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UTILITY OF THE FRAIL QUESTIONNAIRE IN DETECTING HEART FAILURE WITH PRESERVED EJECTION FRACTION

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Abstract: *Objective:* To test the utility of the FRAIL questionnaire as a screening tool for heart failure. *Design:* Cross sectional study. *Setting:* Chinese older people in Hong Kong. *Participants:* Participants aged 60 years and over were recruited from a territory-wide primary care needs assessment for older people based in community centers as well as two nonacute hospitals. *Measurements:* Questionnaire administered included the five-item FRAIL scale, and information regarding sociodemographic data, smoking and alcohol use, history of cardiovascular disease and diabetes, and heart failure symptoms. Handgrip strength, walking speed and 6 minute walk distance were recorded. Cardiac assessment included electrocardiogram, echocardiography, and blood assay for N-terminal prohormone of B-type natriuretic peptide (NT-proBNP). *Results:* The prevalence of diastolic dysfunction was high, being 52% in the robust group, increasing to 65% in the pre-frail and 85% in the frail group. This finding is accompanied by a corresponding increase in NT-proBNP from 64.18 pg/ml in the robust group, to 118.57 pg/ml in the pre-frail and 167.98 pg/ml in the frail group. Three of the five components of the FRAIL scale, fatigue, resistance and ambulation, were associated with increased odds ratios of diastolic dysfunction among those aged 75 years and older, while resistance alone was associated with increased odds ratio among those less than 75 years old. *Conclusion:* Frailty is associated with heart failure with preserved ejection fraction (HFpEF), and frailty screening may be used to detect undiagnosed HFpEF. The findings support the proposal that HFpEF be considered a geriatric syndrome.

Key words: Frailty, heart failure with preserved ejection fraction, FRAIL scale, NT-proBNP.

Introduction

Frailty is well established as a cornerstone of care of older people, characterized by a state of physiological vulnerability to external stimuli, leading to adverse outcomes such as dependency, hospitalization and mortality (1, 2). Many scales are in use, with similar predictive characteristics in the clinical setting. Since the prevalence of pre-frailty and frailty among community-living older people in many countries range from approximately 50% and 10% respectively (3), and reversibility is possible (4, 5) community screening using a quick tool such as the FRAIL scale that does not require professionals to administer has been shown to be useful in detecting conditions that require further management (6, 7).

Inflammageing has been proposed as an underlying etiology of the frailty syndrome as well as cardiovascular diseases (8). For example the prevalence of both heart failure and frailty increase exponentially with age (1, 9). Studies have documented substantial undetected cardiac dysfunction among older community-living adults. A UK study of people aged 85-89 years using domiciliary echocardiography showed that two-thirds had symptomatic dyspnea, with 26% having undiagnosed and significant left ventricular dysfunction, among whom 20% had diastolic dysfunction with preserved ejection fraction (HFpEF) (10). The ARIC study showed an independent relationship between frailty, left ventricular hypertrophy and increased left atrial dimensions among 3991 older adults with a mean age of 75 years (11). In very few studies examining the longitudinal transition from diastolic dysfunction to HF, the 3-year cumulative probability was 11.6% (12), with adjusted hazard ratios ranging from 1.32 (95% CI, 1.01-1.71) (13) to 1.81 (95% CI, 1.01-3.48) (14). Another study documented a close relationship between frailty and sarcopenia in HFpEF, concluding that the management program should include muscular training and nutritional intervention (15). Recent studies have also proposed that HFpEF could be considered as part of the geriatric syndrome, with common underlying etiologies, clinical presentation, and management (16, 17).

The use of a brief questionnaire such as the FRAIL scale in community screening could be implemented on a wide scale, and since three of the constituent questions may be interpreted as symptoms of heart failure, it is possible that this scale may also be used as a screening for undetected heart failure, enabling early detection and management. This question is addressed in a study of community-living older people aged 60 years and over, where cardiological investigations were carried out among three groups according to the FRAIL scale classification: robust, pre-frail, and frail.

