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ASSOCIATION BETWEEN ORTHOSTATIC HYPOTENSION AND FRAILTY IN HOSPITALIZED OLDER PATIENTS: A GERIATRIC SYNDROME MORE THAN A CARDIOVASCULAR CONDITION

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Abstract: *Objectives:* To explore the association between orthostatic hypotension (OH) and frailty for hospitalized older patients and their vulnerable subgroups. *Design:* A prospective, observational cross-sectional study. *Participants:* 693 older patients admitted to a geriatric evaluation and management unit. *Measurements:* Barthel Index, Lawton's instrumental activities of daily living, clinical frailty scale, mini-mental state examination, geriatric depression scale, mini-nutritional assessment, and polypharmacy. *Results:* Overall, the prevalence of OH and frailty was 26% and 36%, respectively. Subjects with OH were older, thinner, more commonly to have weakness, slowness, poorer physical function and higher levels of frailty. The prevalence of OH was substantially increased as higher levels of CFS (p for trend <0.001). Multivariate logistic regression showed significant association between OH and frailty (OR: 1.8, 95% CI: 1.2-2.7), but the association attenuated after adjustment for physical function. (OR: 1.4, 95% CI: 0.7-2.6). Nevertheless, associations between OH and frailty remained significant among vulnerable subgroups like women, subjects having weakness, slowness, poor cognitive function, polypharmacy or any IADL limitation. *Conclusions:* OH in hospitalized older patients was associated with frailty and multiple complex care needs, especially in the vulnerable subgroups. Further study is needed to clarify the roles of OH in clinical practice.

Key words: Frailty, older adults, orthostatic hypotension, comprehensive geriatric assessment.

Introduction

Orthostatic hypotension (OH) is a common but under-recognized condition in older adults that usually co-exist with various complex care needs (1), which may also complicate clinical care for older people. Based on conventional operational definitions, OH is defined as the presence of reduced systolic blood pressure for at least 20 mmHg or 10 mmHg of diastolic blood pressure from supine to standing position (2-4). The reported prevalence of OH in the general population was 5-7 % (5-7), and it became 11-15% among people aged 65 years and over (6, 8), 19% among people aged 80 years and over (6), and even higher among hospitalized older patients (9, 10). OH has been reported to be associated with a wide range of clinical conditions, such as cardiovascular disease, cognitive declines, time to incidental falls, and mortality (11-14). Due to age-related prevalence of OH and the associated adverse health outcomes in older adults, OH has become a clinical challenge and gained extensive research and clinical attentions.

Frailty is an age-related vulnerable state featured by reduced physical reserve, dysregulated homeostasis, poor recovery from stressful events, and cumulative declines in multi-systems (15, 16). Gradually, frailty has become the center of disability prevention and functional re-ablement due to its reversible nature (16). A growing body of evidence showed strong associations between frailty and falls, hospitalization, and mortality when frailty was defined by either phenotypic or index methods (15, 17, 18). Despite the well-developed methodology in frailty assessment, it remains difficult to implement those operational criteria in clinical practice. Therefore, Rockwood, et al., developed a 7-point clinical frailty scale (CFS) and validated its ability in predicting adverse health outcomes,(19), which substantially improved the applications of frailty in clinical settings.

Similar to frailty, OH has also been described as a physical sign that reflected the common pathway of various forms of disordered physiology (4). Although associations between OH and frailty has been observed and OH was proposed to be a biomarker of frailty (9, 12, 20), but no significant association between frailty and OH was identified in a study of 5,692 community-dwelling older adults (7). Therefore, this study aimed to investigate the association between OH and frailty among hospitalized older patients, especially to explore the associations of complex care needs among vulnerable subgroups of these patients.

Methods

Study subjects

The study prospectively enrolled 693 patients aged 65 years admitted to the Geriatric Evaluation and Management Unit

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Table 1
Comparison of characteristics among all participants by orthostatic hypotension

