Original Articles

Innovative clinical pathway shortened the length of hospital stay and prevented readmission in patients with acute decompensated heart failure

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Abstract

Background: With the rapidly aging population in Japan, the number of patients hospitalized for acute decompensated heart failure (ADHF) is increasing. Mitoyo General Hospital created an innovative clinical pathway (CP) for promoting early discharge in patients with ADHF. Major points of the CP were as follows: using tolvaptan as a standard therapy, completing the acute therapies within three days, and starting cardiac rehabilitation from the second day after admission.

Methods: We collected data for patients with ADHF who were admitted to our hospital before introduction of the CP (non-CP group) (April 2014 - July 2015) and after introduction of the CP (CP group) (August 2015 - July 2019). We investigated the impact of the CP on the length of hospital stay (LOHS) and readmission after discharge.

Results: After screening, 593 patients were enrolled in this study. After performing propensity score matching, 129 patients in the non-CP group and 129 patients in the CP group were analyzed. LOHS of patients in the CP group was significantly shorter than that of patients in the non-CP group [20 (14-28) days vs 12 (8-21) days] (P<0.001) without an increase in mortality during hospitalization or an increase in the rate of readmission due to ADHF within 30 days. Use of the CP was an independent negative factor contributing to LOHS for patients with ADHF, even after adjustment of other factors including the use of tolvaptan (P<0.001). The CP significantly decreased the proportions of patients readmitted to hospitals due to

ADHF within 6 months [n=32 (27%) vs n=18 (15%), P=0.026] and 1 year [n=40 (34%) vs n=23 (19%), P=0.009] after discharge compared to the proportion in the non-CP group.

Conclusions: The CP significantly reduced the LOHS of patients without increasing the in-hospital mortality and it also reduced the risk of readmission in the midterm and long-term.

Keywords: clinical pathway, acute decompensated heart failure, tolvaptan, cardiac rehabilitation, prognosis

Introduction

Japan has the highest proportion of elderly people in the world [1]. In previous studies, it was estimated that the number of patients with heart failure (HF) will continue to increase in Japan according to population aging until at least 2040 [2,3]. In addition, the Japanese registry of acute decompensated HF (ADHF), ATTEND, showed that the median length of hospital stay (LOHS) for patients with ADHF in Japan was 21 days [4], which is remarkably longer than that in European countries and the United States (4-9 days) [5–8]. To avoid collapse of the healthcare system due to the "HF pandemic", we need to establish a practical treatment flow that dramatically reduces the LOHS of patients with ADHF without increasing complications, based on clinical evidence.

When patients with ADHF are hospitalized, they generally receive oxygen therapy, peripheral line placement followed by intravenous injection of diuretics and, in addition, urinary catheter insertion. Elderly patients need cardiac rehabilitation to improve their physical performance before discharge. Administration of loop diuretics is a common treatment for ADHF, while several studies conducted in Japan showed that early administration of tolvaptan, an oral vasopressin V2-receptor antagonist, is related to shortening of LOHS in patients with ADHF [9,10]. In addition, previous studies showed that oxygen therapy increased myocardial oxygen delivery only when oxygen saturation in patients was less than 90% and that administration of oxygen at an excessive concentration

resulted in a decrease of cardiac output and an increase of systemic vascular resistance [11,12]. It has also been reported that routine indwelling of a urinary catheter in patients with ADHF was associated with increased urinary tract complications without improving the outcome of HF [13]. Furthermore, a retrospective cohort study of patients with ADHF revealed that patients receiving intravenous fluid infusion had higher rates of subsequent critical care admission, intubation, renal replacement therapy, and in-hospital death than those in patients who received only diuretics [14]. The accumulation of evidence from those studies has shown that oxygen therapy, urinary catheter insertion and intravenous fluid infusion, which are generally used as routine managements for patients with ADHF, do not always improve and sometimes worsen the prognosis of patients. It has also been reported that early initiation of cardiac rehabilitation leads to shortening of LOHS and cost reduction for patients with ADHF [15].

Mitoyo General Hospital is located in Kanonji City, Shikoku region, Japan (Online Figure 1). According to the basic resident register of 2020, people aged 65 years or older accounted for approximately one third [19,567 of 59,342 (33.0%)] of the population of Kanonji City. Based on the previous studies mentioned above, Mitoyo General Hospital introduced an innovative clinical pathway (CP) in August 2015 with the aim of promoting early discharge and improvement of prognosis for patients with ADHF. Since the median LOHS of patients with ADHF in the United States was reported to be 4 days [6,7], the CP was set to complete

acute treatment for HF within 3 days. The CP was introduced to all patients with ADHF except for patients requiring intensive care including administration of positive inotropic agents, mechanical ventilation support and hemodialysis. In this study, we retrospectively investigated the impact of introduction of the CP on LOHS and prognosis with focus on readmission for ADHF after discharge.

