

Supplementary Material

Atrial dysfunction as a contrast-free marker to identify HFpEF in obese diabetics:
Insights from a comprehensive CMR and biomarker assessment

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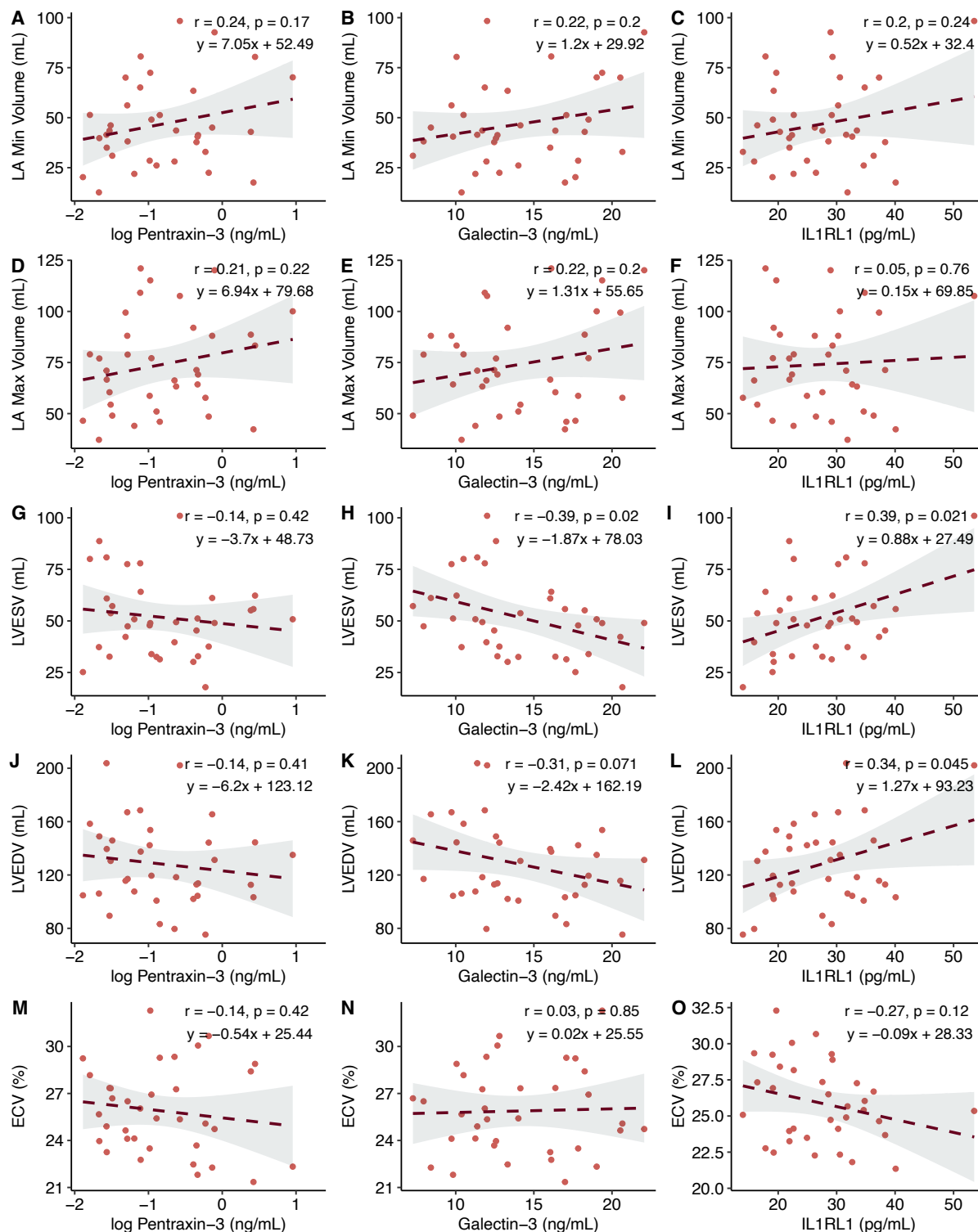
S1. Imaging Parameters for strain analysis

LA volumes and strain were derived from cine CMR images acquired in two-, three-, and four-chamber orientations using a standard retrospectively gated steady-state free precession (SSFP) sequence with breath-holding at end-expiration. The following imaging parameters were used: temporal resolution <35 ms with minimum 30 heart phases, slice thickness 6 mm, inter-slice gap 0 mm, flip angle 45°, acquired voxel size ~1.9 × 1.9 mm (reconstructed: 1.1 × 1.1 mm).

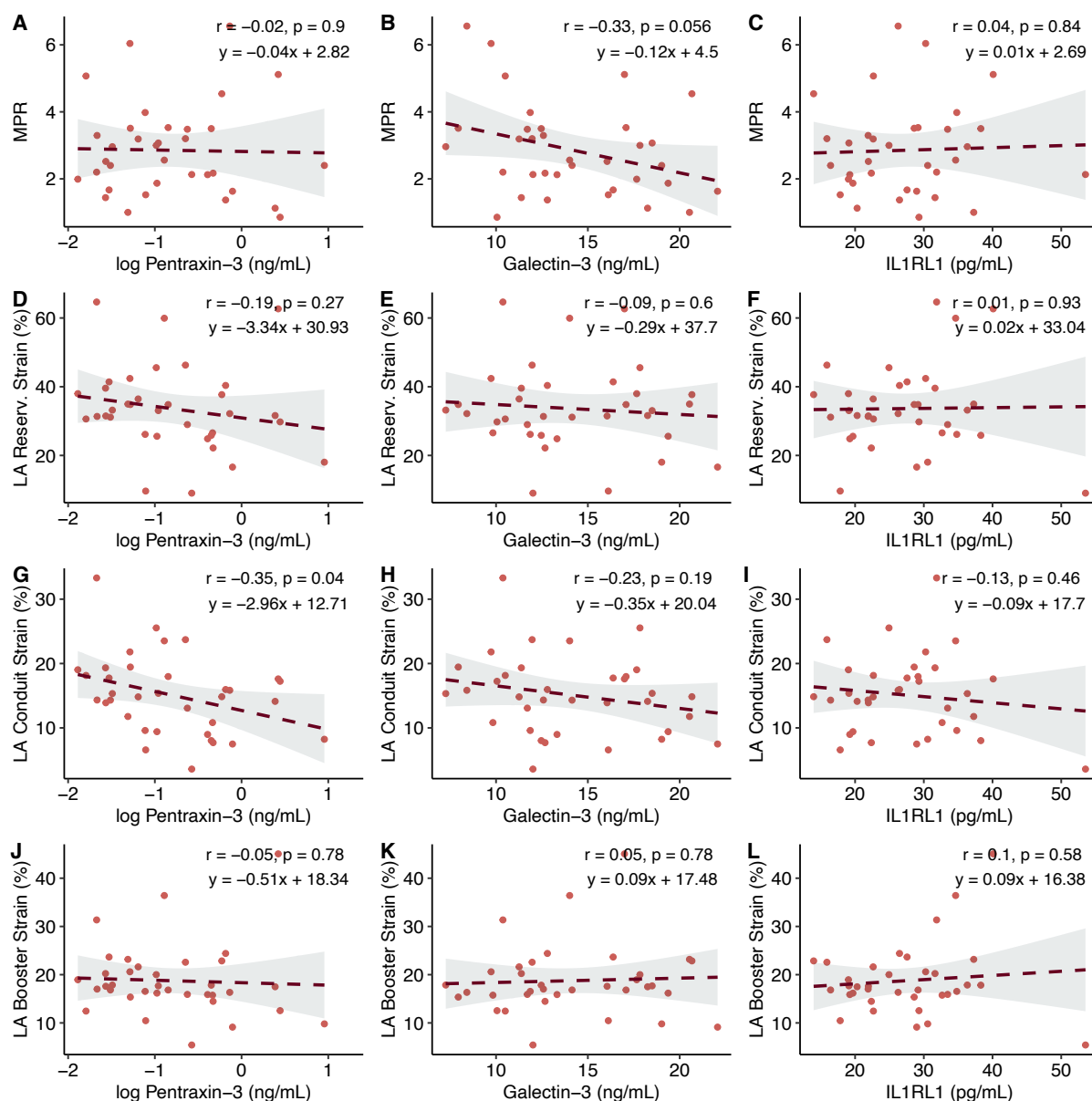
Image post-processing and strain analysis were performed using commercially available software (Medis Suite, Version RE 4.0, Medis Medical Imaging, Leiden, The Netherlands).

