity	82.9% (95% CI:63.5-100%)	100% (95% CI:80.55-100%)	67.7% (95% CI:52.4-83.0)
Specificity	82.2% (95% CI:72.5-91.9%)	82.5% (95% CI:73.3-91.7%)	84.1% (95%CI: 74.8-93.5)
PPV	49.2% (95% CI:34.4-64.0%)	54.3% (95%CI: 41.2-67.3%)	47.0 (95% CI: 31.3-62.7)
NPV	95.9% (95% CI:91.3-100%)	100% (96.7%-100%)	92.6 (95% CI: 89.3-96.0)

Table S3. Bootstrapped AUROC and diagnostic accuracy measures for acute rejection (AR, acute cellular rejection (ACR) + antibody-mediated rejection (AMR)) vs the stable cohort, and combined (AR+ chronic lung allograft dysfunction/neutrophilic-responsive allograft dysfunction (CLAD/NRAD) + allograft infection (INFXN)) vs the stable cohort with correction for single and double lung-transplant (dd-cfDNA fraction thresholds of 0.50%-1.25%).

a) AR vs stable (AUROC: 0.90 (95% CI:0.83-0.98))

	0.50%	0.75%	1.00%	1.25%
Sensitivity	94.74% (86.36-100%)	90.67% (78.75-100%)	89.06% (76.18-100%)	85.13% (70.23-100%)
Specificity	48.31% (35.61-61.01%)	71.20% (59.70-82.71%)	79.07% (68.72-89.41%)	87.91% (79.63-96.19%)
PPV	27.59% (22.37-32.81%)	39.56% (29.51-49.61%)	46.93% (34.11-59.75%)	59.41% (42.37-76.45%)
NPV	97.79% (94.29-100%)	97.35% (94.02-100%)	97.20% (93.99-100%)	96.60% (93.30-99.90%)

b) Combined vs stable. (AUROC 0.76 (95% CI: 0.67-0.86))

	0.50%	0.75%	1.00%	1.25%
Sensitivity	80.56% (69.30-91.82%)	68.36% (55.12-81.60%)	64.84% (51.24-78.44%)	59.23% (45.24-73.22%)
Specificity	50.55% (37.21-63.89%)	72.27% (60.33-84.21%)	80.64% (70.10-91.18%)	88.84% (80.46-97.22%)
PPV	25.30% (19.56-31.04%)	33.88% (23.31-44.46%)	41.04% (26.92-55.16%)	52.46% (32.82-72.09%)
NPV	92.60% (88.23-96.96%)	91.66% (88.22-95.10%)	91.69% (88.58-94.80%)	91.29% (88.46-94.12%)

Figure S1

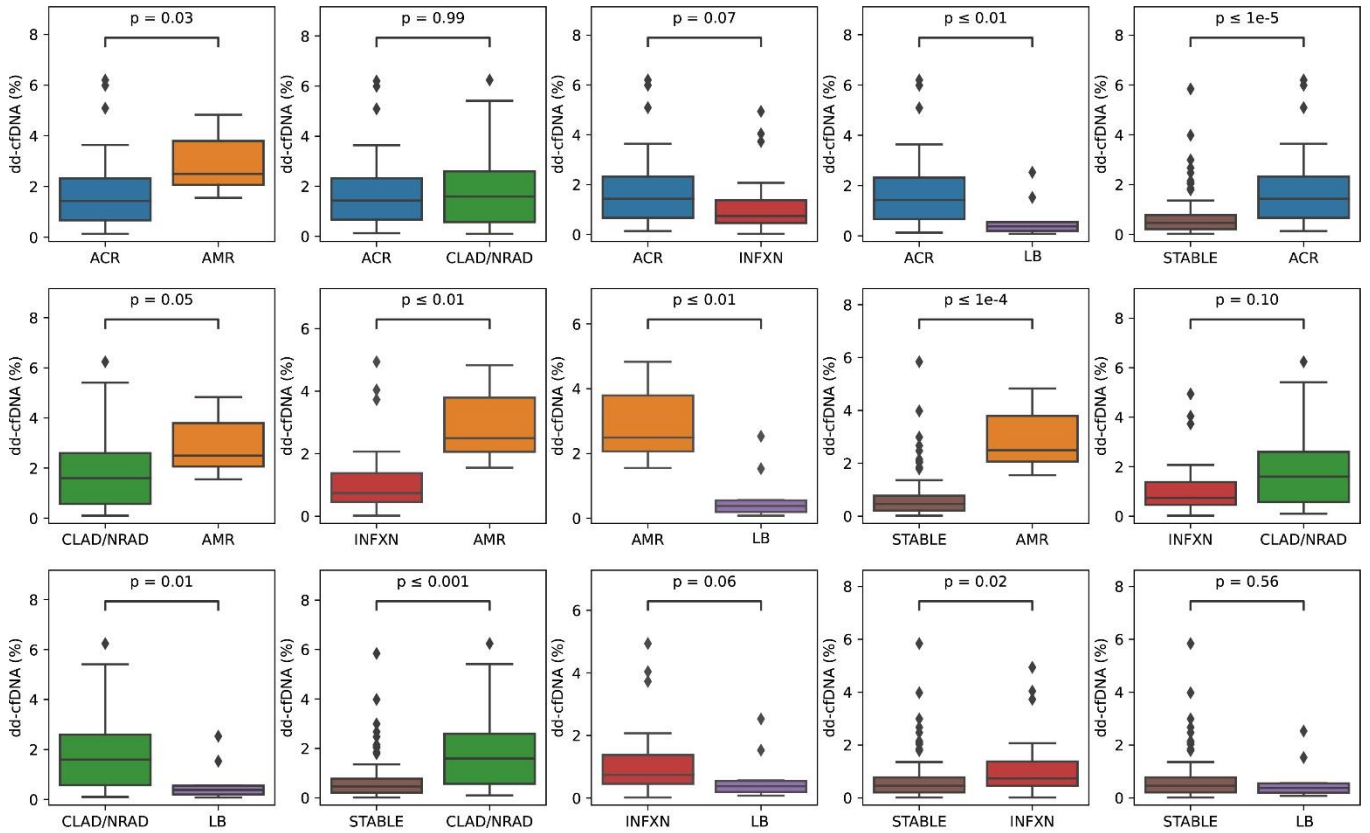


Figure S1: Mann-Whitney-Wilcoxon U test results for dd-cfDNA fraction (%) across clinical-pathologic diagnostic cohorts: acute cellular rejection (ACR), antibody-mediated rejection (AMR), chronic lung allograft dysfunction/neutrophilic-responsive allograft dysfunction (CLAD/NRAD), allograft infection (INFXN), lymphocytic bronchiolitis (LB), and the stable cohort.