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Original Article

Effects of exertional dyspnea on early mobilization of patients with acute decompensated heart failure

YOTA YAMAZAKI, MS^{1)*}, HIROKI YABE, PhD²⁾, KOICHI SAWANO, RPT¹⁾, YUICHI TAWARA, PhD²⁾, SHOHEI OHGI, PhD²⁾

¹⁾ Department of Rehabilitation Technology, Shizuoka City Shimizu Hospital: 1231 Miyakami, Shimizu-ku, Shizuoka, Shizuoka 424-8636, Japan

²⁾ School of Rehabilitation Sciences, Seirei Christopher University, Japan

Abstract. [Purpose] In this study, we investigated the association between exertional dyspnea and length of the mobilization program in patients with acute decompensated heart failure. [Participants and Methods] We recruited all consecutive patients with heart failure who were hemodynamically stabilized after administration of intravenous medication and were able to walk >10 m before admission. Exertional dyspnea was evaluated using the visual analog scale in all patients after the 10-m walk during each session of the mobilization program. Multiple regression analysis was used to determine the factors associated with length of the mobilization program. [Results] Our study included 52 patients. Multiple regression analysis showed that the length of the mobilization program was significantly associated with the visual analog scale on day 3 and the length before the start of the mobilization program; however, the length of the mobilization program showed no significant association with age and blood urea nitrogen levels. The standardized coefficients for the visual analog scale scores on day 3 and the length before the start of the mobilization program were 0.49 and 0.33, respectively. [Conclusion] Exertional dyspnea is a good predictor of the length of the mobilization program. Our findings highlight the importance of evaluation of exertional dyspnea. Key words: Acute decompensated heart failure, Exertional dyspnea, Early mobilization

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INTRODUCTION

Early mobilization is essential for rehabilitation of patients with acute decompensated heart failure (HF). The length of mobilization program leads to decreased physical function, and it is associated with significant adverse events such as quality of life^{1, 2)}, length of hospitalization³⁾, and cardiovascular events⁴⁾. The factors contributing to the length of mobilization program must be clarified.

Recent study have shown that age, length before the start of mobilization program, blood urea nitrogen (BUN), and ventricular tachycardia (VT) and ventricular fibrillation (VF) at admission were related to the length of mobilization program⁴). However, 20-30 percentage (%) of patients with non-compensated HF have exacerbated HF symptoms after hospitalization^{5, 6)}. Therefore, it is difficult to understand the worsening of HF symptoms and the length of mobilization program only by the index at admission. Clinicians need to evaluate post-hospitalization indicators. however, such indicators are unclear.

Exertional Dyspnea, a hallmark symptom of HF, is associated with decreased cardiac output^{7, 8)}, pulmonary function due to pulmonary congestion, pleural effusion^{9, 10}, and skeletal muscle function, such as increased muscle metabolic receptor reflexes^{11, 12}). And exertional dyspnea is related to mortality in patients with HF¹³). Exertional dyspnea is associated with the pathogenesis of HF, the evaluation of exertional dyspnea may help us to predict the degree of improvement in cardiac

*Corresponding author. Yota Yamazaki (E-mail: 18mr08@g.seirei.ac.jp)

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function and whether the length of mobilization program is possible. However, no study has examined exertional dyspnea in terms of the factor of the length of mobilization program in rehabilitation for patients with HF.

The purpose of this study was to identify exertional dyspnea is related to the length of mobilization program in patients with HF.

PARTICIPANTS AND METHODS

We conducted this study according to strengthening the reporting of observational studies in epidemiology Statement¹⁴⁾. We included all consecutive patients between April 2019 and April 2020 who were hemodynamically stabilized after introducing intravenous medication for HF and who were able to walk more than 10-meter (m) before admission in Shizuoka City Shimizu Hospital. We excluded patients who were unable to test and measure due to cognitive decline at admission, who died during hospitalization, or who could not obtain consent to participate in the study (Fig. 1). The medical ethics committee of Shizuoka City Shimizu Hospital approved this study (approval number: 2018-53) by the declaration of Helsinki (2013 revised version), and informed consent was obtained from all patients.

