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Determining the factors for interhospital transfer in advanced heart failure cases

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ABSTRACT

Background: There are some patients with advanced heart failure (HF), for whom implantable left ventricular assist device (LVAD) or heart transplantation (HTx) should be considered. Some of them need to be transferred between hospitals. There are few reports on the interhospital transfer of patients with advanced HF and their subsequent clinical course.
In this study, we investigated the characteristics and clinical course of patients transferred to a LVAD/HTx center, focusing on the distance between hospitals.
Methods: We retrospectively examined 141 patients who were transferred to our hospital, considering the indications of LVAD implantation or HTx. We divided the patients into two groups: those referred <33 km (short-distance) and those referred more than 33 km (long-distance). The primary outcome was the composite outcome of increased catecholamine dose, mechanical support, or renal dysfunction within 1 week of transfer.
Results: Continuous catecholamine infusion was significantly more common in patients in the long-distance group, whereas extracorporeal membrane oxygenation (ECMO) placement was significantly more common in short-distance group.
Patients transferred via long distance had significantly higher rates of increased catecholamine doses, mechanical support including intra-aortic balloon pumping (IABP) and ECMO, and renal dysfunction within 1 week of transfer than patients transferred via short distance. Multivariate analysis showed that low body mass index (BMI) and long distance were independent predictive factors for the primary outcome.
Conclusions: When patients with advanced HF are transferred from far distant hospitals or with low BMI, it may be necessary to devise various measures for interhospital transport.

1. Background

In recent years, various new therapeutic agents for heart failure (HF) have become available, and the range of medical treatment is expanding [1,2]; however, advanced cases of HF remain. It may be necessary to consider left ventricular assist device (LVAD) implantation or heart transplantation (HTx) in cases of advanced HF; however, the number of medical facilities where such interventions are available is limited [3]. Therefore, for cases that require these treatments, it is necessary to determine the appropriate timing for transfer to a specialized facility. Patients with advanced HF may be referred on an outpatient basis, but their condition is not stable and they often need to be transferred between hospitals directly. However, the timing and methods of referral have not been fully established [4], and there are few reports on the interhospital transport of patients with advanced HF and the subsequent clinical course. The purpose of this study was to examine the characteristics and clinical course of patients who have been transferred to referral hospitals, focusing on the distance between hospitals.

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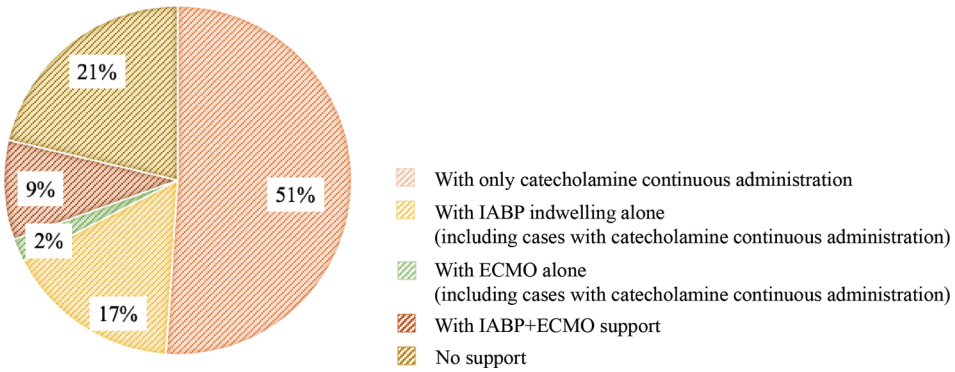

Fig. 1. Patient condition at the transfer to our hospital including catecholamine infusion and/or mechanical circulatory support. IABP; intra-aortic balloon pumping, ECMO; extracorporeal membrane oxygenation.

2. Methods

2.1. Patient selection

Patients with advanced HF who were transferred to the University of Tokyo Hospital between January 1, 2015, and September 30, 2020, considering the indications for interventions such as LVAD implantation or HTx, were recruited. Based on the Declaration of Helsinki, this study was conducted with the approval of the Institutional Review Board of the University of Tokyo Graduate School (assignment number: 2650).

2.2. Evaluation items

This study was followed up until September 30, 2021. Patients were divided into two groups according to the distance between the referral hospital and our hospital. The median distance from the center to all hospitals was 33 km. Therefore, the group was divided into a referral patient group of <33 km (short-distance group: <33 km) and a referral patient group of 33 km or more (long-distance group: ≥33 km).

