Trends in the Management of Acute Heart Failure Requiring Intensive Care

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The aim of the present study was to elucidate trends in managing acute heart failure (AHF) patients who require intensive care over a 19-year period. We evaluated a total of 1,475 AHF patients, comparing patient backgrounds, in-hospital management, and prognosis according to the year of admission (2000s group, n = 608 and 2010s group, n = 867). A multivariate logistic regression analysis revealed that age (≥75 years; odds ratio [OR] 1.334, 95% confidence interval [CI] 1.048 to 1.700), systolic blood pressure (<100 mm Hg; OR 1.934, 95% CI 1.170 to 3.198), left ventricular ejection fraction (>40%; OR 1.441, 95% CI 1.125 to 1.847), and prognostic nutritional index (severe; OR 1.865, 95% CI 1.224 to 2.841) were independently associated with admission in the 2010s group. The use of intra-aortic balloon pumping and noninvasive positive pressure ventilation increased significantly, whereas the need for endotracheal intubation and administration of furosemide and carperitide in the 2010s group decreased significantly compared with the 2000s group. Tolvaptan therapy was introduced from 2010. The duration of intensive care unit admission and total hospitalization in the 2010s group (4 [3 to 6] and 23 [15 to 40] days, respectively) were significantly shorter than in the 2000s group (5 [4 to 8] and 30 [20 to 54] days, respectively). A Kaplan-Meier survival curve analysis showed the survival rate of the 2010s group was significantly poorer compared with the 2000s group (hazards ratio 1.435, 95% CI 1.113 to 1.851). After propensity score matching, the 365-day mortality rates of the 2 groups did not significantly differ. In conclusion, the condition of AHF patients became more critical year by year, leading to poorer long-term prognosis despite improved treatment strategy. These findings will be useful for managing AHF in the next pandemic era. **(Am J Cardiol 2019;124:1076−1084)**

The number of heart failure (HF) patients has been rapidly increasing to a "HF pandemic" level. Approximately 26 million patients worldwide are living with HF, resulting in >1 million hospitalizations each year in both the United States and Europe.[1,2] This HF pandemic also extends to Asia, where it is estimated that >0.37 million patients will newly develop in acute HF (AHF) by 2025.[3,4] HF will become a more serious issue in the near future with its epidemiological transition and population aging. Despite the need for evidence on the epidemiology of HF for managing the next HF pandemic, the available epidemiologic data, evidence, and trends on HF patients during the 2010s are limited, especially in Asia and for patients with severely decompensated AHF. AHF is intrinsically recognized as a heterogeneous condition and its characteristics and management differ according to region and institute. We therefore hypothesized that admission to an intensive care unit (ICU) due to severe AHF during the 2010s would be associated with adverse outcomes due to the characteristic severity of the condition of such patients. In the present study, we evaluated patients with severely decompensated AHF who were admitted to an ICU over a 19-year period and analyzed the trends in characteristics, management, and short-term and long-term prognosis of AHF. These findings may lead to improved prognosis in the next pandemic era.

Methods

We enrolled a total of 1,475 patients admitted to the ICU of the Nippon Medical School Chiba Hokusoh Hospital between January 2000 and December 2018. Patients with HF caused by ST-T elevated myocardial infarction were excluded from the study. Based on the 2016 ECS guidelines for AHF diagnosis, we diagnosed AHF according to plasma natriuretic peptide levels (b-type natriuretic peptide ≥100 pg/ml), a 12-lead electrocardiogram, laboratory measurements (troponins, blood urea nitrogen [BUN], creatinine, sodium, potassium, glucose, liver function, and complete blood counts), and echocardiography.[5] The treating physician at the emergency department diagnosed AHF within 30 minutes of admission. AHF presented as either new-onset or decompensated chronic HF with symptoms

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sufficient to warrant hospitalization. Patients who required any of the following criteria were admitted to the ICU: (1) high-projectile oxygen inhalation, including mechanical support, to treat orthopnea; (2) inotrope or mechanical support due to low blood pressure; and (3) various types of diuretics to improve general or lung edema. The treatment strategy was chosen by each physician. In all cases, diuretics or vasodilators were administered to treat AHF. All patients had a New York Heart Association functional class of either III or IV.

Patients were divided into 2 groups according to their year of admission. Patients admitted from January 2000 to December 2009 were assigned to the 2000s group (n = 608) and those admitted from January 2010 to December 2018 were assigned to the 2010s group (n = 867).

