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THE COMPLEMENTARY ROLE OF NOVEL CARDIAC FIBROSIS BIOMARKERS IN HEART FAILURE PROGNOSIS - A REPORT FROM THE REFERENCE STUDY

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BACKGROUND: The vast data addressing emerging cardiac fibrosis markers as adjunctive to conventional clinical risk factors and natriuretic peptides dosing, led the American College of Cardiology/ American Heart Association to grant Galectin-3 (Gal-3) and Suppression of Tumorigenicity 2 (ST2) evaluation a class II recommendation for heart failure (HF) prognosis, in 2013. Yet, in Europe this endorsement is not valid.

OBJECTIVE: We studied the association of Gal-3 and ST2 with early (defined as the period of 90 days post-discharge) rehospitalization and overall mortality, and long-term overall mortality in HF patients. Additionally, admission aminoterminal B-type natriuretic peptide (NT-proBNP) was considered to test if a multi-marker strategy could yield supplementary information.

METHODS: Gal-3, ST2 and NT-proBNP were assessed in patients hospitalized, to an Internal Medicine ward, with acute decompensated HF in class III or IV of New York Heart Association (NYHA). Subgroup analysis was performed according to the left ventricular ejection fraction (LVEF) in light of the current European Society of Cardiology guidelines. Comparison between patients with and without each of the events was performed for all variables using t test or Wilcoxon Rank test as applicable. Categorical variables were summarized by relative and absolute frequencies, and compared using chi-squared test or Fisher's Exact test as applicable. Univariate Cox proportional hazard model was used to assess the relationship between variables and outcomes. Since there are no standardized cut-offs for Gal-3 and ST2, the multiclass Area Under the Curve Receiver-Operator Characteristic (AUCROC) as defined by Hand and Till was used to evaluate the overall performance of each biomarker as a predictor of the outcomes. The Spearman's correlation coefficient was used to determine the relationship between variables.

RESULTS

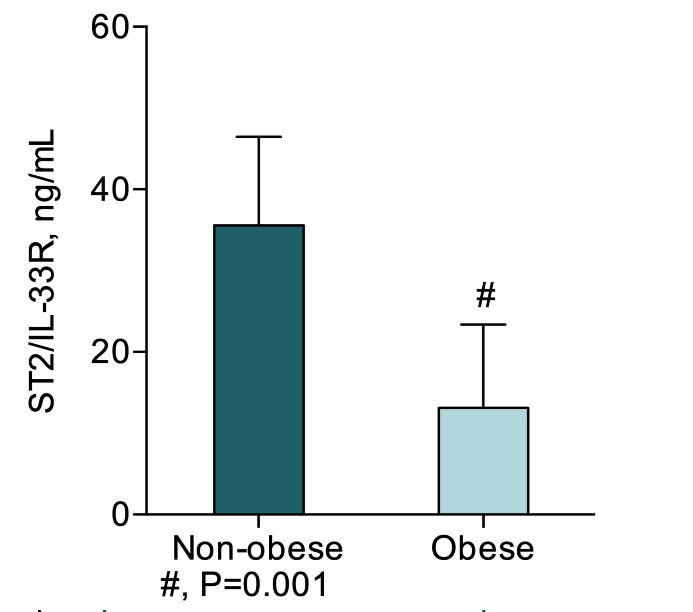
Characteristics	Patients (n=65)
Age, mean (SD)	79.2 ± 10.8
Female Gender, n (%)	37 (56.9)
Hypertension, n (%)	58 (89.2)
Type 2 Diabetes, n (%)	25 (38.5)
Dyslipidemia, n (%)	41 (63.1)
Obesity, n (%)	17 (26.2)
Atrial Fibrillation, n (%)	28 (43.1)
Family History of CVD, n (%)	31 (47.7)
Tabagism, n (%)	21 (32.3)
Chronic Kidney Disease, n (%)	34 (52.3)
GFR (Baseline), median	57.8 (43.8 - 82.2)
GFR (Admission), median	47.9 (33.2 - 68.1)
Previous Acute Myocardial Infarction, n (%)	27 (41.5)
Hypertensive Cardiomyopathy, n (%)	44 (67.7)
Ischemic Cardiomyopathy, n (%)	22 (33.8)
Valvular Cardiomyopathy, n (%)	56 (86.2)
LVEF, mean (SD)	50.38 ± 19.07
NYHA class III, n (%)	43 (66.2)
ACE Inhibitor, n (%)	43 (66.2)
Beta Blocker, n (%)	38 (58.5)
Mineralocorticoid Receptor Antagonists, n (%)	19 (29.2)
Angiotensin II Receptor Blocker, n (%)	11 (16.9)
Loop Diuretic, n (%)	54 (83.1)
Digoxin, n (%)	8 (12.3)
Galectin-3, median	9.82 (7.94 -12.00)
ST2, median	27.22 (15.45-44.39)
NT-proBNP (Admission), median	5701.0 (1867 - 11961)

