Heart Failure in Fabry disease revisited: application of current heart failure guidelines

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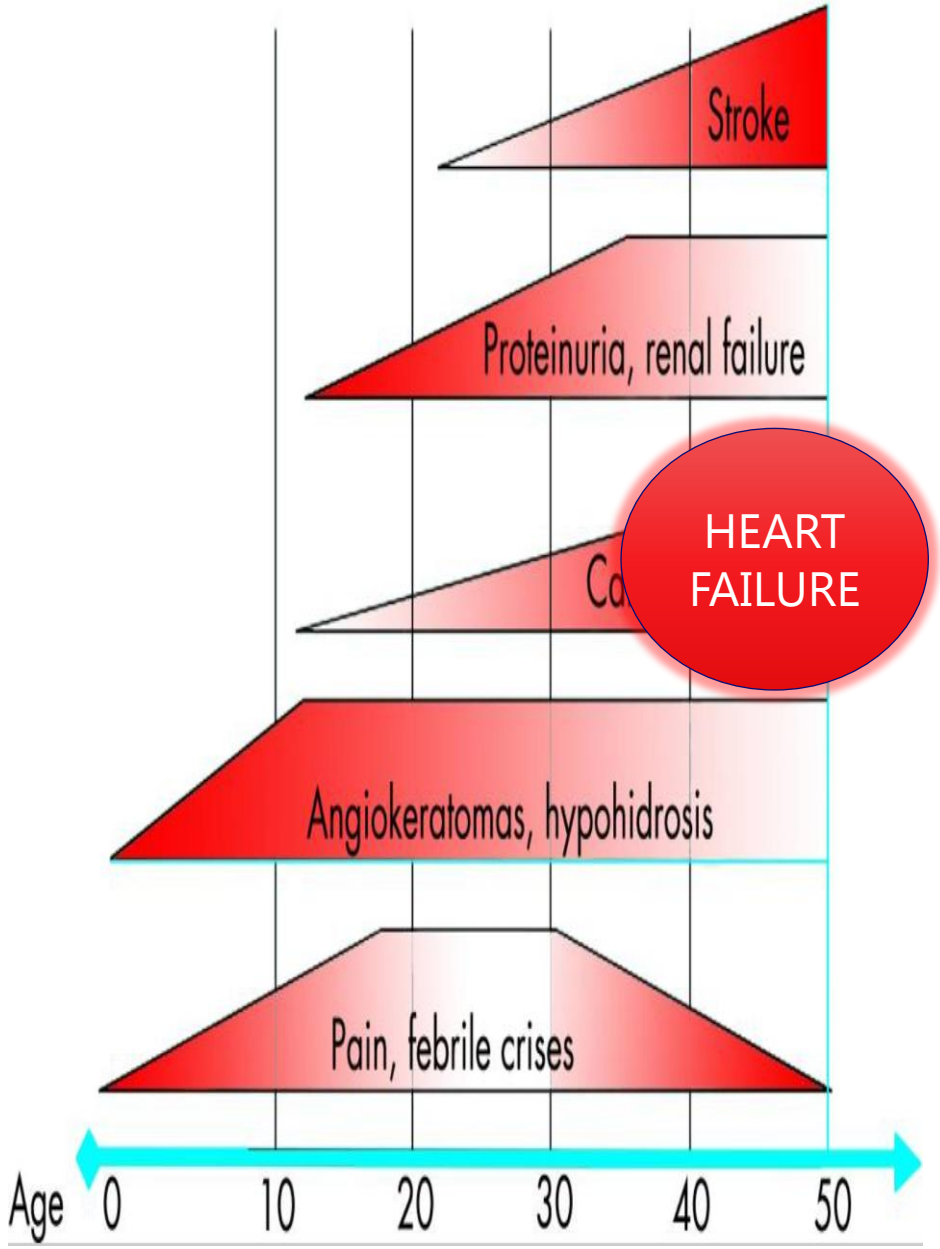
Background

- Fabry disease (FD) is an **X-linked LSD.**
- Caused by mutations in the **GLA gene –>** decreased/absent activity of α-galactosidase A.
- Cardiovascular (CV) manifestations include left **ventricular hypertrophy** (LVH), arrhytmias, valvular and vascular involvement.
- CV complications are the leading cause of **morbidity and mortality**.
- Over time, CV involvement can progress to **heart failure (HF)** - most common CV event in a registry



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Heart failure knowledge gap in FD

- Lack of prospective data regarding HF **prevalence, characteristics and prognosis** in Fabry disease.
- Echocardiography plays a **central role** in HF diagnosis, but echocardiographic alterations are common in Fabry patients.
- Whether currently recommended echocardiographic criteria for HF diagnosis apply in FD is **unknown**.

McDonagh, Theresa A., et al. "2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC." European heart journal 42.36 (2021): 3599-3726.

Aim

- We aimed to evaluate
  - HF **prevalence** and HF **characteristics**
  - Applicability of the **ESC echocardiography criteria** for HF diagnosis
  - **Prognostic value** of echocardiography criteria and HF diagnosis

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Methods

- Prospective observational single-center study.
- All adult (≥18 years) Fabry patients with genetically confirmed disease followed up in the National Referral Center were offered a diagnostic hospitalization to perform a complex assessment of their disease.
- All patients were invited for follow-up, including routine visits at 6-month intervals.

Methods

- **HF definition for echocardiography analysis** was based on meeting both the clinical and laboratory criteria:
  - Symptoms NYHA II–IV or NYHA I on established therapy including diuretics
  - Elevated natriuretic peptides (BNP>35 pg/mL / NTproBNP>125 pg/mL)
- **Echocardiographic criteria** and their cut-off values used were based on the **ESC 2021 HF guidelines** recommendations.
- The **primary endpoint of follow-up was a composite of all-cause mortality and worsening of HF**. The secondary endpoint included all CV hospitalizations.

