



Plasma brain natriuretic peptide level in older outpatients with heart failure is associated with physical frailty, especially with the slowness domain

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Abstract

Objective To determine the association between plasma brain natriuretic peptide (BNP) level in patients with heart failure (HF) and physical frailty as well as with each domain of physical frailty. **Methods** Two hundred and six outpatients of cardiovascular medicine aged 60 years and older who had been hospitalized for HF or had been given a prescription medication for HF were included. Physical frailty was assessed using the following five domains: slowness, weakness, exhaustion, low activity, and shrinking, according to the Cardiovascular Health Study. Patients were divided into nonfrailty and frailty groups according to frailty scores. Plasma BNP level was measured. The 6-min walk test was performed to measure endurance. **Results** Plasma BNP was significantly different between the two groups (frailty group: 158.0 ± 214.7 pg/mL, nonfrailty group: 65.2 ± 88.0 pg/mL, $P < 0.01$). Multivariate logistic regression analysis revealed log-transformed plasma BNP (Log BNP) was significantly associated with physical frailty (OR: 1.68, 95% CI: 1.11–2.56), and Log BNP was significantly associated with the slowness domain (walking speed < 1.0 m/s) of physical frailty (OR: 1.75, 95% CI: 1.15–2.67). Additionally, Log BNP was negatively correlated to the 6-minute walk distance (6MWD) ($\rho = -0.37$, $P < 0.01$), while 6MWD was positively correlated to walking speed ($\rho = 0.66$, $P < 0.01$). **Conclusions** Plasma BNP level was related to physical frailty, especially in the slowness domain. Endurance may intervene in the associations between plasma BNP level and walking speed.

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Keywords: Brain natriuretic peptide; Heart failure; Physical frailty; Walking speed

1 Introduction

Heart failure (HF) has recently been recognized as a major public health problem in industrialized countries with ageing populations.^[1] The number of HF patients is expected to increase as the population ages; indeed, 80% of patients with HF are 65 years-of-age or older.^[2,3] Elderly patients with HF are susceptible to complications, with not only general symptoms such as breathlessness and fatigue,^[4] but also geriatric conditions such as impaired mobility and dementia.^[3] The management of these complications is important because they can exacerbate HF.

In recent years, frailty has attracted attention as a predictor of HF severity. Frailty is defined as a biologic syndrome with decreased physiologic reserve and resistance to stressors, and increased vulnerability to adverse outcomes.^[5,6] The frailty phenotype proposed by Fried, *et al.*^[5] has frequently been used by researchers when identifying physical frailty. It is comprised of five domains: slowness, weakness, exhaustion, low activity, and shrinking.^[5] The prevalence of frailty in community-dwelling elderly people was 6.9% in the United States,^[5] and 11.3% in Japan.^[7] Frail people have an increased risk of sarcopenia,^[8] and a need for long-term care insurance.^[9] Several epidemiological studies have shown that HF is related to frailty. The prevalence of physical frailty in elderly patients with HF was 19%,^[10] and this percentage was higher than in the general elderly population.^[7] In addition, frailty was more predictive of long-term mortality in elderly subjects with HF than in those without HF.^[11] Therefore, the prevention of frailty is important in the management of HF in elderly patients.

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It is necessary to take measures to prevent frailty and domains of physical frailty in high-risk elderly patients with HF preferentially. HF and physical frailty probably share a common pathophysiology that involves inflammatory processes.^[6] Elevated concentrations of inflammatory markers lead to a decline in muscle mass and strength, probably by promoting catabolic processes in muscle cells.^[6,12] We developed two hypotheses for the complex relationship between HF and frailty. Firstly, we hypothesized that plasma brain natriuretic peptide (BNP) level is associated with frailty. Plasma BNP level is frequently used as an index of HF severity. BNP is a cardiac hormone secreted in response to mechanical overload,^[13,14] and reflects cardiac function.^[15] Secondly, we hypothesized that the severity of HF is associated with weakness in physical frailty domains. Weakness is usually defined by grip strength.^[16] It has been suggested that a reduction in lower limb muscle strength is common in patients with HF.^[17] For this reason, we suppose that the inflammatory processes of HF contribute to a decline in grip strength.

