BMJ Open

Plasma NT-proBNP levels associated with cardiac structural abnormalities in asymptomatic health examinees with preserved ejection fraction: a retrospective cross-sectional study

Eun-Hee Nah,[1] Seong Yoon Kim,[2] Seon Cho,[1] Suyoung Kim,[1] Han-Ik Cho[3]

To cite: Nah E-H, Kim SY, Cho S, *et al*. Plasma NT-proBNP levels associated with cardiac structural abnormalities in asymptomatic health examinees with preserved ejection fraction: a retrospective cross-sectional study. *BMJ Open* 2019;**9**:e026030. doi:10.1136/bmjopen-2018-026030

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2018-026030).

Received 16 August 2018
Revised 25 February 2019
Accepted 1 March 2019

[1]Health Promotion Research Institute, Korea Association of Health Promotion, Seoul, South Korea
[2]Division of Cardiology, Department of Internal Medicine, Korea Association of Health Promotion, Seoul, South Korea
[3]MEDIcheck LAB, Korea Association of Health Promotion, Cheongju, South Korea

Correspondence to
Dr Eun-Hee Nah;
cellonah@hanmail.net

ABSTRACT

Objectives Stage B heart failure (HF) is defined as an asymptomatic abnormality of the heart structure or function. The circulating level of N-terminal pro-B-type natriuretic peptide (NT-proBNP) is elevated in symptomatic patients with left ventricular (LV) dysfunction caused by a structural or functional abnormality. This study investigated the association of the NT-proBNP level with echocardiography-detected cardiac structural or diastolic abnormalities in asymptomatic subjects with preserved LV systolic function (ejection fraction >50%).

Methods We retrospectively studied 652 health examinees who underwent echocardiography and an NT-proBNP test at a health-promotion centre in Seoul, between January 2016 and September 2018. The left ventricular mass index (LVMI) and the left atrial dimension (LAD) were used as markers for structural abnormalities, and the mean e' velocity and mitral early flow velocity/early diastolic tissue velocity (E/e') ratio were used as markers for diastolic dysfunction. The plasma NT-proBNP level was measured using electrochemiluminescence immunoassay (DPC Immulite 2000 XPi, Siemens Healthcare Diagnostics, Tarrytown, New York, USA).

Results Subjects with preclinical structural abnormalities were older and had a higher body mass index (BMI), higher blood pressure, lower high-density lipoprotein cholesterol level, higher NT-proBNP level, and higher E/e' ($p<0.05$). Multivariate regression analysis indicated that the factors associated with a higher NT-proBNP level were older age, female sex, lower BMI, higher creatinine level, higher LVMI and higher LAD ($p<0.01$).

Conclusion Diastolic dysfunction is not associated with higher NT-proBNP levels, whereas preclinical cardiac structural abnormalities, as well as older age, female sex, lower BMI, and higher creatinine level, are associated with higher NT-proBNP levels.

Strengths and limitations of this study

- This is the first study to address the association of early stage of preclinical echocardiography-detected cardiac structural or diastolic abnormalities with the N-terminal pro-B-type natriuretic peptide (NT-proBNP) level in a primary healthcare setting.
- The target subjects with potential cardiac structural abnormalities for screening early stage B heart failure would be selected based on the NT-proBNP levels in health check-ups.
- The cross-sectional study design and the relatively small sample mean that further research into the associated causal relationships is needed.

INTRODUCTION

Heart failure (HF) is a clinical syndrome characterised by typical symptoms and signs caused by structural and functional cardiac abnormalities that result in a reduced pumping capability of the heart and its pre- and postloading volumes, stasis of blood flow, and insufficiency of the blood and oxygen supplied to the main organs.[1] The incidence of cardiovascular diseases is increasing, particularly in younger subjects, due to changes in lifestyles and dietary patterns, and there have also been increases in the rates of progression to HF.[2] Systolic dysfunction is frequently present in community-dwelling individuals without recognised symptoms of HF.[3 4] In addition, most subjects with diastolic dysfunction have a normal left ventricular ejection fraction (LVEF), with even moderate or severe isolated diastolic dysfunction being as common as systolic dysfunction.[5–7] Thus, the early recognition and treatment of preclinical structural or functional abnormalities represent a potentially powerful strategy for reducing the incidence of HF.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is produced within myocytes and released into the circulation during increases in the ventricular and atrial pressures.[8 9] The NT-proBNP level is therefore a useful diagnostic marker for cardiac