We compared patient characteristics between groups, including age, gender, body mass index, presence of de novo or recurrent HF, etiology of HF, past medical history (risk factors for atherosclerosis [diabetes mellitus, hypertension, and dyslipidemia], prescription of dialysis, and chronic kidney disease), vital signs (systolic blood pressure [SBP] and heart rate), left ventricular ejection fraction (LVEF) on echocardiography, presence of orthopnea, arterial blood gas data, laboratory data (BUN, creatinine, total bilirubin, sodium, potassium, hemoglobin, brain natriuretic peptide, C-reactive protein [CRP], and other variables), nutritional status (prognostic nutritional index [PNI] and controlling nutritional status [CONUT] score), mechanical support, and medications administered during ICU admission. The duration of ICU and hospital stay as well as in-hospital mortality were also compared between the 2 groups. All data were collected from past medical records. The PNI was calculated according to the following formula: 10 × serum albumin (g/dl) + 0.005 × lymphocyte count (/μl; lower = worse).[6] The CONUT score was calculated using the serum albumin level, lymphocyte count, and total cholesterol (range 0 to 12, higher = worse). In this scoring system, points are assigned to different ranges of laboratory measurements as follows: serum albumin ≥3.5 g/dl, 0 points; 3.49 to 3, 2 points; 2.99 to 2.5, 4 points; and <2.5, 6 points; lymphocyte count ≥1,600 μl^{-1}, 0 points; 1,200 to 1,599, 1 point; 800 to 1,199, 2 points; and <800, 3 points; and total cholesterol ≥180 mg/dl, 0 points; 140 to 179, 1 point; 100 to 139, 2 points; and <100, 3 points.[7] We did not retrieve lymphocyte count and total cholesterol from 192 and 8 patients, respectively. Therefore, the PNI and CONUT score were calculated for 1,283 and 1,275 AHF patients, respectively.

The factors significantly associated with ICU admission in the 2010s group were determined by multivariate logistic regression analysis. We evaluated long-term prognosis, including 365-day all-cause mortality and HF events (all-cause death and readmission for HF), as the primary end point. Patients were routinely followed-up at an outpatient clinic. The prognoses of the patients who were followed at other institutes were determined by telephone contact. We evaluated prognostic value for 365-day mortality and HF events using a Cox regression hazards model and Kaplan-Meier curves. AHF patients who were admitted in 2018 were excluded from the evaluation of the long-term prognosis due to no 1-year follow-up.

We performed all statistical analyses using SPSS 22.0 (SPSS Japan Institute, Tokyo, Japan). All numerical data were expressed as the median (25% to 75% interquartile range), according to normality. We used the Shapiro-Wilk W test to assess normality, Mann-Whitney U test for comparing the 2 groups, and chi-squared test to compare proportions. The p values of <0.05 were considered statistically significant. All clinically relevant factors affecting AHF in patients admitted during the 2010s, including age (≥75 years), SBP (<100 mm Hg), hemoglobin (per 1.0 g/dl increase), BUN (per 1.0 mg/dl increase), CRP (per 1.0 mg/dl increase), prescribed hemodialysis (yes), LVEF upon admission (>40%), and PNI (normal, mild, and severe) were included in the multivariate logistic regression model. We performed the multivariate logistic regression analysis using simultaneous forced entry. A Cox regression analysis determined the hazard ratio for 365-day mortality and HF events. The cumulative survival rates in each group were analyzed using Kaplan-Meier curves and the log-rank test was used to determine statistical differences. After initially analyzing the data, we performed a propensity score-matched analysis to minimize potential patient bias. Each patient was assigned a propensity score based on a multivariate logistic regression model. The covariates in the model included age ≥75 years, LVEF >40%, SBP, serum levels of hemoglobin, BUN, and CRP. The discrimination and calibration abilities of the propensity score model were adequately assessed by receiver-operating characteristic curves (area under the receiver-operating characteristic curve; 0.609) and the Hosmer-Lemeshow test (p = 0.475). Patients in the 2010s and 2000s groups were matched by 2 digits in a 1:1 ratio based on estimated propensity scores of patients who were admitted during the 2010s era.

The research ethics committee of Nippon Medical School Chiba Hokusoh Hospital approved the study protocol. Regarding informed consent, we described the content of the present study in a poster displayed at our institute and shared the content on our homepage where it could be easily seen in accordance with the advice of the ethics committee.

