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,3 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. 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. Despite the growing interest in this field, few data are available on the role of hypertension in the frail and elderly population. In fact, blood pressure values are not constant but with spontaneous oscillations over a day. The exaggerated blood pressure variability representing a decline in homeostatic regulation of blood pressure may indicate a frail state. Hence, we hypothesize that high blood pressure variability may be associated with frail status in older adults. 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 ≥ 130/80 mm Hg, or daytime BP ≥ 135/85 mm Hg, or night time BP ≥ 120/70 mm Hg. 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. The frailty index is characterized by a non-predefined checklist of variables of so-called deficits. It is suggested that a frailty index with at least 30-40 variables is sufficiently accurate for the estimates of frailty. 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.
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. 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.

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. 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. 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).

### Table 1

| 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* |
| Male (%)                         | 35 (56.5)        | 63 (49.6)             | 26 (49.1)            | .413    |
| BMI (kg/m²)                      | 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*   |
| 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*   |
| Number of antihypertensive agents| 2 (1-2)          | 2 (1-3)               | 1 (1-2)              | .007*   |

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.

*Difference found between all groups except pre-frail vs non-frail.

b Difference found between all groups except frail vs pre-frail.

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

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
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). The recordings for each subject were considered invalid if more than 30% of raw data were not obtained. 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.

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. 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. 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 × SD/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 weight/(height)² (kg/m²). 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 ± standard deviation or medium (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 blood pressure, the mean BP in 24-hour, awake, and asleep time frames 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 administrated 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,
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).

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

| 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.
*All groups differ except frail vs pre-frail.
Statistically significant.

### 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. 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. Aging is the accumulation of changes responsible for the advanced disease and adverse outcomes including cognitive decline, falls, and death, 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, but contrary to most studies that higher BMI and smoking were correlated to incident frailty, and the U-shaped relationship between frailty and BMI. 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.

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
of Woo et al., 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, in particular, systolic blood pressure reflects sympathetic nervous system activation. 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., 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.

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* |
| 24-h DBP | 13.2 (10.4-16.2) | 10.0 (8.2-12.4) | 8.3 (6.8-10.3) | <.001* |
| Day SBP | 20.8 (18.9-23.5) | 14.7 (13.2-17.0) | 11.0 (9.5-13.4) | <.001* |
| Day DBP | 13.3 (9.5-17.0) | 10.1 (7.8-13.0) | 9.0 (6.5-11.2) | <.001* |
| Night SBP | 19.4 (14.6-25.6) | 15.1 (10.6-18.9) | 10.9 (8.6-14.4) | <.001* |
| Night DBP | 11.6 (9.1-17.1) | 9.2 (6.9-11.9) | 7.9 (5.5-10.4) | <.001* |
| 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* |
| 24-h DBP | 14.3 (12.7-17.0) | 13.3 (11.0-15.7) | 11.6 (10.0-14.1) | <.001* |
| Day SBP | 12.7 (10.5-14.4) | 11.0 (9.6-13.7) | 10.4 (8.3-11.5) | <.001* |
| Day DBP | 14.1 (12.1-16.8) | 12.7 (10.3-15.1) | 11.0 (9.5-13.6) | <.001* |
| 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* |
| 24-h DBP | 10.7 (9.0-12.6) | 9.8 (8.2-11.9) | 9.1 (7.8-10.9) | <.001* |
| Day SBP | 17.7 (13.5-20.8) | 15.1 (13.3-18.0) | 14.0 (11.6-16.1) | <.001* |
| Day DBP | 10.6 (8.3-12.5) | 9.3 (8.0-11.2) | 8.8 (7.7-10.7) | <.001* |
| 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* |
| Weighed diastolic SD | 8.1 (6.3-9.7) | 7.6 (6.5-9.0) | 7.4 (5.9-8.7) | .048* |

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.
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., 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, 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 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. 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. 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