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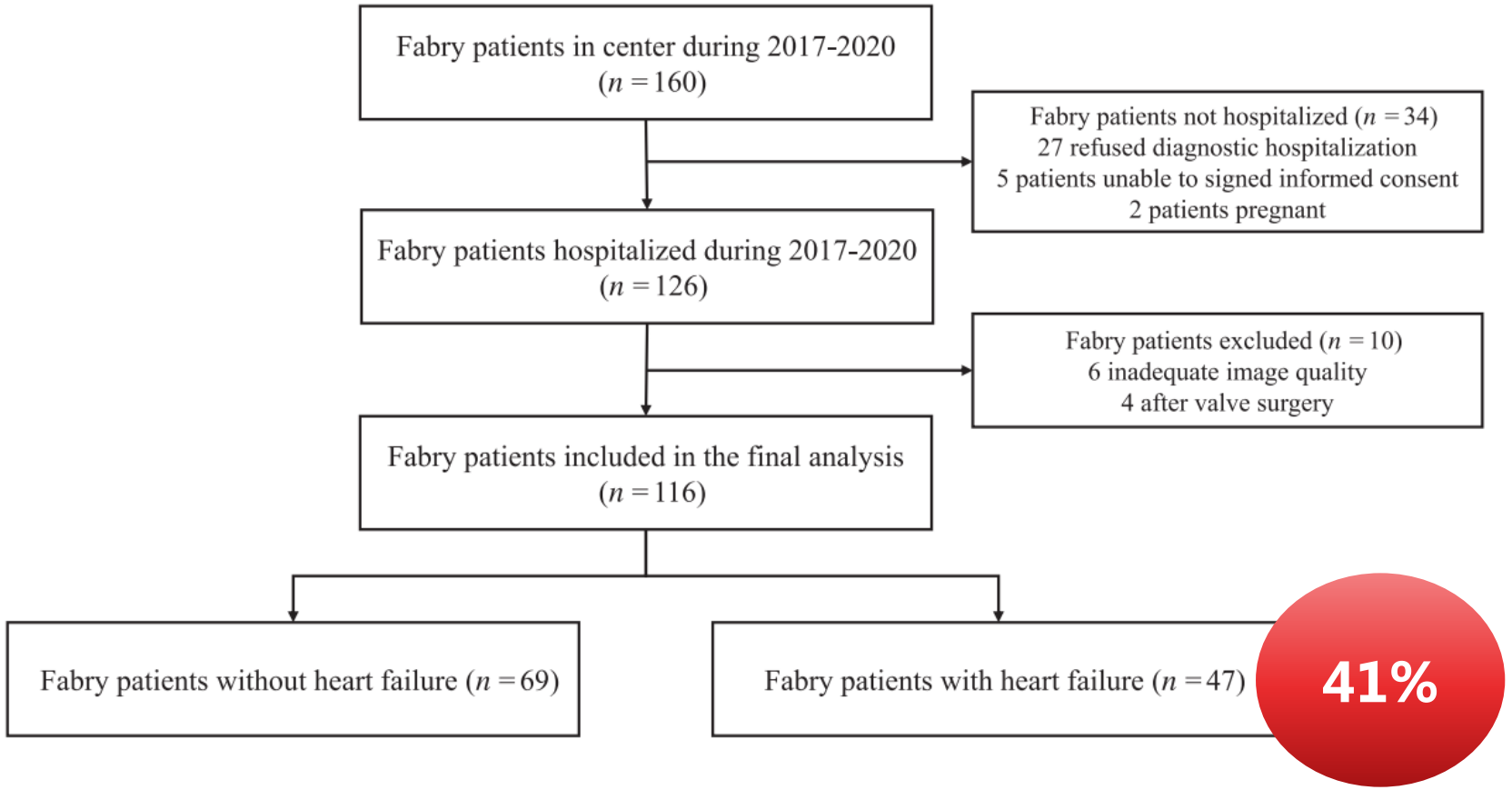
Results

- A total of **116** Fabry patients were included in the final analysis (Figure 1).

Figure 1 Patient flow by the presence or absence of heart failure.



Baseline characteristics

VARIABLE	NO HF GROUP (69)	HF GROUP (47)	P-VALUE
Age (years)	43 ± 14	58 ± 11	<0.001
Male sex	33 % (23)	62 % (29)	<0.007
Meinz Severity Score index	10 [5,18]	24 [19,35]	<0.001
Medical history			
Arterial hypertension	33 % (23)	66% (31)	<0.001
Dyslipidaemia	25 % (17)	57% (27)	<0.001
Coronary artery disease	1.4 % (1)	15 % (7)	0.005

Baseline characteristics

VARIABLE	NO HF GROUP (69)	HF GROUP (47)	P-VALUE
Laboratory values			
eGFR CKD-EPI	103 [88,114]	82 [53,95]	<0.001
NT-pro-BNP	50 [30,100]	402 [179,1306]	<0.001
BNP	26 [12,34]	117 [74,303]	<0.001
Medication			
Enzyme Replacement Therapy	57 % (39)	74 % (35)	0.048
Furosemide	0	28 % (13)	<0.001
Spironolactone	0	8.5 % (4)	0.014
ACEi	25 % (17)	43 % (20)	0.042
AT1 blockers	10 % (7)	15 % (7)	NS
Beta blockers	12 % (8)	51 % (24)	<0.001

Echocardiography characteristics

Variable	No-HF group (69)	HF group (47)	p-value
Structural parameters			
LV mass (g/m2)	76 [61,104]	134 [110,162]	<0.001
Relative wall thickness	0.38 [0.32,0.46]	0.5 [0.43,0.59]	<0.001
LV EF (%)	64 ± 5.5	64 ± 8.8	NS
Global longitudinal strain	20 [17,22]	15 [11,18]	<0.001
LAVi (ml/m2)	30 [25,34]	39 [30,46]	<0.001
LV structural pattern			
Concentric hypertrophy	16% (11)	66% (31)	<0.001
Concentric remodelling	13% (9)	11% (5)	
Excentric hypertrophy	1% (1)	9% (4)	
Normal LV mass	70% (48)	15% (7)	

