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Association between ambulatory blood pressure variability and frailty among older hypertensive patients

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Abstract

Frailty and hypertension often coexist and are increasingly prevalent with advancing age. Although hypertension is independently associated with frailty, whether high blood pressure variability affecting frailty is unclear. In this retrospective study, we consecutively enrolled elderly patients with essential hypertension undergoing 24-hour ABPM. The frailty was assessed by a 38-item frailty index. The parameters of blood pressure variability of ABPM, including ARV, coefficient of CV, SD, and weighed SD were calculated. Ordinal logistic regression was used to investigate the association between blood pressure variability and frailty. A total of 242 hypertensive patients were recruited and divided into the frail group, pre-frail group, and non-frail group. The overall magnitudes of BP variability, assessed by ARV, CV, SD, and weighed SD, were significantly greater in patients with frailty than those with pre-frailty and non-frailty. With adjustment for covariates, ARV of 24-hour, diurnal, and nocturnal SBP were independently associated with frailty (24 hours, OR: 2.48, 95% CI: 2.01-3.07; daytime, OR: 1.83, 95% CI: 1.60-2.10; nighttime, OR: 1.19, 95% CI: 1.12-1.27). The CV of 24-hour, diurnal, and nocturnal SBP was independently associated with frailty in the study (24 hours, OR: 1.2, 95% CI: 1.05-3.07; daytime, OR: 1.19, 95% CI: 1.05-1.34; nighttime, OR: 1.13, 95% CI: 1.03-1.24). For SD and weighed SD, only 24-hour systolic SD was independent risk factor associated with frailty (OR: 1.12, 95% CI: 1.01-1.23). The greater blood pressure variability of SBP, particular ARV and CV, were independent risk factors associated with higher-order frailty status. Longitudinal studies are needed to investigate the causality associations between hypertension and frailty.

1 | INTRODUCTION

Frailty is a multifactorial geriatric syndrome. The age-related cumulative decline across interrelated physiological systems and impaired homeostatic reserves results in the increased vulnerability to stressors, especially exposed to acute or chronic illness.^{1,2}

Accordingly, older adults with frailty are related to an increment risk for the adverse health outcomes, including falls,¹ institutionalization,³ delirium,⁴ disability,⁵ and mortality.⁶ It was estimated that the prevalence rate of frailty was 19.6% in China.⁷ With advancing age, frailty progresses at a great rate, which poses a grave threat to public health.

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In aging population, frailty and hypertension often coexist and are increasingly prevalent in the aging population. Hypertension was much more prevalent in frail individuals (83%) than those without (57.1%), which was independently associated with frailty.⁸ However, the pathophysiological mechanism links between them are complex and not fully understood. They may share the common risk factors such as age and sedentary lifestyle, which may lead to the risk of both frailty and hypertension.⁹ Despite the growing interest in this field, few data are available on the role of hypertension in the frail and elderly population.¹⁰ In fact, blood pressure values are not constant but with spontaneous oscillations over a day.¹¹ The exaggerated blood pressure variability representing a decline in homeostatic regulation of blood pressure may indicate a frail state.¹² Hence, we hypothesize that high blood pressure variability may be associated with frail status in older adults. However, current evidence remains scarce in the field of the association between blood pressure variability and frailty syndrome. In this light, the aim of the present study is to investigate the relationship of frailty syndrome and 24-hour ambulatory blood pressure variability in elderly hypertensive patients. It is important to understand the implications of blood pressure variability for the control and treatment of hypertension in older adults with frailty.

2 | METHODS

2.1 | Participants and study design

In this retrospective study, we enrolled consecutively elderly patients with hypertension, who were admitted to Shanghai East Hospital, Tongji University School of Medicine between June 2019 and December 2019. Inclusion criteria were inpatients with essential hypertension who were over 60 years old undergoing

24-hour ambulatory blood pressure monitoring (ABPM) examination. Exclusion criteria were as follows: (a) patients with diagnosis of secondary hypertension; (b) intolerance for the 24 hours ABPM and BP reading success rate < 70%; (c) incomplete or missing clinical data. Hypertension was defined based on the 2010 Guidelines for Prevention and Treatment of Hypertension in China and the 2020 consensus on the management of hypertension in Asia: (a) systolic blood pressure (SBP) ≥ 140 mm Hg and/or diastolic blood pressure (DBP) ≥ 90 mm Hg; (b) average 24-hour BP $\geq 130/80$ mm Hg, or daytime BP $\geq 135/85$ mm Hg, or night time BP $\geq 120/70$ mm Hg.¹³ Old patients with hypertension who underwent 24-hour ABPM were recruited ($n = 426$). We excluded 21 subjects with secondary hypertension. Of the remaining 405 subjects, we excluded 163 subjects who were missing data of variables in frailty index and/or 24-hour ABPM data, leaving 242 subjects included for analysis. The flowchart of study for participants selection was shown in Figure 1. This study was approved by the ethics committee of Shanghai East Hospital. Requirement for obtaining informed consent from participants was waived due to the retrospective nature of study.