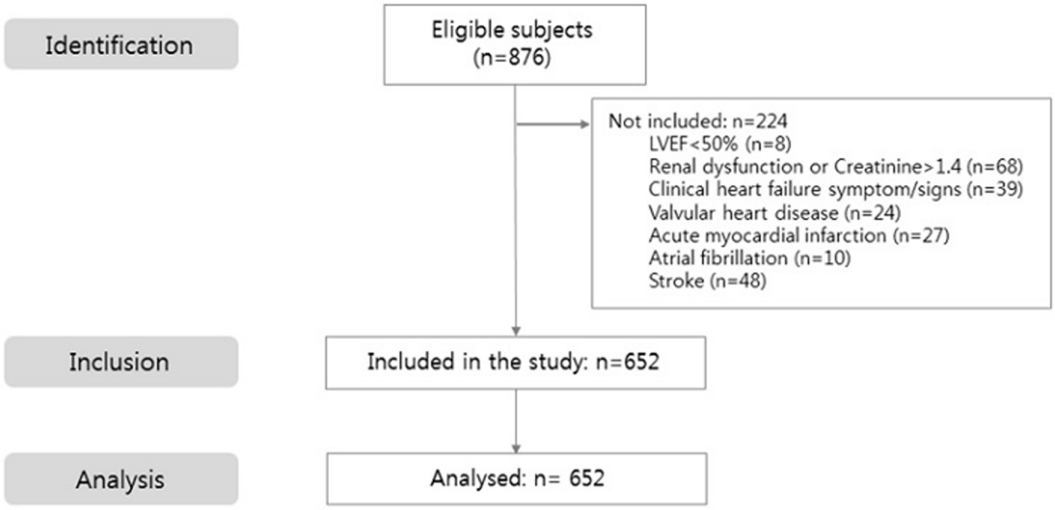

Figure 1 Study flow diagram. LVEF, left ventricular ejection fraction.

insufficiency,[10] ventricular dysfunction[11] and cardiomyopathy.[12] An assay for measuring the NT-proBNP level may also be applied for detecting asymptomatic subclinical cardiac structural or functional impairment. However, few studies have investigated the association between NT-proBNP levels and the early stage of preclinical structural or functional heart abnormalities, which are checked by echocardiography performed as a part of preventive screening programmes in the primary healthcare system.

This study investigated the association of the NT-proBNP level with echocardiography-detected early stage of cardiac structural or diastolic abnormalities in asymptomatic subjects with preserved left ventricular systolic function (LVEF >50%) during health check-ups.

METHODS

Subjects

We retrospectively studied consecutive health examinees aged over 18 year old who underwent echocardiography and an NT-proBNP test during health check-ups at a health-promotion centre in Seoul between January 2016 and September 2018. The study design was retrospective and cross-sectional. The self-reported personal medical history, subjective symptoms and signs, and lifestyle information were obtained from all participants at the time of the health check-ups. Their medical records were also reviewed. Inclusion criterion was preserved left ventricular systolic function (LVEF >50%) determined by echocardiography, without previous cardiac surgery or diagnosed heart disease. Subjects who had echocardiography-detected valvular heart disease, atrial fibrillation, acute myocardial infarction, stroke, renal dysfunction, pregnancy, echocardiography-detected LVEF <50%, or clinical symptoms or signs of HF were excluded from this study. After exclusion, the final sample size was 652 (361 men and 291 women: aged 28–82).

Echocardiography

The echocardiographic investigations were carried out using a Philips/Hewlett-Packard Sono 5500 ultrasound device (Philips Ultrasound, Andover, MA, USA). M-mode, two-dimensional and haemodynamic Doppler images were acquired using a standardised protocol with a 3.5-MHZ transducer. LVEF was calculated using the modified Simpson method.[13] An increased left ventricular mass index (LVMI>115 g/m^2 in men and >95 g/m^2 in women) and an increased left atrial dimension (LAD>41 mm in men and >39 mm in women) were used as markers for structural abnormalities.[14] Cardiac diastolic dysfunction was defined as mitral early flow velocity (E)/early diastolic tissue velocity (e') of ≥13 and a mean e' septal and lateral wall of <9 cm/s.[15]

NT-proBNP measurement

Venous blood was collected in a lithium–heparin tube. The plasma NT-proBNP level was measured using an electrochemiluminescent immunoassay on a DPC Immulite 2000 XPi device (Siemens Healthcare Diagnostics, Tarrytown, NY, USA). The intra-assay and total variances were 3.4% and 4.7%, respectively, and the limit of detection was 10 pg/mL.

