

# World Journal of *Clinical Cases*

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## Contents

Thrice Monthly Volume 9 Number 36 December 26, 2021

## REVIEW

- 11122 Diet and microbiome in the beginning of the sequence of gut inflammation  
*Ceballos D, Hernández-Camba A, Ramos L*

## MINIREVIEWS

- 11148 Stem cell therapy: A promising treatment for COVID-19  
*Zheng ZX*

## ORIGINAL ARTICLE

## Case Control Study

- 11156 Association between serum Sestrin2 level and diabetic peripheral neuropathy in type 2 diabetic patients  
*Mao EW, Cheng XB, Li WC, Kan CX, Huang N, Wang HS, Hou NN, Sun XD*
- 11165 Plasma brain natriuretic peptide, platelet parameters, and cardiopulmonary function in chronic obstructive pulmonary disease  
*Guo HJ, Jiang F, Chen C, Shi JY, Zhao YW*

## Retrospective Cohort Study

- 11173 Analysis of the incidence and influencing factors of hyponatremia before <sup>131</sup>I treatment of differentiated thyroid carcinoma  
*Cao JJ, Yun CH, Xiao J, Liu Y, Wei W, Zhang W*

## Retrospective Study

- 11183 Cognitive magnetic resonance imaging-ultrasound fusion transperineal targeted biopsy combined with randomized biopsy in detection of prostate cancer  
*Pang C, Wang M, Hou HM, Liu JY, Zhang ZP, Wang X, Zhang YQ, Li CM, Zhang W, Wang JY, Liu M*
- 11193 Nomogram based on inflammation-related markers for predicting survival of patients undergoing hepatectomy for hepatocellular carcinoma  
*Pu T, Li ZH, Jiang D, Chen JM, Guo Q, Cai M, Chen ZX, Xie K, Zhao YJ, Liu FB*
- 11208 Association of frailty with in-hospital outcomes in elderly patients with heart failure  
*Kang YP, Chen LY, Zhu JJ, Liu WX, Ma CS*
- 11220 COVID-19 pandemic and exacerbation of ulcerative colitis  
*Suda T, Takahashi M, Katayama Y, Tamano M*
- 11228 Surgical perspectives of symptomatic omphalomesenteric duct remnants: Differences between infancy and beyond  
*Kang A, Kim SH, Cho YH, Kim HY*

- 11237** Clustering cases of *Chlamydia psittaci* pneumonia mimicking COVID-19 pneumonia

Zhao W, He L, Xie XZ, Liao X, Tong DJ, Wu SJ, Liu J

- 11248** Sodium nitroprusside injection immediately before balloon inflation during percutaneous coronary intervention

Yu Y, Yang BP

- 11255** Machine learning approach to predict acute kidney injury after liver surgery

Dong JF, Xue Q, Chen T, Zhao YY, Fu H, Guo WY, Ji JS

- 11265** Application effect for a care bundle in optimizing nursing of patients with severe craniocerebral injury

Gao Y, Liao LP, Chen P, Wang K, Huang C, Chen Y, Mou SY

### Clinical Trials Study

- 11276** Influence of pontic design of anterior fixed dental prosthesis on speech: A clinical case study

Wan J, Cai H, Wang T, Chen JY

### Observational Study

- 11285** Real-world data on the infliximab biosimilar CT-P13 (Remsima®) in inflammatory bowel disease

Huguet JM, Cortés X, Bosca-Watts MM, Aguas M, Maroto N, Martí L, Amorós C, Paredes JM

- 11300** Correlation of periodontal inflamed surface area with glycemic status in controlled and uncontrolled type 2 diabetes mellitus

Anil K, Vadakkekuttikal RJ, Radhakrishnan C, Parambath FC

- 11311** Audiological characteristics and exploratory treatment of a rare condition of acute-otitis-media-associated sudden sensorineural hearing loss

Cao X, Yi HJ

- 11320** Yield of testing for micronutrient deficiencies associated with pancreatic exocrine insufficiency in a clinical setting: An observational study

Jalal M, Campbell JA, Tesfaye S, Al-Mukhtar A, Hopper AD

### Prospective Study

- 11330** Birthing ball on promoting cervical ripening and its influence on the labor process and the neonatal blood gas index

Shen HC, Wang H, Sun B, Jiang LZ, Meng Q

### CASE REPORT

- 11338** Mucormycosis – resurgence of a deadly opportunist during COVID-19 pandemic: Four case reports

Upadhyay S, Bharara T, Khandait M, Chawdhry A, Sharma BB

- 11346** Ductal breast carcinoma metastasized to the rectum: A case report and review of the literature

