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ORIGINAL ARTICLE

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

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Abstract

Aims Fabry disease (FD) is often associated with heart failure (HF). However, data on HF prevalence, prognosis, and applicability of echocardiographic criteria for HF diagnosis in FD remain uncertain.

Methods and results We evaluated patients with genetically proven FD for symptoms and natriuretic peptides indicating HF. We then analysed the diagnostic utility of the currently recommended European Society of Cardiology (ESC) echocardiographic criteria for HF diagnosis and their relationship to natriuretic peptides. Finally, we examined the association between HF and echocardiographic criteria with mortality and cardiovascular events during follow-up. Of 116 patients with FD, 48 (41%) had symptomatic HF (mean age 58 ± 11 years, 62% male). HF with preserved ejection fraction (HF-pEF) was diagnosed in 43 (91%) patients, representing the dominant phenotype. Left ventricular mass index (LVMi) had the highest diagnostic utility (sensitivity 71% and specificity 83%) for HF diagnosis in FD, followed by E/e' $>$ 9 (sensitivity 76% and specificity 78%) and global longitudinal strain (GLS) $<$16% (sensitivity 54% and specificity 88%). Log N-terminal pro-brain natriuretic peptide correlated significantly with LVMi (r = 0.60), E/e' (r = 0.54), and GLS (r = 0.52) (all Ps $<$ 0.001) but not with left ventricular ejection fraction (r = −0.034, P = 0.72). During follow-up (mean 1208 ± 444 days), patients diagnosed with HF had a higher rate of all-cause mortality and worsening HF (33% vs. 1.5%, P $<$ 0.001). Abnormal LVMi, E/e' $>$ 9, and GLS $<$ 16% were all associated with higher all-cause mortality and worsening HF.

Conclusions This study found a high prevalence of symptomatic HF in FD patients. HF-pEF was the dominant phenotype. LVMi, E/e', and GLS yielded the highest diagnostic utility for HF diagnosis and were significantly correlated with natriuretic peptides levels. Echocardiographic criteria proposed by current ESC HF guidelines apply to Fabry patients and predict cardiovascular events. At follow-up, Fabry patients with HF diagnosis had high event rates and significantly worse prognosis than patients without HF.

Keywords Fabry disease; Heart failure; Echocardiography; Left ventricular hypertrophy; Global longitudinal strain; Natriuretic peptides

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Introduction

Fabry disease (FD) (OMIM 301500) is an X-linked lysosomal storage disorder caused by mutations in the GLA gene that lead to decreased or absent enzymatic activity of α-galactosidase A (α-gal A), resulting in progressive accumulation of neutral glycosphingolipids in various tissues.[1] Cardiac involvement is one of the leading causes of morbidity and mortality in FD.[1–3] The cardiovascular (CV) manifestations of FD, including left ventricular (LV) hypertrophy (LVH), rhythm and conduction abnormalities, and valvular and vascular involvement, have been described elsewhere.[1,2] Over time, CV involvement can progress to heart failure (HF), the most common CV event in a large Fabry registry.[3] Moreover, HF is becoming an increasingly important issue with an improved life expectancy of Fabry patients thanks to comprehensive therapy.[4–6] Echocardiography plays a central role in HF diagnosis.[7,8] However, echocardiographic alterations are common in Fabry patients compared with the general population.[1,2] Whether currently recommended echocardio-

graphic criteria for HF diagnosis apply in FD is unknown. Therefore, we aimed to evaluate HF characteristics of Fabry patients and the applicability of the European Society of Cardiology (ESC) echocardiographic criteria for HF diagnosis in our cohort of Fabry patients.[7,8]

Methods

Study design

This prospective analysis is part of a larger systematic diagnostic evaluation programme for patients with genetically confirmed FD who are followed up in the National Referral Center for FD of the General University Hospital in Prague. This prospective cohort has been continuously recruited since 1996. Between 2016 and 2020, all eligible patients ≥18 years were offered a diagnostic hospitalization to perform a complex assessment of FD manifestations. Inpatient management was chosen for logistic reasons. All patients were invited for follow-up, including routine outpatient visits at 6 month intervals. The diagnosis of FD was based on DNA mutation analysis of the GLA gene and α-gal A activity in plasma and leucocytes in male patients. The pathogenicity of a GLA variant was considered if described in the published literature in cases associated with classical multiorgan involvement and, recently, in cases of abnormal lyso-Gb_3 values.

Informed written consent was obtained from all patients and included an agreement with hospitalization, diagnostic procedures, and analysis of anonymized clinical data for scientific purposes. The research was approved by the Ethics Committee of the General Faculty Hospital and First Medical Faculty, Charles University, Prague. The investigation conforms to the principles outlined in the Declaration of Helsinki.

