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Predictive value of attended automated office blood pressure and resting pulse rate for mortality in community-dwelling octogenarians: Minhang study

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Abstract

Systolic blood pressure (SBP) and resting pulse rate (RPR) have been linked to mortality and cardiovascular events in younger population. Till now, no studies simultaneously investigate the non-linear association of SBP and RPR with all-cause and cardiovascular mortality among population aged 80 and older. Data of 2828 eligible participants were selected from electronic health records linked attended automated office blood pressure measurement system. The dose-response relationship between the SBP, RPR, and the risk of all-cause and cardiovascular mortality was analyzed by Cox model with restricted cubic splines. During the 3.6-year follow-up, 442 deaths occurred. Comparing with the optimal SBP (117-145 mmHg), the lower (HR: 1.39, 95% CI: 1.07-1.81) and higher SBP (HR: 1.34, 95% CI: 1.08-1.65) were significantly associated with an increasing risk of all-cause mortality. The higher SBP (>144 mmHg) was associated with cardiovascular mortality, with the HR (95% CI) as 1.51 (1.07-2.12). The faster RPR showed the higher risk of all-cause (HR: 1.36, 95% CI: 1.05-1.76) and cardiovascular (HR: 1.51, 95% CI: 1.07-2.13) mortality. We found both higher SBP and faster RPR were independently associated with all-cause and cardiovascular mortality, and lower SBP was only associated with the increased risk of all-cause mortality in oldest old community-dwelling Chinese population. Our results demonstrate the prognostic importance of both SBP and RPR in the elderly.

Yan Wang, Ling Chen and Minna Cheng: Contribute equally.

1 | INTRODUCTION

High blood pressure (BP), especially high systolic BP (SBP), represents one of the most important risk factors for cardiovascular diseases (CVD), which is the leading cause of mortality in China.[1] Although the benefits of BP-lowering treatment for prevention of all-cause and cardiovascular mortality are well established among young population,[2] the advantages of treatment and optimal therapeutic BP target among elders remain controversial. Several randomized controlled trails (RCTs) have offered proof of benefit on cardiovascular outcomes of BP lowering at older ages,[3] which suggests to reduce the SBP lower than 150 mmHg,[4] even lower than 120 mmHg.[5] On the contrary, observational researches show a positive relationship between lower BP and mortality in the very old, and J- or U-shaped association is reported.[6]

Higher resting pulse rate (RPR) is also linked to all-cause and cardiovascular mortality and morbidity in general population and individuals with cardiovascular disorders.[7] 2018 European guidelines suggest that RPR should also be recorded at the time of BP measurements, and RPR >80 beats/min is considered as an independent cardiovascular risk factor.[8] Longitudinal data from the Framingham Study shows a tendency to decline in RPR with advancing age, particularly in the oldest old,[9] but there is no special PRP suggestion for elders till now.

The population over 80 years old has expanded exponentially over the past 40 years[10]; however, there have been no studies simultaneously investigating the non-linear association of SBP and RPR with all-cause and cardiovascular mortality among population aged 80 and older. Therefore, we carry out a real-world study in Chinese community-dwelling oldest old population, to clarify the predictive value of SBP and RPR in mortality which was defined by a Cox model with restricted cubic splines, by using electronic health records (EHR) linked attended automated office BP (AOBP) measurement system.

2 | METHODS

2.1 | Ethics statement

This study was approved by the Ethics Committee of Ruijin Hospital. Considering this is a retrospective observational study including past information stored in the hospital's EHR, the need for written consent was waived by the Ethics Committee.

2.2 | Data source

All data used in this study were extracted from the outpatient EHR of Xinzhuang town hospital in Minhang district, Shanghai, China. Details of the EHR in the Minhang electronic primary care system had been reported elsewhere.[11] In brief, it was a structured medical archive that records full life cycle health-related information of residents.

The seated brachial BP was taken by nurses in an isolated quiet room after 5 minutes of resting. BP and RPR were recorded in triplicate at 30-second intervals using an automated oscillometric device (Watch BP Office, Microlife) with the appropriate cuff size. All three BP and RPR readings and their average were transferred in real time to the patient's EHR for storage.

