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ASSOCIATION OF BNP WITH FRAILTY IN ELDERLY POPULATION: RUGAO LONGEVITY AND AGEING STUDY

S. YAO[1,5], J. GUO[2,5], G. SHI[2], Y. ZHU[2], Y. WANG[2], X. CHU[2], X. JIANG[3,4], L. JIN[1], Z. WANG[2], X. WANG[1]

1. Ministry of Education Key Laboratory of Contemporary Anthropology, School of Life Sciences and National Clinical Research Center for Aging and Medicine, Huashan Hospital, Fudan University, Shanghai, China; 2. Rugao People's Hospital, Rugao, Jiangsu, China; 3. Key Laboratory of Arrhythmias of the Ministry of Education of China, Tongji University School of Medicine, Shanghai, China; 4. Department of Pathology and Pathophysiology, Tongji University of Medicine, Shanghai, China; 5. These authors contributed equally to this work. Corresponding author: Xiaofeng Wang, Ministry of Education Key Laboratory of Contemporary Anthropology, School of Life Sciences and National Clinical Research Center for Aging and Medicine, Huashan Hospital, Fudan University, Shanghai, 200433, China, xiaofengwang71@163.com; Zhengdong Wang, Rugao People's Hospital, Rugao 226500, Jiangsu, China, wangzhengdongRUGAO@163.com.

Abstract: *Objectives:* To explore the associations of B-type natriuretic peptide (BNP) with physical frailty status as well as each domain of frailty in a general elderly population. *Design:* Cross-sectional analysis of prospective cohort study. *Setting:* All of 31 communities in Jiang'an township. *Participants:* Overall 1338 participants (aged 70-89 years, mean 77.42±4.08 years) without a history of cardiovascular diseases in the third-wave of the aging arm of the Rugao Longevity and Aging Study (RuLAS). *Measurements:* Frailty was defined as the presence of ≥3 domains among five modified Fried's criteria (unintentional weight loss, low physical activity level, weakness (low grip strength), exhaustion, and slowness (slow gait speed)) and pre-frailty as the presence of 1-2 domains. *Results:* The prevalence of frailty and pre-frailty was 10.4% and 53.3%, respectively, in this elderly population. Elevated BNP (≥100 pg/mL) was significantly associated with pre-frailty (OR: 1.61, 95% CI: 1.13-2.29) and frailty (OR: 2.63, 95% CI: 1.61-4.32) after adjustment for covariates. In addition, elevated BNP was associated with low grip strength (OR: 2.00, 95% CI: 1.41-2.82) and low gait speed (OR: 1.62, 95% CI: 1.15-2.28) after adjustment for multiple covariates. Log BNP was inversely associated with grip strength (r= -0.265, p<0.001) and gait speed (r= -0.189, p<0.001). *Conclusion:* Elevated plasma BNP was associated with increased risks of frailty, pre-frailty, and low levels of grip strength and gait speed in the elderly community people.

Key words: Frailty, BNP, grip strength, gait speed, elderly.

Introduction

Frailty is a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes including falls, delirium, disability and mortality (1-3) . Frailty was commonly defined as the presence of ≥3 domains among five modified Fried's criteria (unintentional weight loss, low physical activity level, weakness (low grip strength), exhaustion, and slowness (slow gait speed)) and pre-frailty as the presence of 1-2 domains (4). Several inter-related mechanisms, i.e., ageing related dysfunction of endocrine system (5) low grade inflammatory response (6, 7), changes in IGF signaling and sex hormone (5, 8) had been proposed to be involved in the development of frailty. However, despite an increase in interest in frailty, the pathophysiological changes underline this disorder are not clearly known.