Methods

Study Population

This study was a retrospective study that included patients with ADHF who were admitted to Mitoyo General Hospital before introduction of the CP (non-CP group) (from April 2014 to July 2015) and after introduction of the CP (CP group) (from August 2015 to July 2019). We diagnosed ADHF according to ESC guidelines as a condition characterized by clinical symptoms (breathlessness, ankle swelling and fatigue) accompanied by signs (jugular venous distension, pulmonary crackles, and peripheral edema) due to a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressure [16]. We first excluded the following patients from both groups in this study: (1) patients requiring positive inotropic agents including catecholamine and phosphodiesterase 3 inhibitors due to hemodynamic instability, (2) patients receiving mechanical ventilatory support, (3) patients receiving hemodialysis, (4) patients already taking

tolvaptan before admission, and (5) patients without adequate information. Subsequently, we excluded patients who overlapped with the non-CP group from patients treated according to the CP. Finally, propensity score-matched patients in the two groups were enrolled in this study. This study was conducted according to the principles expressed in the Declaration of Helsinki and approved by the institutional ethics committee of Mitoyo General Hospital (application number: 21-CR01-191). In addition, patients were given the opportunity to opt out of the study via the hospital website.

Clinical Pathway

Major points of the CP for patients with ADHF in Mitoyo General Hospital (Figure 1) were as follows: (A) Use of tolvaptan (7.5 mg/day) for the first three days as a standard therapy of diuretics for patients without hypernatremia (>145 mEq/L) who show a poor response to loop diuretics, (B) use of oxygen therapy for the first 3 days only when transcutaneous oxygen saturation is not maintained at 90% or more, (C) use of intravenous fluid infusion for the first 2 days only when other drugs including diuretics are co-administrated intravenously, (D) use of a urinary catheter for the first 2 days only when patients cannot go to the toilet by themselves due to dyspnea or low activities of daily living, and (E) start of cardiac rehabilitation on the second day after admission unless the patient refuses it. Ordering of all of these therapeutic interventions was performed automatically. Patients with a poor

response to loop diuretics were defined as patients who had already been taking oral loop diuretics at admission and patients in whom physicians determined that there was not a sufficient urine output within 30 minutes after intravenous injection of loop diuretics [17,18]. The use of tolvaptan, intravenous fluid infusion, a urinary catheter and oxygen therapy was continued only when they were necessary for management of ADHF. Cardiac rehabilitation was started at the beginning of the week if the patient was admitted to our hospital on the weekend. Exercise training prescription for patients was decided according to their exercise capacity, age and activity habits as suggested in the statement of European Society of Cardiology [19]. The introduction and continuation of all other treatments were decided by the attending physician.

Data Collection

Information on age, sex, body weight, body mass index, blood pressure, New York Heart Association (NYHA) functional classification, heart rate, blood pressure, medical history, principal cause of HF, general laboratory data, left ventricular ejection function (EF) evaluated by transthoracic echocardiography, HF phenotype according to left ventricular EF [HF with preserved EF (HFpEF) (≥ 50%), HF with mid-range ejection fraction (HFmrEF) (40 – 49%), and HF with reduced ejection fraction (HFrEF) (< 40%)], medication at admission, treatment during the acute phase of ADHF, medication at discharge, total medical cost during

hospitalization, and clinical prognosis was obtained from medical records for the patients. Costs were calculated using the exchange rate from Japanese yen (JPY) to United States dollar (USD) on February 5, 2022 (100 JPY = 0.87 USD). For patients who did not visit to our hospital after discharge, we checked their prognosis by telephone.

Clinical Endpoints

The primary endpoint of this study was LOHS of patients. In addition, mortality during hospitalization and readmission due to HF in the short term (30 days), middle term (6 months) and long term (1 year) after discharge were evaluated. All data were collected by a blinded assessment team (N.A. and N.M.) with no information on the background and prognosis of the patients.

Statistical Analysis

The statistical methods used in this study are shown in Online Data 1.

Data Availability

The data generated or analyzed during this study are available from the corresponding author upon reasonable request.

Results

Basic Characteristics of the Study Patients

Figure 2 shows a flowchart of the selection of patients in this study. After screening of 219 patients admitted before introduction of the CP and 549 patients admitted after introduction of the CP, 191 patients and 402 patients were enrolled as patients in the non-CP group and patients in the CP group, respectively.

The characteristics of the patients in the non-CP group and CP group at admission before propensity score matching are shown in Table 1. The proportions of patients with hypertension (n = 119 [62%] vs n = 204 [51%], P = 0.010), patients with a history of hospitalization for HF (n = 39 [20%] vs n = 38 [10%], P<0.001), and patients using diuretics (n = 104 [55%] vs n = 181 [45%], P = 0.035) were significantly higher in the non-CP group. The serum level of sodium was significantly lower in the non-CP group than in the CP group (137 ± 13 mEq/L vs 139 ± 4 mEq/L, P = 0.007). There was no significant difference in other data including age (81 ± 11 years vs 81 ± 11 years), sex (male) [n = 99 (52%) vs n = 205 (51%)], NYHA functional classification, principal cause of HF, and plasma level of brain natriuretic peptide (BNP). After performing 1:1 propensity score matching, 129 patients were selected in each group. Table 2 shows the characteristics of patients in the non-CP group and CP group at admission after propensity score matching. The mean ages of patients were 81 ± 10 years and 80 ± 11 years, the numbers of male patients were 66 (51%) and 70 (54%),

the numbers of patients with a history of hospitalization for HF were 24 (19%) and 30 (23%), the numbers of patients with ischemic heart disease as a principal cause of ADHF were 32 (25%) and 25 (19%), serum levels of sodium were 137 ± 13 mEq/L and 139 ± 5 mEq/L, plasma levels of BNP were 587 (345-978) pg/ml and 585 (334-1001) pg/ml, left ventricular EF values were 48 ± 19% and 49 ± 20%, and the numbers of patients with HFpEF were 73 (57%) and 83 (64%) in the non-CP group and CP group, respectively. There was no significant difference in characteristics between the two groups after performing propensity score matching.

