ORIGINAL ARTICLE

Heart Failure

Clinical Approach to Shortening Length of Hospital Stay in Elderly Patients With Acute Heart Failure Requiring Intensive Care

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Background: The length of hospital stay (LOHS) after acute heart failure (AHF) is too long in Japan. The clinical approach to shortening LOHS is an urgent issue in the aging Japanese society.

Methods and Results: Of 1,473 AHF patients screened, 596 patients >75 years old were enrolled. They were divided by LOHS: <28 days (<28-day group, n=316) and ≥28 days (≥28-day group, n=280). Systolic blood pressure and serum hemoglobin were significantly higher and serum blood urea nitrogen and creatinine significantly lower in the <28-day group than in the ≥28-day group. Non-invasive positive pressure ventilation (NPPV) use was significantly more frequent in the <28-day group than in the ≥28-day group. Furthermore, newly initiated tolvaptan in <12 h was significantly more frequent in the <28-day group than in the ≥28-day group (P=0.004). On multivariate logistic regression analysis, newly initiated tolvaptan in <12 h (OR, 2.574; 95% CI: 1.146–5.780, P=0.022) and NPPV use (OR, 1.817; 95% CI: 1.254–2.634, P=0.002) were independently associated with the <28-day group. The same result was found after propensity score matching for LOHS.

Conclusions: LOHS was prolonged in patients with severe HF but could be shortened by early tolvaptan treatment.

Key Words: Acute decompensated heart failure; Aging; Hospitalization; Oral vasopressin V2-receptor antagonist; Tolvaptan

Prolonged length of hospital stay (LOHS) in patients with acute heart failure (AHF) is of major public concern in Japan. LOHS after AHF in Japan is >20 days due to Japan's socialized medical system, and is much longer than in any other Western or Asian countries.[1,2] Our previous study suggested that LOHS was decreasing, even though patient condition was becoming more severe,[3] but it was still longer than in other reports from the 2000s.[1,2,4,5] The rapid global increase in the number of HF patients has reached a pandemic level,[6] and AHF is estimated to afflict >0.37 million patients by 2025 in Japan.[7] Aging may be the most important issue when discussing the future of the HF pandemic, given that Japan's population is aging rapidly and that Japanese life expectancy is increasing year by year, compared with Western countries.

Prolonged hospital stay is associated with a decline in activities of daily living (ADL), and with an associated increase in the level of frailty and malnourishment in elderly AHF patients. Management practices to maintain ADL by shortening hospitalization should therefore be considered in the upcoming HF pandemic era. Tolvaptan was introduced in 2010 in Japan, and substantial supporting evidence has subsequently been accumulated to recommend its use in the early phase of AHF.[8] Oral treatment has been shown to have a positive influence on physical function in older AHF patients; indeed, Ueda et al showed that oral medication increased functional independence during hospitalization compared with sustained continuous i.v. infusion, likely because the release from the infusion line enabled the patients to be more mobile.[9] Early tolvaptan treatment therefore might help reduce LOHS in elderly AHF patients.
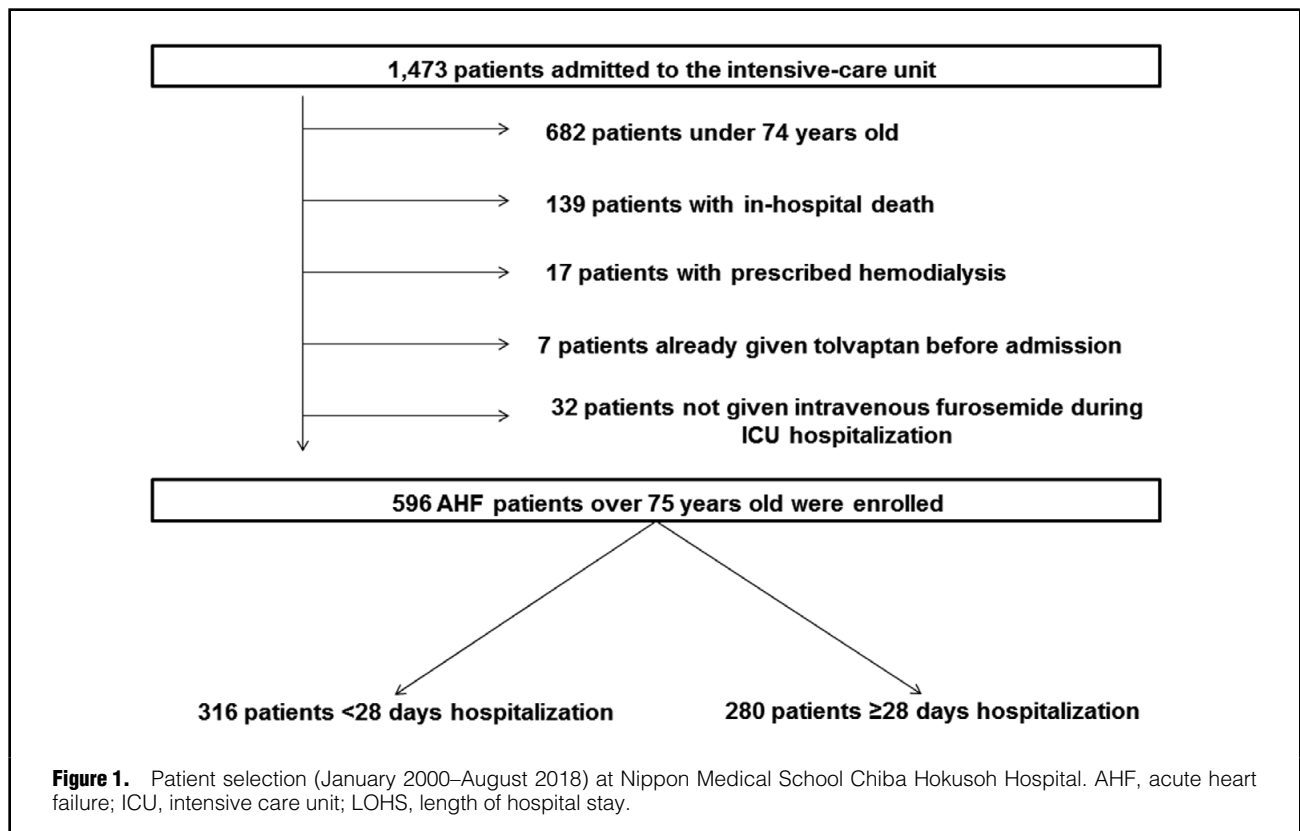
In the present study, we investigated the differences in clinical factors according to LOHS and explored the clinical approach to shortening LOHS in elderly AHF patients who require intensive care.