2.2 | Frailty index measurements

In all subjects, the assessment of frailty was performed using validated frailty index, which is a cumulative deficit approach and was initially proposed in the Canadian Study of Health and Aging.^{14,15} The frailty index is characterized by a non-predefined checklist of variables of so-called deficits.¹⁵ It is suggested that a frailty index with at least 30-40 variables is sufficiently accurate for the estimates of frailty.¹⁶ The variables of frailty index are selected in accordance with the available data in each database.^{14,16} The estimates based on different deficits regimes appear to yield similar results.¹⁴ Although there is no standard set of deficits for constructing frailty

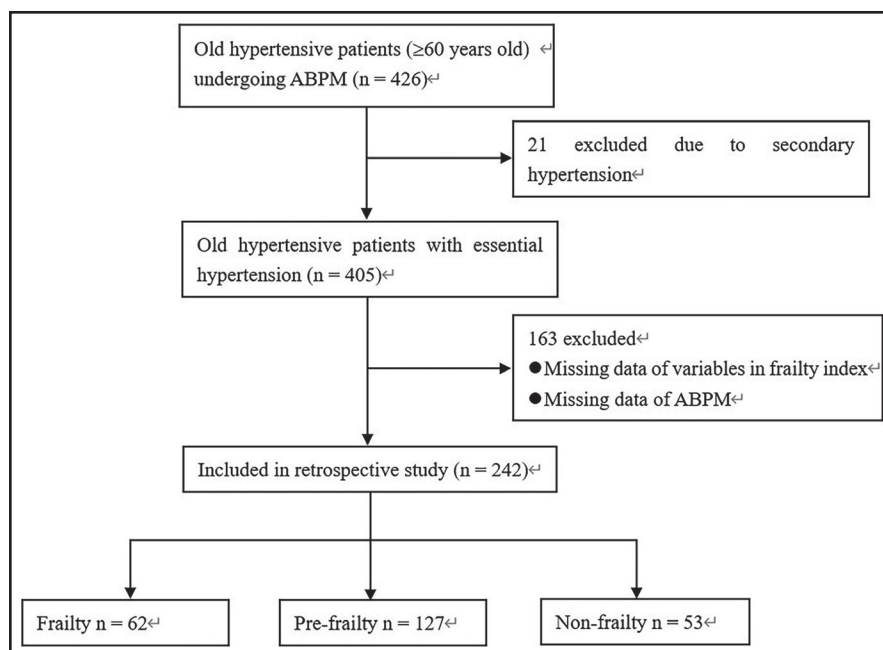


FIGURE 1 Flowchart of the participants. Flowchart depicting the selection of participating individuals for investigation. ABPM, ambulatory blood pressure monitoring

TABLE 1 Main characteristics of study participants according to different frailty status (n = 242)

Parameter	Frailty (n = 62)	Pre-frailty (n = 127)	Non-frailty (n = 53)	P-value
Age (y)	76.92 ± 9.67	72.35 ± 9.31	69.74 ± 8.35	<.001 ^a
Male (%)	35 (56.5)	63 (49.6)	26 (49.1)	.413
BMI (kg/m ²)	23.93 ± 5.04	24.06 ± 3.46	25.22 ± 4.10	.161
Smoker status (%)	10 (16.1)	17 (13.4)	11 (20.8)	.536
Type 2 diabetes (%)	27 (43.5)	54 (42.5)	15 (28.3)	.108
Stroke (%)	26 (41.9)	40 (31.5)	8 (15.1)	.002 ^{a,*}
Glucose (mmol/L)	5.2 (4.5-7.6)	5.3 (4.6-6.9)	5.2 (4.7-6.4)	.217
Serum creatinine (mmol/L)	82.0 (54.8-110.7)	71.1 (59.6-88.1)	71.0 (60.2-83.5)	.924
HDL cholesterol (mmol/L)	1.0 (0.8-1.3)	1.1 (0.9-1.3)	1.0 (0.9-1.9)	.296
LDL cholesterol (mmol/L)	2.5 (1.8-3.0)	2.5 (1.9-3.3)	2.3 (1.8-2.8)	.283
Triglycerides (mmol/L)	1.4 (1.0-2.0)	1.5 (1.0-2.4)	1.6 (1.1-2.6)	.384
Conventional BP (mm Hg)				
SBP	149.00 ± 25.57	144.28 ± 24.79	142.74 ± 22.56	.334
DBP	78.08 ± 11.08	78.05 ± 11.28	81.53 ± 10.92	.137
Antihypertensive agents (%)				
ACEI	8 (12.9)	7 (5.5)	5 (9.4)	.445
ARB	32 (51.6)	76 (59.8)	27 (50.9)	.997
β-blockers	28 (45.2)	61 (48.0)	17 (32.1)	.185
CCB	32 (51.6)	71 (55.9)	23 (43.4)	.421
Diuretics	17 (27.4)	30 (23.6)	5 (9.4)	.022 ^{a,*}
Number of antihypertensive agents	2 (1-2)	2 (1-3)	1 (1-2)	.007 ^{a,*}