Treatments and Prognosis

Treatments and prognosis of the patients with ADHF in the two groups are shown in Table 3. The proportion of patients in whom tolvaptan was used as acute management for ADHF was significantly higher in the CP group than in the non-CP group [n = 39 (30%) vs n = 125 (97%), P<0.001)]. Four patients in the CP group did not receive treatment with tolvaptan according to physicians' decisions. In contrast, the proportions of patients who received intravenous injection of furosemide [n = 99 (77%) vs n = 59 (46%), P < 0.001] and intravenous injection of carperitide [n = 62 (48%) vs n = 4 (3%), P < 0.001] were significantly lower in the CP group than in the non-CP group. The proportion of patients who received oxygen therapy [n = 109 (85%) vs n = 80 (62%), P < 0.001], intravenous fluid infusion [n = 110 (85%) vs n = 83 (64%),

P < 0.001] and a urinary catheter [n = 75 (59%) vs n = 52 (40%), P = 0.006] in the CP group were significantly lower than those in the non-CP group. In patients in whom those treatments were used, the median durations of the use of oxygen therapy [7 (5-13) days vs 5 (3-11) days, P = 0.004], intravenous fluid infusion [7 (5-12) days vs 3 (2-4) days, P < 0.001] and a urinary catheter [7 (4-16) days vs 4 (3-5) days, P < 0.001] were also significantly decreased by using the CP. In addition, the proportion of patients who received cardiac rehabilitation was significantly higher [n = 108 (84%) vs n = 120 (93%), P = 0.031] and the start of cardiac rehabilitation was significantly earlier [5 (3-8) days vs 3 (2-4) days, P < 0.001] in the CP group than in the non-CP group.

The proportion of patients whose maximum level of serum sodium was over 145 mEq/L during hospitalization was significantly higher in the CP group than in the non-CP group [n = 4 (3%) vs n = 16 (12%), P = 0.009]. On the other hand, there was no significant difference between the two groups in the proportion of patients who showed severe hypernatremia (> 150 mEq/L) [n = 0 (0%) vs n = 1 (1%), P = 1.000]. In addition, the ratio of patients who showed worsening renal function (increase of serum creatinine ≥ 0.3 mg/dL) during hospitalization was not significantly different between the two groups [n = 6 (5%) vs n = 4 (3%), P = 0.749].

The proportion of patients using tolvaptan at discharge was significantly higher in the CP group than in the non-CP group [n = 23 (19%) vs n = 75 (61%), P < 0.001]. The proportion

of patients receiving a beta-blocker at discharge was significantly lower in the CP group than in the non-CP group [n = 59 (50%) vs n = 39 (32%), P = 0.006]. There was no significant difference in the percentages of patients receiving other HF treatments at discharge including treatments with an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin II receptor blocker (ARB), mineralocorticoid receptor antagonist (MRA) and diuretics other than tolvaptan. Only one patient in the CP group was taking sodium-glucose co-transporter-2 (SGLT2-I) at discharge.

LOHS was significantly shorter in the CP group than in the non-CP group [20 (14-28) days vs 12 (8-21) days, P < 0.001]. Furthermore, there was no significant difference between the two groups in the proportion of patients who died during hospitalization [n = 10 (8%) vs n = 6 (5%), P = 0.440] and the proportion of patients transferred to a nursing home or another hospital [n = 19 (15%) vs n = 20 (16%), P = 1.000]. In addition, total medical cost needed for patient care during hospitalization was significantly lower in the CP group than in the non-CP group [7,293 (5,373-10,625) USD vs 5,293 (3,344-8,994) USD, P < 0.001]. There was no significant difference in the ADHF readmission rate within 30 days after discharge between the two groups [n = 14 (12%) vs n = 6 (5%), P = 0.063]. On the other hand, the proportions of patients readmitted for ADHF within 6 months and 1 year after discharge in the CP group were significantly lower than those in the non-CP group [n = 32 (27%) vs n = 18 (15%), P = 0.026] [n = 40 (34%) vs n = 23 (19%), P = 0.009]. There was no significant difference between

the two groups in the proportions of patients who died from a cardiovascular event [n = 9 (8%) vs n = 6 (5%), P = 0.434] and from any cause [n = 12 (10%) vs n = 16 (13%), P = 0.549] within 1 year after discharge. Kaplan-Meier analysis showed that ADHF-readmission-free survival rate after discharge was significantly higher in the CP group than in the non-CP group (log-rank, P = 0.008) (Figure 3).

Univariate regression analysis showed that use of the CP was significantly correlated with LOHS for patients with ADHF (standardized regression coefficient = -0.33, P < 0.001). Furthermore, even after adjustment of other general factors affecting the course of HF and the use of tolvaptan as acute treatment for ADHF, use of the CP was an independent negative factor contributing to LOHS for patients with ADHF (standardized regression coefficient = -0.44, P < 0.001) (Table 4). Furthermore, univariate Cox proportional hazards regression analysis showed that use of the CP had a significant impact on readmission due to ADHF [hazard ratio (HR): 0.51, 95% confidence interval (CI): 0.30 - 0.85, P = 0.009]. After adjustment of other conventional factors contributing to the course of HF and the use of tolvaptan at discharge, use of the CP was still an independent factor affecting readmission due to ADHF (HR: 0.43, 95% CI: 0.24 - 0.78, P = 0.005) (Table 5).