B-type natriuretic peptide (BNP) is a neurohormone secreted into the bloodstream mainly by cardiac myocytes in response to increased ventricular wall stress, hypertrophy, and volume overload (9). BNP is useful to help with diagnosis, prognosis, and management of heart failure (10). Besides the well-documented role in the cardiovascular system, BNP has been shown to predict mortality in older adults even without specific cardiac diagnoses (11, 12). Specifically, increased level of BNP were recently found to be associated with activity of daily living (ADL) disability (12, 13) and reduced muscle mass (14) in the elderly population without clinical evidently heart diseases, suggesting that BNP levels increase in response to muscle loss to protect against muscle damage (14, 15). Here we hypothesized that BNP may be related to physical frailty, a key component of which is the progressive loss of skeletal muscle mass, strength, and power. We explore the relationship of plasma BNP level and frailty status as well as each domain of frailty in a general elder population without clinically manifested cardiovascular diseases (CVD).

Methods

Study population

Data were drawn from the third-wave of the aging arm of the Rugao Longevity and Aging Study (RuLAS), a population-based observational two-arm cohort study conducted in Rugao, Jiangsu Province, China. As previously described (16), 1788 elderly adults aged 70-84 years were recruited at baseline from November 2014 to December 2014. Eighteen months later, the second-wave examination was conducted from April 2016 through June 2016 (wave 2). Another eighteen months later, the third-wave examination was conducted from November 2017 to December 2017 (wave 3). Finally, the third-wave examination (wave 3) recruited 1950 participants. In this study, eligible participants met the following criteria were included: 1) 70 ≤ age ≤89 years; 2) with complete information of BNP

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and frailty components; 3) without a history of CVD (angina, myocardial infarction, TIA, stroke, heart failure) and cancers. CVD conditions were assessed through a combination of self-report, medical records of local clinic, and records of social security system and new rural cooperative medical system (NCMS). Finally, 1338 participants were included in this study.

Frailty

Frailty phenotype was defined in the following five domains: weight loss, exhaustion, low activity, weakness and slowness according to Fried (4). Weight loss was considered if the participant responded "yes" to the following question: "Have you lost more than 4,5kg or 5% of weight in the past 12 months?". Exhaustion was considered if the participant responded "yes" to the following question: "Have you felt tired at least 3 or 4 days per week?". Low activity was considered if the participant responded "yes" to the following question: "Do you need help to walk?". Weakness was defined as being below the 20th sex-specific percentile of handgrip strength. Handgrip strength in kilograms was measured using a dynamometer for three trials of each hand. The best performance of these three trials was recorded. The max value of two hands was used in this study. Slowness was defined as being below the 20th sex-specific percentile in gait speed, which was assessed using a TUG test. Briefly, in the TUG test, the participants were asked to stand up from an armchair, walk 3 meters, return, and sit down again. The timing of the test began when the participant's back came off the back of the armchair, and stopped when their buttocks touched the seat of the chair again. Those with three or more of the five factors were defined to be frail, those with one or two factors as pre-frail, and those with no factors as robust people.

Blood biomarkers

Fasting blood samples of all participants were collected by trained nurses during the morning of the survey. Blood-based biomarkers included C reactive protein (CRP; mg/L), homocysteine (HCY; umol/L), Triglyceride (TG; mmol/L), Low Density Lipoprotein (LDL; mmol/L), high density lipoprotein (HDL; mmol/L) and B-type natriuretic peptide (BNP; pg/mL) were measured by a technician in the biochemistry laboratory of the Rugao People's Hospital. Glucose (Glu, mmol/L) was conducted by onsite rapid dipstick test of random blood glucose.

Other covariates

Covariates were collected including demographics (age, gender), blood pressure (BP; mmHg), self-reported hypertension, active exercise, smoking habits, drinking habits, weight, and height. Body mass index (BMI) was calculated by dividing the weight by the square of the height (kg/m2). A participant was categorized as current smoker if he/she reported smoking everyday now, former smoker if he/she had ever smoked continuously for more than 6 months or non-smoker. A participant was categorized as current drinking habit if he/she reported drinking everyday now, former drinking habit if he/she had ever drank continuously for more than 6 months or never drinking habit. A participant was categorized as active exercise if he/she reported doing exercises more than 3 times per week.