The baseline was determined according to the date when the first set of rational OBP was recorded in each individual's EHR. The rational OBP referred to SBP between 70 and 250 mmHg and DBP in the range 40-150 mmHg. The OBP records with atrial fibrillation were also excluded. Overall, the data of 2828 subjects aged 80 years or older were extracted from May 17, 2012 to July 31, 2018. The diagnosis of hypertension and diabetes was depended on the EHR documentation. The antihypertensive treatment was determined according to the latest recorded prescription within one year. Cigarette smoking was defined as smoking at least one cigarette per day for ≥1 year. Alcohol drinking was defined as those who had been drinking for ≥2 days every week during the past 6 months. Smoking and drinking data were obtained through a questionnaire. Body mass index (BMI) was calculated as self-reported weight in kilograms divided by the square of height in meters.

2.3 | Ascertainment of death

We ascertained vital status until July 31, 2018, via the EHR. Furthermore, all death-related information was confirmed based on documents provided by Shanghai Centers for Disease Control and Prevention. The end points considered in the present analysis were all-cause and cardiovascular mortalities, which included mortality from cerebral hemorrhage (International Classification of Diseases, Tenth Revision [ICD-10] codes I60-62 and I69.1), cerebral infarction (ICD-10 codes I63 and I69.3), undetermined cerebral disorders (ICD-10 codes I64 and I67), and cardiac disorders (ICD-10 codes I07, I09-13, I20-I25, I33, I35, I38, I42, and I48-I51).

2.4 | Statistical analysis

For database management and statistical analysis, we used R software (version 3.6.3, R core team) with the R package dplyr, survival, and rms. Quantitative descriptive statistics of the patients were compared among the groups using the *t* test, and categorical variables were compared using chi-square test. To estimate the potential dose-response relationship between the SBP, RPR, and the risk of all-cause and cardiovascular mortality, the two indexes were included as continuous variable in the Cox regression and modeled by a spline regression approach applying restricted cubic spline functions. The cutoff values with the minimum mortality risk were determined according to the estimated parameters of restricted cubic splines after adjustment. Then, we used Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence interval (CI) for SBP and RPR as categorical variables. In basic model, the association of

SBP or RPR with mortality was adjusted with sex, age, BMI, smoking status, drinking status, diabetes, and hypertension, whereas the beta-blocker using was additionally adjusted in the model of RPR. In the full model, the SBP was added to the model including RPR, and vice versa. All *p*-values were 2-tailed, and a *p*-value <.05 was considered statistically significant.

3 | RESULTS

A total of 2828 eligible participants were extracted from EHR, among which 1288 (45.5%) were men (Table 1). A diagnosis of hypertension was documented in 77.9% of the participants, and treatment rate was 96.3%. Average age at baseline was 84.1 years. Compared with men, women were older and had lower frequencies of smoking and drinking. There was no significant difference between males and females in SBP or RPR.

During the follow-up (median: 3.6 years), 442 deaths occurred. Mortality included 198 cardiovascular deaths, with 95 strokes and 103 cardiac deaths. Stroke deaths were due to cerebral infarction in 78 subjects, cerebral hemorrhage in 14 subjects, and other causes in 3 subjects. Cardiac mortality included chronic coronary heart disease (*n* = 65), myocardial infarction (*n* = 15), heart failure (*n* = 12), and various other cardiac disorders (*n* = 11).

In Figure 1, we used restricted cubic splines to flexibly model and visualize the relation of predicted SBP and RPR with mortality. Associations between SBP and all-cause mortality were U-shaped, indicating minimum mortality risk at 135 mmHg for SBP. Compared with individuals with 135 mmHg of SBP, the risk of all-cause mortality was significantly higher in participants with SBP lower than 117 mmHg or higher than 145 mmHg. RPR had a J-shaped association with all-cause mortality, with lowest risk occurring in the range 77-85 beats/min. Meanwhile, the Cox models revealed J-shaped associations of SBP with cardiovascular mortality. The risk of cardiovascular mortality was relatively flat until around 144 mmHg of SBP, and then started to increase rapidly. Compared with individuals with 77 beats/min of RPR, the risk of cardiovascular mortality was significantly higher in participants with RPR lower than 73 beats/min or higher than 86 beats/min. We also tested the interaction of SBP and RPR with all-cause and cardiovascular mortality, whereas a negative relationship between SBP*RPR and mortality was found in the model including both SBP and RPR.

