Models to predict prognosis in older patients with heart failure complicated by pre-frailty and frailty: a pilot prospective cohort study

Takuya Umehara *, Nobuhisa Katayama, Akinori Kaneguchi, Yoshitaka Iwamoto, Miwako Tsunematsu, Masayuki Kakehashi

A B S T R A C T

Introduction: There are no clinical prediction models to predict the prognosis of pre-frailty or frailty in patients with heart failure. We aimed to develop prediction models for the prognosis of pre-frailty and frailty in older patients with heart failure using the classification and regression tree (CART) method; we then tested the predictive accuracies of the developed models.

Methods: Patients with pre-frailty or frailty at admission were divided into improved and non-improved groups. The CART method was used to establish two models: A, which predicted the presence or absence of pre-frailty improvement during hospitalisation; and B, which predicted the presence or absence of frailty improvement during hospitalisation.

Results: Patients with heart failure complicated by pre-frailty (n=28) or frailty (n=156) were included. In model A, the accuracy of predicting pre-frailty improvement was high; the best predictor was single-leg standing time at admission, followed by left ventricular ejection fraction at admission. In model B, the accuracy of predicting frailty improvement was moderate; the best predictor was hand grip strength at admission, followed by estimated glomerular filtration rate at admission, haemoglobin level at admission, and change in single-leg standing time during hospitalisation. The areas under the receiver operating characteristic curves of the CART models were 0.96 and 0.84 in models A and B, respectively.

Conclusion: Although conditions at admission may predict the improvement of pre-frailty and frailty during hospitalisation, cardiac rehabilitation that improves single-leg standing time may help to improve frailty, particularly when conditions at admission are poor.

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New knowledge added by this study

- We developed prediction models for the prognosis of pre-frailty and frailty in older patients with heart failure using classification and regression tree methods.
- Single-leg standing time at admission was the best predictor of pre-frailty improvement, whereas hand grip strength at admission was the best predictor of frailty improvement.
- Change in single-leg standing time during hospitalisation was also a predictor of frailty improvement.

Implications for clinical practice or policy

- Improvements in physical function can help to manage frailty in older patients with heart failure, particularly when conditions at admission are poor.
- Cardiac rehabilitation to prolong single-leg standing time is necessary to improve frailty, particularly when conditions at admission are poor.

Introduction

Heart failure is a major public health problem that has been shown to increase with age, such that incidence rates rapidly increase after 80 years of age.[1] Among older patients with heart failure, 18% to 54% show signs of frailty, a state of reduced physical and cognitive function that results in weakness.[2] There are some overlapping symptoms between heart failure and frailty; they interact to accelerate the vicious cycle of frailty.[3] One study showed that frail patients

老年患者心臟衰竭併發體弱前期和體弱預後的預測模型：試點前瞻性隊列研究

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引言：目前尚無臨床預測模型來預測心臟衰竭患者體弱前期或體弱的預後。本研究旨在使用分類和迴歸樹（CART）開發心臟衰竭老年患者體弱前期或體弱預後的預測模型，以及測試這個模型的預測準確性。

方法：將體弱前期或入院時體弱患者分為改善組和未改善組。利用CART建立兩個模型：模型A預測住院期間是否存在衰弱前期改善，模型B則預測住院期間體弱情況有否改善。

結果：納入心臟衰竭併發體弱前期（n=28）或體弱（n=156）的患者。模型A預測體弱前期改善的準確性很高；最佳預測指標是入院時的單腿站立時間，其次是入院時的左心室射血分數。模型B預測體弱改善的準確性中等，最佳預測指標是入院時的握力，其次是入院時估算的腎小球濾過率、入院時血紅蛋白水平以及住院期間單腿站立時間的變化。CART模型的受試者工作特徵曲線下面積在模型A和B分別為0.96和0.84。

結論：雖然老年患者入院時的情況可能預示其住院期間體弱前期和體弱的改善，但改善單腿站立時間的心臟復康可能有助改善他們的體弱，尤其在入院時條件較差的情況下。

with cardiovascular disease had a 7-year survival rate of 12%, which was much lower than the survival rate in non-frail patients with cardiovascular disease (43%).[4] Moreover, frailty among patients with heart failure has been associated with poor prognosis[5] and reduced cardiac output capacity.[6] Pre-frailty is the first step towards frailty; approximately 34.6% to 46.1% of individuals with pre-frailty progress to frailty in Japan.[7] Therefore, improvements in frailty and pre-frailty are important considerations in the care of older patients with heart failure.

Age,[8] nutrition,[9] walking speed,[9] heart function,[8] and grip strength[10] have been shown to influence frailty improvement among older patients with heart failure. However, the predictive accuracies of such factors remain unknown. Moreover, a combination of the predictors has been suggested to increase their predictive accuracy,[11] although this hypothesis has not yet been tested. Additionally, nutrition,[12] physical function,[12] and quality of life[12] have been reported to influence pre-frailty improvement among community-dwelling older individuals. To our knowledge, there are no reports of factors that influence pre-frailty improvement among patients with heart failure.

