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Original Article

NT-proBNP is associated with age, gender and glomerular filtration rate in a community-dwelling population

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Abstract: Objective: This study assessed the relationship between N-terminal pro-brain natriuretic peptide (NT-proBNP), age, gender, renal function, and obtained the reference range of NT-proBNP in each subgroup by age and gender in a community-dwelling population. Methods: In total, 1499 subjects ranging from 23 to 96 years were included in the study, NT-proBNP, age, gender, eGFR (Estimated Glomerular Filtration Rate) and other relevant indicators were recorded from 5 years of follow-up research. The relationships between NT-proBNP, age, gender, and eGFR were clarified with scientific research and statistical methods. Results: The median age was 61.4 years old, and the median NT-proBNP level was 37.9 pg/mL (interquartile range, 17.025-74.95 pg/mL). Age was divided into 4 groups by 20 year increments. The plasma NT-proBNP concentrations were significantly positively related to age. Gender subgroup analysis showed that the level of NT-proBNP in the female group was higher than that in the male group, while the difference was not statistically significant when the age was over 80. eGFR was divided into two groups based on the critical value of 60 mL/(min·1.73 m^2), the plasma NT-proBNP level (median, 167.5; interquartile range, 82.33-371.05 pg/mL) in the lower eGFR group was significantly higher than that (median, 37.85; interquartile range, 17.2-73.88 pg/mL) in the higher eGFR group. Linear correlation analysis showed that NT-proBNP was negatively correlated with eGFR. However, no significant correlation was found when we compared the NT-proBNP with the eGFR decreasing in 5 years. Conclusions: In the community-dwelling population, NT-proBNP increased with age, and was higher in female subjects less than 80 years old. Furthermore, eGFR was negatively correlated with NT-proBNP. Nonetheless, NT-proBNP was not an independent risk factor for kidney function.

Keywords: NT-proBNP, age, gender, kidney function

Introduction

The cardiac natriuretic hormone plays an important role in regulating homeostasis and cardiovascular remodeling [1]. These peptide hormones induce natriuresis, diuresis, and vasodilatation, and act specifically to counter the effects of the renin-angiotensin-aldosterone system [2]. Diseases that cause atrial dilatation, increased blood volume, increased sodium concentration in blood, and increased angiotensin can stimulate the heart to release BNP/NT-proBNP [3]. Human BNP is made up of 108 amino acids, further biological processing releases the biologically active 32-amino acid peptide and an amino-terminal fragment (NT-proBNP) [4]. NT-proBNP is a biologically inactive metabolite secreted together with its biologically active counterpart BNP from cardiac myocytes in response to cardiac stress [5]. In cardiovascular research, NT-proBNP is associated in particular with heart failure [6], atherosclerosis [7], aortic stenosis [8], renal function [9], diabetes mellitus [10], etc. Besides, NT-proBNP also increased in participants with subclinical cardiac dysfunction [11].

Moreover, our previous studies show that NT-proBNP was associated with troponin T [12] and resting heart rate [13] and holds prognostic value for all-causes of death and major cardiovascular events [14] in a community-dwelling population of China. Until now, the relationship of age and gender and renal function on plasma NT-proBNP levels had not been investigated in Chinese community-dwelling popula-

Table 1. Characteristics depended on NT-proBNP levels in the study sample

Variables	All	NT-proBNP (75%-100%)	NT-proBNP (50%-75%)	NT-proBNP (25%-50%)	NT-proBNP (0%-25%)	P
age	61.4±11.4	56.93±9.46	59.10±10.09	61.56±9.99	66.56±9.93	0
BMI	25.4±3.31	25.57±3.23	26.02±3.55	25.16±3.28	25.24±3.52	0.011
Men	42% (630)	219	150	129	131	0
TC	5.03±0.93	5.05±0.89	5.09±0.89	4.97±0.95	4.92±0.94	0.11
LDL-C	2.91±0.71	2.94±0.66	3.04±0.72	2.91±0.72	2.87±0.71	0.024
smoking	26.3% (394)	123	101	84	86	0
diabetes	20.9% (234)	79	75	74	86	0.027
eGFR (5 years prior)	94.2±11.56	97.12±11.87	96.01±12.73	93.71±11.15	85.77±11.42	0
eGFR (5 years later)	80.2±13.47	84.59±12.36	79.76±14.33	77.61±13.28	73.94±14.67	0

Notes: The following continuous variables are presented as mean ± SD deviation: age, BMI, TC, LDL-C, eGFR. The following categorical variables are presented as counts and percentages: Gender, current smoking, diabetes. Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; TC, total plasma cholesterol.

tions. Therefore, we stratified the relationship between NT-proBNP, age, gender and renal function in a 5-year follow-up study.