To compare the ranges of SBP and RPR with mortality, we underwent Cox proportional hazards models, whereas grouping was based on the estimated parameters of restricted cubic splines after adjustments. For the U-shaped association, we chose two points with statistically significant differences as the grouping boundaries. In the case of J-shaped association, the point with the minimum mortality risk and the inflection point were chosen as the grouping boundaries. We found that baseline BMI was higher in the group with higher SBP, and none of the other baseline characteristics showed significant difference among the three groups of SBP or RPR. In the basic Cox regression model, the prognostic significance of categorized SBP and RPR was analyzed with adjustments applied for sex, age, BMI, smoking and drinking habits, diabetes mellitus, and antihypertensive treatment (Table 2), whereas the beta-blocker using was additionally adjusted in the model of RPR. Comparing with the optimal SBP (117-145 mmHg), the lower (HR: 1.39, 95% CI: 1.07-1.81) and higher SBP (HR: 1.34, 95% CI: 1.08-1.65) were significantly associated with an increasing risk of all-cause mortality. The higher SBP (>144 mmHg) was associated with cardiovascular mortality, with the HR (95% CI) as 1.51 (1.07-2.12). The higher RPR (>86 beats/min) showed the higher risk of both all-cause (HR: 1.36, 95% CI: 1.05-1.76) and cardiovascular mortality (HR: 1.51, 95% CI: 1.07-2.13) in Cox regression. In the fully adjusted model, SBP was further adjusted for RPR, and vice versa. When they were adjusted for each other, the predictive value of both SBP and RPR in relation to all-cause and cardiovascular mortality was unchanged.

TABLE 1 The characteristics of subjects on baseline according to gender

Characteristic	Male	Female	All
Number	1288	1540	2828
Age (y)	83.8 ± 3.2	84.4 ± 3.7*	84.1 ± 3.5
Body mass index (kg/m^2)	23.7 ± 2.9	23.7 ± 3.2	23.7 ± 3.0
Smoking (*N*, %)	96 (7.5)	9 (0.6)*	105 (3.7)
Drinking (*N*, %)	192 (14.9)	20 (1.3)*	212 (7.4)
Hypertension (*N*, %)	998 (77.4)	1204 (78.2)	2202 (77.9)
Diabetes (*N*, %)	322 (25.0)	428 (27.8)	750 (26.5)
Average SBP (mmHg)	136.5 ± 19.4	136.5 ± 19.7	136.5 ± 19.6
Average DBP (mmHg)	72.1 ± 10.6	70.9 ± 10.6*	71.4 ± 10.6
Resting pulse rate (beats/min)	78.9 ± 14.5	79.1 ± 12.7	79.0 ± 12.9
Number of Antihypertensive drugs	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3
Beta-blocker using (*N*, %)	58 (4.5)	80 (5.2)	138 (4.9)
Follow-up days (Median, Q1-Q3)	1265 (586, 1657)	1372 (623, 1682)*	1327 (602, 1667)

*p < .05 compared to male.