Figure 1. Patient selection (January 2000–August 2018) at Nippon Medical School Chiba Hokusoh Hospital. AHF, acute heart failure; ICU, intensive care unit; LOHS, length of hospital stay.

Methods

Subjects

A total of 1,473 patients with AHF who were admitted to the intensive care unit (ICU) of Nippon Medical School Chiba Hokusoh Hospital between January 2000 and December 2018 were screened. Of these, 682 patients <74 years old and 139 patients with in-hospital death were initially excluded from this study. To evaluate the relationship between diuretics and LOHS, we further excluded the following patients: 17 patients prescribed hemodialysis, 7 patients who had already received tolvaptan before admission, and 32 patients who did not use i.v. furosemide during ICU hospitalization (**Figure 1**).

AHF was defined as either new-onset HF or decompensation of chronic HF with symptoms sufficient to warrant hospitalization, resulting in the need for urgent therapy. A clinical history (i.e., symptoms, functional limitation, history of cardiac disease, risk factors, exacerbating factors, comorbidities, and drugs), physical examination (i.e., vital signs, weight and volume status in heart, lung, abdomen, and peripheral vascular region) and initial investigations (i.e., chest radiograph, 12-lead electrocardiogram [ECG], laboratory measurement of troponins, blood urea nitrogen [BUN], creatinine, sodium, potassium, glucose, liver function, and complete blood count) were required for the diagnosis of HF. Furthermore, echocardiography or an abnormal ECG or the presence of pulmonary edema on chest X-ray, and B-type natriuretic peptide (BNP) ≥100 pg/mL or N-terminal pro BNP (Nt-proBNP) ≥300 pg/mL were also required for the diagnose of AHF. The treating cardiologist in the emergency department diagnosed AHF based on

these criteria immediately after admission.[10] All of the patients who presented to the emergency room had a New York Heart Association (NYHA) functional class of either III or IV.

Furthermore, the use of diuretics or vasodilators as a treatment for AHF was carried out in all of the included patients. The patients who required high-flow oxygen therapy (including mechanical support) to treat orthopnea or who required inotropes or mechanical support due to low blood pressure or required various types of diuretics to improve general or lung edema were treated in ICU. We excluded patients with HF due to ST-T segment elevation acute coronary syndrome. There was no limitation in the treatment of AHF, and the treatment strategy was chosen by each of the physicians.

Procedure

The AHF patients were assigned to 2 groups according to LOHS: less than 28 days (<28-day group, n=316) and 28 days or over (≥28 days, n=280). The LOHS cut-off was set to 4 weeks, according to the median LOHS in all cohorts (27 days) and based on the utility of daily clinical practice. The following factors were compared between the 2 groups: patient characteristics (age, gender, presence of de novo or recurrent HF, etiology of HF), risk factors for atherosclerosis (diabetes mellitus, hypertension, and dyslipidemia), vital signs (systolic blood pressure [SBP] and heart rate), status (left ventricular ejection fraction [LVEF] on echocardiography, orthopnea, chronic kidney disease [CKD]), respiratory management, arterial blood gas data, laboratory data, mechanical support during ICU admission, and medication given during ICU admission.