Determination of clinical and laboratory characteristics

All characteristics, including clinical history, electrocardiogram, echocardiography, and biochemistry, were obtained during hospitalization. The clinical laboratory at the General University Hospital in Prague processed all blood specimens. In September 2017, our clinical laboratory switched from brain natriuretic peptide (BNP) to N-terminal pro-BNP (NT-proBNP) evaluation (Elecsys®, Roche Diagnostics, Basel, Switzerland). We used a conversion formula to calculate NT-proBNP from BNP values for the correlation analysis.[9] The estimated glomerular filtration rate (eGFR) for this conversion was calculated using the Cockroft–Gault formula.[10] For other analyses, the Chronic Kidney Disease Epidemiology Collaboration formula was used.[11]

Clinical evaluation of Fabry disease manifestations

To evaluate the multisystemic involvement of FD, we recorded neurological (neuropathic pain or other signs of small fibre neuropathy, history of stroke, and white matter lesions on magnetic resonance imaging), kidney (presence of microalbuminuria, proteinuria, decrease in eGFR, and need for renal replacement therapy), cutaneous (presence of angiokeratomas, hypohidrosis, or hyperhidrosis), ocular (presence of cornea verticillata, Fabry cataract, and vessel tortuosity), gastrointestinal (pain and diarrhoea), and CV manifestations (HF signs and symptoms, arrhythmias, need for cardiac pacing or implantable cardioverter defibrillator implantation, and coronary events). We used the Mainz Severity Score Index (MSSI) to assess overall disease burden.[12]

Heart failure definition

Heart failure definition for echocardiographic analysis in this study was based on meeting the following clinical and laboratory criteria: (i) symptoms New York Heart Association (NYHA) Class II–IV or NYHA Class I on established HF therapy, including diuretics, and (ii) BNP $>$ 35 pg/mL or NT-proBNP $>$ 125 pg/mL.[7]

Echocardiography

Echocardiographic data were recorded using GE Vivid 7 and Vivid 9 systems (GE Healthcare, Chicago, IL), and measurements were performed using EchoPAC Workstation (GE Healthcare). All measurements were performed according to the current recommendations of the European Association of Cardiovascular Imaging and the American Society of Echocardiography.[13] All measurements were performed by a specialist blinded to patient HF status and natriuretic peptide levels. Echocardiographic criteria and their cut-off values used for this analysis were based on the ESC 2021 HF guidelines recommendations.[7] The criteria included assessment of LV ejection fraction (LVEF) to categorize the type of HF and structural alterations [LV mass index (LVMi) ≥115 g/m^2 for men and ≥95 g/m^2 for women], relative wall thickness ($>$0.42), left atrial volume index (LAVi $>$ 34 mL/m^2) and functional alterations at rest (E/e' $>$ 9), pulmonary artery systolic pressure (≥35 mmHg), and/or tricuspid regurgitation velocity (≥2.8 m/s). We also used the GLS cut-off value $<$16% proposed by the ESC 2021 HF guidelines as a marker of impaired longitudinal systolic function.[7] First, we tested the diagnostic utility (sensitivity and specificity) of these echocardiographic criteria for HF diagnosis in our FD population. We further tested the diagnostic accuracy of the ESC Heart Failure Association recommended echocardiography criteria in the Heart Failure

Association Pre-test Assessment, Echocardiography & Natriuretic Peptide, Functional Testing, Final Etiology (HFA–PEFF) diagnostic algorithm.[8] Finally, a correlation analysis was performed to evaluate the strength of the relationship between natriuretic peptide levels and each of the main echocardiographic parameters.

Follow-up and adverse events assessment

All patients were invited for follow-up, including routine outpatient visits at 6 month intervals. Adverse events were collected during the follow-up visit and at any additional clinical assessment required because of patient condition. An episode of worsening HF was defined as an unplanned hospitalization or an urgent visit necessitating intravenous therapy for HF. The primary endpoint for this study was a composite of all-cause mortality and worsening of HF. The secondary endpoint included all CV hospitalizations.

Statistical analysis

Categorical variables were represented using percentages and continuous variables using means ± standard deviation with normally distributed variables and median [25th, 75th percentile] in non-normal distributions. Shapiro–Wilk's test was used to assess normality. Differences in continuous variables were compared by *t*-test or the Mann–Whitney *U* test, as appropriate. The Pearson correlation coefficient was used to determine the relationship between natriuretic peptides and continuous variables. To achieve a more normal distribution, natriuretic peptides were log-transformed before analysis. Sensitivities and specificities were calculated from contingency tables. Differences in event rates were assessed using the Kaplan–Meier estimator with the log-rank test. R software v 4.1.2 (The R Foundation for Statistical Computing, Vienna, Austria) was applied to perform the analyses. A *P*-value <0.05 was considered statistically significant.