So far, there are few studies that have examined the association between HF and frailty in terms of the physical domains of frailty. Thus, the purpose of this study was to determine the association between plasma BNP level and physical frailty as well as with each domain of physical frailty.

2 Methods

2.1 Subjects

This study was performed in the community hospital in Shiga prefecture, Japan. The study subjects were 206 outpatients consulting cardiovascular medicine of our institution aged 60 years and older who had previously been admitted to hospital for management of HF or had already been receiving treatment for HF. For recruitment, we distributed an advertisement requesting patients who were visiting the community hospital for management of HF. Interviews were then performed to exclude patients based on the following criteria: severe pulmonary or musculoskeletal disorders; comorbidities associated with a greater risk of falls such as Parkinson's disease and stroke; and the use of psychotropic drugs. Written informed consent was obtained from each patient in accordance with the guidelines approved by the Kyoto University Graduate School of Medicine and the Declaration of Human Rights, Helsinki, 1975. The study protocol was approved by the ethical committee of the Kyoto University Graduate School of Medicine.

2.2 Anthropometric and clinical data

Age, gender, height, and weight were obtained as an-

thropometric data. We obtained data regarding age and gender directly from the patients and measured the height and weight using standardized height and weight scales. Body mass index (BMI) was calculated by dividing the weight by the square of the height (kg/m^2). Clinical data, such as number of hospitalizations, complications (angina, myocardial infarction, arrhythmia, cardiomyopathy, valvular heart disease, hypertension, dyslipidemia, diabetes mellitus, and chronic obstructive pulmonary disease) and medications (diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and cardiotonic agents) were obtained from the patients' medical records. Physical therapists interviewed the patients and classified their heart failure according to the New York Heart Association (NYHA) Functional Classification system.

2.3 Assessment of physical frailty

We defined the physical frailty phenotype by limitations in the following five domains, according to the Cardiovascular Health Study:^[5] slowness, weakness, exhaustion, low activity, and shrinking. We measured each domain based on a standard used in a previous study.^[18] To measure slowness, each patient's 10-m normal walking speed (m/s) was calculated, and a slow walk was defined as < 1.0 m/s. Patients were asked to walk on a level surface at a comfortable walking speed. Weakness was defined as the average grip strength in each arm of less than 26 kg in men and less than 18 kg in women. Grip strength was measured in kilograms using a handheld dynamometer. Patients gripped the dynamometer with one hand using maximum effort, and no other body movement was allowed. Exhaustion was considered present if the participant responded "yes" to the following question, which included the Kihon-Checklist, a self-reported comprehensive health checklist that was developed by the Japanese Ministry of Health Labor, and Welfare:^[19] "In the last two weeks, have you felt tired without a reason?" If patients answered "yes" to the question, we classified them as being exhausted. We assessed activity level by asking the following two questions: (1) "Do you engage in moderate levels of physical exercise or sports aimed at health?" and (2) "Do you engage in low levels of physical exercise aimed at health?" If a patient answered "no" to both of these questions, we defined them as having low activity.^[7] Shrinking was measured according to self-reports of weight loss in response to the following question:^[19] "Have you lost 2 kg or more in the past 6 months?" If a patient answered, "yes" to this question, then we defined them as having shrinking. We assigned patients to the frailty group if they were affected in at least three of the five domains.

2.4 Blood sampling data

Plasma BNP, serum albumin, sodium, hemoglobin levels as well as the estimated glomerular filtration rate (eGFR) were determined as blood sampling data. Blood samples were collected from the peripheral vein. The blood samples were immediately placed on ice and centrifuged at 4°C, and the plasma was frozen in aliquots and stored at -30°C until assay. All patients had rested in bed in a supine position for at least 30 min just before blood sampling. Plasma BNP level was measured with a chemiluminescence enzyme immunoassay for human BNP, using a commercial kit (TOSOH, Tokyo, Japan). The minimum detectable concentration of human BNP using this system is 4 pg/mL. Each patient's serum creatinine level (Scr) was measured, which was then applied to the formula for eGFR: $eGFR \text{ (mL/min per } 1.73 \text{ m}^2) = 194 \times \text{Scr}^{-1.094} \times \text{Age}^{-0.287} \times 0.739 \text{ (if female)}$. This formula has originated from the MDRD study group and was arranged for Japanese individuals. It is recommended by the Japanese Society of Nephrology.^[20]