As a primary outcome, an increase in the catecholamine dose, mechanical support addition, or renal dysfunction within 1 week of transfer was considered as an exacerbation event of HF. Renal dysfunction was defined by an increase in serum creatinine levels of 0.3 mg/dL or more [5]. In addition, as a secondary outcome, we examined the implantation of the LVAD (including both of extracorporeal and implantable) and death after 1 week of transfer. The need for LVAD implantation was determined by a team consisting of cardiologists, cardiac surgeons, and transplant coordinators based on the following criteria: symptoms of HF did not improve and progressive circulatory failure occurred despite escalating sufficient drug treatment and non-drug treatment.

2.3. Database

Patient characteristics were collected at the time of transfer. The dose of β-blockers was calculated to the corresponding bisoprolol dose, and the dose of loop diuretics was calculated to the corresponding furosemide dose. A blood test was performed when the patient was transferred and evaluated using the standard test method of the University of Tokyo Hospital.

2.4. Statistical method

Numerical data are displayed as mean ± standard deviation or median (interquartile range). For statistical analysis, JMP version Pro 14 (SAS Institute, Cary, NC, USA) was used. Continuous variables were compared using Student's *t*-test or Mann–Whitney *U* test, and categorical variables were compared using Fisher's exact test. The survival rate and free period of LVAD implantation were compared by performing a log-rank test using the Kaplan–Meier analysis. The day of transfer was set as "0 day." Statistical analysis was performed using a two-sided test, the significance level was set at 5%, and the P-value and confidence interval were calculated. For predicting the primary outcome using logistic regression analysis, the cutoff value of each variable was selected using a receiver operating characteristic curve to maximize sensitivity and specificity. Furthermore, univariate analysis was performed, and factors with $p < 0.1$ were used for multivariate analysis to extract significant factors.

3. Results

3.1. Patient background

A total of 141 patients with advanced HF were included in this study. As means of transportation between hospitals, 129 patients were transported by an ambulance, 10 were transported by a helicopter, one was transported by a train, and one was transported by an airplane. The average age of patients with advanced HF at the time of transfer was 42.3 ± 12.1 years, and 100 (71.0%) were male. Regarding the presence of underlying heart disease, 98 (69.5%) patients had non-ischemic dilated cardiomyopathy. The median left ventricular ejection fraction was 17% (12–23%). Regarding medication at the time of transfer, 105 patients (74.4%) were administered beta-blockers, 87 (61.7%) were administered angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists, and 96 (61.7%) were administered mineral corticoid receptor antagonists (68.0%). In addition, 44 (31.2%) patients were treated with an implantable cardioverter defibrillator/cardiac resynchronization therapy defibrillator. As shown in Fig. 1, 72 (51%) patients received continuous catecholamine infusion, 23 (17%) received intra-aortic balloon pumping (IABP) indwelling alone (including cases with continuous catecholamine infusion), three (2%) received extracorporeal membrane oxygenation (ECMO) alone (including cases with continuous catecholamine infusion), 13 (9%) received IABP and ECMO support, and 30 (21%) received no support at the time of transfer.

3.2. Patient background between groups

Based on the distance from the University of Tokyo Hospital to the referral source hospital, the patients with advanced HF were divided into a group of those who were transferred via a hospital <33 km (short-distance group, <33 km) and a group of those who were transferred via a hospital over 33 km (long-distance group, ≥33 km). Patient background characteristics were compared between the two groups (Table 1). The number of referral patients in the short-distance group was 70 and that in the long-distance group was 71. The median age of patients was 41.7 [35.0–51.2] years (short-distance group) and 43.0 [35.0–52.0] years (long-distance group) ($P = 0.44$). The median body mass index was 20.1 [18.6–21.8] kg/m^2 (long-distance group) and 21.8 [19.2–24.3] kg/m^2 (short-distance group), showing a significant difference ($p = 0.012$).

Table 1
Patient characteristics divided into two groups according to the distance between the referral hospital and our hospital.