Ban B, Zhang K, Li JN, Liu TJ, Shi J

- 11355** De Garengeot hernia with avascular necrosis of the appendix: A case report  
*Yao MQ, Yi BH, Yang Y, Weng XQ, Fan JX, Jiang YP*
- 11362** Mature mediastinal bronchogenic cyst with left pericardial defect: A case report  
*Zhu X, Zhang L, Tang Z, Xing FB, Gao X, Chen WB*
- 11369** Difficulties in diagnosing anorectal melanoma: A case report and review of the literature  
*Apostu RC, Stefanescu E, Scurtu RR, Kacso G, Drasovean R*
- 11382** Solid pseudopapillary neoplasm of the pancreas in a young male with main pancreatic duct dilatation: A case report  
*Nakashima S, Sato Y, Imamura T, Hattori D, Tamura T, Koyama R, Sato J, Kobayashi Y, Hashimoto M*
- 11392** Acute myocardial infarction in a young man with ankylosing spondylitis: A case report  
*Wan ZH, Wang J, Zhao Q*
- 11400** Acute appendicitis complicated by mesenteric vein thrombosis: A case report  
*Yang F, Guo XC, Rao XL, Sun L, Xu L*
- 11406** Inguinal endometriosis: Ten case reports and review of literature  
*Li SH, Sun HZ, Li WH, Wang SZ*
- 11419** Dramatic response to immunotherapy in an epidermal growth factor receptor-mutant non-small cell lung cancer: A case report  
*Li D, Cheng C, Song WP, Ni PZ, Zhang WZ, Wu X*
- 11425** Three-dimensional inlay-guided endodontics applied in variant root canals: A case report and review of literature  
*Yan YQ, Wang HL, Liu Y, Zheng TJ, Tang YP, Liu R*
- 11437** Ectopic pregnancy implanted under the diaphragm: A rare case report  
*Wu QL, Wang XM, Tang D*
- 11443** Ear ischemia induced by endovascular therapy for arteriovenous fistula of the sigmoid sinus: A case report  
*Li W, Zhang SS, Gao XR, Li YX, Ge HJ*
- 11448** Giant schwannoma of thoracic vertebra: A case report  
*Zhou Y, Liu CZ, Zhang SY, Wang HY, Varma SN, Cao LQ, Hou TT, Li X, Yao BJ*
- 11457** Severe digital ischemia coexists with thrombocytopenia in malignancy-associated antiphospholipid syndrome: A case report and review of literature  
*Chen JL, Yu X, Luo R, Liu M*
- 11467** Rare spontaneous extensive annular intramural esophageal dissection with endoscopic treatment: A case report  
*Hu JW, Zhao Q, Hu CY, Wu J, Lv XY, Jin XH*

- 11475** Mucinous cystic neoplasm of the liver: A case report  
*Yu TY, Zhang JS, Chen K, Yu AJ*
- 11482** Retroperitoneal parasitic fetus: A case report  
*Xia B, Li DD, Wei HX, Zhang XX, Li RM, Chen J*
- 11487** De novo mutation loci and clinical analysis in a child with sodium taurocholate cotransport polypeptide deficiency: A case report  
*Liu HY, Li M, Li Q*
- 11495** Surgery for hepatocellular carcinoma with tumor thrombosis in inferior vena cava: A case report  
*Zhang ZY, Zhang EL, Zhang BX, Zhang W*

**LETTER TO THE EDITOR**

- 11504** Advantages and issues of concern regarding approaches to peripheral nerve block for total hip arthroplasty  
*Crisci M, Cuomo A, Forte CA, Bimonte S, Esposito G, Tracey MC, Cascella M*

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## Retrospective Study

## Association of frailty with in-hospital outcomes in elderly patients with heart failure

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## Abstract

**BACKGROUND**

Frailty is prevalent in elderly patients with cardiovascular diseases. However, the association between frailty and in-hospital outcomes for elderly patients with heart failure and reduced ejection (HFrEF) remains unknown.

**AIM**

To evaluate the predictive efficacy of frailty, compared with pre-frailty, for adverse events in these patients.

**METHODS**

Elderly patients ( $\geq 60$  years) with HFrEF were assessed. Frailty was evaluated with the Fried phenotype criteria, and physical performance was evaluated based on handgrip strength and the short physical performance battery (SPPB). The composite incidence of adverse events, including all-cause death, multiple organ failure, cardiac shock, and malignant arrhythmia, during hospitalization was recorded.

**RESULTS**

Overall, 252 elderly individuals with HFrEF [mean age:  $69.4 \pm 6.7$  years, male: 169 (67.0%)] were included. One hundred and thirty-five (53.6%) patients were frail and 93 (36.9%) were pre-frail. Frail patients were older, more likely to be female, to have a lower blood pressure, and to present with left ventricular thrombosis ( $P$  all  $< 0.05$ ). Frail patients with HFrEF had a higher incidence of in-hospital mortality (11.9% vs 4.3%,  $P = 0.048$ ). Multivariate analyses showed that female gender (OR = 0.422), aging (OR = 1.090), poor cardiac functional class (OR = 2.167), frailty (OR = 2.379), and lower handgrip strength (OR = 1.106) were independent predictors of in-hospital adverse events ( $P$  all  $< 0.05$ ).



with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent statement:** Due to the retrospective nature of this study, the requirement for informed consent was waived.

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## CONCLUSION

Frailty may be associated with poor in-hospital outcomes for elderly patients with HFrEF. The influence of frailty on long-term prognosis in these patients deserves further investigation.

**Key Words:** Heart failure with reduced ejection fraction; Frailty; Elderly; Adverse events

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**Core Tip:** This retrospective study included 252 elderly individuals with heart failure and reduced ejection who showed a high prevalence of frailty (53.6%) and pre-frailty (36.9%). Female gender, aging, poor cardiac functional class, frailty, and lower handgrip strength were found to be independent predictors of in-hospital adverse events in these patients. Taken together, frailty is prevalent in elderly individuals with heart failure and reduced ejection, and frailty may be associated with poor in-hospital outcomes for these patients.