Table 1. Baseline AHF Patient Characteristics vs. LOHS

	Total (n=596)	LOHS <28 days (n=316)	≥28 days (n=280)	P-value†
Status				
Age (years)	81 (78–86)	81 (78–85)	81 (78–86)	0.562
Gender (male)	335 (56.2)	193 (61.1)	142 (50.7)	0.011
BMI (kg/m²)	22.0 (19.6–24.2)	21.6 (19.6–24.2)	22.2 (19.6–24.3)	0.157
Readmission	200 (33.6)	120 (37.9)	80 (28.6)	0.014
Etiology				
Ischemia	243 (40.8)	122 (38.6)	121 (43.2)	0.253
Hypertensive heart disease	103 (17.2)	57 (18.0)	46 (16.4)	0.604
Cardiomyopathy	46 (7.7)	27 (8.5)	19 (6.8)	0.422
Valvular disease	167 (28.0)	90 (28.5)	77 (27.5)	0.790
Others	34 (5.7)	18 (5.7)	16 (5.7)	0.992
Medical history				
Hypertension	474 (79.5)	254 (80.4)	220 (78.6)	0.585
Diabetes mellitus	228 (38.3)	120 (38.0)	108 (38.6)	0.881
Dyslipidemia	258 (43.2)	126 (39.9)	132 (47.1)	0.074
CKD	323 (54.2)	168 (53.2)	155 (55.4)	0.646
Vital signs				
SBP (mmHg)	160 (136–180)	160 (140–180)	157 (130–180)	0.019
BP ≥140 mmHg	410 (68.8)	233 (73.7)	177 (63.2)	0.006
BP 100–<140 mmHg	167 (28.0)	78 (24.7)	89 (31.8)	0.056
BP <100 mmHg	19 (3.2)	5 (1.6)	14 (5.0)	0.020
Pulse (beats/min)	108 (90–126)	108 (88–126)	108 (92–126)	0.517
LVEF (%)	38 (28–51)	38 (28–50)	38 (30–54)	0.219
Orthopnea	462 (77.5)	238 (75.3)	224 (80.0)	0.201
Arterial blood gas				
pH	7.33 (7.22–7.42)	7.34 (7.22–7.42)	7.33 (7.21–7.42)	0.719
PCO₂ (mmHg)	42.8 (34.2–55.5)	42.9 (34.6–54.7)	42.8 (33.6–57.0)	0.878
PO₂ (mmHg)	92.1 (67.1–137.0)	98.9 (68.2–148.0)	85.8 (66.0–131.3)	0.025
HCO₃⁻ (mmol/L)	22.1 (19.5–24.9)	22.1 (19.6–24.8)	22.2 (18.8–25.1)	0.897
SaO₂ (%)	96 (91–98)	97 (92–98)	95 (90–98)	0.035
Lactate (mmol/L)	1.7 (1.1–3.3)	1.6 (1.1–3.4)	1.8 (1.2–3.1)	0.764
Laboratory data				
Total bilirubin (mg/dL)	0.6 (0.4–0.8)	0.6 (0.4–0.8)	0.6 (0.4–0.8)	0.512
Sodium (mmol/L)	140 (138–142)	140 (137–142)	140 (138–143)	0.450
Potassium (mmol/L)	4.3 (3.9–4.7)	4.3 (3.9–4.7)	4.3 (3.8–4.7)	0.443
Hemoglobin (g/dL)	11.7 (10.1–13.1)	11.9 (10.3–13.3)	11.3 (9.9–12.9)	0.019
BUN (mg/dL)	25.0 (18.7–35.9)	23.5 (18.1–33.6)	26.4 (19.4–38.6)	0.009
Creatinine (g/dL)	1.16 (0.87–1.74)	1.12 (0.84–1.66)	1.21 (0.90–1.77)	0.049
CRP (mg/dL)	0.65 (0.18–2.15)	0.63 (0.17–1.89)	0.71 (0.20–2.36)	0.222
BNP (pg/mL)	860 (477–1,449)	872 (502–1,350)	831 (460–1,546)	0.944
Mechanical support in ICU				
NPPV	317 (53.2)	190 (60.1)	127 (45.4)	<0.001
ETI	100 (16.8)	29 (9.2)	71 (25.4)	<0.001
IABP	5 (0.8)	1 (0.3)	4 (1.4)	0.137
CRRT	38 (6.4)	2 (0.6)	36 (12.9)	<0.001
Medication in ICU				
Carperitide	275 (46.1)	139 (44.0)	136 (48.6)	0.263
Nitroglycerin	360 (60.4)	184 (58.2)	176 (62.9)	0.249
Nicorandil	81 (13.6)	43 (13.6)	38 (13.6)	0.990
Dopamine	98 (16.5)	26 (8.2)	72 (25.7)	<0.001
Dobutamine	100 (16.8)	25 (7.9)	75 (26.8)	<0.001
ACEI/ARB	198 (33.2)	114 (36.1)	84 (30.0)	0.116
β-blocker	143 (24.0)	90 (28.5)	53 (18.9)	0.006
Spironolactone	200 (33.6)	112 (35.4)	88 (31.4)	0.300

Data given as n (%) or median (IQR). †Mann-Whitney U-test or χ² test. ACEI, angiotensin-converting enzyme inhibitor; AHF, acute heart failure; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; CKD, chronic kidney disease; CRP, C-reactive protein; CRRT, continuous renal replacement therapy; ETI, endotracheal intubation; IABP, intra-aortic balloon pumping; ICU, intensive-care unit; LOHS, length of hospital stay; LVEF, left ventricular ejection fraction; NPPV, non-invasive positive pressure ventilation; SBP, systolic blood pressure.

Table 2. Indicators of LOHS <28 Days in AHF Patients

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Baseline patient characteristics						
Age (per 10-year increase)	0.993	0.961–1.027	0.697	1.000	0.965–1.037	0.982
SBP (≥140mmHg)	1.634	1.152–2.316	0.006	1.390	0.954–2.024	0.086
Orthopnea	0.763	0.517–1.125	0.172	0.655	0.423–1.017	0.059
BUN (per 1.0-mg/dL increase)	0.987	0.977–0.996	0.007	0.993	0.976–1.010	0.441
Creatinine (per 0.1-mg/dL increase)	0.982	0.966–0.997	0.022	0.991	0.966–1.017	0.485
Management in ICU						
Tolvaptan newly initiated in <12h	2.927	1.357–6.317	0.006	2.506	1.108–5.669	0.027
NIPPV	1.817	1.312–2.516	<0.001	1.726	1.183–2.516	0.005
Carperitide	0.832	0.602–1.148	0.263	0.835	0.586–1.189	0.835
Dobutamine	0.235	0.144–0.382	<0.001	0.298	0.178–0.499	<0.001
ACEI/ARB	1.317	0.934–1.857	0.116	1.064	0.731–1.548	0.747
β-blocker	1.706	1.159–2.509	0.007	1.527	0.999–2.336	0.051
Spironolactone	1.198	0.851–1.686	0.300	0.946	0.644–1.391	0.779

Abbreviations as in Table 1.