Values are median (IQR), n (%), or mean ± SD. IQR: interquartile range and minimum/maximum, SD: standard deviation, CVD: cardiovascular disease, GFR: glomerular filtration rate, ACE: Angiotensin-Converting-Enzyme.

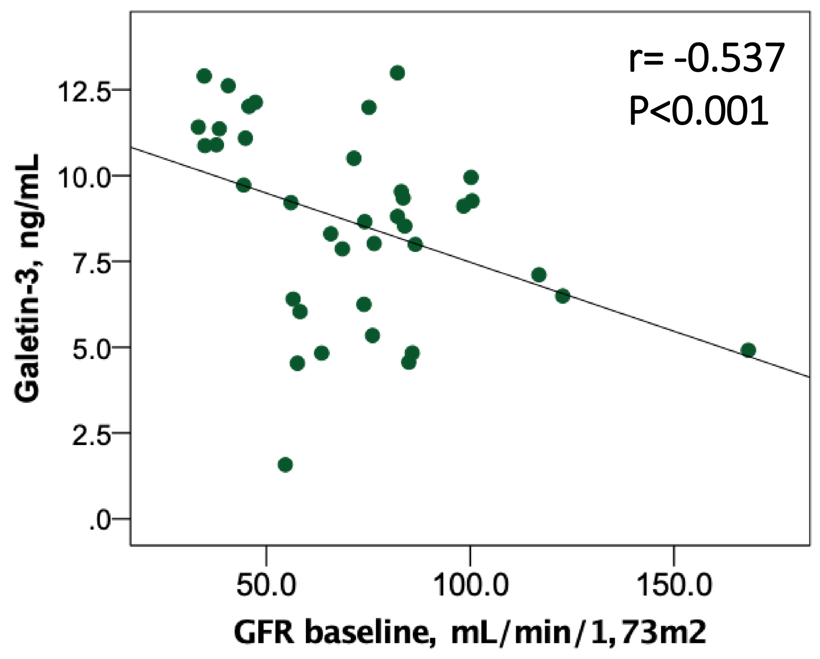
N=65 HF patients
Mean age: 79.2 (SD 10.8)

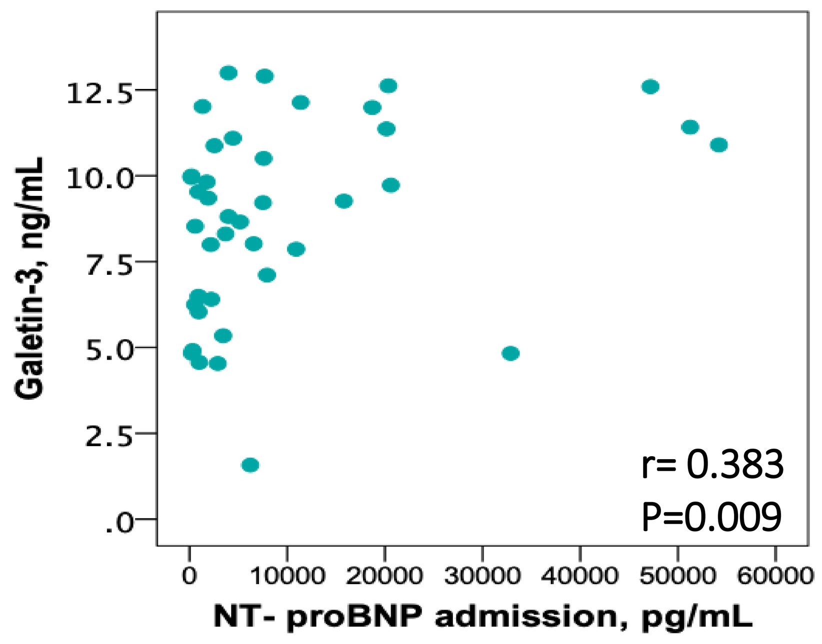
Median follow-up : 13.7 months
[Q1: 6.7 to Q3: 18.9]