1 S2. Pearson Correlation

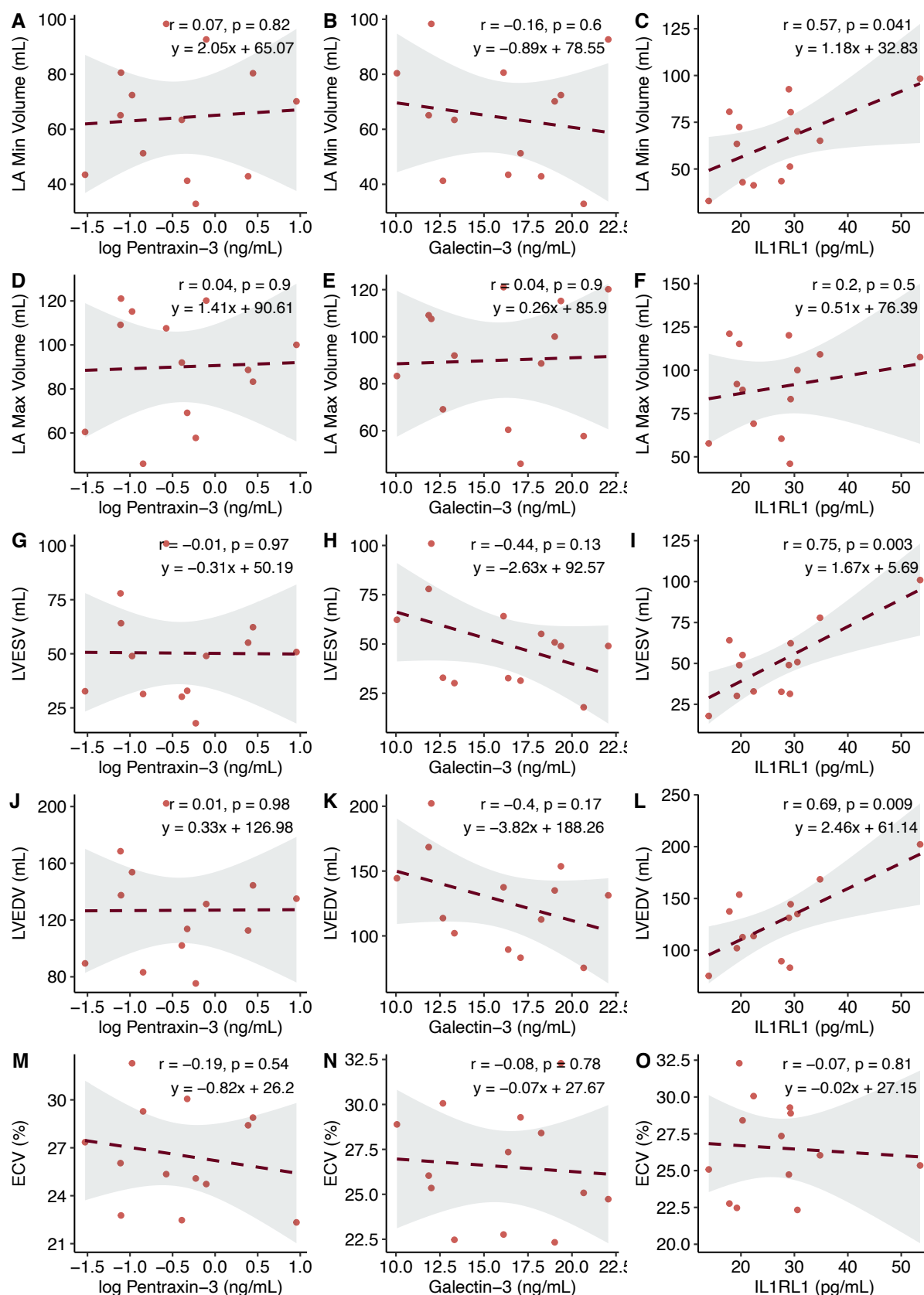
2 2.1 Pearson's Correlation for Serum Biomarkers and CMR Imaging across all study subjects