LVEF was calculated on a Sonos 5500 (Hewlett Packard, Palo Alto, CA, USA) or Vivid I (GE Yokogawa Medical, Tokyo, Japan) using the Teicholz method or Simpson's method at admission. The method of LVEF measurement (Teicholz method or Simpson's method) was decided on a case-by-case basis. Due to severe orthopnea, LVEF was not adequately measured during the acute phase.

Statistical Analysis

SPSS 22.0 (SPSS Japan Institute, Tokyo, Japan) was used for the statistical analysis of all data. All numerical data are expressed as median (IQR). Mann-Whitney U-test was used to compare 2 groups. Comparison of all proportions was done using chi-squared analysis. P<0.05 was considered to be statistically significant.

Multivariate logistic regression modeling was carried out using all clinically relevant factors affecting the shortening of LOHS as follows: age (per 1-year increase in age), ischemic etiology (yes), SBP (per 10-mmHg increase), orthopnea (yes), total bilirubin (per 1.0-mg/dL increase), creatinine (per 0.1-mg/dL increase), tolvaptan treatment in <12h, non-invasive positive pressure ventilation (NIPPV) use, carperitide and dobutamine. The simultaneous forced entry method was selected for the evaluation of multivariate logistic regression analysis.

After initially analyzing the data, a propensity score-matched analysis was carried out to minimize potential patient bias regarding LOHS. The rate of tolvaptan in <12h, which was used for propensity score, was calculated for each patient on multivariate logistic regression based on all clinically important covariates. Patients in the <28-day and ≥28-day groups were matched 1:1 based on the estimated propensity scores of patients who were admitted for <28 days. The covariates in the model included sex, SBP (SBP <100mmHg and ≥140mmHg), serum creatinine, serum BUN, use of NIPPV, carperitide and dobutamine. The discrimination and calibration abilities of the propensity score model were adequately assessed using receiver operating characteristic (ROC) curves (area under the ROC curve [AUC], 0.701) and the Hosmer-Lemeshow test (P=0.189). The effect size between 2 groups is given using the P-value and the standardized difference (Cohen d).

Propensity score matching was conducted on the logit of the propensity score with a caliper width equal to 0.01.
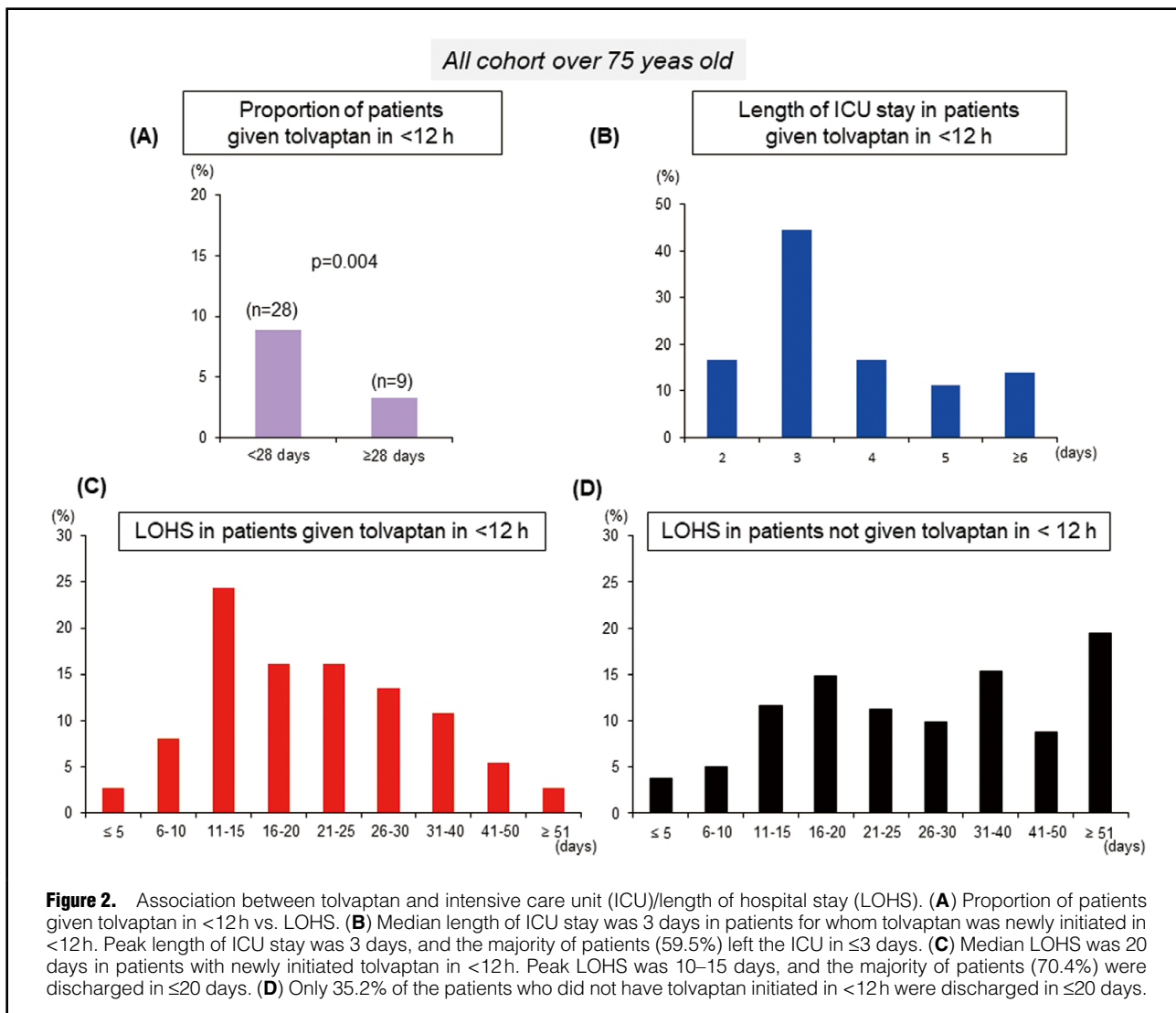
Ethics