Results

Baseline characteristics and concomitant therapy

During the study period, 160 patients with FD were followed up in our centre. Thirty-four patients were excluded from the final analysis because they did not undergo hospitalization (2 were pregnant, 5 had a severe neurological impairment, and 27 refused diagnostic hospitalization). All 126 hospitalized patients underwent echocardiographic examination, but 10 were excluded from the final echocardiographic analysis (6 had inadequate image quality and 4 had prior valve surgery, thereby invalidating the predefined analysis). A total of 116 unique examinations were included in the final analysis (*Figure 1*). Overall, 47 (41%) patients met HF criteria (symptoms and natriuretic peptides elevation). Baseline characteristics according to the presence or absence of HF are listed in *Table 1*. Compared with the non-HF population, patients with HF were frequently older and male and had more comorbidities (coronary artery disease, arterial hypertension, dyslipidaemia, atrial fibrillation, and chronic obstructive pulmonary disease). Patients with HF also had a higher MSSI. As expected, the HF group had significantly worse exercise capacity and tolerance assessed by a 6 min walking test. In addition, patients with HF had significantly lower eGFR. There was no difference in the prevalence of HF in patients with classic compared with late-onset phenotype. *Table 1* shows the concomitant therapy of the two groups. Predictably, the

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

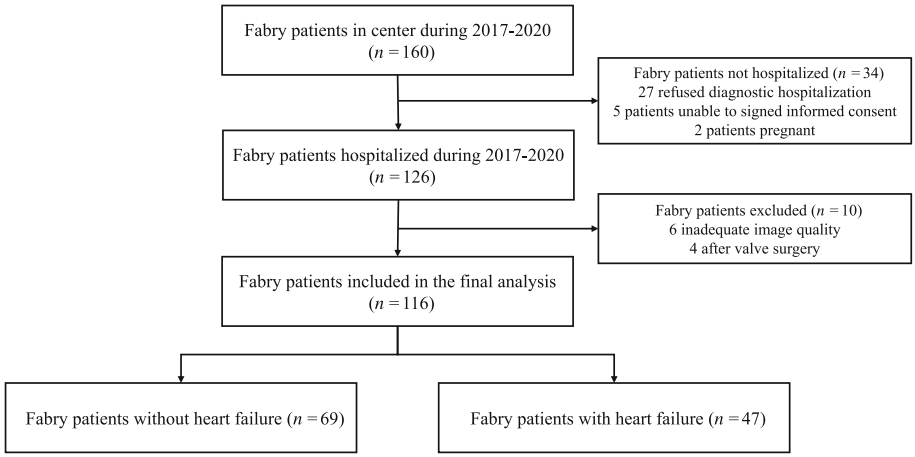

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Table 1 Baseline characteristics of the study population by the presence or absence of HF

Variable	Non-HF group (69)	HF group (47)	*P*-value
Age (years)	43 ± 14	58 ± 11	<0.001
Male sex	33% (23)	62% (29)	<0.007
Weight (kg)	76 [64, 92]	81 [69, 94]	NS
Height (cm)	170 ± 9.3	173 ± 9.5	NS
BMI (kg/m^2)	27 [23, 29]	26 [24, 30]	NS
Systolic BP (mmHg)	129 ± 15	134 ± 20	NS
Diastolic BP (mmHg)	82 ± 11	81 ± 12	NS
Heart rate (b.p.m.)	75 [70, 80]	70 [64, 80]	NS
MSSI total	10 [5, 18]	24 [19, 35]	<0.001
Fabry disease phenotype			
Classic variant	61% (42)	57% (27)	NS
Late-onset variant	39% (27)	43% (20)	
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
Myocardial infarction	0	2.1% (1)	NS
Atrial fibrillation	0	28% (13)	<0.001
Diabetes	5.8% (4)	17% (8)	0.057
COPD	4.3% (3)	17% (8)	0.025
6 min walking test			
Distance	500 [450, 560]	400 [350, 521]	<0.001
Borg scale	1 [0, 3]	3 [1, 4.5]	<0.004
Heart rate (b.p.m.)	91 [80, 101]	81 [72, 95]	0.011
Laboratory values			
eGFR Cockcroft–Gault	114 [99, 140]	93 [60, 110]	<0.001
eGFR CKD-EPI	103 [88, 114]	82 [53, 95]	<0.001
NT-proBNP	50 [30, 100]	402 [179, 1306]	<0.001
BNP	26 [12, 34]	117 [74, 303]	<0.001
CRP	1.4 [0, 3.8]	3 [0, 7.2]	0.047
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
Statins	28% (19)	47% (22)	0.033

ACEi, angiotensin-converting enzyme inhibitor; AT1, angiotensin II receptor type 1; BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HF, heart failure; MSSI, Mainz Severity Score Index; NS, not significant; NT-proBNP, N-terminal pro-brain natriuretic peptide.