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Method

Participants

Participants were recruited from a territory-wide primary care needs assessment for older people based in community centres covering items such as sensory impairment, oral health, frailty, sarcopenia, cognitive and functional impairments, psychological well-being, and polypharmacy using automated data capture followed by computer generated report to guide further action. The project has been described elsewhere (18). Some participants were also recruited from non-acute hospitals in the same region as the study centre. The five item FRAIL scale (Table 1 (6)) was use to classify participants into three groups: robust (score 0), pre-frail (score 1-2), and frail (score ≥3). All participants who did not have any history of heart failure were invited to attend a regional acute hospital (the study centre) as well as a non-acute hospital in the same region for further cardiac assessment, with a final sample size of approximately 100 per frailty group. Medical follow up was offered to all participants if abnormalities in cardiac function were detected, either at the same hospital or referred to hospitals nearer their residential address. Written informed consent was obtained from all participants, and the study was approved by the Chinese University of Hong Kong Clinical Research Ethics Committee.

Table 1
The FRAIL Scale

Item	Scale
Fatigue	Tired all or most of the time during the past four weeks (No/Yes)
Resistance	Difficulty walking up 10 steps without resting or aids (No/Yes)
Ambulation	Difficulty walking several hundred yards alone without aid (500-600 meters) (No/Yes)
Illnesses	5 or more illnesses (No/Yes)
Loss of weight	Weight loss >5% within the past moth (No/Yes)

Robust = 0; Pre-frail=1-2; Frail=3

Assessments

Questionnaire

Information obtained by questionnaire include sociodemographic information, smoking and drinking habit, history of cardiovascular disease and diabetes, and any symptoms of heart failure according to the New York Heart Association classification. Any medications used were recorded.

Physical performance measures

Grip strength was measured using a dynamometer (Jamar Hand Dynamometer 5030JO; Sammons Preston Inc., Bolingbrook, IL, USA) Two readings were taken from each side, and the maximum value of all the measurements was used for analysis. Walking speed was measured using the best time in seconds to complete a walk along a straight line 6 metres long. A warm up period of less than 5 minutes was followed by two walks, and the best time was recorded. The 6 minute walk test was conducted in a 20 metre corridor on a flat hard surface, with every 5 meters marked on the side of the walkway. A cone was placed at each end of the walkway to indicate where the participant had to turn. Participants were encouraged to walk continuously for six minutes, and the distance covered was recorded.

Cardiac function assessment: echocardiography

Study participants underwent transthoracic echocardiographic (TTE) examination using a General Electric VIVID E9 ultrasound system. Left ventricular ejection fraction (Simpson's biplane method) and standard diastolic parameters were measured as per American Society of Echocardiography recommendations (19). Briefly, mitral inflow E and A velocities, tissue Doppler e', deceleration time, left atrial volume index, and tricuspid regurgitation, if available, were considered for grading (0, I–IV) of diastolic dysfunction.

Cardiac function assessment: NT-proBNP level measurements

Patients with frailty and at least Grade II diastolic dysfunction were considered to have HFpEF if they also had concomitant elevated N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) of at least 300 pg/ml (20). Blood specimens were collected in Vacuette Z Serum Separator Clot Activator blood collection tubes (Greiner Bio-One International GmbH, Austria). NT-proBNP levels were measured using the Roche Elecsys e411 analyser in a clinical laboratory at Prince of Wales Hospital, Hong Kong that used Roche-supplied standard reagents and followed a protocol for in vitro diagnosis.

Statistical analysis

Continuous variables with normal distributions were reported by means ± standard deviations (SD), and one-way ANOVA with least significant difference post-hoc test performed for between-group comparisons. Continuous variables with nonparametric distribution were expressed as median (range) and compared using Kruskal-Wallis H Test. Categorical variables were expressed as frequencies, and Chi-square or Fisher's exact test was used for comparison between groups where appropriate. Logistic regression was used to test for associations between binary variables, and the effect sizes were estimated as odds ratios (OR) between groups when comparing individual components of FRAIL scale and diastolic dysfunction. Diastolic dysfunction was categorized as a binary variable based on American Society of Echocardiography recommendations (19). Subanalysis of age used 75 years as