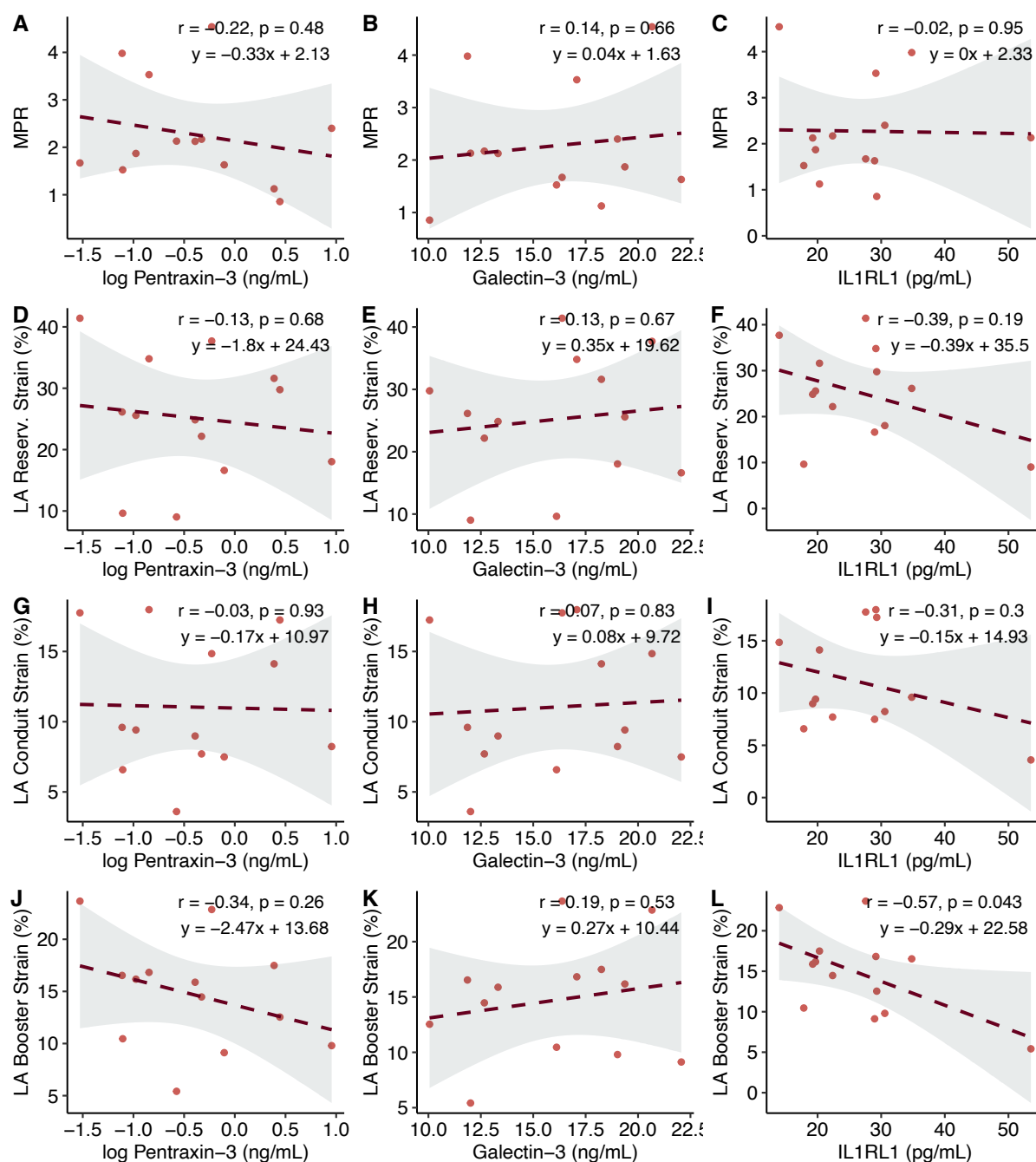
2.2 Pearson's Correlation for Serum Biomarkers and CMR Imaging across all study subjects – continued



2.3 Pearson's Correlation for Serum Biomarkers and CMR Imaging across HFpEF with T2DM cohort only

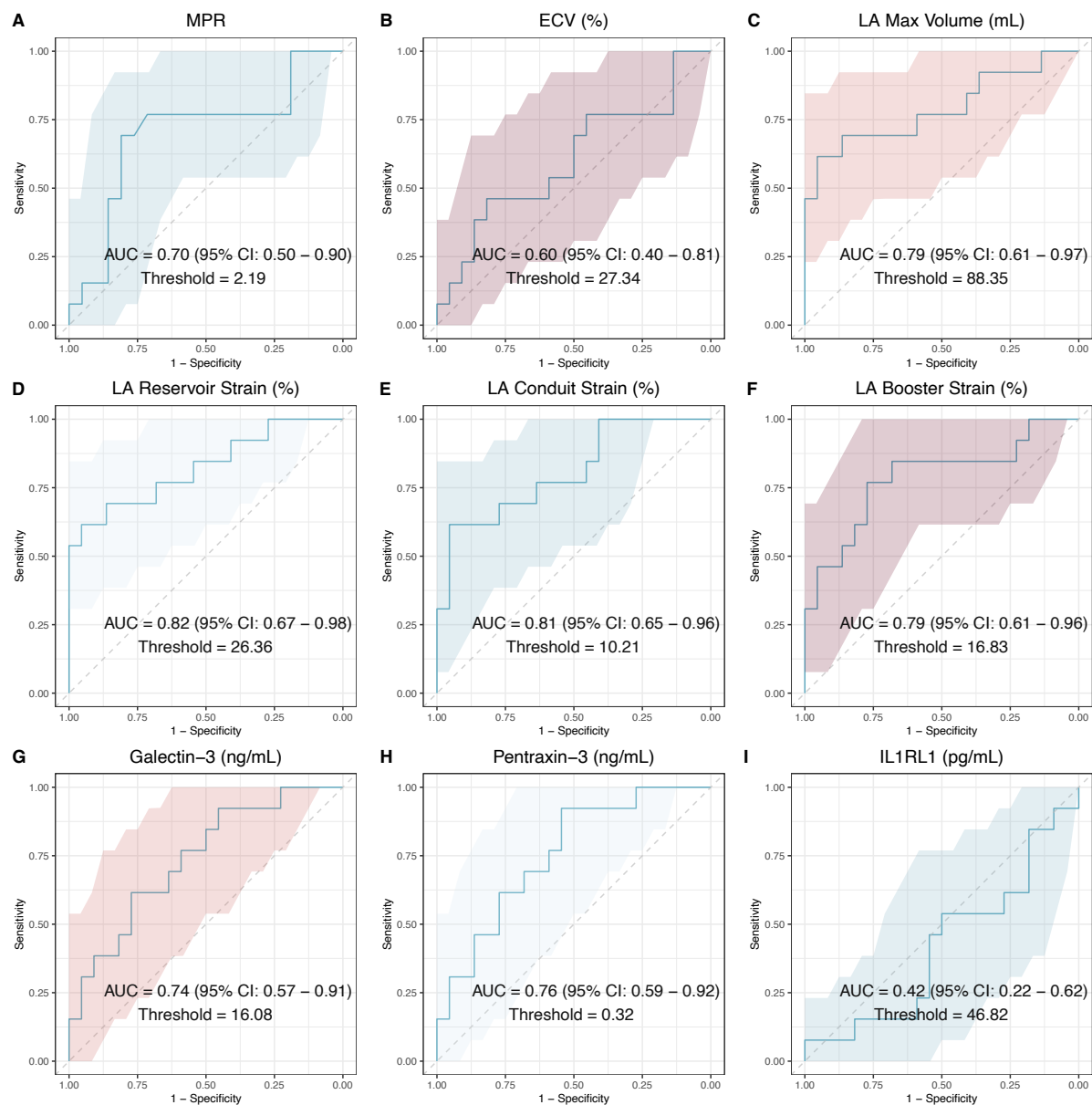


2.4 Pearson's Correlation for Serum Biomarkers and CMR Imaging across HFpEF with T2DM cohort only – continued



1 S3.Receiver Operating Curve Analysis

2 3.1 Visualization



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3.2 Summary of Receiver Operating Analysis Statistics

