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

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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, lower NT-proBNP level, and 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.

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

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.

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insufficiency, ventricular dysfunction and cardiomyopathy. 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. An increased left ventricular mass index (LVMI>115 g/m² in men and >95 g/m² 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. 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.

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 χ² 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 χ² 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/m²)        | 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                         | 78.9±15.7                     | 0.520   |
| eGFR (mL/min/1.73 m²)| 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/m²)        | 71.7±13.3                         | 88.9±18.1                     | <0.001  |
| LAD (mL/m²)        | 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 χ² 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; 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/m²)        | 23.4±3.0                         | 25±3.2                        | <0.001  |
| SBP (mm Hg)        | 116.2±12.6                       | 122±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                       | <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 m²)| 88.9±15.7                   | 84.3±15                       | 0.001   |
| NT-proBNP (pg/mL)  | 35.9±63.5                        | 32.3±32.9                     | 0.476   |
| LVEF (%)           | 66.2±6.9                         | 66.1±6.5                      | 0.131   |
| LVMI (g/m²)        | 69.5±14.2                        | 75.9±15.3                     | <0.001  |
| LAD (mL/m²)        | 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±1.1                       | <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 χ² 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; 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.

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, 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 | Structural abnormality b | Diastolic dysfunction c | Structural abnormality and diastolic dysfunction d | 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/m²) | 23.2±3   | 25.9±2.1                 | 24.6±2.9                | 27.1±3.7                                       | <0.001 | a,c,d              |
| SBP (mm Hg) | 115.7±12.6 | 121.3±11.5                 | 121.6±13.8              | 127.6±12                                       | <0.001 | a,c,d              |
| DBP (mm Hg) | 71.2±8.7 | 73.8                     | 74.8±8.8                | 77.6±8.5                                       | <0.001 | a,b,c,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,c,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,c,d              |
| HDL-C (mmol/L) | 1.6±0.4 | 1.5±0.5                   | 1.5±0.4                | 1.4±0.4                                        | 0.001  | a,c,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 m²) | 89.5±15.8 | 82.3±13.1                 | 83.5±13.9              | 88.3±19.2                                      | <0.001 | b,c,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/m²) | 67.8±12.8 | 88±16.2                   | 73.3±13.1              | 89.1±18.5                                      | <0.001 | a,c,d,b            |
| LAD (mL/m²) | 33±3.9 | 43.5±6.2                   | 34±3.8                 | 40.2±5.2                                       | <0.001 | a,c,d,b, c< b      |
| E/e' | 9.3±2.1 | 10.7±2.4                   | 11.8±3.5               | 13.4±3.5                                       | <0.001 | a,c,d,b, c< b      |
| e' (cm/s) | 8.2±1.1 | 11±12.3                    | 5.4±0.9                | 4.9±1.2                                        | <0.001 | a,c,d,b, c< 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 LDL-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 LDL-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

| Variables | Univariate model | Multivariate model |
|-----------|-----------------|-------------------|
|           | Coeff.* (95% CI) | P value | R² | Coeff.* (95% CI) | P value | R² | Coeff.* (95% CI) | P value | R² |
| 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/m²) | −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 (−0.1 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 | <0.001 | −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 to −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) | 0.041 | 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/m²) | 0.47 (0.26 to 0.69) | 0.041 | 0.028 | 0.28 (0.04 to 0.52) | 0.022 | 0.30 (0.07 to 0.53) | 0.012 |
| LAD (mL/m²) | 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.
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, 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 al21 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

**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.

**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.
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 dilation, ventricular hypertrophy, pulmonary hypertension or valvular heart disease and presented at a tertiary referral centre. Another previous study of PDD 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. 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. 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.

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