Abbreviations: ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; BP, blood pressure; CCB, calcium channel blockers; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

^aDifference found between all groups except pre-frail vs non-frail.

^bDifference found between all groups except frail vs pre-frail.

*Statistically significant; Data are means ± standard deviation, medians (interquartile range), or n (%).

index, variables selected should be in accordance with the core criteria: (a) biological sensible; (b) age-related; (c) not saturate too early; (d) covering a range of systems.^{16,17}

In this study, we constructed a 38-item frailty index using a standardized procedure, and the components were a range of items associated with health status, including diseases, symptoms, disabilities, abnormal laboratory test results, and polypharmacy.^{16,18,19} For any individual, the frailty index was calculated as the fraction X/N, where X is the number of variables presented as deficits and N is the total number of items.^{14,20} The items were coded following the convention of having 0 value if the deficit was absent and 1 value if it was present. The score of frailty index was calculated and presented as the variable ranging between 0, the robust, and 1, the maximum frailty. The higher score of frailty index, the worse frailty

status.¹⁶ In line with previous reports, the frailty status can be classified into three categories: frailty (0.21 < frailty index), pre-frailty (0.10 < frailty index ≤ 0.21), and non-frailty (frailty index ≤ 0.10).²¹⁻²³

2.3 | 24-hour ABPM assessments

All of the elderly hypertensive patients who underwent 24-hour ABPM were performed with a validated oscillometric device (Model TM-2430, AND). The automatic monitor was installed on the non-dominant arm between 07:00 and 09:00 AM for 24 hours during hospital stay. Patients were instructed to maintain their usual activities during the 24-hour monitoring period, but to keep the arm extended and immobile at the time of automatic cuff inflation. The

