Low Variability in Gene Expression Profile Scores Are Associated with Decreased Risk of Adverse Events Post Heart Transplantation: The Mid America Experience

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INTRODUCTION

Endomyocardial biopsy (EMB) is considered the "gold standard" for orthotopic heart transplant (OHT) rejection surveillance. However, EMBs are invasive, uncomfortable for patients, suffers from between-reader variability, and can be affected by sampling errors.

Recent developments in gene expression profiling (GEP) have offered a non-invasive rejection surveillance method[1]. GEP is done by a simple blood test measuring the activity of a 20-gene panel (11 informative genes, 3 normalization genes, 6 control genes). The combined activity of these 11 informative genes yields a linear discriminate algorithm (LDA) score. This is then converted into an ordinal GEP between 0-40 for clinical use using the coefficients included in Table 1. A score less than 34 more than 6 months post OHT is associated with a 99% negative predictive value for rejection. Patients with higher scores undergo EMB and have a 5% risk of rejection.

CARGO II was a large European study of the use of GEP in post OHT rejection surveillance[2]. They hypothesized that the variability in GEP score over time may indicate a more active immune system and may be associated with adverse events[3]. They evaluated a new variable: the GEP Variability Score (GVS). GVS is currently defined by calculating the standard deviation of 4 consecutive LDA scores. A high GVS (over 1.5) has been associated with a higher risk for the Invasive Monitoring Attenuation through Gene Expression (IMAGE[4]) study endpoints (death, re-transplant, and graft failure) for OHT patients within 3 years after the last GEP score[3]. In a recent study at our institution, we observed that a GVS>1.25 calculated from 3 GEP scores (directly preceding the event/most recent if no event) was associated with higher risk for IMAGE outcomes within 20 months of the most recent GEP test[5]. However, myocardial infarction and percutaneous coronary intervention risks have not been evaluated using GVS.

METHODS

PORTRAIT:

- This study is a retrospective review of 391 OHTs performed at Saint Luke's Hospital's Mid-America Heart Institute from January 1, 2007 through December 31, 2016.
- **Hypothesis:** A GEP Variability Score calculated with 3 consecutive LDA scores can predict negative composite outcomes post-transplant according to the IMAGE study along with myocardial infarction and percutaneous intervention.

STUDY POPULATION:

- Our center has been consistently using GEP since 2007 to reduce the number of EMBs using the GEP test beginning at 6 months post OHT (2007) and then 4 months post OHT (2008).
- Between 1/1/2007 and 12/31/2016, 387 patients underwent 391 OHTs at our institution.
- **Inclusions:** We included all patients who had at least 3 consecutive GEP scores beginning at month 6 before they experienced an event or to the date of censure (10/21/2017) (n=354).
- **Exclusions:** Less than 3 consecutive GEP scores after 6 months post OHT (n=36), or an event before 6 months post OHT (n=1).
- 73 out of 354 (21.0%) OHT recipients had an IMAGE-defined event (hemodynamically significant rejection, death, or re-transplant), myocardial infarction, or percutaneous coronary intervention. Of the total 73 events, 5 had antibody mediated rejection with hemodynamic compromise, 3 had acute cellular rejection with hemodynamic compromise, 15 had biopsy negative rejection with hemodynamic compromise, 0 had re-transplant, 29 had death, 3 had myocardial infarction, and 18 had percutaneous coronary intervention.
- Pts were separated into 3 risk groups based on percentiles [(low <20th, GVS <.0.6), (moderate 20th-80th, GVS 0.6-1.5) (high >80th, GVS > 1.5)].

DATA COLLECTION:

- LDA scores, and event data were collected on each patient.
- A patient had a "composite outcome" if one of the following occurred: antibody mediated rejection with hemodynamic compromise, acute cellular rejection with hemodynamic compromise, biopsy negative rejection with hemodynamic compromise, re-transplant, death, myocardial Infarction, or percutaneous coronary intervention.
- Hemodynamic compromise was considered a proportional decrease in ejection fraction of ≥25% from baseline or absolute drop in ejection fraction ≤30% at the time of the rejection episode.
- If patients had multiple composite outcomes, the first event was used.

STATISTICAL ANALYSIS:

- GVS was calculated using the standard deviation of the 3 consecutive LDA scores preceding the composite outcome or the day of censure if no event (Table 1).
- Continuous variables were compared using Student's t-test (Table 2).
- Categorical variables were compared using chi-square or Fisher's exact test (Table 2).
- Kaplan-Meier curves were compared via log rank statistic (Figure 1).
- Youden index was used to determine point that maximizes sensitivity and specificity on the receiver-operator curve (ROC) curve.
- A time to first event analysis was performed using a multivariable Cox model adjusted for age, OHT technique, and donor gender mismatch (Figure 2).