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## INTRODUCTION

Heart failure (HF) is a clinical syndrome that presents as the end stage of various cardiovascular diseases[1], and the incidence has increased in recent decades[2-4]. Despite significant improvements in the management of patients with HF, this disease, particularly HF with reduced ejection fraction (HFrEF), remains one of the leading causes of morbidity and mortality for people all over the world[5]. Accumulating evidence suggests that aging is an important risk factor for the development of HF[6]. Many mechanisms have been proposed to relate aging with the development of HF, among which frailty is suggested to play an important role[7,8]. Frailty, defined as a clinical syndrome characterized by reduced functional capacity, multiple system disorder, impaired regulatory efficacy for homeostasis, and increased vulnerability to stimuli, becomes more prevalent with age[7,9]. People with frailty are vulnerable to diseases and frailty has been associated with increased mortality[10]. Interestingly, previous studies also showed that frailty is prevalent in patients with cardiovascular diseases, including those with ischemic heart disease, atrial fibrillation (AF), and HF [11,12]. Additionally, previous studies showed that frailty is associated with poor prognosis in patients with HF[13]. A previous meta-analysis with 20 observational studies showed that frailty significantly increased the risk of all-cause mortality and hospitalization in HF patients[14]. However, whether frailty, compared to pre-frailty, in elderly patients with HFrEF is also related to an increased risk of adverse events during hospitalization remains unknown[15]. Therefore, we aimed to determine the differences in the clinical characteristics and clinical implications of frailty and pre-frailty in elderly patients with HFrEF in our center.

## MATERIALS AND METHODS

Elderly patients with a confirmed diagnosis of HFrEF who were admitted to the Department of Cardiac Care Unit at the Beijing Anzhen Hospital for HF decompensation between January 1<sup>st</sup>, 2014 and December 30<sup>th</sup>, 2019 were included. The protocol for the study was approved by the Ethics Committee of Beijing Anzhen Hospital before the initiation of the study. Due to the retrospective nature of this study, the requirement for informed consent was waived.



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### Patient inclusion and exclusion criteria

Patients were included if they met all of the following criteria: (1) Age  $\geq 60$  years; (2) Ambulant patients with a confirmed diagnosis of HFrEF according to the criteria of the 2016 European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (with symptoms and signs of HF and LVEF  $< 40\%$ ) [16]; and (3) Complete data on the clinical characteristics, treatment details, and outcome records during hospitalization. All of the included patients were Chinese and the enrolment of patients started in 2014. According to the Chinese laws on the protection of the rights and interests of the elderly population, 60 is defined as the cut-off age for elderly individuals. Accordingly, we used 60 years-old as the cut-off to define elderly patients rather than 75 years-old in this study. The following exclusion criteria were applied: (1) Patients with difficulties in language communication, cognitive impairment, or mental disorders that prevented the comprehensive evaluation of frailty status and physical performance; (2) Long-term bedridden individuals with severe musculoskeletal or neurological diseases that prevented standing or walking; (3) Incomplete clinical or physical performance assessment data; and (4) Patients with unstable hemodynamic parameters, unstable vital signs, or other conditions that prevented the assessment of frailty or physical performance.

### Clinical data definitions and collection

Data regarding the demographic and clinical characteristics of the included patients at admission were extracted from their medical records, including age, gender, systolic and diastolic blood pressure (SBP and DBP), resting heart rate (HR), and the New York Heart Association (NYHA) functional classification. The medical histories of the patients including hypertension, diabetes mellitus (DM), dyslipidemia, AF, peripheral artery disease (PAD), and previous coronary percutaneous intervention (PCI) and coronary artery bypass grafting (CABG) procedures were also recorded. Serum biochemical parameters were obtained on the second day of admission from blood samples collected under a fasting condition. The following parameters were extracted: alanine aminotransferase (ALT), serum creatinine (SCr), fasting plasma glucose (FPG), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and type B natriuretic peptide (BNP). Blood gas analysis (BGA) was performed for each patient on admission and the partial pressure of oxygen ( $\text{PaO}_2$ ) was extracted. On admission, echocardiography was performed for each patient by an experienced physician to evaluate cardiac structure and function. The left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD), LVEF, and the presence of left ventricular (LV) thrombosis were also recorded. All of the patients received evidenced-based medications for HF, which included diuretics, digitalis, beta-blockers, angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and aldosterone receptor antagonists (ARAs) [16].

### Assessment of frailty

A strict evaluation system has been applied for a long time for stage 1 cardiac rehabilitation of patients with HF at the CCU at our institution. Patients who undergo rehabilitation assessment and training must meet the following conditions: (1) Resting heart rate  $< 120$  beats/min; (2) Resting respiratory rate  $< 30$  breaths/min; (3)  $\text{SpO}_2 \geq 90\%$ ; (4) Systolic blood pressure (SBP)  $< 180$  mmHg, diastolic blood pressure (DBP)  $< 110$  mmHg; (5) Weight change within 72 h less than  $\pm 1.8$  kg; (6) Random blood glucose within 5-18 mmol/L; (6) No evidence of new-onset ischemia on the electrocardiogram at rest; (7) No angina attack; (8) No malignant arrhythmia leading to hemodynamic instability; (9) No shock; (10) No acute heart failure due to severe valve disease; (11) No neurological and motor system diseases; and (12) Patients agreed to be evaluated. The assessment was performed on the basis of sufficient treatment and on patients in a stable condition.

Frailty was evaluated within 72 h after admission when the patients were confirmed to be hemodynamically stable by the physicians. In order to reduce bias and ensure consistency during the evaluation, the frailty and physical performance of all included patients were evaluated by the same clinical rehabilitation specialist, who had been trained before the assessment.

