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Five Prognostic Factors for Readmission in Patients Over 75 Years Old with Worsening Heart Failure

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Abstract: Heart failure (HF) is a common disease in elderly patients, particularly in those presenting as readmission for worsening HF. While recent studies have revealed mortality-associated factors in this population, little is known about prognostic factors associated with worsening HF. To investigate this clinical evidence gap in patients aged over 75 years, we retrospectively investigated 165 patients hospitalized for HF at Showa University Hospital, of whom 65 (39.4%) were readmitted for worsening HF. We extracted the candidate variables based on univariate analysis, and then elucidated the independent prognostic factors by multivariate analysis. Compared with non-readmitted patients, readmitted patients with worsening HF had lower left ventricular ejection fraction (LVEF) (39% vs. 50%, $P=0.002$) and body mass index (BMI) (19.9 kg/m^2 vs. 21.4 kg/m^2, $P=0.007$), higher levels of B-type natriuretic peptide (BNP) (478 pg/ml vs. 198 pg/ml, $P<0.001$), and heart rate (HR) (71.0 beats/min vs. 67.0 beats/min, $P=0.021$) upon discharge during the primary admission. Multivariate logistic analysis identified LVEF $<40\%$, BMI <21 kg/m^2, BNP ≥ 500 pg/ml, Charlson score ≥ 3, and HR ≥ 70 beats/min upon initial discharge as independent prognostic factors. Based on these factors, readmission for worsening HF was more frequent in those with our proposed risk score of ≥ 3.0 than in those with a risk score <3.0 ($P<0.001$), and we suggested five prognostic factors for HF patients over 75 years old. Our proposed risk score combines these factors and might predict readmission for worsening HF in the elderly population.

Key words: heart failure, readmission, prognostic factor, elderly, risk score

Introduction

Acute decompensated heart failure (HF) is a leading cause of admission to cardiology units, with the majority of patients improving immediately. However, maintaining a clinical condition by pharmacotherapy is seldom straight forward, and patients often experience readmission for worsening HF[1]. Recently, the Japanese Cardiac Registry of Heart Failure in Cardiology

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(JCARE-CARD) study reported a 27% readmission incidence for worsening HF within 6 months from discharge[2].

HF is especially common in elderly people, with the worldwide increase in incidence with advancing age likened to a pandemic[3]. Unlike younger patients, elderly patients with HF usually have comorbidities[4] that often render them refractory to conventional guideline-based treatment[5].

Recently, potentially inappropriate medications (PIMs) have attracted attention in the optimization of pharmacotherapy for elderly patients, whose frequently decreased ability to metabolize medications make them more prone to therapy-related harm. PIMs in particular have been associated with adverse events due to drug-disease and drug-drug interactions[6], and patients with many diseases are generally treated with many prescriptions, which probably include PIMs. Many countries have developed strategies and criteria for identifying and screening PIMs; however, while one systematic review associated PIMs with readmission[7], a cohort study on HF patients using the Beers criteria found no such association[8]. Therefore, the role of PIMs in readmissions of HF patients is still controversial.

Risk scores[9–11] developed to predict mortality in HF patients are considered useful for decision-making on the intensity of treatment, such as device therapy or palliative care. On the other hand, risk scores for predicting readmission for worsening HF are still under development[12]. Thus, our study aimed to elucidate the relevant prognostic factors for worsening HF in patients over 75 years old to develop a risk score for predicting readmission.

Patients and methods

Study overview

We collected data retrospectively from the medical records of patients ≥75 years old who were hospitalized for HF at Showa University Hospital from January 1, 2016 to December 31, 2018. We excluded any repeat hospitalization for HF during the study period. We explored the prognostic factors for readmission due to worsening HF by comparing clinical indices between readmitted and non-readmitted patients. We excluded the following patient groups from the data analysis: readmitted patients hospitalized premeditatedly or for a reason not related to worsening HF; non-readmitted patients defined as outpatients of Showa University hospital; and, those who were followed-up at clinic, entered a nursing facility, or received home care. We defined the follow-up period as 6 months from discharge, and the last follow-up day was May 30, 2019. Patients who died during the primary hospitalization or were transferred to another hospital were also excluded. The School of Pharmacy, Showa University ETHICAL COMMITTEE (Permit Number 324) approved this research, and information was disclosed with an opt-out clause.