Table 2
Baseline characteristics of participants by frailty states

Variables	Overall (n=306)	Frailty (n=95)	Pre-frailty (n=107)	Robust (n=104)
Socioeconomic demographics				
Age, y	74.73±7.76	79.14±7.68*‡	74.35±7.67†	71.76±5.70
Male gender, % (n)	31.0 (95/306)	15.8 (15/95)§	18.7 (20/107)	57.7 (60/104)
Living alone, % (n)	25.2 (77/306)	38.9 (37/95)§	24.3 (26/107)	13.5 (14/104)
Smoking status, % (n)				
Current smokers	2.6 (8/306)	3.2 (3/95)§	0.9 (1/107)	3.8 (4/104)
Previous smokers	19.0 (58/306)	12.6 (12/95)	12.1 (13/107)	31.7 (33/104)
Nonsmokers	78.4 (240/306)	84.2 (80/95)	86.9 (93/107)	64.4 (67/104)
Alcohol status, % (n)				
Current drinkers	20.3 (62/306)	3.2 (3/95)§	22.4 (24/107)	33.7 (35/104)
Previous drinkers	14.7 (45/306)	18.9 (18/95)	11.2 (12/107)	14.4 (15/104)
Nondrinkers	65.0 (199/306)	77.9 (74/95)	66.4 (71/107)	51.9 (54/104)
Comorbidities				
Hypertension, % (n)	65.7 (201/306)	80.0 (76/95)§	69.2 (74/107)	49.0 (51/104)
Diabetes mellitus, % (n)	28.1 (86/306)	41.1 (39/95)§	26.2 (28/107)	18.3 (19/104)
Ischemic heart disease, % (n)	6.5 (20/306)	13.7 (13/95)§	2.8 (3/107)	3.8 (4/104)
Atrial fibrillation, % (n)	2.9 (9/306)	4.2 (4/95)	2.8 (3/107)	1.9 (2/104)
NYHA class, % (n)				
Class I-II	68.7 (204/306)	27.4 (26/95)§	70.1 (75/107)	99.0 (103/104)
Class III-IV	33.3 (102/306)	72.6 (69/95)	29.9 (32/107)	1.0 (1/104)
Medication, % (n)				
Antiplatelets	23.2 (71/306)	29.5 (28/95)§	26.2 (28/107)	14.4 (15/104)
Anticoagulants	1.3 (4/306)	3.2 (3/95)	0	1.0 (1/104)
Statins	40.5 (124/306)	45.3 (43/95)	40.2 (43/107)	36.5 (38/104)
Beta blockers	18.6 (57/306)	24.2 (23/95)	18.7 (20/107)	13.5 (14/104)
ACE inhibitors/ARBs	26.5 (81/306)	29.5 (28/95)	28.0 (30/107)	22.1 (23/104)
CCBs	40.9 (125/306)	48.5 (46/95)	43.9 (47/107)	30.8 (32/104)
Diuretics	5.2 (16/306)	9.5 (9/95)	4.7 (5/107)	1.9 (2/104)
Nitrates	4.6 (14/306)	8.4 (8/95)§	4.7 (5/107)	1.0 (1/104)
Physical fitness				
Handgrip strength normalized by BMI	0.76±0.29	0.62±0.19*‡	0.69±0.24†	0.95±0.31
Gait speed, m/sec	0.86±0.24	0.69±0.19*‡	0.83±0.21†	1.05±0.16
6-minute walk distance, m	327.54±97.65	249.94±82.17*‡	318.66±84.19†	405.25±55.84

One-way ANOVA used when comparing normally distributed continuous variables between groups; *P <0.05, frail vs. pre-frail individuals; †P <0.05, pre-frail vs. robust individuals; ‡P <0.05), frail vs. robust individuals; §P <0.05, Pearson Chi-square test or Fisher's exact test across frail, pre-frail and robust groups where appropriate

the cut-point. A two-sided P <0.05 was considered statistically significant. IBM SPSS Version 24.0 (Armonk, New York, USA) software was used for statistical analyses.