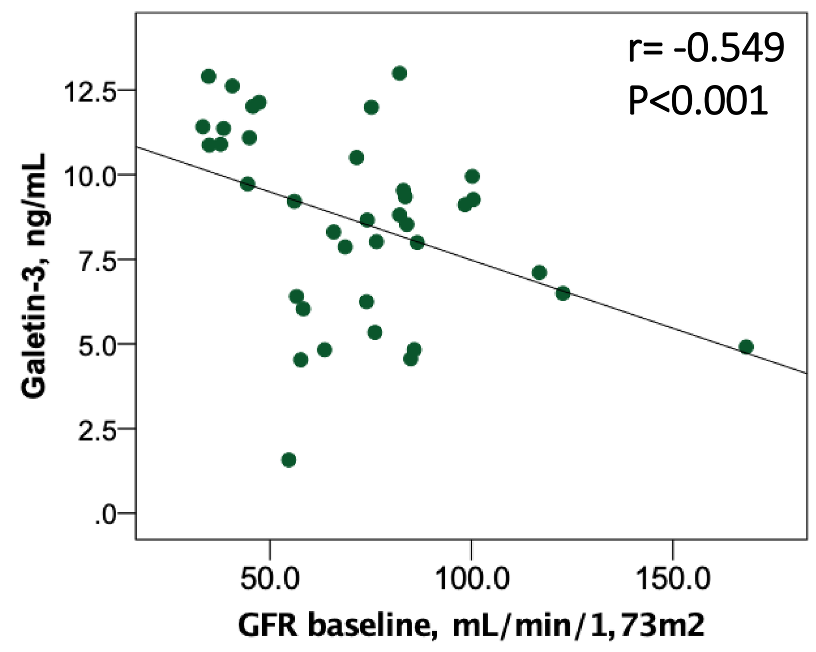
- Spearman's correlation indicated a significant negative relation between:
  - ST2 levels and baseline GFR (Coefficient: -0.418, P<0.001)
  - ST2 levels and admission GFR (Coefficient: -0.438, P<0.001).



- An association between ST2 and long-term mortality was acknowledged (HR: 4.846, 95% CI: 1.396-16.825, P-value=0.013).



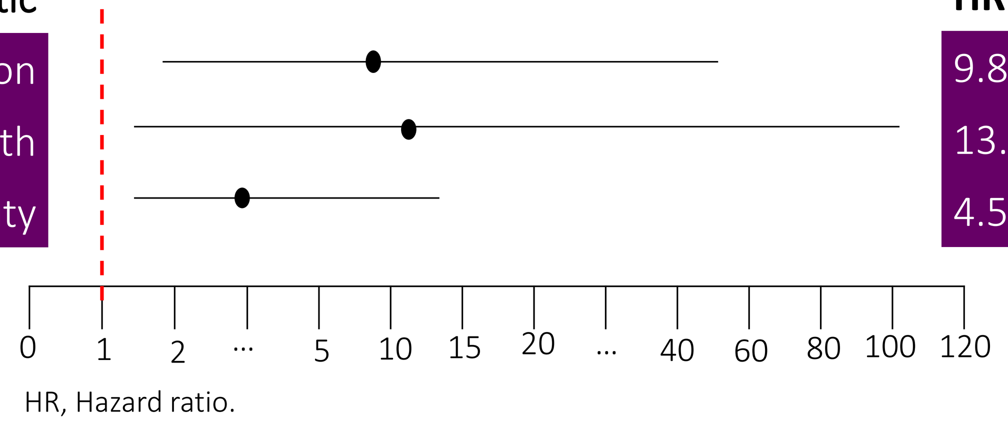




GALECTIN-3

Forest Plot of Hazard Ratios by Patient Subgroups

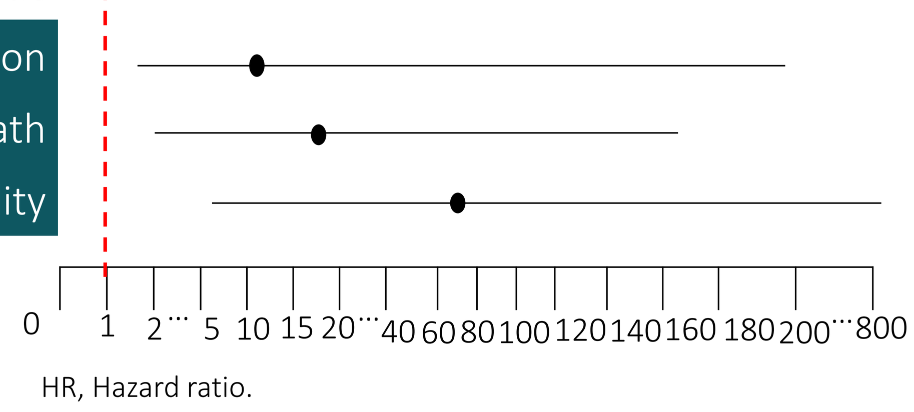
Characteristic	HR	95% CI	P value
Early rehospitalization	9.89	2.0-48.20	0.005
Early death	13.73	1.65-114.23	0.015
Long-term mortality	4.50	1.59-12.66	0.004