The Research Ethics Committee of Nippon Medical School Chiba Hokusoh Hospital approved the study protocol. Given that it was a retrospective study, written informed consent was waived. The ethics committee also advised as follows: (1) a description of the content of the present study was displayed in a poster at the present institute; and (2) the content was shared on our homepage where it could be easily seen by anyone. The present study was performed in accordance with the Declaration of Helsinki.

Results

Patient Characteristics and Factors Associated With Shortened LOHS

The subjects included 335 men (56.2%) with a median age of 81 years, and 200 (33.6%) of the patients had been re-admitted for HF. A total of 243 patients (40.8%) had ischemic heart disease, and most patients also had orthopnea in an emergency setting (n=462, 77.5%). Median LVEF on admission was 38.0%.

The <28-day group had a higher proportion of men than the ≥28-day group; in addition, patients with re-admission were significantly more frequent, and SBP was higher than in the ≥28-day group. The patients with SBP ≥140mmHg were significantly more frequent while those with SBP <100mmHg were less frequent in the <28-day group than in the ≥28-day group. Regarding laboratory data, serum hemoglobin was significantly higher and serum BUN and creatinine significantly lower in the <28-day group than in the ≥28-day group (**Table 1**). Regarding AHF management, NIPPV was used significantly more frequently, while the need for endotracheal intubation (ETI) was significantly reduced in the <28-day group compared with the ≥28-day group. Continuous renal replacement therapy (CRRT) was used significantly less frequently in the <28-day group than in the ≥28-day group. Furthermore, dopamine and dobutamine treatment were significantly less frequent in the <28-day group than in the ≥28-day group (**Table 1**).

Figure 2. Association between tolvaptan and intensive care unit (ICU)/length of hospital stay (LOHS). (**A**) Proportion of patients given tolvaptan in <12 h vs. LOHS. (**B**) Median length of ICU stay was 3 days in patients for whom tolvaptan was newly initiated in <12 h. Peak length of ICU stay was 3 days, and the majority of patients (59.5%) left the ICU in ≤3 days. (**C**) Median LOHS was 20 days in patients with newly initiated tolvaptan in <12 h. Peak LOHS was 10–15 days, and the majority of patients (70.4%) were discharged in ≤20 days. (**D**) Only 35.2% of the patients who did not have tolvaptan initiated in <12 h were discharged in ≤20 days.

This suggests that LOHS differed depending on severity of patient condition and AHF management.

On multivariate logistic regression analysis, newly initiated tolvaptan in <12 h (OR, 2.574; 95% CI: 1.146–5.780, P=0.022), use of NPPV (OR, 1.817; 95% CI: 1.254–2.634, P=0.002) and dobutamine (OR, 0.297; 95% CI: 0.178–0.496, P<0.001) were independently associated with the <28-day group (**Table 2**). New initiation of tolvaptan in <12 h was significantly more frequent in the <28-day group than in the ≥28-day group (P=0.004) (**Figure 2A**). The median length of ICU stay and of LOHS was 3 days and 20 days, respectively, in patients with tolvaptan newly initiated in <12 h (**Figure 2B,C**). The peak length of ICU stay was 3 days in patients with tolvaptan newly initiated in <12 h, and the majority of patients (59.5%) left the ICU in ≤3 days (**Figure 2B**). Moreover, peak LOHS was 10–15 days in patients with tolvaptan newly initiated in <12 h, and the majority of patients (70.4%) were discharged in ≤20 days (**Figure 2C**). Meanwhile, only 35.2% of patients who did not have tolvaptan initiated in <12 h were discharged in ≤20 days (**Figure 2D**).

Given that patient condition, including the management

of HF, was an independent factor associated with LOHS, propensity score matching was performed to adjust for the severity of patient condition. After estimated propensity scores were used to match 187 patients each from the <28- and ≥28-day groups (**Table 3**), the main result was the same (**Figure 3**). New initiation of tolvaptan in <12 h was significantly more frequent in the propensity score-matched <28-day group than in the ≥28-day group (P=0.029, **Figure 3A**). Median length of ICU stay and of LOHS was 3 days and 16.5 days, respectively, in patients with tolvaptan newly initiated in <12 h (**Figure 3B,C**). Peak length of ICU stay was 3 days in patients with tolvaptan newly initiated in <12 h, and half of the patients (50.0%) left the ICU in ≤3 days (**Figure 3B**). Peak LOHS was 11–20 days in patients with tolvaptan newly initiated in <12 h and more than half of the patients (64.3%) were discharged in ≤20 days (**Figure 3C**). Meanwhile, only one-third of patients (32.9%) who did not have tolvaptan newly initiated in <12 h were discharged in ≤20 days (**Figure 3D**). Furthermore, on multivariate logistic regression analysis only newly initiated tolvaptan in <12 h (OR, 3.939; 95% CI: 1.065–14.570, P=0.040) was independently associated with the propensity