In this study, we used the classification and regression tree (CART) method,[13] which facilitates the establishment of clinical prediction models that can identify the best combinations of medical signs, symptoms, and other findings to predict prognoses or treatment outcomes.[13] Several clinical prediction models have been developed using the CART method to predict mortality in patients with heart failure.[14,15] However, no clinical prediction models have been established to predict the prognosis of patients with heart failure complicated by pre-frailty and frailty.

Here, we aimed to use the CART method to develop models that could predict the prognosis of older patients with heart failure complicated by pre-frailty and frailty, then confirm the predictive accuracies of those models.

Methods

Study design

This pilot prospective cohort study followed the STROBE reporting guidelines. All included patients provided written informed consent to participate in the study. Identifying information was not collected to protect each patient's privacy. This study was performed in accordance with the Declaration of Helsinki.

Setting

Recruitment, follow-up, and data collection were performed at two acute hospitals (Saiseikai Kure Hospital, Kure, Japan; Kure Kyosai Hospital, Kure, Japan) between July 2018 and December 2019. Potential participants were recruited by therapists at the rehabilitation department.

Patients

This study included patients who met the following inclusion criteria: age ≥65 years; hospitalisation for the treatment of heart failure; and presence of pre-frailty or frailty. The exclusion criteria were complications during hospitalisation and/or severe dementia (defined as a revised Hasegawa's Dementia Scale score ≤9).

Intervention

Cardiac rehabilitation was performed by physical or occupational therapists to improve physical condition, restore walking ability during hospitalisation, and expand the activities of daily living. Rehabilitation programmes were established by physical or occupational therapists in accordance with physicians' orders. Initially, aerobic exercises and resistance training programmes were provided according to each patient's physical condition. Exercise intensity was determined using multiple indices, including target heart rate (convenient method: resting heart rate + 20 bpm), talk test, and Borg scale (11-13) for the chest and lower limbs. The type of exercise was modified (ie, duration extended

and load increased) with consideration of each patient's symptoms and haemodynamics. If necessary, functional exercises (eg, neuromuscular facilitation, joint range of motion, and muscle strengthening exercises), exercises for activities of daily living, and psychological support were implemented for patients and their families. Exercises for activities of daily living were customised according to the functions that each patient needed for discharge. Overall, the duration and frequency of intervention were 30 minutes to 1 hour per day and 5 days per week, respectively.

Variables

Variables included demographic and clinical characteristics, frailty assessment results, and physical function. Demographic characteristics included age, sex, body mass index, living arrangement (with family members or alone), New York Heart Association class, medical history (eg, heart failure, coronary artery disease, valvular disease, hypertension, diabetes mellitus, dyslipidaemia, atrial fibrillation, chronic renal dysfunction, and/or stroke), cognitive function assessed using the revised Hasegawa's Dementia Scale, Life-Space Assessment score, interval from admission to initiation of cardiac rehabilitation, interval from admission to rehabilitation room entry, and length of hospital stay. Hasegawa's Dementia Scale scores of 21-30, 15-20, 10-14, and ≤9 were regarded as normal, suspected dementia, mild to moderate dementia, and severe dementia, respectively.[16] The Life-Space Assessment developed by Baker et al[17] was used to evaluate life-space mobility. Up to 120 points were assigned based on the degree of independence in each life-space level during the month prior to the assessment; higher scores were considered indicative of broader life-space and/or greater independence.

Clinical characteristics included blood data, cardiac function, and pharmacotherapy. Blood data included the Geriatric Nutritional Risk Index, brain natriuretic peptide level, estimated glomerular filtration rate (eGFR), and haemoglobin (Hb) level. Cardiac function was evaluated using left ventricular ejection fraction (LVEF), as determined by echocardiography. Pharmacotherapy data included whether patients were receiving dopamine, dobutamine, noradrenaline, phosphodiesterase III inhibitor, or diuretics.

Frailty was assessed using the following five conditions based on the Cardiovascular Health Study (CHS) Index: slow gait speed, weakness, exhaustion, low activity, and weight loss.[18] Slow gait speed was defined as <1.0 m/s. Weakness was assessed using maximum grip strength according to sex-specific cut-offs (<26 and <18 kg for men and women, respectively). Exhaustion was assessed using the question "During the past 2 weeks, have you felt tired without a specific reason?" A positive response to this question (ie, "yes") was considered indicative of exhaustion. Physical activity was evaluated using the question "Do you engage in low levels of physical activity to improve your health?" A negative response to this question (ie, "no") was considered indicative of a low activity level. Weight loss was assessed using the question "Have you lost 2 kg or more in the past 6 months?" A positive answer to this question was considered indicative of weight loss. There are various criteria for assessing frailty; Fried's frailty phenotype model[18] and the accumulated deficit model established by Mitnitski et al[19] are well known. The CHS criteria and the Frailty Index were developed based on the above frailty phenotype model and accumulated deficit model, respectively. Furthermore, a Japanese version of the CHS criteria (J-CHS) has been established,[20] and its validity has been confirmed.[21] Thus, we selected the J-CHS to assess frailty. Patients with none of the above conditions were considered non-frail (robust), patients with one to two conditions were considered pre-frail, and patients with three conditions or more were considered frail.[22]