	All	OH(-)	OH(+)	p
n	693	512	181	
Age (years)	81.2±8.2	80.3±8.0	83.6±8.2	<0.001
Men	400(57.7)	277(54.1)	123(68.0)	0.001
Married	517(74.6)	386(75.4)	131(72.4)	0.423
Education (years)	10.9±4.8	10.9±4.7	11.1±4.9	0.563
Smoke	168(24.2)	112(21.9)	56(30.9)	0.014
Drink	141(20.4)	101(19.7)	40(22.1)	0.496
Body mass index (kg/m2)	23.6±3.4	23.7±3.4	23.4±3.3	0.374
Handgrip strength (kg)	26.3±9.5	26.7±9.5	25.1±9.2	0.052
Gait speed (m/s)	0.9±0.3	0.9±0.3	0.8±0.3	<.001
Weakness	229(33.0)	151(29.5)	78(43.1)	0.001
Slowness	290(41.9)	197(38.5)	93(51.4)	0.003
Dynapenia	362(52.2)	247(48.2)	115(63.5)	<.001
CFS	4.1±1.2	3.9±1.2	4.5±1.3	<.001
CFS1-4	440(63.5)	352(68.8)	88(48.6)	<.001
CFS5-7	253(36.5)	160(31.3)	93(51.4)	
Urinary Incontinence	171(24.7)	111(21.7)	60(33.2)	0.002
Polypharmacy	369(53.3)	253(49.4)	116(64.1)	0.001
Hypertension	480(69.3)	355(69.3)	125(69.1)	0.945
Fall	140(20.2)	96(18.8)	44(24.3)	0.109
MNA	12.0±2.1	12.1±2.1	11.7±2.4	0.063
MMSE	24.5±5.3	24.9±5.1	23.6±5.6	0.004
Geriatric depression scale	2.5±2.7	2.6±2.8	2.4±2.4	0.517
Activity of daily livings	94.6±12.5	95.8±10.9	90.9±15.7	<.001
IADL	6.1±2.4	6.4±2.2	5.3±2.8	<.001

Numerical variable expressed as mean ± standard deviation and categorical variable expressed as number (%). OH denotes orthostatic hypotension; CFS denotes clinical frailty scale; MNA denotes mini-nutrition assessment short form; MMSE denotes mini-mental state examination; IADL denotes instrumental activity of daily living; Bold type characters denote statistical significance.

(GEMU) of Zhejiang Hospital between Jan 2017 and Mar 2018. All patients received comprehensive geriatric assessments (CGA) and frailty assessment at admissions by well-trained research nurses. The performance and reporting format was adherent to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (21). The institutional review board of Zhejiang Hospital approved the whole study and all participants signed the written informed consent. All study design and conducted procedures were carried out in accordance with the ethical principles of the Helsinki Declaration.

Comprehensive geriatric assessment and frailty assessment

In this study, CGA was performed by well-trained nurses according to the previous protocol (22). Demographic characteristics collected in this study included age, sex, current smoking in the past six month (yes versus no), and current alcohol drinking in the past six month (yes versus no). Barthel Index was used to measure the activities of daily living(ADL) (23); Lawton's instrumental activities of daily living scale was used to measure the instrumental activities of daily living (IADL) (24). Chinese version of mini-mental state examination (MMSE) was used to evaluate cognitive function, and a MMSE score <24 in literate older adults and <15 in illiterate ones were defined as cognitive impairment. (25). Chinese version of Geriatric Depression Scale-15 (GDS) was used to detect their depressive symptoms (26); mini-nutritional assessment-short form (MNA) was used to define nutritional status (27). The International Consultation on Incontinence Questionnaire-Urinary Incontinence-Short Form (ICIQ-UI-SF) ≥6 was defined as urinary incontinence (28). Polypharmacy was defined as the concomitant use of ≥5 drugs (29). Dominant side handgrip strength was measured by digital dynamometers for three times with an allowed pre-trial at a seated position (30), and the maximum value was selected for analysis. Weakness was defined as <26 kg for men and <18 kg for women (31). Walking speed was measured as a static-start and non-decelerating stop in 6-meter distance, and those who with walking speed <0.8 meter/second were defined as having slowness (31). In this study, frailty was assessed by

7-point clinical frailty scale (CFS), and the score ≥5 points was considered as frailty (19).

Measurement of orthostatic hypotension

OH was evaluated when participants rested in supine position for 10 minutes and then stood up with aids if necessary by research nurses as necessary. Within 3 minutes of standing at orthostatic position, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using the mercury sphygmomanometer. OH was defined as the presence of reduction in systolic blood pressure for at least 20 mmHg or diastolic blood pressure for at least 10 mmHg, or both (2).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation whereas categorical data were expressed as number (percentage). Comparisons between continuous variables were performed by Student's t test or Mann-Whiney U test when appropriate and the comparisons between categorical data were done by Chi square test or Fisher-Exact test when appropriate. Logistic regression was used to explore the association between OH and frailty. All statistical analyses were conducted by the SAS software (version 9.4, SAS Institute Inc, Cary, NC). A p-value from two-sided tests < 0.05, and 95% CIs not spanning the null hypothesis values were considered statistically significant.

Results

Prevalence and demographic characteristics

Table 1 summarized the demographic and clinical characteristics of all participants stratified by the presence of OH or not. Among all subjects, 181 (26.1%) of them had OH, and they were more likely to be thinner, having weakness, slowness, lower levels of physical function and higher levels of frailty. Both OH and frailty were increased with advancing age (both p for trend<0.001) (Figure 1), and the prevalence of OH was substantially increased as higher levels of CFS (p for trend <0.001) (Figure 2).