Statistical analysis

Statistical analyses were performed using SAS V.9.4 (SAS Institute). Differences in the characteristics of the study subjects were analysed according to the presence of structural abnormalities using Student's t-test or the χ^2 test. In addition, differences in the characteristics of the study subjects were analysed according to the presence of diastolic dysfunction using Student's t-test or the χ^2 test. Differences in the characteristics of those with structural abnormality, diastolic dysfunction or both abnormalities were analysed using analysis of variance. Univariate (crude) and multivariate (adjusted) regression analyses were performed to determine the variables affecting an increased NT-proBNP level. Variables considered in the

Table 1 Characteristics of study subjects according to the presence of structural abnormalities

Variables	No structural abnormality (n=560)	Structural abnormality (n=92)	P value
Age (year)	57.7±8.9	60.8±8.8	0.017
Male sex, N (%)	309 (55.2)	52 (56.5)	0.432
BMI (kg/m^2)	24.2±3.0	26.9±3.5	<0.001
SBP (mm Hg)	119.8±13.7	126.6±12.1	<0.001
DBP (mm Hg)	73.7±8.9	76.9±8.6	0.003
Hb (g/L)	147.7±14.6	146.3±16.5	0.965
FBS (mmol/L)	5.9±1.5	6.2±1.5	0.289
TC (mmol/L)	5.4±1.1	5.2±1.0	0.110
TG (mmol/L)	1.4±0.9	1.6±1.1	0.125
HDL-C (mmol/L)	1.5±0.4	1.4±0.4	<0.001
LDL-C (mmol/L)	3.2±1	3.1±0.9	0.236
Creatinine (µmol/L)	78.5±15.2	76.9±15.7	0.520
eGFR (mL/min/1.73 m^2)	85.3±14.7	87.3±18.4	0.639
NT-proBNP (pg/mL)	29.6±27.5	55.8±91.5	0.015
LVEF (%)	66±6.5	64.9±7.3	0.807
LVMI (g/m^2)	71.7±13.3	88.9±18.1	<0.001
LAD (mL/m^2)	33.7±3.9	40.8±5.5	<0.001
E/e'	11±3.4	13±3.5	0.002
e' (cm/s)	6.2±1.6	5.9±5.4	0.950

Continuous variables are expressed as mean±SD values and were compared using Student's t-test. Categorical variables are expressed as N (%) values and were analysed using the χ^2 test.
BMI, body mass index; DBP, diastolic blood pressure; e', mean e' septal and lateral wall velocity; E/e', mitral early flow velocity/early diastolic tissue velocity; eGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; Hb, haemoglobin; HDL-C, high-density lipoprotein cholesterol; LAD, left atrial dimension; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

Table 2 Characteristics of study subjects according to the presence of diastolic dysfunction

Variables	No diastolic dysfunction (n=182)	Diastolic dysfunction (n=470)	P value
Age (year)	52.6±8.8	60.3±8.1	<0.001
Male sex, n (%)	93 (51.1)	268 (57.0)	0.172
BMI (kg/m^2)	23.4±3	25±3.2	<0.001
SBP (mm Hg)	116.2±12.6	122.6±13.7	<0.001
DBP (mm Hg)	71.4±8.6	75.3±8.8	<0.001
Hb (g/L)	144±15.2	148.9±14.5	<0.001
FBS (mmol/L)	5.6±1	6.1±1.6	<0.001
TC (mmol/L)	5.4±1	5.4±1.1	0.958
TG (mmol/L)	1.2±0.8	1.5±1	<0.001
HDL-C (mmol/L)	1.6±0.4	1.5±0.4	<0.001
LDL-C (mmol/L)	3.2±1	3.2±1	0.996
Creatinine (µmol/L)	76.3±15.5	79±15.2	0.040
eGFR (mL/min/1.73 m^2)	88.9±15.7	84.3±15	0.001
NT-proBNP (pg/mL)	35.9±63.5	32.3±32.9	0.476
LVEF (%)	65.2±6.9	66.1±6.5	0.131
LVMI (g/m^2)	69.5±14.2	75.9±15.3	<0.001
LAD (mL/m^2)	33.9±5.1	35±4.7	0.007
E/e'	9.4±2.1	12±3.6	<0.001
e' (cm/s)	8.4±3.6	5.3±1	<0.001

Continuous variables are expressed as mean±SD values and were compared using Student's t-test. Categorical variables are expressed as N (%) values and were analysed using the χ^2 test.
BMI, body mass index; DBP, diastolic blood pressure; e', mean e' septal and lateral wall velocity ; E/e', mitral early flow velocity/early diastolic tissue velocity; eGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; Hb, haemoglobin; HDL-C, high-density lipoprotein cholesterol; LAD, left atrial dimension; LDL-C, low-density liporotein cholesterol; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