Variables

We collected data on variables considered potential prognostic factors for readmission due to worsening HF, as follows: age; gender; clinical scenario and New York Heart Association classification upon admission; vital signs, weight, medications, echocardiography data, and laboratory data upon discharge; status of comorbidities; length of stay; past HF admission; and socioeco-

nomic status. Charlson scores were calculated as an index of comorbidity status[13], based on the International Classification of Diseases 10th revision. The medications upon discharge included only those prescribed by the physicians and excluded those that were taken on an as-needed basis. PIMs upon discharge were assessed using three criteria : 1) Beers criteria[6] ; 2) Screening Tool of Persons Prescription (STOPP)[14] ; and 3) Screening Tool of Persons Prescription-Japan (STOPP-J)[15]. Missing data were excluded from statistical analysis.

Statistical analysis

All continuous variables were presented as mean ± standard deviation or as a median (interquartile range). All categorical variables were presented as frequency (percentage). For comparisons of continuous variables, unpaired Student's t-test was used for parametrically distributed data, and the Mann-Whitney U-test was used for non-parametrically distributed data. Fisher's exact test was used to compare categorical variables.

We developed a risk score for predicting readmission in three steps. First, we identified the candidate variables associated with readmission for worsening HF using univariate analysis. Variables with a $P < 0.2$ by univariate analysis and those that were clinically important were chosen as the candidate variables. Second, we extracted the prognostic factors by stepwise multivariate logistic regression analysis and excluded candidate variables showing $P \geq 0.05$. Continuous candidate variables included in the regression equation were categorized as dichotomous variables, based on receiver operating characteristic (ROC) curves. Considering the collinearity, we used variance inflation factors. The degree of association between the prognostic factors and readmission for worsening HF was expressed as odds ratios (OR) and 95% confidence intervals (CI). Third, we developed a risk score for predicting readmission for worsening HF, based on the logistic regression equation. The weight given to each variable was based on the natural logarithm of the OR[16].

We evaluated the discrimination ability of our proposed risk score using the area under the ROC (AUROC) curve and 95% CI. Based on the risk score that gave the maximum sum of the sensitivity and specificity on the ROC curve, we stratified HF patients into 2 groups. The incidences of readmission for worsening HF in both groups were analyzed by the Kaplan-Meier method and were compared using the log rank test.

All analyses were two-tailed, and $P < 0.05$ was considered to be statistically significant. Statistical analyses were performed using EZR version 1.37 (Jichi Medical University, Saitama, Japan)[17].

Results

Figure 1 shows the study population flowchart. Of the 340 patients discharged, 99 patients could not become outpatients of Showa University hospital and 75 patients were readmitted for reasons excluding worsening HF. We therefore included 165 patients in our study. During the study period, there were 65 (39.4%) patients readmitted for worsening HF.

Table 1 details the patients' baseline characteristics. Compared with non-readmitted patients, those who were readmitted for worsening HF had a lower body mass index (BMI) (19.9 kg/m^2