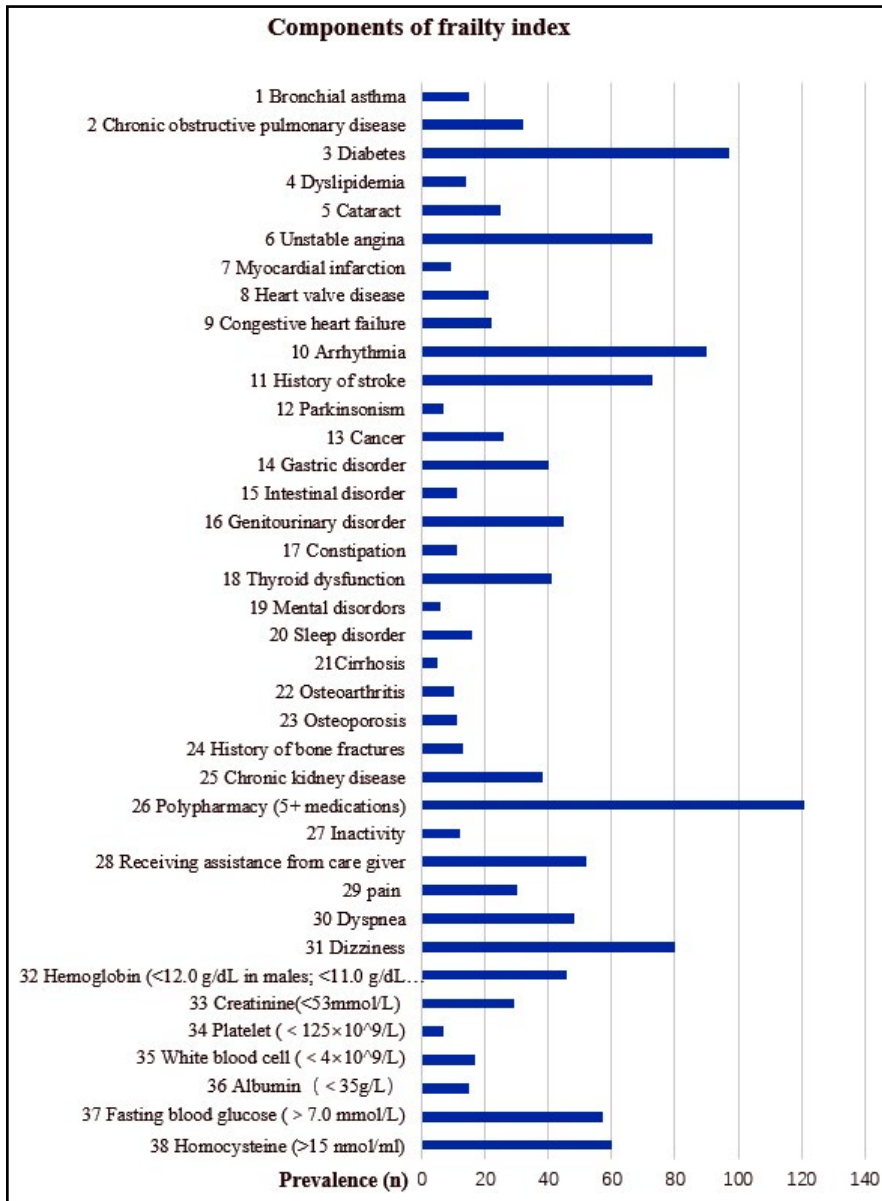


FIGURE 2 Component of frailty index. The 38-item frailty index used to assess frailty status in this study

blood pressure readings were recorded at 30-minute intervals during daytime (6:00 AM to 10:00 PM) and at 60-minute intervals during nighttime (10:00 PM to 6:00 AM).^{24,25} The recordings for each subject were considered invalid if more than 30% of raw data were not obtained.^{25,26} Values of systolic readings lower than 70 mm Hg or >260 mm Hg, diastolic readings lower than 40 mm Hg or >150 mm Hg, were automatically discarded from the recording.^{27,28}

2.4 | Blood pressure variability measurements

All ambulatory BP readings obtained were used to calculate 24-hour, diurnal, and nocturnal BP arithmetic mean values as well as variability values. Mean BP values indicated the average levels of SBP and DBP. Pulse pressure (PP) was measured as the difference between

SBP and DBP. Nocturnal SBP dipping was calculated as follows: (diurnal SBP-nocturnal SBP) × 100/diurnal SBP, and the dipper pattern was defined as SBP decline on average by 10%-20%, which is considered as a normal status.^{29,30} The variability of SBP and DBP values was measured by the following common metrics, including the average real variability (ARV), the coefficient of variation (CV), the standard deviation (SD), and the weighed SD of SBP and DBP. ARV is the mean of absolute changes between successive blood pressure readings and was calculated using the following formula:

$$ARV = \frac{1}{N-1} \sum_{k=1}^{N-1} |BP_{k+1} - BP_k|,$$

where N is the total valid numbers of blood pressure readings, and BP_k and BP_{k+1} denote two adjacent BP measurements.³¹ Data were

extracted to calculate SD, which measures the dispersion of a data set around the mean values. Weighed SD over 24 hours was calculated with the following formula: Weighed SD = (SD of diurnal BP × daytime + SD of nocturnal BP × nighttime)/Total recording length.³² CV was calculated as $100 \times \text{SD}/\text{mean blood pressure of SBP and DBP}$.³³

2.5 | Clinical data collection

All the inpatients received multidimensional evaluations consisting of sociodemographic and clinical data collection. They also underwent standard laboratory tests and conventional blood pressure measurements in sitting position (office BP). Baseline data were collected for each participant enrolled in our study. Age, sex, smoking status, body mass index (BMI), and conventional blood pressure were obtained. BMI was calculated as $\text{weight}/(\text{height})^2$ (kg/m^2). Other medical records including clinical diagnoses, history of diseases, disability, symptoms, signs, blood tests, and prescriptions were also collected. All baseline data collected was shown in Table 1. Components of frailty index were presented in Figure 2.

2.6 | Statistical analysis

All statistical analyses were performed using SPSS statistical package, version 24 for Windows. Continuous variables were expressed as mean \pm standard deviation or median (interquartile range), and categorical variables as absolute and relative frequencies. Kolmogorov test was applied to evaluate distribution normality. Comparisons of differences among the three groups were carried out by using ANOVA test with Bonferroni post hoc for continuous normal distributed variables, non-parametric Kruskal-Wallis tests for continuous variables with skewed distribution, and chi-square test for categorical variables. Ordinal logistic regression model was applied to investigate the association between 24-hour blood pressure variability and frailty. Two sets of models were tested: unadjusted model and adjusted model for each outcome. In the adjusted models, the covariate factors such as age, sex, BMI, the administered numbers of antihypertensive agents, the mean value and PP of 24-hour ambulatory blood pressure were controlled to eliminate the potential effects of confounding factors. P value $< .05$ was considered to be statistically significant.