Table 3. Baseline AHF Patient Characteristics After Propensity Matching

	Total (n=374)	LOHS <28 days (n=187)	LOHS ≥28 days (n=187)	Standardized difference
Status				
Age (years)	81.9±4.8	81.9±5.0	81.8±4.6	0.02
Gender (male)	197 (52.6)	99 (52.9)	98 (52.4)	0.01
Etiology				
Ischemia	153 (40.9)	70 (37.4)	83 (44.3)	−0.14
Hypertensive heart disease	69 (18.4)	36 (19.3)	33 (17.6)	0.04
Cardiomyopathy	22 (5.9)	13 (7.0)	9 (4.8)	0.09
Valvular disease	107 (28.6)	56 (29.9)	51 (27.3)	0.06
Medical history				
CKD	194 (51.6)	93 (49.7)	101 (54.0)	−0.09
Vital signs				
SBP (mmHg)	158.3±34.6	156.5±32.9	160.0±36.2	−0.10
BP ≥140mmHg	252 (67.4)	124 (66.3)	128 (68.4)	−0.05
BP 100–<140mmHg	113 (30.2)	59 (31.6)	54 (28.9)	0.06
BP <100mmHg	9 (2.4)	4 (2.1)	5 (2.7)	−0.04
LVEF (%)	41.4±17.1	40.5±16.7	42.3±17.6	−0.10
Orthopnea	289 (77.2)	141 (75.4)	148 (79.1)	−0.09
Laboratory data				
Total bilirubin (mg/dL)	0.70±0.50	0.68±0.37	0.72±0.61	−0.08
Hemoglobin (g/dL)	11.6±2.2	11.6±2.2	11.6±2.3	0.01
BUN (mg/dL)	28.8±15.2	29.4±16.5	28.2±13.9	0.08
Creatinine (g/dL)	1.40±0.97	1.45±1.08	1.35±0.85	0.09
CRP (mg/dL)	2.9±10.9	3.1±14.7	2.7±4.7	0.04
BNP (pg/mL)	1,093.9±940.0	1,128±957	1,059±923	0.07
Mechanical support in the ICU				
NPPV	195 (52.1)	99 (52.9)	96 (52.3)	0.03
Medication in ICU				
Carperitide	171 (45.7)	89 (45.7)	82 (43.9)	0.08
Nicorandil	51 (13.6)	27 (14.4)	24 (12.8)	0.05
Dobutamine	39 (10.4)	18 (9.6)	21 (11.2)	−0.05
ACEI/ARB	129 (34.5)	65 (34.8)	64 (34.2)	0.01
β-blocker	80 (21.4)	47 (25.1)	33 (17.6)	0.18
Spironolactone	120 (32.1)	57 (30.5)	63 (33.7)	−0.07

Data given as n (%) or mean±SD. Abbreviations as in Table 1.

score-matched <28-day group (**Table 4**).

Discussion

The major findings of the present study were that the early initiation of tolvaptan and the use of NPPV were independently associated with shorter LOHS, and that dobutamine use was independently associated with prolonged LOHS. Given that the severity of patient condition was found to be associated with prolonged LOHS in the elderly cohort, we performed a propensity score-matched analysis to evaluate the difference in management according to LOHS. After propensity score matching of the baseline data, the early use of tolvaptan remained associated with shortened LOHS. The oral diuretic tolvaptan might play an important role in maintaining ADL by shortening the duration of hospitalization for elderly AHF patients in Japan.

LOHS After AHF in Japan

Regional differences in LOHS have been described in several registries.[1] Median LOHS after AHF in the USA was 4.3–6.4 days in the ADHERE and OPTIMIZE-HF registries, which was extremely short in comparison with other countries.[4,11] It was also relatively short compared with the median 9 days in Europe in the EHFS II registry and 7 days in Africa in the THESUS-HF registry.[5,12] Median LOHS in the Asia-Pacific region was 6 days in the ADHERE-AP database,[13] and the median LOHS in Korea was 8 days, while the average LOHS in Taiwan was 15 days.[14,15]

The LOHS in Japan is extremely long in comparison with other countries. Major Japanese registries of hospitalized HF (e.g., ATTEND registry and CHART-2 study) have documented hospitalization durations of around 30 days,[16,17] consistent with the present data. In the present study, median LOHS was 27 days. The AHF trends indicate that the LOHS is decreasing year by year, despite a worsening patient condition.[3] The present hospitalization duration, however, is still longer than in other reports from the 2000s.[1,2,4,5]