analysis included age, sex, body mass index (BMI), systolic blood pressure, diastolic blood pressure, haemoglobin (Hb), fasting blood sugar (FBS), triglyceride, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), creatinine, LVEF, LVMI, LAD, early diastolic mitral inflow velocity/early diastolic mitral annular velocity (E/e') and e'. We used a multiple linear regression model to control for effects of included age, sex, BMI, blood pressure, Hb, FBS, blood lipid, creatinine, LVEF, LVMI, LAD, E/e' and e' (model 1). An additional regression model adjusted for age, sex, BMI, creatinine, LVMI and LAD was used to identify increased NT-proBNP levels in the multivariate model (model 2). Wilcoxon rank-sum tests were performed to compare mean NT-proBNP levels between sexes, and between those with and without structural abnormalities in each age groups, respectively. In addition, Wilcoxon rank-sum test was used to compare those with diastolic dysfunction with those without diastolic dysfunction. Logarithmic transformations were applied to the NT-proBNP level. Area under the receiver operating curve (AUROC) was calculated to measure the performance of NT-proBNP in predicting the cardiac structural abnormalities. A p value of <0.05 was considered statistically significant.

Patient and public involvement

Patients were not involved in the recruitment to and in the conduct of the study. Results will be disseminated to study participants through annual information events.

Table 3 Characteristics of study subjects according to the presence of structural abnormalities and/or diastolic dysfunction

Variables	Normal[a] (n=167)	Structural abnormality[b] (n=15)	Diastolic dysfunction[c] (n=393)	Structural abnormality and diastolic dysfunction[d] (n=77)	P value	Multiple comparison
Age (year)	52.5±8.8	54.8±8.9	59.9±8	62±8.3	<0.001	a, b<c, d
Male sex, n (%)	82 (49.1)	11 (73.3)	227 (57.8)	41 (53.3)	0.129	–
BMI (kg/m^2)	23.2±3	25.9±2.1	24.6±2.9	27.1±3.7	<0.001	a<d
SBP (mm Hg)	115.7±12.6	121.3±11.5	121.6±13.8	127.6±12	<0.001	a<d
DBP (mm Hg)	71.2±8.7	73±8	74.8±8.8	77.6±8.5	<0.001	a, b<d
Hb (g/L)	143.7±15.1	147.3±16.6	149.4±14.1	146.1±16.6	<0.001	–
FBS (mmol/L)	5.6±1	5.5±1	6.1±1.6	6.4±1.5	<0.001	b<d
TC (mmol/L)	5.4±1	5.1±1.3	5.4±1.1	5.3±0.9	0.631	–
TG (mmol/L)	1.2±0.8	0.9±0.7	1.4±1	1.7±1.1	<0.001	b<d
HDL-C (mmol/L)	1.6±0.4	1.5±0.5	1.5±0.4	1.4±0.4	0.001	a>d
LDL-C (mmol/L)	3.2±1	3.2±1	3.3±1	3.1±0.9	0.618	–
Creatinine (µmol/L)	75.4±15.1	85.5±18.2	79.7±15.2	75.2±14.7	0.001	a, d<b
eGFR (mL/min/1.73 m^2)*	89.5±15.8	82.3±13.1	83.5±13.9	88.3±19.2	<0.001	b<a
NT-proBNP (pg/mL)*	27.1±16	132.9±195.2	30.7±31.1	40.8±40	0.005	a, c,d<b
LVEF (%)*	65.3±6.3	63.8±12	66.3±6.6	65.2±6.2	0.272	–
LVMI (g/m^2)*	67.8±12.8	88±16.2	73.3±13.1	89.1±18.5	<0.001	a,c<b,d
LAD (mL/m^2)*	33±3.9	43.5±6.2	34±3.8	40.2±5.2	<0.001	a,c<d < b
E/e'*	9.3±2.1	10.7±2.4	11.8±3.5	13.4±3.5	<0.001	a<b,c<d
e' (cm/s)*	8.2±1.1	11±12.3	5.4±0.9	4.9±1.2	<0.001	d,c<a < b

*Welch's ANOVA (not equal variance) was used.
BMI, body mass index; DBP, diastolic blood pressure; e', mean e' septal and lateral wall velocity; E/e', mitral early flow velocity/early diastolic tissue velocity; eGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; Hb, haemoglobin; HDL-C, high-density lipoprotein cholesterol; LAD, left atrial dimension; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

RESULTS

Six hundred fifty-two of the 876 eligible subjects were analysed (figure 1). The median age of the study subjects was 58 years (range 28–82 years). Echocardiography revealed structural abnormalities in 92 (14.1%) of the subjects, who were older (60.8±8.8 vs 57.7±8.9 years [mean±SD], p<0.017) and had a higher BMI, higher blood pressure, lower HDL-C level, higher NT-proBNP level (55.8±91.5 vs 29.6±27.5 pg/mL, p=0.015) and higher E/e' ratio (13.0±3.5 vs 11.0±3.4) in echocardiography (table 1).