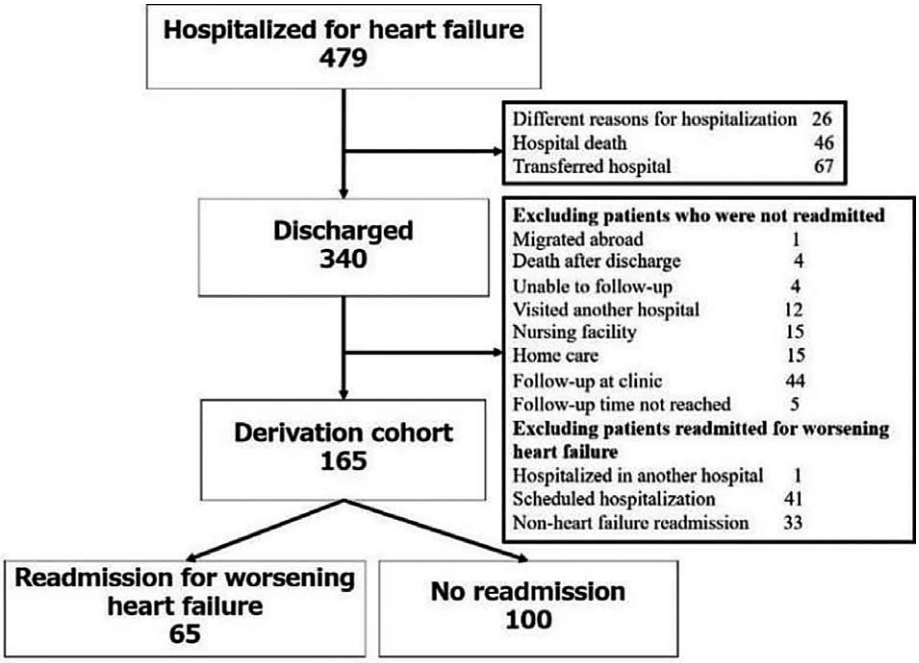

Fig. 1. Patient flowchart

vs. 21.4 kg/m^2), left ventricular ejection fraction (LVEF) (39% vs. 50%), and higher B-type natriuretic peptide (BNP) levels (478 pg/ml vs. 198 pg/ml); diastolic blood pressure (DBP) (64.0 mmHg vs. 61.0 mmHg); serum creatinine (1.3 mg/dl vs. 1.1 mg/dl); and heart rate (HR) (71.0 beats/min vs. 67.0 beats/min) upon discharge. The Charlson score was numerically higher in patients readmitted for worsening HF than in the non-readmitted patients ($P = 0.039$). With regard to the medications upon discharge, patients who were readmitted for worsening HF received less prescriptions for angiotensin converting enzyme (ACE) / angiotensin receptor blocker (ARB) (40% vs. 60%, $P = 0.017$) and mineralocorticoid receptor antagonist (MRA) (31% vs. 49%, $P = 0.024$). On the other hand, upon discharge, the number of medications and the number of STOPP-J PIMs were not significantly different between the groups.

Based on the univariate analysis, we adopted 17 candidate variables, including male gender, systolic blood pressure, BMI, LVEF, BNP, DBP, serum creatinine, HR, hypertension, atrial fibrillation, length of stay, HF hospitalization history, alone (Home environment), Charlson score, ACE/ARBs, MRAs, and loop diuretics. The results of the multivariate logistic regression analysis are shown in Table 2. Of the 17 candidate variables, 5 variables (Charlson score ≥ 3, LVEF $< 40\%$, BMI < 21 kg/m^2, HR ≥ 70 beats/min, and BNP ≥ 500 pg/ml) were extracted as the prognostic factors. The ROC curves and the risk scores for each prognostic factor are shown in Figure 2. At an AUROC curve of 0.81 (95% CI 0.75-0.88), the sum of the sensitivity and specificity was maximum at a risk score of 3.0 points. The Kaplan-Meier curves are shown in Figure 3. Readmissions for worsening HF were more frequent in patients with a risk score ≥ 3.0 points than in those with risk scores < 3.0 points (log-rank, $P < 0.001$).

Table 1. Baseline characteristics of the patients

	Readmission for worsening HF (n=65)	No readmission (n=100)	*P*
Age (years)†	85.6±5.3	84.7±5.2	0.259
Male	24 (37)	51 (51)	0.081
Vital signs at discharge			
Systolic BP (mmHg)	118 (105-132)	110 (100-126)	0.056
Diastolic BP (mmHg)	64.0 (57.0-72.0)	61.0 (54.0-68.0)	0.046*
Heart rate (beats/min)	71.0 (67.0-80.0)	67.0 (59.0-78.0)	0.021*
BMI (kg/m^2)	19.9 (17.9-22.1) (n=61)	21.4 (19.7-23.3) (n=94)	0.007*
NYHA classification (admission) II	7 (11)	10 (10)	Reference
III	12 (18)	35 (35)	0.236
IV	46 (71)	55 (55)	0.797
Laboratory data at discharge			
Hemoglobin (g/dl)	11.0±1.7	11.3±1.9	0.362
Serum creatinine (mg/dl)	1.3 (1.0-1.7)	1.1 (0.9-1.4)	0.008[b]*
BNP (pg/ml)	478 (233-689)	198 (106-313)	<0.001*
Echocardiography at discharge			
LVEF (%)	39 (32-53)	50 (39-58)	0.002*
Comorbidity			
Hypertension	51 (78)	89 (89)	0.077
Diabetes mellitus	16 (25)	20 (20)	0.564
Ischemic heart failure	35 (54)	52 (52)	0.873
Atrial fibrillation	24 (37)	51 (51)	0.081
Charlson score	3.0 (2.0-5.0)	3.0 (1.8-4.0)	0.039*
Length of stay (days)	19 (14-34)	19 (14-26)	0.175
HF hospitalization history	27 (42)	31 (31)	0.184
Home environment	(n=61)	(n=94)	
With son or daughter	30 (49)	56 (60)	Reference
Old couple	16 (26)	23 (24)	0.552
Alone	15 (25)	15 (16)	0.192
Medication at discharge			
Medications (n)	9.8±3.6	9.9±3.5	0.966
STOPP-J PIMs (n)	2.0 (1.0-3.0)	2.0 (2.0-3.0)	0.719
STOPP PIMs (n)	1.0 (0-2.0)	2.0 (0-2.0)	0.912
Beers PIMs (n)	0 (0-2.0)	0 (0-1.0)	0.732
ACE inhibitors/ARBs	26 (40)	60 (60)	0.017*
MRAs	20 (31)	49 (49)	0.024*
β blockers	57 (88)	80 (80)	0.288
Loop diuretics	58 (89)	96 (96)	0.114
Statins	30 (46)	44 (44)	0.873