Physical function was assessed using the Short Physical Performance Battery score, 10-metre walk time, single-leg standing time, and hand grip strength. Patients performed the Short Physical Performance Battery test in the following sequence, in accordance with the National Institute on Aging protocol: standing balance tests, gait test (4 m), and chair stand test (five repetitions). The sum of the three test components comprised the final Short Physical Performance Battery score, which ranged from 0 to 12; a score of 12 indicated optimal lower extremity function.[23,24] Moreover, 10-m walk time was measured at a comfortable walking speed to assess walking ability. The 10-m walk test has demonstrated high validity and reliability in multiple populations, including healthy older individuals and patients with stroke, neurological disorders, or orthopaedic dysfunction.[25,26] Measurements were performed twice at an interval of 30 s; the smaller value was used to indicate walking ability. Standing balance was evaluated by measuring single-leg standing time, which reflects the ability to maintain the body's centre of gravity within its base of support. A stopwatch was used to measure the duration that a patient could stand on one leg with their eyes open and hands on their waist, without any assistance or falling. A second trial was performed if the result of the first trial was <60 s.[27] Hand grip strength (kg) was measured using a digital hand grip strength dynamometer (TKK-5101; Takei Scientific Instruments, Tokyo, Japan or 12B3X00030; Tsutsumi Works, Chiba, Japan). Accordingly, patients were asked to squeeze the dynamometer with maximum effort during two trials for each hand. The maximum

value (rounded to the nearest 0.1 kg) for either the left or right hand was used for subsequent analyses.[28]

Demographic and clinical characteristics were assessed upon admission or each time, whereas cognitive function and Life-Space Assessment were assessed during the first physical therapy session. Frailty and physical function were assessed upon initial entry into the rehabilitation room and at discharge. The amount of change in physical function (discharge–initial) was calculated.

Bias

To reduce selection bias, outcomes were selected based on the methods of previous studies.[16-28] To reduce measurement bias, the first author (T Umehara) was not involved in participant enrolment or data collection. Patients received explanations about the purpose of the study but did not receive information concerning the hypothesis tested.

Statistical analysis

Classification and regression tree analysis[29] was used to predict the primary outcomes. Patients with pre-frailty at admission were categorised into an improved group and a non-improved group: patients who were non-frail at discharge were assigned to the improved group, whereas patients who were pre-frail or frail were assigned to the non-improved group. Similarly, patients with frailty at admission were categorised into an improved group and a non-improved group: patients who were non-frail or pre-frail at discharge were assigned to the improved group, whereas patients who were frail were assigned to the non-improved group. Binary trees were used to recursively split predictor variables based on answers to yes/no questions for each variable. All statistical distributions were considered without limitation to linear relationships between outcome variables and predictor variables. These algorithms have been used to develop prediction models in various fields.[30-32] The CART method with the Gini index was used for the following models: A, which predicted the presence or absence of pre-frailty improvement during hospitalisation; and B, which predicted the presence or absence of frailty improvement during hospitalisation. Pre-frailty or frailty improvement was the dependent variable, whereas demographic and clinical characteristics, pharmacotherapy, and amount of change in physical function were the independent variables. The accuracies of the CART models were evaluated using the area under the receiver operating characteristic curve (AUROC). The method proposed by Delong et al[33] was used to identify optimal cut-off points. Subsequently, the sensitivity, specificity, positive likelihood ratio (PLR), and negative likelihood ratio (NLR) were calculated. To assess model validity, cross-validation was performed as follows: the sample was divided into 10 subgroups and the model developed from nine subgroups was used to test the 10th subgroup; this was repeated for all 10 combinations and the rates of misclassification were averaged. Model validity was considered high when the misclassification rates were similar before and after cross-validation. The accuracies of the CART models were evaluated using the AUROC developed from each method. The maximum Youden index (sensitivity + specificity – 1) was defined as the optimal cut-off point. All statistical analyses were performed using SPSS (Windows version 23.0; IBM Corp, Armonk [NY], United States) and the significance level was set at 5%.

Sample size

Sample size calculations were conducted using MedCalc statistical software, version 19.2 (MedCalc Software bvba, Ostend, Belgium). Before plotting an AUROC, the following values were established: statistical significance ($P<0.05$), alpha (0.05), statistical power (0.80), and the AUROC value to be included in the null hypothesis (0.5). The AUROC could distinguish between non-predictive ($AUROC<0.5$), less predictive ($0.5<AUROC<0.7$), moderately predictive ($0.7<AUROC<0.9$), highly predictive ($0.9<AUROC<1$), and perfectly predictive ($AUROC=1$).[34] In this study, an AUROC value of 0.7 was considered indicative of superior statistical discrimination. The frailty improvement ratio (ie, positive/negative ratio) considerably varied among previous studies.[35-37] Therefore, the positive/negative ratio used here was set at 1:1-5. Moreover, a large sample size was needed to allow for the possibility of stratified analysis. Thus, 62 to 120 patients with frailty were required: 20-31 and 31-100 in the improved and non-improved groups, respectively.

Results

Figure 1 shows the flowchart of patient recruitment. Among the 30 patients with pre-frailty, two with severe dementia were excluded; 28 patients were included in the analysis. Among the 161 patients with frailty, five with severe dementia were excluded; 156 patients were included in the analysis. The patient characteristics are summarised in Tables 1 and 2 (patients with pre-frailty and patients with frailty, respectively).

