

# NT-pro-BNP in patients with left ventricular hypertrabeculation/non-compaction

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## Abstract

**Aims** Left ventricular hypertrabeculation/non-compaction (LVHT) is a cardiac abnormality of unknown pathogenesis and frequently associated with neuromuscular disorders. The N-terminal fragment of the pro brain natriuretic peptide (NT-pro-BNP) is a prognostic marker in heart failure whose relevance in LVHT patients is largely unknown. The aim of the study was to assess the role of NT-pro-BNP levels as prognostic markers in LVHT.

**Methods and results** Data of LVHT patients were collected in a database from one echocardiographic laboratory since 1996. The hospital information system was screened for measurements of NT-pro-BNP levels, and their association with clinical and echocardiographic baseline parameters was retrospectively assessed. During follow-up, the endpoints were death and heart transplantation. In 113 patients (median age 57 years, 24% women), data about NT-pro-BNP measurements were found, ranging from 8 to 121 152 (median 2029) ng/L. High NT-pro-BNP levels were associated with heart failure, valvular abnormalities, diabetes mellitus, hypertension, angina pectoris, number of LVHT-affected segments, end-diastolic diameter, and systolic dysfunction. During a follow-up of 73 ( $\pm 64$ ; 0–237) months, 35% of the patients reached an endpoint. High NT-pro-BNP levels were associated with the occurrence of an endpoint ( $P < 0.001$ ). By multivariate analysis, predictors for endpoints were increased age ( $P = 0.0025$ ), atrial fibrillation ( $P = 0.0023$ ), natural logarithm of NT-pro-BNP levels ( $P = 0.0073$ ), diabetes mellitus ( $P = 0.014$ ), and thromboembolic events before diagnosis ( $P = 0.0347$ ).

**Conclusions** Also in LVHT patients, high NT-pro-BNP levels are indicators for death and heart transplantation.

**Keywords** Heart failure; Cardiomyopathy; Echocardiography; Biomarkers

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## Introduction

Left ventricular (LV) hypertrabeculation (LVHT), also called non-compaction, is a cardiac abnormality of unknown pathogenesis. Normally, the left ventricle shows up to three trabeculations, but in the case of LVHT, it has more than three trabeculations. LVHT affects frequently the apex, the lateral and inferior wall segments of the left ventricle.<sup>1</sup> LVHT can be diagnosed by echocardiography, magnetic resonance imaging (MRI), cardiac computed tomography, or ventriculography.<sup>2,3</sup> There are variable diagnostic criteria for echocardiography and MRI, and in the absence of a diagnostic golden standard, it is difficult to determine the prevalence of LVHT.<sup>4</sup>

The most common clinical presentations of LVHT are heart failure, arrhythmia, thromboembolism, and sudden cardiac death. LVHT is frequently associated with neuromuscular disorders and congenital cardiac diseases.<sup>4,5</sup>

The mortality rate of LVHT is estimated at 0.5% to 9.6% per year, and factors like the severity of heart failure, LV dysfunction, increased age, neuromuscular diseases, sinus tachycardia, and atrial fibrillation have been identified as indicators for death or heart transplantation in patients with LVHT.<sup>5–8</sup>

The N-terminal fragment of the pro brain natriuretic peptide (NT-pro-BNP) is a useful marker for diagnosis and prognosis of acute and chronic heart failure.<sup>9,10</sup> Different classification systems are used to distinguish normal from

pathologic NT-pro-BNP levels (Table 1). The classification of the European Society of Cardiology uses a cut-off level of 125 ng/L for chronic heart failure.<sup>9</sup> The classification of Stämpfli et al. is age and gender dependent.<sup>11</sup> The department for Clinical Chemistry and Laboratory Medicine, where the study was carried out, uses a classification according to the manufacturer's recommendations.<sup>12</sup>

It is largely unknown how NT-pro-BNP acts in patients with LVHT and if NT-pro-BNP could be of prognostic relevance in these patients. Only few studies investigated the long-term prognostic relevance of NT-pro-BNP in LVHT.<sup>11,13,14</sup>

The aim of the present study was to investigate NT-pro-BNP levels in adult patients with LVHT, considering the different classification systems, and to assess if NT-pro-BNP is a prognostic marker for mortality or heart transplantation.