	short-distance group (<33km) (N=70)	long-distance group (≧33km) (N=71)	*P* value
Age (years old)	40.0 [35.0–51.3]	44.0 [35.0–52.0]	0.44
Sex (male)	50 (71.4 %)	50 (70.4 %)	0.90
BMI (kg/m^2)	21.8 [19.2–24.3]	20.1 [18.6–21.8]	0.012 ‖
BSA (DuBois, m^2)	1.66 [1.54–1.82]	1.65 [1.53–1.75]	0.28
Systolic BP (mmHg)	94 [86–110]	90 [84–100]	0.090
Diastolic BP (mmHg)	60 [53–68]	60 [52–66]	0.62
Heart rate (beats/min)	88 [74–108]	86 [76–98]	0.83
By transport			
ambulance, *n* (%)	70 (100 %)	59 (83.1 %)	0.0050 ‖
helicopter, *n* (%)		0 (0 %)	10 (14.1%)
ballet train, *n* (%)	0 (0 %)	1 (1.4 %)	
airplane, *n* (%)	0 (0 %)	1 (1.4 %)	
Medical history			
Hypertension	6 (8.6 %)	10 (14.1 %)	0.30
Diabetes	11 (15.8 %)	17 (23.9 %)	0.22
Dyslipidemia	15 (21.4 %)	19 (26.8 %)	0.46
Atrial fibrillation	15 (21.4 %)	9 (12.7 %)	0.17
Stroke	8 (11.4 %)	6 (8.5 %)	0.55
Smoking	33 (47.1 %)	37 (52.1 %)	0.56
ICD/CRTD	17 (24.3 %)	27 (38.0 %)	0.078
Duration of HF (days)	601 [63–3849]	2230 [178–3744]	0.11
Etiology			
DCM, *n* (%)	47 (67.1 %)	51 (71.8 %)	0.55
HCM, *n* (%)	1 (1.4 %)	3 (4.2 %)	0.32
ICM, *n* (%)	4 (5.7 %)	6 (8.4 %)	0.53
Myocarditis, *n* (%)	11 (15.7 %)	3 (4.2 %)	0.023 ‖
Others *	7 (10 %)	8 (11.3 %)	0.88
Family history	3 (4.2 %)	8 (11.3 %)	0.12
Support at transfer			
With catecholamine	46 (65.7 %)	57 (81.4 %)	0.035 ‖
With IABP	21 (30.0 %)	15 (21.8 %)	0.27|
With ECMO	13 (18.6 %)	3 (4.3 %)	0.0079 ‖
Echocardiographic data			
LVEF (%)	17.0 [11.0–22.3]	17.0 [12.8–23.0]	0.60
LVDd (mm)	64.8 ± 12.3	67.7 ± 12.8	0.18
LVDs (mm)	58.8 ± 13.2	61.7 ± 13.8	0.19
IVST (mm)	7.0 [6.0–8.0]	8.0 [7.0–8.8]	0.12
PWT (mm)	8.0 [7.0–9.0]	7.0 [6.0–9.0]	0.29
LAD (mm)	43.7 ± 10.6	45.3 ± 10.8	0.46
Medication management at transfer			
β blocker	46 (65.7 %)	59 (83.1 %)	0.018 ‖
ACEi/ARB	38 (54.3 %)	49 (69.0 %)	0.072
MRA	50 (58.1 %)	55 (77.5 %)	0.016 ‖
Loop diuretics	53 (75.7 %)	67 (94.4 %)	0.0019 ‖
Tolvaptan	25 (35.7 %)	37 (52.1 %)	0.049 ‖
Carperitide	11 (15.7 %)	7 (9.9 %)	0.30
SGLT2 inhibitor	2 (2.9 %)	2 (2.8 %)	0.99
Laboratory data			
Albumin (g/dL)	3.4 [2.9–3.9]	3.7 [3.3–3.9]	0.071
Total protein (g/dL)	6.5 [5.7–7.1]	6.6 [6.0–7.1]	0.27
AST (U/L)	34 [21–76]	28 [19–36]	0.017 ‖
ALT (U/L)	29 [16–96]	27 [13–41]	0.15
γGTP (U/L)	71 [37–133]	72 [42–149]	0.88
Total cholesterol (mg/dL)	149.6 ± 44.0	155.3 ± 41.2	0.56
Total bilirubin (mg/dL)	1.1 [0.7–1.8]	1.1 [0.7–1.5]	0.22
Creatinine (mg/dL)	0.93 [0.73–1.21]	0.89 [0.69–1.21]	0.63
eGFR ml/min/1.73m^2)	60.1 [49.6–90.5]	66.8 [44.2–88.6]	0.88
Sodium (mmol/L)	136.5 ± 4.1	135.6 ± 4.7	0.58
Potassium (mmol/L)	4.33 ± 0.59	4.30 ± 0.51	0.93
CRP (mg/dL)	1.13 [0.20–5.17]	0.38 [0.08–1.64]	0.0071 ‖
White blood cell (×1000/μL)	7.2 [5.7–9.4]	6.6 [5.3–8.8]	0.30
Lymphoid (×1000/μL)	1.2 [0.9–1.7]	1.1 [0.8–1.5]	0.22
Hemoglobin (g/dL)	12.3 ± 2.5	12.4 ± 2.0	0.51
Platelet (×10000/μL)	18.8 ± 8.5	21.7 ± 10.3	0.16
Hemoglobin A1c (%)	5.8 [5.4–6.2]	5.8 [5.4–6.2]	0.69
BNP (pg/mL)	421.9 [199.3–966.0]	523.5 [217.0–974.0]	0.80