2.5 Measurement of endurance

We performed the 6-min walk test to measure endurance,^[21] because its association with frailty in HF patients was shown in a previous report.^[22] It is a reliable and well-validated test in HF patients, and was completed according to the American Thoracic Society guidelines.^[23] Measurement was carried out in a flat, straight, unimpeded 30 m long hallway, with chairs positioned at both ends to provide places for patients to rest. Patients were permitted to use a walker or cane if needed. They were instructed to walk as much as possible, but were allowed to slow down or stop as necessary. At the end of 6 min, the patient was told to "stop" and the 6-minute walk distance (6MWD) was recorded.

2.6 Statistical analysis

Prior to the analysis, we classified patients into the following two groups according to their physical frailty score: nonfrailty and frailty. We examined the differences between the frailty group and the nonfrailty group using the unpaired *t*-test for age, BMI, number of hospitalizations, and eGFR, and the Mann-Whitney *U*-test for plasma BNP, serum albumin, sodium, hemoglobin levels, and 6MWD because they were not normally distributed. Differences in gender, NYHA class, complications, medications, and ratios corresponding to each domain of physical frailty were evaluated by Chi-square tests. As the distribution of plasma BNP levels was positively skewed, these data were transformed logarithmically. A multivariate logistic regression analysis

was performed to investigate whether the log-transformed plasma BNP levels (Log BNP) were independently associated with physical frailty adjusted for age, gender, and BMI. Subsequent multivariate logistic regression analyses were performed to determine the independent association between each domain of physical frailty and Log BNP adjusted for age, gender, and BMI. In addition, we analyzed the association between Log BNP and 6MWD. We also analyzed the association between 6MWD and any domain of physical frailty that was independently associated with Log BNP in subsequent multivariate logistic regression analyses. Odds ratios (ORs) with 95% confidence intervals (CI) were presented. Statistical analyses were carried out by using SPSS Statistics for Mac OS, version 22.0 (IBM Corp, Armonk, NY, USA), with a significance threshold of 0.05.

3 Results

The anthropometric data for patients stratified by frailty group are shown in Table 1. The patient's mean age was 73.7 ± 7.3 years, and 143 patients were men (63 were women). The nonfrailty group had 172 patients (83.5%) and the frailty group had 34 patients (16.5%). The frailty group was significantly older ($P < 0.01$), had larger number of hospitalizations ($P = 0.02$), and had lower eGFR ($P < 0.01$) compared to the nonfrailty group. The plasma BNP level (frailty group: 158.0 ± 214.7 pg/mL, nonfrailty group: 65.2 ± 88.0 pg/mL, $P < 0.01$), 6MWD (frailty group: 359.9 ± 122.7 m, nonfrailty group: 476.9 ± 99.9 m, $P < 0.01$), and hemoglobin (frailty group: 12.2 ± 1.8 g/dL, nonfrailty group: 13.3 ± 1.4 g/dL, $P < 0.01$) were significantly different in the two groups. Significantly more patients in the frailty group had valvular heart disease ($P = 0.02$) and were administered prescription diuretics ($P = 0.04$). Moreover, they were impaired in all domains of physical frailty ($P < 0.05$).

In the multivariate logistic regression analyses, Log BNP was significantly associated with physical frailty (OR: 1.68, 95% CI: 1.11–2.56, $P = 0.02$, Table 2). In the subsequent multivariate logistic regression analyses, Log BNP was significantly associated with the slowness domain of physical frailty (OR: 1.75, 95% CI: 1.15–2.67, $P = 0.01$, Table 3), but not with any of the other four domains.

Based on the results of the multivariate logistic regression analyses, Spearman correlation coefficients were calculated between Log BNP and 6MWD, and between 6MWD and walking speed. Log BNP had a significant negative correlation with 6MWD ($\rho = -0.37$, $P < 0.01$, Figure 1). Additionally, 6MWD was significantly positively correlated with walking speed ($\rho = 0.66$, $P < 0.01$, Figure 2).

Table 1. Characteristics of patients in the nonfrailty and frailty groups.