This study was a single-center prospective study. Patient characteristics, including age, gender, body mass index, etiology of HF, medication history, comorbidities, laboratory values, echocardiography, blood sampling, and chest X-rays were collected from medical records at admission (Fig. 2). On echocardiography, the left ventricular ejection fraction (LVEF) and E/e' were measured. Hemoglobin, BUN, creatinine, glomerular filtration rate, and brain natriuretic peptide were measured by blood sampling. The cardiothoracic ratio was investigated using chest X-ray data. Urine volume and body weight from the first 10-m walk to 3 days after admission were also investigated daily from medical records. We calculated the amount of change in body weight (Δ Weight) and mean urine output difference between the weight measurements at each time point and the previous time point. Mean urine output was calculated by dividing the difference in urine output between the day of admission and the first day after the 10-m walk test was available, and between the first day (day 1) and 3 days after the first 10-m walk (day 3) by the length of days required to reach each time point.



Fig. 1. Schematic representation of the study cohort inclusion process.



Fig. 2. Measurement protocols.

We proceeded with mobilization program based on a standardized rehabilitation program for HF patients¹⁵⁾ (Fig. 2). The initiation criteria for mobilization program^{1, 2)} were as follows: (1) no resting HF symptoms such as dyspnea, (2) no hemodynamically unstable arrhythmia, (3) no symptoms due to low output syndrome, (4) no state of shock, (5) no Swan-Ganz catheter insertion, and (6) no active myocardial ischemia. Mobilization program progresses in the order of the stage: sitting position, standing position, 10-m, 30-m, 50-m, 80-m, and 80-m \times 3 sets every day. The criteria for not proceeding with these stages were as follows: (1) new HF symptoms, (2) increased arrhythmias, or rhythm changes to atrial fibrillation, (3) increased heartbeats (>30 beats/min), (4) a decrease in percutaneous oxygen saturation below 90%, (5) excessive blood pressure changes, and (6) ischemic ST changes. Furthermore, the Borg Scale was used as the acceptable condition for exertion dyspnea until the Borg Scale 13, the progression criterion for mobilization program, was reached. The completion of the length of mobilization program was examined as the length of days from the start program to achieve 80 m \times 3 sets or the maximum continuous walking distance before admission.

We investigated exertional dyspnea using the Visual Analog Scale (VAS) after the 10-m walk. The VAS was measured for day 1 and day 3. For this assessment, patients were asked to evaluate their general well-being by marking a 10-cm vertical line, with the top labeled "no dyspnea" and the bottom labeled "worst you have ever dyspnea". We scored the patients' markings on a scale of 0 to 100 by measuring the distance in millimeters from the bottom of the line¹⁶.

All data are shown as the mean \pm standard deviation. Pearson's product-moment correlation coefficient and Spearman's rank correlation coefficient for the length of mobilization program and other variables were calculated. Multiple regression analysis was performed using the length of mobilization program as a dependent variable and significant variables in correlation analysis as independent variables. In the present study⁴, in addition to the items that were significant in the correlation analysis, age, BUN, and the length before start of the mobilization program, which has been shown in previous studies to affect the the length of mobilization program, were also considered independent variables. If there was a variable with a correlation coefficient of r>0.8 between the independent variables, one of them was chosen and submitted as an independent variable to avoid multicollinearity¹⁷). The variable increase method with the likelihood ratio test was used to select the variables. All significant determinations were based on a risk rate of 5%. All statistical analyses were performed with SPSS Statistics Base 22.0 (Tokyo, Japan).

RESULTS

Fifty-four patients, excluding 8 who were unable to be tested and measured due to cognitive decline at admission, participated in the study. Two patients dropped out after hospitalization due to death, and there were 52 patients in the study (Fig. 1). The patient characteristics are summarized in Table 1. The mean age was 77.7 ± 11.6 years, and the body mass index was 23.6 ± 4.0 kg/m². The post-hospitalization progress in this study is summarized in Table 2. The length before start of mobilization program was 1.9 ± 1.7 days, the length of mobilization program was 6.0 ± 4.9 days, and the length of hospital stay was 28.0 ± 12.8 days.