## Patients and methods

The present study represents a subgroup analysis of subsequent patients in whom LVHT was diagnosed in one echocardiographic laboratory using the criteria of Stöllberger et al.<sup>1</sup> Previous findings from this cohort have been published.<sup>15</sup>

Included in this retrospective study were LVHT patients with at least one measurement of NT-pro-BNP, obtained between 2007 and 2016 in the department for Clinical Chemistry and Laboratory Medicine. The decision for measurement of NT-pro-BNP was made by the treating physicians according to clinical needs and not according to a protocol. At least one measurement of NT-pro-BNP and a maximum of four consecutive measurements were recorded. NT-pro-BNP levels were

**Table 1** Cut-off levels of different classifications of NT-pro-BNP levels and distribution among the included 113 patients

	Classifications (n = 113)	Frequency	Percent
ESC	Low levels, <125 ng/L	13	11.5
	High levels, >125 ng/L	100	88.5
CCLM	Normal levels	14	12.4
	Pathological levels <sup>a</sup>	99	87.6
Stämpfli	Group 1 <sup>b</sup>	14	12.4
	Group 2 <sup>c</sup>	41	36.3
	Group 3 (2001 to 10 000 ng/L)	39	34.5
	Group 4 (>10 000 ng/L)	19	16.8

ESC = classification system of the European Society of Cardiology.<sup>9</sup> CCLM = classification system according to the manufacturer's recommendations, used by the department for Clinical Chemistry and Laboratory Medicine, where the study was carried out.<sup>12</sup> Stämpfli = classification system, used in the publication of Stämpfli et al.<sup>11</sup>

<sup>a</sup>Women: until age 44, ≥116 ng/L; age 45–54, ≥169 ng/L; age 55–64, ≥247 ng/L; age 65–74, ≥285 ng/L; age 75–120, ≥738 ng/L. Men: until age 44, ≥63 ng/L; age 45–54, ≥84 ng/L; age 55–64, ≥161 ng/L; age 65–74, ≥241 ng/L; age 75–120, ≥486 ng/L.

<sup>b</sup>Women: <age 60, ≤164 ng/L; ≥age 60, ≤225 ng/L. Men: <age 60, ≤100 ng/L; ≥age 60, ≤172 ng/L.

<sup>c</sup>Women: <age 60, 165–2000 ng/L; ≥age 60, 226–2000 ng/L. Men: <age 60, 101–2000 ng/L; ≥age 60, 173–2000 ng/L.

measured in blood plasma with electrochemiluminescence immunoassay analyser 'ECLIA' using the 'Cobas' analyser at the department for Clinical Chemistry and Laboratory Medicine.<sup>12</sup>

Excluded were LVHT patients in whom we could not find any NT-pro-BNP measurements in the records of the department for Clinical Chemistry and Laboratory Medicine.

Two-dimensional and Doppler echocardiographic criteria for the diagnosis of LVHT were >3 trabeculations protruding from the LV wall, apically to the papillary muscles, visible in one echocardiographic image plane at end-diastole; trabeculations from the non-compacted part of a two-layered myocardial structure, best visible at end-systole; and intertrabecular spaces perfused from the ventricular cavity, as visualized on colour Doppler imaging. Trabeculations were defined as structures moving synchronously with the ventricular contractions, distinct from ventricular bands, false tendons, and prominent papillary muscles. The location of LVHT was assessed and categorized as apical if it involved the LV apex or as anterior, lateral, or posterior, if it involved the anterior, lateral, or posterior parts of the LV wall.

The cardiac phenotype was classified as 'dilated' if the LV end-diastolic diameter (LVEDD) was >57 mm and LV fractional shortening (FS) was ≤25%; 'hypertrophic' if LVEDD was ≤57 mm, FS > 25%, and LV posterior wall and interventricular septal thickness were both >13 mm; 'intermediate' if LVEDD was >57 mm and FS > 25% or if LVEDD was ≤57 mm and FS ≤ 25%; and 'normal' if LVEDD was ≤57 mm, FS > 25%, and interventricular septal thickness and LV posterior wall ≤ 13 mm.