Material and methods

Study population and design

A 5-year follow-up study was carried out on a community-dwelling population in the Pingguoyuan area, Shijingshan district in Beijing, People's Republic of China. A total of 1,859 permanent residents who had a routine health examination between September 1, 2007, and January 31, 2009 were recruited in the study. However, 31 of the patients had arrhythmia, mental illness, severe systemic disease and were bedridden were excluded from the study.

In this study, eGFR (Estimated Glomerular Filtration Rate) evaluation was performed in 1,792 subjects. According to the exclusion criteria, a total of 141 patients with coronary heart disease (unstable angina pectoris, myocardial infarction, coronary artery revascularization), congestive heart failure, and cerebrovascular diseases (transient ischemic attack or stroke) were excluded. Among these, a total of 1,499 NT-proBNP subjects (mean age 61 years, range 23-96 years) were available for analysis. The study was reviewed by the ethics committee of the Chinese People's Liberation Army (PLA) General Hospital, and each participant signed informed consent.

Clinical data collection

The basic data of the volunteers were obtained through standardized questionnaires which included name, gender, age, chronic medical history, life history, family history, etc. The height, weight and blood pressure were measured in clinic. Height was measured in centimeters, weight in kilograms, and blood pressure in millimeters of mercury. Smoking was defined as smoking at least one cigarette per day for a year or more. The relevant laboratory measures such as NT-proBNP and creatinine were taken on an empty stomach in the morning.

Biomarker variable determination

All subjects underwent comprehensive laboratory evaluation, including blood lipids, liver and kidney function indicators. Blood samples were taken on an empty stomach between 8 and 10 a. m, and stored at -80°C after centrifugation for further tests. The test indicator reagent companies and test methods are detailed in our previous articles [13].

Definition of variables

Body mass index (BMI) was calculated by dividing weight (kg) by height (kg/m^2). Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg, or the use of antihypertensive drugs. Diabetes mellitus was defined as a fasting glucose ≥7.0 mmol/L, non-fasting glucose ≥11.1 mmol/L, or use of antihyperglycemic medication. The estimated glomerular filtration rate (eGFR) was calculated with the CKD-EPI equation as follow [15]: GFR = 141 × min (sCr/k, 1) α × max (sCr/k, 1) -1.209 × 0.993Age × 1.018 (if female) × 1.159 (if black), where k is

Table 2. Plasma NT-proBNP by age and gender in normal subjects

Gender NT-proBNP	n	ALL Median (25th, 7 th)	n	Age 21-40 Median (25th, 75th)	n	Age 41-60 Median (25th, 75th)	n	Age 61-80 Median (25th, 75th)	n	Age 81-100 Median (25th, 75th)
Women	780	45.3 (23.7, 83.15)	28	34.15 (18.48, 49.05)	410	37.15 (18.75, 68.35)	335	56.4 (29.9, 98.7)	7	128.9 (28.55, 549.78)
Men	719	30 (11.2, 65.9)	29	16.0 (7.9, 21.6)	367	19.45 (8.18, 35.6)	311	41.9 (17.1, 85.93)	12	189.85 (63.25, 362.58)
All	1499	37.9 (17.03, 74.95)	57	22.6 (13.7, 46.7)	777	28.85 (13.33, 51.13)	646	48.6 (23.9, 92.2)	19	178.1 (50.65, 269.13)

Notes: The median 25th and 75th percentiles are shown.