Discussion

The major findings of this study were as follows: (1) the CP for promoting early discharge of

ADHF patients significantly reduced the LOHS of patients (median LOHS of 8 days) and total medical cost during hospitalizations (median cost of 2,000 USD) without increasing in-hospital mortality and readmission within 30 days, (2) even after adjustment of other factors including the use of tolvaptan, use of the CP was an independent negative factor contributing LOHS for patients with ADHF and (3) the CP also significantly reduced the risk of readmission for ADHF within 6 months and 1 year after discharge.

Characteristics of Patients' Background

The subjects of this study were elderly patients with a mean age of over 80 years, and HFpEF accounted for more than half of the phenotypes of HF. In the Prevention of Renal and Vascular Endstage Disease (PREVEND) study and the Framingham Heart Study, in which the average ages of patients were 49 years and 58 years, respectively, the majority of the phenotypes of HF were HFrEF, whereas in Cardiovascular Health Study, in which the average age of patients was 73 years, HFpEF accounted for 53% of the phenotypes of HF [20]. Those studies and our study suggest that the proportion of patients with HFpEF increases with advance of age in patients with HF. The results of our study are expected to have great implications for the treatment of HF in the current aging society, in which HFpEF is expected to account for the majority HF phenotypes.

Characteristics of Medications for HF in This Study

We included the use of tolvaptan as a standard therapy of the CP in this study. The high ratio of patients showing hypernatremia in the CP group compared to that in the non-CP group was likely to be caused by the introduction of tolvaptan. On the other hand, only one patient showed severe hypernatremia (> 150 mEq/L) in the CP group. These results showed the safety of tolvaptan as a standard therapy for heart failure patients without hypernatremia at admission. In addition, it was remarkable that only 4 patients (3%) in the CP group were treated with carperitide, while almost half of the patients in the non-CP group were treated with carperitide. This gap between the two groups was probably based on the concept of the CP that aims to simplify the management of ADHF. We also found low ratios of patients receiving an ACE-I or ARB and patients receiving MRA (both approximately 30% respectively), and patients receiving a beta-blocker (≤50%) in both groups. There were several possible reasons for the low introduction rates of these drugs for patients in this study. First, as we mentioned above, approximately 60% of the patients were diagnosed as having HFpEF. Since there is no established treatment other than diuretics for improving the prognosis of patients with HFpEF, it was quite conceivable that physicians did not prescribe these drugs to the patients with HFpEF. Second, because the mean age and estimated glomerular filtration rate of the patients in this study were approximately 80-81 years and 46-47 ml/min/1.73 m^2 respectively, it was possible that elderly patients with decreased renal

function did not show sufficient tolerance to the introduction of an ACE-I, ARB or MRA, for which there is a risk of increase in the serum level of potassium. On the other hand, the lower ratio of patients receiving a beta-blocker at discharge in the CP group than in the non-CP group may have resulted from insufficient introduction of a beta-blocker during hospitalization due to early discharge of patients in the CP group. In addition, there was almost no patient receiving a SGLT2-I at discharge in our study. It was estimated that since patients who were admitted to our hospital from April 2014 to July 2019 were enrolled in our study, we could not apply the latest evidence of SGLT2-I as a treatment for HFrEF [21–23].

Clinical Impact of the CP on Patients with ADHF

This study showed that introduction of the CP resulted in shorter LOHS and reduction of medical costs during hospitalization for patients with ADHF. According to one of the largest Japanese registries of HF, the median period of LOHS was 21 days [4]. In addition, a previous study showed that the median cost per patient with HF was 8,089 (5,362 – 12,787) USD per hospitalization according to data of a Japanese registry [24]. Therefore, the median LOHS (20 days) and the median medical cost (7,293 USD) in patients in the non-CP group in our study are generally reasonable in Japan, and 8 days reduction in the LOHS and 2,000 USD reduction in the medical cost by using the CP are considered to have a great impact on the management of inpatients with ADHF.

In the EVEREST trial, one of the world's largest randomized controlled trials in which the impact of tolvaptan on ADHF was evaluated, it was shown that administration of tolvaptan within 48 hours of admission resulted in significant amelioration of symptoms of HF including dyspnea and edema [25]. However, the trial also showed that there was no significant improvement of clinical symptoms 1 week after the start of tolvaptan administration in patients with HF. On the other hand, our study showed that introduction of the CP significantly contributed to shortening of the LOHS even after correction by confounding factors including the use of tolvaptan during the acute phase. In our study, it is possible that early decongestion by tolvaptan ameliorated symptoms of HF, which led to early release of patients from management with oxygen therapy, intravenous fluid infusion and urinary catheters and subsequently resulted in the achievement of early initiation and promotion of cardiac rehabilitation.

Furthermore, in the present study, introduction of the CP not only shortened LOHS of patients with ADHF but also significantly reduced readmission rate for ADHF within 6 months and 1 year without increasing readmission rate within 30 days after discharge. On the other hand, a post-hoc analysis of the EVEREST trial showed that longer LOHS was correlated with lower risk for 30-day readmission for HF [26]. This may be because the CP used in our study included not only administration of tolvaptan but also early initiation of cardiac rehabilitation in the schedule, which prevented deterioration of cardiopulmonary function.