BMI; body mass index, BSA; body surface area, BP; blood pressure, ICD/CRTD; implantable cardioverter defibrillator/cardiac resynchronization therapy defibrillator, HF; heart failure, DCM; dilated cardiomyopathy, HCM; hypertrophic cardiomyopathy, ICM; ischemic cardiomyopathy, IABP; intra-aortic balloon pumping, ECMO; extracorporeal membrane oxygenation, LVEF; left ventricular ejection, fraction, LVDd; left ventricular end-diastolic dimension, LVDs; left ventricular end-systolic dimension, IVST; interventricular septum end-diastolic thickness, PWT; posterior left ventricular wall end-diastolic thickness, LAD; left atrial dimension, ACEi; angiotensin-converting enzyme inhibitor, ARB; angiotensin II receptor blocker, MRA; mineralocorticoid receptor antagonist, SGLT2; sodium glucose transporter 2, AST; aspartate aminotransferase, ALT; alanine aminotransferase, γGTP; γ-glutamyl transpeptidase, eGFR; estimated glomerular filtration rate, CRP; C-reactive protein, BNP; brain natriuretic peptide.

* Others including restricted cardiomyopathy, sarcoidosis, structural heart disease, arrhythmogenic right ventricular cardiomyopathy, anthracycline-induced cardiomyopathy, and tachycardia induced cardiomyopathy.

‖ $P < 0.05$.

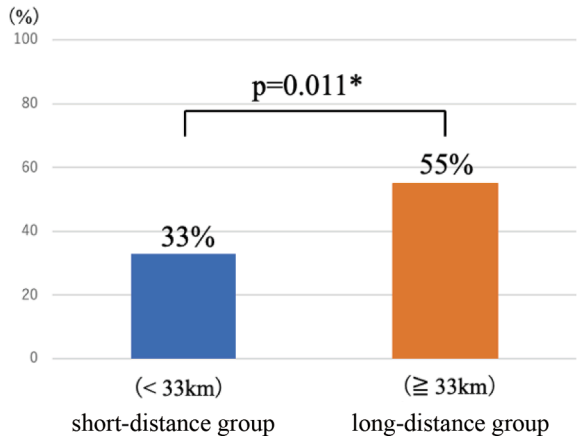

Fig. 2. Primary outcome in short- and long-distance groups from our hospital. There were more primary outcome events in patients transferred via long distance than short distance.

Blood tests showed significantly higher aspartate aminotransferase (AST) (p = 0.017) and C-reactive protein (CRP) (p = 0.0071) levels in the short-distance group. In the short-distance group, all the patients were transported between hospitals by an ambulance, whereas in the long-distance group, they were transported by an ambulance, helicopters, trains, and airplanes. In addition, continuous catecholamine infusion was significantly more common in patients in the long-distance group (65.7% vs. 81.4%; p = 0.035), whereas ECMO support was significantly more common in patients in the short-distance group (18.6% vs. 5.0%; p = 0.0079). Regarding medications, the usage of beta-blockers (65.7% [short-distance group] vs. 83.1% [long-distance group]; p = 0.018), mineral corticoid receptor antagonists (58.6% [short-distance group] vs. 77.5% [long-distance group]; p = 0.016), loop diuretics (75.7% [short-distance group] vs. 94.4% [long-distance group]; p = 0.0019), and tolvaptan (36.3% [short-distance group] vs. 54.1% [long-distance group]; p = 0.034) were significantly different between the groups, with patients in the long-distance group having been highly administered with guideline-directed therapeutic agents for HF. Echocardiographic parameters were not significantly different between the two groups. In addition, a significantly higher rate of fulminant myocarditis, as an underlying heart disease, was observed in the short-distance group (p = 0.023).

3.3. Clinical course of advanced HF

Regarding primary outcomes, 62 (43.9%) patients had primary outcomes of increased catecholamine support, mechanical support, or