The frailty phenotype proposed by Fried *et al* [17] was used to evaluate the frailty status of the included patients with HFrEF as previously described. Briefly, this tool includes the following five components for evaluating the frailty status of an individual [17]: (1) Underweight or sarcopenia: defined as weight loss of  $\geq 4.5$  kg in the past 12 mo; (2) Reduced handgrip strength: defined as handgrip strength  $< 20\%$  of the

average value for the population with the same age, sex, and body mass index (BMI) and assessed according to the reference range for reduced grip strength in different genders and BMIs in the Fried frailty assessment table; (3) Reduced exercise capacity: defined as self-reported symptoms of fatigue; (4) Reduced gait speed: assessed based on the 4.5 m walking time for people of different genders and heights listed in the Fried frailty assessment table; and (5) Low physical activity: defined as low daily consumption of calories ( $< 20\%$  of the average level),  $< 383$  kcal/wk for men and  $< 270$  kcal/wk for women. The patients were categorized as frail if they fulfilled  $\geq$  three of the components and as pre-frail if they satisfied one or two components[17]. Patients were considered non-frail if they fulfilled none of the components[17].

### Assessment of physical performance

For the physical performance assessment, the International Physical Activity Questionnaire (IPAQ), the handgrip strength test, and the short physical performance battery (SPPB) were used.

The IPAQ evaluates the degree of self-reported physical activity decline *via* a questionnaire with good reliability and validity[18]. The weekly caloric consumption of patients was evaluated according to their physical activity status within one week before admission. The data were collected by a trained cardiologist using the IPAQ short questionnaire, and the BMI and body surface area were calculated at the same time. The contents of the IPAQ short questionnaire included exercise intensity, exercise form, and exercise time within 7 d. Exercise intensity was determined according to the patient's responses and expressed as the metabolic equivalent (MetS, 1 MetS = 1.05 kcal/kg per hour). The energy consumption for physical activity in 7 d was estimated.

The CAMRY electronic grip strength meter was used for the measurement of handgrip power and the recommended method in the "Chinese National Physique Measurement Standard Manual" was adopted. Briefly, the patients remained in a standing position with both feet together and the arms drooping vertically. During the measurement, the grip force meter did not contact the body or clothes and the patients were not allowed to bend the arm or bend down when exerting force. Both hands were tested twice and the maximum value was recorded.

The SPPB includes three tests, namely a balance test, a strength test (chair standing test), and a movement test (4-m gait test)[19]. The balance test was conducted during the first phase and the second phase consisted of a 4-m walking speed test. The time required to walk at a normal walking speed for 4 min was recorded. In the third phase, the chair standing test was conducted. The participants crossed their arms in front of their chest and attempted to stand up from the chair once. The time to stand was recorded five times. Each component of the SPPB was scored from 0 to 4, with a total score of 0 to 12[19].

### Outcomes

The in-hospital mortality of patients in each group was recorded, and the primary causes of in-hospital mortality were categorized as cardiac shock, malignant arrhythmia, and multiple organ failure (MOF). The diagnosis of cardiac shock was in accordance with the definition in the 2016 ESC Guidelines on the Diagnosis and Treatment of Acute Heart Failure[20]. Malignant arrhythmia included high-grade (Mobitz II or third degree) atrioventricular block[21], sustained ventricular tachycardia, and ventricular fibrillation[22]. MOF was defined as physiological dysfunction of more than one organ or system.

### Statistical analysis

Continuous variables were presented as means and SDs if normally distributed, and the differences between groups were analyzed with the independent *t* test. Continuous variables with skewed distribution were presented as medians and interquartile range (IQR) and compared with the Mann-Whitney *U* test. Categorized variables were presented as numbers and proportions, and comparisons between groups were analyzed with the Chi-square test. The composite incidence of adverse events, including all-cause death, multiple organ failure, cardiac shock, and malignant arrhythmia, during hospitalization was recorded. Patient characteristics, frailty status, and physical performance were compared in a univariate analysis between patients with and without adverse events during hospitalization. Multivariate logistic regression analyses were performed to evaluate the potential predictors of in-hospital adverse events, focusing on the frailty status and parameters related to physical performance. A *P* value  $< 0.05$  was considered statistically significant. Statistical

analyses were performed with SPSS 22.0 Software.

## RESULTS

### **Patient characteristics**

Overall, 526 patients were screened, and 252 elderly [mean age:  $69.4 \pm 6.7$  years, male: 169 (67.0%)] patients with HFrEF were included in the final analyses. The flowchart of patient enrollment is shown in [Figure 1](#). According to the definition of frailty by Fried *et al* [17], 135 (53.6%) patients were categorized as frail, 93 as pre-frail (36.9%), and 24 (9.5%) as non-frail. Since the number of non-frail patients was limited, we compared the characteristics of patients with frailty and pre-frailty. As shown in [Table 1](#), patients with frailty were older ( $70.7 \pm 7.2$  years *vs*  $68.8 \pm 5.8$  years,  $P = 0.039$ ), were more likely to be female (32.6% *vs* 26.9%,  $P = 0.022$ ), had lower SBP ( $107.71 \pm 21.03$  mmHg *vs*  $114.01 \pm 23.39$  mmHg,  $P = 0.035$ ) and DBP ( $66.90 \pm 13.57$  *vs*  $72.03 \pm 12.06$ ,  $P = 0.004$ ), had larger LVEDD ( $56.81 \pm 9.01$  mm *vs*  $54.46 \pm 7.66$  mm,  $P = 0.036$ ), and were more likely to present with LV thrombosis (20% *vs* 9.7%,  $P = 0.036$ ) than those with pre-frailty. Other characteristics were not statistically different between frail and pre-frail patients with HFrEF, including NYHA class, previous medical history of cardiovascular diseases, and biochemical parameters.