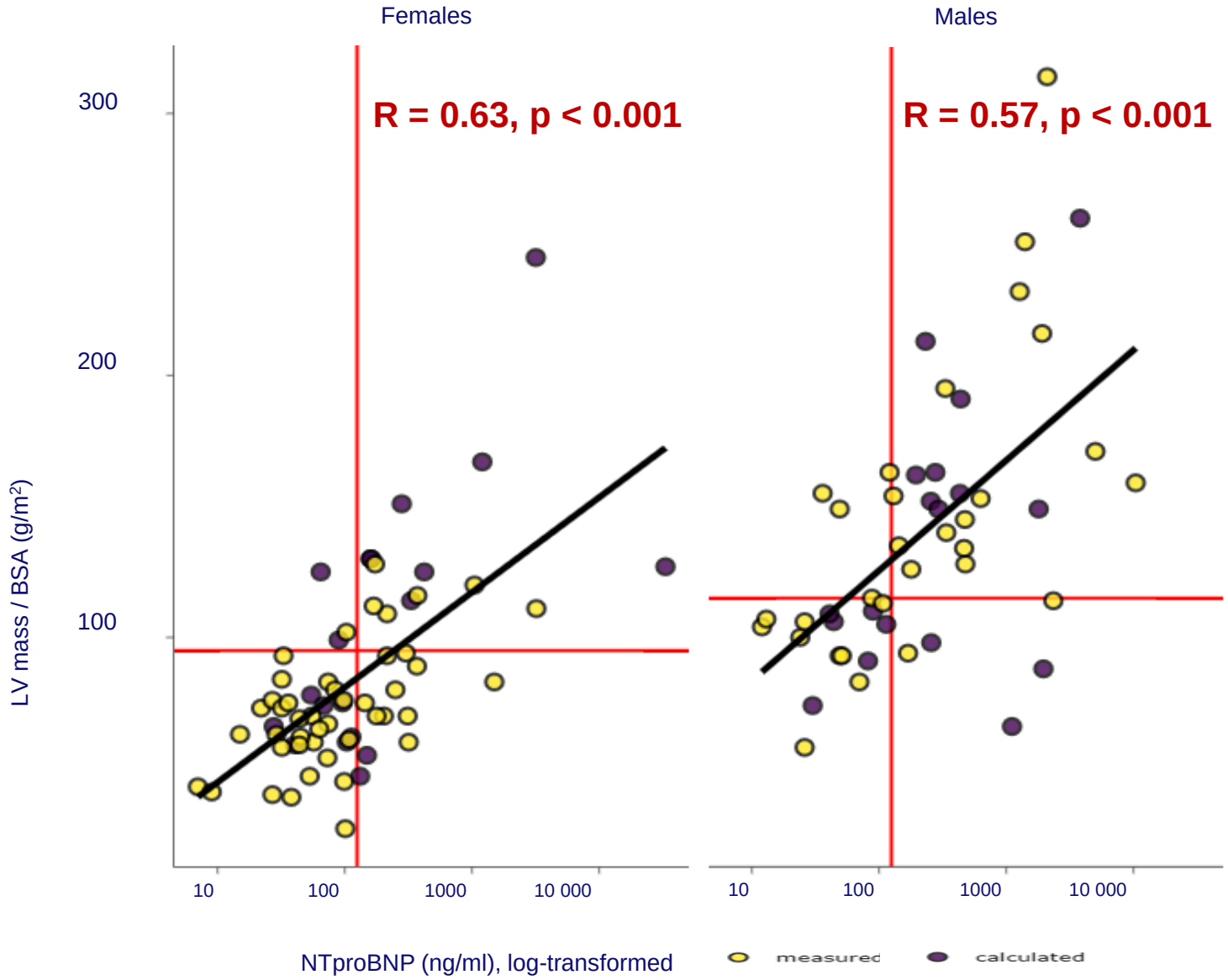
Echocardiography characteristics

VARIABLE	NO-HF GROUP	HF GROUP	P-VALUE
Diastolic function			
Grade I dysfunction	54% (33)	66% (21)	<0.001
Grade II dysfunction	2% (1)	22% (7)	
Grade III dysfunction	0% (0)	9% (3)	
Systolic function			
Preserved EF	100% (69)	91% (43)	0.048
Mildly reduced EF	0	6.4% (3)	
Reduced EF	0	2.1% (1)	