HF population was more frequently treated by specific therapy, furosemide, spironolactone, beta-blockers, and statins.

Echocardiographic characteristics

Echocardiographic characteristics based on the presence or absence of HF are presented in *Table 2*. There were significant differences in all HF echocardiographic criteria except of LVEF between the HF and non-HF groups. Despite the preserved LVEF in most patients, GLS alteration was significantly more common in the HF group. The leading LV structural pattern in the HF group was LV concentric hypertrophy, with fewer patients presenting with concentric remodelling and eccentric hypertrophy. Although diastolic dysfunction is prevalent in FD, only three patients from the entire FD population had a restrictive filling pattern.

2021 European Society of Cardiology Guidelines for the diagnosis and treatment of heart failure

Analysis of the diagnostic utility of the current echocardiographic criteria for an HF-pEF diagnosis[7] in our cohort of Fabry patients is summarized in *Table 3*. The highest diagnostic accuracy had abnormal LVMi followed by E/e' > 9 and GLS < 16%.

Recommendation for heart failure with preserved ejection fraction diagnosis (Heart Failure Association diagnostic algorithm)

Analysis of the diagnostic accuracy of the currently recommended echocardiographic criteria for HF-pEF[8] diagnosis is summarized in *Table 4*. The highest diagnostic accuracy had abnormal E/e' > 9, followed by criteria for LVH.

Table 2 Echocardiographic characteristics of the study population by the presence or absence of HF

Variable	Non-HF group (69)	HF group (47)	*P*-value
Structural parameters			
LV mass (g/m^2)	76 [61, 104]	134 [110, 162]	<0.001
Relative wall thickness	0.38 [0.32, 0.46]	0.50 [0.43, 0.59]	<0.001
LVEF (%)	64 ± 5.5	64 ± 8.8	NS
GLS	20 [17, 22]	15 [11, 18]	<0.001
LAVi (mL/m^2)	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)	
Eccentric hypertrophy	1% (1)	9% (4)	
Normal LV mass	70% (48)	15% (7)	
Functional parameters			
Mitral E velocity (cm/s)	70 [57, 83]	67 [54, 80]	NS
Mitral A velocity (cm/s)	51 ± 15	59 ± 16	0.008
Deceleration time	181 [154, 202]	205 [168, 259]	0.012
Septal e′ (cm/s)	8.0 [5.7, 10]	4.7 [3.5, 5.5]	<0.001
Lateral e′ (cm/s)	10.0 [8.3, 14]	7.7 [6, 9]	<0.001
Mitral E/e′ ratio	7.6 [6.3, 8.8]	10.0 [9.2, 14]	<0.001
Diastolic function			
Normal	44% (27)	3% (1)	<0.001
Grade I dysfunction	54% (33)	66% (21)	
Grade II dysfunction	2% (1)	22% (7)	
Grade III dysfunction	0% (0)	9% (3)	
Systolic function			
Preserved EF	100% (69)	91% (43)	0.048
Mid-range EF	0	6.4% (3)	
Reduced EF	0	2.1% (1)	
Significant valvular disease	0% (0)	2.1% (1)	NS

EF, ejection fraction; GLS, global longitudinal strain; HF, heart failure; LAVi, left atrial volume index; LV, left ventricular; LVEF, left ventricular ejection fraction; NS, not significant.

Table 3 Diagnostic utility of recommended echocardiographic criteria for HF-pEF diagnosis (ESC HF guidelines 2021) in FD

HF criterion	Accuracy	Sensitivity	Specificity	PPV	NPV	*N*
LVMi ≥ 115 g/m^2 men and ≥95 g/m^2 women	0.78	0.71	0.83	0.71	0.83	111
E/e′ > 9	0.77	0.76	0.78	0.68	0.84	111
GLS < 16%	0.76	0.54	0.88	0.71	0.77	103
RWT > 0.42	0.74	0.79	0.71	0.624	0.84	111
LAVi > 34 mL/m^2	0.68	0.59	0.74	0.57	0.75	110
TR > 2.8 m/s	0.68	0.20	1.0	1.0	0.66	63
PASP > 35 mmHg	0.63	0.20	0.97	0.83	0.61	57

ESC, European Society of Cardiology; FD, Fabry disease; GLS, global longitudinal strain; HF, heart failure; HF-pEF, heart failure with preserved ejection fraction; LAVi, left atrial volume index; LVMi, left ventricular mass index; *N*, number of patients with valid measurement; NPV, negative predictive value; PASP, pulmonary artery systolic pressure; PPV, positive predictive value; RWT, relative wall thickness; TR, tricuspid regurgitation.