Data given as mean±SD, median (IQR) or n (%). †Age of the patients range from 75 to 99. ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, b-type natriuretic peptide; BP, blood pressure; HF, heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PIMs, potentially inappropriate medications; SD, standard deviation; STOPP, Screening Tool of Person's Prescription; STOPP-J, Screening Tool of Person's Prescription-Japan. *$P<0.05$

Table 2. Prognostic factors for readmission for worsening HF based on multivariate analysis

	OR	95% CI	*P*
Charlson score ≥ 3	2.38	1.04–5.44	0.040
LVEF＜40%	2.41	1.02–5.66	0.044
BMI＜21kg/m^2	2.63	1.20–5.79	0.016
HR≥70beats/min	3.64	1.62–8.17	0.002
BNP≥500pg/ml	5.41	1.91–15.3	0.001

ACE, angiotensin converting enzyme ; ARB, angiotensin receptor blocker ; BMI, body mass index ; BNP, b-type natriuretic peptide ; BP, blood pressure ; CI, confidence interval ; HF, heart failure ; HR, heart rate ; LVEF, left ventricular ejection fraction ; MRA, mineralocorticoid receptor antagonist.
P＜0.05, by stepwise logistic regression analysis.
Candidate variables : Male gender, Systolic BP ≥110 mmHg, Diastolic BP ≥70 mmHg, HR ≥70 beats/min, serum creatinine ≥1.2 mg/dL, BNP ≥500 pg/mL, BMI ＜21 kg/m^2, LVEF ＜40%, Hypertension, Atrial fibrillation, Carlson score ≥3, Length of stay ≥28 days, HF hospitalization history, Alone, ACE inhibitors/ARBs, MRAs, Loop diuretics