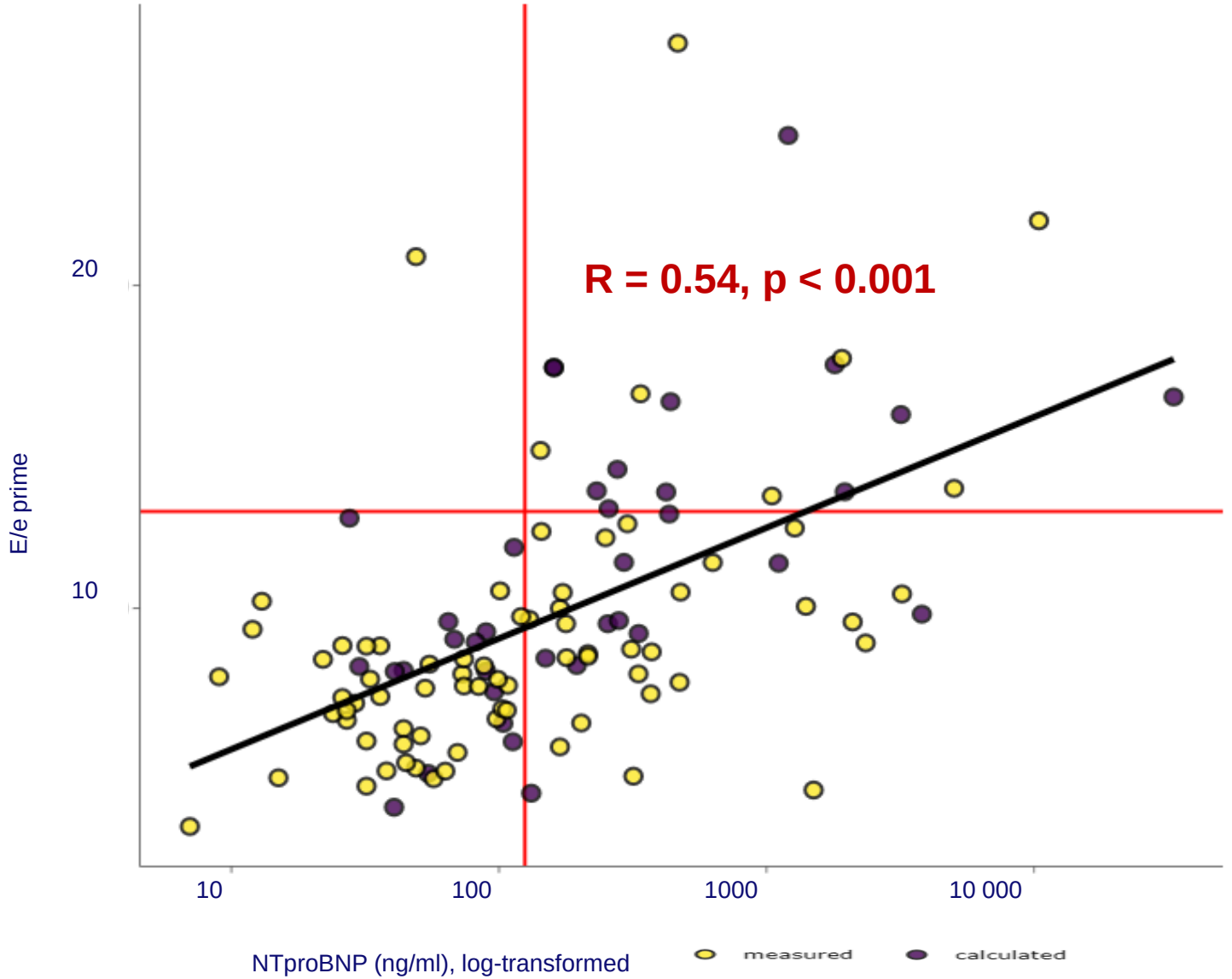
Diagnostic utility of echocardiographic criteria for HF-pEF (ESC HF guidelines 2021)

HF criterion	Accuracy	Sensitivity	Specificity	PPV	NPV
LVMi ≥115 g/m² m, ≥95 g/m² f	0.79	0.74	0.83	0.74	0.83
E/e´ > 9	0.78	0.77	0.78	0.71	0.83
GLS < 16%	0.77	0.60	0.88	0.76	0.77
RWT > 0.42	0.73	0.77	0.71	0.64	0.82
LAVi > 34 mL/m²	0.70	0.63	0.74	0.62	0.75
TR > 2.8 m/s	0.68	0.25	1.0	1.0	0.64
PASP > 35 mmHg	0.63	0.25	0.97	0.88	0.60

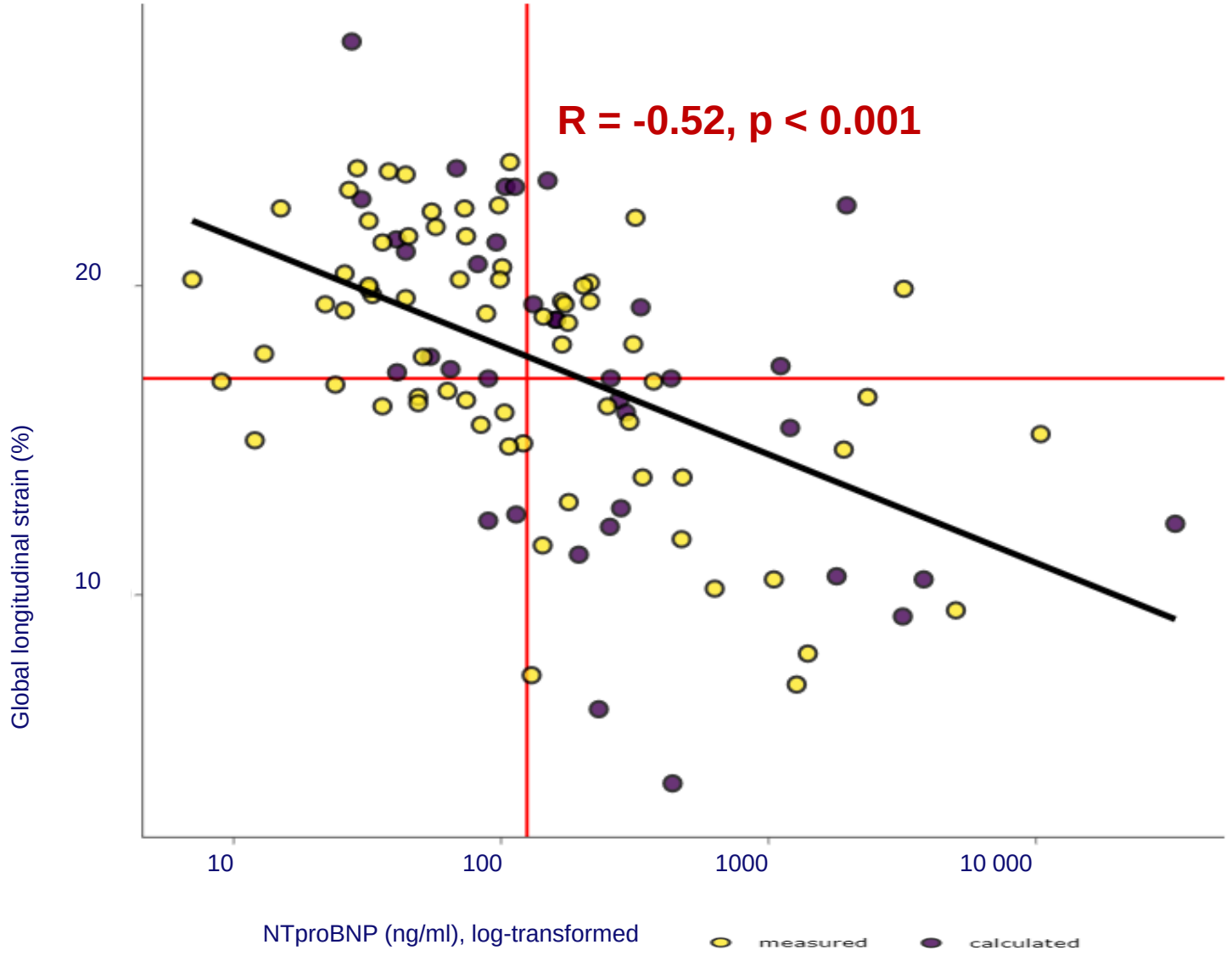
Correlation analysis of NT-pro-BNP and LVMi



