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Screening for asymptomatic heart failure with preserved ejection fraction in Mongolian population at high risk

Objective The goals of the present study were to assess the prevalence of asymptomatic heart failure with preserved ejection fraction (HFpEF) in subjects at high risk of developing HF and to define the diagnostic accuracy of NT-pro BNP assay compared with echocardiography in this setting.

Material and methods This cross-sectional study included subjects aged from 35 to 64 years, with high risk of HF, who had no clinical symptoms of HF. Risk factors of HF were detected by clinical examinations. NT-pro BNP determination was performed using immunoassay analyzer (FIA8000, Getein Bio Medical Inc, China),. The cut-off point for NT-pro BNP was 125 pg/ml. Diagnosis of HFpEF was based on criteria recommended by 2016 ESC heart failure guidelines. Diastolic dysfunction was assessed according to the algorithm proposed in the joint recommendations of the ASE/EACVI.

Results 602 patients with risk factors of HF were included in the study, of which 256 (42.5%) were males and 346 (57.5%) females. The mean age was 51.71±8.07 years. 83 patients (13.8%) showed elevated NT-pro BNP levels of ≥125 pg/ml. Our study has shown that NT-pro BNP concentration was positively correlating with age, both systolic and diastolic blood pressure, left ventricular mass and E/e' ratio and negatively correlating with waist circumference, body mass index, left ventricular EF and E/A ratio in asymptomatic population. The likelihood of positive NT-pro BNP test was independently ($p<0.05$) associated with age, hypertension and diabetes. The diagnosis of asymptomatic HFpEF was confirmed in 12.3% of studied population. A cutoff value of 125 pg/ml for NT-proBNP concentration showed the following diagnostic re-abilities in identifying asymptomatic HFpEF: sensitivity 85.0%, specificity 88.6% and area under curve 0.92 (95% CI 0.86–0.98).

Conclusion Subjects with raised NT-pro BNP level (≥125 pg/ml) were more likely to have a confirmed diagnosis of asymptomatic HFpEF after screening. In summary, in at-risk population, natriuretic peptide based screening combined with echocardiography identifies high prevalence of asymptomatic HFpEF.

Keywords Heart failure; natriuretic peptide; screening; diastolic dysfunction; echocardiography; NT-pro BNP; HFpEF

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Introduction

The prevalence of cardiovascular diseases (CVD) among Mongolian population has increased 5 times during the last 20 years [1]. The prevalence of heart failure (HF) and its associated morbidity and mortality have increased exponentially over recent decades. The increasing prevalence of HF remains a major public health concern underlining the need for an effective prevention strategy [2]. The HF has poor prognosis and high mortality rate (40–50% after 5 years) especially if the symptoms are due to left ventricular (LV) systolic dysfunction [3].

Given the growing epidemic of HF with preserved ejection fraction (HFpEF), it may be the time to broaden the aim of screening to focus on the identification of patients with asymptomatic LV diastolic dysfunction. According to the 2016 ESC acute and chronic heart failure guidelines, circulating levels of NT-proBNP (N-Terminal pro-B-type natriuretic peptide) can be used as an initial diagnostic test. The cut-off value of NT-proBNP for patients without acute HF is 125 pg/ml [4].

Lastly, the use of natriuretic peptide analysis as a screening element prior to echocardiography in patients with

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suspected HF attended in primary care can provide support for the initial suspected diagnosis. NT-proBNP can be useful in screening, diagnosis, treatment monitoring and to inform prognosis of HF. Levels of NT-proBNP have been shown to be elevated in patients with cardiac dysfunction [5].

The prevalence of diastolic HF among population is higher than the prevalence of systolic HF [6]. The LV diastolic dysfunction increases with age and cardiovascular risk exposure. Subjects with asymptomatic LV dysfunction are estimated to be found in 3~4% of the general population. An early diagnosis of asymptomatic HFpEF is needed to guide appropriate treatment strategies, to delay or reverse progression of disease and considerably improve the prognosis of HF.

The purposes of the present study were to assess the prevalence of asymptomatic HFpEF in subjects at high risk of developing HF and to define the diagnostic accuracy of NT-proBNP assay compared with echocardiography in this setting.