As shown in Table 3, the length of mobilization program was significantly correlated with the length before start of the mobilization program (r=0.41), VAS on day 1 (r=0.48), and VAS on day 3 (r=0.60). The other variables did not show a significant correlation in Table 3. VAS on day 1 and VAS on day 3 (r=0.83) showed a significant positive correlation (r>0.80). This significant positive correlation was only seen between VAS on day 1 and day 3 (p<0.05). There was no such correlation (r>0.80, and p<0.05) observed among the other independent variables. In the dependent variable of multiple logistic regression, the VAS on day 3, age, length before the start of the mobilization program, and BUN were selected to account for multicollinearity. The results of the multiple regression analysis are shown in Table 4. The length of mobilization program showed a significant relationship with VAS on day 3 and the length before the start of the mobilization program (p<0.05 for the model χ^2 test). The standardized coefficients for VAS on day 3 and the length before the start of the mobilization program (p<0.05 for the model χ^2 test). The standardized coefficients for VAS on day 3 and the length before the start of the mobilization program were 0.49 and 0.33, respectively.

DISCUSSION

In this study, the length of mobilization program showed that significant relationships with the VAS score of exertional dyspnea and length before the start of mobilization program. This result suggests that exertional dyspnea may be a new index for predicting the length of mobilization program in patients with HF.

Exertional dyspnea in HF is a physical assessment that physical therapists can evaluate in routine clinical work, and it is one of the indexes that reflects the pathology of HF. Exertional dyspnea in HF is associated with two pathologies: pulmonary congestion due to increased pulmonary venous pressure and decreased blood flow to skeletal muscles. In patients with HF, exertional dyspnea reflects various pathologies of cardiac^{8, 9}, pulmonary^{10, 11}, and skeletal muscle function^{18–22}, and the degree of exertional dyspnea in the early phase of hospitalization might reflect the extent of these pathologies. As HF gets worse and fluid collects, most people will have stronger exertional dyspnea. When the HF status is worse, the length of the mobilization program were longer²). Therefore, the stronger exertional dyspnea is, the longer the length of mobilization program.

In clinical work, a patient who will be longer the length of mobilization program needs additional individualized interventions to prevent deconditioning²²⁾. Recent studies have shown that endurance training^{23–25)}, resistance training^{24, 25)}, physical activity^{26–28)}, neuromuscular electrical stimulation^{29–31)}, and leg cycles³²⁾ are effective in treating patients with HF. Such interventions for patients with HF may prevent poor physical function, poor quality of life^{1, 2)}, and longer hospital stays³⁾. In cases that delay mobilization program, individualized additional interventions might be necessary.

In conclusion, exertional dyspnea in the early phase of hospitalization was significantly associated with the length of mobilization program. This study has several limitations. First, some participants in this study were characteristic. Participants in this study were more likely to have heart failure patients with congestive pathology than with cardiogenic shock^{33, 34}).

Table 1. Patient characteristics

Research items	All participants
n	52
Age, years	77.7 ± 11.6
Male, n (%)	31 (60)
BMI, kg/m ²	23.6 ± 4.0
NYHA class (II/III/IV), n (%)	4 (8)/25 (48)/23 (44)
Etiology of HF	
Ischemic heart disease, n (%)	11 (22)
Valvular heart disease, n (%)	11 (22)
Hypertension, n (%)	11 (22)
Dilated cardiomyopathy, n (%)	4 (8)
Other, n (%)	14 (26)
Medical history	
Hytertension, n (%)	36 (69)
Diabetes, n (%)	13 (25)
Chronic kidney disease, n (%)	9 (18)
Chronic obstructive pulmonary disease, n (%)	8 (16)
Atrial fibrillation, n (%)	19 (36)
History of hospitalization for HF, n (%)	13 (25)
Cardiothoracic ratio (%)	57.8 ± 7.4
LVEF (%)	51.8 ± 14.1
E/e'	17.4 ± 5.0
Hemoglobin, mg/dL	11.8 ± 2.6
BUN, mg/dL	26.3 ± 11.8
Cr, mg/dL	1.31 ± 0.50
eGFR, mL/min/1.73 m ²	43.4 ± 14.2
BNP, pg/dL	696.9 ± 460.2
Dopamine hydrochloride, n (%)	1 (2)
Dobutamine hydrochloride, n (%)	7 (13)
Noradrenaline, n (%)	0 (0)
PDE-inhibitor, n (%)	0 (0)
Nitrate, n (%)	12 (23)
Carperitide, n (%)	35 (68)
Loop diuretic, n (%)	50 (97)
NPPV, n (%)	7 (13)
Cardiopulmonary support, n (%)	0 (0)
Acute blood purification therapy, n (%)	0 (0)