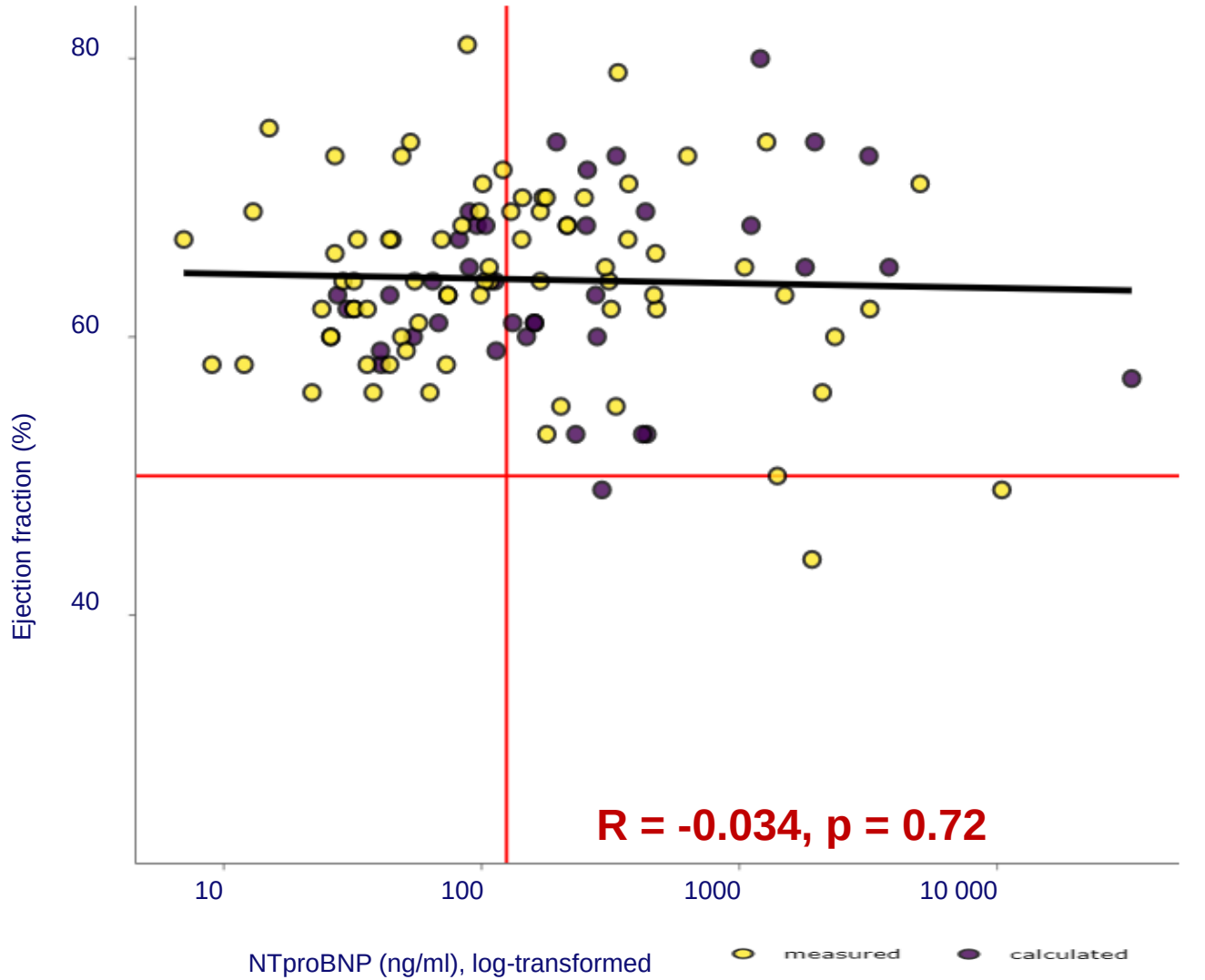
Correlation analysis of NT-pro-BNP and E/e´