Material and methods

The cross-sectional study was carried out for a period of ten months (November 2017 to August 2018) in Express diagnostic and Cardiovascular centers in the city of Ulaanbaatar (Mongolia). The eligible participants were health checkup examinees, aged from 35 to 64 years, with high risk for HF, who had no symptoms of HF and agreed to the study. We excluded patients with previous diagnosis and clinical symptoms of HF and history of myocardial infarction and subjects with LV ejection fraction (LVEF) <50%. Among the 628 participants initially enrolled in the study, 15 passed away, 8 subjects withdrew their consents and 3 patients had LVEF <50%, leaving 602 patients eligible for analysis.

All patients gave their written informed consent to take part in the study. Research ethical permission was obtained from the local ethics committee of Mongolian National University of Medical Sciences and Biomedical ethics committee of Ministry of Health, Mongolia.

High risks for HF included arterial hypertension, diabetes, obesity, excessive drinking of alcohol, smoking and family history of CVD. We defined the following cardiovascular risk factors according to clinical examination and laboratory test results: obesity as the body mass index (BMI) ≥30 kg/m^2, hypertension as having a blood pressure of ≥130/80 mmHg on two separate examinations or usage of antihypertensive agents, diabetes mellitus as fasting glucose ≥7.0 mmol/l usage of insulin or anti-diabetic drugs.

Smoking was defined as current smoking, family history as history of CVD or sudden cardiac death before the age of 55 years of the father or any other first-degree male relative or before the age of 65 years of the mother or any other first degree female relative. Excessive drinking of alcohol is defined as 15 or more standard drinks a week for men and as 8 or more standard drinks a week for women. Abdominal obesity is defined as waist circumference ≥90 cm for men and ≥80 cm for women.

A 10 ml venous blood sample was drawn into an EDTA tube. NT-proBNP determination was performed using immunoassay analyzer (FIA8000, Getein Bio Medical Inc, China), which utilizes reagent strip to obtain quantitative NT-proBNP results in whole blood or plasma. The test results were obtained in 15 min. Plasma NT-proBNP values are expressed in pg/ml (analytical range, 100–35000 pg/ml). The cut-off point for NT-proBNP was 125 pg/ml.

Echocardiographic study was carried out with a General Electric Vivid 7 system using a 3.5 MHz transducer. The LVEF was calculated from apical four chamber view using the Simpson's method. Parameters from M-mode, 2D trans thoracic echocardiography, Doppler tissue imaging of the septal and lateral wall at the mitral annulus, and Doppler color analysis were used. Parameters of LV diastolic function assessed using standard techniques included tissue Doppler at the lateral and medial mitral annulus.

The early diastolic mitral annular wall velocity (e' velocity) was measured and E/e' was calculated. From the mitral inflow profile, the E deceleration time, the early diastolic mitral flow velocity (E), and atrial contraction (A) wave velocity were measured. The early-to-atrial LV filling ratio (E/A) was calculated.

According to HF guidelines of the European Society of Cardiology, we defined HFpEF as a LVEF ≥50% and elevated NT-pro-BNP value as >125 pg/ml and plus at least 1 additional following criterion: left atrial volume index (LAVI) >34 ml/m^2 or a LV mass index (LVMI) ≥115 g/m^2 for males, ≥95 g/m^2 for females or diastolic dysfunction. Diastolic dysfunction was assessed according to the ASE/EACVI recommendations for the evaluation of LV diastolic function by echocardiography.

Statistical analysis

All statistical analyses were made with Statistical Package for the Social Sciences SPSS version 24.0. All continuous data were tested for normality using the Kolmogorov – Smirnov test. Since the Kolmogorov – Smirnov testing identified that NT-proBNP was non-normal distributed, non-parametric tests were used throughout the analysis. We used Mann-Whitney U test as a nonparametric tool. The Kruskal-Wallis test was used to make multiple comparisons assessment. All continuous values were presented as mean ± standard deviation. Differences between the study groups were analyzed with the chi-square test for categorical variables. P-value less than 0.05 is considered as statistically significant. A multivariate logistic regression and odds ratio (OR) (95% confidence interval (CI)) analysis were performed to identify

the contribution of major cardiovascular risk factors for elevated NT-proBNP level in the study. Pearson's correlation coefficient as a statistical method was used to calculate correlation of echocardiographic parameters with NT-proBNP levels.