	All, <i>n</i> = 206	Nonfrailty, <i>n</i> = 172	Frailty, <i>n</i> = 34	<i>P</i> value
Age ^b , yrs	73.7 ± 7.3	72.6 ± 6.7	79.2 ± 7.8	< 0.01**
Males ^a	143 (69.4%)	120 (69.8%)	23 (67.6%)	0.81
BMI ^b , kg/m ²	23.5 ± 3.3	23.7 ± 3.3	22.7 ± 3.2	0.11
NYHA ^a				0.09
I	108 (52.4%)	93 (54.1%)	15 (44.1%)	
II	79 (38.3%)	67 (39.0%)	12 (35.3%)	
III	17 (8.3%)	11 (6.4%)	6 (17.6%)	
IV	2 (1.0%)	1 (0.6%)	1 (3.0%)	
Hospitalizations ^b , times	2.0 ± 1.8	1.9 ± 1.7	2.7 ± 2.2	0.02*
Blood samples				
BNP ^c , pg/mL	80.5 ± 122.8	65.2 ± 88.0	158.0 ± 214.7	< 0.01**
Serum ^c albumin, g/dL	4.0 ± 0.3	4.0 ± 0.2	4.0 ± 0.4	0.18
Sodium ^c , mEq/L	140.0 ± 3.0	140.2 ± 2.9	139.8 ± 3.2	0.29
Hemoglobin ^c , g/dL	13.1 ± 1.5	13.3 ± 1.4	12.2 ± 1.8	< 0.01**
eGFR ^b , mL/min per 1.73 m ²	57.2 ± 17.5	59.1 ± 17.0	47.9 ± 17.0	< 0.01**
Complication ^a				
Angina	134 (65.0%)	111 (64.5%)	23 (67.6%)	0.73
Myocardial infarction	50 (24.3%)	41 (19.9%)	9 (26.5%)	0.74
Arrhythmia	45 (21.8%)	34 (19.8%)	11 (32.4%)	0.11
Cardiomyopathy	7 (3.4%)	7 (4.1%)	0 (0.0%)	0.23
Valvular heart disease	20 (9.7%)	13 (7.6%)	7 (20.6%)	0.02*
Hypertension	100 (48.5%)	82 (47.7%)	18 (52.9%)	0.57
Dyslipidemia	71 (34.5%)	63 (36.6%)	8 (23.5%)	0.14
Diabetes mellitus	42 (20.4%)	34 (19.8%)	8 (23.5%)	0.62
COPD	4 (1.9%)	4 (2.3%)	0 (0.0%)	0.37
Medication ^a				
Diuretic	45 (21.8%)	33 (19.2%)	12 (35.3%)	0.04*
ACEI	25 (12.1%)	19 (11.0%)	6 (17.6%)	0.28
ARB	76 (36.9%)	65 (37.8%)	11 (32.4%)	0.55
Beta-blocker	66 (32.0%)	54 (31.4%)	12 (35.3%)	0.66
Cardiotonic agent	7 (3.4%)	5 (2.9%)	2 (5.9%)	0.38
6MWD ^c , m	457.6 ± 112.4	476.9 ± 99.9	359.9 ± 122.7	< 0.01**
Each domain of frailty ^a				
Slowness	37 (18.0%)	15 (8.7%)	22 (64.7%)	< 0.01**
Weakness	31 (15.0%)	13 (7.6%)	18 (52.9%)	< 0.01**
Exhaustion	151 (73.3%)	121 (70.3%)	30 (88.2%)	0.03*
Low activity	72 (35.0%)	49 (27.9%)	24 (70.6%)	< 0.01**
Shrinking	31 (15.0%)	13 (7.6%)	18 (52.9%)	< 0.01**

Data are presented as mean ± SD or *n* (%). **P* < 0.05, ***P* < 0.01. ^aAssessed by Chi-square tests; ^bAssessed by unpaired *t*-test; ^cAssessed by Mann Whitney *U*-test. Nonfrailty was defined as frailty score of 0 to 2, frailty was score 3 or greater. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BMI: body mass index; BNP: B-type natriuretic peptide; eGFR: estimated glomerular filtration rate; COPD: chronic obstructive pulmonary disease; NYHA: New York Heart Association; 6MWD: six-minutes walk distance.