Results

The number of AHF patients who required ICU admission increased after 2011 and the percentage of patients of ≥75 years of age also increased after 2009 (Figure 1). Therefore, the characteristics of AHF patients may have changed from the 2000s to the 2010s. Because of the infectious disease pandemic in 2014, ICU beds were closed for 1 month, which targeted patients during the ICU bed shutdown following the pandemic. This unusual situation caused the dip in features in 2014.

The whole AHF patient cohort consisted of 974 (66.0%) male patients. The median age was 74 years. A total of 504 (34.2%) patients were readmitted for HF, 607 (41.2%) had ischemic heart disease, and 868 (58.8%) had nonischemic heart disease, including cardiomyopathy (n = 188), hypertensive heart disease (n = 234), and valvular heart disease (n = 339). Most patients (93.2%) were classified as New York Heart Association class IV. The median LVEF upon admission was 37.0% (Table 1). Patients were significantly

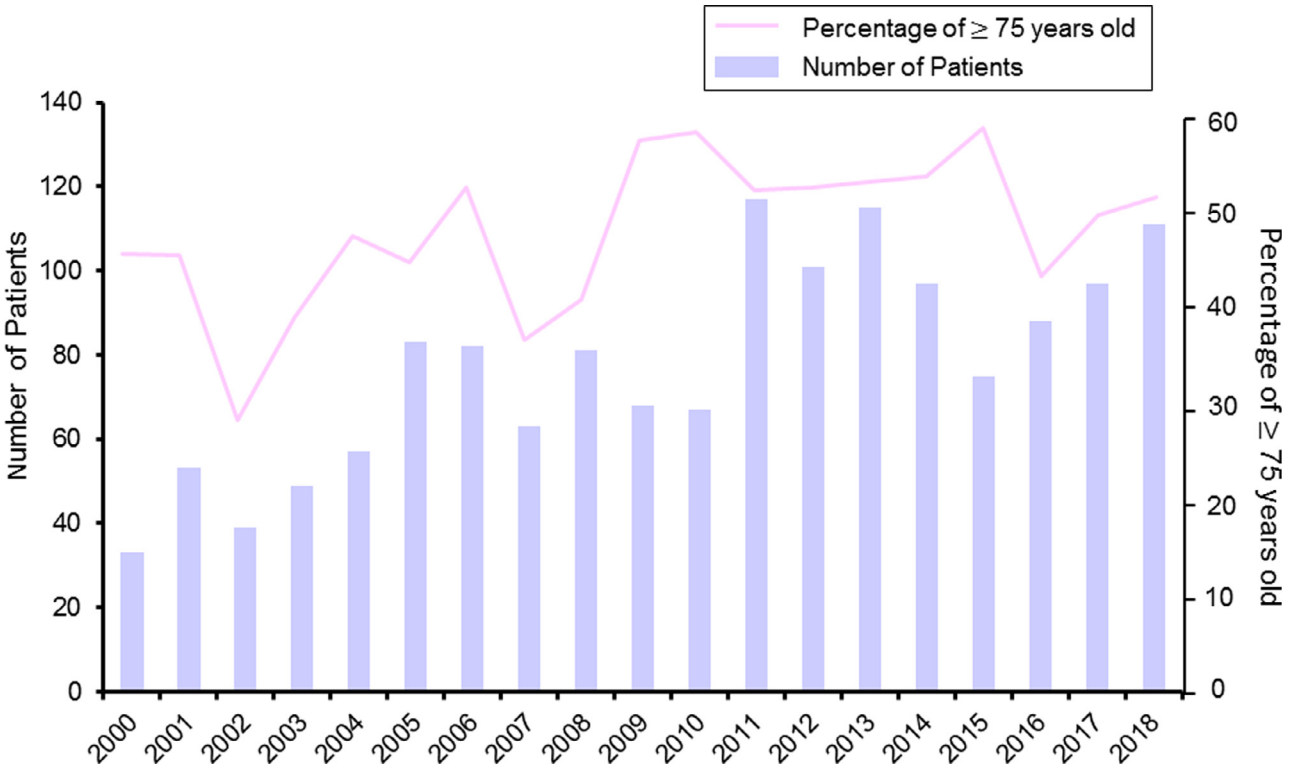

Figure 1. The distribution of AHF patients and the percentage of patients of >75 years of age. The number of AHF patients increased from 2011 and the percentage of AHF patients of ≥75 years of age was >50% from 2009.