Multivariate logistic regression

Multivariate logistic regression showed significant association between OH and frailty, but the association attenuated after adjustment for physical function (Table 2). The associations between OH and components of physical frailty, e.g. weakness, and slowness, were all insignificant after adjustment for physical function (data not shown). Age and sex-adjusted logistic regression showed that fall was associated with frailty (OR 2.0 95% CI 1.3-3.1, p=0.02), but not OH (OR 1.3, 95% CI 0.8-1.9, p=0.246). However, associations between OH and frailty remained statistically significant among subgroups, including women, having weakness or slowness, poor cognitive function, having polypharmacy or any IADL limitation (Figure 3).

Figure 1
Prevalence and trend of frailty and orthostatic hypotension by age

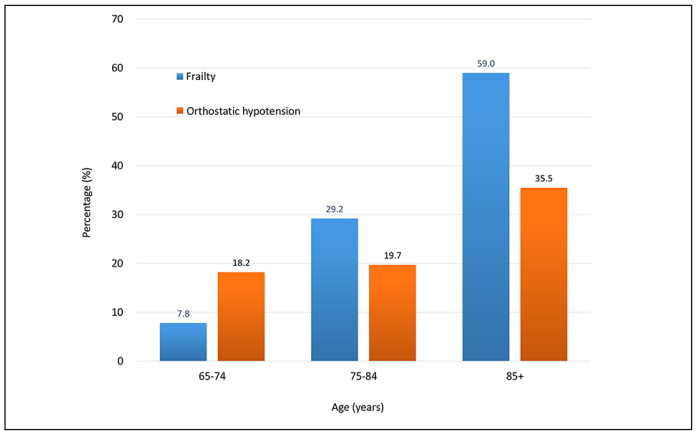


Figure 2
Prevalence of orthostatic hypotension across levels of clinical frailty scale

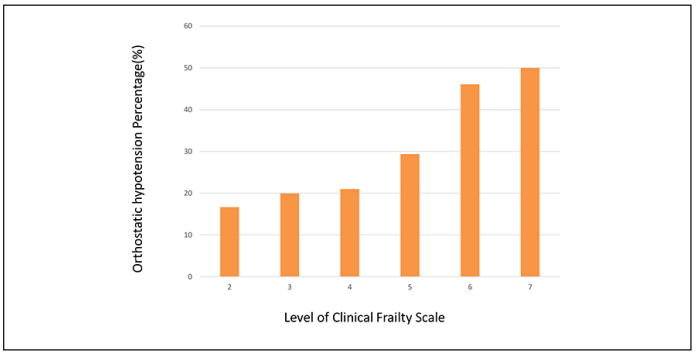
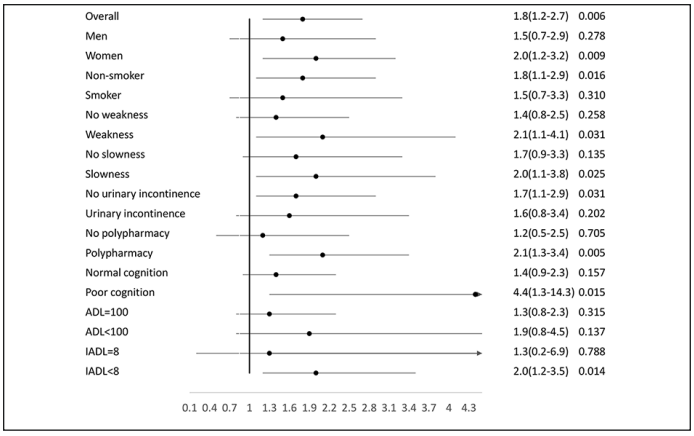


Figure 3
Forest plot showing odds ratios obtained by age and sex adjusted logistic regression according to present or absent of orthostatic hypotension



Discussion

Results of this study clearly showed the association of OH and frailty among hospitalized older patients, but the

Table 2
Logistic regression to explore the association between orthostatic hypotension and frailty

	Model I	Model 2	Model 3	Model 4	Model 5
Dependent=Frailty(CFS≥5)					
OH	1.8(1.2-2.7)	1.8(1.2-2.7)	1.8(1.2-2.7)	1.6(1.0-2.5)	1.4(0.7-2.6)
Dependent=OH					
CFS(per point)	1.8(1.2-2.7)	1.3(1.1-1.6)	1.3(1.1-1.6)	1.3(1.1-1.6)	1.2(0.9-1.5)

OH denotes orthostatic hypotension. CFS denotes clinical frailty scale; Model 1: adjusted for age, sex; Model 2: model 1+ smoke, drink, education; Model 3: model 2+ hypertension, urinary inconstancy; Model 4: model 3+ Mini-mental state examination; Model 5: model 4+ Instrumental activity of daily living

associations attenuated when physical disability was considered. Nevertheless, the association remained significant in the vulnerable subgroups having polypharmacy, weakness, slowness, poor cognitive function or IADL impairment. Since frailty was considered as a "pre-disability" state, so the association may be attenuated when patients became physically disabled. Therefore, it may be more appropriate to conclude that OH was associated with declined physical function, from frailty to disability.