Figure 2 shows CART model A, which predicted the presence or absence of pre-frailty improvement during hospitalisation. Among the 28 patients with pre-frailty, seven experienced improvements. Single-leg standing time at admission was identified as the best single discriminator for pre-frailty improvement (≤4.4 or >4.4 s). Among patients with single-leg standing time of >4.4 s at

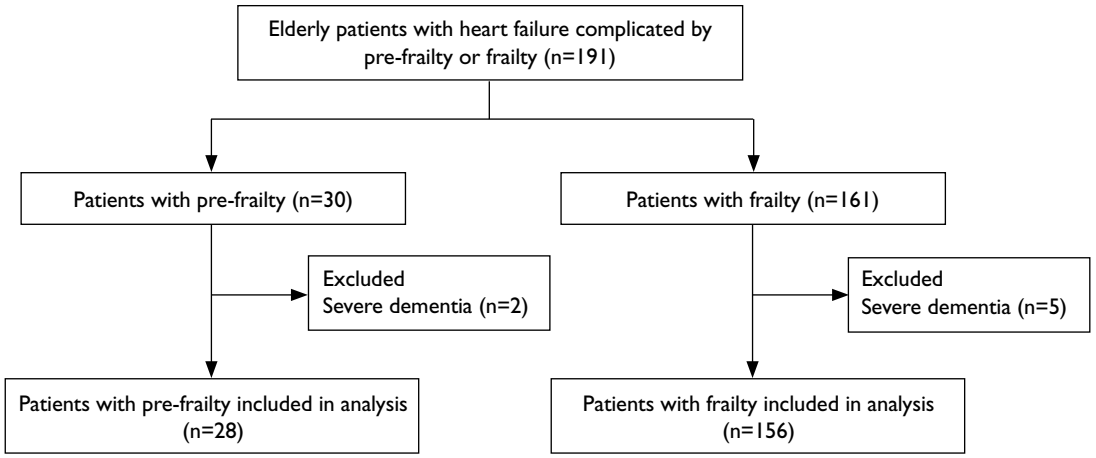

FIG 1. Flowchart depicting the recruitment of older patients with heart failure complicated by pre-frailty and frailty

admission, the next predictor was LVEF (≤36.8% or >36.8%). Our CART analysis resulted in the establishment of three terminal nodes. The terminal node with the highest probability of a favourable outcome (pre-frailty improvement) was defined as rank 1, whereas the terminal node with the lowest probability of a favourable outcome was defined as rank 3. Based on the AUROC (95% confidence interval [CI]), this CART model had an accuracy of 0.96 (95% CI=0.89-1.00), with an optimal cut-off point of rank 1 (sensitivity: 85.7%, specificity: 95.2%, PLR: 18.0, and NLR: 0.15). The misclassification rates before and after cross-validation were 7.1% and 28.6%, respectively.

Figure 3 shows CART model B, which predicted the presence or absence of frailty improvement during hospitalisation. Among the 156 patients with frailty, 57 experienced improvements. Hand grip strength at admission was identified as the best single discriminator for frailty improvement (≤16.8 or >16.8 kg). Among patients with hand grip strength of >16.8 kg at admission, the next predictor was eGFR (≤27.0 or >27.0 mL/min/1.73 m^2). Among patients with hand grip strength of ≤16.8 kg at admission, the next predictor was eGFR (≤83.5 or >83.5 mL/min/1.73 m^2). Among patients with eGFR ≤83.5 mL/min/1.73 m^2, the next predictor was Hb level (≤14.3 or >14.3 g/dL). Among patients with Hb level ≤14.3 g/dL, the next predictor was change in single-leg standing time (≤4.9 or >4.9 s). Our CART analysis resulted in the establishment of six terminal nodes. The terminal node with the highest probability of a favourable outcome (frailty improvement) was defined as rank 1, whereas the terminal node with the lowest probability of a favourable outcome was defined as rank 6. Based on the AUROC (95% CI), this CART model had an accuracy of 0.84 (95% CI=0.78-0.91), with an optimal cut-off point of rank 4 (sensitivity: 70.1%, specificity: 86.9%, PLR: 5.3, and NLR: 0.3). The misclassification rates before and after cross-validation were 19.2% and 35.3%, respectively.

Discussion

Model A predicted pre-frailty improvement with high accuracy; it identified single-leg standing time at admission as the best predictor, followed by LVEF. Notably, changes in physical function during hospitalisation were not identified as predictors. These results suggest that conditions at admission strongly influence pre-frailty improvement during hospitalisation; moreover, improvement can be expected among patients with good physical function (single-leg standing time >4.4 s) and cardiac function (LVEF >36.8%) at admission. To our knowledge, no study has examined the factors that influence pre-frailty improvement among patients with heart failure. However, one study found that physical function, nutrition, and quality of life were factors that influenced pre-frailty improvement among community-dwelling older individuals.[12] The above findings suggest that although physical function is a common factor that influences pre-frailty improvement among older patients with heart failure and community-dwelling older individuals, cardiac function specifically influences pre-frailty improvement among patients with heart failure.