older and the rates of hypertension, diabetes mellitus, and dyslipidemia were significantly higher in the 2010s than in the 2000s group. Interestingly, hemodialysis was prescribed for a significantly greater number of patients in the 2010s group (Table 1). The clinical data on admission are noted in Table 2. The 2010s group included significantly greater numbers of patients with an SBP of <100 mm Hg and patients with a preserved LVEF. In the 2010s group, heart rate, pH value, and serum hemoglobin level were significantly lower, whereas serum BUN and CRP levels were significantly higher. Interestingly, there were significant differences between the 2 groups in factors reflecting nutritional status. The nutritional status of the 2010s group was significantly worse than that of the 2000s group. Regarding

Table 1
Baseline of the patients' characteristics according to the year of admission

Variable	Total (n = 1,475)	Year of admission		p Value
		2000s (2000 to 2009, n = 608)	2010s (2010 to 2018, n = 867)	
Age (years old)	74 (65-81)	73 (64-80)	75 (67-81)	0.016
Men	974 (66.0%)	401 (66.0%)	573 (66.1%)	0.956
BMI (kg/m^2)	22.9 (20.4-25.3)	22.4 (20.4-24.9)	23.1 (20.4-25.6)	0.074
Readmission	504 (34.2%)	195 (32.1%)	309 (35.6%)	0.163
Social vulnerable	640 (43.3%)	255 (41.9%)	385 (44.4%)	0.262
Ischemia	607 (41.2%)	252 (41.4%)	355 (40.9%)	0.872
Hypertensive heart disease	234 (15.8%)	105 (17.3%)	129 (14.9%)	0.219
Cardiomyopathy	188 (12.7%)	78 (12.8%)	110 (12.7%)	0.937
Valvular disease	339 (23.0%)	139 (22.9%)	200 (23.1%)	0.950
Others	102 (6.9%)	32 (5.3%)	70 (8.1%)	0.037
Hypertension	1101 (74.6%)	434 (71.4%)	667 (76.9%)	0.018
Diabetes mellitus	653 (44.3%)	234 (38.5%)	419 (48.3%)	<0.001
Dyslipidemia	703 (47.7%)	250 (41.1%)	453 (52.2%)	<0.001
Prescribed hemodialysis	57 (3.9%)	16 (2.6%)	41 (4.7%)	0.040
CKD	764 (52.0%)	299 (49.0%)	465 (54.0%)	0.101

BMI = body mass index; CKD = chronic kidney disease.
The p values between the 2000s and the 2010s groups were determined using the Mann-Whitney U test or the chi-square test.
All numerical data are expressed as the median (25% to 75% interquartile range).

Table 2
Vital signs, blood examination, and nutritional status according to the year of admission