Correlation analysis of NT-pro-BNP and GLS

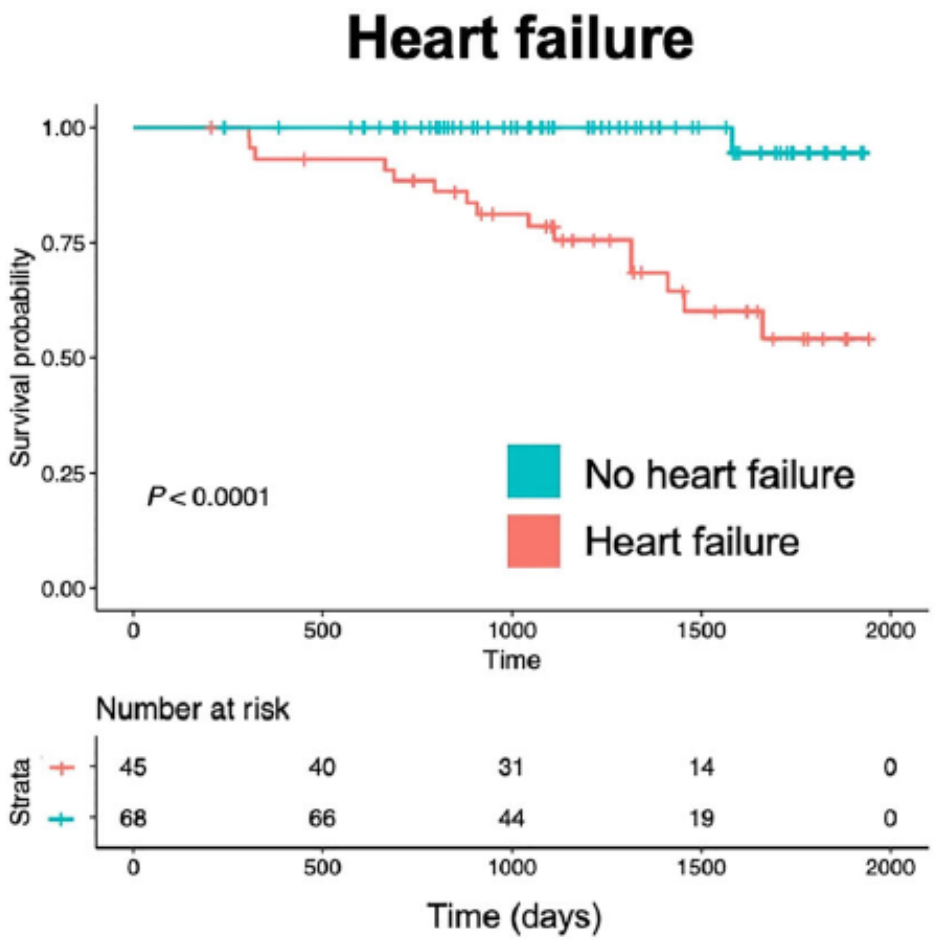


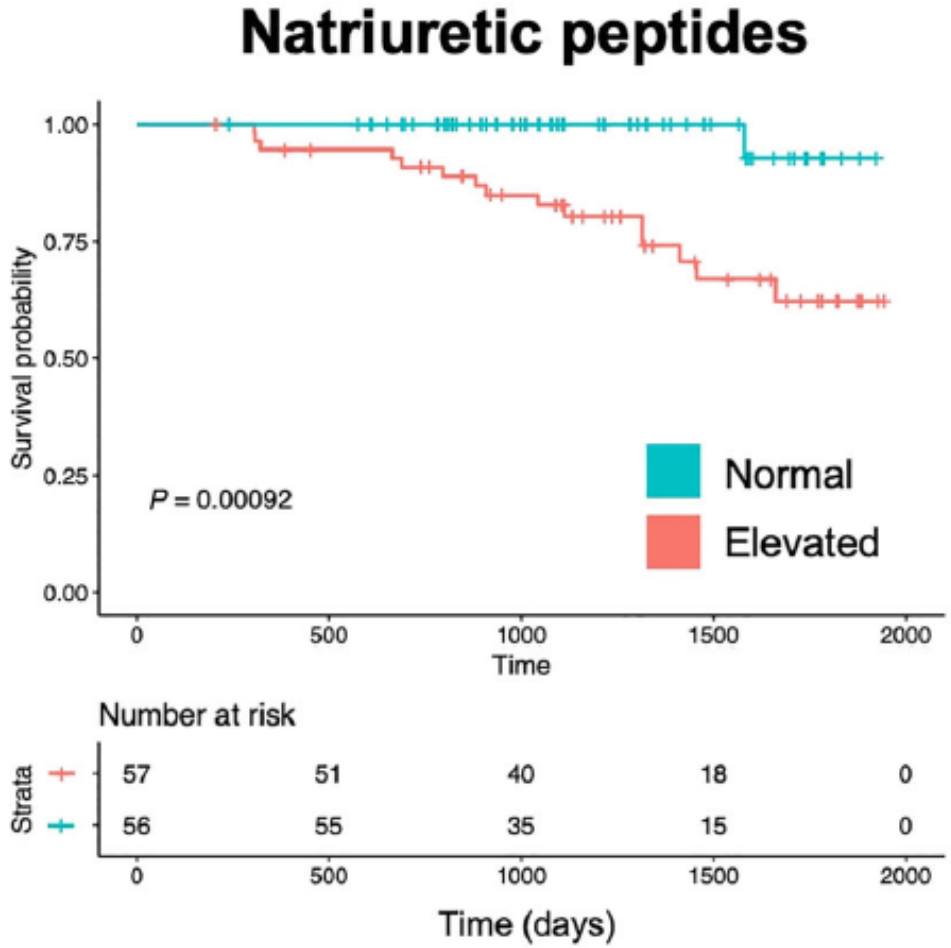
Correlation analysis of NT-pro-BNP and LV EF