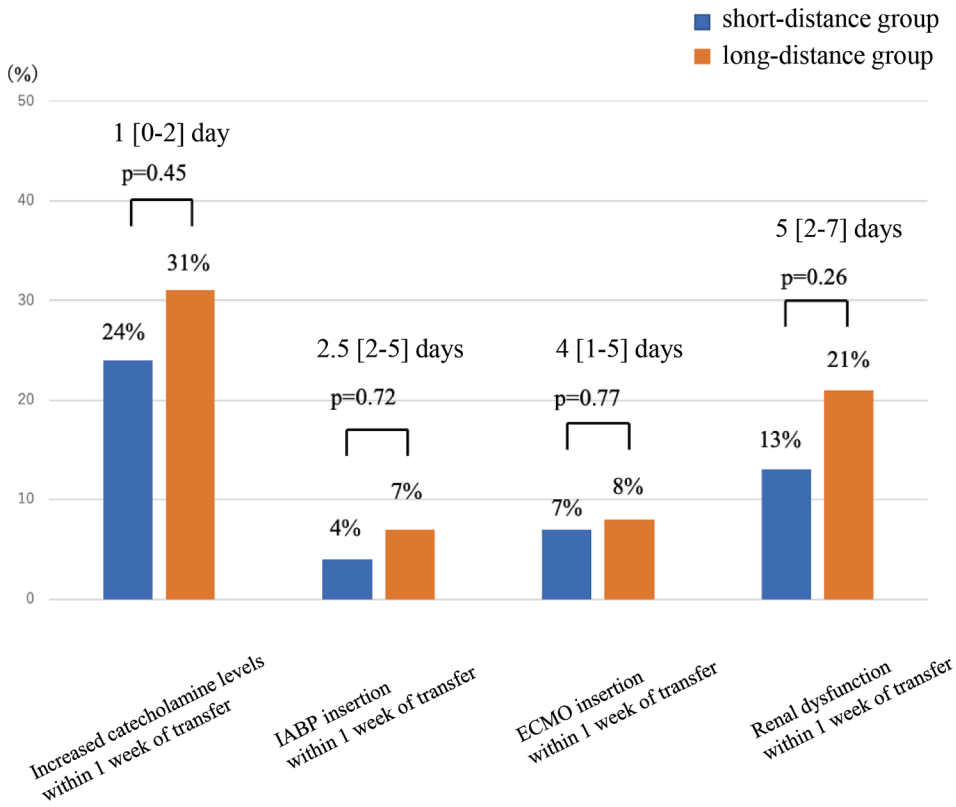

Fig. 3. Difference in each factor in primary outcomes between short- and long-distance groups. There was no significant difference in each factor in primary event between two groups. IABP; intra-aortic balloon pumping, ECMO; extracorporeal membrane oxygenation.

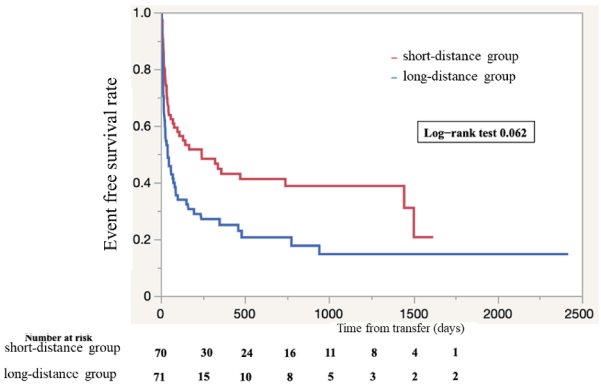

Fig. 4. Secondary outcome in short- and long-distance groups from our hospital. There were no significant differences in event-free survival curves of the secondary outcome measures between two groups.

renal dysfunction within 1 week of transfer (Fig. 2). Fig. 3 shows that within 1 week of transfer, 39 (27.7%) patients required increased catecholamine dose, eight (5.7%) required IABP insertion, and 11 (7.8%) required ECMO implantation. In contrast, 24 patients (17.0%) had renal dysfunction.

Based on the occurrence of primary outcome events, referral patients in the long-distance group had a higher percentage of catecholamine addition, additional mechanical support including IABP/ECMO, and renal dysfunction than patients in the short-distance group ($p = 0.011$). However, based on the individual events included in the primary outcome, no events were identified that occurred with a significant difference between the short- and long-distance groups. Regarding secondary outcomes, 93 patients were implanted with an LVAD and 14 died. There was no significant difference in the secondary outcomes between the two groups ($p = 0.062$) (Fig. 4). Univariate regression analysis predicting primary outcomes showed that age, low body mass index (BMI), long distance, catecholamine support, and implantable cardioverter defibrillator/cardiac resynchronization therapy were the determining factors (Table 2). Multivariate analysis using these parameters showed that low BMI and long distance were independent predictive factors for the primary outcome.

4. Discussion

In this study, although the ECMO support ratio was different between the two groups, there was no significant difference in the characteristics. However, the clinical outcome after transfer, which included an addition of HF treatment within 1 week and the risk of deterioration of renal function, was significantly higher in the long-distance group.

In this study, we focused on the distance between hospitals and evaluated the characteristics of transfer in patients with advanced HF. The distance cutoff value was determined considering that the median distance of hospitals in this study was 33 km. However, the population distribution also differs around 33 km; therefore, the difference in the medical environment of different transfer sources might affect the results in this study. The quality of medical care provided for acute myocardial infarction (AMI), such as the level of medical staff, varies depending on the population density [6].

In the cardiovascular field, studies have been conducted on the transfer of hospitals for AMI and acute aortic dissection (DA) and indicated the importance of early accurate diagnosis and transfer to a facility that can handle treatment as soon as possible [7,8]. The pathology in our study differs from AMI and DA in two aspects: First, unlike acute diseases such as AMI and DA, advanced HF has a time axis that follows an acute exacerbation in a relatively chronic course. Second, the number of medical facilities in the former is overwhelmingly large, which is also the case in Europe and the United States [9]. Therefore, previous

Table 2
Monovariate and multivariate regression analysis of factors that determined the risk of primary outcome.