Data are presented as mean \pm SD or n (%). BNP: brain natriuretic peptide; BMI: body mass index; BUN: blood urea nitrogen; Cr: creatinine; E/e': early diastolic mitral annulus velocity (e') estimated by tissue Doppler and the ratio of the trans-mitral early peak velocity (E) by pulsed wave Doppler over e'; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; NPPV: noninvasive positive pressure ventilation; NYHA: New York Heart Association; PDE, phosphodiesterase.

Table 1	2.	Post-hosp	italiz	zation	progress
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Research items	All participants	
∆Weight, kg		
From hospitalization to day 1	-1.3 ± 2.5	
From day 1 to day 3	-1.0 ± 1.2	
Average urine output, ml		
From hospitalization to day 1	$2,742.1 \pm 2,173.2$	
From day 1 to day 3	$1{,}606.3 \pm 1{,}107.6$	
Dyspnea on exertion VAS, mm		
VAS on day 1	22.4 ± 18.1	
VAS on day 3	15.3 ± 18.0	
The length before start of mobilization program, day	1.9 ± 1.7	
The length of mobilization program, day	6.0 ± 4.9	
The length of hospital stay, day	28.0 ± 12.8	

Data are presented as mean \pm SD or n (%). Δ weight: weight change; VAS: visual analog scale.

Table 3.	Correlation	with the	length of	f mobilization	program

Research items	r
Age	0.90
BMI	-0.08
NYHA class	0.26
Cardiothoracic ratio	0.37
LVEF	0.15
E/e'	-0.08
Hemoglobin	-0.18
BUN	0.14
Cr	0.03
eGFR	-0.30
BNP	0.11
Hospitalization for HF in past	-0.30
The length before start of the ambulation	0.41*
VAS on Day 1	0.48*
VAS on Day 3	0.60*
Δ Weight from hospitalization to day 1	-0.17
∆Weight from day 1 to day 3	-0.57
Average urine output from hospitalization to day 1	-0.80
Average urine output from day 1 to day 3	-0.13

*p<0.05.

BMI: body mass index; BNP: brain natriuretic peptide; BUN: blood urea nitrogen; Cr: creati-nine; E/e': early diastolic mitral annulus velocity (e') estimated by tissue Doppler and the ratio of the trans-mitral early peak velocity (E) by pulsed wave Doppler over e'; eGFR: estimated glomerular filtration rat; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; r: correlation coefficient; VAS: visual analog scale; ∆Weight: weight change.

Table 4. Multiple regression analyses on the length of mobilization program

Research items	b	95% CI
VAS on Day 3	0.49	0.06-1.21*
Age	0.21	0.02 - 0.58
The length before the start of mobilization program	0.33	0.19-1.62*
BUN	0.45	0.36-0.76

*p<0.05.

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b: standardized regression coefficient; BUN: blood urea nitrogen; CI: confidence interval; VAS: visual analog scale.

Additional studies on patients with HF, mainly due to low cardiac output, are needed. Second, the survey was conducted by a single institution, which may lead to selection bias. Third, factors influencing exertional dyspnea need to be studied further. Unmeasured confounding factors might have affected the results in the length of mobilization program. Fourth, this study may not be sufficiently blinded. Dyspnea is a subjective assessment, which may lead to measurement bias. Therefore, blinding is desirable. This study suggests that exertional dyspnea is a good predictor of mobilization program. HF patients with severe exertional dyspnea in the early phase of hospitalization should be considered for individualized interventions in addition to early mobilization.

Conflict of interest

All authors declare no conflicts of interest.