| Parameter | Unadjusted OR (95% CI) | P value | Adjusted 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.
both lower mean SBP and DBP than non-frail patients. 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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REFERENCES
1. Fried LP, Xue QL, Cappola AR, et al. Nonlinear multisystem physiological dysregulation associated with frailty in older women: implications for etiology and treatment. J Gerontol A Biol Sci Med Sci. 2009;64:1049-1057.
2. Rockwood K, Mitnitski A, Song X, et al. Long-term risks of death and institutionalization of elderly people in relation to deficit accumulation at age 70. J Am Geriatr Soc. 2006;54:975-979.
3. Eeles EM, White SV, O’Mahony SM, et al. The impact of frailty and delirium on mortality in older inpatients. Age Ageing. 2012;41:412-416.
4. Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. Lancet. 2013;381:752-762.
5. Fialkova M, Mitnitski A, Kirkland SA, et al. The impact of social vulnerability on the survival of the fittest older adults. Age Ageing. 2012;41:161-165.
6. Materson BJ, Garcia-Estrada M, Preston RA. Hypertension in the frail elderly. J Am Soc Hypertens. 2016;10:536-541.
7. El Mokadem M, Bosshardt H, Cattani A, et al. Correlation between blood pressure variability and subclinical target organ damage in patients with essential hypertension. J Hum Hypertens. 2019. https://doi.org/10.1038/s41371-019-0286-8. [Epub ahead of print].
8. Capelli L, Mitnitski A, Gahlbauer EA, et al. Standard procedure for creating a frailty index. BMC Geriatr. 2008;8:24.
9. Song X, Mitnitski A, Rockwood K. Prevalence and 10-year outcomes of frailty in older adults in relation to deficit accumulation. J Am Geriatr Soc. 2009;61:1049-1057.
10. Fried LP, Xue QL, Cappola AR, et al. Nonlinear multisystem physiological dysregulation associated with frailty in older women: implications for etiology and treatment. J Gerontol A Biol Sci Med Sci. 2009;64:1049-1057.
11. Rockwood K, Mitnitski A, Song X, et al. Long-term risks of death and institutionalization of elderly people in relation to deficit accumulation at age 70. J Am Geriatr Soc. 2006;54:975-979.
12. Eeles EM, White SV, O’Mahony SM, et al. The impact of frailty and delirium on mortality in older inpatients. Age Ageing. 2012;41:412-416.
13. Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. Lancet. 2013;381:752-762.
14. Fialkova M, Mitnitski A, Kirkland SA, et al. The impact of social vulnerability on the survival of the fittest older adults. Age Ageing. 2012;41:161-165.
15. Materson BJ, Garcia-Estrada M, Preston RA. Hypertension in the frail elderly. J Am Soc Hypertens. 2016;10:536-541.
16. El Mokadem M, Bosshardt H, Cattani A, et al. Correlation between blood pressure variability and subclinical target organ damage in patients with essential hypertension. J Hum Hypertens. 2019. https://doi.org/10.1038/s41371-019-0286-8. [Epub ahead of print].
17. Woo J, Yu R, Tsoi K, et al. Variability in repeated blood pressure measurements as a marker of frailty. J Nutr Health Aging. 2018;22:1122-1127.
18. Kario K, Park S, Chia YC, et al. 2020 Consensus summary on the management of hypertension in Asia from the HOPE Asia Network. J Clin Hypertens (Greenwich). 2020;22:351-362.
19. Fried LP, Xue QL, Cappola AR, et al. Nonlinear multisystem physiological dysregulation associated with frailty in older women: implications for etiology and treatment. J Gerontol A Biol Sci Med Sci. 2009;64:1049-1057.
20. Rockwood K, Mitnitski A, Song X, et al. Long-term risks of death and institutionalization of elderly people in relation to deficit accumulation at age 70. J Am Geriatr Soc. 2006;54:975-979.
21. Fialkova M, Mitnitski A, Kirkland SA, et al. The impact of social vulnerability on the survival of the fittest older adults. Age Ageing. 2012;41:161-165.
22. Blodgett J, Theou O, Kirkland S, et al. Frailty in NHANES: comparison of frailty index and phenotype. Arch Gerontol Geriatr. 2015;60:446-470.
23. Pajewski NM, Williamson JD, Applegate WB, et al. Characterizing frailty status in the systolic blood pressure intervention trial. J Gerontol A Biol Sci Med Sci. 2016;71:649-655.
24. Hoover M, Rotermann M, Sammartin C, et al. Validation of an index to estimate the prevalence of frailty among community-dwelling seniors. Health Rep. 2013;24:10-17.
25. JU MS, Lee S, Bae I, et al. Effects of aroma massage on home blood pressure, ambulatory blood pressure, and sleep quality in
26. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens. 2018;36:1953-2041.

27. Li S, Wang X, Zhao L, et al. The characteristics of 24-hour ambulatory blood pressure monitoring and its relationship with cardiovascular target organ damage in Chinese Han patients with concomitant type 2 diabetes and hypertension. Blood Press Monit. 2019;24:167-173.