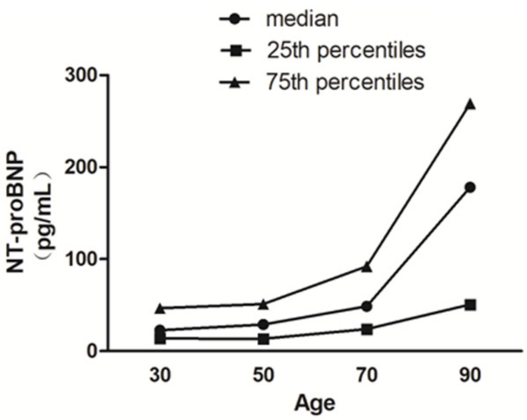

Figure 1. Relationship between NT-proBNP concentration and age. The nomogram demonstrates the 25th, 50th, 75th percentiles for BNP according to age.

0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of sCr/k or 1 and max indicates the maximum of sCr/k or 1.

Statistical analysis

The data were processed using SPSS for Windows software version 21.0 (SPSS, Chicago, IL, USA). The normal distribution continuous variables were represented by mean ± standard deviation, while the non-normal distribution variables by median and quartile. Differences in continuous variables are tested by parametric (t test or One-way ANOVA) or nonparametric tests (Kruskal-Wallis test). Differences in proportions were tested using chi-square test and Fisher's exact test. The Pearson distribution test was used for correlation analysis. The null hypothesis was rejected at the 95% confidence interval, with P<0.05 considered significant.

Results

Characteristics

Altogether, 1499 participants were included in the present study. The mean ± SD age of participants in the study was 61.4±11.4 years. The characteristics of the study population are summarized in **Table 1**.

Distribution of NT-proBNP concentrations

The distribution of NT-proBNP was revealed in the existing population data. Among the 1499 participants, the NT-proBNP concentration of 95% (1363) was greater than 5 pg/mL. The range of detectable NT-proBNP concentrations was 0-3,076 pg/mL with a median value of 37.9 pg/mL (interquartile range, 17.025-74.95 pg/mL).

The association of NT-proBNP with age and gender in the study sample

Age was divided into 4 groups by 20 year intervals. The distribution of the subjects by age/gender and corresponding NT-proBNP is shown in **Table 2**. The median value of NT-proBNP was 22.6 pg/mL (interquartile range, 13.7-46.7 pg/mL) in the 21-40 age group, 28.85 pg/mL (interquartile range, 13.33-51.13 pg/mL) in the 41-60 age group, 48.6 pg/mL (interquartile range, 23.9-92.2 pg/mL) in the 61-80 age group, and 171.8 pg/mL (interquartile range, 50.65-269.13 pg/mL) in the older than 80 age group, The plasma NT-proBNP concentrations were significantly positively related to age (P<0.01, **Figure 1**). Similarly, significant differences remained when we divided the group by gender (**Figure 2**), the plasma NT-proBNP levels ranged between 0 and 1,639 pg/mL (median, 45.3; interquartile range, 23.7-83.15 pg/mL; n=780) in females, and between 0 and 3,076 pg/mL (median, 30.0; interquartile range, 11.2-65.9 pg/mL; n=719) in male volunteers. The level of NT-proBNP in the female group was higher than that in the male group (P<0.01). However, age subgroup analysis showed that the difference was not statistically significant when the age was over 80 (**Figure 3**).

eGFR was negativly correlated with NT-proBNP, and NT-proBNP was not an independent risk factor for kidney function

eGFR calculated by the CKD-EPI equation was used to reflect kidney function. To explore the correlation between NT-proBNP and eGFR, subjects were divided into two groups based on whether eGFR was higher than 60 mL/(min·1.73 m^2) (shown in **Table 3**). The plasma NT-proBNP level (median, 167.5; interquartile range, 82.33-371.05 pg/mL) in the lower eGFR group significantly exceeded that (median, 37.85; interquartile range, 17.2-73.88 pg/mL) in the higher eGFR group (P<0.01) (**Figure 4A**). Linear correlation analysis showed that NT-proBNP was negatively correlated with eGFR (P<0.01, r=-0.26). A five-year follow-up