Variable	AUC (95% CI)	Threshold	Sens	Spec	PPV	NPV	Accuracy
Perfusion & Fibrosis							
MPR	0.70 (0.50–0.90)	2.19	0.69	0.81	0.69	0.81	0.76
ECV (%)	0.61 (0.40–0.81)	27.34	0.46	0.82	0.60	0.72	0.69
Function							
LA Max Vol (mL)	0.79 (0.61–0.97)	88.35	0.62	0.95	0.89	0.81	0.83
LA Reservoir Strain (%)	0.83 (0.67–0.98)	26.36	0.62	0.95	0.89	0.81	0.83
LA Conduit Strain (%)	0.81 (0.65–0.96)	10.21	0.62	0.95	0.89	0.81	0.83
LA Booster Strain (%)	0.79 (0.62–0.96)	16.83	0.77	0.77	0.67	0.85	0.77
Serum Biomarkers							
Galectin-3 (ng/mL)	0.74 (0.57–0.91)	16.08	0.62	0.77	0.62	0.77	0.71
Pentraxin-3 (ng/mL)	0.76 (0.59–0.92)	0.32	0.92	0.55	0.55	0.92	0.69
IL1RL1 (pg/mL)	0.42 (0.22–0.62)	46.82	0.08	1.00	1.00	0.65	0.66

AUC = Area under the curve. CI = Confidence interval. ECV = Extracellular volume fraction. Galectin-3 = Galectin-3. IL1RL1 = Interleukin-1 receptor-like 1. LA Booster Strain = Left atrial booster strain. LA Conduit Strain = Left atrial conduit strain. LA Max Vol = Left atrial maximum volume. LA Reservoir Strain = Left atrial reservoir strain. mL = Millilitres. MPR = Myocardial perfusion reserve. ng = Nanograms. NPV = Negative predictive value. pg = Picograms. Pentraxin-3 = Pentraxin-3. PPV = Positive predictive value. Sens = Sensitivity. Spec = Specificity.

Sensitivity Analyses for subgroup pf patients without medical history for atrial arrhythmia

S4. Sensitivity analysis for subgroup without atrial arrhythmia

4.1 Patient Characteristics for subgroup of patients without medical history for atrial arrhythmia

Variable	n	Obese without CVD n = 6 ¹	T2DM n = 16 ¹	HFpEF with T2DM n = 10 ¹	p-value ²
Demographics					
Age (years)	32	62 ± 2	61 ± 11	68 ± 4	0.178
Female	32	2 (33%)	1 (6.3%)	3 (30%)	0.191
Body Mass Index (kg/m ²)	32	27.7 ± 1.3	30.6 ± 3.1	31.9 ± 4.6	0.071
Comorbidities					
Arterial Hypertension	32	0 (0%)	12 (75%)	10 (100%)	<0.001
Hypercholesterolemia	32	0 (0%)	3 (19%)	0 (0%)	0.191
Diabetic Burden (years)	26	NA ± NA	7.9 ± 6.4	11.9 ± 11.5	0.268
Atrial Fibrillation	32	0 (0%)	0 (0%)	0 (0%)	-
Atrial Ectopic Tachycardia	32	0 (0%)	0 (0%)	0 (0%)	-
Medication					
ACE inhibitors	35	0 (0%)	5 (31%)	3 (30%)	0.291
Angiotensin II Receptor Blockers	35	0 (0%)	7 (44%)	6 (60%)	0.057
Beta Blockers	35	0 (0%)	3 (19%)	4 (40%)	0.158
Calcium Channel Blockers	35	0 (0%)	7 (44%)	4 (40%)	0.142
SGLT2 Inhibitors	35	0 (0%)	5 (31%)	3 (30%)	0.291
GLP-1 Receptor Agonists	35	0 (0%)	4 (25%)	1 (10%)	0.299
Oral antidiabetics	35	0 (0%)	16 (100%)	10 (100%)	<0.001
Insulins	35	0 (0%)	3 (19%)	0 (0.0%)	0.191
Statins	35	0 (0%)	8 (50%)	3 (30%)	0.084
Other lipid-lowering agents	35	0 (0%)	2 (13%)	2 (20%)	0.504
Diuretics	35	0 (0%)	5 (31%)	3 (30%)	0.291

Anticoagulants	35	0 (0%)	0 (0%)	1 (10%)	0.321
Antiplatelets	35	0 (0%)	4 (25%)	2 (20%)	0.406
Labs					
Hemoglobin (g/dL)	32	14.53 ± 1.17	14.46 ± 1.13	13.78 ± 1.21	0.296
Total Protein (g/dL)	32	7.15 ± 0.40	7.31 ± 0.28	7.21 ± 0.41	0.545
Creatinine (mg/dL)	32	0.87 ± 0.14	0.99 ± 0.21	1.08 ± 0.26	0.181
Hemoglobin A1c (%)	16	5.23 ± 0.29	6.29 ± 1.53	6.53 ± 0.85	0.041
NT-proBNP (pg/mL)	31	6 ± 2	6 ± 3	48 ± 26	<0.001
Cardiac Magnetic Resonance					
LVEDV (mL)	32	133 ± 27	127 ± 30	122 ± 32	0.773
LVSV (mL)	32	79 ± 9	75 ± 23	76 ± 17	0.915
LVEF (%)	32	61 ± 9	59 ± 9	63 ± 7	0.488

¹ Mean ± SD; n (%)

² One-way ANOVA; Pearson's Chi-squared test

1 4.2 Findings for subgroup pf patients without medical history for atrial arrhythmia

Variable	n	Obese without CVD n = 6 ¹	T2DM n = 16 ¹	HFpEF with T2DM n = 10 ¹	p- value ²
Perfusion & Fibrosis					
MPR	31	3.63 ± 1.62	3.05 ± 1.41	2.41 ± 1.20	0.239
ECV (%)	32	26.73 ± 1.81	25.03 ± 2.65	26.12 ± 3.32	0.377
Atrial Morphology & Function					
Minimum LA Volume (mL)	32	35 ± 17	37 ± 13	65 ± 18	<0.001
Maximum LA Volume (mL)	32	63 ± 21	65 ± 16	91 ± 28	0.011
LA Reservoir Strain (%)	32	41 ± 12	38 ± 11	26 ± 10	0.021
LA Conduit Strain (%)	32	21.2 ± 6.3	16.1 ± 4.8	11.8 ± 4.6	0.004
LA Booster Strain (%)	32	19 ± 7	22 ± 8	15 ± 5	0.093
Serum Biomarkers					
Galectin-3 (ng/mL)	32	10.6 ± 3.7	13.8 ± 3.3	16.6 ± 3.9	0.010
Pentraxin-3 (ng/mL)	32	0.21 ± 0.05	0.52 ± 0.35	0.82 ± 0.74	0.063
Interleukin-1 Receptor-Like 1 (pg/mL)	32	28 ± 6	28 ± 8	25 ± 7	0.619
¹ Mean ± SD; n (%)					
² One-way ANOVA					