The prevalence of OH was 26% in this study, which was similar to the 22% in a previous study (9), and was higher than the 5-19% among community-dwelling older people (5, 6, 8, 32). In this study, OH was significantly associated with older age, presence of weakness, slowness, urinary incontinence, poor cognitive function, depressive symptoms, as well as functional impairment in both ADL and IADL. Based on these associations, OH met the core concept of geriatric syndrome (33), and may be an emerging one that needs clinical attentions. Nevertheless, recommendations for assessment of OH among older people remained inconsistent in different guidelines. The European Society for Hypertension recommended routine OH assessment for all older adults, but the National Institute for Health and Care Excellence (NICE) recommended OH assessment only when patients presented with symptoms of orthostatic intolerance (34, 35). OH and frailty may share the common physiological pathway in relation to physical disability (4), and most older adults with OH did not present with OH-associated symptoms (36). Therefore, OH in hospitalized older patients may be considered as the consequence of functional impairment, instead of cardiovascular dysregulation. Probably, OH was resulted from impaired venous returned secondary to the reduced muscle mass and strength among frail older people.

Frailty may be defined by phenotypic methods (15), or index methods (37), and both methods were of great prognostic importance in research and public health. However, both methods were difficult to be implemented in clinical settings. On the contrary, CFS was an easy, convenient instrument that fit clinical applications. Moreover, CFS has good correlation with frailty index and similar ability to predict adverse outcomes for older patients (19, 38). CFS-defined frailty also reflected the reversible and dynamic nature of frailty, and has been adopted as the instrument to evaluate the therapeutic effects of post-acute care for frail older adults in Taiwan's National Health Insurance services (39).

Associations between OH and frailty in the previous studies were inconstant that a study of 510 older hospital inpatients disclosed significant association between them (9), as well as the Canadian Study of Health and Aging of 1,347 community-dwelling older adults (12). However, The Irish Longitudinal Study on Ageing (TILDA) failed to establish the association between OH and frailty by either phenotypic or index methods, but OH was defined by measurements of sit-to-stand blood pressure instead of supine-to-stand position in this study (7). To the best of our knowledge, this is the first study to establish association between OH and frailty by using CFS. In particular, the association between OH and frailty was stronger among vulnerable subgroups of these patients, i.e. older, current smokers, presented with weakness, slowness, polypharmacy, and physical disability. Findings of this study were similar to previous ones that defined frailty by phenotypic approach of cumulative deficits (9, 20). Besides, OH has been reported to be associated with cognitive impairment (40), and similar association also existed between frailty and cognitive impairment (41). From this study, we observed stronger association between OH and frailty among patients with poorer cognitive function, and the synergistic effect also appeared in vulnerable subgroups of weakness, slowness, and polypharmacy. Therefore, more clinical attentions should be paid for OH, especially among older patients with multiple comorbid conditions and geriatric syndromes. In addition to adverse clinical outcomes, OH also predicted the decline of motor function (42), which may be resulted from the development of weakness and slowness, the core components of frailty. Although both frailty and OH were predictive for adverse outcomes for older patients, Romero-Ortuno, et al., argued that frailty was superior to OH in predicting falls (20). Nevertheless, OH may also serve to be a biomarker for frailty because loss of muscle mass and strength may cause reduced venous return and subsequent OH (9). Therefore, OH in older hospitalized patients demonstrated strong links with declined physical function and impairments in other functional domains, rather than a simple cardiovascular condition.

Despite all the efforts went into this study, there were still some limitations. First, the cross-sectional study design limited the possibility to establish the causal relationship between

OH and frailty. Although results supported that OH may be a consequence of functional impairment, further longitudinal study is needed for confirmation. Second, this study was an observational design and participants were enrolled from one single hospital, which may limit the potential for extrapolating study results. Third, in this study, OH was defined by single measurement of blood pressure, and the prevalence may differ by multiple measurements.

Conclusions

OH was common among hospitalized older patients, and was significantly associated with frailty and vulnerable subgroups of multiple comorbid conditions or geriatric syndromes. Further longitudinal study is needed to evaluate the causal relationship between frailty and OH, as well as the potential synergistic effects on adverse outcomes.

Ethical Standards Disclosure: The institutional review board of Zhejiang Hospital approved the whole study and signed informed consent were obtained from all participants. The design and procedures of the study were performed in accordance with the principles of the Declaration of Helsinki.

Statement of Potential Conflict of Interest: No potential conflict of interest was reported by the authors.

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