Clinical, electrocardiographic, and echocardiographic data were collected at time of LVHT diagnosis.

All patients were invited for a neurological investigation comprising the history and a clinical examination. If there were indications for a polyneuropathy, an established screening programme including blood, cerebrospinal fluid investigation, and sometimes nerve biopsy was carried out. If there were indications for a myopathy, a screening was initiated, including muscle enzymes, electromyography, and occasionally muscle biopsy. Neuromuscular disorders were assessed as 'specific' if a diagnosis could be established. Cases where no specific diagnosis could be established were assessed as 'neuromuscular disorder of unknown aetiology'.

Follow-up was carried out every year, either by personal contact with the patients, their general practitioner/internist, or search in the hospital's documentation system. Follow-up parameters included thromboembolic events, implantation of cardiac devices (antibradycardic pacemakers, defibrillators, or cardiac resynchronization devices), death, and heart transplantation. Endpoints were defined as the occurrence of death and heart transplantation. The follow-up ended in December 2018.

For statistical analysis, group comparisons were carried out by using the  $\chi^2$  test and Fisher's exact test, if applicable, for

**Table 2** Baseline characteristics, follow-up data, and high NT-pro-BNP levels according to the classification systems

Characteristics (baseline data)	Study population (n = 113)	NT-pro-BNP Levels				
		CCLM	ESC	Stämpfli		
		Pathological (n = 99)	High (n = 100)	Group 2 (n = 41)	Group 3 (n = 39)	Group 4 (n = 19)
Age at diagnosis, years, median (IQR)	57 (45–69)	59 (48–72)	59 (48–71)	50 (40–59)	63 (54–73)	73 (62–86)
Male, n (%)	86 (76)	74 (75)	74 (74)	28 (68)	31 (80)	15 (79)
Outpatient status at baseline, n (%)	30 (27)	25 (25)	25 (25)	16 (39)	8 (21)	1 (5)
Comorbidities/symptoms at baseline						
Thromboembolic events before diagnosis, n (%)	14 (12)	13 (13)	13 (13)	4 (10)	7 (18)	2 (11)
Angina pectoris, n (%)	31 (27)	23 (23)	23 (23)	12 (29)	8 (21)	3 (16)
Oedema, n (%)	40 (35)	39 (39)	39 (39)	9 (22)	17 (44)	13 (68)
Exertional dyspnoea, n (%)	85 (75)	80 (81)	81 (81)	26 (63)	36 (92)	19 (100)
Palpitations/vertigo/syncope, n (%)	33 (29)	27 (27)	28 (28)	13 (32)	8 (21)	6 (32)
Asymptomatic, n (%)	5 (4)	4 (4)	4 (4)	3 (7)	1 (3)	0 (0)
Diabetes mellitus, n (%)	32 (28)	32 (32)	32 (32)	9 (22)	13 (33)	10 (53)
Arterial hypertension, n (%)	56 (50)	52 (53)	53 (53)	19 (46)	19 (49)	15 (79)
Heart failure, n (%)	88 (78)	85 (86)	86 (86)	31 (76)	36 (92)	19 (100)
NYHA I/II, n (%)	32 (28)	29 (29)	30 (30)	19 (46)	10 (26)	1 (5)
NYHA III/IV, n (%)	56 (50)	56 (57)	56 (56)	12 (29)	26 (67)	18 (95)
Neuromuscular disorder present, n (%)	53 (47)	45 (46)	46 (46)	17 (42)	20 (51)	9 (47)
Coronary artery disease, n (%)	31 (27)	31 (31)	31 (31)	10 (24)	15 (39)	6 (32)
Device						
Device before diagnosis, n (%)	10 (9)	9 (9)	9 (9)	2 (5)	4 (10)	3 (16)
ECG abnormalities						
Tall QRS complex, n (%)	40 (35)	39 (39)	39 (39)	18 (44)	15 (39)	6 (32)
Left bundle branch block, n (%)	24 (21)	22 (22)	23 (23)	7 (17)	7 (18)	8 (42)
Ventricular ectopic beats, n (%)	9 (8)	9 (9)	9 (9)	2 (5)	5 (13)	2 (11)
Atrial fibrillation, n (%)	23 (20)	23 (23)	23 (23)	6 (15)	12 (31)	5 (26)
Left anterior hemiblock, n (%)	15 (13)	15 (15)	15 (15)	6 (15)	7 (18)	2 (11)
Right bundle branch block, n (%)	3 (3)	3 (3)	3 (3)	1 (2)	2 (5)	0 (0)