Statistical analysis

Analyses of variance (ANOVA) and Kruskall-Wallis test (when appropriate) were used to compare descriptive characteristics and biomarkers between robust individuals, pre-frail individuals and frail individuals. Multinomial logistic regressions were performed to investigate the relationship between BNP and frailty status. Multivariate logistic regressions were performed to investigate the relationship between BNP and each domain of frailty (weight loss, exhaustion, low activity, weakness and slowness). Odds ratios (ORs) and 95% confidence intervals (CI) were documented. Pearson correlation coefficient was used to investigate the relationship between LogBNP and grip strength and gait speed of TUG test. A p-value of < 0.05 was considered to be statistically significant. All analyses were performed using SPSS version 20.

Results

Of the 1338 participants, 139 (10.4%) with ≥3 components were characterized as frail, 713(53.3%) as pre-frail (1 or 2 components), and the remaining 486(36.3%) as robust. Frailty was more prevalent among women and participants who never drink alcohol (Table 1). Those deemed frail were older (79.40±4.22 years vs. 77.87±4.07 in the pre-frail group vs 76.20±3.70 in the robust group), had a higher level of CRP (5.37 mg/L vs 2.43 mg/L vs 2.21 mg/L), HCY (19.43 umol/L vs 16.60 umol/L vs 15.52 umol/L) and BNP (67.00 pg/ml vs 55.00 pg/ml vs 39.50pg/ml) (Table 1).

Participants were allocated into different groups by three different methods in order to evaluate the relationship between plasma BNP and frailty status. First of all, participants were divided into quartiles. The lowest quartile (Quartile 1) was used as the reference category. The highest quartile (Quartile 4) was significantly associated with pre-frail status (OR: 1.67, 95% CI: 1.13-2.47) and frail status (OR: 2.04, 95% CI: 1.09-3.81) compared to robust status. Secondly, participants were divided into three categories: <10th percentile, 10-90th percentile, >90th percentile (17). The 10-90th percentile was used as reference category. The >90th percentile was significantly associated with pre-frail status (OR: 1.78, 95% CI: 1.05-3.02) frail status (OR: 2.29, 95% CI: 1.16-4.23) compared to robust status. Lastly, participants with a BNP level ≥100 pg/mL were divided into elevated BNP group; the others were divided into normal BNP group(18). The normal BNP group was used as reference category. Elevated BNP was significantly associated with pre-frail status (OR: 1.61, 95% CI: 1.13-2.29) and frail status (OR: 2.63, 95% CI: 1.61-4.32) compared to robust status