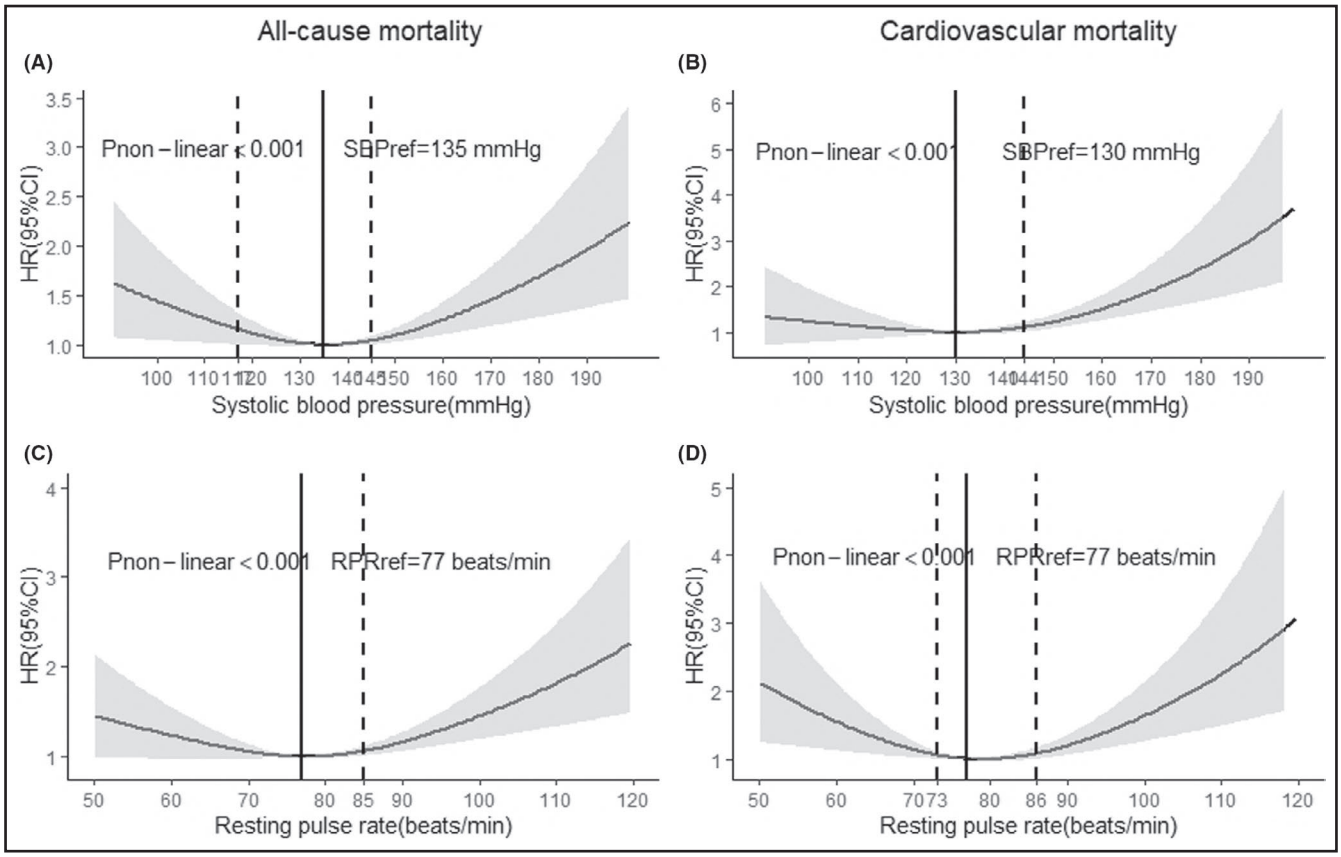

FIGURE 1 Association of systolic blood pressure and resting pulse rate with all-cause and cardiovascular mortality. (A) systolic blood pressure and all-cause mortality. (B) systolic blood pressure and cardiovascular mortality. (C) resting pulse rate and all-cause mortality. (D) resting pulse rate and cardiovascular mortality. Hazard ratios are indicated by solid lines and 95% CIs by shaded areas. Reference point is lowest value for systolic blood pressure and resting pulse rate. All models were adjusted for cofounders in Table 2

4 | DISCUSSION

Based on the standardized AOBP in EHR, we underwent a retrospective real-world cohort analysis on the association of SBP and RPR with all-cause and cardiovascular mortality in Chinese community-dwelling outpatients aged 80 years and above. We found a U-shaped relationship of SBP, as well as a J-shaped association of RPR, with all-cause mortality. Additionally, the SBP over 144 mmHg and RPR over 86 beats/mins was associated with an increased risk of cardiovascular mortality.

