

Clinical Validation of a Novel Assay for Galectin-3 for Risk Assessment in Acutely Destabilized Heart Failure

Christopher deFilippi*, Robert Christenson*, Ravi Shah†, Anju Bhardwaj†, and James L. Januzzi†

* University of Maryland School of Medicine, Baltimore, MD

† Massachusetts General Hospital, Harvard University, Boston, MA

Disclosures

- Christopher deFilippi: Siemens^{1,2,3}, Roche Diagnostics^{1,2,3}, BG Medicine^{1,2}
- Robert Christenson: Siemens^{1,2,3}, BG Medicine^{1,2,3}
- James Januzzi: Siemens^{1,2,3}, Roche Diagnostics^{1,2,3}, BG Medicine^{1,2}
- Ravi Sah: Nothing to disclose
- Anju Bhardwaj: Nothing to disclose

1. Grant support
2. Consulting
3. Speaking honorarium

Galectin-3 background

- Galectin-3 is a structurally unique 30 kDa member of a family of multifunctional beta-galactoside-binding lectins
- Expression of galectin-3 has been associated with the epithelium and inflammatory cells including macrophages, neutrophils and mast cells
- Galectin-3 has been implicated in a variety of biological processes important in heart failure including myofibroblast proliferation, fibrogenesis, tissue repair, cardiac remodeling, and inflammation
- Extracellular gal-3 mediates cell migration and cell-cell interactions
- Induces cardiac fibroblast proliferation, collagen I deposition and ventricular dysfunction