Table 2. Association between BNP and physical frailty by multivariate logistic regression analysis.

	Physical frailty	
	OR (95% CI)	<i>P</i> value
Log BNP	1.68 (1.11–2.56)	0.02*
Age	1.11 (1.04–1.18)	< 0.01**
Gender	-	0.95
Female	1 [Reference]	-
Male	0.98 (0.41–2.32)	-
BMI	0.94 (0.83–1.07)	0.36

P* < 0.05, *P* < 0.01. BNP: brain natriuretic peptide; Log BNP: log-transformed values of BNP.

4 Discussion

The current cross-sectional study was performed to determine the association between plasma BNP level and physical frailty as well as each domain of physical frailty. It is a new and interesting finding that plasma BNP level was related to physical frailty, especially the slowness domain. Several epidemiological studies have demonstrated a relationship between HF and frailty.^[7,11] However, none of these studies examined the association between plasma BNP level and each domain of physical frailty.

In this study, 16.4% of patients had physical frailty. This finding is approximately in line with a previous report,^[10] in which elderly patients with HF had frailty more frequently than community-dwelling elderly people in another recent study.^[7] We showed that the frailty group had significantly higher plasma BNP level, and the severity of HF was related to physical frailty. The frailty group was significantly older and had a shorter 6MWD than the nonfrailty group in this study. These results are also consistent with prior reports.^[24]

This study indicates a connection between plasma BNP level and the slowness domain of physical frailty. Additionally, we found correlations between plasma BNP level and 6MWD, and between 6MWD and walking speed. Altogether, it is likely that exercise tolerance intervenes in the associations between plasma BNP level and walking speed. Previous studies also indicated that plasma BNP level was associated with endurance.^[25] Thus, it seems that physical activity may intervene in the correlation between endurance and walking speed in this study. Certainly, a recent study showed that the main factor associated with limited physical activity in the daily lives of chronic obstructive pulmonary disease patients was 6MWD.^[26] Similarly, it seems that deterioration in endurance leads to limited physical activity, which in turn leads to slow walking speed in elderly patients

Table 3. Association between BNP and each domain of physical frailty by multivariate logistic regression analysis.

	Slowness		Weakness		Exhaustion		Low activity		Shrinking	
	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
Log BNP	1.75 (1.15–2.67)	0.01*	1.07 (0.70–1.64)	0.75	0.91 (0.67–1.24)	0.56	1.29 (0.97–1.72)	0.08	1.28 (0.87–1.90)	0.22
Age	1.13 (1.06–1.20)	<0.01**	1.17 (1.09–1.26)	<0.01**	1.01 (0.96–1.06)	0.66	0.97 (0.93–1.02)	0.21	1.05 (0.99–1.11)	0.11
Gender	-	0.15	-	0.33	-	0.13	-	0.90	-	0.47
Female	1 [Reference]	-	1 [Reference]	-	1 [Reference]	-	1 [Reference]	-	1 [Reference]	-
Male	0.54 (0.24–1.24)	-	0.64 (0.26–1.56)	-	0.57 (0.28–1.18)	-	1.04 (0.56–1.97)	-	1.39 (0.56–3.44)	-
BMI	1.04 (0.92–1.17)	0.54	0.90 (0.79–1.03)	0.13	1.08 (0.97–1.20)	0.15	1.04 (0.95–1.13)	0.45	0.82 (0.71–0.94)	0.01*

* $P < 0.05$, ** $P < 0.01$. BMI: body mass index; BNP: brain natriuretic peptide; Log BNP: log-transformed values of BNP.