Therefore, in our study, maintenance of cardiopulmonary function by cardiac rehabilitation may have contributed to the prevention of HF readmission in the short term and long term. However, evaluation of cardiopulmonary function by objective tools including cardiopulmonary exercise testing was not routinely performed at the time of discharge and it is therefore unclear to what extent early start of cardiac rehabilitation contributed to the prevention of readmission of patients in this study. Further studies are needed to reach a conclusion regarding the effect of early initiation of cardiac rehabilitation on prevention of readmission for HF.

Study Limitations

There were several limitations in this study. First, this study was a retrospective study with a relatively small sample size performed in a single center, and it was not a randomized controlled trial. Although the data were corrected as much as possible by performing propensity score matching and multivariate analysis, there was still a possibility that the background of patients remained biased, and it may have affected the results of this study. Second, patients requiring intensive support for maintaining the stability of respiration and circulation were excluded from this study, and we therefore, we could not assess the impact of the CP on patients with severe heart failure. Third, we could not individually evaluate the impact of each item included in the CP on LOHS and prognosis in patients with HF. In

addition, the CP introduced in this study did not include a specific method for evaluating fluid overload in the patients. For example, the routine use of diuretics is not recommended for patients with clinical scenario 1 heart failure [27], which is sometimes not accompanied by severe fluid overload. We need to update the CP to reflect the evaluation of fluid volume status in each patient in order to avoid risks of dehydration and collapse of circulation. Finally, we could not obtain information on treatments and medical costs for patients after discharge in our study because not all of the patients continued visiting our hospital. The ratio of patients who were still taking tolvaptan at discharge was higher in the CP group, and loss of information for patients after discharge was therefore an important limitation of this study.

Conclusions

The CP for promoting early discharge significantly shortened the LOHS and reduced medical costs for elderly patients with ADHF without increasing in-hospital mortality and readmission rate in the short term and decreased the readmission rate in the middle term and long term after discharge. Our study suggested that the CP used in this study can contribute to the resolution of problems including a lack of beds and rising healthcare costs associated with the "HF pandemic" in an aging society.

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Figure legends

Figure 1. Clinical pathway for promoting early discharge for patients with acute decompensated heart failure.

Figure 2. Flowchart of patient selection.

ADHF: acute decompensated heart failure; CP: clinical pathway.

Figure 3. Kaplan-Meier curve for heart failure-related readmission within 1 year after discharge.

ADHF: acute decompensated heart failure; CP: clinical pathway.

Tables

Table 1. Characteristics of patients in the non-CP group and the CP group at admission before matching by propensity scores.

	Non-CP group (n = 191)	CP group (n = 402)	P-value
Clinical characteristics			
Age, years	81 ± 11	81 ± 11	0.910
Sex (male), n (%)	99 (52)	205 (51)	0.861
Body weight, kg	56 ± 15	56 ± 16	0.688
Body mass index, kg/m^2	21.7 ± 4.4	21.5 ± 4.3	0.769
NYHA functional classification			
II, n (%)	5 (3)	18 (5)	0.364
III, n (%)	113 (59)	226 (56)	0.535
IV, n (%)	73 (38)	158 (39)	0.857
Heart rate, beats per minute	89 ± 25	86 ± 24	0.164
Systolic blood pressure, mm Hg	141 ± 30	142 ± 26	0.715
Diastolic blood pressure, mm Hg	78 ± 19	81 ± 19	0.057
Medical history			

Hypertension, n (%)	119 (62)	204 (51)	0.010
Diabetes mellitus, n (%)	42 (22)	90 (22)	1.000
Dyslipidemia, n (%)	44 (23)	88 (22)	0.752
Atrial fibrillation, n (%)	77 (40)	173 (43)	0.593
Previous PCI or CABG, n (%)	35 (18)	49 (12)	0.058
Cardiac resynchronization therapy, n (%)	2 (1)	0 (0)	0.103
Hospitalization for heart failure, n (%)	39 (20)	38 (10)	<0.001
Principal cause of heart failure			
Ischemic heart disease, n (%)	43 (23)	64 (16)	0.053
Laboratory data			
Hemoglobin, g/dl	11.4 ± 2.2	11.7 ± 2.2	0.157
Serum sodium, mEq/L	137 ± 13	139 ± 4	0.007
Plasma BNP, pg/ml	624 (352-988)	569 (350-991)	0.292
eGFR, ml/ min/ 1.73 m^2	46 ± 24	47 ± 20	0.722
Left ventricular ejection fraction, %	49 ± 18	50 ± 18	0.788
HF phenotype			
HFpEF, n (%)	114 (60)	245 (61)	0.788

HFmrEF, n (%)	26 (14)	54 (13)	1.000
HFrEF, n (%)	51 (27)	103 (26)	0.841
Medication			
ACEI or ARB, n (%)	78 (41)	146 (36)	0.319
Beta-blocker, n (%)	61 (32)	108 (27)	0.207
MRA, n (%)	35 (18)	59 (15)	0.279
Diuretic, n (%)	104 (55)	181 (45)	0.035
Oral hypoglycemic agent, n (%)	47 (25)	78 (19)	0.162
SGLT2 inhibitor, n (%)	1 (1)	2 (1)	1.000

Values are expressed as mean±standard deviation, median and interquartile range or absolute number of cases (relative percentage) as appropriate.