### **Physical performance evaluation**

Compared to pre-frail patients, frail patients with HFrEF showed lower handgrip strengths stratified by sex (men:  $23.8 \pm 4.1$  kg *vs*  $25.1 \pm 4.2$  kg,  $P = 0.056$ , and women:  $17.9 \pm 3.4$  kg *vs*  $21.2 \pm 4.5$  kg,  $P = 0.003$ ; [Table 2](#)). Moreover, frail patients with HFrEF showed poor performance in the balance, walking, and strength portions of the SPPB evaluation (all  $P < 0.001$ , [Table 2](#)). Finally, the overall SPPB score was lower in frail patients with HFrEF than in those with pre-frailty ( $7.24 \pm 1.72$  *vs*  $8.95 \pm 1.44$ ,  $P < 0.001$ , [Table 2](#)), indicating the poor physical performance of frail patients compared to pre-frail patients with HFrEF.

### **Incidence of in-hospital mortality**

The overall in-hospital mortality of elderly patients with HFrEF in this study was 8.7%, including four patients with pre-frailty and 16 patients with frailty (11.9% *vs* 4.3%,  $P = 0.048$ ; [Table 3](#)). Further analysis of the causes of hospital death showed that 10 patients with frailty died of MOF, and only one patient with pre-frailty died of MOF (7.4% *vs* 1.1%,  $P = 0.028$ ; [Table 3](#)). There was no significant difference in cardiogenic shock and malignant arrhythmia between patients with pre-frailty and frailty ( $P = 0.971$  and  $0.517$ ).

### **Clinical characteristics and physical performance in patients with and without adverse events**

Comparisons of the clinical characteristics and physical performance in patients with and without adverse events are shown in [Table 4](#). Univariate analysis showed that patients with adverse events during hospitalization were older, more likely to have a poor NYHA class (all  $P < 0.05$ ) compared to those without in-hospital adverse events. Moreover, patients with adverse events were more likely to be frail (72.1% *vs* 51.4%,  $P = 0.002$ ; [Table 4](#)), to have lower handgrip ( $22.26 \pm 5.34$  kg *vs*  $23.04 \pm 4.44$  kg,  $P = 0.030$ ), and to have lower total SPPB scores ( $7.50 \pm 2.04$  *vs*  $8.18 \pm 1.61$ ;  $P = 0.006$ ).

### **Predictors of in-hospital adverse events in elderly patients with HFrEF**

Multivariate logistic analyses were performed using SBP and the significant variables in [Table 4](#) as well as female gender and LVEF, two of the established prognostic parameters for HFrEF. The results showed that female gender [odds ratio (OR) = 0.422, 95%CI: 0.189–0.943,  $P = 0.035$ ], aging (OR = 1.090, 95%CI: 1.029–1.154,  $P = 0.003$ ), poor NYHA class (OR = 2.167, 95%CI: 1.320–3.559,  $P = 0.002$ ), frailty (OR = 2.379, 95%CI: 1.196–4.733,  $P = 0.014$ ), and lower handgrip strength (OR = 1.010, 95%CI: 1.020–1.212,  $P = 0.030$ ) were independent predictors of in-hospital adverse events in elderly patients with HFrEF ([Table 5](#)), but not the total SPPB score, SBP, or LVEF (all  $P > 0.05$ ).

**Table 1 Characteristics of the included elderly patients with heart failure and reduced ejection according to the frailty status**