Variable	Total (n = 1,475)	Year of admission		p Value
		2000s (2000 to 2009, n = 608)	2010s (2010 to 2018, n = 867)	
Systolic blood pressure (mm Hg)	160 (129-184)	160 (130-182)	160 (127-186)	0.521
SBP ≥140 mm Hg	980 (66.4%)	403 (66.3%)	577 (66.6%)	0.955
SBP 100 mm Hg to <140 mm Hg	380 (25.8%)	178 (29.3%)	202 (23.3%)	0.011
SBP <100 mm Hg	114 (7.7%)	27 (4.4%)	87 (10.0%)	<0.001
Pulse (beats/min)	87 (70-101)	86 (70-100)	87 (70-102)	<0.001
LVEF (%)	36 (25-49)	34 (24-44)	38 (27-50)	<0.001
LVEF >40%	577 (39.3%)	208 (34.4%)	369 (42.7%)	0.001
Orthopnea	1,169 (79.3%)	497 (81.7%)	672 (77.5%)	0.050
pH	7.34 (7.22-7.43)	7.33 (7.20-7.42)	7.35 (7.23-7.43)	0.013
PCO_2 (mm Hg)	41.3 (33.4-54.6)	43.7 (34.2-56.9)	39.6 (33.0-53.6)	<0.001
PO_2 (mm Hg)	90.9 (68.0-136.0)	85.7 (65.3-123.0)	96.8 (70.4-143.5)	<0.001
HCO_3^- (mmol/L)	21.8 (19.2-24.3)	22.0 (19.5-24.3)	21.7 (19.0-24.3)	0.350
SaO_2 (%)	96 (91-98)	95 (89-98)	97 (92-99)	<0.001
Lactate (mmol/L)	1.8 (1.1-3.5)	1.4 (1.0-3.1)	1.8 (1.1-3.5)	0.489
Total bilirubin (mg/dl)	0.6 (0.4-0.9)	0.6 (0.4-0.8)	0.6 (0.4-0.9)	0.777
Sodium (mmol/L)	140 (137-142)	140 (137-142)	140 (137-142)	0.908
Potassium (mmol/L)	4.3 (3.9-4.7)	4.2 (3.9-4.7)	4.3 (3.9-4.8)	0.188
Hemoglobin (g/dl)	12.3 (10.5-14.1)	12.5 (10.8-14.4)	12.2 (10.2-13.9)	0.003
BUN (mg/dl)	24.4 (18.0-36.7)	22.5 (17.6-32.1)	25.8 (18.4-41.0)	<0.001
Creatinine (g/dl)	1.20 (0.90-1.84)	1.17 (0.92-1.72)	1.21 (0.89-1.99)	0.141
CRP (mg/dl)	0.66 (0.20-2.43)	0.56 (0.20-1.90)	0.72 (0.21-3.04)	0.029
BNP (pg/ml)	831 (452-1,427)	801 (401-1,365)	847 (475-1,488)	0.087
PNI	43.3 (38.4-48.3)	44.3 (39.8-48.0)	42.6 (37.6-48.5)	0.022
CONUT score	3 (1-5)	3 (1-4)	3 (1-5)	0.009
Albumin (g/dl)	3.6 (3.3-3.9)	3.8 (3.4-4.1)	3.5 (3.2-3.8)	<0.001
Lymphocyte count (/μl)	1,306 (802-1,890)	1,253 (866-1,677)	1,387 (731-2,210)	0.001
Total cholesterol (mg/dl)	166 (139-195)	169 (143-195)	164 (138-195)	0.076

BNP = brain natriuretic peptide; BUN = blood urea nitrogen; CONUT = controlling nutritional status; CRP = C-reactive protein; LVEF = left ventricular ejection fraction measured by echocardiography; PNI = prognostic nutritional index; SBP = systolic blood pressure.

The p values between the 2000s and the 2010s groups were determined using the Mann-Whitney U test or the chi-square test.

All numerical data are expressed as the median (25% to 75% interquartile range).

AHF management, in the 2010s group, NPPV was used significantly more frequently, whereas the need for endotracheal intubation decreased significantly. Intra-aortic balloon pumping (IABP) was used significantly more frequently in the 2010s group. Administration of furosemide and carperitide decreased significantly in the 2010s group and tolvaptan therapy was newly suggested from 2010. Administration of nitroglycerin and dopamine decreased significantly in the 2010s group (Table 3).

The multivariate logistic regression analysis revealed that age (≥75 years; odds ratio [OR] 1.334, 95% confidence interval [CI] 1.048 to 1.700, p = 0.019), SBP (<100 mm Hg; OR 1.934, 95% CI 1.170 to 3.198, p = 0.010), LVEF (>40%; OR 1.441, 95% CI 1.125 to 1.847, p = 0.004), and PNI (severe; OR 1.865, 95% CI 1.224 to 2.841, p = 0.004) were independently associated with ICU admission of AHF patients in the 2010s group (Table 4). These results suggest that AHF patients admitted in the 2010s were categorized as clearly aging, HF preserved LVEF, and malnourished. Furthermore, the number of patients with a low SBP who required IABP also increased. The severity of the condition of individual AHF patients admitted in the 2010s may have been exacerbated compared with the 2000s. The duration of ICU admission and total hospitalization in the 2010s group (ICU; 4 [3 to 6] days, total; 23 [15 to 40] days) was significantly shorter than in the 2000s group (ICU; 5 [4 to 8] days, total; 30 [20 to 54] days).

The median follow-up period was 365 (116 to 365) days. There were 140 (9.5%) in-hospital deaths and 270 (18.3%) patients died within 365 days. The rates of in-hospital mortality in the 2 groups did not significantly differ. The Kaplan-Meier curves for the eras of admission are shown in Figure 2. The rate of all-cause mortality in the 2010s group was significantly higher than in the 2000s group (p = 0.005) and the number of HF events in the 2010s group tended to be higher than in the 2000s group (p = 0.065; Figure 2).