Table 1
Demographic characteristics of participants by frailty status

	Robust n=486	Pre-frail n=713	Frail n=139	Total participants n=1338
Age***	76.20±3.70	77.87±4.07	79.40±4.22	77.42±4.08
Gender**				
Male	255(52.5%)	317(44.5%)	56(40.3%)	628(46.9%)
Female	231(47.5%)	396(55.5%)	83(59.7%)	710(53.1%)
BMI(kg/m2)	24.07±3.40	23.91±3.56	23.57±3.79	23.93±3.53
SBP(mmHg)	154.66±21.39	155.22±21.53	151.84±23.11	154.66±21.66
DBP(mmHg)	80.09±10.90	79.84±10.45	78.97±11.61	79.84±10.74
Active exercises (>3/week)	109(24.9%)	159(24.4%)	23(18.3%)	291(24.0%)
Self-report hypertension*	194(39.9%)	334(46.8%)	71(51.1%)	599(44.8%)
Smoking habits				
Never	364(75.4%)	569(80.9%)	107(78.1%)	1040(78.6%)
Current	76(15.7%)	80(11.4%)	18(13.1%)	174(13.2%)
Former	43(8.9%)	54(7.7%)	12(8.8%)	109(8.2%)
Drinking habits***				
Never	287(59.5%)	489(69.7%)	112(82.3%)	888(67.3%)
Current	130(27.0%)	158(22.5%)	16(11.8%)	304(23.0%)
Former	65(13.5%)	55(7.8%)	8(5.9%)	128(9.7%)
Each domain of frailty				
Weight loss***	0(0.0%)	123(17.3%)	67(48.2%)	190(14.2%)
Exhaustion***	0(0.0%)	373(52.3%)	114(82.0%)	487(36.4%)
Low activity***	0(0.0%)	61(8.6%)	77(55.4%)	138(10.3%)
Weakness ***	0(0.0%)	175(24.5%)	97(69.8%)	272(20.3%)
Slowness***	0(0.0%)	204(28.6%)	106(76.3%)	310(23.2%)
Biomarker				
BNP(pg/ml)#***	39.50(24.00-68.00)	50.00(27.00-93.50)	67.00(30.00-129.00)	47.00(26.00-87.00)
BNP≥100 pg/ml ***	66(13.6%)	163(22.9%)	53(38.1%)	282(21.1%)
CRP(mg/L)**	2.21±4.30	2.43±5.43	5.37±6.46	2.65±9.77
HCY(umol/L)***	15.52±7.48	16.60±9.19	19.43±10.79	16.50±8.86
Triglyceride(mmol/l)	1.35±1.03	1.45±1.04	1.39±0.74	1.40±1.01
LDL(mmol/l)	2.83±0.64	2.81±0.61	2.69±0.56	2.80±0.62
HDL(mmol/l)	1.89±0.46	1.85±0.44	1.80±0.47	1.86±0.45
Glucose(mmol/L)	5.80±1.33	5.85±1.62	5.93±1.67	5.84±1.53

*p <0.05; **p<0.01; ***p <0.001. #: presented by median (25%-75%).

(Table 2).

In the further analyses, elevated BNP was significantly associated with the weakness domain (low grip strength) (OR: 2.00, 95% CI: 1.41-2.82) and slowness domain (low gait speed) of frailty (OR: 1.62, 95% CI: 1.15-2.28) (Table 3).

Spearman correlation coefficients were calculated between Log BNP and grip strength and gait speed of TUG test. Log BNP had a significant negative correlation with grip strength($r=-0.265$, $p<0.001$, Figure 1) and gait speed of TUG test ($r=-0.189$, $p<0.001$, Figure 2).

Table 2
Association between BNP and frailty status by logistic regression analysis

	Pre-frail Relative to Robust				Frail Relative to Robust			
	Model 1		Model 2		Model 1		Model 2	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Quartile 1	Reference		Reference		Reference		Reference	
Quartile 2	0.83(0.60-1.15)	0.263	0.92(0.65-1.31)	0.642	0.70(0.38-1.29)	0.251	0.76(0.40-1.46)	0.414
Quartile 3	0.91(0.66-1.28)	0.6	1.03(0.72-1.48)	0.873	0.76(0.42-1.38)	0.375	0.78(0.41-1.53)	0.486
Quartile 4	1.49(1.04-2.13)	0.03	1.67(1.13-2.47)	0.011	2.04(1.16-3.59)	0.013	2.04(1.09-3.81)	0.026
BNP<10%	1.53(1.04-2.27)	0.033	1.52(0.99-2.32)	0.054	1.01(0.45-2.23)	0.989	1.35(0.59-3.08)	0.476
BNP10-90%	Reference		Reference		Reference		Reference	
BNP>90%	1.77(1.11-2.83)	0.016	1.78(1.05-3.02)	0.033	2.29(1.24-4.23)	0.008	2.29(1.16-4.23)	0.018
BNP<100pg/ml	Reference		Reference		Reference		Reference	
BNP≥100pg/ml	1.55(1.12-2.14)	0.008	1.61(1.13-2.29)	0.008	2.74(1.75-4.30)	<0.001	2.63(1.61-4.32)	<0.001

Model 1 was adjusted for gender and age; Model 2 was adjusted for gender, age, BMI, smoking habits, drinking habits, self-report hypertension, active exercises, CRP, HCY, LDL, HDL, TG, Glu.