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; BNP: brain natriuretic peptide; CABG: coronary artery bypass grafting; CP: clinical pathway; eGFR: estimated glomerular filtration rate; HFmrEF: heart failure with mid-range ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association; PCI; percutaneous coronary intervention; SGLT2: sodium-glucose co-transporter-2.

Table 2. Characteristics of patients in the non-CP group and the CP group at admission after matching by propensity scores.

	Non-CP group (n = 129)	CP group (n = 129)	P-value
Clinical characteristics			
Age, years	81 ± 10	80 ± 11	0.722
Sex (male), n (%)	66 (51)	70 (54)	0.708
Body weight, kg	55 ± 14	55 ± 14	0.917
Body mass index, kg/m^2	21.6 ± 4.4	21.1 ± 3.8	0.486
NYHA functional classification			
II, n (%)	5 (4)	5 (4)	1.000
III, n (%)	110 (85)	110 (85)	1.000
IV, n (%)	14 (11)	14 (11)	1.000
Heart rate, beats per minute	87 ± 24	83 ± 22	0.166
Systolic blood pressure, mm Hg	136 ± 27	139 ± 25	0.363
Diastolic blood pressure, mm Hg	77 ± 18	80 ± 17	0.187
Medical history			
Hypertension, n (%)	77 (60)	63 (49)	0.104

Diabetes mellitus, n (%)	27 (21)	26 (20)	1.000
Dyslipidemia, n (%)	30 (23)	25 (19)	0.543
Atrial fibrillation, n (%)	61 (47)	59 (46)	0.901
Previous PCI or CABG, n (%)	26 (20)	16 (12)	0.128
Cardiac resynchronization therapy, n (%)	2 (2)	0 (0)	0.498
Hospitalization for heart failure, n (%)	24 (19)	30 (23)	0.444
Principal cause of heart failure			
Ischemic heart disease, n (%)	32 (25)	25 (19)	0.368
Laboratory data			
Hemoglobin, g/dl	11.4 ± 2.3	11.6 ± 2.2	0.376
Serum sodium, mEq/L	137 ± 13	139 ± 5	0.130
Plasma BNP, pg/ml	587 (345-978)	585 (334-1001)	0.683
eGFR, ml/ min/ 1.73 m^2	47 ± 24	46 ± 20	0.864
Left ventricular ejection fraction, %	48 ± 19	49 ± 20	0.826
HF phenotype			
HFpEF, n (%)	73 (57)	83 (64)	0.252
HFmrEF, n (%)	15 (12)	7 (5)	0.117

HFrEF, n (%)	41 (33)	39 (31)	0.686
Medication			
ACEI or ARB, n (%)	53 (41)	42 (33)	0.197
Beta-blocker, n (%)	47 (36)	39 (30)	0.355
MRA, n (%)	29 (23)	25 (19)	0.646
Diuretic, n (%)	72 (56)	70 (54)	0.900
Oral hypoglycemic agent, n (%)	30 (23)	25 (19)	0.543
SGLT2 inhibitor, n (%)	0 (0)	0 (0)	NA (*)

Values are expressed as mean ± standard deviation, median and interquartile range or absolute number of cases (relative percentage) as appropriate.

*: The statistical analysis could not be performed because there was no patient taking a SGLT2 inhibitor at admission in both groups.

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; BNP: brain natriuretic peptide; CABG: coronary artery bypass grafting; CP: clinical pathway; eGFR: estimated glomerular filtration rate; HFmrEF: heart failure with mid-range ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; MRA: mineralocorticoid receptor antagonist; NA: not analyzed; NYHA: New York Heart Association; PCI; percutaneous coronary intervention; SGLT2: sodium-glucose co-transporter-2.

Table 3. Treatments and prognosis of patients with ADHF in the non-CP group and the CP group.

	Non-CP group (n = 129)	CP group (n = 129)	P-value
Acute management			
Tolvaptan, n (%)	39 (30)	125 (97)	<0.001
Furosemide (intravenous injection), n (%)	99 (77)	59 (46)	<0.001
Carperitide, n (%)	62 (48)	4 (3)	<0.001
Oxygen therapy, n (%)	109 (85)	80 (62)	<0.001
Duration of using oxygen therapy (*), days	7 (5-13)	5 (3-11)	0.004
Intravenous fluid infusion, n (%)	110 (85)	83 (64)	<0.001
Duration of using intravenous fluid infusion (*), days	7 (5-12)	3 (2-4)	<0.001
Urinary catheter, n (%)	75 (59)	52 (40)	0.006
Duration of using urinary catheter (*), days	7 (4-16)	4 (3-5)	<0.001
Cardiac rehabilitation, n (%)	108 (84%)	120 (93%)	0.031
Start day of cardiac rehabilitation (*), days	5 (3-8)	3 (2-4)	<0.001

Hypernatremia			
Serum sodium > 145 mEq/L, n (%)	4 (3)	16 (12)	0.009
Serum sodium > 150 mEq/L, n (%)	0 (0)	1 (1)	1.000
Worsening renal function			
Increasing of serum Cre ≥ 0.3 mg/dL, n (%)	6 (5)	4 (3)	0.749
Heart failure treatment at discharge			
ACEI or ARB, n (%)	39 (33)	37 (30)	0.679
Beta-blocker, n (%)	59 (50)	39 (32)	0.006
MRA, n (%)	35 (29)	34 (28)	0.778
Diuretic (except for tolvaptan), n (%)	93 (78)	100 (81)	0.632
Tolvaptan, n (%)	23 (19)	75 (61)	<0.001
SGLT2 inhibitor, n (%)	0 (0)	1 (1)	1.000
Clinical outcome and cost during hospitalization			
Length of hospital stay, days	20 (14-28)	12 (8-21)	<0.001
In-hospital death, n (%)	10 (8)	6 (5)	0.440
Total medical cost during hospitalization, USD	7293 (5373-10625)	5293 (3344-8994)	<0.001
Discharge disposition			