Correlation analysis of the N-terminal pro-brain natriuretic peptide values and echocardiographic criteria

The overall linear relationship between log (NT-proBNP) and echocardiographic parameters for HF diagnosis is shown in *Figure 2A–2D*. The strongest correlation was found between log (NT-proBNP) and LVMi (*Figure 2A*). There was also a highly significant negative correlation between log (NT-proBNP) and GLS (*Figure 2B*); a correlation between log (NT-proBNP) and LVEF was not observed (*Figure 2C*). A significant correlation with a higher magnitude of variance was found for E/e′ (*Figure 2D*).

Follow-up and event analysis

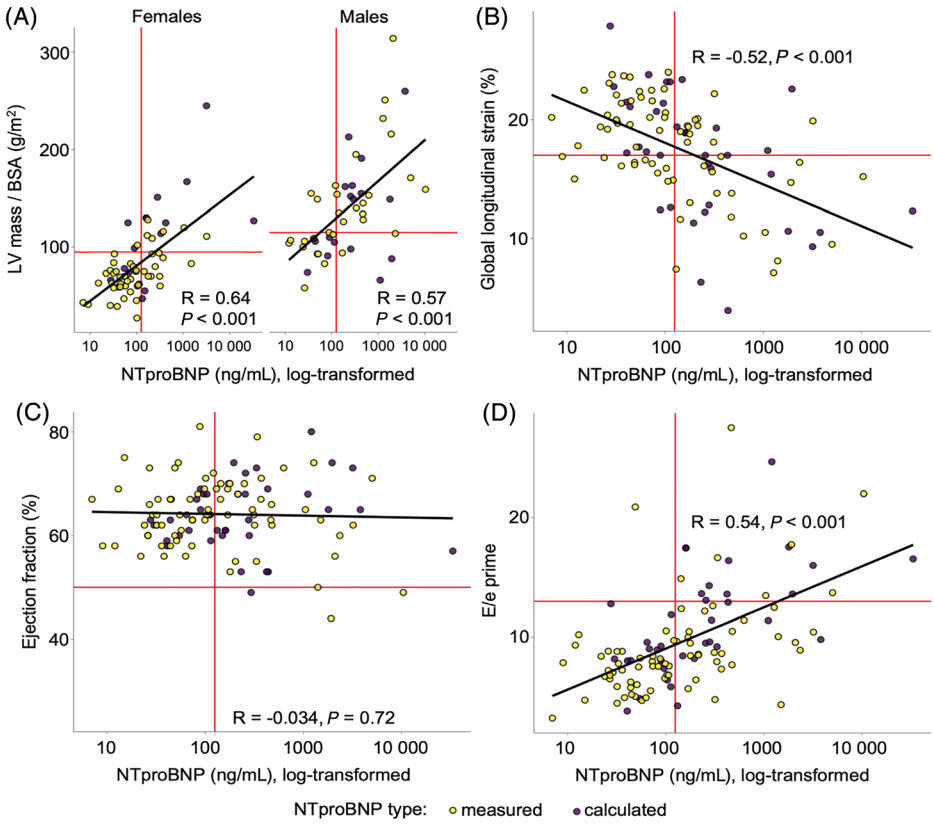
Follow-up was completed in 113 of 116 patients, and the average length was 1208 ± 444 days. During follow-up, 16 (14%) patients had reached the primary endpoint and 37 (33%) the secondary endpoint. Patients diagnosed with HF had a significantly worse primary outcome (*Figure 3*, $P < 0.001$). The same was true for patients with elevated natriuretic peptides, LVH, LAVi > 34 mL/m^2, E/e′ > 9, and GLS < 16% (*Figure 3*). Patients with an HF diagnosis and those with elevated natriuretic peptides, LVH, LAVi > 34 mL/m^2, E/e′ > 9, and GLS < 16% also had a significantly worse secondary outcome (*Figure 4*).

Table 4 Diagnostic utility of the recommended echocardiographic criteria for HF-pEF diagnosis (HFA–PEFF diagnostic algorithm) in FD

HF criterion	Accuracy	Sensitivity	Specificity	PPV	NPV	*N*
E/e′ ≥ 9	0.77	0.76	0.78	0.68	0.84	111
E/e′ ≥ 15	0.68	0.19	0.99	0.89	0.67	111
Septal e′ < 7 or lateral e′ < 10	0.67	0.93	0.51	0.53	0.92	111
LAVi > 29 mL/m^2	0.57	0.78	0.45	0.46	0.78	110
LAVi > 34 mL/m^2	0.68	0.59	0.74	0.57	0.75	110
LVMi ≥ 115 g/m^2 men and ≥95 g/m^2 women or RWT > 42 or wall diameter ≥ 12 mm	0.75	0.88	0.67	0.62	0.90	111
LVMi ≥ 149 g/m^2 men and ≥122 g/m^2 women and RWT > 42	0.70	0.40	0.88	0.68	0.71	111

FD, Fabry disease; HF, heart failure; HF-pEF, heart failure with preserved ejection fraction; LAVi, left atrial volume index; LVMi, left ventricular mass index; *N*, number of patients with valid measurement; NPV, negative predictive value; PPV, positive predictive value; RWT, relative wall thickness.