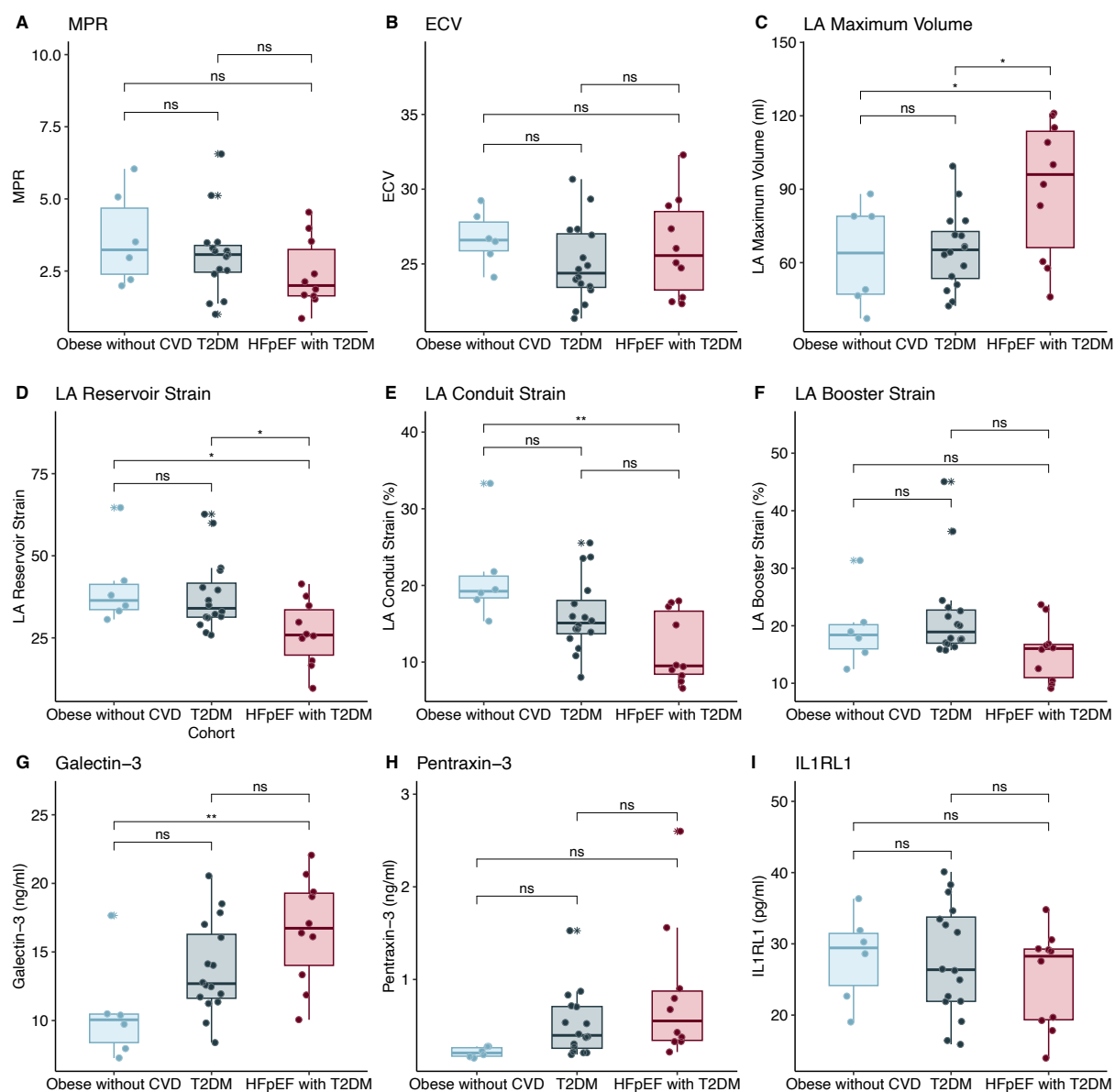
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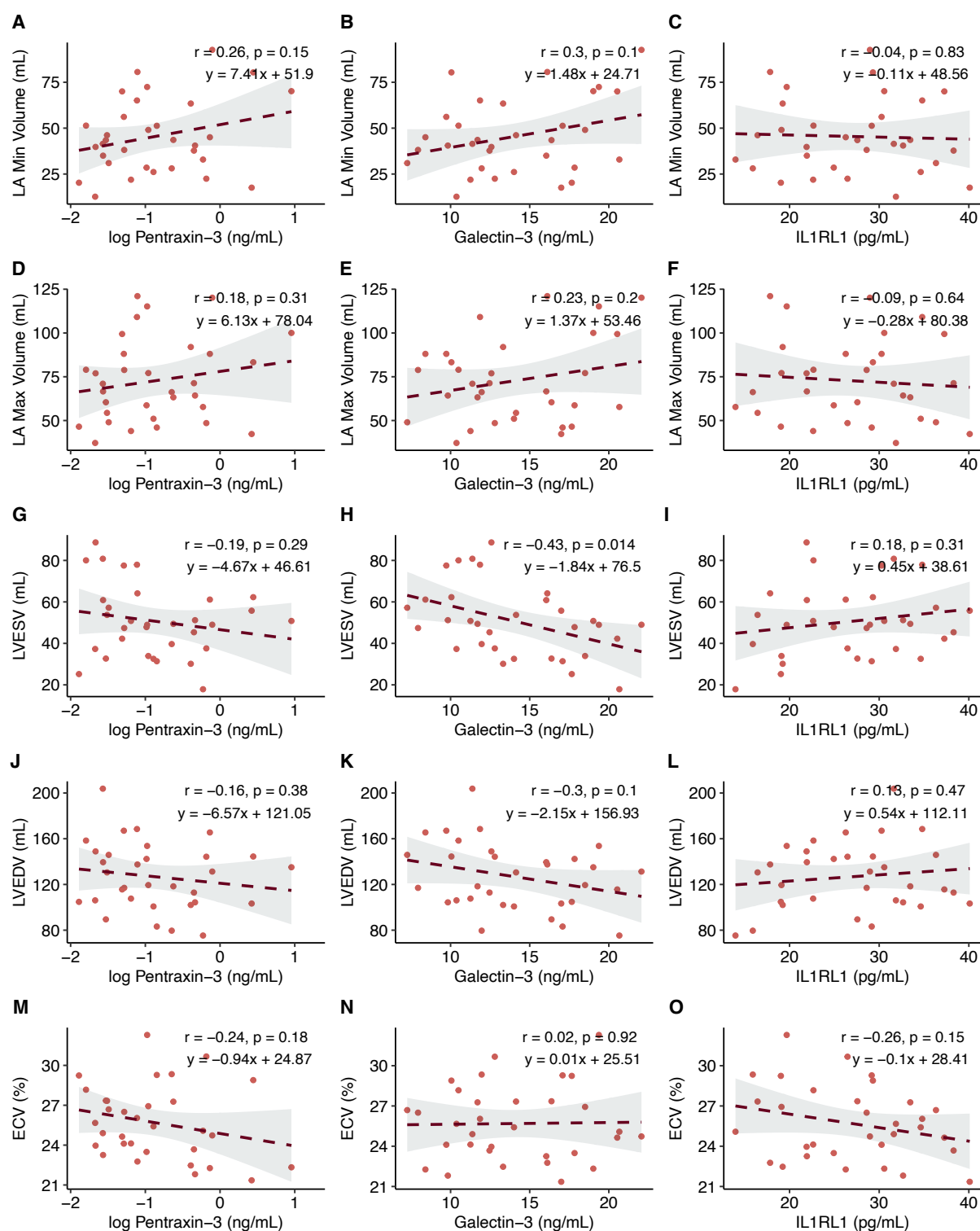
4.3 Logistic Regression Analyses for subgroup of patients without medical history for atrial arrhythmia