Results

The baseline characteristics of participants by frailty status are shown in Table 2. Older age, living alone, abstinence from smoking and alcohol use, were associated with increasing levels of frailty. Prevalence of hypertension, diabetes mellitus, ischaemic heart disease, and atrial fibrillation was also higher

Table 3
Cardiac function by frailty states

Variables	Overall (n=306)	Frailty (n=95)	Pre-frailty (n=107)	Robust (n=104)
Systolic dysfunction (LVEF <50%)	4.3% (13/304)	6.5% (6/93)	2.8% (3/107)	3.8% (4/104)
LVEF 40-49%	2.3% (7/304)	2.2% (2/93)	1.9% (2/107)	2.9% (3/104)
LVEF <40%	2.0% (6/304)	4.3% (4/93)	0.9% (1/107)	1.0% (1/104)
Diastolic dysfunction (LVEF ≥50%)	67.0% (205/306)	85.3% (81/95)*	65.4% (70/107)	51.9% (54/104)
Grade I diastolic dysfunction	47.7% (146/306)	57.9% (55/95)	42.1% (45/107)	44.2% (46/104)
Grade II-IV diastolic dysfunction	19.6% (60/306)	27.4% (26/95)*	23.4% (25/107)	8.7% (9/104)
NT-proBNP, pg/ml	113.87	167.98	118.57	64.18
(range)	(9.13-6517.81)	(9.13 – 6517.81)*‡	(15.07 – 3639.89)†	(14.97 – 4769.75)
Prevalence of HFpEF	9.8% (30/306)	16.8% (16/95)*	10.3% (11/107)	2.9% (3/104)

Kruskal-Wallis H test was performed on nonparametric variables between subgroups; *P <0.05, Pearson Chi-square test or Fisher's exact test across frail, pre-frail and robust groups where appropriate; † P <0.05, pre-frail vs. robust individuals; ‡ P <0.05, frail vs. robust individuals

Table 4
Risk of diastolic dysfunction associated with individual components of the FRAIL score stratified by age

Frailty individual components	Univariate logistic regression		Univariate logistic regression stratified by age			
			Age ≥75 years old (n=148)		Age <75 years old (n=158)	
	OR	95% CI	OR	95% CI	OR	95% CI
Fatigue	2.87†	1.67 – 4.93	3.25*	1.26 – 8.41	1.51	0.73 – 3.15
Resistance	3.49†	2.11 – 5.76	2.57*	1.03 – 6.42	2.06*	1.05 – 4.05
Ambulation	3.57†	2.09 – 6.09	3.05*	1.25 – 7.47	1.78	0.84 – 3.79
Illnesses	1.51	0.47 – 4.80	0.35	0.10 – 1.25	N/A	N/A
Loss of weight	1.62	0.76 – 3.46	2.06	0.73 – 5.79	0.91	0.28 – 2.94

OR, odds ratio; CI, confidence interval; * P value <0.05; † P value <0.01.

with increasing frailty, as with use of various medications. Grip strength, walking speed and 6 minute walk distance were all lower with increasing levels of frailty. Although the prevalence of systolic dysfunction was low and there was no significant difference between the three groups, the prevalence of diastolic dysfunction was high, being 52% in the robust group, increasing to 65% in the pre-frail and 85% in the frail group (Table 3). This finding is accompanied by a corresponding increase in NT-proBNP from 64.18 pg/ml in the robust group, to 118.57 pg/ml in the pre-frail and 167.98 pg/ml in the frail group (Table 3). The prevalence of HFpEF was also statistically different between the frailty groups, being highest in the frail group (16.8%, 10.3% and 2.9% respectively). When each of the five components of the FRAIL scale was examined for significant association with diastolic dysfunction, only fatigue, resistance, and ambulation were associated with increased odds ratios of diastolic dysfunction among those aged 75 years and older, while resistance alone was associated with an increased odds ratio among those less than 75 years old (Table 4).