Diagnostic utilities were calculated using the sensitivity, specificity, negative and positive predictive values, negative and positive likelihood ratios. Receiver operating characteristic (ROC) and area under the curves (AUC) were calculated for measurement of the natriuretic peptide's performance in predicting HF at screening.

Results

A total of 602 patients with risk factor of HF were included in the study, of which 256 (42.5%) were males and 346 (57.5%) were females. The mean age and age ranges were 51.71±8.07 and 35–64 years old respectively. The distribution of baseline characteristics was different between male and female (Table 1). Diabetes, excessive drinking of alcohol and smoking in male were significantly higher than in female. Abdominal obesity and family history of CVD in female were significantly higher than in male.

NT-proBNP levels were measured in 602 participants during our study. 83 patients (13,8%) showed elevated NT-proBNP levels of ≥125 pg/ml. The mean NT-proBNP level among the 83 patients with positive test was 313.08±120.70 pg/ml (range 131–689 pg/ml). The distribution of risk factors for HF was different between normal and elevated NT-proBNP groups (Table 2). The aging and percentages of hypertension, diabetes and excessive drinking of alcohol in elevated NT-proBNP group were significantly higher than in normal NT-proBNP group. Although there was no significant sex difference in the prevalence of participants with NT-proBNP levels of ≥125 pg/ml. The percentage of subjects with NT-proBNP levels of ≥125 pg/ml was non-significantly lower in males than in females.

The contribution of risk factors to the progression of HF was analyzed using multivariate logistic regression analysis. The statistical analysis was carried out using all the cardiovascular risk factors (age, gender, hypertension, diabetes, abdominal obesity, BMI ≥30 kg/m², excessive drinking of alcohol, smoking and family history) as independent variables and elevated NT-proBNP level as dependent variable.

Using multivariate analysis (Table 3), the likelihood of positive NT-proBNP test was independently associated with age, hypertension and diabetes. Based on OR, hypertension showed 3.4 times greater risk for HF than other cardiovascular risk factors studied.

Clinical and echocardiographic parameters correlating with NT-proBNP levels are shown in Table 4. Correlation analysis demonstrated that age, systolic and diastolic blood pressure, LVM, LAVI, inter-ventricular septum thickness at diastole and E/e' ratio all positively correlated with NT-

Table 1. Baseline participant's characteristics

Characteristics	Male (n=256)	Female (n=346)	All participants (n=602)	p value
Age, mean (SD), years[a]	51.74±8.49	50.81±10.05	51.71±8.07	556
Age group, n (%)				
35–44	66 (25.8)	81 (23.4)	147 (24.4)	083
45–54	84 (32.8)	144 (41.6)	228 (37.9)	
55–64	106 (41.4)	121 (35.0)	227 (37.7)	
Arterial hypertension, n (%)	197 (76.9)	246 (72.0)	446 (74.1)	167
Diabetes mellitus, n (%)	77 (30.1)	76 (21.9)	153 (25.4)	024*
Excessive drinking of alcohol	146 (55.1)	90 (26.0)	236 (39.2)	0001*
Smoking, n (%)	128 (50.0)	34 (9.8)	162 (26.9)	0001*
Obesity (BMI ≥30 kg/m²)	109 (42.6)	159 (45.9)	268 (44.5)	557
Abdominal obesity, n (%)	202 (78.9)	301 (87.0)	503 (83.5)	008*
Family history of CVD, n (%)	61 (23.8)	141 (40.7)	202 (33.5)	001

** – p value is calculated with Chi–Square test,
[a] – Mann–Whitney U test and considered significant as <0.05,
BMI – body mass index. CVD – cardiovascular disease.

Table 2. The distribution of risk factors for HF between normal and elevated NT-pro BNP levels

Risk factors	NT-pro BNP, <125 pg/ml (n=519), n (%)	NT-pro BNP, ≥125 pg/ml (n=83), n (%)	p value
Age group			
35–44	136 (26.2)	11 (13.2)	0001*
45–54	206 (39.7)	22 (26.6)	
55–64	177 (34.1)	50 (60.2)	
Gender			
Male	224 (43.1)	32 (38.5)	431
Female	295 (56.9)	51 (61.5)	
Hypertension	371 (71.5)	75 (90.4)	0001*
Diabetes mellitus	141 (27.2)	12 (14.4)	039*
Abdominal obesity	436 (84.0)	67 (80.7)	453
Obesity (BMI >30 kg/m²)	232 (44.7)	36 (43.3)	714
Excessive drinking of alcohol	212 (40.8)	24 (28.9)	039*
Smoking	139 (26.8)	23 (27.7)	859
Family history of CVD	172 (33.1)	30 (36.1)	607

* – p value is calculated with Chi–Square test and considered significant as <0.05.

