

## Postprint: Correlation Between Disease Duration and Autonomic Nervous System Impairment in Primary Care Elderly Hypertensive Patients in Ningxia Hui Autonomous Region Using Single-Lead Wearable ECG Devices

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### Abstract

**Background:** Hypertension is a major chronic disease managed in primary healthcare institutions in China. Cardiac autonomic dysfunction is a primary cause of blood pressure dysregulation and adverse cardiovascular events. Therefore, exploring the relationship between elderly hypertensive patients and the autonomic nervous system using efficient and portable single-lead wearable ECG devices in primary healthcare institutions can provide simple, efficient, low-cost, and sustainable appropriate methods and objective evidence for the management of hypertensive patients and the prevention and control of cardiovascular diseases at the primary level.

**Objective:** To explore the correlation between disease duration and autonomic nerve impairment in elderly hypertensive patients in primary healthcare institutions of Ningxia Hui Autonomous Region using single-lead wearable ECG devices.

**Methods:** A total of 2137 hypertensive patients aged over 65 years from 20 primary healthcare institutions in Ningxia Hui Autonomous Region, whose data were collected via single-lead wearable ECG devices and uploaded to a cloud platform from January 2022 to December 2022, were selected as study subjects. Data including 72-hour ECG recordings, basic patient information, mental health status, and lifestyle factors collected by the cloud platform were gathered. Based on the heart rate variability (HRV) time-domain parameter standard deviation of all normal-to-normal RR intervals (SDNN), autonomic nerve impairment was categorized into a normal group (SDNN > 100ms) with 470 cases and an abnormal group (SDNN ≤ 100ms) with 1667 cases. Confounding factors

were adjusted using 1:1 propensity score matching with a caliper value of 0.02. Inverse probability of treatment weighting was used as a reference to validate the matching effect of propensity score matching. Univariate and multivariate logistic regression analyses were employed to examine the relationship between hypertension duration and autonomic nerve injury. Furthermore, the effectiveness of propensity score matching was verified. Sensitivity subgroup analyses before and after matching were conducted based on hypertension duration and autonomic nerve injury. Additionally, restricted cubic spline (RCS) analysis was used to test for nonlinear association and dose-response effect between hypertension duration and autonomic nerve impairment.

Results: A total of 479 cases of grade 1 hypertension and 1658 cases of grade 2 hypertension were collected. Disease duration was <5 years in 1203 cases, 5-10 years in 753 cases, 10-15 years in 110 cases, 15-20 years in 41 cases, 20-30 years in 26 cases, and ≥30 years in 4 cases. Multivariate logistic regression analysis revealed that autonomic nerve impairment in hypertensive patients was positively correlated with disease duration both before and after matching ( $P<0.001$ ). Subgroup analysis showed that before and after matching, the correlation between disease duration and autonomic nerve impairment was stronger in hypertensive patients under 80 years old, with lower education level, and without comorbid coronary heart disease; and in female hypertensive patients with comorbid obstructive sleep apnea (OSA), with statistically significant differences ( $P<0.05$ ) and significant interaction effects ( $P<0.05$ ). However, RCS analysis showed no nonlinear relationship between disease duration and autonomic nerve impairment in hypertensive patients before and after matching.

Conclusion: Disease duration is positively correlated with autonomic nerve impairment in elderly hypertensive patients at the primary care level in Ningxia Hui Autonomous Region. Primary healthcare institutions should strengthen health education for patients and improve treatment compliance, which can delay autonomic nerve impairment in hypertensive patients.

## Full Text

### **Study on the Correlation between the Course of Hypertension and Autonomic Nervous System Damage in Elderly Patients in Primary Care Institutions in Ningxia Hui Autonomous Region Based on Single-Lead Wearable Electrocardiogram Device**

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## Abstract

### Background

Hypertension is a major chronic disease managed by primary healthcare institutions in China. Cardiac autonomic dysfunction is a primary cause of blood pressure dysregulation and adverse cardiovascular events. Therefore, exploring the relationship between elderly hypertensive patients and the autonomic nervous system using efficient and portable single-lead wearable electrocardiogram (ECG) devices in primary care settings can provide a simple, efficient, low-cost, and sustainable approach with objective evidence for hypertension management and cardiovascular disease prevention.

### Objective

To investigate the correlation between the duration of hypertension and autonomic nervous system damage in elderly hypertensive patients in primary care institutions of Ningxia Hui Autonomous Region using single-lead wearable ECG devices.