Diastolic dysfunction was detected using echocardiography in 470 (72.0%) of the subjects. These subjects were older and had a higher BMI, higher blood pressure, higher FBS, higher triglycerides, and lower HDL-C levels. However, the NT-proBNP level did not differ significantly between subjects with and without diastolic dysfunction (table 2). Although subjects with both structural abnormality and diastolic dysfunction were older, higher blood pressure, higher FBS, higher triglyceride, higher LVMI, higher E/e', and lower e' compared with one of structural abnormality or diastolic dysfunction, NT-proBNP was higher in subjects with structural abnormality only (table 3).

In a univariate model, older age, lower LDL-C level, higher creatinine level, higher LVMI and higher LAD were associated with an increased NT-proBNP level. In a multivariate model, older age, female sex, lower BMI, higher creatinine level, higher LVMI and higher LAD were associated with an increased NT-proBNP level (p<0.01). While sex was not associated with the NT-proBNP level in a univariate model, female sex was associated with an increased NT-proBNP level (p=0.002) in the multivariate model (table 4). Among subjects in all age ranges (aged ≤45, 46–60 and aged ≥61 years), women showed higher NT-proBNP levels than men (figure 2). A structural abnormality defined by higher LVMI and/or higher LAD was associated with an increased NT-proBNP level (p<0.01), but the E/e' ratio and mean e' velocity were not associated with the NT-proBNP level. In subjects aged 46–60 and ≥61 years, those with structural abnormality showed a higher NT-proBNP level (p=0.002 and p=0.004, respectively) (figure 3).

Figure 4 shows the receiver operating curve for assessing the performance of NT-proBNP in predicting cardiac structural abnormalities. AUROC was 0.625 (95% CI 0.566 to 0.684). The cut-off for NT-proBNP at 21.0 pg/

Table 4 Regression analysis of the variables affecting an increased NT-proBNP level

	Univariate model			Multivariate model					
				Model 1			Model 2		
Variables	Coeff.* (95% CI)	P value	R^2	Coeff.* (95% CI)	P value	R^2	Coeff.* (95% CI)	P value	R^2
Age (year)	0.97 (0.6 to 1.33)	<0.001	0.040	0.58 (0.15 to 1.01)	0.008	0.153	0.51 (0.13 to 0.89)	0.009	0.140
Sex (ref: female)	−0.52 (−7.27 to 6.23)	0.879	<0.001	−17.31 (−28.12 to −6.51)	0.002		−19.47 (−28.5 to −10.45)	<0.001	
BMI (kg/m^2)	−0.26 (−1.3 to 0.78)	0.626	<0.001	−1.97 (−3.2 to −0.74)	0.002		−2.34 (−3.47 to −1.21)	<0.001	
SBP (mm Hg)	0.14 (−0.1 to 0.39)	0.258	0.002	−0.25 (−0.61 to 0.1)	0.165				
DBP (mm Hg)	0.27 (−0.11 to 0.64)	0.164	0.003	0.48 (−0.06 to 1.01)	0.081				
Hb (g/L)	−0.14 (−0.37 to 0.08)	0.216	0.002	−0.15 (−0.45 to 0.15)	0.338				
FBS (mmol/L)	−0.97 (−3.22 to 1.28)	0.396	0.001	−0.44 (−2.71 to 1.84)	0.707				
TG (mmol/L)	−2.34 (−5.81 to 1.13)	0.186	0.003	−2.01 (−5.8 to 1.78)	0.298				
HDL-C (mmol/L)	−1.72 (−10.2 to 6.77)	0.691	<0.001	−0.76 (−9.82 to 8.31)	0.870				
LDL-C (mmol/L)	−3.62 (−6.96– −0.27)	0.034	0.007	−2.95 (−6.2 to 0.3)	0.075				
Creatinine (µmol/L)	0.36 (0.14 to 0.58)	0.001	0.016	0.70 (0.4 to 0.99)	<0.001		0.68 (0.4 to 0.97)	<0.001	
LVEF (%)	−0.01 (−0.51 to 0.49)	0.968	<0.001	0.12 (−0.37 to 0.6)	0.637				
LVMI (g/m^2)	0.47 (0.26 to 0.69)	<0.001	0.028	0.28 (0.04 to 0.52)	0.022		0.30 (0.07 to 0.53)	0.012	
LAD (mL/m^2)	2.11 (1.43 to 2.79)	<0.001	0.054	2.58 (1.79 to 3.37)	<0.001		2.63 (1.85 to 3.41)	<0.001	
E/e’	0.65 (−0.33 to 1.63)	0.191	0.003	−0.14 (−1.24 to 0.97)	0.806				
e’ (cm/s)	−0.54 (−1.87 to 0.8)	0.430	0.001	0.38 (−1.04 to 1.81)	0.597				