Table 3
Association between elevated BNP and each domain of frailty by logistic regression analysis

	Weight loss		Exhaustion		Low activity		Weakness		Slowness	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Model 1	1.26(0.85-1.87)	0.258	1.16(0.87-1.56)	0.32	1.47(0.92-2.26)	0.082	2.09(1.50-2.92)	<0.001	1.73(1.25-2.40)	0.001
Model 2	1.26(0.85-1.88)	0.257	1.11(0.82-1.49)	0.511	1.47(0.95-2.27)	0.085	1.96(1.40-2.75)	<0.001	1.70(1.22-2.38)	0.002
Model 3	1.23(0.82-1.85)	0.328	1.09(0.80-1.47)	0.585	1.37(0.87-2.14)	0.175	2.00(1.41-2.82)	<0.001	1.62(1.15-2.28)	0.006

Model 1 was adjusted for gender and age; Model 2 was adjusted for gender, age, BMI, smoking habits, drinking habits, self-reported hypertension and active exercises; Model 3 was adjusted for gender, age, BMI, smoking habits, drinking habits, self-reported hypertension and active exercises, CRP, HCY, LDL, HDL, TG and Glu.

Figure 1
Relationship between Log BNP and grip strength in all participants. In this study, Log BNP was correlated significantly to grip strength (r= -0.265, p<0.001)

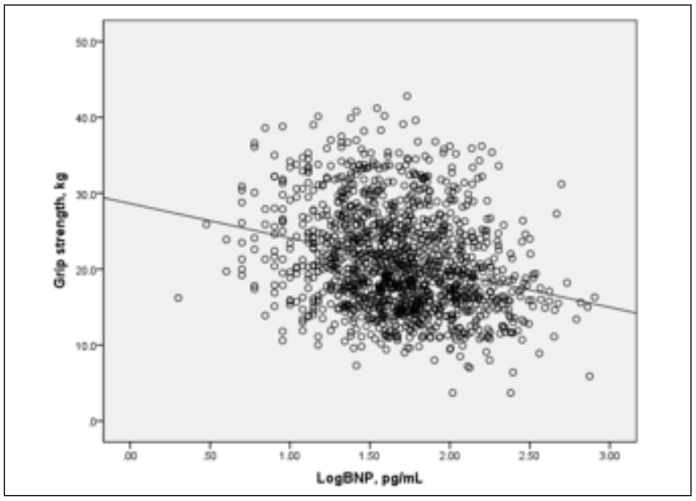
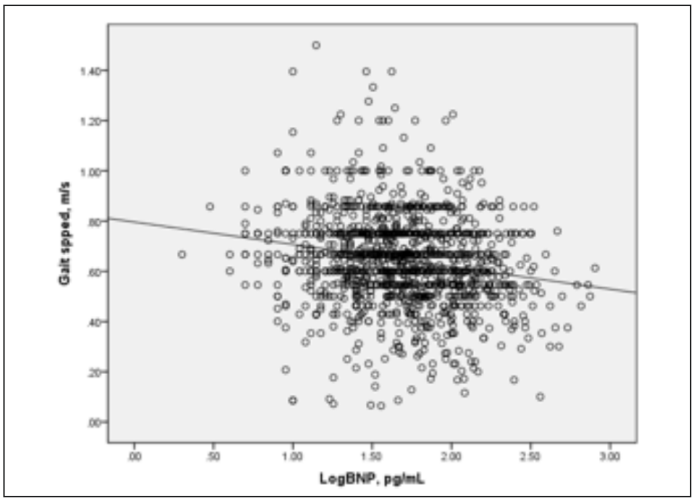


Figure 2
Relationship between Log BNP and gait speed of TUG test in all participants. In this study, Log BNP was correlated significantly to gait speed of TUG test (r= -0.189, p<0.001).