	Frail ( <i>n</i> = 135)	Pre-frail ( <i>n</i> = 93)	<i>P</i> value
Demographic factors			
Age (yr)	70.7 ± 7.2	68.8 ± 5.8	0.039
Female, <i>n</i> (%)	44 (32.6)	25 (26.9)	0.022
NYHA Class			
III, <i>n</i> (%)	70 (51.9)	57 (61.3)	0.249
IV, <i>n</i> (%)	44 (32.6)	23 (24.7)	0.010
Medical history			
Hypertension, <i>n</i> (%)	78 (57.8)	48 (51.6)	0.358
DM, <i>n</i> (%)	57 (42.2)	29 (31.2)	0.091
Dyslipidemia, <i>n</i> (%)	34 (25.2)	17 (18.3)	0.219
AF, <i>n</i> (%)	40 (29.6)	18 (19.4)	0.080
PAD, <i>n</i> (%)	9 (6.7)	8 (8.6)	0.585
CABG, <i>n</i> (%)	15 (11.1)	11 (11.8)	0.867
PCI, <i>n</i> (%)	24 (17.8)	18 (19.4)	0.763
Clinical parameters			
SBP (mmHg)	107.71 ± 21.03	114.01 ± 23.39	0.035
DBP (mmHg)	66.90 ± 13.57	72.03 ± 12.06	0.004
HR (bpm)	88.16 ± 20.41	89.39 ± 19.77	0.653
ALT (U/L) <sup>1</sup>	39 (23, 79)	35 (20, 71)	0.347
SCr (μmol/L)	109.70 ± 65.63	102.67 ± 54.03	0.395
FPG (mmol/L)	9.01 ± 6.32	8.49 ± 4.18	0.499
TG (mmol/L) <sup>1</sup>	1.4 (0.9, 1.8)	1.5 (1.0, 2.1)	0.082
LDL-C (mmol/L)	2.59 ± 0.77	3.44 ± 1.51	0.455
HDL-C (mmol/L)	1.05 ± 0.31	0.99 ± 0.31	0.901
PaO <sub>2</sub> (mmHg)	96.85 ± 33.03	101.12 ± 38.93	0.374
BNP (μmol/L) <sup>1</sup>	712 (329, 1422)	542 (307, 925)	0.189
Echocardiography			
LVEDD (mm)	56.81 ± 9.01	54.46 ± 7.66	0.036
LVESD (mm)	41.97 ± 11.03	41.89 ± 9.98	0.956
LVEF (%)	33.79 ± 6.06	34.03 ± 5.64	0.753
LV thrombosis, <i>n</i> (%)	27 (20)	9 (9.7)	0.036
Medications			
Diuretics, <i>n</i> (%)	101 (74.8)	73 (78.5)	0.521
ARAs, <i>n</i> (%)	90 (66.7)	55 (59.1)	0.246
ACEIs/ARBs, <i>n</i> (%)	75 (55.6)	53 (57.0)	0.830
Beta-blockers, <i>n</i> (%)	114 (84.4)	76 (81.7)	0.588
Digitalis, <i>n</i> (%)	51 (37.8)	23 (24.7)	0.039
Anticoagulants, <i>n</i> (%)	65 (48.1)	33 (35.5)	0.058

<sup>1</sup>Data are presented as medians and interquartile ranges.

NYHA: New York Heart Association; DM: Diabetes mellitus; AF: Atrial fibrillation; PAD: Peripheral artery disease; CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate; ALT: Alanine

aminotransferase; SCr: Serum creatinine; FPG: Fasting plasma glucose; TG: Triglyceride; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; BNP: Type B natriuretic peptide; LVEDD: Left ventricular end-diastolic dimension; LVESD: Left ventricular end-systolic dimension; LVEF: Left ventricular ejection fraction; LV: Left ventricular; ARAs: Aldosterone Receptor Antagonists; ACEIs: Angiotensin converting enzyme inhibitors; ARBs: Angiotensin II receptor blockers.

**Table 2 Physical performance of the included patients evaluated by short physical performance battery according to the frailty status (mean  $\pm$  SD)**

	Frail ( <i>n</i> = 135)	Pre-frail ( <i>n</i> = 93)	<i>P</i> value
Handgrip strength (kg)			
Men	23.8 $\pm$ 4.1	25.1 $\pm$ 4.2	0.056
Women	17.9 $\pm$ 3.4	21.2 $\pm$ 4.5	0.003
Balance test	3.08 $\pm$ 0.68	3.42 $\pm$ 0.61	< 0.001
Four-meter gait test	2.19 $\pm$ 0.82	2.70 $\pm$ 0.76	< 0.001
Chair stand test	1.96 $\pm$ 0.77	2.83 $\pm$ 0.70	< 0.001
Overall SPPB score	7.24 $\pm$ 1.72	8.95 $\pm$ 1.44	< 0.001

SPPB: Short physical performance battery; SDs: Standard deviations.

**Table 3 Incidence of in-hospital mortality and the major causes of mortality during hospitalization according to the frailty status of the patients**

	Frail ( <i>n</i> = 135)	Pre-frail ( <i>n</i> = 93)	<i>P</i> value
In-hospital death	16 (11.9)	4 (4.3)	0.048
Cardiac shock	3 (2.2)	2 (2.4)	0.971
Malignant arrhythmia	3 (2.2)	1 (1.1)	0.517
MOF	10 (7.4)	1 (1.1)	0.028

MOF: Multiple organ failure.

## DISCUSSION

In this study of admitted elderly patients with HFrEF, we found that frailty and pre-frailty were common in this population, with a prevalence of 53.6% and 36.9%. Moreover, compared to patients with pre-frailty, frail patients with HFrEF were more likely to be female, to have lower blood pressure, and to present with LV thrombosis. Importantly, frail patients with HFrEF had a higher composite incidence of in-hospital adverse events. Additionally, compared with pre-frailty, frailty was associated with poor in-hospital outcomes in elderly patients with HFrEF. Although the results should be validated in multicenter prospective cohort studies, these results suggest that frailty may be associated with poor prognosis during hospitalization in elderly patients with HFrEF. Future studies are needed to determine whether early rehabilitation targeting frailty can improve the clinical outcomes in elderly patients with HFrEF.