Home, n (%)	100 (78)	103 (80)	0.761
Nursing home or other hospital, n (%)	19 (15)	20 (16)	1.000
Clinical outcome after discharge			
Readmission due to ADHF within 30 days, n (%)	14 (12)	6 (5)	0.063
Readmission due to ADHF within 6 months, n (%)	32 (27)	18 (15)	0.026
Readmission due to ADHF within 1 year, n (%)	40 (34)	23 (19)	0.009
Cardiovascular death within 1 year, n (%)	9 (8)	6 (5)	0.434
All-cause death within 1 year, n (%)	12 (10)	16 (13)	0.549

Values are expressed as median and interquartile range or absolute number of cases (relative percentage) as appropriate.

*: in the cases of using those treatments

ACEI: angiotensin-converting enzyme inhibitor; ADHF: acute decompensated heart failure; ARB: angiotensin II receptor blocker; CP: clinical pathway; USD: United States dollars.

Table 4. Impact of CP on length of hospital stay evaluated by univariate and multiple regression analyses.

	B	SE_B	β	95% CI of B	P-value
Model 1	-0.48	0.09	-0.33	-0.65 to -0.31	<0.001
Model 2	-0.47	0.09	-0.32	-0.64 to -0.30	<0.001
Model 3	-0.49	0.09	-0.34	-0.66 to -0.32	<0.001
Model 4	-0.50	0.09	-0.34	-0.67 to -0.32	<0.001
Model 5	-0.65	0.12	-0.44	-0.90 to -0.41	<0.001

Model 1: unadjusted.

Model 2: adjusted for age and sex.

Model 3: adjusted for prevalence of atrial fibrillation, principal cause of heart failure (ischemic heart disease or not), and history of admission due to heart failure in addition to adjustments in Model 2.

Model 4: adjusted for phenotype of heart failure (HFrEF or not), NYHA functional class, eGFR and plasma level of BNP (log-transformed) at admission in addition to adjustments in Model 3.

Model 5: adjusted for tolvaptan use as acute therapy in addition to adjustments in Model 4.

B: regression coefficient; β: standardized coefficient of B; BNP: brain natriuretic peptide; CI: confidence interval; CP: clinical pathway; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; SE_B: standard error of

B.

Table 5. Impact of CP on readmission due to heart failure within 1 year after discharge evaluated by Cox proportional hazard models.

	Hazard ratio	95% CI	P-value
Model 1	0.51	0.30 to 0.85	0.009
Model 2	0.51	0.31 to 0.86	0.011
Model 3	0.43	0.25 to 0.73	0.002
Model 4	0.42	0.25 to 0.71	0.001
Model 5	0.43	0.24 to 0.78	0.005

Model 1: unadjusted.

Model 2: adjusted for age and sex.

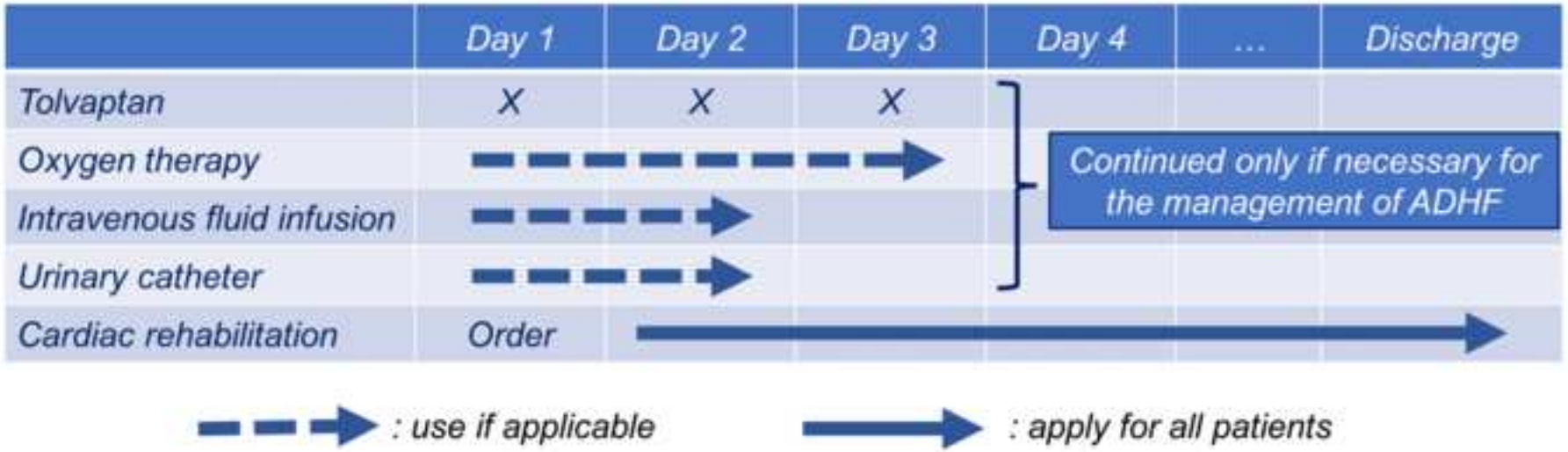
Model 3: adjusted for prevalence of atrial fibrillation, principal cause of heart failure (ischemic heart disease or not), and history of repeated admission due to heart failure in addition to adjustments in Model 2.