3 | RESULTS

The baseline characteristics of the participants are described in Table 1. A total of 242 patients were enrolled in our studies, including 124 (51.2%) men and 118 (48.8%) women. Age ranged from 60 to 96 years old; mean age was 73.03 ± 9.38 years. In total, there were 62 (25.62%) patients considered frail, 127 (54.48%) pre-frail, and 53 (21.90%) non-frail. Frail patients were generally older compared to

pre-frail and non-frail old adults ($P < .001$). The three groups were homogeneous regarding to general characteristics, including gender, BMI, and smoking status ($P > .05$). The frail and pre-frail patients presented with more prevalence of stroke compared to the non-frail patients, but no difference was observed for patients subjected to type 2 diabetes among the three groups ($P = .108$). There was no statistically significant difference between conventional blood pressure in sitting position among the subgroups ($P > .05$). The numbers of antihypertensive agents administered in frail group were found to be significantly different as compared with the other two groups ($P = .007$). The use of angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) of all subjects was 8.3% and 55.8% respectively, with no differences between groups ($P = .445$ and $.997$). The other common antihypertensive agents used were β -blockers in 43.8% ($P = .185$), calcium channel blocker (CCB) in 52.1% ($P = .421$), and diuretics in 24.0% ($P = .022$). The administrations of β -blockers and CCB were similarly in three groups ($P > .05$). Frail and pre-frail patients used more diuretics, but no difference was found among them (Table 1).

Regarding the average values of 24-hour ambulatory blood pressure, the mean BP in 24-hour, awake, and asleep time frames were found to be significantly different among the groups. There was higher average of SBP in the frail and pre-frail groups as compared with non-frail group over the three time frames ($P = .014$, $.023$ and $.014$, respectively), while lower average of DBP was found among frail and pre-frail individuals than those among non-frail over 24 hours, wakefulness, and sleep ($P = .012$, $.009$ and $.049$, respectively). PP values of SBP and DBP over the three time frames were higher in the frail and pre-frail groups than non-frail group ($P = .01$, $.01$ and $.015$, respectively). However, nocturnal SBP dipping and dippers also did not differ among groups ($P > .05$) (Table 2).

The overall magnitudes of blood pressure variability, including ARV, CV, SD, and weighed SD, were found significant greater in patients with frailty than those with pre-frailty and non-frailty. The increased ARV of SBP and DBP over 24-hour, awake, and asleep time frames were significantly different between three subgroups ($P < .001$). With regard to CV and SD over 24 hours and daytime, but not nighttime, the significant differences were detected between study groups ($P < .001$). A significant increase in the values of weighed systolic and diastolic SD was observed in the frail group ($P < .001$ and $P < .05$, respectively) (Table 3).

Ordinal logistic regression analysis was used to evaluate the association between BP variability and frailty. The statistically significant parameters (P value $< .05$) in univariate analysis, considered as potential confounding factors, were incorporated into analysis modeling. Majority of results from unadjusted and adjusted analyses were similar, other than for systolic SD and weighed SD, which were only found significantly associated with frailty in unadjusted analyses. With adjustment for covariates, ARV of 24-hour, diurnal, and nocturnal SBP were independently significant associated with frailty (24 hours, odds ratio [OR]: 2.48, 95% confidence interval [CI]: 2.01-3.07; daytime, OR: 1.83, 95% CI: 1.60-2.10; nighttime, OR: 1.19, 95% CI: 1.12-1.27). Likewise,

Parameter	Frailty	Pre-frailty	Non-frailty	P value
SBP (mm Hg)				
24-h systolic mean	138.97 ± 17.54	135.94 ± 15.59	130.53 ± 12.15	.014 ^{†,a}
Day systolic mean	139.52 ± 17.56	136.94 ± 15.89	131.55 ± 12.73	.023 ^{†,a}
Night systolic mean	137.11 ± 20.65	132.38 ± 18.59	126.98 ± 14.24	.014 ^{†,a}
DBP (mm Hg)				
24-h diastolic mean	74.26 ± 15.88	73.94 ± 9.13	77.70 ± 9.79	.012 ^{†,a}
Day diastolic mean	73.27 ± 9.05	74.80 ± 9.44	78.62 ± 10.20	.009 ^{†,a}
Night diastolic mean	70.31 ± 9.19	70.98 ± 10.34	74.51 ± 9.70	.049 ^{†,a}
PP (mm Hg)				
24-h PP	63.0 (54.0-72.0)	60.0 (51.0-69.0)	54.0 (48.0-63.0)	.01 ^{†,a}
Day PP	63.0 (54.0-72.0)	60.0 (51.0-69.0)	54.0 (48.0-60.0)	.01 ^{†,a}
Night PP	63.0 (51.0-72.8)	60.0 (48.0-72.0)	54.0 (45.0-66.0)	.015 ^{†,a}
Nocturnal SBP dipping (mm Hg)	2.0 ± 10.4	3.4 ± 9.4	2.8 ± 8.9	.635
Dipper status (%)	14 (22.6)	33 (26.0)	11 (20.8)	.854

Note: Data are means ± standard deviation, medians (interquartile range), or n (%).