Parameter	Monovariate		Multivariate	
	Odds ratio (95 % Confidence interval)	*P* value	Odds ratio (95 % Confidence interval)	*P* value
Age (≧40 y/o)	2.33 (1.17–4.64)	0.016*	1.47 (0.65–3.34)	0.36
Sex (male)	1.33 (0.63–2.79)	0.45		
BMI (<19.15 kg/m^2)	1.96 (0.91–4.22)	0.087*	2.74 (1.13–6.62)	0.026 *
Hypertension	1.31 (0.46–3.73)	0.61		
Diabetes	1.62 (0.71–3.72)	0.26		
Dyslipidemia	1.18 (0.54–2.56)	0.68		
Atrial fibrillation	1.10 (0.45–2.65)	0.84		
Stroke	1.31 (0.43–3.95)	0.63		
Distance ≧33 km)	2.49 (1.26–4.93)	0.0089 *	2.69 (1.22–5.93)	0.014 *
Duration of HF ≧492日)	1.21 (0.61–2.41)	0.57		
Systolic BP (<101 mmHg)	1.25 (0.60–2.64)	0.55		
Heart rate (≧77 bpm)	1.49 (0.72–3.11)	0.29		
Catecholamine support	2.32 (1.04−5.18)	0.040*	2.11 (0.84–5.32)	0.11
IABP support	1.40 (0.65–2.99)	0.39		
ECMO support	1.78 (0.62–5.09)	0.28		
ICD/CRTD	2.13 (1.03–4.40)	0.040*	1.59 (0.71–3.56)	0.26
LVEF (<15 %)	1.58 (0.80–3.12)	0.18		
Albumin (<3.3 g/dL)	1.65 (0.82–3.32)	0.16		
eGFR (<78.4 ml/min/ 1.73m2)	2.09 (0.99–4.40)	0.052	1.57 (0.67–3.72)	0.30
BNP ≧1519 pg/mL)	1.98 (0.71–5.53)	0.19		
CRP ≧2.72 mg/L)	1.77 (0.79–3.95)	0.17		
Sodium level (<138 mmol/L)	1.20 (0.60–2.40)	0.61		
Hemoglobin (<14.7 g/ dL)	1.32 (0.90–5.97)	0.082	1.81 (0.61–3.72)	0.28

BMI; body mass index, HF; heart failure, BP; blood pressure IABP; intra-aortic balloon pumping, ECMO; extracorporeal membrane oxygenation, ICD/CRTD; implantable cardioverter defibrillator/cardiac resynchronization therapy defibrillator, LVEF; left ventricular ejection fraction, eGFR; estimated glomerular filtration rate, BNP; brain natriuretic peptide, CRP; C-reactive protein.
* $P < 0.1$.

studies' findings on these acute diseases cannot be directly applied to advanced HF, but it may be the case that a network of treatable medical institutions and prompt cooperation between medical institutions are required. It is thus necessary to individually consider an appropriate medical institution network for HF [10].

Patients transferred via short distance tended to have a higher mechanical support rate (IABP, ECMO) at the time of transfer, whereas those transferred via long distance tended to have a higher catecholamine support rate. As the size (number of beds) of the hospital from which the patient was transferred via short or long distance did not change significantly (data not shown), the treatment that can be handled was presumed to be comparable; however, in the group of patients transferred via long distance, catecholamine was used more frequently to strengthen their drug treatment. Regarding the medication of patients, there was a significant difference in the administration of HF drugs and diuretics among patients transferred via long distance. It was suggested that the short-distance group might consider transfer at a relatively early time, while the timing of transfer is relatively late in the long-distance group.

Patients with advanced HF are transferred to another hospital for advanced medical treatment such as LVAD implantation and HTx based on the judgment that medical treatment at the current hospital is difficult [11]. Although there are some recommendations regarding patient transfer [12,13], there are restrictions due to various disparities; problems such as regional characteristics of medical distribution make such transfers complicated [14], and it is extremely difficult to make an appropriate judgment in the setting in which there is no clear judgment standard. Furthermore, the lack of understanding of the actual conditions of transfer itself and the clinical course after transfer, such as the transfer procedure and adverse effect due to transfer, may raise the hurdle for the judgment at the transfer source.

