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Cardiovascular Outcomes in Initial and Sustained Orthostatic Hypotension: A Retrospective Cohort Study

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ABSTRACT

Classic orthostatic hypotension (OH) is a common geriatric disorder and is associated with cardiovascular risk. There is so far too few data available on the prognostic importance of initial OH and the comparison with sustained OH. This study investigated cardiovascular outcomes in initial and sustained OH in a cohort of patients aged ≥50 years. The study included 435 participants; 94 (21.6%) patients had initial (43, 45.7%) or sustained (51, 54.3%) OH, diagnosed by an active orthostatic test using the CNAP monitor. The median follow-up period was 65 months (inter-quartile range, 30 to 71). One hundred and fifty-nine (36.6%) of the patients had the primary outcome (a composite of major adverse cardiovascular events [MACE] and death from any cause), among which 142 (32.6%) had MACE, and 21 (4.8%) died. Analysis through Kaplan–Meier and further Cox regression models for multivariable adjustment both showed that, initial OH increased both the risk of the primary outcome and MACE (HR 2.20, 95% CI 1.39 to 3.50; HR 2.38, 95% CI 1.48 to 3.84), while didn't increase the mortality. In contrast, sustained OH increased both the risk of the primary outcome and MACE (HR 1.77, 95% CI 1.17 to 2.69; HR 1.71, 95% CI 1.09 to 2.70), as well as the mortality (HR 3.32, 95% CI 1.29 to 8.50). In conclusion, the preliminary exploration of this relatively small-sample study indicates that, OH, no matter initial or sustained OH, increased the cardiovascular risk in patients aged ≥50 years, while only sustained OH increased the risk of mortality.

1 | Introduction

Orthostatic hypotension (OH) is an important medical problem that is particularly common in elderly patients with multiple comorbidities and polypharmacy [1, 2]. Classic OH, also known as sustained OH, is defined as a sustained reduction in systolic blood pressure (BP) by at least 20 mmHg and/or reduction in diastolic BP by 10 mmHg within 3 min of standing or 60° head-up tilt [3]. OH is an independent risk factor of mortality and cardiovascular comorbidities linked to increased hospital admissions [4, 5]. A meta-analysis of 15 cohort studies found that individuals with OH had a higher risk of developing heart failure, atrial fibrillation, coronary heart disease, and myocardial infarction [5]. In a number of population-based longitudinal and prospective studies, OH has been a consistent predictor of a higher risk of coronary events, ischemic stroke, cardiovascular disease, and asymptomatic atrial fibrillation [4]. These study findings suggest that OH may be a robust yet under-recognized risk factor of cardiovascular disease-related morbidity and mortality, especially among older adults. Improvements in hemodynamic profiling with continuous BP measurements have helped to uncover sub-types such as sustained OH and initial OH. Initial OH is defined as a transient BP decrease (>40 mmHg systolic and/or >20 mmHg diastolic BP within 15 s of standing) [6]. Initial OH used to be under-reported in epidemiological studies evaluating the initial BP response to standing, due to its requirement for