WPW syndrome, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Sinustachycardia, n (%)	21 (19)	20 (20)	20 (20)	7 (17)	9 (23)	4 (21)
Echocardiographic findings						
LV end-diastolic diameter, mm, median (IQR)	60 (55–68)	62 (56–69)	62 (56–69)	59 (53–67)	62 (57–72)	68 (60–69)
LV fractional shortening, %, median (IQR)	20 (15–30)	20 (13–26)	20 (14–26)	24 (15–31)	19 (15–22)	16 (11–20)
Interventricular septal thickness, mm, median (IQR)	11 (10–14)	11 (10–14)	11 (10–14)	11 (10–13)	11 (10–14)	13 (11–14)
LV posterior wall thickness, mm, median (IQR)	12 (10–14)	12 (10–14)	12 (10–14)	12 (10–13)	12 (11–14)	12 (10–13)
Valvular abnormalities, n (%)	80 (71)	76 (77)	76 (76)	25 (61)	32 (82)	19 (100)
LVHT location						
Apical, n (%)	111 (98)	97 (98)	98 (98)	41 (100)	37 (95)	19 (100)
Anterior wall, n (%)	9 (8)	9 (9)	9 (9)	3 (7)	4 (10)	2 (11)
Posterior wall, n (%)	23 (20)	22 (22)	22 (22)	8 (20)	9 (23)	5 (26)
Lateral wall, n (%)	76 (67)	69 (70)	70 (70)	23 (56)	31 (80)	16 (84)
Septal wall, n (%)	7 (6)	6 (6)	6 (6)	0 (0)	4 (10)	2 (11)
LVHT affecting >2 ventricular parts, n (%)	26 (23)	24 (24)	24 (24)	6 (15)	9 (23)	9 (47)
Cardiac phenotype						
Dilated, n (%)	59 (52)	59 (60)	59 (59)	17 (42)	25 (64)	17 (90)
Hypertrophic, n (%)	8 (7)	5 (5)	5 (5)	4 (10)	1 (3)	0 (0)
Intermediate, n (%)	30 (27)	24 (24)	25 (25)	13 (32)	11 (28)	1 (5)
Normal, n (%)	16 (14)	11 (11)	11 (11)	7 (17)	2 (5)	1 (5)
Follow-up						
Death, n (%)	38 (34)	35 (35)	36 (36)	8 (20)	16 (41)	12 (63)
Heart transplantation, n (%)	2 (2)	2 (2)	2 (2)	0 (0)	2 (5)	0 (0)
Thromboembolic event after diagnosis, n (%)	7 (6)	6 (6)	6 (6)	3 (7)	2 (5)	1 (5)
Device after diagnosis, n (%)	24 (21)	23 (23)	23 (23)	6 (15)	12 (31)	4 (21)

LV, left ventricular; LVHT, left ventricular hypertrabeculation/non-compaction; NYHA, New York Heart Association.

ESC = classification system of the European Society of Cardiology.<sup>9</sup> CCLM = classification system according to the manufacturer's recommendations, used by the department for Clinical Chemistry and Laboratory Medicine, where the study was carried out.<sup>12</sup> Stämpfli = classification system, used in the publication of Stämpfli et al.<sup>11</sup>

categorical variables. For continuous variables, the *t*-test was used for comparing the mean of two groups, if normal distribution was given. Otherwise, the Mann–Whitney *U* test for comparing the median of two groups and the Kruskal–Wallis test for comparing three groups was used. Kaplan–Meier and Cox regression analysis were used to assess the prognostic validity of NT-pro-BNP on the incidence of death or heart transplantation. The multivariate analysis was conducted by applying Cox proportional hazard regression. While all other parameters are timed at diagnosis, we use the time-dependent NT-pro-BNP value at last measurement in the multivariate analysis to account for the change of NT-pro-BNP values across measurements. Model building followed purposeful variable selection<sup>16,17</sup> using likelihood ratio test and the Akaike information criterion, if applicable. The final model included the variables age at diagnosis, natural logarithm of NT-pro-BNP values, diabetes mellitus, atrial fibrillation, and thromboembolic event before diagnosis. All statistical analyses were performed by using the statistical software Stata 16 and Microsoft Excel.<sup>18</sup>

The study was approved by the institutional review board of the community of Vienna (EK 17-145-VK 13 October 2017, extension 15 January 2019).