REFERENCES

- Tsutsui H, Isobe M, Ito H, et al. Japanese Circulation Society and the Japanese Heart Failure Society Joint Working Group: JCS 2017/JHFS 2017 Guideline on diagnosis and treatment of acute and chronic heart failure—digest version. Circ J, 2019, 83: 2084–2184. [Medline] [CrossRef]
- 2) JCS Joint Working Group: Guidelines for rehabilitation in patients with cardiovascular disease (JCS 2012). Circ J, 2014, 78: 2022–2093. [Medline] [CrossRef]
- Cops J, Haesen S, De Moor B, et al.: Exercise intervention in hospitalized heart failure patients, with emphasis on congestion-related complications: a review. Heart Fail Rev, 2020, 25: 257–268. [Medline] [CrossRef]
- Ishikawa K, Fukushima A, Yokota T, et al.: Clinical impact and associated factors of delayed ambulation in patients with acute heart failure. Circ Rep, 2020, 1: 179–186. [Medline] [CrossRef]
- 5) O'Connor CM, Mentz RJ, Cotter G, et al.: The PROTECT in-hospital risk model: 7-day outcome in patients hospitalized with acute heart failure and renal dysfunction. Eur J Heart Fail, 2012, 14: 605–612. [Medline] [CrossRef]
- 6) Metra M, Teerlink JR, Felker GM, et al.: Dyspnoea and worsening heart failure in patients with acute heart failure: results from the Pre-RELAX-AHF study. Eur J Heart Fail, 2010, 12: 1130–1139. [Medline] [CrossRef]
- Laveneziana P, O'Donnell DE, Ofir D, et al.: Effect of biventricular pacing on ventilatory and perceptual responses to exercise in patients with stable chronic heart failure. J Appl Physiol, 2009, 106: 1574–1583. [Medline] [CrossRef]
- 8) Smith JR, Olson TP: Ventilatory constraints influence physiological dead space in heart failure. Exp Physiol, 2019, 104: 70-80. [Medline] [CrossRef]
- Malfatto G, Caravita S, Giglio A, et al.: Pulmonary congestion at rest and abnormal ventilation during exercise in chronic systolic heart failure. J Am Heart Assoc, 2015, 4: e001678. [Medline] [CrossRef]
- Reddy YN, Obokata M, Wiley B, et al.: The haemodynamic basis of lung congestion during exercise in heart failure with preserved ejection fraction. Eur Heart J, 2019, 40: 3721–3730. [Medline] [CrossRef]
- Witte KK, Notarius CF, Ivanov J, et al.: Muscle sympathetic nerve activity and ventilation during exercise in subjects with and without chronic heart failure. Can J Cardiol, 2008, 24: 275–278. [Medline] [CrossRef]
- Van Iterson EH, Snyder EM, Johnson BD, et al.: Influence of the metaboreflex on pulmonary vascular capacitance in heart failure. Med Sci Sports Exerc, 2016, 48: 353–362. [Medline] [CrossRef]
- Selvaraj S, Claggett B, Pozzi A, et al.: Prognostic implications of congestion on physical examination among contemporary patients with heart failure and reduced ejection fraction: PARADIGM-HF. Circulation, 2019, 140: 1369–1379. [Medline] [CrossRef]
- 14) von Elm E, Altman DG, Egger M, et al. STROBE Initiative: The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet, 2007, 370: 1453–1457. [Medline] [CrossRef]
- 15) Izawa H, Yoshida T, Ikegame T, et al. Japanese Association of Cardiac Rehabilitation Standard Cardiac Rehabilitation Program Planning Committee: Standard cardiac rehabilitation program for heart failure. Circ J, 2019, 83: 2394–2398. [Medline] [CrossRef]
- 16) Grant S, Aitchison T, Henderson E, et al.: A comparison of the reproducibility and the sensitivity to change of visual analogue scales, Borg scales, and Likert scales in normal subjects during submaximal exercise. Chest, 1999, 116: 1208–1217. [Medline] [CrossRef]
- 17) Tsushima E: Medical Data Analysis in SPSS, 2nd ed. 2016.
- Pavasini R, Serenelli M, Celis-Morales CA, et al.: Grip strength predicts cardiac adverse events in patients with cardiac disorders: an individual patient pooled meta-analysis. Heart, 2019, 105: 834–841. [Medline] [CrossRef]
- Homma I, Eklund G, Hagbarth KE: Respiration in man affected by TVR contractions elicited in inspiratory and expiratory intercostal muslces. Respir Physiol, 1978, 35: 335–348. [Medline] [CrossRef]
- 20) O'Donnell DE, Banzett RB, Carrieri-Kohlman V, et al.: Pathophysiology of dyspnea in chronic obstructive pulmonary disease: a roundtable. Proc Am Thorac Soc, 2007, 4: 145–168. [Medline] [CrossRef]
- Dubé BP, Agostoni P, Laveneziana P: Exertional dyspnoea in chronic heart failure: the role of the lung and respiratory mechanical factors. Eur Respir Rev, 2016, 25: 317–332. [Medline] [CrossRef]
- 22) Hamilton RD, Winning AJ, Perry A, et al.: Aerosol anesthesia increases hypercapnic ventilation and breathlessness in laryngectomized humans. J Appl Physiol, 1987, 63: 2286–2292. [Medline] [CrossRef]
- 23) Kitzman DW, Brubaker PH, Herrington DM, et al.: Effect of endurance exercise training on endothelial function and arterial stiffness in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. J Am Coll Cardiol, 2013, 62: 584–592. [Medline] [CrossRef]
- 24) Motoki H, Nishimura M, Kanai M, et al.: Impact of inpatient cardiac rehabilitation on Barthel Index score and prognosis in patients with acute decompensated heart failure. Int J Cardiol, 2019, 293: 125–130. [Medline] [CrossRef]
- 25) Reeves GR, Whellan DJ, O'Connor CM, et al.: A novel rehabilitation intervention for older patients with acute decompensated heart failure: the REHAB-HF pilot study. JACC Heart Fail, 2017, 5: 359–366. [Medline] [CrossRef]