Abbreviations: DBP, diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure.

^a All groups differ except frail vs pre-frail.

[†]Statistically significant.

the CV of 24-hour, diurnal, and nocturnal SBP was significantly associated with frailty in the study (24 hours, OR: 1.2, 95% CI: 1.05-3.07; daytime, OR: 1.19, 95% CI: 1.05-1.34; nighttime, OR: 1.13, 95% CI: 1.03-1.24). With respect to SD, only 24-hour systolic SD after adjustment had significant association with frailty status (OR: 1.12 95% CI: 1.01-1.23), while SD of SBP during wakefulness and sleep did not ($P > .05$). No significant association between weighed SD and frailty has been found in the adjusted analysis. ($P > .1$) (Table 4).

4 | DISCUSSION

In our study, we included 242 inpatients with hypertension older than 60 years, and grouped them into frail, pre-frail, and non-frail patients. The overall prevalence of frailty among hospitalized patients was 25.62%, evaluated by the combined frailty index. The results in the current study were in line with previous published ones that the prevalence of frailty ranged from 18% to 54% among different regions in China in clinical settings.³⁴ The results showed subjects in the frail group were significantly older than that in the pre-frail and non-frail groups. In line with previous studies, we observed the strong association between ageing and frailty status.^{35,36} Aging is the accumulation of changes responsible for the advanced

TABLE 2 The characteristics of 24-h ambulatory blood pressure of elderly hypertensive patients by the level of frailty

disease and adverse outcomes including cognitive decline, falls, and death,^{37,38} which could explain the facts that elderly individuals who accumulate more deficits and undergo more adverse events tend to be frailer as age increases.

In the present study, we did not observe a difference in gender between groups. Also, there was no difference in the degree of obesity and smoking status among three groups, the results were consistent with previous findings from Brail and Singapore,^{36,39} but contrary to most studies that higher BMI and smoking were correlated to incident frailty,⁴⁰ and the U-shaped relationship between frailty and BMI.^{41,42} The reason accounting for this discrepancy between studies may be due to the relatively small sample size and more selected hospitalized population judged by our inclusion and exclusion criteria. The pre-frail and frail patients are more likely to use diuretics, and this finding was in accordance with results of previous study which demonstrated that diuretic administration was associated with frailty.⁴³

The main findings in current study are that the frail elderly tended to have greater short-term blood pressure variability, which were assessed by ARV, CV, SD, and weighed SD. Results showed that 24-hour and daytime BP variability were associated with frailty in the older adults. For the nocturnal blood pressure variability, only ARV was found to have significant association with frailty in contrast to CV and SD. Our results were partially consistent with that

TABLE 3 The characteristics of 24-h blood pressure variability of elderly hypertensive patients by the level of frailty

Parameter	Frailty	Pre-frailty	Non- frailty	P value
ARV (mm Hg)				
24-h SBP	20.6 (18.6-22.5)	15.3 (13.4-17.0)	11.6 (10.2-13.4)	<.001 ^a
24-h DBP	13.2 (10.4-16.2)	10.0 (8.2-12.4)	8.3 (6.8-10.3)	<.001 ^a
Day SBP	20.8 (18.9-23.5)	14.7 (13.2-17.0)	11.0 (9.5-13.4)	<.001 ^a
Day DBP	13.3 (9.5-17.0)	10.1 (7.8-13.0)	9.0 (6.5-11.2)	<.001 ^a
Night SBP	19.4 (14.6-25.6)	15.1 (10.6-18.9)	10.9 (8.6-14.4)	<.001 ^a
Night DBP	11.6 (9.1-17.1)	9.2 (6.9-11.9)	7.9 (5.5-10.4)	<.001 ^a
CV (mm Hg)				
24-h SBP	12.8 (10.7-15.0)	11.8 (10.1-13.9)	10.5 (8.7-12.4)	<.001 ^a
24-h DBP	14.3 (12.7-17.0)	13.3 (11.0-15.7)	11.6 (10.0-14.1)	<.001 ^a
Day SBP	12.7 (10.5-14.4)	11.0 (9.6-13.7)	10.4 (8.3-11.5)	<.001 ^a
Day DBP	14.1 (12.1-16.8)	12.7 (10.3-15.1)	11.0 (9.5-13.6)	<.001 ^a
Night SBP	10.5 (8.5-13.0)	10.8 (7.2-13.5)	9.6 (7.5-11.5)	.288
Night DBP	12.1 (8.8-15.7)	12.3 (8.6-14.9)	11.45 (8.4-14.1)	.581
SD (mm Hg)				
24-h SBP	18.2 (13.8-21.0)	16.0 (13.7-18.3)	14.1 (11.8-16.2)	<.001 ^a
24-h DBP	10.7 (9.0-12.6)	9.8 (8.2-11.9)	9.1 (7.8-10.9)	<.001 ^a
Day SBP	17.7 (13.5-20.8)	15.1 (13.3-18.0)	14.0 (11.6-16.1)	<.001 ^a
Day DBP	10.6 (8.3-12.5)	9.3 (8.0-11.2)	8.8 (7.7-10.7)	<.001 ^a
Night SBP	13.7 (11.4-18.1)	13.5 (9.2-18.4)	12.2 (9.6-15.0)	.135
Night DBP	8.6 (6.0-11.3)	8.3 (5.4-10.7)	8.5 (6.0-10.5)	.838
Weighed SD (mm Hg)				
Weighed systolic SD	16.9 (13.4-18.9)	14.9 (12.6-17.3)	13.4 (11.7-15.1)	<.001 ^a
Weighed diastolic SD	8.1 (6.3-9.7)	7.6 (6.5-9.0)	7.4 (5.9-8.7)	.048 ^a