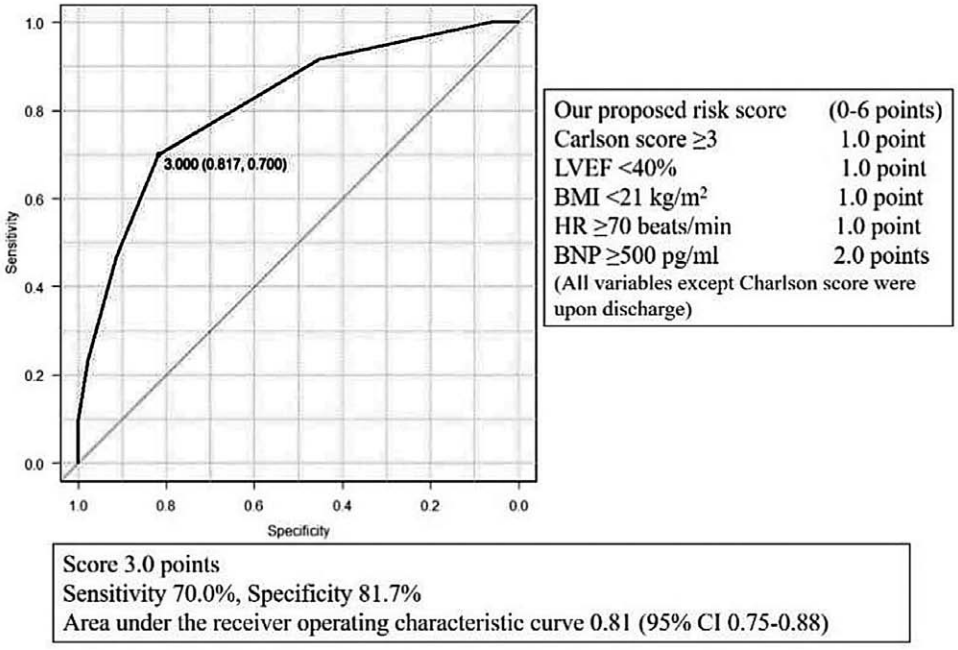

Fig. 2. Discrimination of the considered risk score for predicting readmission for worsening heart failure
The Area under the ROC curve is 0.81 (95% CI 0.75–0.88). The considered risk score ranges from 0–6 points. At 3.0 point, the maximum sum of the sensitivity and specificity is 70.0% and 81.7%, respectively. BMI, body mass index; BNP, B-type natriuretic peptide; HR, heart rate; LVEF, left ventricular ejection fraction; ROC, receiver-operating characteristic.

Discussion

Herein, we elucidated five prognostic factors that were associated with readmission for worsening HF in elderly patients. The number of discharge medications that fulfilled the SOPP-J criteria for PIMs was not extracted as a prognostic factor. Hamaguchi *et al.*[18] previously

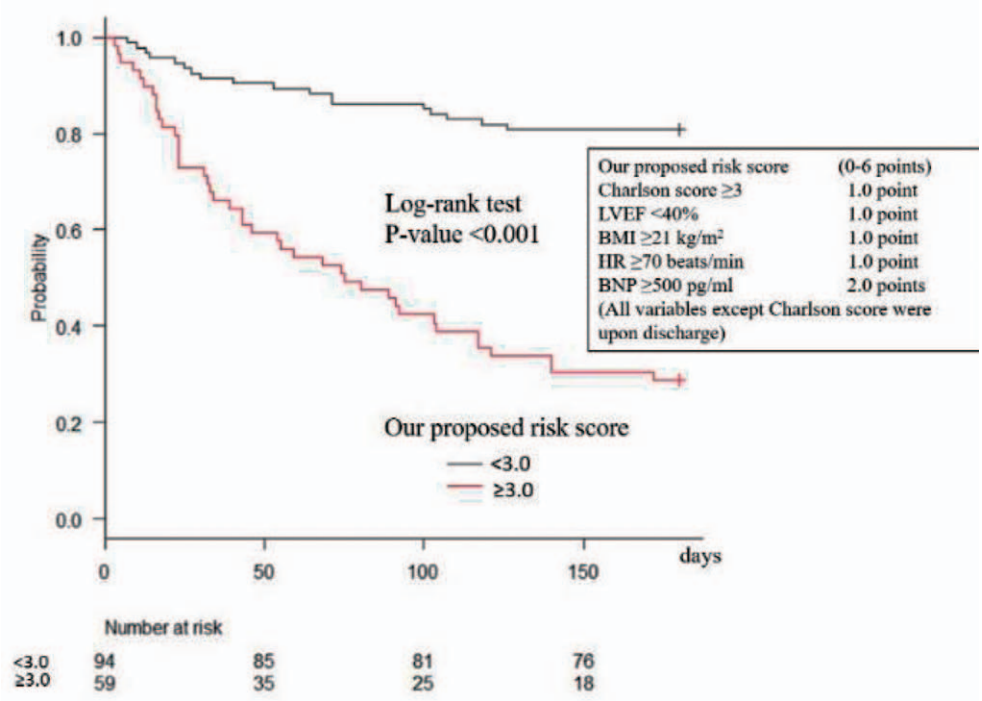

Fig. 3. Incidence rates of readmission for worsening heart failure according to our proposed risk scores
The Kaplan-Meier curve for the time to readmission for worsening heart failure was less decreased for our proposed risk score of < 3.0 points than for our proposed risk score of ≥ 3.0 points. BMI, body mass index; BNP, B-type natriuretic peptide; HR, heart rate; LVEF, left ventricular ejection fraction