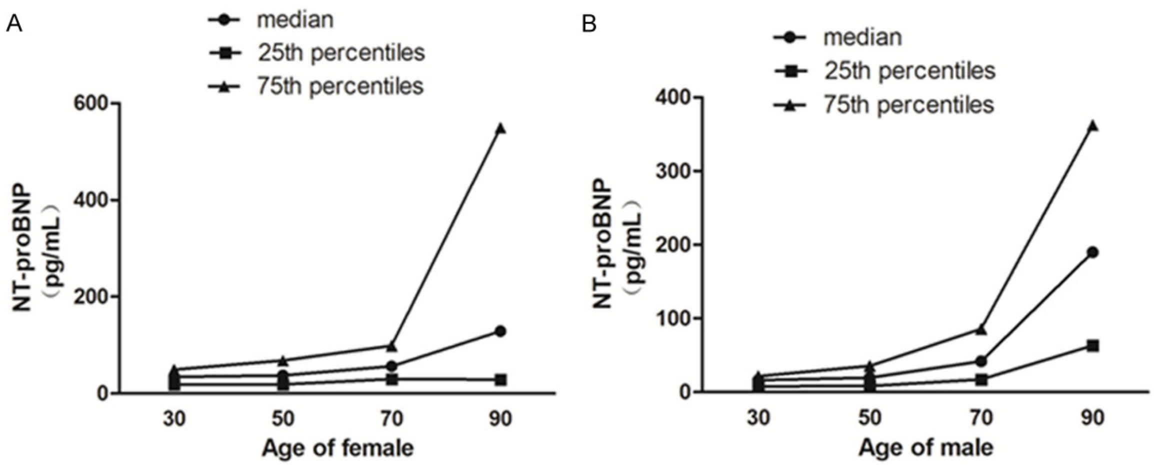

Figure 2. NT-proBNP concentration as a function of age for each gender and assay system. The nomogram demonstrates the 25th, 50th, 75th percentiles for BNP according to age: (A) Age of females; (B) Age of males.

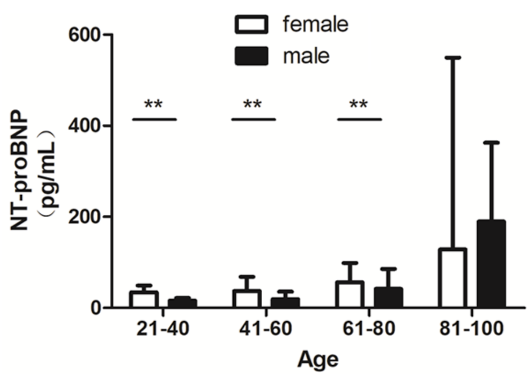

Figure 3. NT-proBNP concentrations according to age and gender.

study found that an identical correlation also occurred between NT-proBNP and eGFR five years later (P<0.01, r=-0.24) (**Figure 4B**). Moreover, we explored whether higher NT-proBNP could aggravate the deterioration of renal function. However, no significant correlation was found when we compared the NT-proBNP with the eGFR decreasing in 5 years (P=0.26). This means NT-proBNP did not cause kidney function to deteriorate, which indicated that NT-proBNP was not an independent risk factor for kidney function.

Discussion

In this study, we demonstrated for the first time that in a community-dwelling asymptomatic Chinese population, the distribution of NT-proBNP was a skewed distribution, which was expressed in terms of median and interquartile numbers, instead of mean and standard deviation. The NT-proBNP median value was 37.9 pg/mL (interquartile range, 17.025-74.95 pg/mL) in the Chinese community-dwelling population, which was consistent with reports of Jens Peter Goetze [4], who explored that the median concentration of NT-proBNP is within 10 pmol/L in healthy volunteers of Denmark. In addition, NT-proBNP in Jens Peter Goetze's study was found to increase with age. In our study, we divided the subjects into four subgroups according to age and found a similar tendency (median value was 22.6 pg/mL in the 21-40 age group, 28.85 pg/mL in the 41-60 age group, 48.6 pg/mL in the 61-80 age group, 178.1 pg/mL in the 81-100 age group). The positive correlation between NT-proBNP and age was also found in Japan [16] and still existed in very old people [17]. The explanation that NT-proBNP (BNP) concentration increases in response to age-related alterations was possibly due to increasing diastolic dysfunction, cardiac size, renal function or functions that are not detectable by current techniques [18]. Moreover, the NT-proBNP in healthy children, adolescents, and young adults was also explored and suggests that there is a significant peak at the age of 12 or 13 years in females, and 13 or 14 years in males [19]. It is more likely that sex hormones such as estrogen may regulate the cardiac natriuretic peptide system by affecting the renin-angiotensin system directly or indirectly through endocrine and/or paracrine effects [20].