GALECTIN-3 & NT-proBNP

Forest Plot of Hazard Ratios by Patient Subgroups

Characteristic	HR	95% CI	P value
Early rehospitalization	11.98	1.96-73.2	0.007
Early death	18.84	2.19-161.8	0.007
Long-term mortality	78.03	7.60-801.9	<0.001



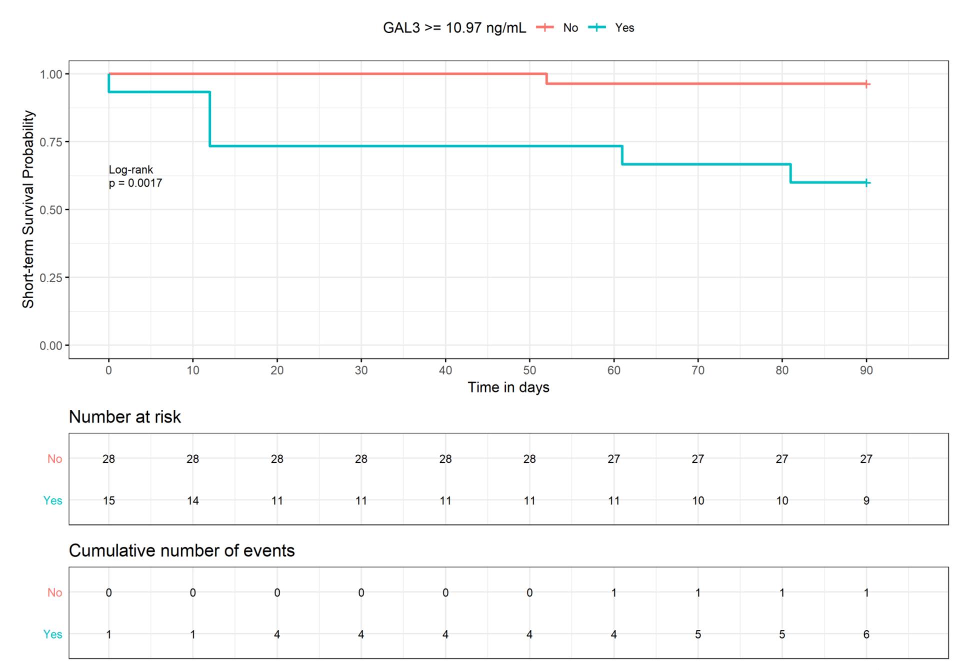


Figure 1 - Short-term mortality - Kaplan Meier: GAL3 ≥10.97 ng/mL

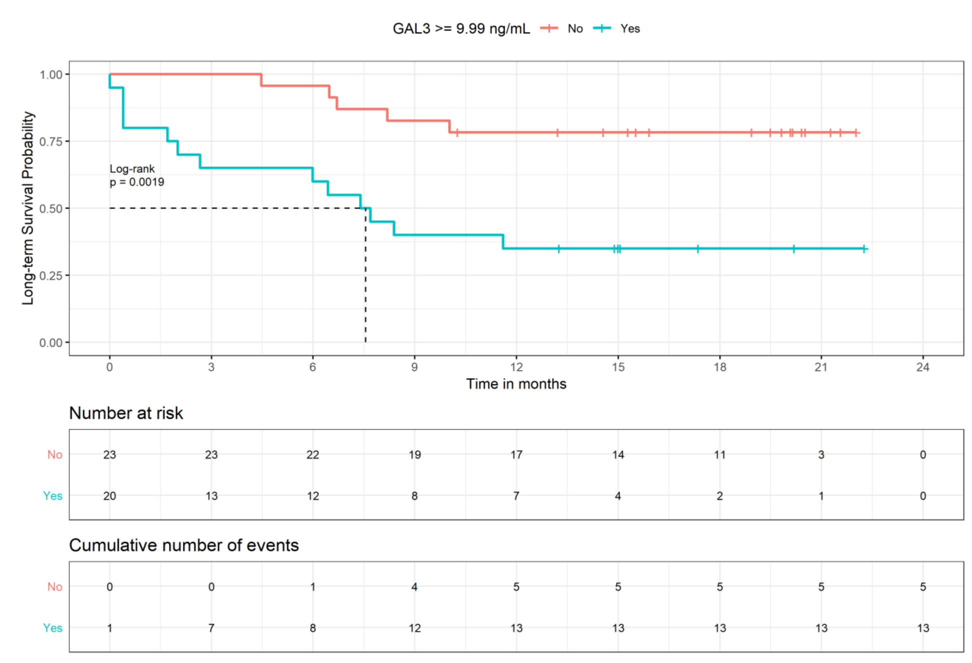


Figure 2 - Long-term mortality - Kaplan Meier: GAL3 ≥9.99 ng/mL

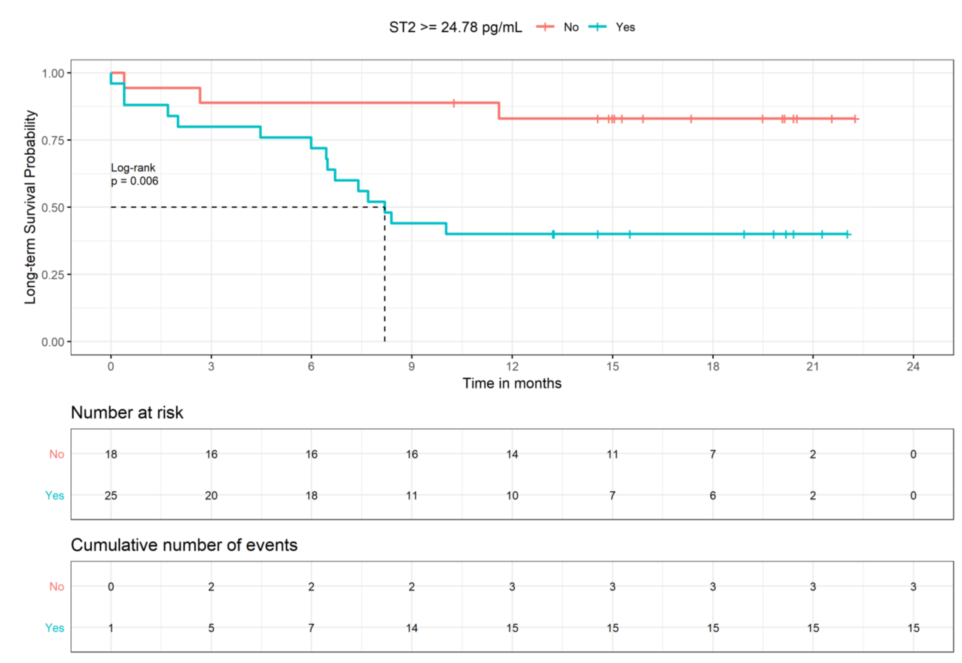


Figure 3 - Long-term mortality - Kaplan Meier: sST2 ≥24.78 pg/mL

Long-term mortality

6-fold risk: sST2 ≥24.78pg/mL and Admission NT-proBNP ≥21336ng/L
HR: 5.953, 95% CI: 1.683-21.055, P-value=0.006

6.2-fold risk: sST2 ≥24.78pg/mL and Gal-3 ≥9.99 ng/mL
HR: 6.209, 95% CI: 2.393-16.114, P-value<0.001

Long-term mortality for HFrEF

16-fold risk: Gal-3 ≥9.99 ng/mL and sST2 ≥24.78pg/mL
HR: 15.782, 95% CI: 1.593-156.322, P-value=0.018

Long-term mortality for HFpEF

5-fold risk: Gal-3 ≥9.99 ng/mL and sST2 ≥24.78pg/mL
HR: 5.2, 95% CI: 1.223-22.187, P-value=0.026

CONCLUSION:

- High Gal-3 determinations correlated with early rehospitalization, early mortality and long-term mortality; whereas ST2 predicted long-term mortality.
- Combined analysis with elevated NT-proBNP values further increased the outcomes' risk.
- Our findings support the assumption that promising novel biomarkers Gal-3 and ST2 may be useful for HF risk stratification.
- Furthermore, a multi-marker strategy appears to add information, as a synergism between natriuretic peptides and the cited biomarkers was documented.