## Results

In 301 patients, LVHT was diagnosed in the echocardiographic laboratory since 1995. In 113 of these patients (median age 57, 76% men), at least one NT-pro-BNP measurement was found, why they were included in the present study. The diagnosis of LVHT was additionally confirmed by cardiac MRI in 41 of the 113 included patients. Baseline and follow-up parameters are listed in *Table 2*.

The NT-pro-BNP levels ranged from 8 to 121 152 ng/L (median 2029 ng/L, interquartile range 636–6218 ng/L). The frequency distribution according the classification systems did not show any variations (*Table 1*). Most of the patients (89%) showed elevated NT-pro-BNP levels.

NT-pro-BNP was measured in most patients (64%) within a month before or after the date of LVHT diagnosis. For two patients (2%), the closest measurement took place 5 and 2 months, respectively, before the LVHT diagnosis. For five patients (4%), the first measurement was within 12 months after LVHT diagnosis; for 13 patients (12%), between 12 and 60 months after LVHT diagnosis; for 7 patients (6%), between 60 and 120 months; for 11 patients (10%), between 120 and 180 months; and for 3 more patients (3%), between 180 and 201 months. In 62 of these 113 patients, at least two measurements; in 40 of the 62 patients, at least three; and in 26 of the 40 patients, four measurements were found. Of the 62 patients with at least two measurements were 24

patients with increasing NT-pro-BNP levels and 38 patients with decreasing NT-pro-BNP levels.

Neurologically investigated were 75 of the 113 included patients. In seven patients, a specific neuromuscular disorder was found: metabolic myopathy *n* = 5, Becker's muscular dystrophy *n* = 1, and myotonic dystrophy type 1 *n* = 1. The neurological investigation was normal in 22 patients. In 46 patients, a neuromuscular disorder of unknown aetiology was found.

High NT-pro-BNP levels according to all classification systems, as presented in *Table 1*, were associated with increased age, angina pectoris, diabetes mellitus, heart failure, oedema, exertional dyspnoea, valvular abnormalities, increased LVEDD, and systolic dysfunction (*Table 3*). Dependent on the classification system, there were associations between high NT-pro-BNP levels and inpatient status at baseline, tall QRS complexes, arterial hypertension, atrial fibrillation, LVHT affecting the lateral wall, and LVHT affecting >2 ventricular

**Table 3** *P* values indicating the association of high NT-pro-BNP levels with baseline and follow-up parameters

Characteristics	CLLM	ESC	Stämpfli
<b>Baseline data</b>			
Age at diagnosis, years	<b>0.0006</b>	<b>0.0002</b>	<b>&lt;0.0001</b>
Outpatient status at baseline	0.5180	0.3253	<b>0.0219</b>
<b>Comorbidities/symptoms</b>			
Angina pectoris	<b>0.0204</b>	<b>0.0066</b>	<b>0.0490</b>
Oedema	<b>0.0179</b>	<b>0.0307</b>	<b>0.0003</b>
Exertional dyspnoea	<b>0.0009</b>	<b>0.0004</b>	<b>&lt;0.0001</b>
Diabetes mellitus	<b>0.0097</b>	<b>0.0182</b>	<b>0.0039</b>
Arterial hypertension	0.0934	<b>0.0424</b>	<b>0.0108</b>
Heart failure	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>
NYHA I/II	0.7537	0.3443	<b>0.0041</b>
NYHA III/IV	<b>&lt;0.0001</b>	<b>0.0001</b>	<b>&lt;0.0001</b>
<b>ECG abnormalities</b>			
Tall QRS complex	<b>0.0179</b>	<b>0.0307</b>	0.0745
Atrial fibrillation	0.0694	0.0670	<b>0.0493</b>
<b>Echocardiographic findings</b>			
Valvular abnormalities	<b>0.0006</b>	<b>0.0018</b>	<b>&lt;0.0001</b>
Left ventricular enddiastolic diameter, mm	<b>0.0001</b>	<b>0.0004</b>	<b>0.0002</b>
Left ventricular fractional shortening, %	<b>0.0001</b>	<b>0.0001</b>	<b>&lt;0.0001</b>
<b>LVHT-affected segments</b>			
Lateral wall	0.2216	0.1159	<b>0.0106</b>
LVHT affecting >2 ventricular parts	0.5164	0.7291	<b>0.0485</b>
<b>Cardiac phenotype</b>			
Dilated	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>
Hypertrophic	0.0589	<b>0.0480</b>	0.0646
Intermediate	0.1935	0.3253	0.0978
Normal	<b>0.0276</b>	<b>0.0194</b>	<b>0.0058</b>
<b>Follow-up data</b>			
Death	0.3772	0.2131	<b>0.0026</b>