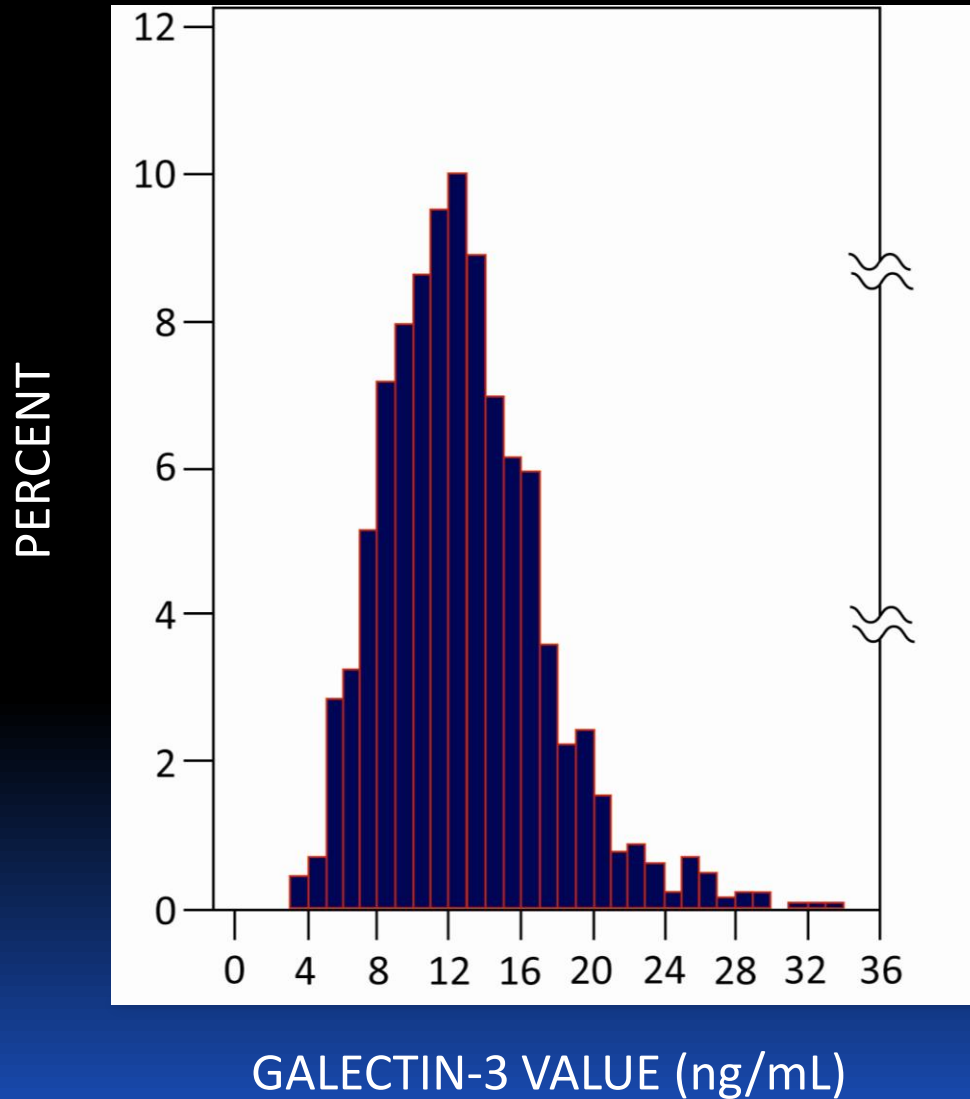


*Galectin-3 (human) structure
[source: Consortium for Functional
Glycomics]*

Development of a high-precision galectin-3 ELISA assay

- Equivalent values for serum or EDTA plasma specimens
- Limit of Detection = 1.13 ng/mL; Limit of Quantitation = 1.32 ng/mL (at CV of 20%)
- Total Imprecision
 - 11.98% at 6.1 ng/mL; 7.66% at 20.7 ng/mL; 7.95% at 72.2 ng/mL
- Measurement range: 1.32 to 96.6 ng/mL
- Stability of stored samples
 - 15 days at room temperature (22—28°C) or refrigerated (2—8°C)
 - At least 6 months at either -20°C or -70°C
 - At least 6 freeze-thaw cycles

Galectin-3 normal reference interval




In a study of 1,099 healthy volunteers, the mean (\pm SD) plasma galectin-3 level was 13.3ng/mL (\pm 6.6ng/mL) with a median value of 12.4ng/mL. The 97.5th percentile level of galectin-3 was 26.2ng/mL.



Hypothesis

“Galectin-3, a lectin involved in inflammation and fibrosis, will be independently prognostic for long-term mortality in patients with acute decompensated heart failure, and additive to other biomarkers of risk for this indication.”