Variable	Univariable Logistic Regression		Multivariable Logistic Regression*	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Hemodynamics & Fibrosis				
ECV (%)	1.09 (0.82, 1.45)	0.545	-	-
MPR	0.61 (0.28, 1.11)	0.150	-	-
Function				
LV EDV (mL)	0.99 (0.96, 1.02)	0.538	-	-
LA Max Vol (mL)	1.06 (1.02, 1.11)	0.011	1.21 (1.04, 1.27)	0.015
LA Reservoir Strain (%)	0.85 (0.72, 0.95)	0.022	0.71 (0.44, 0.91)	0.047
LA Conduit Strain (%)	0.77 (0.60, 0.93)	0.017	0.58 (0.32, 0.85)	0.024
LA Booster Strain (%)	0.80 (0.61, 0.96)	0.045	0.72 (0.49, 0.93)	0.034
Serum Biomarkers				
Galectin-3 (ng/mL)	1.29 (1.05, 1.67)	0.025	1.26 (0.98, 1.71)	0.097
Pentraxin-3 (ng/mL) [†]	3.21 (1.06, 12.2)	0.055	-	-
IL1RL1 (pg/mL)	0.95 (0.84, 1.05)	0.317	-	-
*Included the respective variable significant in univariable logistic regression and additionally accounted for age, sex and BMI.				
[†] Values for log-transformed Pentraxin-3.				

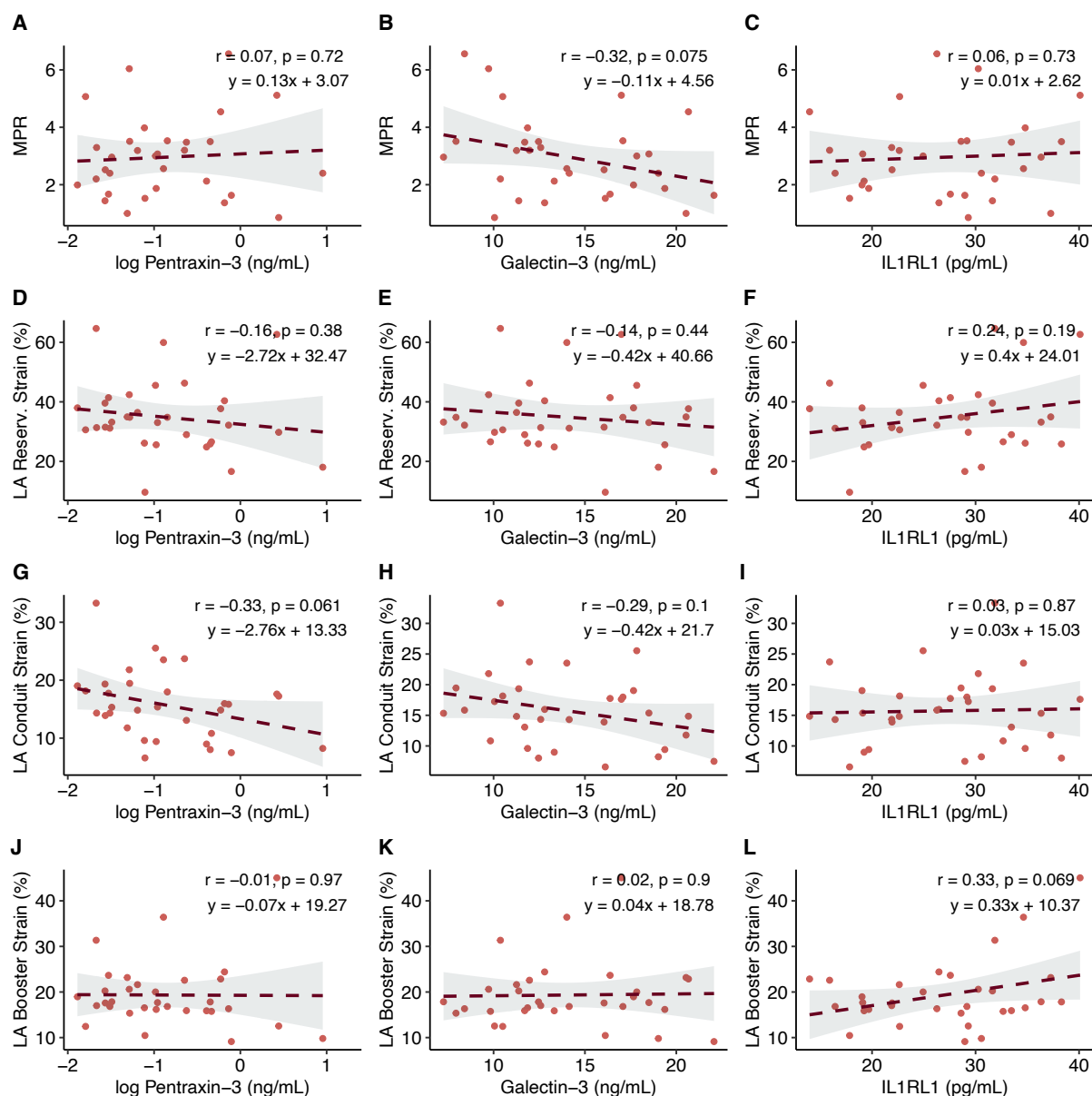
4.4 Comparative analysis of Serum Biomarkers and CMR Imaging across Subgroup of patients without medical history for atrial arrhythmia