### Methods

A total of 2,137 hypertensive patients aged 65 years or older from 20 primary care institutions in Ningxia Hui Autonomous Region were enrolled between January 2022 and December 2022. Participants' 72-hour ECG data and basic information, mental health status, and lifestyle data were collected via a cloud platform using single-lead wearable ECG devices. Autonomic nerve damage was assessed based on heart rate variability (HRV) time-domain parameters, specifically the standard deviation of all normal sinus RR intervals (SDNN). Patients were divided into a normal group (SDNN > 100 ms, n = 470) and an abnormal group (SDNN ≤ 100 ms, n = 1,667). Propensity score matching was performed at a 1:1 ratio to adjust for confounding factors, with a caliper value of 0.02. Inverse probability weighting was used as a reference to validate the matching effect. Univariate and multivariate logistic regression analyses were conducted to examine the relationship between hypertension duration and autonomic nerve damage. Subgroup analyses were performed before and after matching based on hypertension duration and autonomic nerve damage. Restricted cubic spline (RCS) analysis was used to test for nonlinear associations and interaction effects

between hypertension duration and autonomic nerve damage.

### Results

Among the patients, 479 had grade 1 hypertension and 1,658 had grade 2 hypertension. Disease duration distribution was as follows: 1,203 patients (<5 years), 753 patients (5-10 years), 110 patients (10-15 years), 41 patients (15-20 years), 26 patients (20-30 years), and 4 patients (>30 years). Multivariate logistic regression analysis revealed a positive correlation between autonomic nerve damage and hypertension duration both before and after matching ( $P < 0.001$ ). Subgroup analysis showed that before matching, the correlation was stronger in patients under 80 years, those with lower education levels, and those without comorbid coronary heart disease ( $P < 0.05$ ), with significant interaction effects ( $P < 0.05$ ). After matching, the correlation was more pronounced in female patients and those with comorbid obstructive sleep apnea (OSA) ( $P < 0.05$ ), also with significant interaction effects ( $P < 0.05$ ). However, RCS analysis showed no nonlinear relationship between hypertension duration and autonomic nerve damage before or after matching.

### Conclusion

In elderly hypertensive patients from primary care institutions in Ningxia Hui Autonomous Region, the duration of hypertension is positively correlated with autonomic nerve damage. Primary care institutions should strengthen health education to improve treatment adherence, which may delay autonomic nerve damage in hypertensive patients.

**Keywords:** Hypertension; Elderly; Disease course; Autonomic nerve; Primary health service centers; Single-lead wearable electrocardiogram monitoring

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### Introduction

Hypertension is a leading cause of premature death and cardiovascular disease worldwide [1], with up to one-third of hypertension-related deaths associated with sudden cardiac death [2]. China has 245 million hypertensive patients [3], and effective management of grade 1-2 hypertensive patients could prevent an estimated 803,000 cardiovascular events annually [3]. In China, the prevalence of hypertension among adults is approximately 27.5%, but it reaches 54.4%, 65.2%, and 66.7% in those aged 60-<70, 70-<80, and >80 years, respectively [4]. With severe population aging, managing elderly hypertensive patients and assessing their cardiovascular risk is a core strategy to curb the epidemic of cardiovascular and cerebrovascular diseases and reduce complications such as stroke, coronary heart disease, and heart failure [5].

Cardiac autonomic dysfunction is a major cause of blood pressure dysregulation and adverse cardiovascular events [6], not only promoting the development and progression of hypertension [7] but also interacting reciprocally with target organ damage to the heart, brain, kidneys, and blood vessels [8-9]. Therefore,

autonomic nerve damage can serve both as an adjunct diagnostic marker for hypertension [10] and as a predictor of hypertensive events and target organ damage [11]. Heart rate variability (HRV), the phenomenon of periodic variation in sinus rhythm over time due to autonomic tone changes, objectively reflects autonomic nervous system regulation of the heart and blood vessels [12] and is a recognized quantitative indicator for cardiovascular disease prevention and sudden cardiac death risk prediction [13-14]. Among its time-domain parameters, the standard deviation of NN intervals (SDNN) serves as a surrogate marker for the severity of autonomic nerve damage [15]. Studies show that  $SDNN < 100$  ms not only indicates autonomic nerve damage but also predicts the progression of cardiovascular events and target organ damage in hypertensive patients [16-17].