LV, left ventricular; LVHT, left ventricular hypertrabeculation/non-compaction; NYHA, New York Heart Association.

ESC = classification system of the European Society of Cardiology.<sup>9</sup> CLLM = classification system according to the manufacturer's recommendations, used by the department for Clinical Chemistry and Laboratory Medicine, where the study was carried out.<sup>12</sup> Stämpfli = classification system, used in the publication of Stämpfli *et al.*<sup>11</sup> Cut-off levels are given in *Table 1*. Significant associations are given in bold.

segments (Table 3). NT-pro-BNP levels were not associated with presence or absence of neuromuscular disorders.

Follow-up ranged from 0 to 237 months with a mean follow-up of 73 ( $\pm 64$ ) months. During follow-up, 38 patients (34%) died (Figure 1), 2 patients (2%) underwent heart transplantation, 24 patients (21%) received a device, and 7 patients (6%) suffered from a stroke/embolism. Among the 24 patients who received a device, the first NT-pro-BNP measurement was done before device implantation in 16 patients and after device implantation in 8 patients. The mean time interval between measurement and device implantation was 2.6 years (range 0–11 years). Patients who received a device, suffered from a stroke/embolism, or underwent heart transplantation did not differ regarding NT-pro-BNP levels from patients without these events.

The mean NT-pro-BNP levels at first measurement differed between patients who suffered from an endpoint and patients with no endpoint (13 125 vs. 3640 ng/L;  $P = 0.0002$ ). No difference could be found between NT-pro-BNP levels of patients with a cardiac and non-cardiac cause of death. Kaplan–Meier estimator and log rank test showed differences in the survival curves according to the Stämpfli classification ( $P < 0.001$ ) (Figure 2). The groups with high NT-pro-BNP levels ( $>10\,000$  ng/L) and (2000–10 000 ng/L) achieved a hazard ratio of 8.2 ( $P < 0.001$ ) and 3.1 ( $P = 0.0048$ ), respectively, relative to those with pro-BNP levels below 2000 ng/L. Taking into account the change of NT-pro-BNP levels across measurements during follow-up, the hazard ratio of the group with the highest pro-BNP levels even increased to 13.0 ( $P < 0.0001$ ), while the hazard ratio of the group with pro-BNP levels between 2000 and 10 000 ng/L remained relatively stable (hazard ratio 2.8,  $P = 0.01$ ).

In the multivariate model, significant parameters for the occurrence of death or heart transplantation were logarithm of NT-pro-BNP levels at last measurement ( $P = 0.0073$ ), increased age at diagnosis ( $P = 0.0025$ ), diabetes mellitus

( $P = 0.0137$ ), atrial fibrillation ( $P = 0.0023$ ), and thromboembolic event before diagnosis ( $P = 0.0347$ ).