Figure 2 Correlation analysis of the relationship between natriuretic peptide levels and the main echocardiographic parameters: (A) left ventricular (LV) mass index, (B) global longitudinal strain (GLS), (C) ejection fraction, and (D) E/e′. BSA, body surface area; NT-proBNP, N-terminal pro-brain natriuretic peptide.



Discussion

This study demonstrates several important findings. First, our study shows a high prevalence of symptomatic HF in a large cohort of Fabry patients despite the high rate of treatment with enzyme replacement therapy. This result aligns with several published studies showing progressive structural heart disease and CV complications in FD despite ERT.[14,15] The prevalence of HF in this study is higher than previous registry investigations reporting HF symptoms in up to 25% of patients.[2,3] This difference may be explained by two factors. First, our study included adults only. Second, we used a systematic assessment of all FD patients with detailed recordings of signs and symptoms of HF including routine natriuretic peptides measurement. Moreover, the current ESC HF diagnostic criteria were applied, whereas registries rely on reported HF symptoms and events that may underestimate the true prevalence of HF. HF was more prevalent in Fabry male patients, although a considerable proportion (38%) of patients with HF were women. This finding confirms that

Figure 3 Kaplan–Meier survival analysis of all-cause mortality and heart failure (HF) worsening according to HF diagnosis, natriuretic peptides, left ventricular (LV) mass index, left atrial (LA) volume index (LAVi), E/e', and global longitudinal strain (GLS).