The issue of transfer in the field of emergency medicine has been relatively debated [15,16]. In a previous study, a database was used to examine the transfer of 1124 cases in 5 years; 66% of patients were transferred for surgical treatment, while 25% were transferred for professional treatment. Although the events during the transfer were examined, events in the clinical course after transfer were not examined [15]. In addition, another study found that among patients transferred to the intensive care unit (ICU), those who were transferred via the emergency room (ER) at the original hospital had a better prognosis than those who were transferred via the ICU [17]. In the current study, the type of bed in the original hospital for patients with HF was unknown, but the prognosis was compared between patients who entered the coronary care unit (CCU) at the time of transfer or within 1 week after the transfer and those who did not. The result was that there were no significant differences in LVAD implantation and the incidence of death (data not shown). This suggests that if the patient's condition at the time of transfer is properly judged, treatment with a CCU is not always necessary.

In addition, regarding the transfer of hospitals with ECMO installed, it has been reported that 11% of the adverse events associated with the transfer were problems such as a decrease in tidal volume, and 5.6% of problems were related to the circulatory system, including bleeding [18]. It has been concluded that the patients can be safely transferred regardless of the distance, but the clinical course after the transfer has not been verified. In addition, the prognosis for ECMO-equipped transfer to cardiogenic shock is very poor, with a 1-year survival report of 33% [19]. In the current study, of the 16 patients (11%) who were transferred with ECMO, eight required an increase in the catecholamine dose within 1 week after transfer, which was a significant difference compared to that of the patients transferred without ECMO ($p = 0.036$). Although the transfer itself can be relatively safe, it is suggested that it affects the clinical course thereafter.

A comparison of blood test findings between the group of patients transferred via short distance and those transferred via long distance showed a significant increase in CRP and AST levels in the patients transferred via short distance. This result suggests that fulminant myocarditis has a high proportion of background diseases in the short-distance group; thus, there is a high risk of increased inflammatory response and hemodynamic disruption after transfer. This may also explain a large number of ECMO installations.

A spoke-hub-and-node (SHN) model has been reported for HF [19]. The SHN model is a model for building organizations in primary care, hospital health care, and specialized care in advanced care, explaining patient stratification and patient flow. A spoke-hub is formed around the center of advanced HF, forming a huge medical area, but in HF with a relatively chronic course, 70–80% are treated as primary care located in the spoke. If additional treatment or consultation is required, the patient will be treated at a community hospital located on the hub or a core