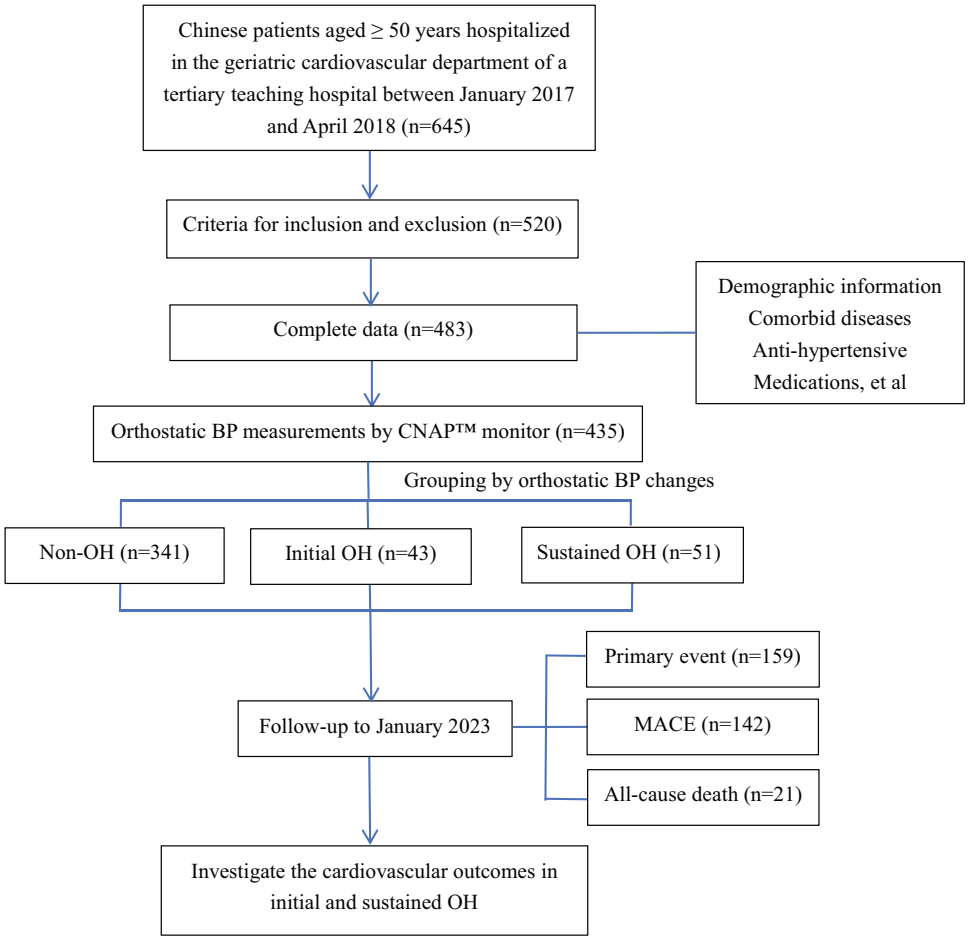

FIGURE 1 | Study flow diagram displaying the process of cohort identification and follow-up. BP, blood pressure; MACE, major adverse cardiovascular events; OH, orthostatic hypotension.

specialized equipment for measurement. Up to now, limited data are available regarding the prognostic importance of initial OH and the comparison between that and sustained OH. Therefore, this study aimed to investigate cardiovascular outcomes in initial and sustained OH through a retrospective cohort study.

2 | Methods

2.1 | Participants

This study was conducted in the geriatric cardiovascular department of a tertiary teaching hospital between January 2017 and April 2018. During this period, all consecutive patients hospitalized in the geriatric cardiovascular department were screened. The inclusion criteria were as follows: (1) patients aged ≥50 years (in both sexes); (2) those who had the ability to stand up actively from the supine position and keep fit for 3 min; and (3) those who had the ability to cooperate well with the measurements by the CNAP monitor. Patients were excluded if they (1) were unable to stand for 3 min; (2) needed immediate treatment; (3) had a cognitive disorder, thus were not able to provide informed consent; (4) had irregular heart rhythm such as atrial fibrillation; and (5) had incomplete follow-up data. All patients were followed up via face-to-face or telephone visits at intervals of 6 months up to January 2023. A flow chart of the study is shown in Figure 1.

This study was approved by the institutional review board and ethics committee of the participating center (registration number: 2023[049-001]). Data from the participants and investigators were anonymized.

2.2 | Protocol

Patients' demographic information, medical comorbidities, medications, and associated clinical data were extracted from the medical records in the geriatric cardiovascular department during the study period. The diagnoses of hypertension, coronary heart disease, dyslipidemia, and diabetes mellitus were conducted according to the associated guidelines [7–11]. All participants underwent measurement of body mass index (BMI) and serum creatinine.

For continuous measurements, a CNAP monitor (CN Systems Medizintechnik AG, Graz, Austria), which is a continuous noninvasive arterial pressure measurement device, was used. Based on the volume clamp method, this device monitors the blood flowing (measured by light absorption) into the finger and translates blood flow oscillations sensed by the encircling finger cuff into continuous pulse pressure waveforms and beat-to-beat BP values. The CNAP monitor has been validated for arterial BP and heart rate measurements [12].