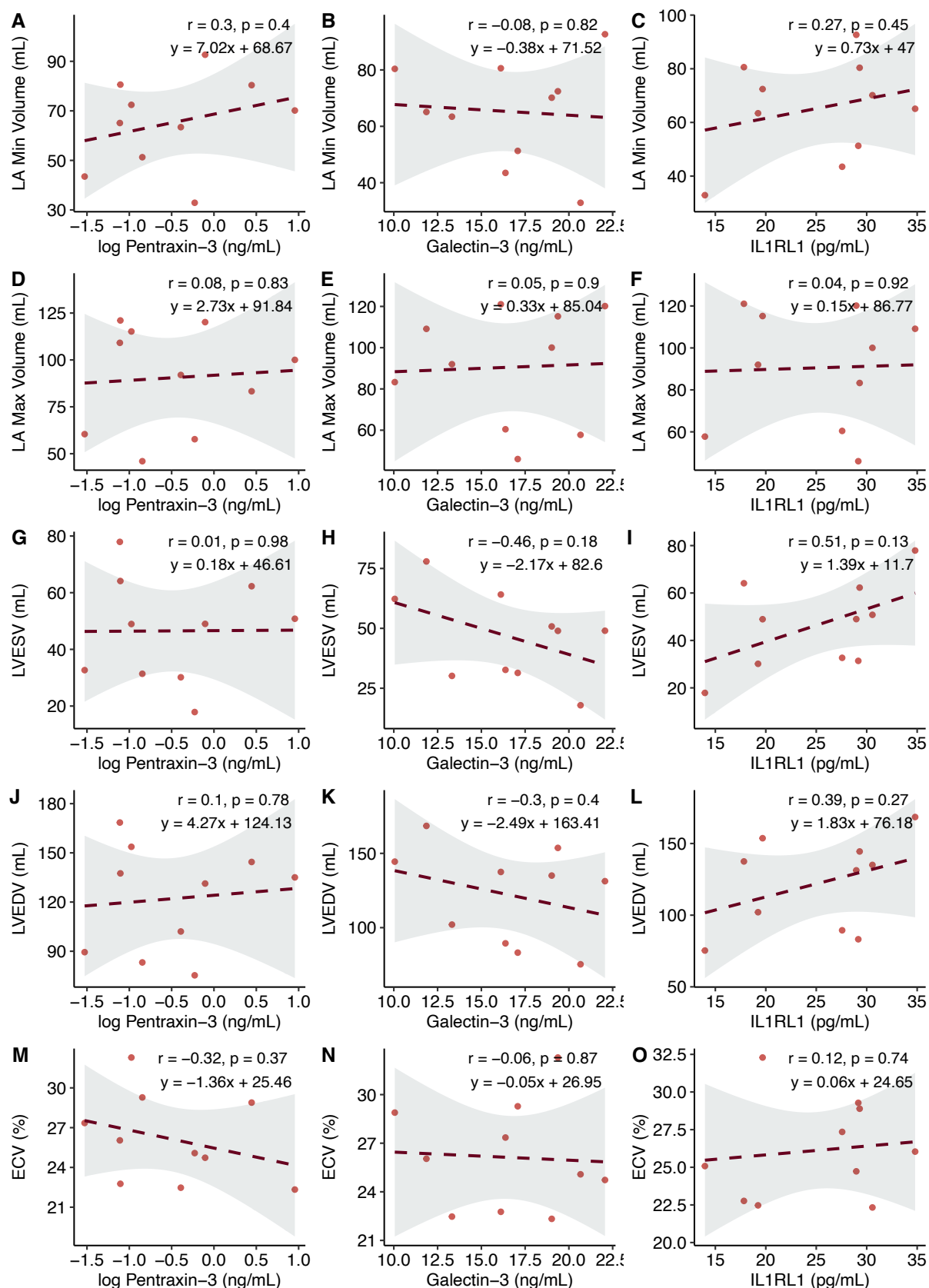
4.5 Pearson's Correlation for Serum Biomarkers and CMR Imaging across Subgroup of patients without medical history for atrial arrhythmia



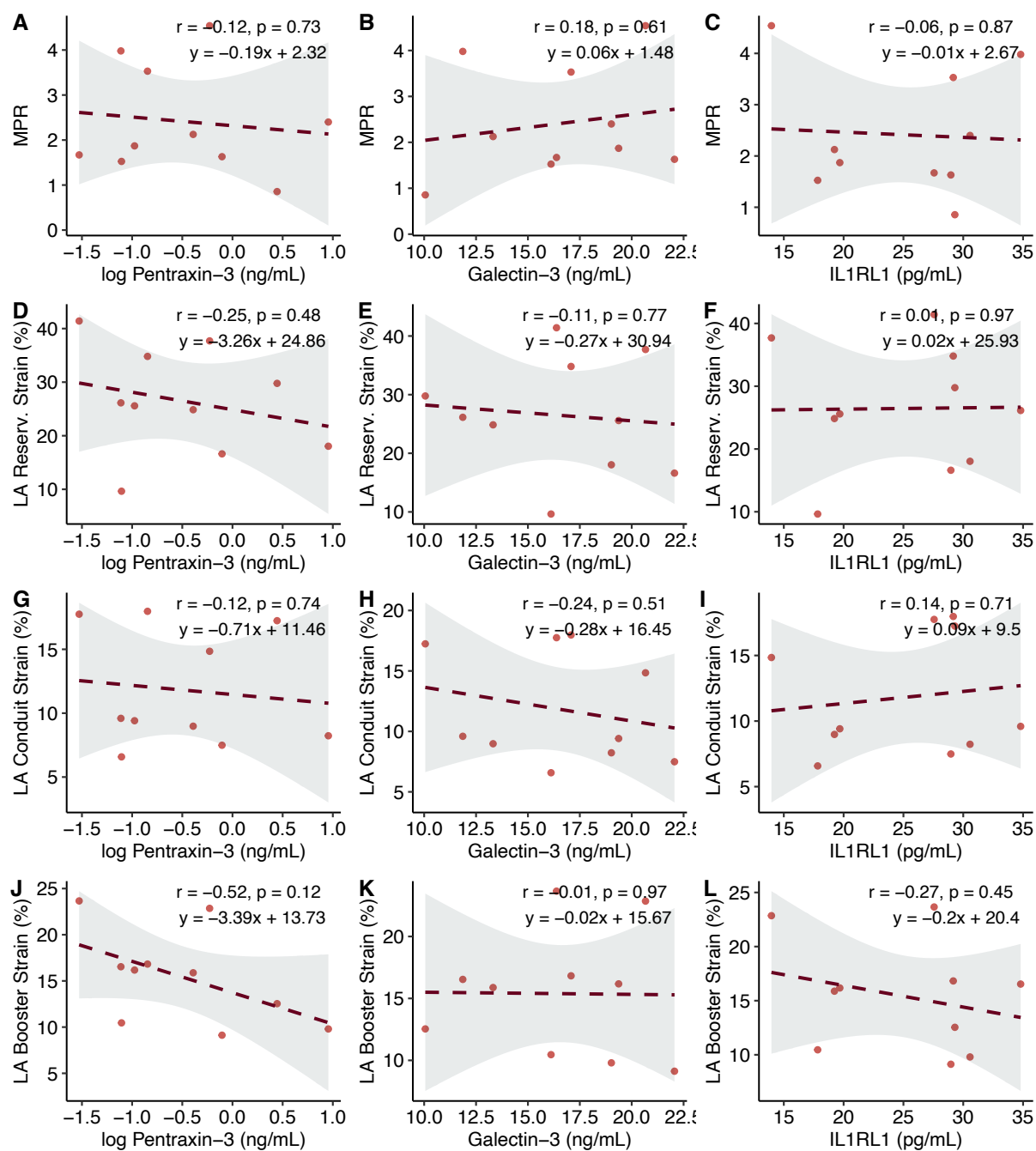
4.6 Pearson's Correlation for Serum Biomarkers and CMR Imaging Subgroup of patients without medical history for atrial arrhythmia – continued