The risks and benefits of treating hypertension in individuals older than 80 years were still uncertain. The HYVET trail was the only antihypertensive therapy trial to date specifically designed to patients over 80 years old, which indicated that targeting BP under 150/90 mmHg would reduce the rate of all-cause and cardiovascular death in very elderly patients.[4] The subgroup study of SPRINT on persons aged 75 years or older demonstrated that a treatment goal for SBP of less than 120 mmHg reduced incident CVD by 33% and total mortality by 32%.[5] Contrary to the results from RCTs, the Umer cohort study[12] of people age ≥85 years showed that a baseline SBP <120 mmHg was associated with higher mortality than any other BP categories. The population-based cohort study using EHR of 144 403 participants ≥80 years in the United Kingdom[13] found that SBP <120 mmHg was associated with a greater risk of mortality when compared to a SBP between 120 to 139 mmHg. In the study investigated, the associations of BP levels with clinical events in older patients ~85 years old receiving home medical care, Koujiya and colleagues[14] found that SBP below 124 mmHg group showed a significantly higher rate of required hospitalization. The divergence of BP-lowering suggestions from RCTs and epidemiologic studies, as well as the different optimal target BPs derived from observational researches, could be induced by several reasons, such as the frailty status,[15] the comorbidity suffered,[16] and the BP trajectory at the end of life.[17] Additionally, the different research subjects enrolled would also lead the conclusion to divergent terminals, whereas the patients included in RCTs were always with higher BP (HYVET) or at increased risk for CVD (SPRINT), and the participants in the observational studies were always population-based. It had been noticed that higher SBP predicted a higher risk from CVD, and lower SBP predicted a higher risk of death from non-cardiovascular causes,[18] so that the subjects in RCTs were more prone to benefit from BP-lowering treatment. In consistence with prior cohort studies, we confirmed the existence of a U-shaped correlation between SBP and all-cause mortality.[12,19] With the help of Cox model with restricted cubic splines, we found that the optimal

TABLE 2 All cause and cardiovascular mortality versus different level of blood pressure and resting pulse rate in the community oldest population

		Basic model		Full model	
Variables	**Death/At risk**	**HR (95%CI)**	***p* Value**	**HR (95%CI)**	***p* Value**
All cause mortality					
Systolic blood pressure					
Lower (<117 mmHg)	74/393	1.39 (1.07-1.81)	**.015**	1.39 (1.07-1.81)	**.014**
Middle (117-145 mmHg)	223/1634	Reference		Reference	
Higher (>145 mmHg)	145/801	1.34 (1.08-1.65)	**.006**	1.33 (1.08-1.64)	**.008**
Resting pulse rate					
Lower (<77 beats/min)	199/1303	1.15 (0.90-1.46)	.635	1.14 (0.90-1.46)	.274
Middle (77-85 beats/min)	100/733	Reference		Reference	
Higher (>85 beats/min)	143/792	1.36 (1.05-1.76)	**.028**	1.35 (1.04-1.74)	**.023**
Cardiovascular mortality					
Systolic blood pressure					
Lower (<130 mmHg)	63/1090	0.98(0.68-1.40)	.912	0.98 (0.69-1.41)	.921
Middle (131-144 mmHg)	57/893	Reference		Reference	
Higher (>144 mmHg)	78/845	1.51 (1.07-2.12)	**.019**	1.50 (1.06-2.11)	**.021**
Resting pulse rate					
Lower (<73 beats/min)	70/921	1.34 (0.95-1.87)	.094	1.29 (0.92-1.81)	.143
Middle (73-86 beats/min)	65/1174	Reference		Reference	
Higher (>86 beats/min)	63/733	1.51 (1.07-2.13)	**.020**	1.44 (1.01-2.04)	**.042**

Note: Cox proportional hazards models were applied. The basic model was adjusted with sex, age, BMI, smoking status, drinking status, diabetes and hypertension, whereas the beta-blocker using was additionally adjusted in the model of resting pulse rate. In the full model, the SBP was added to the model including resting pulse rate, and vice versa.

Bold indicates statistical significant value (P < 0.05).