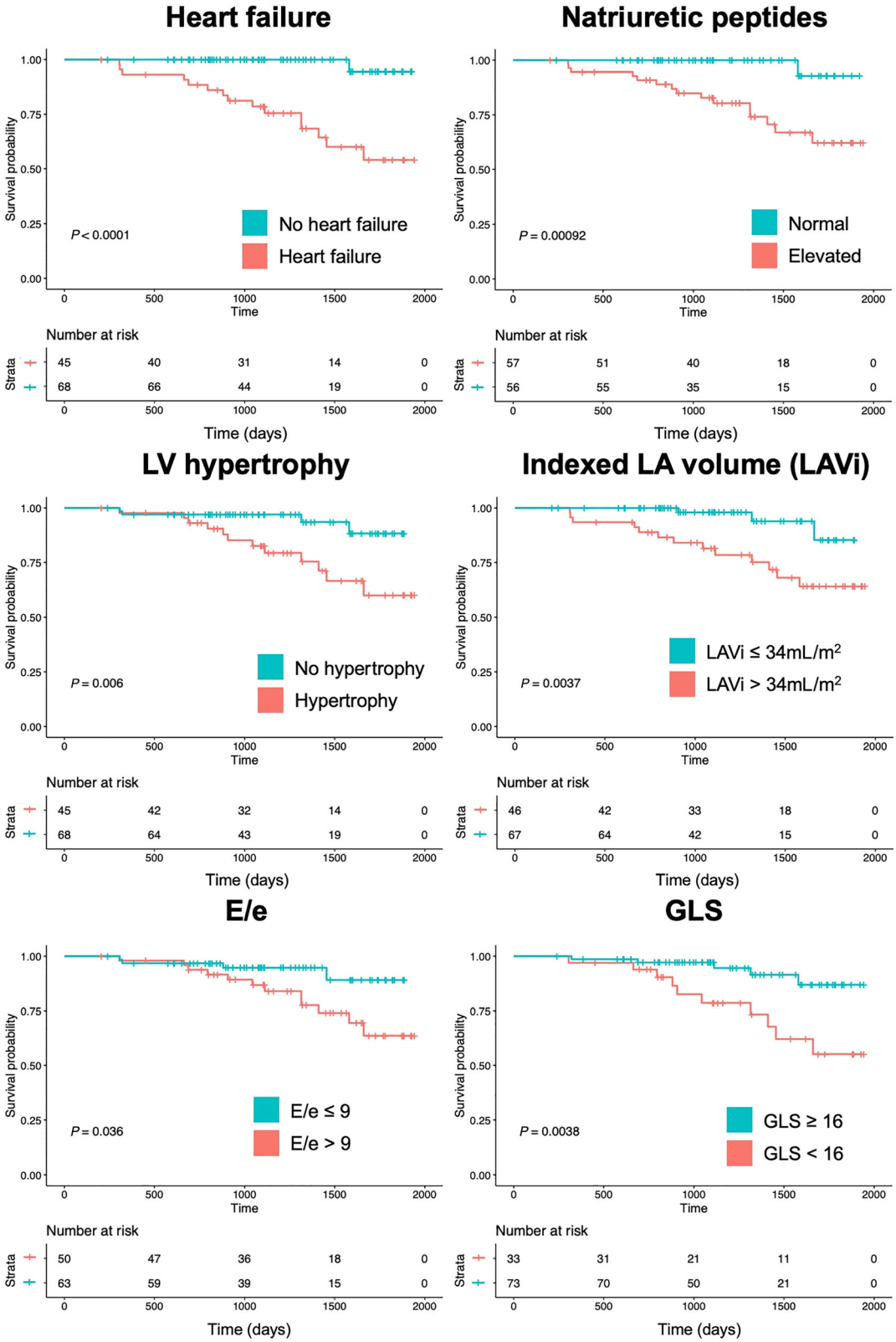


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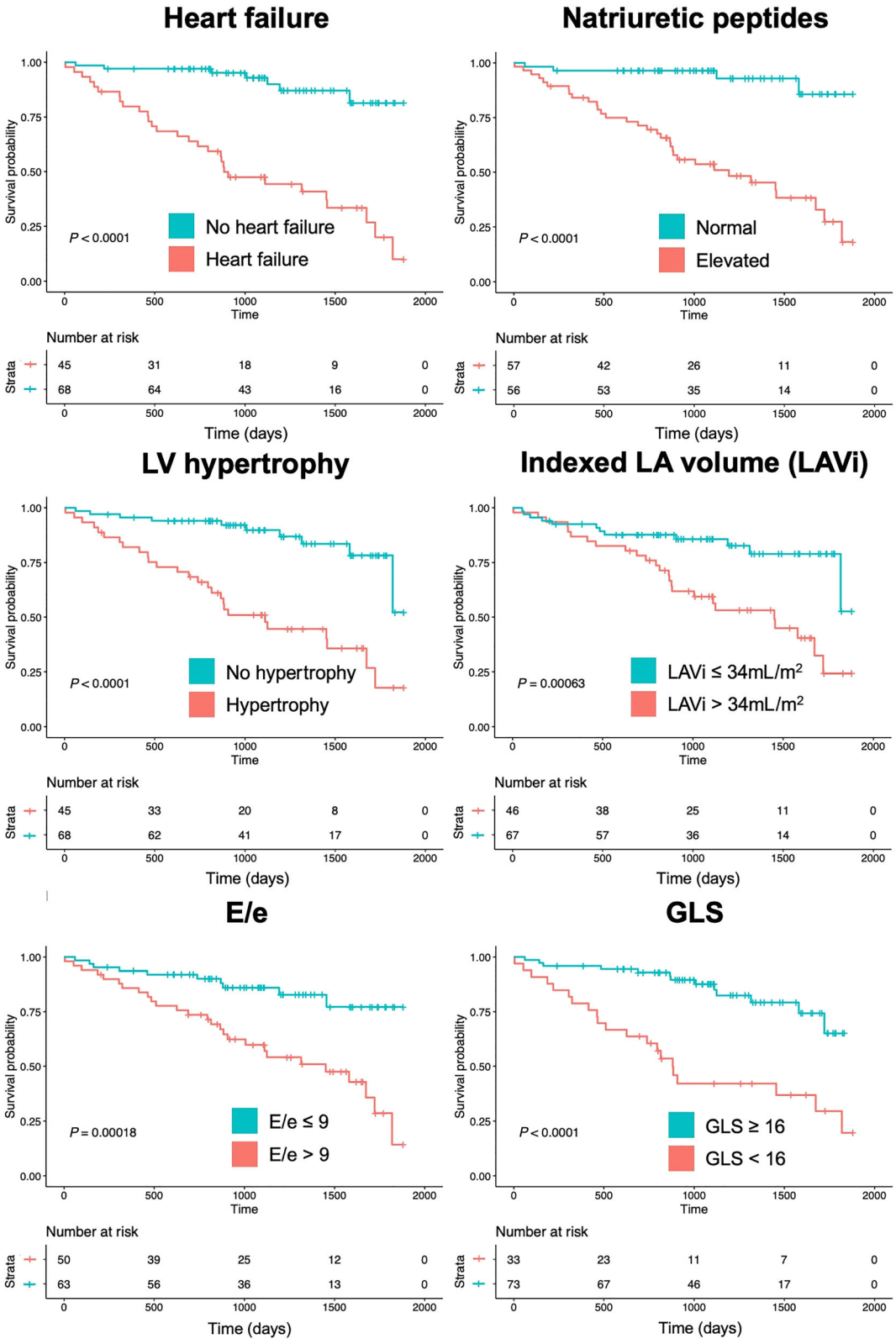
Figure 4 Kaplan–Meier survival analysis of cardiovascular hospitalizations according to heart failure diagnosis, natriuretic peptides, left ventricular (LV) mass index, left atrial (LA) volume index (LAVi), E/e', and global longitudinal strain (GLS).



