Table S1. List of abbreviations and their definitions

Abbreviation	Definition
AA	archetypal analysis
AMR	antibody-mediated rejection
AMATs	alternative macrophage activation transcripts
ATAGC	Alberta Transplant Applied Genomics Centre
AUC	area under the curve
BAT	B cell-associated transcripts
CAV	cardiac allograft vasculopathy
cIRIT	cardiac injury and repair transcripts
DAMP	damage-associated molecular pattern transcripts
DSA	donor-specific antibody
EMB	endomyocardial biopsy
HT	heart parenchymal transcripts
HT1	heart parenchymal transcripts set 1
HT2	heart parenchymal transcripts set 2
IGT	immunoglobulin transcripts
INTERHEART	Diagnostic and Therapeutic Applications of Microarrays in Heart Transplantation, a Multicenter Study (ClinicalTrials.gov Identifier: NCT02670408)
Injury archetype	archetypal model for assessing cardiac injury
IRRAT	injury-and-repair transcripts
IRITD3	injury-repair induced transcripts day 3
IRITD5	injury-repair induced transcripts day 5
ISHLT	International Society for Heart and Lung Transplantation
LVEF	left ventricular ejection fraction
MCAT	mast cell transcripts
MMDx	Molecular Microscope Diagnostic System
NR	no rejection
NR-Early injury	no rejection with early posttransplant injury
NR-Minor	no rejection with minor injury
NR-Normal	no rejection biopsies
NRI	net classification indices
pABMR	possible AMR
PCA	principal component analysis
PC1	principal component 1
PC2	principal component 2
pTCMR	possible TCMR
RATs	rejection-associated transcripts
SOC	standard-of-care
TCMR	T cell-mediated rejection

Table S2. Biopsy characteristics and patient demographics

Biopsy characteristics	All (1320 biopsies)
Days to biopsy posttransplant (TxBx)	
Mean	759
Median (range)	184 (4 – 10 150)
Days to most recent follow-up after biopsy	
Mean	644
Median (range)	313 (1 – 3854)
Indication for biopsy	
Clinical including follow-up (% of known)	327 (25%)
Protocol biopsy (% of known)	824 (62%)
Not stated (% of total)	169 (13%)
Patient demographics	All (645 patients)
Mean patient age (range)	49 (1 – 80)
Age > 65 years (Count)	56
Mean donor age (range)	41 (6 – 71)
Patient sex	
Male (% of known)	446 (69%)
Female (% of known)	197 (31%)
Unknown	2
Donor sex	
Male (% of known)	326 (67%)
Female (% of known)	159 (33%)
Not available (% of total)	160 (25%)
Patient had a previous failed heart transplant	4 (1%)
Heart status at last follow-up	
Alive at last follow-up (% of known)	475 (88%)
Deceased (% of known)	60 (11%)
Failed and retransplanted (% of known)	4 (1%)
Not available (% of total)	106 (17%)
Primary disease[a]	
Dilated Cardiomyopathy (% of known)	284 (44%)
Hypertrophic Cardiomyopathy (% of known)	32 (5%)
Restrictive Cardiomyopathy (% of known)	14 (2%)
Other Cardiomyopathies	48 (7%)
Congenital Heart Defect (% of known)	33 (5%)
Coronary Artery Disease (% of known)	91 (14%)
Other (% of known)	143 (22%)
Not available (% of total)	0 (0%)

[a]Some patients received more than one primary diagnosis

Table S3. Histologic diagnoses and modified archetype sign-outs in 1320 endomyocardial biopsies

Histology diagnosis[a]		N (% of 1320)
No Rejection		519 (39%)
TCMR		113 (9%)
AMR		71 (5%)
Mixed (AMR + TCMR)		14 (1%)
All AMR (including Mixed)		***85 (6%)***
Possible TCMR		411 (31%)
Possible AMR		150 (11%)
Incomplete		42 (3%)
Modified rejection sign-out categories[b]		**N (% of 1320)**
NR-Normal		462 (35%)
NR-Minor		359 (27%)
NR-Early-injury		32 (2%)
TCMR-related including mixed	Mixed	13 (1%)
	TCMR	76 (6%)
	Possible TCMR	38 (3%)
AMR-related (no TCMR)	AMR	179 (14%)
	Possible ABMR	161 (12%)

[a] Biopsy labels were converted as follows:
pAMR1, pAMR1I+, pAMR1H+   Possible AMR
pAMR2, pAMR3   AMR
TCMR2R, TCMR3R   TCMR

[b] Halloran PF, Madill-Thomsen KS, Aliabadi-Zuckermann A, et al. Many heart transplant biopsies currently diagnosed as no rejection have mild molecular antibody-mediated rejection-related changes. *J Heart Lung Transplant.* 2021;In press. https://doi.org/10.1016/j.healun.2021.08.004.

Table S4. Added 3-year graft survival predictive value of injury archetype scores vs rejection archetype scores.

Prediction tested	Type of test	Comparison	Result	P value[c]
3-year graft survival	Multivariable Cox regression	Injury archetype scores[b] + rejection archetype scores[a]	Injury scores **add** predictive value compared to rejection archetype scores alone.	3.8E-5
		Rejection archetype scores[a] + Injury archetype scores[b]	Rejection archetype scores **add** predictive value to injury scores alone.	2.6E-5

[a] Rejection archetype scores include the TCMR, AMR, Early-injury (injury without rejection), and Minor.