In China's three-tier healthcare system, primary care institutions (community health service centers/stations, township hospitals, and village clinics) are the main front for elderly hypertension management. Understanding the relationship between disease duration and autonomic nerve damage in hypertensive patients managed at the primary care level can inform precise prevention and control measures, thereby improving blood pressure control rates and reducing cardiovascular morbidity and mortality. Wearable ECG devices have demonstrated unique advantages in the full lifecycle management of cardiovascular diseases [18-19]. Single-lead wearable ECG devices, in particular, are widely used in primary care due to their simple application, comfort, and portability, which improve patient compliance and experience [20-21]. However, their limited lead configuration and cloud platform functionality restrict their application scope. This study innovatively utilized single-lead wearable ECG devices to collect 72-hour ECG data from hypertensive patients aged 65+ in Ningxia's primary care institutions, using SDNN as an indicator of autonomic nerve damage. Combined with patient data collected via the cloud platform, we analyzed the relationship between disease duration and autonomic nerve damage to provide a simple, efficient, low-cost, and sustainable approach for hypertension management and cardiovascular disease prevention.

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## Methods

**Study Population and Design** We enrolled 2,137 hypertensive patients aged 65 years or older from 20 primary care institutions in Ningxia Hui Autonomous Region between December 2021 and December 2022. Inclusion criteria were: (1) age  $\geq 65$  years; (2) history of grade 1 or 2 hypertension; (3) regular use of antihypertensive medication under primary care physician guidance; and (4) no cognitive impairment. Exclusion criteria were: (1) incomplete ECG data, basic information, lifestyle habits, or mental health data; and (2) never having received antihypertensive drug treatment. The study adhered to the Declaration of Helsinki and was approved by the Ethics Committee of Yinchuan First People's Hospital (KT-2021-116). All participants provided informed consent.

**Hypertension Classification and Disease Duration** Hypertension grading and diagnosis dates were obtained from the patient management cloud platform. Classification followed the *Chinese Guidelines for the Management of Hypertension in the Elderly 2023* [5]: Grade 1 hypertension (systolic 140-159 mmHg and/or diastolic 90-99 mmHg) and Grade 2 hypertension (systolic 160-179 mmHg and/or diastolic 100-109 mmHg). Disease duration was calculated from diagnosis date to data collection date and categorized as <5 years, 5-10 years, 10-15 years, 15-20 years, 20-30 years, and  $\geq 30$  years.

**Arrhythmia Diagnosis and SDNN Analysis** Primary care physicians fitted patients with a single-lead wearable dynamic ECG recorder (Model 401, Sichuan Medical Device Registration No. 20212070096) manufactured by Chengdu Xinhui Juyuan Technology Co., Ltd. to collect 72-hour ECG data uploaded to the cloud platform. Professional ECG physicians accessed the data, excluded unrecognizable interference, correctly mislabeled RR intervals (normal sinus and arrhythmic), diagnosed arrhythmia types, and analyzed SDNN values automatically calculated by the system algorithm [22].

**Assessment and Grouping of Autonomic Nerve Damage** Based on HRV time-domain parameter SDNN, patients were grouped into normal (SDNN  $\geq 100$  ms) and abnormal (SDNN < 100 ms) groups [22].

**Assessment of Other Variables** Covariates were collected via the patient management cloud platform: (1) Basic information: age, sex, BMI, ethnicity, occupation, education level, urban/rural residence, and medical history [diabetes, coronary heart disease, and stroke diagnosed according to respective guidelines [23-25]]. (2) Obstructive sleep apnea (OSA): Assessed using the apnea-hypopnea index (AHI) calculated via cyclic variation of heart rate (CVHR) technology [26]; moderate-to-severe OSA was defined as AHI  $\geq 15$  events/hour (CVHR shows high sensitivity and specificity for moderate-to-severe OSA [26-27]). (3) Mental health: Normal defined as Self-Rating Depression Scale (SDS) score < 53 and Self-Rating Anxiety Scale (SAS) score < 50; abnormal as SDS  $\geq 53$  and/or SAS  $\geq 50$  [28-29]. (4) Lifestyle: Smoking (never, former [quit >5 years], current), alcohol consumption (never, former [quit >5 years], current), tea drinking (never, occasionally [ $< 3$  days/week], regularly [ $\geq 4$  days/week]), and exercise (never, short duration [ $< 1$  hour/day], long duration [ $\geq 1$  hour/day]).