Discussion

The findings of this study shows that frailty is associated with diastolic dysfunction, the association accounted for by three of the FRAIL screening questions: fatigue, difficulty in walking up 10 steps and several hundred yards on the level alone without resting or aids, the odds ratios being greater with increasing levels of frailty. The latter is clinically manifested in reduced walking speed, grip strength, and cardiorespiratory fitness (indicated by the 6 minute walk test). Frailty and all these parameters have been shown to increase mortality and other adverse health outcomes such as use of health services, mobility limitations, and falls (2). Therefore diastolic dysfunction may not be regarded as an age-related change without clinical consequences, but as a result of a common underlying pathophysiological process that gives rise to all these phenomena. Indeed diastolic dysfunction may account for some of the symptoms included as an indicator of frailty. Conversely, frailty screening may be considered of relevance in screening for undiagnosed heart failure among older people living in the community. Undiagnosed pathology

is not uncommon since there tends to be under reporting of symptoms (21).

The association between frailty and HFpEF has been observed in two other studies in Japan and the US, using other measures of frailty (11, 15). HFpEF has been proposed to be a geriatric syndrome, in view of its increasing prevalence with age, and association with a broad range of cardiac abnormalities with inflammation as a common underlying cause (16, 17). Higher levels of circulating inflammatory markers such as interleukin-6, tumor necrosis factor, and C- reactive protein were observed in frail older people (22) and associated with poorer physical function (23). Therefore HFpEF may be considered as a biomarker of frailty.

The findings have clinical significance, in that frailty screening using this simple questionnaire may be used as a screening tool for diagnosis of HFpEF among community-living older people. Since frailty predisposed to self-care dependency, and people with dependency and chronic cardiac/respiratory conditions are frequent users of acute care (24), timely detection of both conditions may enable early intervention in avoiding acute admissions. Frailty may be reversible, and intervention studies involving lifestyle modification have been carried out and guidelines formulated (25, 26). Currently, there is no pharmacological treatment for HFpEF, and management also revolves around nutrition and exercise training (15). Apart from meticulous work-up and careful exclusion of potential underlying etiologies that might explain HFpEF as guided by clinical history, physical examination and an index of suspicion (27), there is a possibility that the frailty prevention programmes may provide benefits through improvement in diastolic function.

There are limitations in this study. It is cross-sectional in nature and there is no data on subsequent progress of participants in terms of changes in frailty status and symptoms, and other longer term outcomes such as dependency and use of hospital services. We did not analyse in detail the influence of different drugs on frailty and cardiac function. Nevertheless, the association between three questions of the FRAIL scale and HFpEF was clearly documented.

Conclusion

Frailty is associated with HFpEF, and frailty screening may be used to detect undiagnosed HFpEF. The findings support the proposal that HFpEF be considered a geriatric syndrome.

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Conflicts of interest: The authors declare no conflicts of interest.

Ethical standards: Written informed consent was obtained from all participants, and the study was approved by the Chinese University of Hong Kong Clinical Research Ethics Committee.