Model B predicted frailty improvement with moderate accuracy; it identified hand grip strength at admission as the best predictor, followed by eGFR, Hb level, and change in single-leg standing time during hospitalisation. Thus, frailty improvement can be expected among patients with good hand grip strength and/or renal function at admission.

TABLE 1. Characteristics of patients with pre-frailty*

Variable	Category	Pre-frailty improved group (n=7)	Pre-frailty non-improved group (n=21)	P value
Admission (baseline)				
Age, y		74.4 ± 5.5	83.0 ± 9.3	0.30†
Sex	Male/female	2/5	13/8	0.13‡
Body mass index, kg/m^2		22.8 ± 2.4	23.4 ± 5.0	0.68†
Living with family	Yes/no	0/7	7/14	0.27‡
New York Heart Association class		2.3 ± 0.8	2.4 ± 1.0	0.91§
Medical history				
Heart failure	Yes/no	3/4	16/5	0.10‡
Coronary artery disease	Yes/no	3/4	8/13	0.82‡
Valvular disease	Yes/no	0/7	5/16	0.15‡
Hypertension	Yes/no	5/2	14/7	0.82‡
Diabetes mellitus	Yes/no	4/3	10/11	0.66‡
Dyslipidaemia	Yes/no	3/4	10/11	0.83‡
Atrial fibrillation	Yes/no	2/5	8/13	0.65‡
Chronic renal failure	Yes/no	2/5	9/12	0.50‡
Stroke	Yes/no	0/7	2/19	0.66‡
Pharmacotherapy				
Dopamine	Yes/no	0/7	0/21	
Dobutamine	Yes/no	0/7	1/20	0.56‡
Noradrenaline	Yes/no	0/7	0/21	
Phosphodiesterase III inhibitor	Yes/no	1/6	1/20	0.40‡
Diuretic	Yes/no	4/3	5/16	0.10‡
Geriatric Nutritional Risk Index score		100.1 ± 5.3	91.5 ± 14.6	0.03†
Brain natriuretic peptide level, pg/mL		932.5 ± 801.4	513.9 ± 330.5	0.19§
eGFR, mL/min/1.73 m^2		48.7 ± 27.7	43.4 ± 22.0	0.61†
Hb level, g/dL		12.9 ± 1.9	12.2 ± 2.0	0.40†
LVEF, %		50.5 ± 21.6	47.1 ± 16.4	0.68†
HDS-R score		29.0 ± 1.9	23.2 ± 6.7	<0.01†
LSA score		94.3 ± 29.9	48.0 ± 30.9	<0.01†
Interval from admission until initiation of cardiac rehabilitation, d		6.4 ± 4.5	2.3 ± 2.1	0.05†
Interval from admission until rehabilitation room entry, d		8.6 ± 5.0	3.3 ± 2.7	0.03†
Length of stay, d		19.7 ± 6.2	21.9 ± 12.4	0.66‡
Initial				
Frailty status	Frail/pre-frail/non-frail	0/7/0	0/21/0	
SPPB score		9.7 ± 1.7	7.1 ± 3.2	0.01†
10-Metre walk time, s		10.3 ± 1.7	15.0 ± 5.9	0.00†
Single-leg standing time, s		13.9 ± 11.6	3.6 ± 5.2	0.06†
Hand grip strength, kg		29.2 ± 10.0	19.6 ± 8.8	0.02†
Discharge				
Frailty status	Frail/pre-frail/non-frail	0/0/7	0/21/0	
SPPB score		11.3 ± 0.8	8.7 ± 2.8	0.02§
10-Metre walk time, s		8.4 ± 1.1	14.3 ± 7.5	<0.01†
Single-leg standing time, s		21.7 ± 13.6	6.2 ± 12.1	0.01†
Hand grip strength, kg		31.3 ± 9.9	20.3 ± 8.9	0.01†
Change				
SPPB score		1.6 ± 1.6	1.6 ± 1.7	1.00†
10-Metre walk time, s		-1.8 ± 1.8	-0.7 ± 4.2	0.49†
Single-leg standing time, s		7.9 ± 11.8	2.6 ± 10.8	0.17§
Hand grip strength, kg		2.2 ± 2.5	0.7 ± 2.6	0.17§

Abbreviations: eGFR = estimated glomerular filtration rate; Hb = haemoglobin; HDS-R = revised Hasegawa's Dementia scale; LSA = Life-Space Assessment; LVEF = left ventricular ejection fraction; SPPB = Short Physical Performance Battery