Discussion

To our best knowledge, this is the first population-based study to investigate the associations of plasma BNP with frailty as well as each domain of frailty. We observed that elevated level of plasma BNP was associated with increased risk of frailty, especially with the weakness (low grip strength) and slowness (low gait speed) domain.

Although data was scarce with respect to the relationship between BNP and the phenotype of frailty in the general population, the association was observed in hospital patient cohorts. In a cohort of 238 prevalent hemodialysis patients, high NT-proBNP was associated with decreased levels of the indexes for muscle mass (19). In 260 outpatients of heart failure, Shu et al found that increased plasma BNP level was associated with increased risk of frailty (20). In the leiden 85-plus study, Petra et al found that participants aged 85 years without heart failure and with high NT-proBNP had a higher ADL disability score at baseline and had an accelerated annual increase in ADL disability score (12). In participants aged ≥80 years, Ueda et al found a cross-sectional association of increased level of NT-proBNP with the ADL disability (13).

In the Newcastle 85+ study, using a cross-sectional sample of 852 individuals aged 85, Carmen et al explored the U shape effects of NT-pro-BNP with adverse outcomes. They found that high level of NT-pro-BNP (>90% percentile) was associated with increased risk of disease count and mortality (17). Similarly but on the other side, low level of NT-pro-BNP (<10% percentile) was associated with decreased risk of disability count (17). We using this category of BNP in our sample and found the increased risk of pre-frailty in BNP <10% percentile and frailty in BNP>90% percentile.

In the present study, we additionally found that BNP was inversely associated with two frailty domains-grip strength and gait speed of TUG test. Similar associations was also found in the outpatients of heart failure where increased plasma BNP level was associated with slow walking speed, and short 6-minute walk distance (5). In a population-based study including 1,431 apparently healthy middle-aged to elderly subjects, Yamashita et al found that after adjusting of multiple confounding parameters, BNP level is inversely associated with thigh muscle cross-sectional area (CSA) instead of visceral fat area (14).

The mechanisms links BNP with physical frailty and its component phenotype (grip strength and gait speed) is unclear at this stage. Several possible mechanisms may help to explain the associations. 1) BNP is primarily secreted by cardiomyocytes upon excessive stretch, increased transmural pressure, or direct injury. These homodynamic changes mechanically stimulate BNP secretion and was associated with the loss of muscle mass (15). 2) BNP is also secreted from satellite cells within the ischemic skeletal muscle in response to blood pressure load, which regulates the regeneration of neighboring endothelia (21). 3) Elevated BNP could stimulate excessive release of free fatty acids which impair insulin sensitivity and muscle lipotoxicity (22). 4) Elevated BNP levels in the circulation may produce increased energy dissipation and oxidative capacity by skeletal muscle (22).

In this study, we adjusted multiple covariates including high physical activity level, hypertension, and metabolic biomarkers since these factors elevate plasma BNP level, especially in the elderly individuals (9, 23) . Limitation of this study should also be mentioned. This study is a cross-sectional analysis that prohibit causal inference.

In conclusion, the present study shows a significant association between elevated plasma BNP and frailty in a general elder population. Elevated plasma was especially related to weakness and slowness among the five domains of frailty. It suggests that BNP is an important biomarker of frailty. More attention should be focused on those elders who had a decreased grip strength and gait speed with higher BNP levels.

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Conflict of interest statement: The authors declare no conflicts of interests.

Ethical standard: The Human Ethics Committee of the School of Life Sciences, Fudan University, Shanghai, People's Republic of China, approved the present study. Written informed consent was obtained from all participants prior to the study.

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