Previous studies have shown that the prevalence of frailty varies considerably in patients with HF. A systematic review of eight studies with 5522 HF patients aged between 70 and 79 years showed that the prevalence of frailty in these studies ranged from 18%-54%, which may be related to the different populations studied and different criteria used for the diagnosis of frailty[23]. A recent study including 467 consecutive HF patients assessed with three frailty tools showed that the prevalence of frailty varies from 30% to 52% according to the tools used[24]. Regardless of the diagnostic tools used, the prevalence of frailty in HF patients is significant higher than that in controls[24]. A previous meta-analysis of 26 studies involving 6896 patients with HF showed an overall estimated prevalence of frailty in 44.5% of HF patients. The prevalence was slightly lower among studies that used Physical Frailty measures (42.9%, *Z* = 9.05; *P* < 0.001) and slightly higher among studies that used Multidimen-

**Table 4 Patient characteristics and the composite outcome of in-hospital adverse events: Results of univariate analysis**

	With AEs (n = 86)	Without AEs (n = 142)	P value
Female, n (%)	30 (34.9)	39 (27.5)	0.279
NYHA Class III/IV, n (%)	79 (91.9)	115 (80.9)	0.010
Frailty, n (%)	62 (72.1)	73 (51.4)	0.002
Hypertension, n (%)	54 (62.8)	72 (50.7)	0.075
DM, n (%)	33 (38.4)	53 (37.3)	0.874
Dyslipidemia, n (%)	18 (20.9)	33 (23.2)	0.685
AF, n (%)	28 (32.6)	30 (21.1)	0.055
Age (yr)	72.05 ± 7.46	68.65 ± 5.90	< 0.001
Handgrip strength (kg)	22.26 ± 5.34	23.04 ± 4.44	0.030
Overall SPPB score	7.50 ± 2.04	8.18 ± 1.61	0.006
SBP (mmHg)	110.87 ± 23.24	109.92 ± 21.62	0.759
DBP (mmHg)	69.34 ± 15.13	68.78 ± 11.92	0.772
PaO <sub>2</sub> (mmHg)	99.23 ± 47.56	98.20 ± 25.87	0.853
LVEF (%)	33.74 ± 6.45	33.97 ± 5.53	0.786

AEs: Adverse events; NYHA: New York Heart Association; DM: Diabetes mellitus; AF: Atrial fibrillation; SPPB: Short physical performance battery; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; LVEF: Left ventricular ejection fraction; LV: Left ventricular.

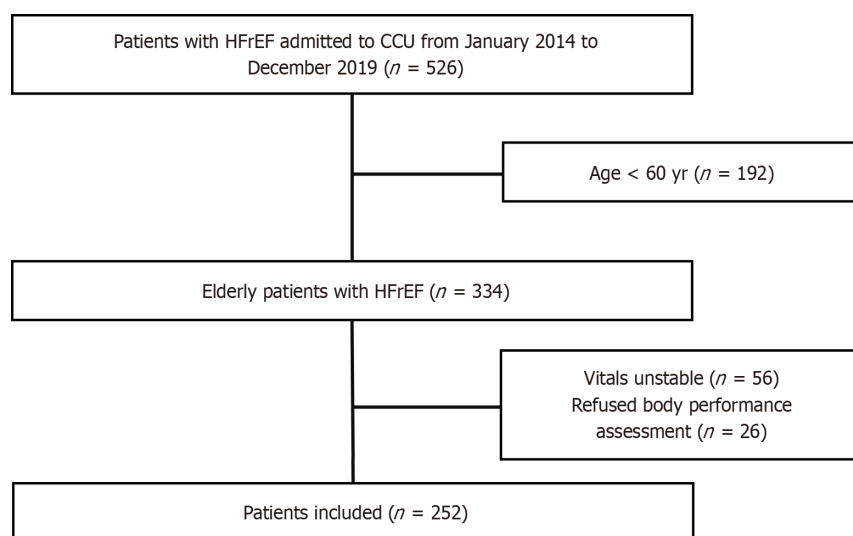
**Table 5 Potential predictive efficacy of frailty on the composite outcome of in-hospital adverse events: results of multivariate logistic regression analysis**

	SE	OR	95%CI	P value
Female	0.410	0.422	0.189-0.943	0.035
Age	0.029	1.090	1.029-1.154	0.003
NYHA Class III/IV	0.253	2.167	1.320-3.559	0.002
Frailty	0.351	2.379	1.196-4.733	0.014
Overall SPPB Score	0.100	0.945	0.776-1.150	0.570
Handgrip strength	0.047	1.106	1.010-1.212	0.030
SBP	0.007	1.003	0.989-1.017	0.656
LVEF	0.027	0.990	0.939-1.042	0.694

SE: Standard error; OR: Odds ratio; CI: Confidence interval; AEs: Adverse events; SPPB: Short physical performance battery; SBP: Systolic blood pressure; LVEF: Left ventricular ejection fraction.

sional Frailty measures (47.4%,  $Z = 5.66$ ;  $P < 0.001$ )[25]. The Fried frailty phenotype used to diagnose frailty and pre-frailty[17] in our study is a well-validated tool and has been comprehensively used in the era of geriatric medicine. Moreover, the Fried frailty phenotype has been recommended as a diagnostic tool for frailty in the Chinese population by the Chinese Geriatric Society[26]. Our results showed that the prevalence of frailty was 53.6% in our cohort, which is similar to the findings in previous studies. We found that the prevalence of pre-frailty in elderly patients with HFrEF was 36.9%. A previous study that also used the Fried frailty phenotype showed that in old patients with stable HF (mean age 85.2 years)[27], the prevalence of pre-frailty was 40.1%, which is slightly higher than the value in our population. In addition, we found that compared to patients with pre-frailty, patients with frailty were more likely to be female. Female gender has been identified as an independent risk factor for the incidence of in-hospital adverse events in elderly patients with HFrEF. These findings are also consistent with previous studies showing that women





**Figure 1** Flowchart of patient inclusion process.

may have higher odds for frailty than men of the same age[28].