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symptomatic cardiac involvement in adult women with FD is relatively common. In addition, the role of comorbidities in Fabry patients was important. Our results showed significantly higher rates of arterial hypertension, coronary artery disease, atrial fibrillation, and renal impairment in the HF group. All these factors play a potentially important role in HF development and modify its management.[7]

Cardiac hypertrophy is the predominant cause of depressed contractility and diastolic filling impairment in FD.[16] Accordingly, increased LVMi was identified as the most frequent structural alteration in our HF patients. Only one patient from the entire cohort had HF with reduced ejection fraction (EF), and few patients had mildly reduced HF.[7] Echocardiographic analysis also confirms that contractility impairment is usually masked by LVH structural changes and longitudinal systolic dysfunction assessed by GLS was prevalent in our Fabry patients. Although diastolic dysfunction is frequent in FD, only three patients from the entire FD population in our cohort had a restrictive filling pattern on echocardiography despite including Fabry patients with advanced cardiomyopathy. This result firmly argues against the classification of FD among causes of restrictive cardiomyopathy.

Further analysis of the diagnostic utility of the currently recommended echocardiographic criteria for HF diagnosis showed good applicability of current ESC HF guidelines[7] and the ESC HF-pEF diagnostic algorithm[8] in the FD cohort. The highest diagnostic accuracy from the currently recommended ESC HF guidelines with acceptable sensitivity and specificity had abnormal LVMi $\geq$ 115 g/m^2 for men and $\geq$95 g/m^2 for women. Good diagnostic accuracy of absolute values of GLS $<$ 16% for HF detection in our Fabry patients further supports the importance of routine GLS assessment in clinical practice. Using an E/e' cut-off point $>$9 led to good sensitivity and specificity for HF diagnosis compared with E/e' $\geq$ 15, which displayed high specificity but very low sensitivity for HF diagnosis in FD. This finding agrees with the modifications in echocardiographic parameters for HF-pEF in the recently issued 2021 ESC HF guidelines.[7]

Our analysis revealed significant correlations between natriuretic peptide levels and the echocardiographic criteria, including LVMi, GLS, and E/e'. As anticipated in FD, in whom most patients fulfil the criteria for HF-pEF or HF with mid-range EF, a correlation between natriuretic peptide levels and LVEF was not observed. These results confirm previous studies showing that natriuretic peptide levels are good markers of cardiac involvement and diastolic dysfunction in FD[17,18] and underscore the importance of routine natriuretic peptides measurements in FD, which may help its severity assessment. This information may help clinicians in complex decision-making process to initiate FD specific therapy, enzyme replacement,[4,5] or molecular chaperone (migalastat).[6,19]

Finally, our follow-up data showed a considerable risk of mortality and episodes of worsening HF, as well as high rates of CV hospitalizations in FD patients with an established HF diagnosis. In addition, patients with elevated natriuretic peptides, abnormal LVMi, LAVi, GLS $<$ 16%, and E/e' $>$ 9 had higher mortality rates, HF worsening, and CV hospitalizations than their counterparts. These results confirm the prognostic value of natriuretic peptides and these echocardiographic criteria in FD. Current recommendations on HF management in FD are largely based on expert consensus,[16] suggesting the need for further studies on HF therapy in this specific population.

Strengths and limitations

The primary strength of our study is the prospective design. Another strength is that the Czech Republic has a single centre for FD, which provides detailed clinical, echocardiographic, and biochemical records for a substantial group of Fabry patients. However, our study has several limitations. In our study, 34 of 160 Fabry patients were not capable or refused diagnostic hospitalization and thus were not included in the analysis. Furthermore, elevated natriuretic peptides are not specific for HF and can be affected by decreased renal function in Fabry patients. Finally, the conversion from BNP to NT-proBNP represents another limitation of our study.

Conclusions

This study found a high prevalence of HF in adult patients (in both hemizygous men and heterozygous women) with FD. HF with preserved EF was the dominant phenotype. LVH associated 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 were significantly correlated with natriuretic peptide levels. These echocardiographic criteria were also predictive of all-cause mortality, HF worsening, and CV hospitalizations during follow-up. Proposed echocardiographic criteria in the recently updated ESC HF guidelines and recommendations are applicable for Fabry patients. HF diagnosis in FD is associated with a high risk of death, HF worsening, and CV hospitalization at follow-up, suggesting the need for further studies to improve knowledge of HF therapy in this specific population.

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Conflict of interest

D.R. reports consulting honoraria from Sanofi Genzyme. J.M. reports consulting honoraria from Sanofi Genzyme, Takeda, and Amicus. G.D. reports consulting honoraria from Sanofi Genzyme, Takeda, Amicus, and Protalix. A.L. reports consulting honoraria from Sanofi Genzyme, Takeda, Amicus, and AVROBIO.

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