- 26) Long L, Mordi IR, Bridges C, et al.: Exercise-based cardiac rehabilitation for adults with heart failure. Cochrane Database Syst Rev, 2019, 1: CD003331. [Medline]
- 27) Hamer M, O'Donovan G, Stamatakis E: Association between physical activity and sub-types of cardiovascular disease death causes in a general population cohort. Eur J Epidemiol, 2019, 34: 483–487. [Medline] [CrossRef]
- 28) Zores F, Iliou MC, Gellen B, et al.: Physical activity for patients with heart failure: position paper from the heart failure (GICC) and cardiac rehabilitation (GERS-P) Working Groups of the French Society of Cardiology. Arch Cardiovasc Dis, 2019, 112: 723–731. [Medline] [CrossRef]
- 29) Groehs RV, Antunes-Correa LM, Nobre TS, et al.: Muscle electrical stimulation improves neurovascular control and exercise tolerance in hospitalised advanced heart failure patients. Eur J Prev Cardiol, 2016, 23: 1599–1608. [Medline] [CrossRef]
- 30) Notarius CF, Millar PJ, Keir DA, et al.: Training heart failure patients with reduced ejection fraction attenuates muscle sympathetic nerve activation during mild dynamic exercise. Am J Physiol Regul Integr Comp Physiol, 2019, 317: R503-R512. [Medline] [CrossRef]
- Jones S, Man WD, Gao W, et al.: Neuromuscular electrical stimulation for muscle weakness in adults with advanced disease. Cochrane Database Syst Rev, 2016, 10: CD009419. [Medline]
- 32) Shiba N, Nochioka K, Miura M, et al. CHART-2 Investigators: Trend of westernization of etiology and clinical characteristics of heart failure patients in Japan—first report from the CHART-2 study. Circ J, 2011, 75: 823–833. [Medline] [CrossRef]
- 33) Tsutsui H, Tsuchihashi-Makaya M, Kinugawa S, et al. JCARE-CARD Investigators: Clinical characteristics and outcome of hospitalized patients with heart failure in Japan. Circ J, 2006, 70: 1617–1623. [Medline] [CrossRef]
- 34) Shiga T, Suzuki A, Haruta S, et al. HIJ-HF II Investigators: Clinical characteristics of hospitalized heart failure patients with preserved, mid-range, and reduced ejection fractions in Japan. ESC Heart Fail, 2019, 6: 475–486. [Medline] [CrossRef]