Follow-up and event analysis

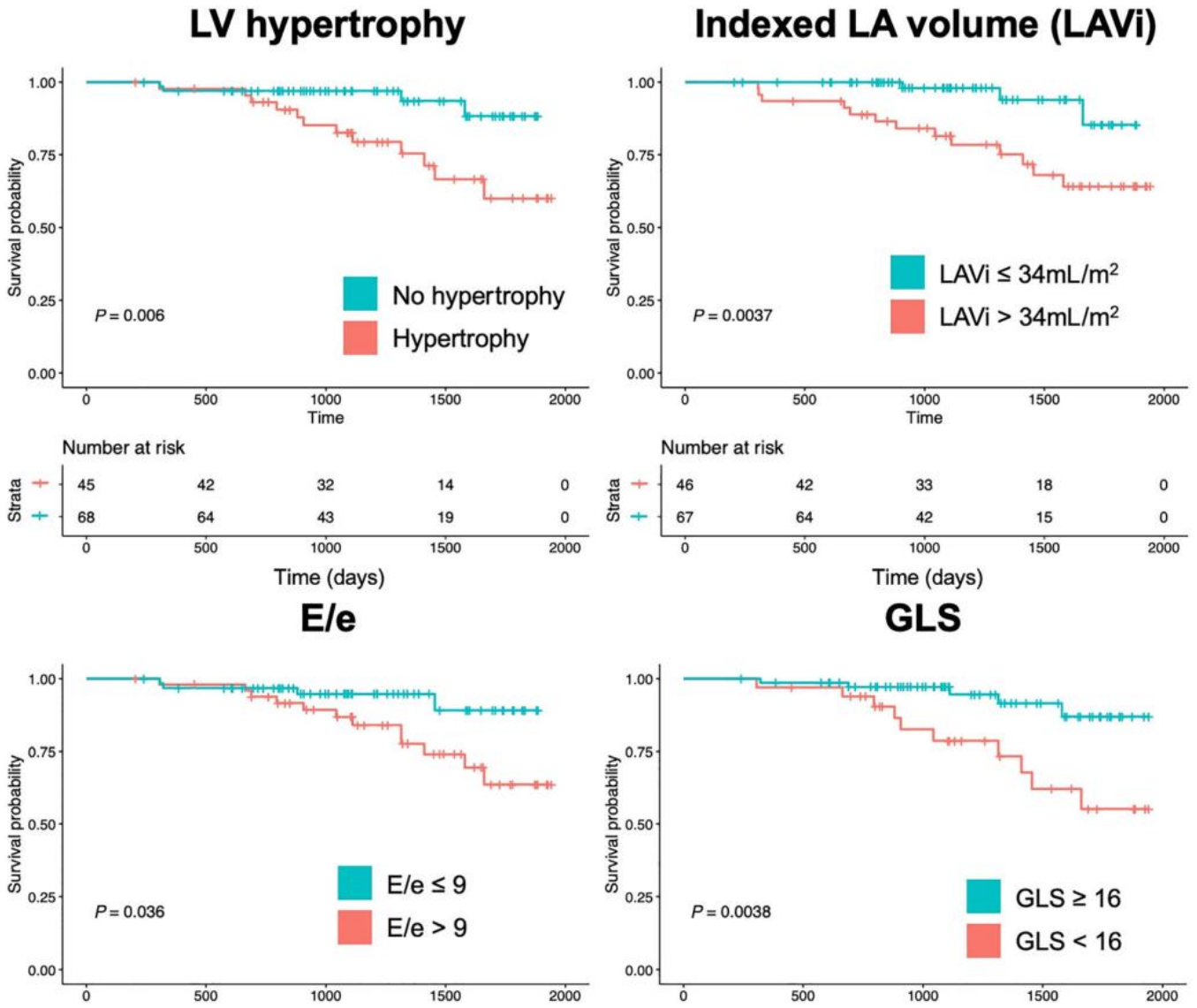
- Follow-up completed **113 of 116 patients** (average length 3.3 years).
- Primary outcome = all-cause mortality and HF worsening.