Note: Data are medians (interquartile range).

Abbreviations: ARV, average real variability; BPV, blood pressure variability; CV, coefficient of variation; SD, standard deviation.

^aAll groups differ.

^bDifference found between all groups except pre-frail vs non-frail.

*Statistically significant.

of Woo et al.,¹² who conducted a longitudinal cohort study on 1156 older community dwellers in Hong Kong. Participants took part in repeated BP measurements three times a week during one year. They evaluated visit-to-visit BP variability and calculated BP variability as a whole single marker of frailty by machine learning. The results indicated that high blood pressure variability was associated with frailty (OR 1.57; 95% CI 1.05-2.37), in spite of that this significance only found in subgroup analysis of women. The inadequate sample size for men who only accounting for 25% of all participants appears to be attributed to the results in the study. The potential underlying mechanism of association between frailty and increased blood pressure variability remains unclear, but it may be explained by the decline in homeostatic mechanisms that a frail individual tends to be more physiologically dysregulated in achieving a satisfactory blood pressure control.⁴⁴ A frailty state may represent a reduced regulation of biological homeostasis in blood pressure when

exposed to stressors, leading to the great variability in blood pressure measurements.

In this study, ordinal logistic regression analysis showed that 24-hour, daytime and nighttime systolic ARV and CV, but not diastolic parameters, were independently associated with frailty. A possible explanation for this may be that sympathetic nervous system is an important regulator of short-term blood pressure,⁴⁵ in particular, systolic blood pressure reflects sympathetic nervous system activation.⁴⁶ However, it has been suggested that the sympathetic nervous activity was decreased in older adults with frailty.⁴⁷ This finding was supported by Giannattasio et al.,⁴⁸ who observed dysregulated sympathetic nervous system and impaired baroreceptor modulations among older adults. Hence, the greater variability of systolic blood pressure may become the independent risk factor of frailty.

In our study, ARV and CV performed better than SD and weighed SD. The 24-hour, diurnal, and nocturnal ARV and CV of SBP were

Parameter	Unadjusted		Adjusted	
	OR (95% CI)	P value	OR (95% CI)	P value
ARV				
24-h SBP	2.19 (1.86-2.58)	<.001*	2.48 (2.01-3.07)	<.001*
24-h DBP	0.96 (0.87-1.07)	.491	0.95 (0.84-1.08)	.42
Day SBP	1.79 (1.59-2.01)	<.001*	1.83 (1.60-2.10)	<.001*
Day DBP	0.94 (0.87-1.01)	.097	0.93 (0.85-1.01)	.096
Night SBP	1.15 (1.09-1.21)	<.001*	1.19 (1.12-1.27)	<.001*
Night DBP	1.03 (0.98-1.10)	.25	1.06 (0.98-1.13)	.104
CV				
24-h SBP	1.13 (1.0-1.27)	.049*	1.2 (1.05-1.37)	.006*
24-h DBP	1.1 (0.99-1.21)	.07	1.08 (0.97-1.20)	.174
Day SBP	1.15 (1.03-1.29)	.012*	1.19 (1.05-1.34)	.005*
Day DBP	1.08 (0.99-1.18)	.072	1.07 (0.97-1.17)	.167
Night SBP	1.05 (0.97-1.13)	.269	1.13 (1.03-1.24)	.032*
Night DBP	1 (0.92-1.07)	.89	0.94 (0.86-1.02)	.117
SD				
24-h SBP	1.2 (1.10-1.31)	<.001*	1.12 (1.01-1.23)	.026*
24-h DBP	0.98 (0.86-1.11)	.727	1.13 (0.98-1.31)	.092
Day SBP	1.07 (1.01-1.14)	.043*	1 (0.93-1.08)	.991
Day DBP	0.91 (0.82-1.01)	.082	1.01 (0.90-1.14)	.874
Night SBP	1.08 (1.01-1.15)	.018*	1.07 (1.00-1.14)	.064
Night DBP	0.93 (0.84-1.02)	.132	0.95 (0.85-1.07)	.405
Weighed SD				
Weighed SBP	1.13 (1.04-1.22)	.005*	1.04 (0.95-1.14)	.416
Weighed DBP	0.86 (0.75-0.98)	.026*	0.97 (0.83-1.12)	.653