* Data are shown as mean ± standard deviation or No., unless otherwise specified

† Unpaired *t* test

‡ Chi squared test

§ Mann-Whitney *U* test

TABLE 2. Characteristics of patients with frailty*

Variable	Category	Frailty improved group (n=57)	Frailty non-improved group (n=99)	P value
Admission (baseline)				
Age, y		84.4 ± 7.9	85.5 ± 8.1	0.25†
Sex	Male/female	25/32	72/27	<0.01‡
Body mass index, kg/m²		21.2 ± 3.5	22.1 ± 3.4	0.09†
Living with family	Yes/no	14/43	34/65	0.49‡
New York Heart Association class		2.7 ± 0.9	2.8 ± 1.0	0.45†
Medical history				
Heart failure	Yes/no	43/14	75/24	0.56‡
Coronary artery disease	Yes/no	25/32	42/57	0.50‡
Valvular disease	Yes/no	18/39	30/69	0.50‡
Hypertension	Yes/no	51/6	81/18	0.15‡
Diabetes mellitus	Yes/no	24/33	37/62	0.34‡
Dyslipidaemia	Yes/no	24/33	43/56	0.50‡
Atrial fibrillation	Yes/no	32/25	53/46	0.44‡
Chronic renal failure	Yes/no	17/40	44/55	0.05‡
Stroke	Yes/no	5/52	11/88	0.43‡
Pharmacotherapy				
Dopamine	Yes/no	6/51	9/90	0.49‡
Dobutamine	Yes/no	2/55	2/97	0.57‡
Noradrenaline	Yes/no	0/57	1/98	0.45‡
Phosphodiesterase III inhibitor	Yes/no	2/55	4/95	0.87‡
Diuretic	Yes/no	19/38	25/74	0.28‡
Geriatric Nutritional Risk Index score		89.8 ± 14.0	92.3 ± 12.3	0.24†
Brain natriuretic peptide level, pg/mL		803.1 ± 849.1	940.8 ± 1190.0	0.65†
eGFR, mL/min/1.73 m²		43.7 ± 22.7	36.0 ± 19.5	0.02†
Hb level, g/dL		12.3 ± 5.1	11.7 ± 5.3	0.29†
LVEF, %		49.1 ± 18.3	54.9 ± 16.9	0.06†
HDS-R score		22.5 ± 6.4	20.1 ± 7.3	0.05†
LSA score		40.6 ± 27.0	36.3 ± 68.6	0.03†
Interval from admission until initiation of cardiac rehabilitation, d		3.3 ± 3.7	3.2 ± 2.7	0.62†
Interval from admission until rehabilitation room entry, d		4.6 ± 3.5	5.2 ± 4.0	0.42†
Length of stay, d		26.1 ± 16.3	26.3 ± 14.4	0.70†
Initial				
Frailty status	Frail/pre-frail/non-frail	57/0/0	99/0/0	
SPPB score		6.4 ± 2.8	4.6 ± 2.9	<0.01†
10-Metre walk time, s		16.3 ± 5.5	21.4 ± 12.3	<0.01†
Single-leg standing time, s		3.6 ± 4.6	1.7 ± 3.4	<0.01†
Hand grip strength, kg		18.1 ± 7.2	13.4 ± 5.7	<0.01†
Discharge				
Frailty status	Frail/pre-frail/non-frail	0/57/0	99/0/0	
SPPB score		9.0 ± 2.7	6.4 ± 2.8	<0.01†
10-Metre walk time, s		11.5 ± 3.8	16.9 ± 9.5	<0.01†
Single-leg standing time, s		5.8 ± 7.0	2.5 ± 4.7	<0.01†
Hand grip strength, kg		18.7 ± 7.4	13.7 ± 5.4	<0.01†
Change				
SPPB score		2.7 ± 2.0	1.8 ± 3.0	0.03†
10-Metre walk time, s		-4.8 ± 4.3	-4.6 ± 7.1	0.28†
Single-leg standing time, s		2.2 ± 5.4	0.8 ± 4.4	0.06†
Hand grip strength, kg		0.6 ± 2.5	0.3 ± 2.9	0.84†

Abbreviations: eGFR = estimated glomerular filtration rate; Hb = haemoglobin; HDS-R = revised Hasegawa's Dementia scale; LSA = Life-Space Assessment; LVEF = left ventricular ejection fraction; SPPB = Short Physical Performance Battery

* Data are shown as mean ± standard deviation or No., unless otherwise specified

† Mann-Whitney *U* test

‡ Chi squared test

However, the cut-off values for eGFR, an index of renal function, considerably differed between patients with good (>16.8 kg) and poor (≤16.8 kg) hand grip strength (27 and 83.5 mL/min/1.73 m^2, respectively). A previous study also showed that older patients with heart failure who had higher hand grip strength were more likely to experience frailty improvement.[10] Although no association has been identified between renal function and frailty, renal function is known to influence improvements in exercise capacity among patients with heart failure.[38] Moreover, our results showed that, despite the presence of poor physical and renal function at admission, patients with a high Hb level (>14.3 g/dL) were likely to improve from frailty. Although there is no published literature concerning an association between Hb level and frailty, a low Hb level has been shown to cause fatigability,[39,40] which is one of the criteria for assessing frailty using the CHS. Furthermore, the Hb level reportedly influences improvements in exercise capacity among patients with heart failure.[38]

Despite poor hand grip strength, weak renal function, and a low Hb level at admission, frailty improvement was observed in most patients whose single-leg standing time during hospitalisation was >4.9 s. In previous studies that sought to predict frailty improvement among older patients with heart failure, investigators mostly focused on conditions at admission without considering changes during hospitalisation.[41] The present results indicate that, despite the presence of poor conditions at admission, patients can recover from frailty by improving physical function during hospitalisation; therefore, rehabilitation is essential during hospitalisation. Resistance training is known to improve single-leg standing time among older individuals.[42] Thus, we recommend cardiac rehabilitation, including resistance training, to improve frailty among older patients with heart failure.