Model 1: adjust for age, sex, BMI, blood pressure, Hb, FBS and blood lipid creatinine.
Model 2: adjusted for age, sex, BMI, creatinine, LVMI and LAD.
*Regression coefficient: the usual interpretation of a regression coefficient is the average change in the outcome variable when the corresponding predictor variable is changed by one unit.
BMI, body mass index; DBP, diastolic blood pressure; e’, mean e’ septal and lateral wall velocity; E/e’, mitral early flow velocity/early diastolic tissue velocity; FBS, fasting blood sugar; HDL-C, high-density lipoprotein cholesterol; HB, haemoglobin; LAD, left atrial dimension; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

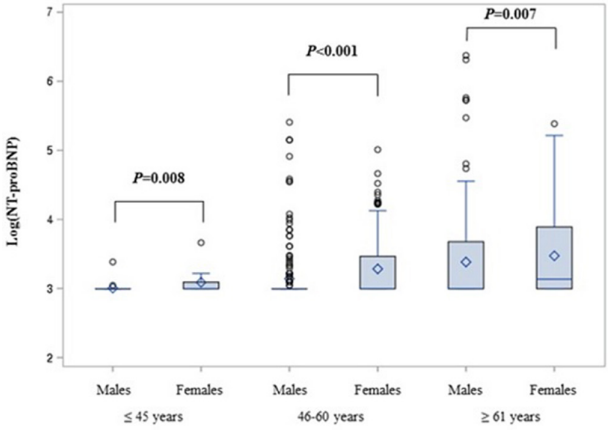

Figure 2 NT-proBNP levels according to sex and age categories. Box limits and horizontal lines within boxes represent interquartile ranges and the median, respectively. The upper and lower whiskers indicate the 97.5th and 2.5th percentiles, respectively. NT-proBNP, N-terminal pro-B-type natriuretic peptide.

mL had a sensitivity of 51.1% (95% CI 40.9% to 61.3%), a specificity of 69.3% (95% CI 65.5%–73.1%), a positive predictive value of 21.5% (95% CI 16.0% to 26.9%) and a negative predictive value (NPV) of 89.6% (95% CI 86.7% to 92.5%) in predicting cardiac structural abnormalities.

DISCUSSION

This study investigated the association between NT-proBNP levels with echocardiography-detected early stage of cardiac structural abnormalities and diastolic dysfunction in asymptomatic subjects with preserved left ventricular systolic function in a primary healthcare setting. Subjects with structural abnormalities that were not yet apparent were older and had a higher BMI, higher blood pressure, lower HDL-C level, or greater impairment of diastolic function in echocardiography. Furthermore,

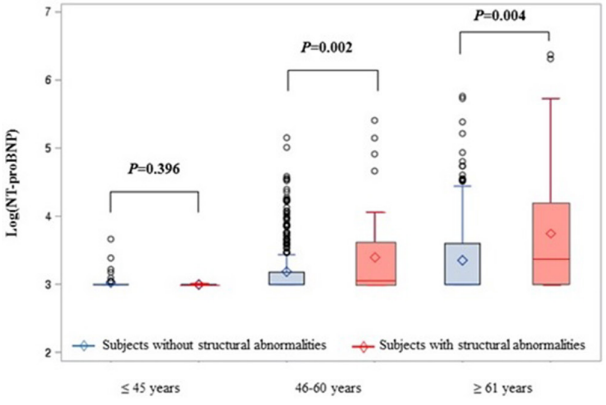

Figure 3 NT-proBNP levels of subjects with and without structural abnormalities according to age categories. Box limits and horizontal lines within boxes represent interquartile ranges and the median, respectively. The upper and lower whiskers indicate the 97.5th and 2.5th percentiles, respectively. NT- proBNP, N-terminal pro-B-type natriuretic peptide.

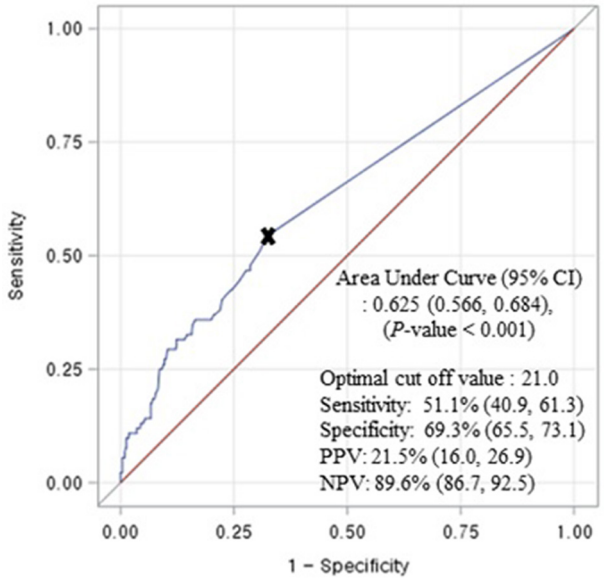

Figure 4 Receiver operating characteristic curve and cut-off value of N-terminal pro-B-type natriuretic peptide in predicting cardiac structural abnormalities. NPV, negative predictive value; PPV, positive predictive value.