SBP for oldest old should be 117-145 mmHg. We also noticed that only the participants with higher SBP (>144 mmHg), but not those with lower SBP, had an increased risk of cardiovascular mortality. The potential for side effects with antihypertensive therapy in oldest old had been noticed for a long time, including orthostatic hypotension,[20] accelerated cognitive decline,[21] and etc Although the aggressive BP lowering in the SPRINT trail did reduce the risk of cardiovascular events and all-cause mortality in robust elders, the incidence of kidney injury and syncope were still high. The PARTAGE study found that the institutionalized individuals older than 80 years who were with lower SBP and under the treatment with 2 or more BP-lowering agents resulted in a higher risk of mortality.[22] In our community-based oldest population, 11.2% of the elders under BP-lowering treatment had BP <117 mmHg who had 1.4 times of risk for all-causes mortality comparing with those with optimal SBP. Considering the inertial treatment and the excessive concern on high BP during daily medical care, the geriatricians should pay more attention to the BP monitoring and adjusted the treatment regimen timely, in order to avoid the harms from aggressive reduction in BP.

Several studies had suggested that increased RPR was risk factor for both cardiovascular and non-cardiovascular mortality in general population; however, evidence was rare on the relationship between RPR and mortality in oldest old. In the study of 7147 participants aged ≥65 years, Legeai and colleagues[23] found that RPR is an independent risk marker of mortality but not of incident cardiovascular events in community-dwelling elderly. Li and colleagues[24] found RPR to be associated with both all-cause and cardiovascular mortality in a community-dwelling population aged 60 years or older. Stessman and colleagues[25] performed a cohort study in a population aged from 70 to 85, and found that rising RPR was associated with greater mortality. Our finding extended the observations to the population aged 80 and older. We also firstly showed the dose-responds relation between RPR and mortality, which indicated that the optimal RPR was 77 beats/min. We also found that those with RPR of greater than 86 beats/min had a higher risk of all-cause and cardiovascular mortality. The mechanism by which higher RPR predicted the adverse cardiovascular outcomes was not well understood, which might due to autonomic dysfunction and sympathetic over activity.[26,27] In elderly adults, high RPR might also be a reflection of poorer physical fitness and impaired cardiac functional reserve.[28] RPR was a fundamental physiological parameter and convenient to measure during daily medical care, however, measurement of RPR had rarely been recommended in guidelines on risk assessment of CVD and few of the EHR had the documentary of RPR. Our findings based on EHR indicated the independently predictive value of RPR, which justified

the necessity of recording RPR and using it to comprehensively evaluate the fitness of elders.

First limitation of the present study is its observational design, which precluded us from drawing definitive conclusions. Unlike most epidemiological cohort studies, we used uniform AOBP measurement system and standard procedure, which guaranteed that the quality of SBP and RPR measurements were as precise as in RCTs. Secondly, considering this was an EHR-based study, numerous subjects did not have laboratory test results within 6 months of BP measurements, so the plasma lipid and glucose levels were not included in the Cox regression models. However, the common risk factors, such as sex, age, BMI, and history of smoking and diabetes, were included. Thirdly, the average RPR in this population was high comparing to the previous studies, which may be induced by the low using rate of beta-blockers, so that generalizing the results to all of the oldest population required further confirmation.

In conclusion, the present study provided new evidence from an observation study by a Cox model with restricted cubic splines. We found both higher SBP and faster RPR were independently associated with all-cause and cardiovascular mortality, and lower SBP was only associated with the increased risk of all-cause mortality in oldest old community-dwelling Chinese population. Our results justified the importance of recording and integrated management of both SBP and RPR during daily medical activities. Further studies with larger sample size and longer follow-up duration were warranted to develop a prediction algorithm for mortality and nonfatal events that include SBP, RPR, and other cardiovascular risk factors.

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CONFLICT OF INTEREST

The authors declared no conflicts of interest.

AUTHOR CONTRIBUTIONS

Yan Wang, MD, PhD and Ling Chen, MD conceived and draft the manuscript. Dingliang Zhu, MD, PhD and Yan Wang, MD, PhD designed the study. Yajuan Wang, MD, Dewei An, MD, Enheng Cai, MD, Jin Zhang, MD, and Xiaofeng Tang, MD involved in data cleaning, data analysis, mortality follow-up, and verification. Yan Li, MD and Dingliang Zhu, MD, PhD contributed to critical revision or important intellectual content. All authors have read and approved the final manuscript.

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