Continuous noninvasive orthostatic BP measurements were performed by two fixed-trained researchers. The orthostatic test was assessed by actively standing up for 3 min after a 5-min supine resting period. All orthostatic tests were conducted between 9:00–11:00 a.m. and 2:00–5:00 p.m. during the day, and more than 2 h after meals to avoid possible interference with postprandial hypotension. An appropriately sized finger cuff of the CNAP monitor was affixed to each participant's finger, and the measurement hand was placed at the heart level. The beat-to-beat measurements of systolic BP, diastolic BP, and heart rate of all participants were performed and recorded in the supine position and within 15 s and 3 min after directly active standing, without special stops in a sitting position. Initial OH was defined as a transient decrease in systolic BP by >40 mmHg and/or diastolic BP by >20 mmHg within 15 s of active standing, with BP recovery between 15 s and 3 min of standing (decrease in systolic BP <20 mmHg and diastolic BP <10 mmHg). Sustained OH was defined as a sustained decrease in systolic BP by ≥20 mmHg and/or diastolic BP by ≥10 mmHg at 3 min after standing.

2.3 | Primary and Secondary Outcomes

The primary outcome was a composite of major adverse cardiovascular events (MACE) and death from any cause during the follow-up period. The secondary outcomes included MACE and death from any cause as two separate outcomes. MACE was defined as cardiovascular death, myocardial infarction, angina pectoris, heart failure, or atrial fibrillation.

2.4 | Statistical Analysis

IBM SPSS (version 22.0; IBM Corp, Armonk, NY) was used for the statistical analyses. Continuous variables are presented as the mean ± standard deviation (SD) or median (lower quartile, upper quartile) and were compared using an independent Student's *t*-test or the Mann–Whitney U-test. Categorical variables are presented as percentages (%) and were compared using Pearson's χ^2-test or Fisher's exact test. Multiple comparisons were performed using one-way ANOVA or the Kruskal–Wallis test with Dunn's or LSD post hoc test, and Bonferroni correction was performed to correct for multiple comparisons. Kaplan–Meier analysis was used to evaluate the timing of outcome occurrences and a Log-rank test was conducted. After adjusting for variables that were known to be strongly associated with the outcomes or differed significantly by univariate analysis, multivariate Cox proportional hazards models were developed to identify the predictors of outcomes. Hazard ratios (HRs) and 95% confidence intervals (CIs) were obtained from Cox proportional hazards regression models. A p value of <0.05 was considered to be statistically significant for all tests. Figures were manufactured by R version 4.3.3.

3 | Results

3.1 | Patient Characteristics

Of the 645 patients hospitalized during the study period, 56 could not stand for 3 min or needed immediate treatment, 18 had a cognitive disorder and were not able to provide informed consent, 50 had an irregular heart rhythm, 48 did not undergo the orthostatic test, and 37 had incomplete follow-up data. Finally, we included 435 patients in the present analysis. The patients were followed for a median of 65 months (inter-quartile range, 30 to 71), for a total of 23 166 patient months of follow-up. Participants' characteristics are shown in Table 1. The mean age was 70.5 ± 12.3 years, and 78.6% were male. A total of 94 (21.6%) patients had OH (initial or sustained), and among them, 43 (45.7%) had initial OH, and 51 (54.3%) had sustained OH. Nineteen of the 51 patients with sustained OH had a decrease of >40 mmHg in systolic BP and/or >20 mmHg in diastolic BP within 15 s of active standing.

No significant differences in sex, BMI, medical history of hypertension, coronary heart disease, dyslipidemia, anti-hypertensive medication use, or serum creatinine were observed between the non-OH, initial OH, and sustained OH groups (p values > 0.05). In contrast, significant differences were observed in age and comorbidity of diabetes among the groups ($p = 0.005$ and 0.009, respectively). Compared to the patients in the non-OH and initial OH groups, the patients with sustained OH were older (75.8 ± 10.2 vs. 69.9 ± 12.2 years; $p = 0.001$ and 75.8 ± 10.2 vs. 70.1 ± 14.3 years; $p = 0.024$). Compared to the patients in the non-OH and sustained OH groups, the patients with initial OH were less likely to have comorbid diabetes (14.0% vs. 32.3%; p 0.013 and 14.0% vs. 43.1%; $p = 0.003$).