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Table 3. Risk factors for elevated NT-proBNP levels (≥125 pg/ml)

Risk factors	NT-proBNP			
	cOR (CI 95%)	p value	aOR	p value
Gender				
Female	1	-	1	-
Male	1.2 (0.7–1.9)	411	1.4 (0.7–2.5)	335
Age				
35–44	1	-	1	-
45–54	1.3 (0.6–2.8)	472	1.1 (0.5–2.2)	098
55–64	3.4 (1.8–6.9)	0001**	2.9 (1.4–4.8)	005*
Arterial hypertension				
No	1		1	
Yes	3.4 (1.5–7.6)	003*	2.1 (0.5–9.4)	331
Diabetes				
No	1	-	1	-
Yes	0.4 (0.2–0.9)	025*	2.2 (0.5–8.1)	231
Abdominal obesity				
No	1	-	1	-
Yes	1.2 (0.7–1.9)	021*	1.1 (0.9–2.1)	05
Excessive drinking of alcohol				
No	1	-	1	-
Yes	0.6 (0.4–1.0)	042*	0.6 (0.3–1.2)	151
Smoking habit				
No	1	-		-
Yes	1.1 (0.6–1.1)	0.851	1.3 (0.7–2.4)	443
Family history of cardiovascular disease				
No	1	-		-
Yes	1.1 (0.6–1.7)	0.783	1.3 (0.7–2.1)	431

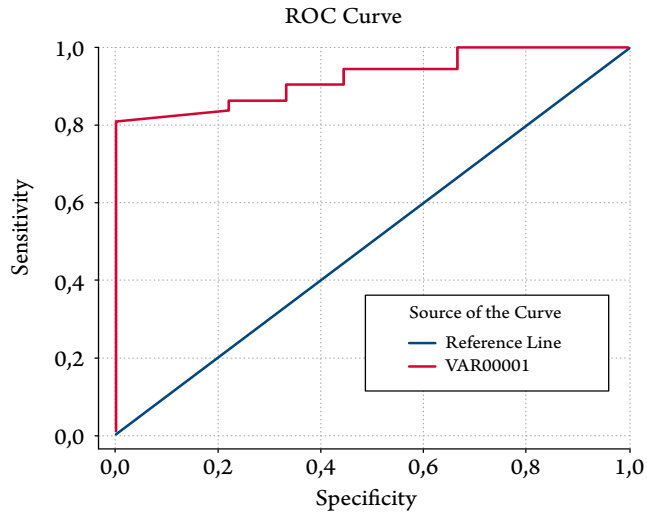
1 – reference value, cOR – crude odds ratio,
aOR – adjusted odds ratio, * – p value is <0.05.

Table 4. Correlation between NT-proBNP levels and clinical, echocardiographic parameters

Parameters	Mean±SD	r (against NT-pro BNP levels)	p value
Age (years)	51.71±8.07	0.134	001*
BMI (kg/m²)	30.3±6.8	–0.013	798
Waist (cm)	99.6±15.7	–0.110	007*
SBP mean (mm Hg)	132.5±20.9	0.198	0001*
DBP mean (mm Hg)	87.4±12.6	0.101	036*
LVEF (%)	62.9±7.7	–0.313	001*
E/A ratio	0.77±0.30	–0.187	016*
E/e'	9.46±2.61	0.201	009*
LAVI (ml/m²)	32.6±5.43	0.324	001*
IVSd (cm)	1.04±0.55	0.163	037*
LVPWd (cm)	0.86±0.48	0.151	052
LV mass (gr/m²)	195.9±48.9	0.190	014

** – difference is significant. SPS – systolic blood pressure,
DBP – diastolic blood pressure, LVEF – left ventricular ejection fraction,
E/A – ratio of the early mitral inflow (E) to late (A) ventricular filling velocities, E/e' – ratio between early mitral inflow velocity and mitral annular early diastolic velocity, LAVI – left atrial volume index,
IVSd – interventricular septum thickness at end-diastole,
LVPWd – left ventricular posterior wall thickness at end-diastole,
LV mass – left ventricular mass.