28. Su D, Guo Q, Gao Y, et al. The relationship between red blood cell distribution width and blood pressure abnormal dipping in patients with essential hypertension: a cross-sectional study. BMJ Open. 2016;6:e010456.

29. Yano Y, Kario K. Nocturnal blood pressure and cardiovascular disease: a review of recent advances. Hypertens Res. 2012;35:695-701.

30. Shin J, Kario K, Chia YC, et al. Current status of ambulatory blood pressure monitoring in Asian countries: a report from the HOPE Asia Network. J Clin Hypertens (Greenwich). 2020;22:384-390.

31. Mena L, Pintos S, Queipo NV, et al. A reliable index for the prognostic significance of blood pressure variability. J Hypertens. 2005;23:505-511.

32. Boardman H, Lewandowski AJ, Lazdam M, et al. Aortic stiffness and blood pressure variability in young people: a multimodality investigation of central and peripheral vasculature. J Hypertens. 2017;35:513-522.

33. Parati G, Ochoa JE, Lombardi C, et al. Assessment and management of blood-pressure variability. Nat Rev Cardiol. 2013;10:143-155.

34. Liang YD, Zhang YN, Li YM, et al. Identification of frailty and its risk factors in elderly hospitalized patients from different wards: a cross-sectional study in China. Clin Interv Aging. 2019;14:2249-2259.

35. Yang F, Chen QW. Evaluation of frailty and influencing factors in old people in hospital institution: evidence for a phenotype of frailty. Medicine (Baltimore). 2018;97:e9634.

36. Bastos-Barbosa RG, Ferrioli E, Coelho EB, et al. Association of frailty syndrome in the elderly with higher blood pressure and other cardiovascular risk factors. Am J Hypertens. 2012;25:1156-1161.

37. Harman D. Free radical theory of aging: history. Exs. 1992;62:1-10.

38. Wassenaar TM, Yaffe K, van der Werf YD, et al. Associations between modifiable risk factors and white matter of the aging brain: insights from diffusion tensor imaging studies. Neurobiol Aging. 2019;80:56-70.

39. Wang X, Lu Y, Li C, et al. Associations of lifestyle activities and a heathy diet with frailty in old age: a community-based study in Singapore. Aging (Albany NY). 2020;12:288-308.

40. Woods NF, LaCroix AZ, Gray SL, et al. Frailty: emergence and consequences in women aged 65 and older in the Women’s Health Initiative Observational Study. J Am Geriatr Soc. 2005;53:1321-1330.

41. Chen C, Winterstein AG, Fillingim RB, et al. Body weight, frailty, and chronic pain in older adults: a cross-sectional study. BMC Geriatr. 2019;19:143.

42. Hubbard RE, Lang IA, Llewellyn DJ, et al. Frailty, body mass index, and abdominal obesity in older people. J Gerontol A Biol Sci Med Sci. 2010;65:377-381.

43. Welsh TJ, Gladman JR, Gordon AL. The treatment of hypertension in people with dementia: a systematic review of observational studies. BMJ Open. 2014;14:19.

44. Ferrucci L, Cavazzini C, Corsi A, et al. Biomarkers of frailty in older persons. J Endocrinol Invest. 2002;25:10-15.

45. Head GA. The sympathetic nervous system in hypertension: assessment by blood pressure variability and ganglionic blockade. J Hypertens. 2003;21:1619-1621.

46. Ceccato I, Lecce S, Cavallini E, et al. Motivation and social-cognitive abilities in older adults: convergent evidence from self-report measures and cardiovascular reactivity. PLoS One. 2019;14:e0218785.

47. Shibasaki K, Ogawa S, Yamada S, et al. Association of decreased sympathetic nervous activity with mortality of older adults in long-term care. Geriatr Gerontol Int. 2014;14:159-166.

48. Giannattasio C, Ferrari AU, Mancia G. Alterations in cardiovascular control mechanisms with ageing. J Hypertens Suppl. 1994;12:S13-S17.

49. Pierdomenico SD, Di Nicola M, Esposito AL, et al. Prognostic value of different indices of blood pressure variability in hypertensive patients. Am J Hypertens. 2009;22:842-847.

50. Benetos A, Petrovic M, Strandberg T. Hypertension management in older and frail older patients. Circ Res. 2019;124:1045-1060.

51. Lakatta EG. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part III: cellular and molecular clues to heart and arterial aging. Circulation. 2003;107:490-497.

52. Anker D, Santos-Eggimann B, Zwahlen M, et al. Blood pressure in relation to frailty in older adults: a population-based study. J Clin Hypertens (Greenwich). 2019;21:1895-1904.

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