Sustained OH group had higher supine systolic BP compared to non-OH and initial OH (126.6 ± 15.7 vs. 117.9 ± 15.7 mmHg; $p = 0.001$ and 126.6 ± 15.7 vs. 115.7 ± 13.4 mmHg; $p = 0.001$), while no difference was seen in supine diastolic BPs and heart rates among the three groups. As expected from the definition, in non-OH group, the decrease of orthostatic systolic and diastolic BP within 15 s was less than those in initial (−11 .0 [−18.0, 0] vs. −28.0 [−36.0, −21.0] mmHg; $p < 0.001$ and −7.0 [−11.0, 0] vs. 22.0 [−25.0, −20.0] mmHg; $p < 0.001$) and sustained OH (−11 .0 [−18.0, 0] vs. −20.0 [−34.0, −10.0] mmHg; $p < 0.001$ and −7.0 [−11.0, 0] vs. −15.0 [−21.0, −9.0] mmHg; $p < 0.001$). The decrease of orthostatic systolic BP within 15 s between initial and sustained OH showed no significant difference, while the decrease of diastolic BP in initial OH was larger than that in sustained OH (−22.0 [−25.0, −20.0] vs. −15.0 [−21.0, −9.0] mmHg; $p < 0.001$). Sustained OH tended to have larger orthostatic systolic and diastolic BP declines at 3 min, compared to non-OH (−19.0 [−26.0, −10.0] vs. 4.0 [−4.0, 13.0] mmHg; $p < 0.001$ and −11.0 [−15.0, −10.0] vs. 4.0 [−1.0, 12.0]; $p < 0.001$) and initial OH (−19.0 [−26.0, −10.0] vs. 0 [−7.0, 8.0] mmHg; $p = 0.002$ and −11.0 [−15.0, −10.0] vs. 0 [−7.0, 7.0]; $p < 0.001$), however less orthostatic HR change at 3 min (4.0 [0, 9.0] vs. 7.0 [4.0, 11.0] beats/min; $p < 0.001$ and 4.0 [0, 9.0] vs. 8.0 [3.0, 11.0] beats/min; $p = 0.036$).

3.2 | Outcomes

In the entire cohort, 159 (36.6%) of the patients had the primary outcome. The Kaplan–Meier analysis showed initial OH and sustained OH had significantly higher rates than non-OH (initial OH vs. non-OH, $p = 0.004$; sustained OH vs. Non-OH, $p < 0.001$; Figure 2A), with rates of 32.0%, 51.2%, and 54.9% for non-OH, initial OH, and sustained OH, respectively. No

TABLE 1 | Characteristics of patients stratified by the types of OH.

Variable	Non-OH ($n = 341$)	Initial OH ($n = 43$)	Sustained OH ($n = 51$)	Overall p value
Demographic				
Male, n (%)	264 (77.4)	38 (88.4)	40 (78.4)	0.256
Age, years	69.9 ± 12.2[b]	70.1 ± 14.3[c]	75.8 ± 10.2[b,c]	**0.005**
BMI, kg/m^2	25.0 ± 3.1	24.9 ± 3.3	24.7 ± 4.0	0.868
Comorbid diseases, n (%)				
Hypertension	243 (71.3)	26 (60.5)	42 (82.4)	0.063
Coronary heart disease	181 (53.1)	19 (44.2)	32 (62.7)	0.195
Dyslipidemia	273 (80.1)	34 79.1)	39 (76.5)	0.836
Diabetes mellitus	110 (32.3)[a]	6 (14.0)[a,c]	22 (43.1)[c]	**0.009**
Medications, n (%)				
ACEI/ARB	153 (44.9)	15 (34.9)	21 (41.2)	0.434
Beta-blockers	179 (52.5)	22 (51.2)	26 (51.0)	0.970
Calcium antagonists	123 (36.1)	14 (32.6)	20 (39.2)	0.799
Diuretics	35 (10.3)	2 (4.7)	6 (11.8)	0.454
alpha-receptor blockers	56 (16.4)	8 (18.6)	15 (29.4)	0.080
Number of anti-hypertensive medications	1.0(1.0, 2.0)	1.0(1.0, 2.0)	2.0 (1.0, 2.0)	0.523
Clinical parameters				
Serum creatinine, μmol/L	92.6 ± 54.5	85.6 ± 14.1	97.0 ± 27.7	0.563
Supine systolic BP, mmHg	117.9 ± 15.7[b]	115.7 ± 13.4[c]	126.6 ± 15.7[b,c]	**<0.001**
Supine diastolic BP, mmHg	68.8 ± 9.2	70.2 ± 7.2	68.7 ± 8.8	0.593
Supine HR, beats/min	65.6 ± 10.4	65.7 ± 11.4	64.7 ± 9.7	0.833
Orthostatic systolic BP change within 15 s, mmHg	−11 .0 (−18.0, 0)[a,b]	−28.0 (−36.0, −21.0)[a]	−20.0 (−34.0, −10.0)[b]	**<0.001**
Orthostatic diastolic BP change within 15 s, mmHg	−7.0 (−11.0, 0)[a,b]	−22.0 (−25.0, −20.0)[a,c]	−15.0 (−21.0, −9.0)[a,b,c]	**<0.001**
Orthostatic HR change within 15 s, beats/min	9.0 (5.0, 13.0)[b]	9.0 (4.0, 15.0)[c]	6.0 (2.0, 10.0)[b,c]	**0.003**
Orthostatic systolic BP change at 3 min, mmHg	4.0 (−4.0, 13.0)[b]	0 (−7.0, 8.0)[c]	−19.0 (−26.0, −10.0)[b,c]	**<0.001**
Orthostatic diastolic BP change at 3 min, mmHg	4.0 (−1.0, 12.0)[a,b]	0 (−7.0, 7.0)[a,c]	−11.0 (−15.0, −10.0) [b,c]	**<0.001**
Orthostatic HR change at 3 min, beats/min	7.0 (4.0, 11.0)[b]	8.0(3.0, 11.0)[c]	4.0 (0, 9.0)[b,c]	**0.002**