**Statistical Analysis** Data were collected via a proprietary patient management cloud platform. Statistical analysis was performed using RStudio 4.1.1 and Python. Normally distributed continuous variables were expressed as mean  $\pm$  standard deviation and compared using t-tests or one-way ANOVA. Categorical variables were expressed as percentages and compared using  $\chi^2$  tests. Propensity score matching at 1:1 ratio with a caliper of 0.02 was used to adjust for confounders, with inverse probability weighting as a reference to validate matching

effectiveness. Univariate and multivariate logistic regression analyses examined the relationship between hypertension duration and autonomic nerve damage. Subgroup and sensitivity analyses were conducted before and after matching. RCS analysis tested for nonlinear associations and interaction effects.  $P < 0.05$  was considered statistically significant.

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## Results

**Baseline Characteristics Before and After Matching** Before matching, the cohort included 479 grade 1 and 1,658 grade 2 hypertensive patients. Disease duration distribution was: 1,203 patients (<5 years), 753 (5-10 years), 110 (10-15 years), 41 (15-20 years), 26 (20-30 years), and 4 ( $\geq 30$  years). Significant differences between groups were observed in sex, age, urban/rural distribution, education level, occupation, and comorbidities including coronary heart disease, diabetes, supraventricular premature beats, and sinoatrial block ( $P < 0.05$ ) (Table 1).

To reduce bias and confounding, we performed 1:1 propensity score matching (caliper = 0.02). After matching, 445 patients were successfully matched in each group. Validation using inverse probability weighting showed good balance, with standardized mean differences (SMD)  $< 0.1$  for all variables except BMI grouping (SMD = 0.109), which was considered acceptable given its distribution relative to the outcome (Table 2). The data distribution after matching and weighting is shown in Figure 1 [Figure 1: see original paper].

**Multivariate Logistic Regression Analysis of Hypertension Duration and Autonomic Nerve Damage Baseline by Disease Duration Segments (Before Matching):** Significant differences were observed across duration groups in age, age grouping, urban/rural distribution, education level, occupation, coronary heart disease history, stroke history, parasystole, ventricular pre-excitation, and SDNN abnormality ( $P < 0.05$ ) (Supplementary Table 1).

**Multivariate Analysis:** Using SDNN grouping as the dependent variable (normal = 0, abnormal = 1) and hypertension duration as the independent variable, we constructed three logistic regression models adjusting for significant covariates (Table 3). Before matching, hypertension duration was positively associated with autonomic nerve damage in the overall population ( $P < 0.001$ ), grade 1 hypertension ( $P < 0.001$ ), and grade 2 hypertension ( $P < 0.001$ ). After matching, this association persisted albeit slightly attenuated ( $P < 0.001$  for all groups). Notably, grade 1 hypertensive patients showed a stronger association between disease duration and autonomic damage than grade 2 patients both before and after matching (Table 4).

**Subgroup Analysis Before and After Matching** To assess potential heterogeneity, we performed subgroup analyses. Before matching, the association was stronger in patients aged <80 years, those with lower education levels, and those without coronary heart disease ( $P < 0.05$ ), with significant interaction effects ( $P < 0.05$ ). After matching, the association was more pronounced in female patients and those with OSA ( $P < 0.05$ ), also with significant interaction effects ( $P < 0.05$ ). Forest plots of subgroup interactions are shown in Figure 2 and Figure 3 [Figure 3: see original paper].

**Nonlinear Association Analysis** RCS analysis based on Model 3 visualized the relationship between hypertension duration and autonomic nerve damage. No nonlinear association was detected before or after matching ( $P = 0.0554$  and  $P = 0.2902$ , respectively). However, grade 2 hypertensive patients experienced autonomic damage earlier than grade 1 patients: the risk transition occurred at 4 years for grade 2 versus 5.3 years and 10.3 years for grade 1 patients before and after matching, respectively (Figure 4 [Figure 4: see original paper]).

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## Discussion

**Relationship Between Hypertension Duration and Autonomic Nerve Damage** Previous studies have shown that hypertensive patients exhibit varying degrees of autonomic dysfunction [30], which is independent of other hypertension causes [31] and correlates with ventricular remodeling [32]. Tao et al. [33] found that autonomic damage severity correlates with hypertension severity through HRV time-domain analysis. While hypertension pathogenesis primarily involves increased sympathetic activity [34], with sympathetic tone positively correlating with blood pressure elevation [35], research demonstrates that cardiac autonomic control is dominated by vagal tone under normal conditions, with sympathetic and vagal activity mutually inhibiting to maintain dynamic balance [36-37]. In hypertension, autonomic dysfunction reduces vagal tone while sympathetic dominance prevails [38]. Vagal suppression plays a crucial role in prehypertension and its progression [39], and comprehensive autonomic assessment requires evaluating both sympathetic and vagal components [37]. SDNN, used in this study, is a recognized indicator of combined sympathetic and vagal tone [22]. Additionally, grade 1 hypertensive patients demonstrate lower disease awareness and treatment adherence than grade 2 patients [40], and medication adherence is essential for blood pressure control [41-42].