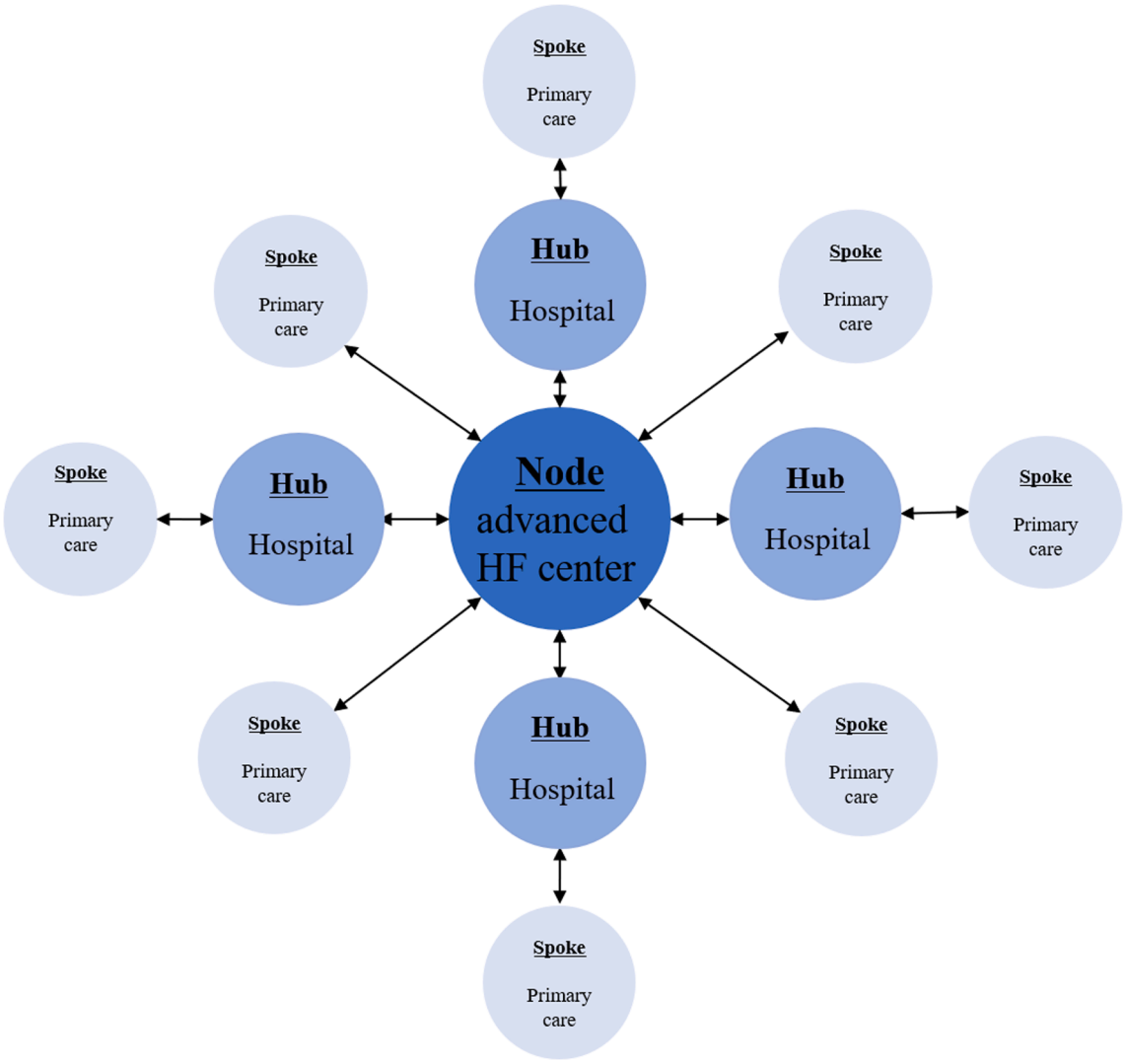

Fig. 5. The Spoke-Hub-and-Node (SHN) model for heart failure (HF) care.This is a conceptual scheme of interhospital collaborations among clinics (spoke), community hospitals, and university hospitals (hub), centered on advanced HF center (node).

hospital; if the condition becomes severe and further treatment needs to be strengthened, the patient will be transferred to the center located at the node. The SHN model has also been proposed abroad for other chronic diseases such as renal failure and has been reported to optimize acute bed utilization and cost. In Japan, it is necessary to use the SHN model to stratify patients with advanced HF and consider optimizing medical resources. We showed that a medical area is formed by hospitals (hubs) such as community hospitals, university hospitals, and medical institutions (spoke), such as clinics and primary care hospitals, centered on the advanced HF center (node) (Fig. 5).

It is necessary to understand that the background differs depending on the case, such as the severity and treatment of patients with HF, transportation means and routes, transportation distance and time, and the risk of exacerbation of the condition due to hospital transfer. Even if temporary deterioration of the condition is predicted after transfer, the necessity of transfer itself does not change; however, it is necessary to consider how to prevent the deterioration of the condition after transfer. It is also important to increase the number of doctors who can respond appropriately by sharing knowledge and experience about HF among doctors and to raise awareness among doctors so that the patients can be transferred at the right time.

4.1. Limitations of this study

This was a retrospective study conducted in Japan, and the number of subjects was relatively small. There are very few LVAD and HTx facilities, and studies on the transfer of patients with advanced HF are limited; therefore, it is still very difficult to make an appropriate decision regarding the time of transfer. It is crucial to conduct studies on a larger scale, including more facilities. In addition, the burden on hospital transfer is now evaluated based on the distance between hospitals, whereas in other studies, it was evaluated based on the transfer time, which may differ greatly depending on the means of transfer; therefore, it is necessary to consider what best reflects the burden of transfer. Indeed, the transfer time might correspond to the impacts on the clinical course after transfer more accurately than transfer distance. We will further collect the data about it in the next investigation.

In addition, as only the patients who were transferred to our hospital were analyzed, it is not possible to compare the clinical course of the patients who were not transferred. A more appropriate transfer method and timing can be examined by including cases that are not originally transferred to another hospital. Previous reports on the transfer of HF in Europe and the United States have reported that the choice of transfer itself has disparities among gender and race [20,21], and it is necessary to investigate such disparities in Japan. Moreover, it is not possible to

compare whether the exacerbation of HF is due to the burden of transfer or the natural course of HF.

5. Conclusions

The distance between hospitals and low BMI were independent prognostic factors for the exacerbation of HF in interhospital transfer of advanced HF cases.

6. Ethics approval and consent to participate

This study was conducted with the approval of the Institutional Review Board of the University of Tokyo Graduate School (assignment number: 2650). Due to nature of retrospective study, written informed consent was waived.

7. Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

8. Declarations

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CRediT authorship contribution statement

Koichi Narita: Conceptualization, Methodology, Data curation, Validation, Writing – original draft, Writing – review & editing. **Eisuke Amiya:** Conceptualization, Methodology, Validation, Data curation, Writing – review & editing. **Masaru Hatano:** Supervision. **Junichi Ishida:** Data curation. **Shun Minatsuki:** Data curation. **Masaki Tsuji:** Data curation. **Chie Bujo:** Data curation. **Nobutaka Kakuda:** Data curation. **Yoshitaka Isotani:** Data curation. **Minoru Ono:** Supervision. **Issei Komuro:** Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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