Note: P values in bold mean $p < 0.05$ and were considered to be statistically significant.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; HR, heart rate; OH, orthostatic hypotension.

[a]Significant difference between non-OH and initial OH.

[b]Significant difference between non-OH and sustained OH.

[c]Significant difference between initial OH and sustained OH.

significant difference was shown between initial and sustained OH ($p > 0.05$). The rates of MACE in the non-OH, initial OH, and sustained OH groups were 28.7% ($n = 98$), 48.8% ($n = 21$), and 45.1% ($n = 23$), respectively. The Kaplan–Meier curve is presented in Figure 2B and illustrates that the initial and sustained OH curve is significantly steeper than the non-OH curve ($p = 0.002$, 0.006), while there was no difference between initial and sustained OH ($p > 0.05$). In contrast, as for mortality, the patients with sustained OH had a higher rate than the ones with initial OH and without OH (sustained OH vs. non-OH, $p < 0.001$; sustained OH vs. initial OH, $p = 0.029$; Figure 2C), with mortality of 3.5% ($n = 12$), 2.3% ($n = 1$), and 15.7% ($n = 8$) for non-OH, initial OH, and sustained OH, respectively. However, no difference was seen between initial OH and non-OH ($p > 0.05$).

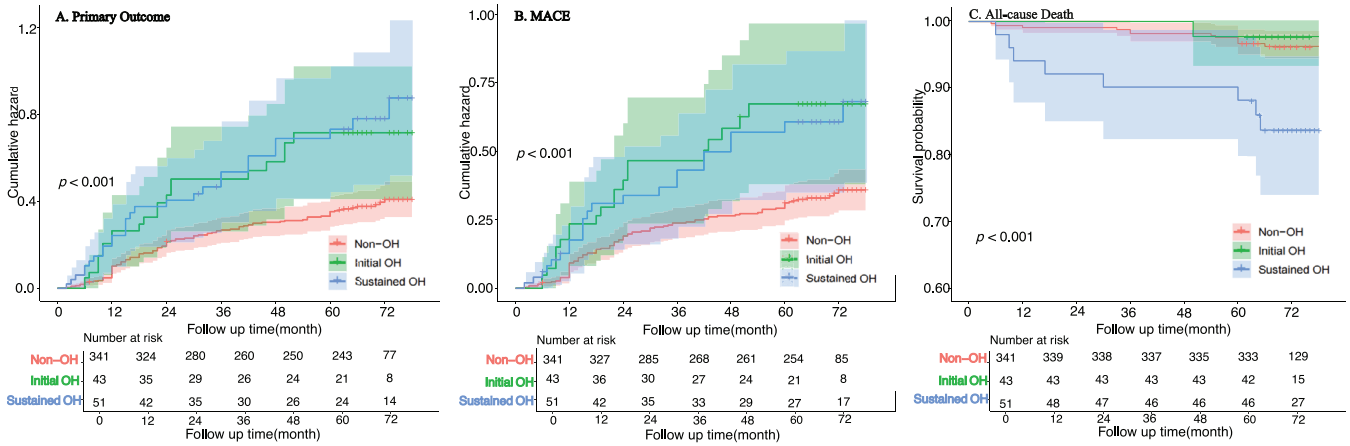

FIGURE 2 | Primary outcome and MACE and all-cause death. Shown is the cumulative hazard of the primary outcome, defined as a composite of major adverse cardiovascular events (MACE) and death from any cause (Panel A), and MACE, defined as cardiovascular death, myocardial infarction, angina pectoris, heart failure or atrial fibrillation (Panel B). Also shown is all-cause mortality (Panel C). MACE, major adverse cardiovascular events; OH, orthostatic hypotension.