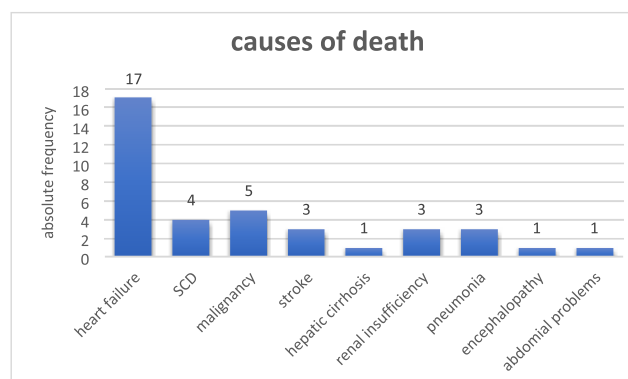
## Discussion

This study shows that in LVHT patients, high NT-pro-BNP levels were associated with heart failure, valve abnormalities, hypertension, angina pectoris, dyspnoea, and oedema. Additionally, there was an association between higher NT-pro-BNP levels and the number of LVHT-affected ventricular segments as well as with higher LVEDD and lower LV FS. An association between higher NT-pro-BNP levels and the occurrence of the endpoint—death or heart transplantation—was shown. Patients with NT-pro-BNP levels above 10 000 ng/L at time of diagnosis (or at first measurement) achieved a hazard ratio of 8.2 regarding death and heart transplantation relative to those with NT-pro-BNP levels below 2000 ng/L. NT-pro-BNP levels were significant predictors for an endpoint in a multivariate model.

Three different classifications of NT-pro-BNP were used in this study to present possible variations of their reference levels. The frequency distribution of these classifications did not show any variations. Most of the patients (89%) showed elevated NT-pro-BNP levels.

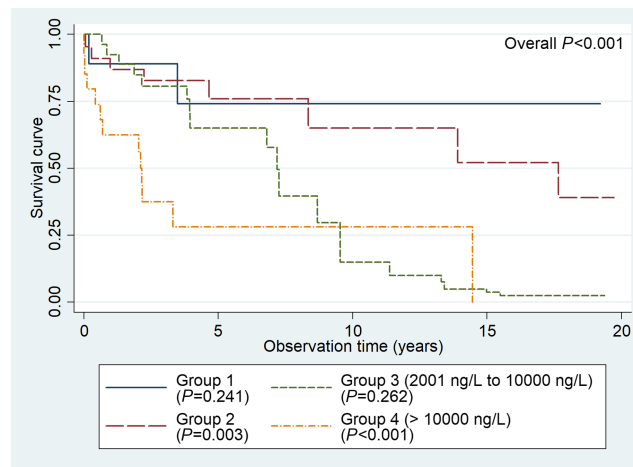
The median NT-pro-BNP level in our study was 2029 ng/L. Our study population showed higher NT-pro-BNP levels than the patients in a previous study, which reported a median NT-pro-BNP of 292 ng/L in patients without endpoint and 6416 ng/L with endpoint.<sup>11</sup> This difference may be explained by the higher age (average age 57 vs. 43 years) and the higher rate of patients with New York Heart Association (NYHA) III and IV (33% NYHA III; 30% NYHA IV versus 12% NYHA III/IV) at time of diagnosis in our study compared with Stämpfli's patients.<sup>11</sup> In Chinese LVHT patients with coronary artery

**Figure 1** Figure of the absolute frequencies of the causes of death.





**Figure 2** Survival curves of the included patients with left ventricular hypertrabeculation/non-compaction according to the Stämpfli classification at first measurement.<sup>11</sup> The classification of the groups is listed in *Table 1*.



disease, NT-pro-BNP levels were higher than in patients without.<sup>14</sup> In Slovenian LVHT patients, those with an impairment of myocardial perfusion, assessed by technetium-99m tetrofosmin, had higher NT-pro-BNP than those without perfusion abnormalities.<sup>19</sup>