The clinical implications of our findings are as follows. Thus far, no algorithms have been established concerning pre-frailty and frailty improvements in older patients with heart failure. Using the CART method, we developed models that could predict the prognosis of older patients with heart failure complicated by pre-frailty and frailty. These models will provide useful information for patients and caregivers. Many of the factors extracted in this study were only assessed at the time of initial rehabilitation. Thus, the prognoses of patients with pre-frailty and patients with frailty can be inferred (to some extent) at the time of initial rehabilitation. Additionally, an increase in single-leg standing time during hospitalisation was associated with frailty improvement. For older patients with heart failure who show signs of frailty, interventions to increase single-leg standing time may help to improve frailty. The PLR and NLR were used to assess the diagnostic performances of the CART models; these parameters revealed that both model A (pre-frailty) and model B (frailty) had good performance. However, our data should be interpreted cautiously because of the small number of patients with pre-frailty.

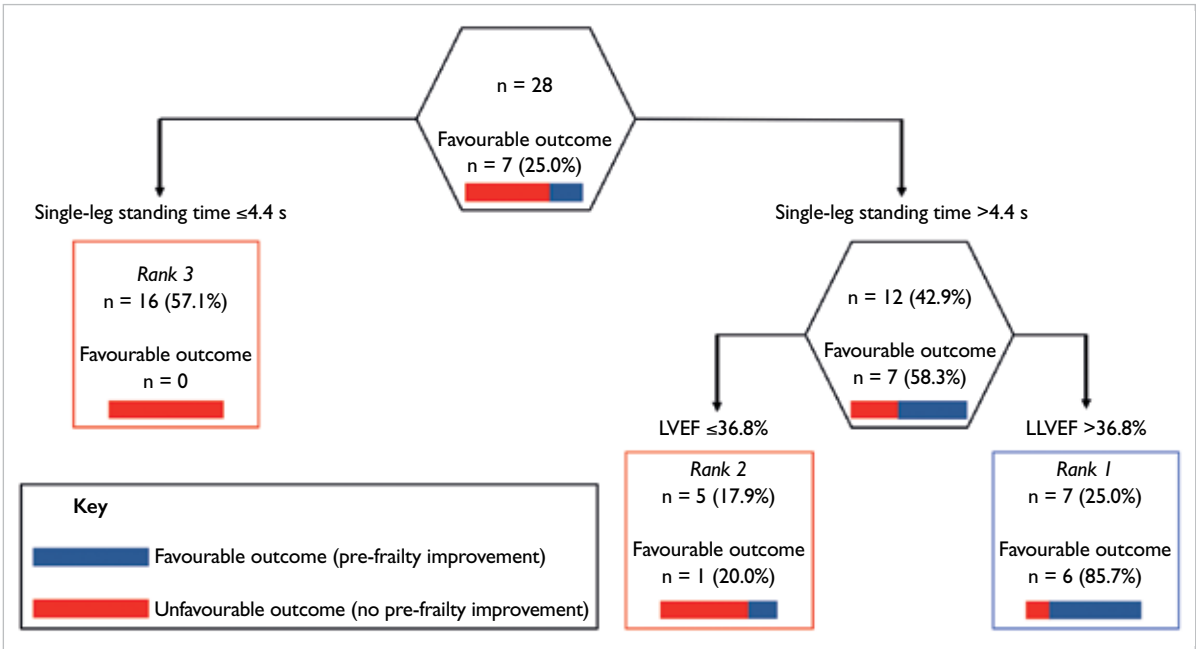

FIG 2. Model to predict the presence or absence of pre-frailty improvement during hospitalisation
Abbreviation: LVEF = left ventricular ejection fraction