TABLE 2 | Effect of OH types on primary and secondary outcomes.

OH types	HR	95% CI	*p* value
Primary outcomes			
Non-OH	1(ref)		
Initial OH	2.20	1.39 to 3.50	**0.001**
Sustained OH	1.77	1.17 to 2.69	**0.007**
MACE			
Non-OH	1(ref)		
Initial OH	2.38	1.48 to 3.84	**<0.001**
Sustained OH	1.71	1.09 to 2.70	**0.020**
Mortality			
Non-OH	1(ref)		
Initial OH	0.49	0.06 to 3.88	0.495
Sustained OH	3.32	1.29 to 8.50	**0.013**

Note: P values in bold mean $p < 0.05$ and were considered to be statistically significant.

Abbreviations: CI, confidence interval; HR, Hazard ratios; MACE, major adverse cardiovascular events; OH, orthostatic hypotension.

3.3 | Prognostic Value After Multi-Variable Adjustment

After conducting Cox univariate analysis on the factors in Table 1 that may be related to the primary and secondary outcomes, meaningful factors with $p < 0.05$, such as gender, age, coronary heart disease, number of anti-hypertensive medications, and OH types, were selected for further multivariate analysis using the Cox model. After the adjustment above, initial OH remained associated with primary outcomes and MACE (HR 2.20, 95% CI 1.39 to 3.50; HR 2.38, 95% CI 1.48 to 3.84), but not with overall mortality (HR 0.49, 95% CI 0.06 to 3.88; Table 2). However, the association between sustained OH and primary outcomes, MACE, as well as overall mortality, remained significant, with an adjusted HR of 1.77 (95% CI 1.17 to 2.69), 1.71(95% CI 1.09 to 2.70), and 3.32(95% CI 1.29 to 8.50), respectively. In the Cox regression models, we also observed that age, coronary heart disease, and serum creatinine were associated with the primary outcome, with HR of, respectively, 1.03 (95% CI 1.01 to 1.04), 2.58 (95% CI 1.77 to 3.76), and 1.01 (95% CI 1.00 to 1.01). Similarly, we found an HR of 3.11 (95% CI 2.13 to 4.53) of coronary heart disease, and 1.00 (95% CI 1.00 to 1.01) of serum creatinine associated with MACE. As for mortality, age and serum creatinine were found to be associated with it, with adjusted HR of 1.18 (95% CI 1.11 to 1.26) and 1.01 (95% CI 1.00 to 1.01), respectively, while there was no statistically significant association with other factors. The HRs for the other covariates included in the regression analysis can also be found in online Supporting Information.

4 | Discussion

The study results show that OH is common in patients ≥50 years and is present in up to 21.6% of the studied patients, among whom 45.7% had initial OH and 54.3% had sustained OH, consistent to the prevalence in previous studies, which varies to the population characteristics, comorbidities, and medications [13–14]. Basic characteristics' comparison showed that, the patients with sustained OH tended to be older, compared to non-OH and initial OH. Population-based studies have showed that, the recovery of BP after active standing is often delayed in older adults [15], which may due to a normal physiological decline in baroreceptor sensitivity and the age-associated increased prevalence of autonomic neurodegenerative diseases, such as diabetes-related autonomic neuropathy [14]. As a consequence, the patients with sustained OH in this study also showed higher comorbidity of diabetes in our study. Surprisingly, the rate of comorbidity of diabetes was even higher in non-OH compared to the initial OH in the study. On one hand, immediately BP' drop, sometimes even with seeing black spots, upon standing appears to also be fairly common in the youth population [16]; on the other, orthostatic BP dysregulation in patients with diabetes, especially the elderly, could manifest as OH, as well as orthostatic hypertension in this population [17–18]. Community studies have shown that sustained OH is associated with medications, such as diuretics

and alpha-receptor blockers, especially in elderly individuals [19], while there was no significant difference in anti-hypertensive medications between three groups, which may be due to the limited sample size in our study and the low number of the patients taking diuretics and α-receptor blockers (because we had already avoided the use of such medications on frail patients in the geriatric ward).