These findings suggest that primary care physicians should emphasize vagal function modulation to balance cardiac autonomic tone, which may be more important than simply reducing sympathetic tone. Enhanced health education for grade 1 hypertensive patients is needed to improve disease awareness and medication adherence. Although no nonlinear relationship was found, grade 2 patients experienced earlier autonomic damage (at 4 years) compared to grade 1

patients (5.3 and 10.3 years), indicating the need for earlier autonomic screening in grade 2 patients.

**Factors Influencing the Relationship Between Hypertension Duration and Autonomic Damage** In males, sympathetic activity correlates positively with total peripheral resistance and negatively with cardiac output [43]. In females, sympathetic activity influences blood pressure primarily through  $\beta$ -adrenergic receptor-mediated vasodilation [44]. With aging, female  $\beta$ -adrenergic receptor sensitivity declines [45], and estrogen levels that promote vasodilation decrease [46], leading to reduced SDNN [47-48].

Elderly hypertensive patients aged  $\geq 80$  years have higher frailty prevalence [49], and increased blood pressure variability (BPV) correlates with frailty [50]. Elevated BPV indicates enhanced sympathetic-mediated vascular reactivity [51], and frail elderly hypertensive patients often have multiple comorbidities affecting autonomic function [52-54]. Thus, in very elderly patients, autonomic damage correlates more closely with frailty than disease duration. Frailty screening is crucial as it determines benefit from blood pressure reduction [55], and U-shaped relationships between blood pressure and mortality in very elderly patients warrant simultaneous BPV and HRV assessment for precise treatment planning [56].

Coronary heart disease causes acute autonomic imbalance through myocardial ischemia [57], but comorbid patients often receive  $\beta$ -blockers and ACE inhibitors with sympatholytic effects [5], plus statins that inhibit sympathetic excitation [58]. Higher awareness of coronary disease improves treatment adherence [3,59]. OSA disrupts nocturnal autonomic function [60], and when combined with hypertension, exacerbates autonomic damage. Most OSA patients in this study were identified via CVHR technology but remained untreated due to low awareness and treatment rates [61].

Lower education limits access to hypertension knowledge, which independently affects medication adherence [62-64]. Lower socioeconomic status reduces health service accessibility [65-68] and creates chronic stress that activates the autonomic system [67]. Health education significantly improves treatment adherence in primary care hypertensive patients [69], and policy interventions are needed to improve healthcare access for low-income populations. These measures benefit patients and families while significantly impacting hypertension management and cardiovascular disease prevention [3,70].

**Strengths and Limitations** This study's strengths include using propensity score matching with inverse probability weighting validation to improve credibility and generalizability. Subgroup analyses avoided heterogeneity and helped refine management strategies. Unlike previous studies comparing HRV between hypertensive and normotensive individuals [10,17,31], we segmented hypertension duration and integrated grading to provide objective evidence for primary care management. The real-world design reflects clinical practice, and data

from single-lead wearable ECG devices and the cloud platform enable efficient, low-cost, continuous arrhythmia screening and autonomic function assessment, facilitating stratified management and reducing patient burden.

Limitations include lack of data on income, medication types, and adherence. OSA diagnosis relied on algorithmic assessment from the wearable device, which, while validated for moderate-to-severe OSA [26] and reliable in multiple studies [21,71-73], was not confirmed by polysomnography due to limited access and reimbursement. Finally, we used only SDNN rather than multiple HRV parameters for comprehensive sympathetic and vagal assessment, which should be addressed in future research.

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## Conclusion

In elderly hypertensive patients in Ningxia' s primary care institutions, disease duration is positively correlated with autonomic nerve damage, suggesting that hypertension duration is an independent risk factor for autonomic damage. Strengthening health education to improve treatment adherence and blood pressure control can delay autonomic nerve damage in hypertensive patients.

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### Supplementary Material

**Supplementary Table 1.** Baseline characteristics of patients by disease duration segment before matching

*Note: Figure translations are in progress. See original paper for figures.*

*Source: ChinaXiv – Machine translation. Verify with original.*