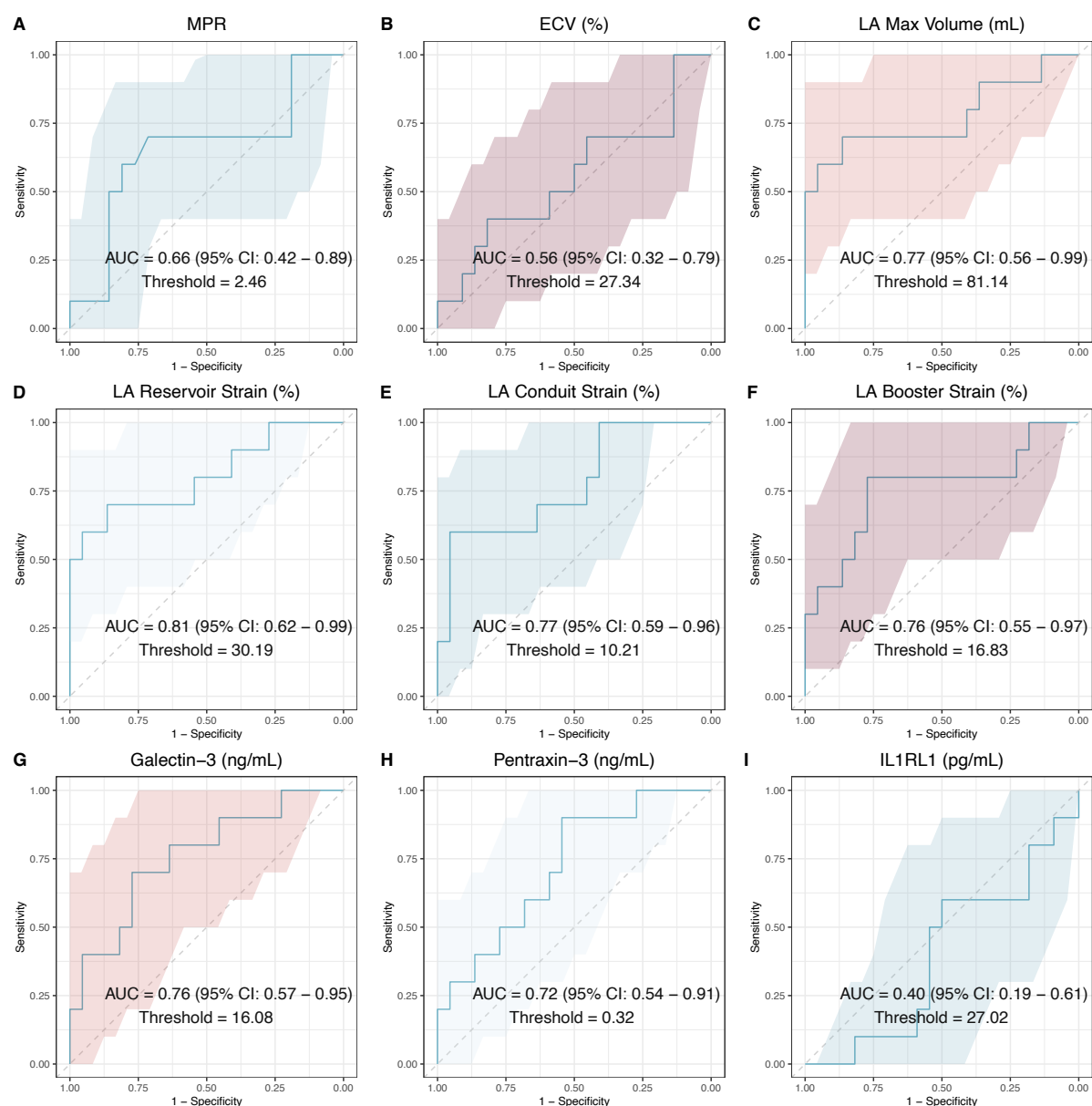
4.7 Pearson's Correlation for Serum Biomarkers and CMR Imaging across HFpEF with T2DM cohort without medical history for atrial arrhythmia only



4.8 Pearson's Correlation for Serum Biomarkers and CMR Imaging across HFpEF with T2DM cohort without medical history for atrial arrhythmia only – continued



4.9 Visualization of Receiver Operating Analysis across HFpEF with T2DM cohort without medical history for atrial arrhythmia only



4.10 Summary of Receiver Operating Analysis Statistics across HFpEF with T2DM cohort without medical history for atrial arrhythmia only

Variable	AUC (95% CI)	Threshold	Sens	Spec	PPV	NPV	Accuracy
Perfusion & Fibrosis							
MPR	0.66 (0.42–0.89)	2.46	0.70	0.71	0.54	0.83	0.71
ECV (%)	0.56 (0.32–0.79)	27.34	0.40	0.82	0.50	0.75	0.69
Function							
LA Max Vol (mL)	0.77 (0.56–0.99)	81.14	0.70	0.86	0.70	0.86	0.81
LA Reservoir Strain (%)	0.81 (0.62–0.99)	30.19	0.70	0.86	0.70	0.86	0.81
LA Conduit Strain (%)	0.77 (0.59–0.96)	10.21	0.60	0.95	0.86	0.84	0.84
LA Booster Strain (%)	0.76 (0.55–0.97)	16.83	0.80	0.77	0.62	0.89	0.78
Serum Biomarkers							
Galectin-3 (ng/mL)	0.76 (0.57–0.95)	16.08	0.70	0.77	0.58	0.85	0.75
Pentraxin-3 (ng/mL)	0.72 (0.54–0.91)	0.32	0.90	0.55	0.47	0.92	0.66
IL1RL1 (pg/mL)	0.40 (0.19–0.61)	27.02	0.60	0.50	0.35	0.73	0.53

AUC = Area under the curve. CI = Confidence interval. ECV = Extracellular volume fraction. Galectin-3 = Galectin-3. IL1RL1 = Interleukin-1 receptor-like 1. LA Booster Strain = Left atrial booster strain. LA Conduit Strain = Left atrial conduit strain. LA Max Vol = Left atrial maximum volume. LA Reservoir Strain = Left atrial reservoir strain. mL = Millilitres. MPR = Myocardial perfusion reserve. ng = Nanograms. NPV = Negative predictive value. pg = Picograms. Pentraxin-3 = Pentraxin-3. PPV = Positive predictive value. Sens = Sensitivity. Spec = Specificity.