Note: Adjustment for age, sex, BMI, the administered numbers of antihypertensive agents, the mean value and pulse pressure of ambulatory blood pressure.

Abbreviations: ARV, average real variability; BMI, body mass index; CI, confidence interval; CV, coefficient of variation; DBP, diastolic blood pressure; OR, odds ratio; SBP, systolic blood pressure; SD, standard deviation.

*Statistically significant.

independently significant associated with frailty, whereas SD and weighed SD were not significant associated with frailty with the exception of 24-hour systolic SD. This finding was in line with Pierdomenico et al.,⁴⁹ who evaluated the impacts of ARV and SD on cardiovascular outcomes in hypertensive patients. The results showed that ARV, but not SD, which had more useful prognostic values and was an independent predictor of cardiovascular events in hypertensive patients. Our finding was also in accordance with that of Mena,³¹ who evaluated the prognostic significance of BPV by 24 hours ambulatory BP monitoring, particularly comparing performance of ARV verse SD among 312 participants, suggesting that ARV may have better prognostic value which may be a more reliable parameter of BP variation than SD.

In this study, we also reported that the average values and PP of ambulatory SBP and DBP. The average ambulatory SBP during wakefulness, sleep period, and over 24 hours were higher, while

TABLE 4 Ordinal logistic regression analyses of association between frailty and blood pressure variability

average DBP of the three time frames was lower among the frail and pre-frail subjects than the non-frail patients. Correspondingly, PP values were significantly greater in the frail and pre-frail groups than in the non-frail group. The findings may be explained by large arterial stiffness increases with advancing age.⁵⁰ Frail and pre-frail individuals are older adults who may be subjected to the deteriorated structural and functional changes of arteries, such as arterial wall hypertrophy, and calcifications and atherosclerotic lesions formation, which are main determinants of decline in elastic properties.⁵¹ Therefore, the age-related pathological alterations may account for the changes of ambulatory SBP and DBP. Yet, our study failed to show an association between frailty and nocturnal SBP dipping, potentially due to the low sensitivity to frailty or the selected population of elderly hospitalized patients. Our findings are only partially consistent with what we expected based on previous study, which showed that frail individuals had

both lower mean SBP and DBP than non-frail patients.⁵² Although the discrepancies may lie in the variations in selection bias of the study population, the association between mean blood pressure and frailty status is still highly debated. Further studies in this area are warranted.

To the best of our knowledge, this is the first study reporting on the associations between the frailty syndrome and some specific types of 24-hour ABPV, and we strongly emphasize the warranty for further studies to clarify underlying mechanism between them.

4.1 | Study limitations

Our study may have some potential limitations. First, this study was an observational and retrospective design, and it is still unclear whether high blood pressure variability is a cause or a consequence of frailty syndrome. Second, although frailty index is the most commonly used tool with good diagnostic accuracy, to date, there is not gold standard for frailty assessment. Third, all the subjects were the elderly inpatients from a single center, which may not represent older adults in community or in other clinical settings. Finally, the participants with lacking or missing medical records were excluded from this analysis, which would cause selection bias since this exclusion was not at random.

5 | CONCLUSIONS

Frailer patients showed higher mean SBP values and lower mean DBP values of 24-hour ABPM. The systolic blood pressure variability, particularly ARV and CV, were independent risk factors for frailty. Further longitudinal research with larger sample is warranted to investigate the potential mechanism and causality associations between essential hypertension and frailty.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

J.H. and Z.Y. involved in conceptualization. J.H. and Z.Y. involved in data acquisition. Z.Y., C.X., G.S., L.Q., and Y.H. involved in data analysis. Z.Y., Z. X., L. H., and L. J. involved in data interpretation. J.H. and Z.Y. involved in draft writing and revising. All authors have read and agreed to the published version of the manuscript.

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