Model 4: adjusted for phenotype of heart failure (HFrEF or not) in addition to adjustments in Model 3.

Model 5: adjusted for taking MRA, beta-blocker, diuretics (except for tolvaptan) and tolvaptan at discharge in addition to the adjustment in Model 4.

CI: confidence interval; CP: clinical pathway; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist.

Figure 1



Treatments	Details
Tolvaptan	Use of tolvaptan (7.5 mg/day) for first three days as a standard therapy of diuretics for patients without hypernatremia (>145 mEq/L) who show a poor response to loop diuretics.
Oxygen therapy	Use oxygen therapy for the first 3 days only when transcutaneous oxygen saturation cannot be maintained at 90% or more.
Intravenous fluid infusion	Use intravenous fluid infusion for the first 2 days only when other drugs including diuretics are co-administrated intravenously
Urinary catheter	Use a urinary catheter for the first 2 days only when patients cannot go to the toilet by themselves due to dyspnea or low activities of daily living.
Cardiac rehabilitation	Start cardiac rehabilitation on the second day after admission unless the patient refuses it.

Figure 2

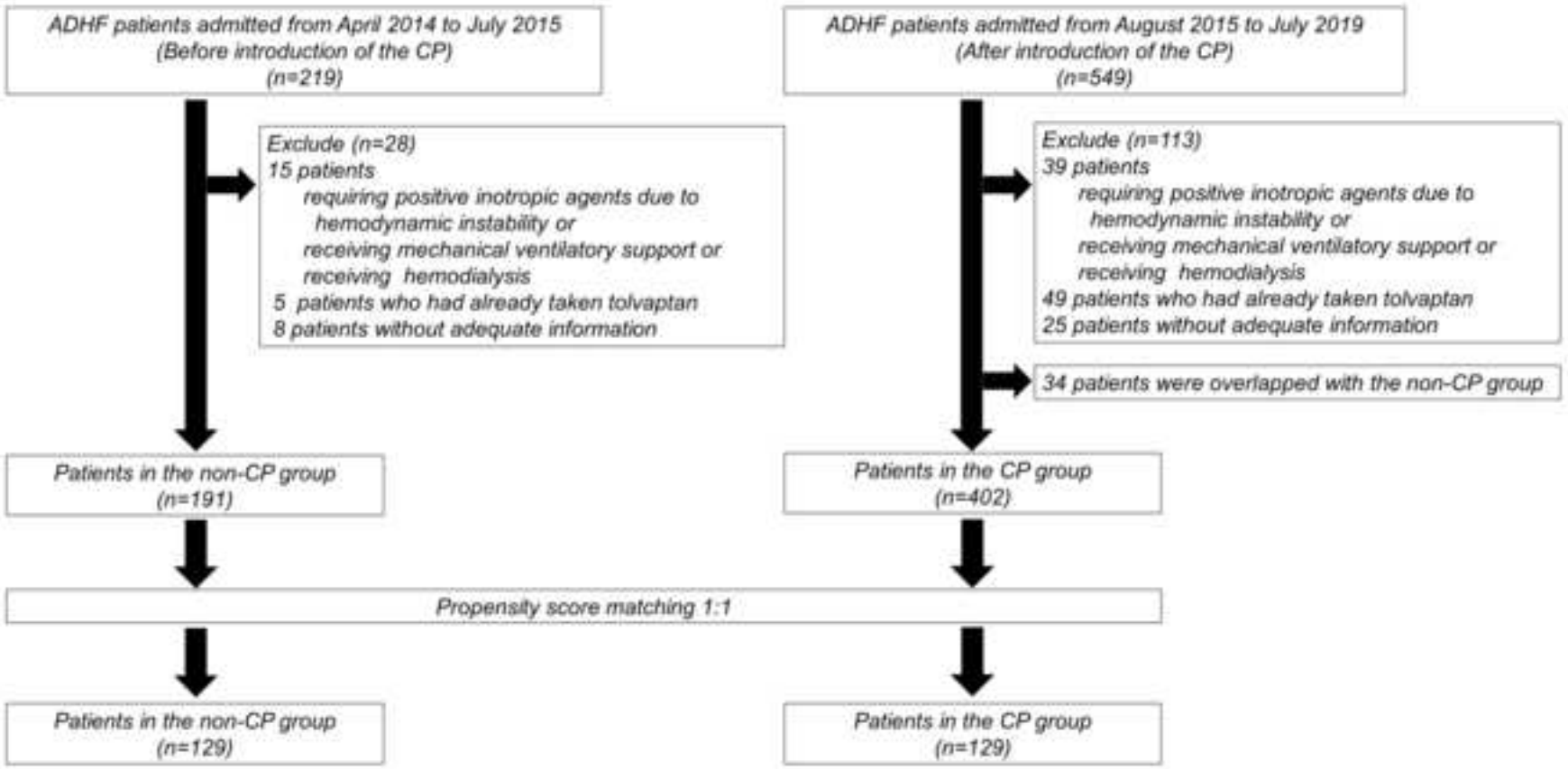


Figure 3