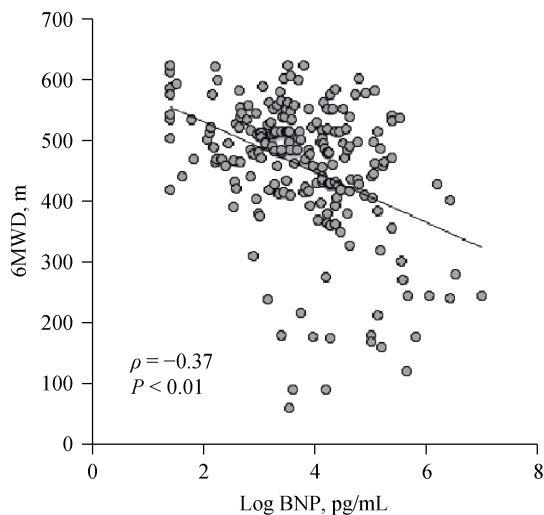


Figure 1. Relationship between Log BNP and 6MWD in all participants. In this analysis, Log BNP was correlated significantly with 6MWD ($\rho = -0.37$, $P < 0.01$). 6MWD: 6-minute walk distance; Log BNP: log-transformed values of brain natriuretic peptide.

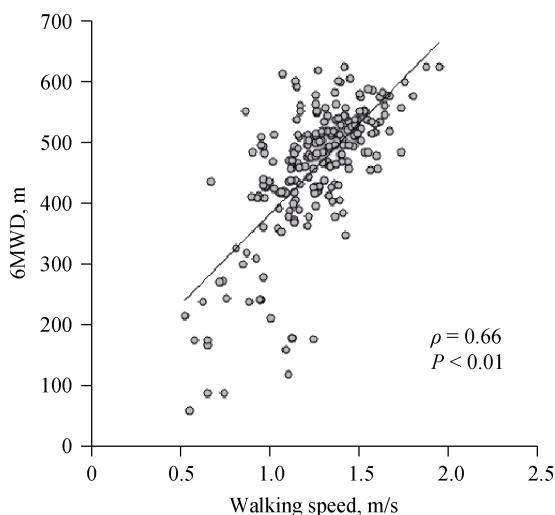


Figure 2. Relationship between walking speed and 6MWD in all participants. In this analysis, walking speed was correlated significantly with 6MWD ($\rho = 0.66$, $P < 0.01$). 6MWD: 6-minute walk distance.

with HF. In summary, the increase in plasma BNP level is associated with deterioration in endurance, which in turn contributes to slow walking speed.

On the other hand, plasma BNP level was not related to weakness in this study. This may be due to patient characteristics; participants in this study were stable outpatients with HF in whom activities of daily living was maintained to some extent. Moreover, more than 90% of them were in NYHA class I or II. Thus, it is likely that the patients did not have muscle weakness associated with a decrease in cardiac function. In fact, in a previous study,^[17] the HF patients who had reduced lower limb muscle strength were in NYHA class III and had fatigue or breathlessness. Further studies of this class of HF patients are required to determine the association between plasma BNP level and weakness in greater detail.

It is important to prevent frailty and to decrease mortality in elderly patients with HF.^[11] However, it is difficult to provide interventions for all HF patients. Therefore, based on the results of this study, it may be effective to increase the everyday physical activity of patients with a high plasma BNP level, depending, in particular, on the endurance of patients, so that a decrease in walking speed is prevented.

Furthermore, nutrition such as vitamin D is associated with both HF and frailty. It has been indicated that vitamin D deficiency is high prevalent in HF patients and associated with mortality,^[27] and that vitamin D levels may contribute to lower endurance and frailty.^[28] Although we did not measure the serum vitamin D in this study, it is important to develop a comprehensive intervention program (physical activity and nutrition supplementation). As the association between the frailty and the severity of HF are considered to be interactive, both preventing of frailty and improving HF are important for decreasing mortality. The intervention program should be developed in accord with these points. It will also be necessary to develop an intervention program that healthcare workers can introduce into the treatment of HF patients in future.

There were several limitations to this study. First, the diagnosis of HF was based on the history of hospitalization and the prescription of drugs, not on the gold standard Framingham Heart Study HF diagnosis criteria.^[29] Second, the cross-sectional design prevented us from establishing causal associations between the severity of HF and each element of physical frailty. Therefore, causal relationships cannot be determined from this study. Thus, the results of the present study should be interpreted with caution. Third, the findings in this study should be considered preliminary owing to the relatively small sample size, which may introduce some error of inference, reduce the power of analysis, and limit generalization.

The present study shows a detailed association between HF and physical frailty. Plasma BNP level was especially related to slowness among the five domains of physical frailty. Further investigations, such as a prospective study, are required to confirm our results.

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