suggested that lower estimated glomerular filtration, nitrate use, and no hypertensive heart failure were associated with readmission for worsening HF in patients ≥ 80 years old with HF. Our results thus add further evidence to validate the previous study. To the best of our knowledge, our study was the first to consider the risk score for predicting readmission for worsening HF in elderly patients. Unlike the predictive formula of Sakamoto *et al*[19], comprising 50 parameters, our proposed and simple risk score might more easily drive the readmission for worsening HF in five factors. Our proposed risk score of ≥ 3.0 points sufficiently discriminated those patients who needed readmission for worsening HF.

A study by Lai *et al*[7]. supported our results on the absence of an association between readmission for worsening HF and the number of discharge medications that fulfilled the STOPP-J criteria. Based on the STOPP-J criteria, the PIMs identified loop diuretics in 154 (93%) patients and spironolactone in 66 (40%) patients (data not shown). These medications have been frequently used for HF treatment. However, in another setting, some of the medications that fulfilled the STOPP-J criteria and were associated with worsening HF, such as non-steroidal anti-inflammatory drugs[20] and pioglitazone[21], could also play in the readmission for worsening HF. The Charlson score is calculated by the sum of weighted score assigned to 17 comorbidities separately, based on the relative risk of mortality. This assignment included HF and chronic kid-

ney disease, which means patients with both disease have Charlson score ≥ 3. A meta-analysis suggested that chronic kidney disease was associated with all-cause death in HF patients[22]. This study partly supported our result on the association of Charlson score ≥ 3 with readmission for worsening HF. Shama *et al*[23]. suggested that lower BMI was associated with cardiac mortality in patients with HF. Their results supported our finding that a BMI < 21 kg/m^2 was associated with readmission for worsening HF. The decrease of BMI may express malnutrition, and malnutrition is an independent prognostic factor in HF patients[24]. A prior study based on the JCARE-CARD registry suggested few differences in the incidence of readmission for worsening HF between LVEF ≥ 50% and LVEF < 40%[25]. Their results may seem to contradict our results. However, this difference may be accounted for by our inclusion criterion of patients ≥ 75 years old. In the BEAUTIFUL study, subanalyses of the morbidity mortality with the ivabradine in patients with coronary disease and left ventricular dysfunction suggested that a HR > 70 beats/min was associated with admission for worsening HF in patients with LVEF < 40%[26]; their results was similar to ours. van Veldhuisen *et al.*[27] suggested that a high BNP was associated with readmission for worsening HF. Their results supported our finding that a BNP ≥500 pg/ml was associated readmission for worsening HF. A recent study showed that BNP-targeted treatment has no effect the readmission for worsening HF in patients ≥ 75 years old[28]. We may decrease the readmission for worsening HF by monitoring Charlson Score, BMI, LVEF, and HR in addition to BNP. In a systematic review that included 10 studies on the use of risk scores to predict readmission in HF patients[12], the range of the AUROC curves was 0.60 to 0.82. The discrimination of our considered risk score was relatively good, but may have been overfitting, because it was evaluated using the derivation cohort. To evaluate the extent of overfitting, a validation study on another cohort is needed.

Our study had some limitations. First, we analyzed a relatively small sample size, mainly due to the exclusion criteria for readmitted and non-readmitted patients. Excluding the discharged patients except outpatients of Showa University Hospital, we prevented the possibility discharged patients being readmitted to another hospital. Second, our study was based on a single setting, and thus might not be applicable to the general population. However, compared with prior studies, our study identified similar prognostic factors for HF patients. Third, based on the retrospective nature of data collection from the medical records, the proper intake of the prescribed medications after discharge was not verified. Further studies are needed to evaluate the association between medication adherence and the prognosis of elderly HF patients.

In conclusion, in HF patients ≥ 75 years old, the Charlson score ≥ 3, LVEF < 40%, BMI < 21 kg/m^2, HR ≥ 70 beats/min, and BNP ≥ 500 pg/ml were associated with readmission for worsening HF. Therefore, the considered risk score, which comprises these prognostic factors, might predict the readmission for worsening HF in patients ≥ 75 years old.

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Conflict of interest disclosure

The authors have no conflicts of interest to declare.

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