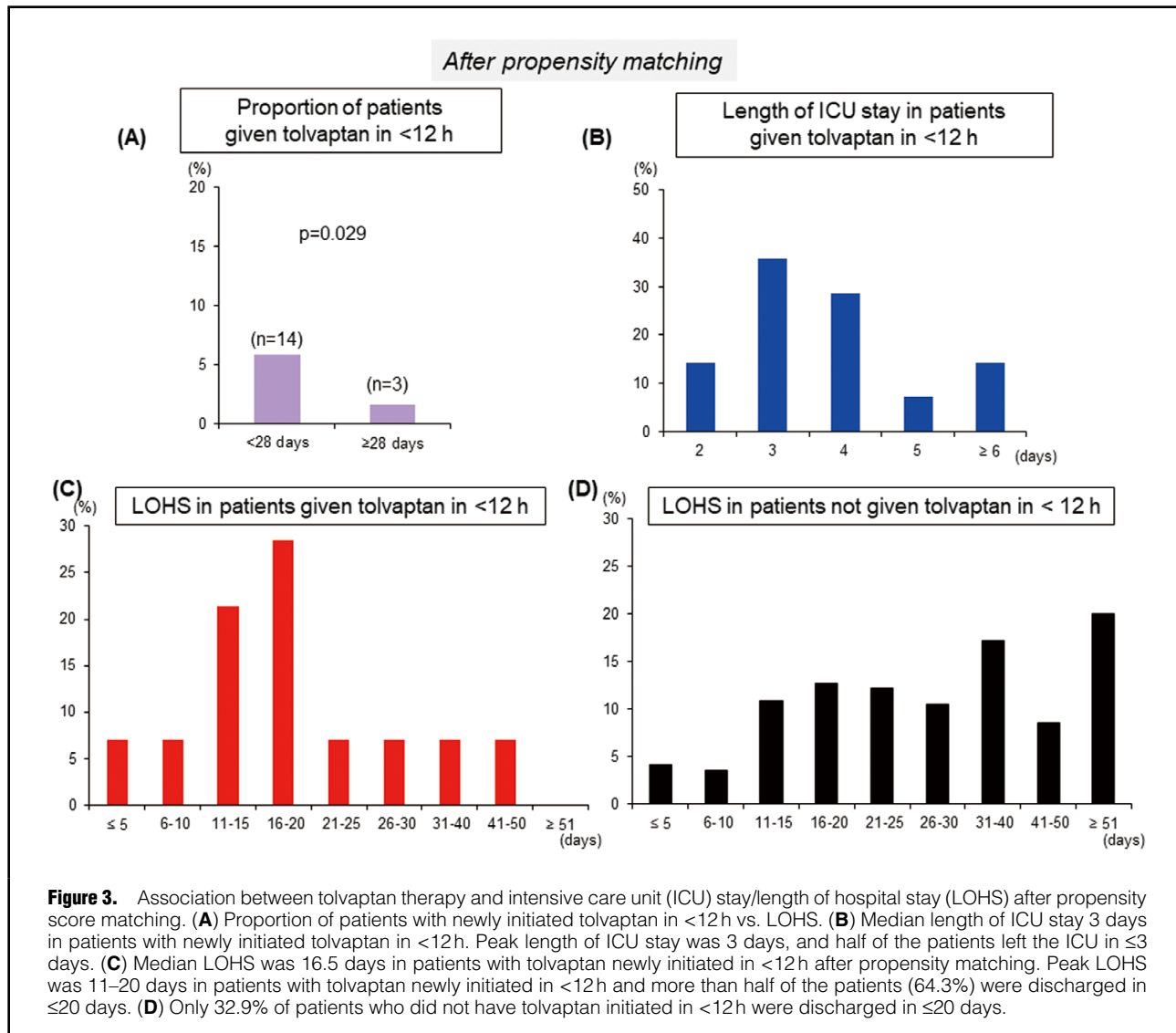The prolonged LOHS after AHF in Japan may be due to inpatient disease management programs and Japan's

Figure 3. Association between tolvaptan therapy and intensive care unit (ICU) stay/length of hospital stay (LOHS) after propensity score matching. (**A**) Proportion of patients with newly initiated tolvaptan in <12 h vs. LOHS. (**B**) Median length of ICU stay 3 days in patients with newly initiated tolvaptan in <12 h. Peak length of ICU stay was 3 days, and half of the patients left the ICU in ≤3 days. (**C**) Median LOHS was 16.5 days in patients with tolvaptan newly initiated in <12 h after propensity matching. Peak LOHS was 11–20 days in patients with tolvaptan newly initiated in <12 h and more than half of the patients (64.3%) were discharged in ≤20 days. (**D**) Only 32.9% of patients who did not have tolvaptan initiated in <12 h were discharged in ≤20 days.

Table 4. Multivariate Indicators of LOHS <28 Days in AHF Patients After Propensity Score Matching

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Baseline patient characteristics						
Age (per 10-year increase)	1.030	0.962–1.047	0.880	1.020	0.959–1.047	0.934
Ischemia etiology	0.750	0.496–1.133	0.172	0.715	0.465–1.099	0.0126
SBP (per 10-mmHg increase)	0.971	0.916–1.030	0.329	0.961	0.904–1.023	0.961
Orthopnea	0.763	0.472–1.235	0.272	0.787	0.464–1.335	0.787
Total bilirubin (per 1.0-mg/dL increase)	0.808	0.497–1.312	0.388	0.802	0.514–1.250	0.330
Creatinine (per 0.1-mg/dL increase)	1.010	0.989–1.032	0.357	1.010	0.988–1.033	0.380
Management in ICU						
Tolvaptan newly initiated in <12 h	3.833	1.052–13.971	0.042	3.939	1.065–14.570	0.040
NPPV	1.066	0.711–1.600	0.756	1.081	0.696–1.678	0.730
Carperitide	1.163	0.774–1.747	0.468	1.257	0.821–1.925	0.292
Dobutamine	0.842	0.433–1.637	0.612	0.891	0.448–1.774	0.891

Abbreviations as in Table 1.

socialized medical system. The main difference between Japan and other countries is its socialized medical system. Universal health insurance is the system used in Japan, hence almost the entire elderly cohort was able to receive medical care equally. Reports from low- and middle-income regions, including Africa, the Middle East, and South America, have described issues with insurance coverage for patients with AHF.[18,19] Regarding insurance coverage, surprisingly, 34.9% of AHF patients lack medical insurance in Asia, including China, India, Malaysia, and the Philippines, with rates of 48.6% reported for Africa, including Nigeria, South Africa, Sudan, Uganda, and Mozambique; 30.6% in the Middle East, including Saudi Arabia, Egypt, and Qatar; and 26.1% in South America, including Argentina, Chile, Colombia, and Ecuador.