The effect of gender on NT-proBNP was also remarkable. In this study, we found that the

Table 3. Plasma NT-proBNP by eGFR in normal subjects

Group	Median (25th, 75th)	P
eGFR≤60 mL/(min·1.73 m^2)	167.5 (82.33, 371.05)	P<0.05
eGFR>60 mL/(min·1.73 m^2)	37.85 (17.2, 73.88)	

Notes: eGFR calculated by CKD-EPI equation.

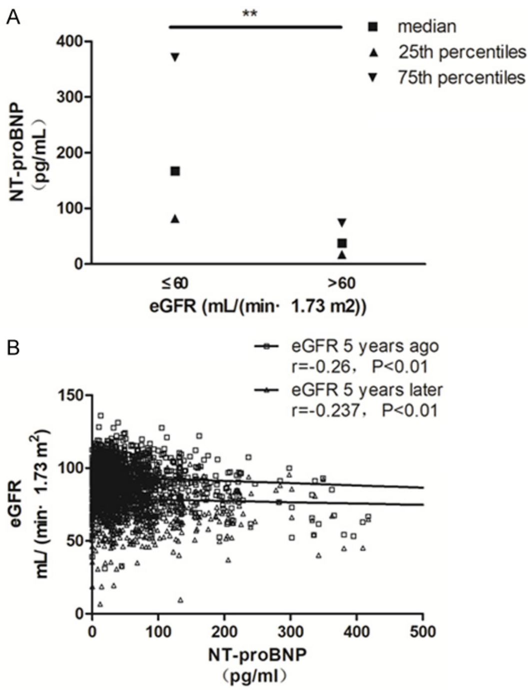

Figure 4. Relationship between NT-proBNP and renal function. A. NT-proBNP concentrations according to eGFR; B. Correlation analysis between NT-proBNP and eGFR.

level of NT-proBNP in women was significantly higher than that in men in the subgroup of under 80 years old, independent of other factors. Gender-related differences in endothelin and angiotensin-converting enzyme activity have been reported to be associated with differences in distribution of NT-proBNP [21, 22]. However, the subgroup analysis found no such difference among people over 80. In contrast, it appeared that NT-proBNP levels in male was higher than that in females over 80, although there was no statistically significant difference. Our results were consistent with those of Poortvliet, R, which assessed the level of NT-proBNP in very old age in the Netherlands [17]. However, the mechanism of why NT-proBNP in males is higher than that in females in the elderly aged over 80 remains to be further explored.

Furthermore, in our study, we explored the difference in NT-proBNP level between the two groups by dividing renal function at eGFR:60 mL/(min·1.73 m^2). The result showed that the level of NT-proBNP was negatively related with eGFR, which was consistent with Sven Linzbach, MD et al, who found a strong negative correlation between the creatinine- and cystatin C-based GFR estimations with serum NT-proBNP [23]. Similarly, Poortvliet, R and others have also reported a negative correlation in older adults [17]. In their study, a cross-sectional analysis was conducted and showed that NT-proBNP was negatively correlated with kidney function; however, a five-year follow-up study showed interesting results. NT-proBNP changes over five years was divided into an increased group and non-increased group, with no statistically significant difference in eGFR change found between the two groups. In other words, the lower kidney function could reflect the higher level of NT-proBNP, whereas the high-level NT-proBNP did not further aggravate renal function. Our research also confirmed this theory. We found that NT-proBNP was negatively correlated with eGFR whether it was five years prior or five years later, while higher NT-proBNP did not lead to more eGFR decrease five years later. This means that NT-proBNP did not cause deterioration of kidney function. We suspect the decline in renal function was due to age, and the NT-proBNP was related to age, therefore, renal function and NT-proBNP were negatively correlated; but as a cardiac hormone secretion, NT-proBNP cannot directly lead to a decline in kidney function.

Conclusion

In conclusion, the present study showed that in a community-dwelling population, NT-proBNP increased with age and was higher in women subjects less than 80 years old. Furthermore, eGFR was negatively correlated with NT-proBNP; but NT-proBNP was not an independent risk factor for kidney function.

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Disclosure of conflict of interest

None.

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