In our study, LVHT patients with one affected segment had lower mean NT-pro-BNP levels than patients with three affected segments. A correlation between high NT-pro-BNP levels and a higher number of trabeculations has been described by Tizón-Marcos et al. in apparently healthy patients.<sup>20</sup> The reason for this phenomenon has not been clarified. Probably, formation of trabeculations is a compensatory answer to systolic dysfunction or volume overload, due to reduced adhesion of cardiomyocytes, an ineffective attempt to overcome a metabolic defect, a 'weak' myocardium, or the need to enlarge the endocardial surface to increase stroke volume or improve oxygenation.<sup>4</sup> An increase in the number of trabeculations would result in an increase of the endocardial surface. Because NT-pro-BNP is released from endocardial cells, an increase in the endocardial surface may lead to an increase in NT-pro-BNP levels in situations of pressure or volume overload. A further study, however, using cardiac MRI in patients with dilated cardiomyopathy found that the LV sphericity index, defined by the ratio LV short-axis length to long-axis length, was inversely correlated with LV ejection fraction and positively with the BNP level but not correlated with the global trabeculation index.<sup>21</sup>

Different neuromuscular disorders with varying degrees of cardiac involvement have been described in association with LVHT.<sup>4</sup> Only few data are available about NT-pro-BNP and neuromuscular disorders in LVHT. In the literature, a boy with Duchenne muscular dystrophy, LVHT, and elevated NT-pro-BNP level (7795 pg/mL) is reported.<sup>22</sup> High NT-pro-BNP levels in patients with muscular dystrophy may be explained as a consequence of high LV wall stress due to the markedly thin

LV wall.<sup>22</sup> In the present study, we did not find an association between the presence of neuromuscular disorders and NT-pro-BNP levels, similarly to a pilot study from our cohort.<sup>13</sup> Most probably, in our cohort, patients with and without neuromuscular disorders both had systolic dysfunction and high LV wall stress. LVHT patients with and without neuromuscular disorders did not differ regarding the prevalence of systolic dysfunction and number of LVHT-affected ventricular segments.<sup>23</sup>

It is already known that patients with heart failure and systolic dysfunction show elevated NT-pro-BNP levels.<sup>9</sup> For LVHT patients, the association of high NT-pro-BNP levels with heart failure, valvular abnormalities, and electrocardiographic abnormalities has already been reported.<sup>11,13,14,19</sup> The present study substantiates these findings by showing a difference between the groups of all three classifications regarding LVEDD and systolic function.

Patients who received a device, suffered from a stroke/embolism, or underwent heart transplantation did not differ regarding NT-pro-BNP levels from patients without these events. In the survival analysis, however, patients with the combined endpoint of death or heart transplantation had higher NT-pro-BNP levels than the patients without endpoint. These discrepancies may be explained by the low number of events and by selection bias since measurement of NT-pro-BNP levels was not performed according to a protocol. In addition, not all patients with NYHA III or IV advanced heart failure received devices because of various reasons like multiple comorbidities, advanced age, low life expectancy, or refusal of the patient.

There are only two studies that investigated the mortality and the prognostic relevance of NT-pro-BNP in LVHT.<sup>11,13</sup> Stämpfli et al. found a difference of the mean NT-pro-BNP levels between patients with and without endpoint regarding all-cause mortality, which was also found in our study.<sup>11</sup> On

the contrary, a pilot study from our cohort did not show any prognostic relevance of NT-pro-BNP levels in LVHT patients, which may be explained by the small number of patients ( $n = 19$ ), by their high rate of systolic dysfunction, and the high rate of patients receiving cardiac electronic devices.<sup>13</sup>

Limitations are the small number of patients, NT-pro-BNP levels not measured according to a protocol but according to clinical needs, and renal function and pharmacotherapy not recorded. Genetic testing was only carried out in selected cases and not systematically. Follow-up investigations were not carried out by personal contact in each patient; this is why we might have missed some events. Due to the small number of events, especially heart transplantations, no definite conclusions can be drawn from our findings.

In conclusion, high NT-pro-BNP levels are associated with heart failure and systolic dysfunction in LVHT patients. The results of the present study indicate that patients with higher NT-pro-BNP levels may have a shorter survival time than patients with lower NT-pro-BNP levels.

## Ethics approval

The study was approved by the institutional review board of the community of Vienna (EK 17-145-VK 13 October 2017, extension 15 January 2019).

## Conflict of interest

None declared.

## Availability of data and material

Data are available in the LVHT Database of Klinik Landstrasse (former 'Krankenanstalt Rudolfstiftung').

## Code availability

Data are stored by using Microsoft Excel.

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