we have demonstrated that diastolic dysfunction is not associated with higher NT-proBNP levels, whereas preclinical cardiac structural abnormalities, as well as older age, female sex, lower BMI and higher creatinine level, are associated with higher NT-proBNP levels.

We observed associations of diastolic dysfunction with cardiovascular risk factors, such as higher BMI, blood pressure, FBS, and triglycerides, and lower HDL-C levels. These results are consistent with reports of the presence of diastolic dysfunction being closely associated with cardiovascular diseases.[16–18] Furthermore, subjects with diastolic dysfunction exhibited elevated LVMI and LAD, which indicate the presence of structural abnormalities. These findings support the finding that a hypertrophied ventricle is more likely to exhibit diastolic dysfunction and a chronic increase in the left atrium (LA) pressure associated with diastolic dysfunction, and would be expected to lead to atrial enlargement.[19]

NT-proBNP is released into the circulation in response to a stretched myocardium resulting from any cardiac structural abnormalities.[20] Hung *et al*[21] demonstrated an association between any structural anomaly and NT-proBNP levels, which was consistent with our finding of the NT-proBNP level being associated with subclinical cardiac structural abnormalities. Our AUROC suggests a threshold level of 21.0 pg/mL to exclude early stage of subclinical structural abnormalities in health check-ups. Compared with the previously recommended cut-off value of 32.8 pg/mL,[21] our newly proposed cut-off value is much lower with fairly acceptable NPV. However, we found no association between preclinical diastolic dysfunction (PDD) and the circulating NT-proBNP level. These differences might be due to differences between the included subjects: our study subjects participated in

routine health check-ups and pre-excluded any echocardiography-detected valvular heart disease or pulmonary hypertension, while the subjects included in the previous study had aortic root dilatation, ventricular hypertrophy, pulmonary hypertension or valvular heart disease and presented at a tertiary referral centre. Another previous study of PDD[22] found that while advanced diastolic dysfunction with a normal LVEF was independently associated with structural abnormalities (increased LVMI and left atrial volume index [LAVI]) and increased circulating NT-proBNP, the structural abnormalities and NT-proBNP levels did not differ between normal controls and patients with mild diastolic dysfunction.

Among subjects with a normal LVEF and no HF diagnosis, a higher severity of diastolic dysfunction was associated with a higher mean LVMI and LAVI.[19] Our subjects with diastolic dysfunction had relatively low mean LVMI or LAD values, and they are therefore likely to have had only mild diastolic dysfunction. Our observations suggest that the association between PDD and circulating NT-proBNP levels may vary according to the severity of diastolic dysfunction. Therefore, the screening of preclinical structural or functional abnormalities based on NT-proBNP levels could be optimised by targeting subjects with potentially advanced diastolic dysfunction, which encompasses those who are older and have cardiovascular risk factors such as obesity, hypertension, higher blood glucose or dyslipidaemia in health check-ups.

Our study has some limitations. Its cross-sectional design and relatively small sample mean that further research is needed into the associated causal relationships. Nevertheless, power calculation using G* power 3.1 with an effect size f^2 of 0.2 (recommended by Cohen) showed the efficiency of sample size as the power of 0.85, which seems to be available in drawing conclusions of this study. Data on potential clinical correlates of diastolic dysfunction, such as exercise tolerance, were not included. Moreover, the echocardiographic evaluation was performed using a minimal data set that did not include detailed echocardiographic data on diastolic function. American Society of Echocardiography 2016 guidelines recommended the four variables for identifying diastolic dysfunction: annular e' velocity, average E/e' ratio, LA maximum volume index, and peak tricuspid regurgitation (TR) velocity. Moreover, the average E/e' ratio, which was used in the present study, was recommended for simplification on the basis of the writing group's collective expert opinion.[15] Inclusion of other variables will be considered to differentiate between normal and abnormal diastolic functions in the future study.

In conclusion, the findings of this study suggest that NT-proBNP levels are associated with preclinical cardiac structural but not with diastolic dysfunction, which is applicable to early stage B HF among the four categories defined by the American College of Cardiology/American Heart Association.[23]

Acknowledgements The authors would like to thank the participants who made this study possible.