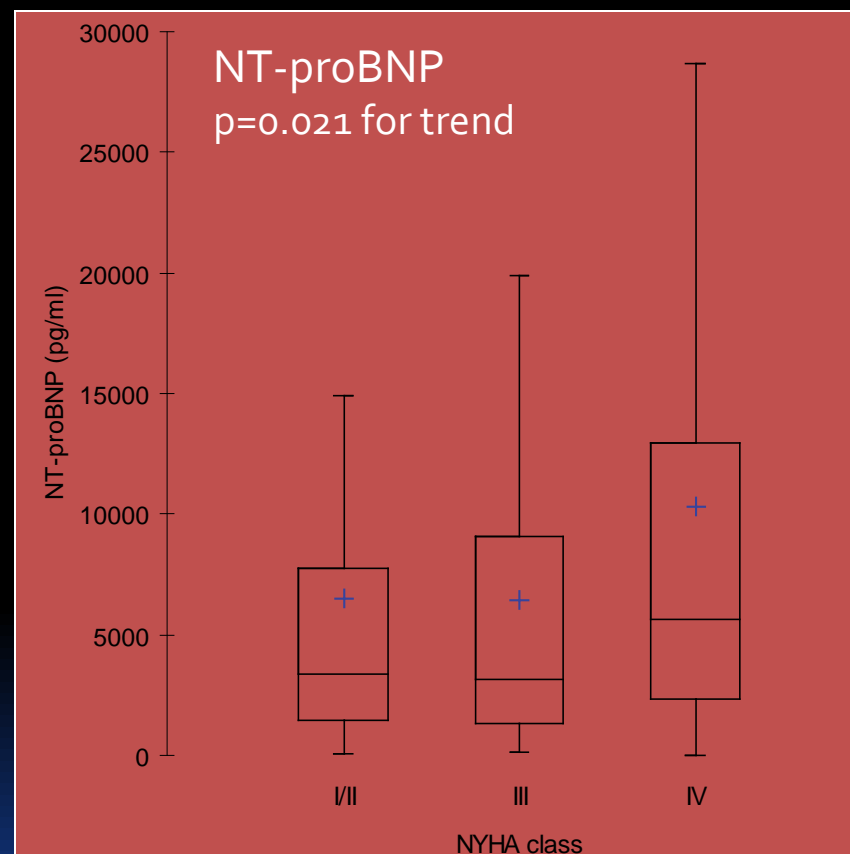
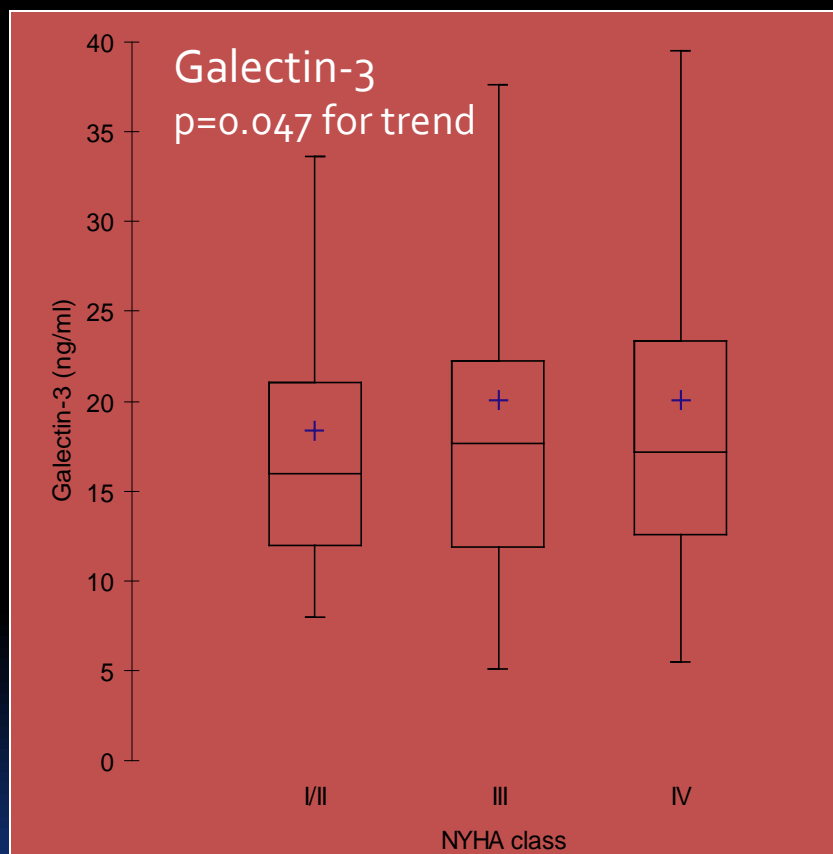
Methods

- 310 patients presenting to the ED with dyspnea and ultimately the adjudicated diagnosis of acute decompensated heart failure (ADHF)
- Galectin-3 and NT-proBNP measured during index presentation to the ED
- Patients followed for up to four years for all-cause mortality
- Independent prognostic value and synergism of the two biomarkers for mortality was determined