Our study showed that compared to HFrEF patients with pre-frailty, patients with frailty had a higher incidence of in-hospital mortality. The difference between the incidences of in-hospital mortality in the two groups was mainly driven by death related to MOF, which may reflect the overall poor clinical status of patients with frailty not limited to the cardiovascular system. Regarding the clinical characteristics of HFrEF patients with frailty and pre-frailty, no significant difference was observed for LVEF, renal and liver function at admission, or the use of evidence-based medications for HF. This finding suggests that frailty could predict the in-hospital outcome for these patients independent of the above clinical characteristics. The presence of frailty, characterized by impaired mobility, fatigue, underweight, and sarcopenia, may overlap with the symptoms of some chronic diseases, particularly in patients with HF[29]. Currently, the mechanisms for the association between frailty and poor outcomes in HF patients remain unknown. However, experimental studies demonstrated that frailty is characterized by overactivated inflammation, which is also recognized as a key pathophysiological feature of ventricular remodeling and myocardial injury[30]. Pathophysiologically, frailty may lead to cardiac overload and an overactivated inflammatory response, thereby worsening the cardiac function[31, 32]. In addition, patients with HF exhibit reduced peripheral perfusion, sarcopenia, and reduced functional preservation of multiple organs, all of which are key features of frailty[31,32]. Future studies are warranted to determine the key molecular mechanisms underlying this association. More importantly, from the clinical perspective, future studies are needed to determine whether early rehabilitation targeting frailty can improve the clinical outcomes for elderly patients with HFrEF.

We used handgrip strength and SPPB to evaluate the physical performance of the elderly patients with HFrEF. Although we found that patients with frailty had lower handgrip strength and SPPB scores compared to those with pre-frailty, only lower handgrip strength was an independent predictor of increased risk of in-hospital adverse events in our study population. The limitation of SPPB evaluation is that it focuses on lower-extremity function. For patients with severe clinical conditions such as decompensated HF, the discrimination of SPPB for physical performance may be less sensitive to handgrip strength. Our results are consistent with those from the PURE study, which included 139691 patients and showed that for every 5 kg reduction in handgrip strength, the risk of all-cause death increased by 16% and the risk of cardiovascular disease increased by 7%[33].

Our study has limitations. Firstly, no consensus has been reached regarding the optimal tool for the evaluation of frailty. Although the Fried frailty phenotype tool has been well validated and recommended, the tool includes physical domains only and does not include components related to cognitive function, which has been confirmed as an important determinant of functional performance in elderly individuals[34]. Secondly, although we used multivariate analyses to adjust the potential confounding factors, we could not exclude the existence of unadjusted residual factors, which may confound the association between frailty and in-hospital outcomes for the patients. In



addition, the patients were evaluated during hospitalization with no subsequent follow-up. The influence of frailty on the long-term outcomes for these patients should be investigated in the future. Moreover, the proportion of patients using digitalis was significantly higher in the frail group than in the pre-frail group, and it has been reported that digitalis increased death in women with HF, which may confound the results. In addition, the blood concentration levels of digitalis were not available for the included patients, although none of the included patients suffered from digitalis toxicity.

Finally, a causative relationship between frailty and poor in-hospital outcomes in elderly patients with HFrEF could not be established based on our results since the study is observational. Clinical trials are needed to determine the influence of early rehabilitation targeting frailty on the clinical outcomes for these patients.

## CONCLUSION

In conclusion, the results of our study showed that frailty and pre-frailty are common in elderly patients with HFrEF, and that frailty, compared to pre-frailty, may be associated with poor in-hospital outcomes. These results should be validated in multicenter prospective cohort studies, and studies are needed to determine whether early rehabilitation targeting frailty can improve the clinical outcomes for elderly patients with HFrEF.

## ARTICLE HIGHLIGHTS

### **Research background**

Frailty is prevalent in elderly patients with cardiovascular diseases. However, the association between frailty and in-hospital outcomes for elderly patients with heart failure and reduced ejection (HFrEF) remains unknown.

### **Research motivation**

Frailty has been included in geriatric comprehensive assessment, which may not only be useful for evaluation of the functional status of elderly patients, but also contribute to the prognostic efficacy for patients with HFrEF.

### **Research objectives**

To evaluate the predictive efficacy of frailty, compared with pre-frailty, for adverse events in these patients.

### **Research methods**

Elderly patients ( $\geq 60$  years) with HFrEF were assessed. Frailty was evaluated with the Fried phenotype criteria, and physical performance was evaluated based on handgrip strength and the short physical performance battery (SPPB). The composite incidence of adverse events, including all-cause death, multiple organ failure, cardiac shock, and malignant arrhythmia, during hospitalization was recorded.

### **Research results**

Frailty and pre-frailty were common in this population, with a prevalence of 53.6% and 36.9%. Moreover, compared to patients with pre-frailty, frail patients with HFrEF were more likely to be female, to have lower blood pressure, and to present with left ventricular thrombosis. Importantly, frail patients with HFrEF had a higher composite incidence of in-hospital adverse events. Additionally, compared with pre-frailty, frailty was associated with poor in-hospital outcomes in elderly patients with HFrEF.

### **Research conclusions**

Frailty may be associated with poor prognosis during hospitalization in elderly patients with HFrEF.

### **Research perspectives**

The results should be validated in multicenter prospective cohort studies. Future studies are needed to determine whether early rehabilitation targeting frailty can improve the clinical outcomes in elderly patients with HFrEF.

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