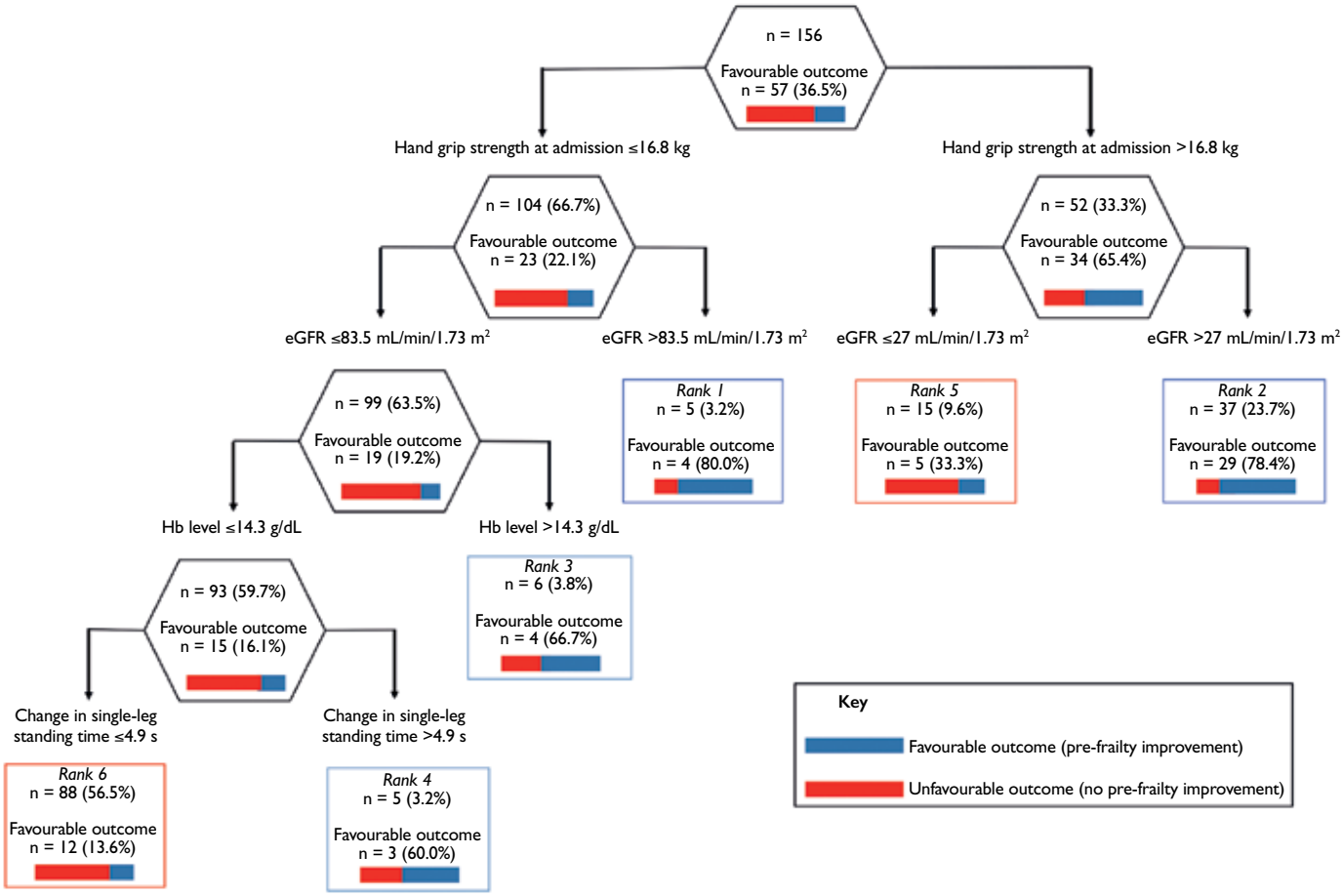

FIG 3. Model to predict the presence or absence of frailty improvement during hospitalisation
Abbreviations: eGFR = estimated glomerular filtration rate; Hb = haemoglobin

There were several notable weaknesses and limitations in this study. First, the sample size was limited; the numbers of patients with pre-frailty and frailty were 28 and 156, respectively. Therefore, this study should be regarded as a pilot prospective cohort study. Despite the moderate to high accuracies of models A and B, more large-scale studies are needed to enhance the generalisability of our results. Second, three aspects of frailty exist, namely physical, social, and mental frailty; mental frailty was not considered in this study. A previous study reported that patients with multifaceted frailty, including physical, mental, and social frailty, had worse prognoses compared with patients who had physical frailty alone.[5] Therefore, additional studies are needed to develop models that predict improvements in multifaceted frailty, including mental frailty. Third, interventions were customised for each patient; they were not uniform. However, physical therapists in both study hospitals received 2 weeks of training in cardiac rehabilitation, and the methods of cardiac rehabilitation were standardised as much as possible. Fourth, we used the J-CHS to measure frailty; the use of this tool to assess patients with heart failure is potentially controversial. The J-CHS was developed for older adults and has been used in multiple studies.[7,21] Additionally, the reliability and validity of this tool have been confirmed.[21] We thus consider this use of the J-CHS to be appropriate. Fifth, this study was performed in an unblinded manner, and we could not completely rule out the potential for bias. However, to reduce the measurement bias, the first author (T Umehara) was not involved in participant enrolment or data collection. Sixth, a selection bias might have been present because patients were only recruited at two hospitals in Japan. Caution is needed when generalising our results, particularly to patients in other countries.

Conclusion

By using the CART method, we developed moderately to highly accurate prediction models for pre-frailty

and frailty improvement among older patients with heart failure. Model A, which predicted pre-frailty improvement, showed that patients with good single-leg standing time and cardiac function at admission are likely to experience pre-frailty improvement. Furthermore, Model B, which predicted frailty improvement, showed that patients with good hand grip strength, excellent renal function, and/or a high Hb level at admission are likely to experience frailty improvement. Notably, despite the presence of poor conditions at admission, frailty improvement may occur in patients who show improvement in single-leg standing time during hospitalisation. Overall, our results suggest that cardiac rehabilitation to prolong single-leg standing time is necessary to improve frailty, particularly when conditions at admission are poor.

Author contributions

Concept or design: All authors.
Acquisition of data: T Umehara and N Katayama.
Analysis or interpretation of data: T Umehara, M Tsunematsu, M Kakehashi.
Drafting of the manuscript: T Umehara, A Kaneguchi and Y Iwamoto.
Critical revision of the manuscript for important intellectual content: T Umehara, A Kaneguchi, Y Iwamoto.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Ethics approval

The study was approved by the Ethics Committees of Saiseikai Kure Hospital (Ref 127) and Kure Kyosai Hospital (Ref 31-17). Patients provided written informed consent to participate.

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