In these countries, it is assumed that some AHF patients cannot afford a prolonged hospital stay due to the expense. They thus have no choice but to shift their treatment to outpatient care in the early phase, despite still being decompensated with persistent congestion. Therefore, the issues still remaining after acute-phase treatment, including complete compensation of AHF (complete decongestion); detailed investigation of the etiology; medical or interventional treatment of the etiologic disease; and rehabilitation and adjustment of the medication dosage, are shifted to the outpatient clinic in almost all Western and Asian counties.

In Japan, especially at the present institute, the physician decides on the length of hospitalization in order to perform detailed investigations of the etiology, attempt prudent rehabilitation, and adjust the medication dosage. Elderly AHF patients can then, as a result, have a decline in ADL, and an increase in the level of frailty and of malnourishment, due to prolonged hospitalization; in contrast, short hospitalization has not been shown to be associated with worse outcomes,[20,21] and LOHS was also not associated with adverse mid-term outcomes in the present study (data not shown). Management practices to maintain the ADL by shortening hospitalization should be enacted in the upcoming HF pandemic era. The rapid reduction of congestion by oral treatment might be one way to help reduce LOHS for elderly AHF patients.

Tolvaptan and LOHS Shortening

The ideal management and clinical approach to reducing LOHS in the HF pandemic will be an essential issue for Japanese society to address. We have shown that LOHS could be reduced by early tolvaptan initiation. An association between tolvaptan and LOHS has also been indicated in several previous studies.[22–24] The beneficial effect of tolvaptan in early vs. late treatment has been reported as follows: Matsukawa et al suggested that tolvaptan be started in ≤3 days to reduce LOHS, while Kiuchi et al suggested that tolvaptan be started in ≤4 days to reduce LOHS.[22,24] Furthermore, Kinoshita et al compared LOHS between patients who received tolvaptan therapy in <24h and those on standard therapy and concluded that intiation of tolvaptan therapy in <24h helped reduce LOHS in patients with AHF >80 years old.[23] This study concept is similar to that in the present study.

The novelty of the present study therefore lies in the timing of tolvaptan (from the super acute phase: in <12h) and in the enrolled patient cohort (requiring intensive care, with more severely ill patients targeted). We hence suggest the immediate initiation of tolvaptan, at the same time as furosemide, especially in elderly AHF patients in ICU,

although there might be some general concerns. Tolvaptan is a selective vasopressin 2 receptor antagonist that acts on the distal nephrons and causes a loss of electrolyte-free water, to induce water diuresis. This mechanism of action can sometimes result in an increase in serum sodium level. All patients enrolled in the present study were treated in the ICU, where laboratory examinations can be performed frequently, and where patients are seen by a number of physicians and are monitored often. In a previous study, we presented evidence to support that tolvaptan should be initiated in <12h for patients with severely decompensated AHF.[8] Thus, tolvaptan might be a candidate diuretic for use at an earlier phase to achieve quick decongestion in elderly patients with AHF who require intensive care.

The main reason for hospitalization in the ICU is congestion, rather than low cardiac output.[25] Therefore, decongestion is the mainstay of treatment for patients with AHF requiring intensive care. The long-term management of decongestion has mainly been i.v. loop diuretics. I.v. carperitide was also used for decongestion in the 2000s.[26] Oral medication, however, has the beneficial effect of freeing patients from the restriction of the infusion line, thereby improving ADL from the early phase of AHF. Freedom from the infusion line might also help prevent delirium in elderly patients, and complication with delirium is the main reason for prolonged hospital stay in the ICU.[27] Tolvaptan therapy from the super acute phase exerts a rapid effect on decongestion, releasing patients from restriction of the infusion line and improving ADL. These effects help reduce LOHS and decrease medical costs in severely decompensated AHF patients >75 years old.

Study Limitations

There are several limitations associated with this study. First, the subjects were limited to patients admitted to the ICU, and excluded those admitted to general wards. The patients were treated in a closed ICU at the institute, where all of the physicians are cardiologists. Thus, the majority of severely decompensated AHF patients were admitted to the ICU. There are no proposed clear criteria, however, regarding the dose of high-flow oxygen, inotropes, and diuretics, therefore the admission criteria may also have differed annually. The responsible physician ultimately decided whether each patient should be admitted to the ICU or general ward, therefore a patient bias with regard to ICU stay may have existed. Second, the present study was a single-center study, and was not a prospective randomized controlled trial. Therefore unmeasured variables might affect the results. Moreover, the major findings of this study might be influenced by the difficulty in standardizing care for the patients. Finally, the present study was not designed to evaluate the impact of tolvaptan on LOHS, and the number of patients treated with tolvaptan in <12h was not sufficient to test this question.

Conclusions

LOHS was prolonged by severe patient condition on admission. Reducing LOHS was not shown to be associated with adverse mid-term outcomes in the present study. The immediate initiation of tolvaptan was independently associated with shortened LOHS. The oral diuretic tolvaptan might help maintain ADL by shortening the duration of hospitalization for elderly AHF patients who require intensive care.

Disclosures

The authors declare no conflicts of interest.

IRB Information

This study was approved by the Research Ethics Committee of Nippon Medical School Chiba Hokusoh Hospital (reference no. 543-1).

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