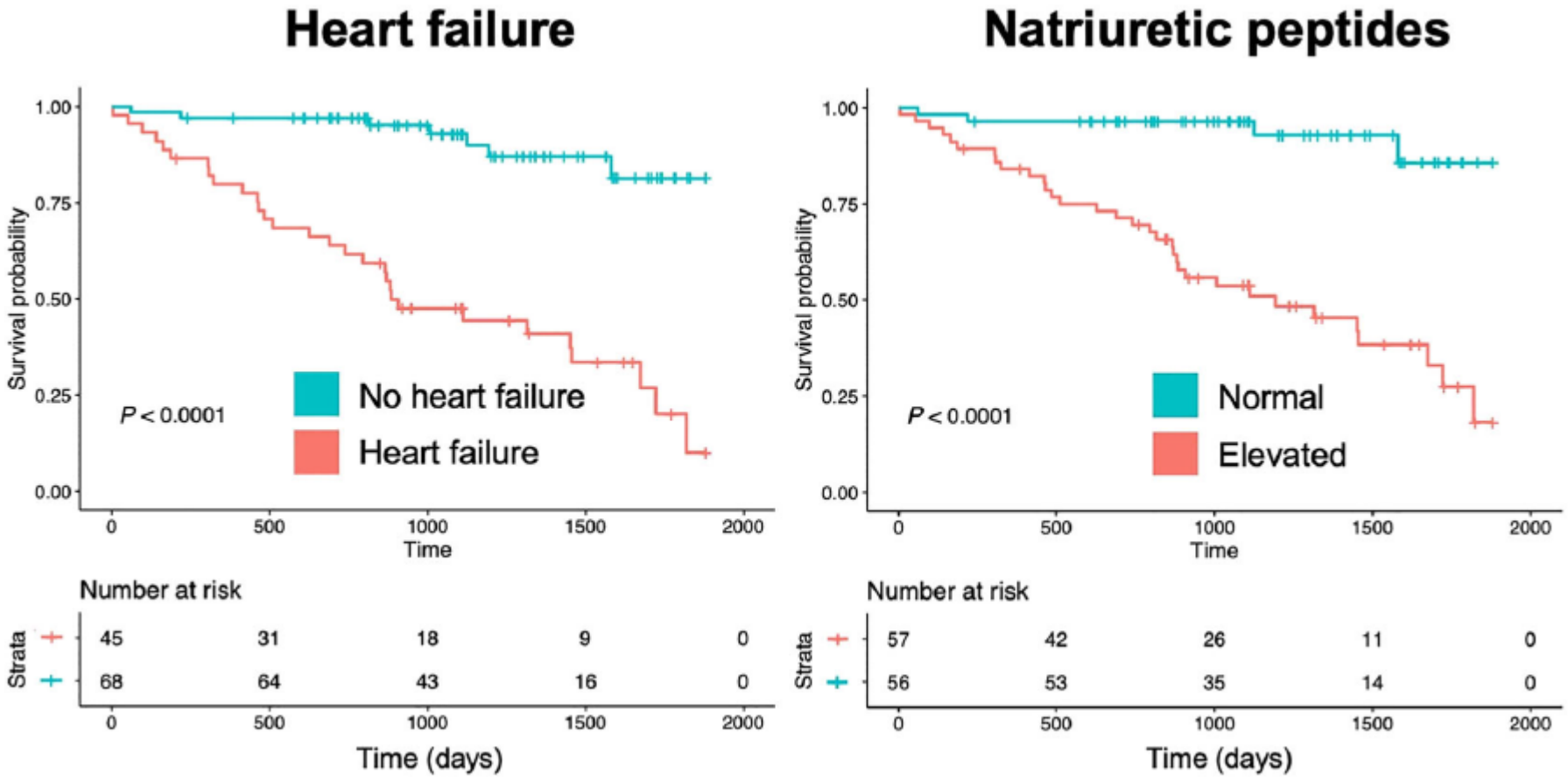
Follow-up and event analysis

- Primary outcome – main echocardiography parameters



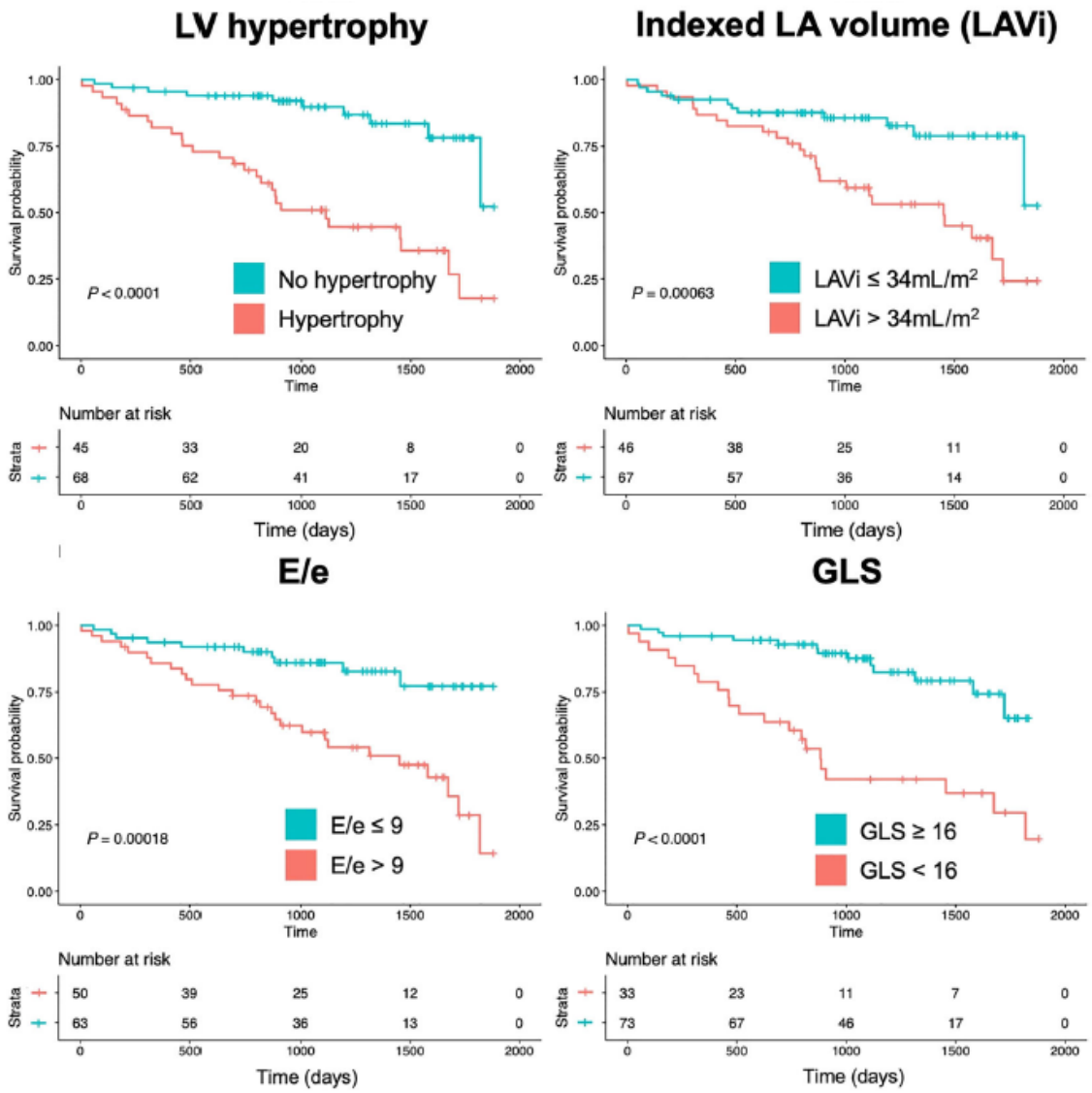
Follow-up and event analysis

- Secondary outcome = all CV hospitalizations



Follow-up and event analysis

- Secondary outcome = all CV hospitalizations



Limitations

- In our study, 34 of 160 Fabry patients were not capable or refused diagnostic hospitalization and thus were not included in the analysis.
- Elevated natriuretic peptides are not specific for HF and can be affected by decreased renal function in Fabry patients.
- The conversion of BNP to NT-proBNP for the purpose of correlation analysis.

Conclusions

- This study found a **high prevalence of HF (41%)** in adult patients with FD.
- **HFpEF** is the dominant phenotype.
- **LVH** with mild-to-moderate diastolic dysfunction is the leading cause of HF.
- **LVMi, E/e', and GLS** yielded the highest diagnostic utility for HF diagnosis and are significantly correlated with NT-pro-BNP levels and predictive of all-cause mortality and CV events.
- Echocardiographic criteria in the ESC HF **guidelines are applicable** for FD.
- HF diagnosis in FD is associated with a **high risk of death and CV events.**
- There is a great need for further studies to improve the knowledge of **HF therapy.**

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ORIGINAL ARTICLE

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