Figure 1. Area under the receiver operating characteristic curve (0.923) for NTpro-BNP cut-off of 125 pg/ml



proBNP levels, whereas waist circumference, BMI, LVEF and E/A ratio were all negatively correlating with it.

A total of 166 subjects (83 with elevated NT-proBNP levels and 83 with normal NT-proBNP levels) underwent heart ultrasound examination. Echocardiography showed diastolic dysfunction or increased LAVI or increased LVM were present in 74/83 subjects with elevated NT-proBNP levels (89.2%) and in 9/83 subjects with normal NT-proBNP levels (10.8%). Diastolic dysfunction was divided into 3 degrees. The most common degree of diastolic dysfunction was B-grade I (64%).

The diagnosis of HFpEF was confirmed by NT-proBNP test and echocardiography in 74/602 (12.3%) of studied participants at high risk for HF.

The sensitivity and specificity of NT-pro BNP test in HF diagnosis were calculated using 2x2 table. A cutoff value of 125 pg/ml for NT-proBNP concentration showed the following diagnostic re-abilities in identifying LV diastolic dysfunction: sensitivity 85.0%, specificity 88.6%, diagnostic accuracy 86.7%, negative predictive value 84.3%, positive predictive value 89.1%, likelihood ratio for positive test results 6.96 and likelihood ratio for negative test results 0.17.

ROC curve showed effectiveness of baseline NT-proBNP in predicting a diagnosis of HF at screening in the population. The ROC curve obtained for the diagnosis of diastolic HF AUC was 0.923 (95% CI 0.86–0.98) (Fig. 1).

Discussion

NT-proBNP levels were measured in 602 participants. Approximately 14% of the cases in asymptomatic population showed raised NT-proBNP levels of ≥125 pg/ml. According to Russian study overall 17.9% of examines had elevated NT-proBNT levels (14.2 and 20.3% among men and women

respectively). The difference may be due to the cut-off value, which in this study was 100 pg/ml [7].

In our study, the likelihood of positive NT-proBNP test was independently associated with age, hypertension and diabetes. Shalnova S. A. et al. [7] reported that elevated NT-proBNP level was significantly associated with gender, age, smoking, myocardial infarction and hypertension (blood pressure ≥160/95 mm Hg).

We have shown that NT-proBNP concentration was positively correlating with age, both systolic and diastolic blood pressure, LVM and E/e' ratio and negatively correlating with waist circumference, BMI, LVEF and E/A ratio in an asymptomatic population. Recent study [8] demonstrated that age, systolic blood pressure, pulse pressure, hypertension, smoking habit were all positively correlating with NT-proBNP levels, whereas male sex, BMI, waist circumference, were all negatively correlating with it. The results are comparable with the results of the present study.

In our study AUC of the NT-proBNP value for the diagnosis of LV diastolic dysfunction was 0.923 (95% CI 0.86–0.98) which was similar to other studies [9, 10]. Median NT-proBNP concentration in patients with diastolic dysfunction in our study was 289 (131-689) pg/ml respectively. These values differ from those reported by Jose´ M. Verdu et al. [11] who described a median NT-proBNP concentration at 715 [510.5–1575] pg/ml, which can be explained by the older mean age of participants and inclusion of symptomatic patients in the study.

The prevalence of HFpEF (12.3%) in the present study was higher than those (0.9–6.6%) in previous studies [2, 9]. The difference may be due to the inclusion of subjects aged 35–64 years with high risk for HF in current study.

The major limitations of our study were the following: we involved in present study only subjects aged 35 to 64 years with high risk of HF, several factors such as renal function and cardiac rhythm were not recorded in this study, which may have had some influence on the NT-proBNP levels.

Conclusions

Subjects with raised NT-proBNP level (≥125 pg/ml) were more likely to have a confirmed diagnosis of diastolic HF after screening. In summary, in an at-risk population, natriuretic peptide based screening combined with echocardiography identifies a high prevalence of asymptomatic HFpEF.

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