[b] Injury archetype scores include the Mild-injury, Moderate-injury, Severe-injury, and Late-injury scores.
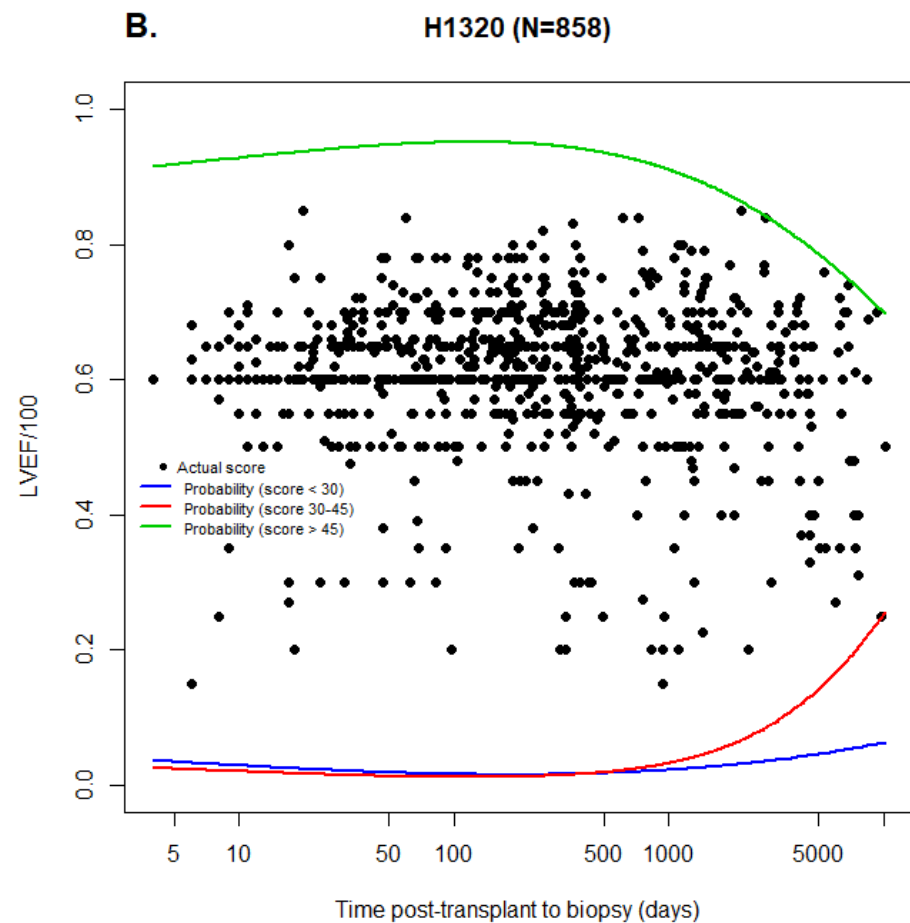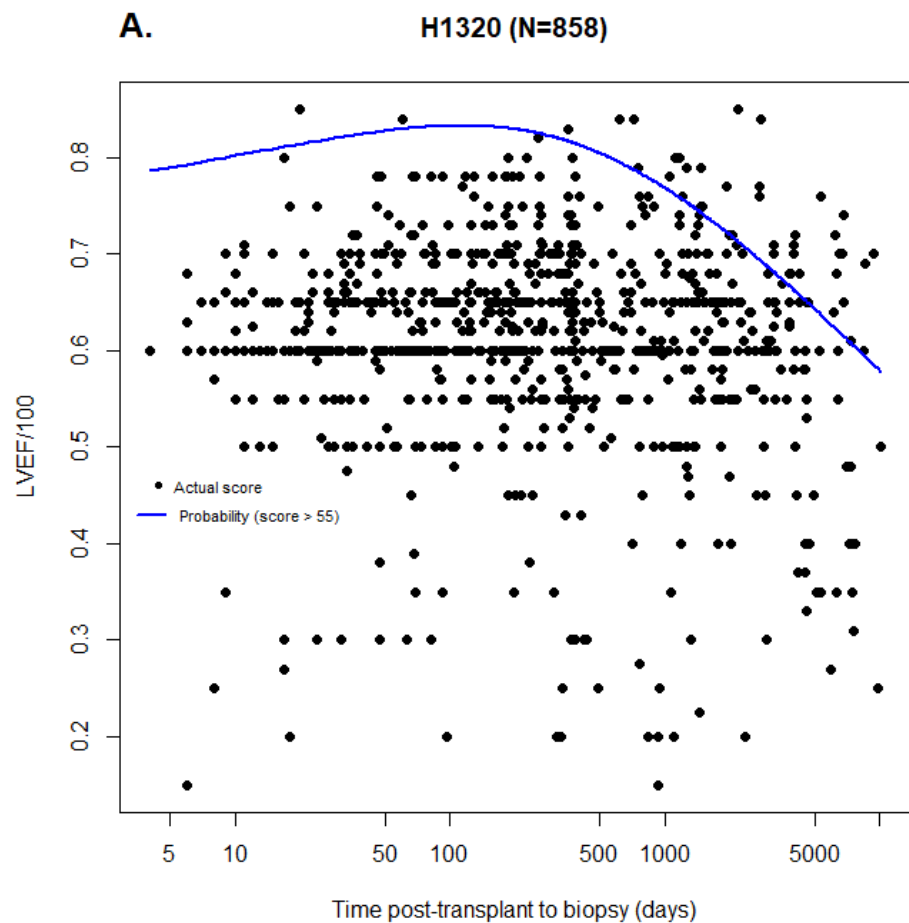
[c] Comparisons done by likelihood ratio tests.

Figure S1. Relationships between injury-induced transcript set scores, time posttransplant, and archetypal injury states. The biopsy population is plotted by the LVEF/100 values (y-axis) and time posttransplant (x-axis). Actual scores are represented by black dots, while the probability that the biopsy's LVEF will be **A)** greater than 55, or **B)** with 3 thresholds at <30, 30-45, or >45 are shown as splined lines.