Contributors All of the authors participated in designing this study. SC and SYK performed data collection. SK undertook the statistical analyses. E-HN, SYK, H-IC and SK analysed and interpreted the data. E-HN wrote the first draft of the manuscript, which was reviewed by all of the other authors, who also provided further contributions and suggestions.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Ethics approval This study was approved by the Institutional Review Board of the Korea Association of Health Promotion (approval no. 130750-201807-HR-016).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

REFERENCES

1. Ponikowski P, Voors AA, Anker SD, *et al*. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;37:2129–200.
2. Felker GM, Anstrom KJ, Adams KF, *et al*. Effect of natriuretic peptide–guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA* 2017;318:713–20.
3. Davies M, Hobbs F, Davis R, *et al*. Prevalence of left-ventricular systolic dysfunction and heart failure in the Echocardiographic Heart of England Screening study: a population based study. *Lancet* 2001;358:439–44.
4. Mosterd A, Hoes AW, de Bruyne MC, *et al*. Prevalence of heart failure and left ventricular dysfunction in the general population; The Rotterdam Study. *Eur Heart J* 1999;20:447–55.
5. Mureddu GF, Agabiti N, Rizzello V, *et al*. Prevalence of preclinical and clinical heart failure in the elderly. A population-based study in Central Italy. *Eur J Heart Fail* 2012;14:718–29.
6. Fischer M, Baessler A, Hense HW, *et al*. Prevalence of left ventricular diastolic dysfunction in the community. Results from a Doppler echocardiographic-based survey of a population sample. *Eur Heart J* 2003;24:320–8.
7. Kuznetsova T, Herbots L, López B, *et al*. Prevalence of left ventricular diastolic dysfunction in a general population. *Circ Heart Fail* 2009;2:105–12.
8. Yu J, Oh PC, Kim M, *et al*. Improved early risk stratification of patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention using a combination of serum soluble ST2 and NT-proBNP. *PLoS One* 2017;12:e0182829.
9. Hall C. Essential biochemistry and physiology of (NT-pro)BNP. *Eur J Heart Fail* 2004;6:257–60.
10. Coats CJ, Parisi V, Ramos M, *et al*. Role of serum N-terminal pro-brain natriuretic peptide measurement in diagnosis of cardiac involvement in patients with anderson-fabry disease. *Am J Cardiol* 2013;111:111–7.
11. Paulus WJ, Tschöpe C, Sanderson JE, *et al*. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007;28:2539–50.
12. Gehle P, Robinson PN, Heinzel F, *et al*. NT-proBNP and diastolic left ventricular function in patients with Marfan syndrome. *Int J Cardiol Heart Vasc* 2016;12:15–20.
13. Folland ED, Parisi AF, Moynihan PF, *et al*. Assessment of left ventricular ejection fraction and volumes by real-time, two-dimensional echocardiography. A comparison of cineangiographic and radionuclide techniques. *Circulation* 1979;60:760–6.

14. Lang RM, Badano LP, Mor-Avi V, *et al*. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;16:233–71.
15. Nagueh SF, Smiseth OA, Appleton CP, *et al*. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016;29:277–314.
16. Kane GC, Karon BL, Mahoney DW, *et al*. Progression of left ventricular diastolic dysfunction and risk of heart failure. *JAMA* 2011;306:856–63.
17. From AM, Scott CG, Chen HH. The development of heart failure in patients with diabetes mellitus and pre-clinical diastolic dysfunction a population-based study. *J Am Coll Cardiol* 2010;55:300–5.
18. Ren X, Ristow B, Na B, *et al*. Prevalence and prognosis of asymptomatic left ventricular diastolic dysfunction in ambulatory patients with coronary heart disease. *Am J Cardiol* 2007;99:1643–7.
19. Redfield MM, Jacobsen SJ, Burnett JC, *et al*. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA* 2003;289:194–202.
20. Mueller T, Gegenhuber A, Poelz W, *et al*. Comparison of the Biomedica NT-proBNP enzyme immunoassay and the Roche NT-proBNP chemiluminescence immunoassay: implications for the prediction of symptomatic and asymptomatic structural heart disease. *Clin Chem* 2003;49:976–9.
21. Hung TC, Wang KT, Yun CH, *et al*. Value of serum N-terminal B-type natriuretic peptide in asymptomatic structural heart disease in Taiwanese population: Comparisons with current ESC Guidelines. *Int J Cardiol* 2017;231:195–200.
22. Abhayaratna WP, Marwick TH, Smith WT, *et al*. Characteristics of left ventricular diastolic dysfunction in the community: an echocardiographic survey. *Heart* 2006;92:1259–64.
23. Yancy CW, Jessup M, Bozkurt B, *et al*. ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Voll Cardiol* 2013;2013:e147–239.