In this study, we found that both sustained and initial OH increased the cardiovascular risk in patients more than 50 years old, while only sustained OH increased the risk of mortality. Our results on sustained OH were consistent with the conclusions of multiple large, prospective cohort studies: sustained OH for community-dwelling adults are associated with future risk of adverse health outcomes, including frailty [20], cardiovascular diseases [21], and early death [22]. Previous studies on initial OH focused on its association with syncope, especially in young adults [23]. In contrast, our results on initial OH revealed its association with the cardiovascular risk in mid-age and elderly people, filling a gap that was unexplored in previous studies. Specifically, initial OH increased both the risk of the primary outcome and MACE in patients ≥50 years. These results suggest that for mid-age and elderly people with multiple comorbidities and polypharmacy, an immediate drop of BP in less than 3 min to a certain extent is enough to increase the risk of adverse cardiovascular outcomes. In addition, our results show that initial OH did not increase all-cause mortality, suggesting that patients with initial OH may have partially preserved autonomic nervous function for fast recovery of BP and thus are less frail than patients with sustained OH [15]. Compared to initial OH, sustained OH may represent a more severe form of OH. Although the pathophysiology underlying the association of initial or sustained OH with increased cardiovascular risk remains not entirely understood, prolonged hypoperfusion of the heart and the brain [14] may play a role in the pathophysiological mechanism.

In the study, we also observed that coronary heart disease was associated with primary outcome and MACE, as coronary heart disease is a crucial threat to the elderly and public death, and is closely related to myocardial infarction, angina pectoris, heart failure, atrial fibrillation, and cardiovascular death [8]. Besides, the study showed that serum creatinine, a traditional and reliable estimation of renal function [24], was positively associated with primary outcome, MACE, and all-cause mortality. Numerous studies have also shown that patients with chronic kidney disease exhibit an elevated cardiovascular risk manifesting as coronary artery disease, heart failure, arrhythmias, and sudden cardiac death, ranging from stage 1 to 6, as chronic kidney disease causes a systemic, chronic proinflammatory state contributing to vascular and myocardial remodeling processes resulting in atherosclerotic lesions, vascular calcification, and vascular senescence as well as myocardial fibrosis and calcification of cardiac valves [25–27]. With the rise of cardiovascular risk, chronic kidney disease is also associated with a higher risk of mortality, and has become the third fastest-growing cause of death worldwide [28].

Our study had some limitations. First, the participants were the patients hospitalized in the geriatric cardiovascular department. Although we documented a systematic evaluation of combined internal medicine diseases and focused on adverse cardiovascular outcomes, we did not evaluate neurological diseases, such as Parkinson's disease and dementia, which may also be associated with sub-types of OH and neurological adverse outcomes [29]. Second, this was a single-center retrospective cohort study with a limited sample size, and some confounding factors were not fully discussed or addressed. The conclusions need to be further validated in a large-scale, prospective study involving a more diverse population.

5 | Conclusions

The preliminary exploration of this relatively small-sample study indicates that OH, no matter initial or sustained OH, increased the cardiovascular risk in patients ≥50 years. Therefore, both types of OH should not be overlooked in clinical practice. When necessary, beat-to-beat BP measurements are needed to help us identify initial OH. However, only sustained OH increased the risk of mortality, while initial OH didn't increase it. Therefore, sustained OH after 3 min of changing position may represent the severity of OH, deserves more attention, and, if necessary, appropriate clinical intervention.

Author Contributions

Hui Geng, Meilin Liu, and Xiahuan Chen contributed to the conception and design of the study. Hui Geng contributed to data collection, performed the data analyses, wrote the main manuscript text, and prepared the tables. Dingfeng Fang prepared the figures. Meilin Liu supervised the project and participated in the revision of the manuscript. The authors read and approved the final manuscript.

Acknowledgments

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Ethics Statement

The study was approved by the ethics committee of Peking University First Hospital (registration number: 2023[049-001]).

Consent

Informed consent was obtained from all participants.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The dataset generated in the current study is available from the authors upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.