References

1. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013;381(9868):752-762.
2. Vermeiren S, Vella-Azzopardi R, Beckwee D, Habbig AK, Scafoglieri A, Jansen B, et al. Frailty and the Prediction of Negative Health Outcomes: A Meta-Analysis. Journal of the American Medical Directors Association 2016;17(12):1163.e1-e.17.
3. Gray WK, Richardson J, McGuire J, Dewhurst F, Elder V, Weeks J, et al. Frailty Screening in Low- and Middle-Income Countries: A Systematic Review. Journal of the American Geriatrics Society 2016;64(4):806-823.
4. Gill TM, Gahbauer EA, Allore HG, Han L. Transitions between frailty states among community-living older persons. Archives of Internal Medicine 2006;166(4):418-423.
5. Lee JSW, Auyeung TW, Leung J, Kwok T, Woo J. Transitions in Frailty States Among Community-Living Older Adults and Their Associated Factors. Journal of the American Medical Directors Association 2014;15(4):281-286.
6. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. J Nutr Health Aging 2012;16(7):601-8.
7. Woo J, Yu R, Wong M, Yeung FN, Wong M, Lum C. Frailty Screening in the Community Using the FRAIL Scale. Journal of the American Medical Directors Association 2015;16(5):412-419.
8. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nature Reviews Cardiology 2018;15(9):505-522.
9. Roger VL. Epidemiology of Heart Failure. Circulation Research 2013;113(6):646-659.
10. Yousaf F, Collerton J, Kingston A, Kenny A, Davies K, Jagger C, et al. Prevalence of left ventricular dysfunction in a UK community sample of very old people: the Newcastle 85+ study. Heart 2012;98(19):1418-23.
11. Nadruz W, Jr., Kitzman D, Windham BG, Kucharska-Newton A, Butler K, Palta P, et al. Cardiovascular Dysfunction and Frailty Among Older Adults in the Community: The ARIC Study. J Gerontol A Biol Sci Med Sci 2017;72(7):958-964.
12. Vogel MW, Slusser JP, Hodge DO, Chen HH. The Natural History of Preclinical Diastolic Dysfunction A Population-Based Study. Circulation-Heart Failure 2012;5(2):144-151.
13. Lam CS, Lyass A, Kraigher-Krainer E, Massaro JM, Lee DS, Ho JE, et al. Cardiac dysfunction and noncardiac dysfunction as precursors of heart failure with reduced and preserved ejection fraction in the community. Circulation 2011;124(1):24-30.
14. Kane GC, Karon BL, Mahoney DW, Redfield MM, Roger VL, Burnett JC, Jr., et al. Progression of left ventricular diastolic dysfunction and risk of heart failure. JAMA 2011;306(8):856-63.
15. Kinugasa Y, Yamamoto K. The challenge of frailty and sarcopenia in heart failure with preserved ejection fraction. Heart 2017;103(3):184-189.
16. Upadhya B, Taffet GE, Cheng CP, Kitzman DW. Heart failure with preserved ejection fraction in the elderly: scope of the problem. J Mol Cell Cardiol 2015;83:73-87.
17. Upadhya B, Pisani B, Kitzman DW. Evolution of a Geriatric Syndrome: Pathophysiology and Treatment of Heart Failure with Preserved Ejection Fraction. J Am Geriatr Soc 2017;65(11):2431-2440.
18. Cheung JTK, Yu R, Wu Z, Wong SYS, Woo J. Geriatric syndromes, multimorbidity, and disability overlap and increase healthcare use among older Chinese. BMC Geriatr 2018;18(1):147.
19. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Journal of the American Society of Echocardiography 2016;29(4):277-314.
20. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37(27):2129-2200.
21. Rosen S, Koretz B, D.B. R. Presention of Disease in Old Age. In: Fillit H, Rockwood K, Woodhouse K, editors. Brocklehurst's Textbook of Geriatric Medicine and Geronotology. 7th Edition ed. Philadelphia USA: Saunders; 2010. p. 205-210.
22. Tang Y, Fung E, Xu A, Lan HY. C-reactive protein and ageing. Clin Exp Pharmacol Physiol 2017;44 Suppl 1:9-14.
23. Ma L, Sha G, Zhang Y, Li Y. Circulating interleukin-6 and adiponectin as physiological correlates of frailty in Chinese older adults. J Frailty Aging 2018;7(Suppl 2):S7-S8.
24. Dollard J, Harvey G, Dent E, Trotta L, Williams N, Beilby J, et al. Older People Who Are Frequent Users of Acute Care: A Symptom of Fragmented Care? A Case Series Report on Patients' Pathways of Care. J Frailty Aging 2018;7(3):193-195.
25. Ngandu T, Lehtisalo J, Solomon A, Levalahti E, Ahtiluoto S, Antikainen R, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet 2015;385(9984):2255-2263.
26. Dent E, Lien C, Lim WS, Wong WC, Wong CH, Ng TP, et al. The Asia-Pacific Clinical Practice Guidelines for the Management of Frailty. Journal of the American Medical Directors Association 2017;18(7):564-575.
27. Zakeri R, Cowie MR. Heart failure with preserved ejection fraction: controversies, challenges and future directions. Heart 2018;104(5):377-384.