Baseline characteristics

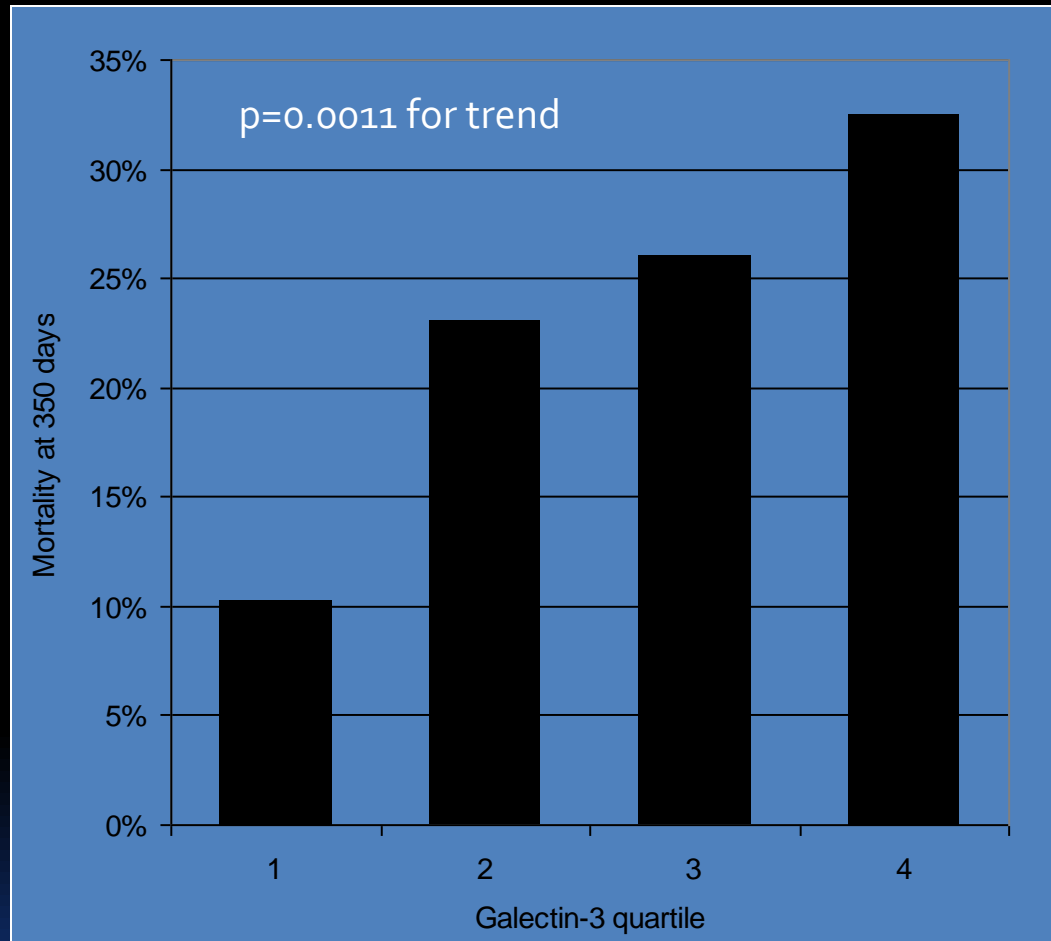
Number of Subjects, N	310
Age, mean (SD), yrs	68.2 (14.4)
Female, N (%)	120 (39%)
Race, N (%)	
Caucasian	215 (69%)
Black	85 (27%)
Hispanic	9 (3%)
Other	1 (1%)
NYHA, N (%)	
Class I	22 (7%)
Class II	40 (13%)
Class III	125 (40%)
Class IV	122 (39%)
LVEF, mean (SD)	44.2 (17.9)
BMI, mean (SD), kg/m ²	29.2 (7.6)
Hypertension, N (%)	214 (69%)
Diabetes, N (%)	130 (42%)
Smoker, N (%)	63 (20%)
NT-proBNP, median (IQR), pg/ml	4204 (1756-9883) [based on N=270 values]
Galectin-3, median (IQR), ng/ml	17.1 (12.0-22.3)

Galectin-3 and NT-proBNP by NYHA class



(blue crosses represent means)

Mortality at 350 days, by galectin-3 quartile



Total Deaths/Number in Category:

1: 8/78

2: 18/78

3: 20/77

4: 25/77

TOTAL: 71 deaths at T=350 days out of 310 subjects

Galectin-3 baseline quartiles:

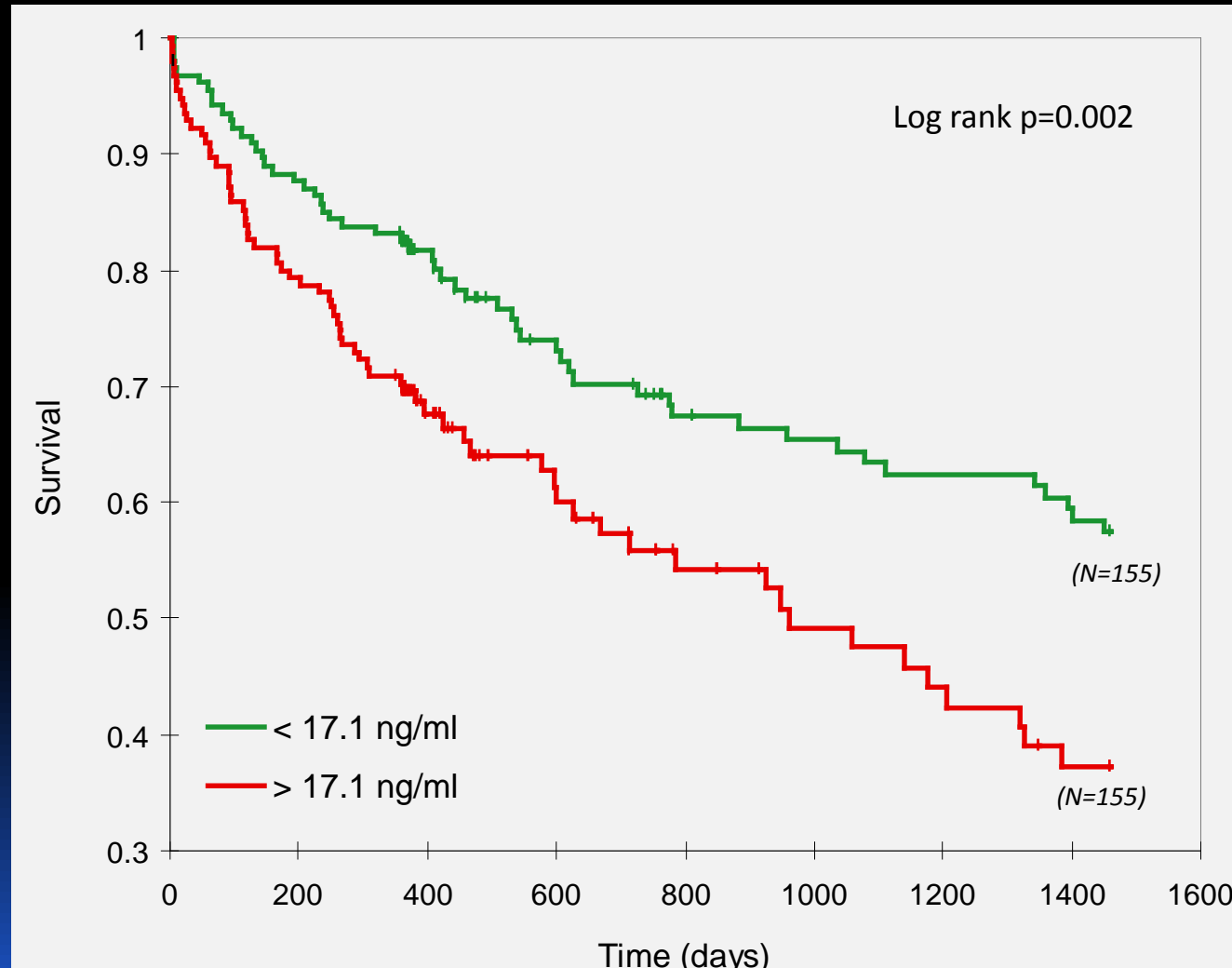
1: < 12.0 ng/ml

2: 12.0-17.1 ng/ml

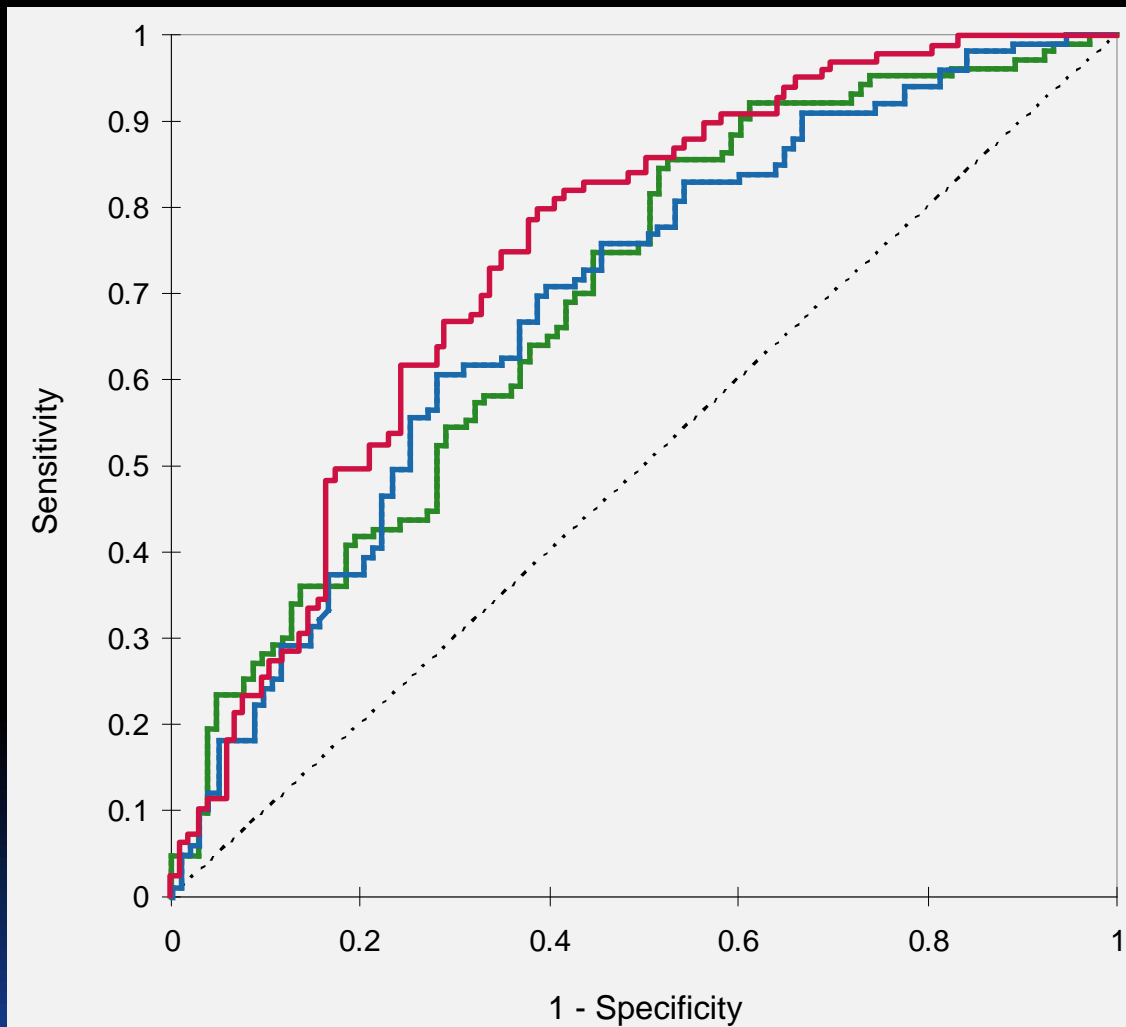
3: 17.2-22.3 ng/ml

4: > 22.3 ng/ml

Kaplan Meier curves for survival, by galectin-3 median



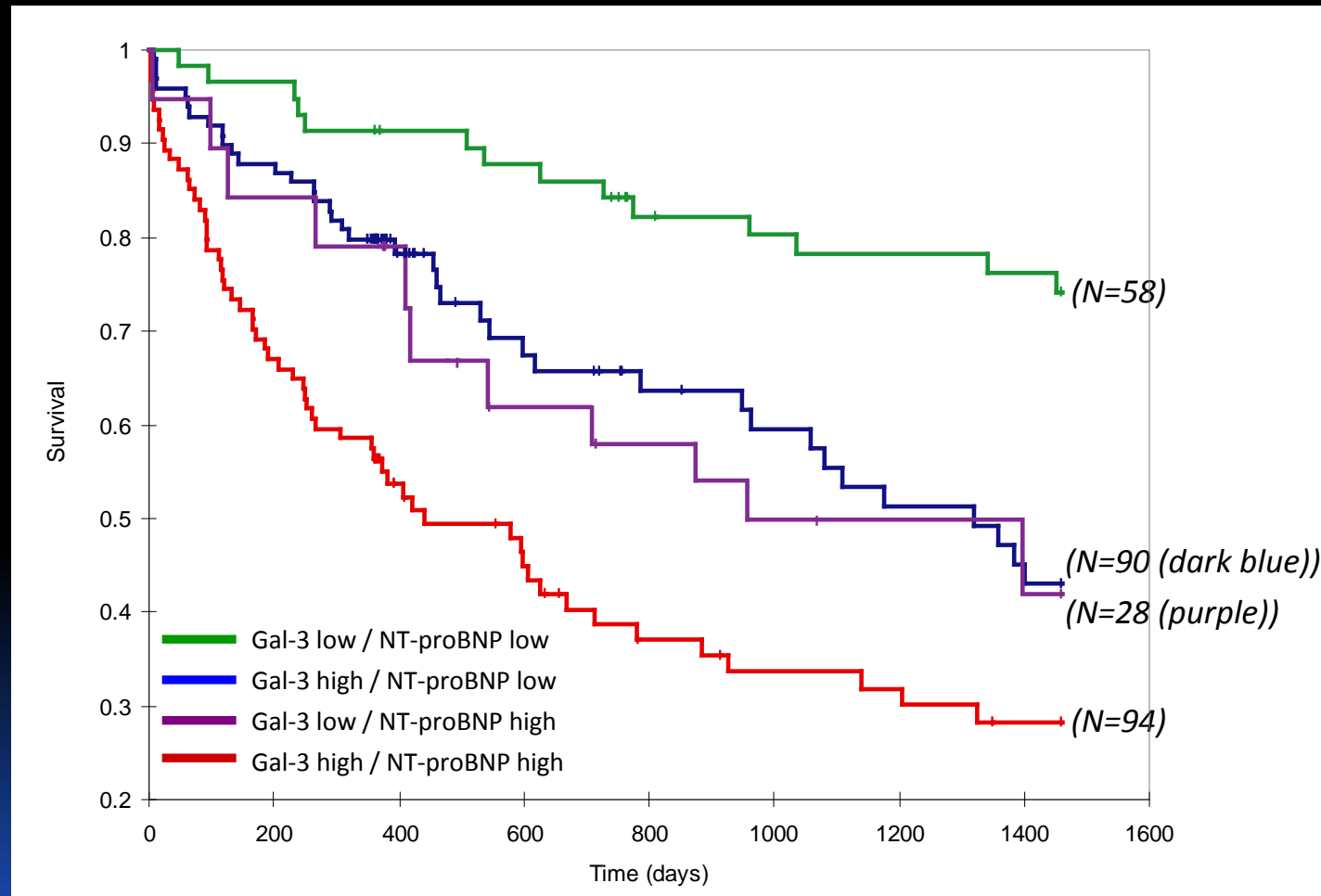
ROC curve for mortality at 800 days



- Gal-3 and NT-proBNP (AUC = 0.741), $p=0.052$ vs. Gal-3 and $p=0.043$ vs. NT-proBNP
- Galectin-3 (AUC = 0.693)
- NT-proBNP (AUC = 0.689)

Kaplan Meier curves for survival, by galectin-3 and NT-proBNP categories

ROC-curve-derived cutpoints for markers: (12.4ng/mL for Gal-3; 5876 pg/mL for NT-proBNP)