DISCLOSURES

- Andrew Kao: G; C; Respicardia, CareDx, Sensible Medical, BioVentrix.

RESULTS

Table 1. Variables and Equations

Variable	Equation
Linear Discriminate Algorithm (LDA)	LDA= 105.96 +1.413 * C_T{IL1R2,FLT3,ITGAM} -1.639 * C_T{MIR,WDR40A} +0.344 * C_T{PF4,G6b} -1.340 * C_T{ITGA4} -0.838 * C_T{PDCD1} -0.684 * C_T{RHOU} -0.739 * C_T{SEMA7A}
Gene Expression Profile (GEP) Score	$GEP\ Score = 40x \frac{e^{(0.234+0.408XLDA)}}{1+e^{(0.234+0.408XLDA)}}$
Gene Expression Profile Variability Score (GVS)	$GVS = \sigma = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N}(x_i-\mu)^2}$

Table 2. Baseline Demographics of OHT Patients with vs. without a Composite Outcome

	Total	Composite Outcome		P-Value
		Yes	No	
	n = 354	n = 73	n = 281	
Female Gender	85 (24.0%)	16 (21.9%)	69 (24.6%)	0.638
Age at Transplant (years)	51.56 ± 12.39	46.29 ± 14.39	52.92 ± 11.46	< 0.001
Ischemic Time (minutes)	165.40 ± 51.99	162.58 ± 51.60	166.13 ± 52.16	0.603
Transplant Technique				0.023
Biatrial	16 (4.5%)	4 (5.5%)	12 (4.3%)	
CMBA*	181 (51.1%)	47 (64.4%)	134 (47.7%)	
Bicaval	157 (44.4%)	22 (30.1%)	135 (48.0%)	
Annuloplasty (at Transplant)	331 (93.5%)	64 (87.7%)	267 (95.0%)	0.023
Pre-transplant PVR (Woods units)	1.94 ± 0.83	2.01 ± 0.88	1.92 ± 0.81	0.454
Calculated GVS	1.09 ± 1.67	1.54 ± 3.48	0.98 ± 0.58	0.010

*CMBA= Cabrol Modified Biatrial

Figure 1. 6-year Freedom from Composite Outcome for Cardiac Transplants with Low, Intermediate, and High GVS

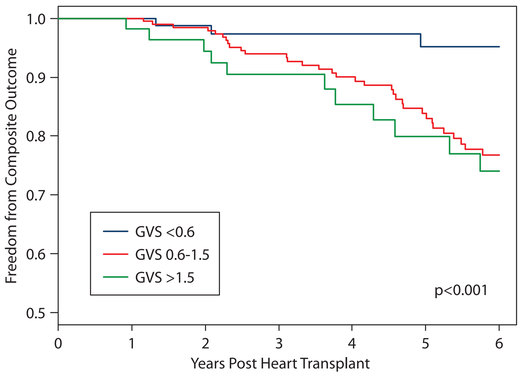
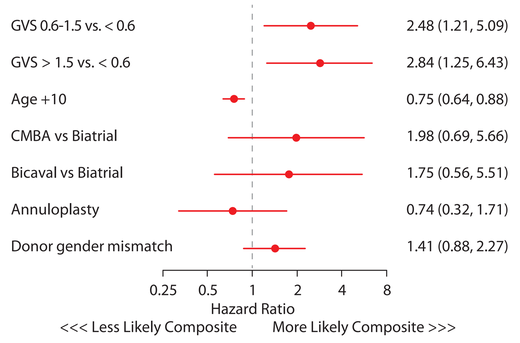


Figure 2. Impact of Different Factors on Likelihood of Experiencing Composite Outcomes



CONCLUSION

GVS based on 3 consecutive GEP scores beginning at 6 months post OHT can predict IMAGE outcomes plus MI and PCI post OHT. When compared to the low risk group, the high risk group [HR=2.84 (1.25, 6.43) p<0.02] and moderate risk group [HR=2.48 (1.21, 5.09) p<0.02] experienced significantly more composite outcomes. GVS <0.6 was associated with low risk of adverse events.

LIMITATIONS

- This study is a retrospective single-center review and thus has the limitations of a non-randomized work. However, these patients were cared for using the same protocol-driven care and were not subject to any selection bias.
- Larger multi-center studies of this will be needed to further validate these findings.

REFERENCES

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