Time to death

Cox Regression Analysis

Variable	Hazard Ratio (95% CI)	Chi-Square	p-value
log(Galectin-3)	2.18 (1.36, 3.51)	10.5	0.001
age	2.30 (1.45, 3.67)	12.5	0.0004
log(CRP)	1.18 (1.04, 1.35)	6.5	0.011
NYHA class	1.36 (1.05, 1.77)	5.5	0.019
log(NT-proBNP)	1.21 (1.02, 1.42)	4.9	0.026
log(creatinine)	0.81 (0.46, 1.43)	0.5	0.4
gender	1.05 (0.71, 1.54)	0.1	0.8
race, black	1.78 (0.90, 1.45)	1.9	0.079
race, Hispanic	0.76 (0.23, 2.44)	0.1	0.6

Notes:

- For age, hazard ratio is relative to younger category (age \leq 69.0 yrs). For race, hazard ratios are relative to Caucasian race category. For gender, hazard ratio is relative to female gender. For NYHA, hazard ratio is per increasing NYHA class.

Conclusions

- A high precision assay for Galectin-3 has now been developed
- Galectin-3 levels are typically elevated in dyspnea patients with ADHF and associated with a gradient of increased risk for death
- Galectin-3 levels are independent predictors of mortality
- Galectin-3 and NT-proBNP levels provide synergistic prognostic information and may ultimately be useful to further stratify patients