Interestingly, after estimated propensity scores were used to match 553 patients each from the 2010s and 2000s groups (Table 5), the rates of 365-day mortality and the number of HF events did not differ between the 2 groups (Figure 2). The duration of ICU admission and total hospitalization in the 2010s group (ICU; 3 [3 to 5] days, total; 22 [15 to 38] days) were significantly shorter than those in the 2000s group (ICU; 5 [4 to 8] days, total; 31 [5 to 8] days; Table 5).

Discussion

Aging was clearly an important characteristic of AHF patients in the 2010s group in the present study. It is well

Table 3
In-hospital management and short-term prognosis according to the year of admission

Variable	Total (n = 1,475)	Year of admission		p Value
		2000s (2000 to 2009, n = 608)	2010s (2010 to 2018, n = 867)	
NPPV	727 (49.3%)	140 (23.0%)	587 (67.7%)	<0.001
ETI	321 (21.8%)	188 (30.9%)	133 (15.3%)	<0.001
IABP	75 (5.1%)	11 (1.8%)	64 (7.4%)	<0.001
CRRT	203 (13.8%)	73 (12.0%)	130 (15.0%)	0.107
Furosemide	1,360 (92.2%)	583 (95.9%)	777 (89.6%)	<0.001
Carperitide	654 (44.3%)	344 (56.6%)	310 (35.8%)	<0.001
Tolvaptan	136 (9.2%)	0 (0.0%)	136 (15.6%)	<0.001
Nitroglycerin	853 (57.8%)	475 (78.1%)	378 (43.6%)	<0.001
Nicorandil	197 (13.4%)	71 (11.7%)	126 (14.5%)	0.120
Dopamine	280 (19.0%)	218 (35.9%)	62 (7.2%)	<0.001
Dobutamine	332 (22.5%)	152 (25.0%)	180 (20.8%)	0.058
ACE-I/ARB	541 (36.7%)	248 (40.8%)	293 (33.8%)	0.007
β-blocker	381 (25.8%)	129 (21.2%)	252 (29.1%)	0.001
Spironolactone	532 (36.1%)	199 (32.7%)	333 (38.4%)	0.028
Statin	458 (31.1%)	169 (27.8%)	289 (33.3%)	0.026
ICU hospitalization (days)	4 (3-7)	5 (4-8)	4 (3-6)	<0.001
Total hospitalization (days)	27 (17-45)	30 (20-54)	23 (15-40)	<0.001
In-hospital mortality	140 (9.5%)	53 (8.7%)	87 (10.0%)	0.418

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CRRT = continuous renal replacement therapy; ETI = endotracheal intubation; IABP = intra-aortic balloon pumping; ICU = intensive care unit; NPPV = noninvasive positive pressure ventilation.

The p values between the 2000s and the 2010s groups were determined using the Mann-Whitney U test or the chi-square test.

All numerical data are expressed as the median (25% to 75% interquartile range).

known that Japan's population is aging faster and that Japanese life expectancy is increasing year by year compared with Western countries. A large number of registries were established in Western and Asian countries during the 2000s.[8–13] The Japanese registries in the 2000s revealed that the mean age was 69 to 73 years,[8–10] whereas the mean age in Asian and Western registries was 67 years[11] and 70 to 72 years,[12,13] respectively. There were various differences in the factors recorded in these registries, for example, the type of HF (acute or chronic) and regional characteristics. However, the admission era was almost the same. The mean age of the patients in these registries was <75 years of age, whereas that in the 2010s was 75 years of age in the present study. In studies on 3 large-scale AHF registries (ATTEND/WET-HF/REALITY-AHF),[14–16] Shiraishi et al[17] reported the same trends: the mean age increased to >75 years from 2012. The age of AHF patients is expected to continuously increase in correlation with population aging in the near future.

Malnutrition is also a common complication associated with aging in patients with HF due to low nutritional intake or malabsorption due to intestinal edema, anorexia, liver dysfunction, and cytokine-induced hypercatabolism.[18] Some nutritional parameters are associated with prognosis of patients with AHF.[19–21] Based on trends in the present study, nutritional improvement is an expected key issue in

Table 4
The multivariate logistic model of the clinical findings associated with admission during the 2010s

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p Value	OR	95% CI	p Value
Including factors						
Age (≥75 years)	1.361	1.105-1.676	0.004	1.334	1.048-1.700	0.019
SBP (<100 mm Hg)	2.400	1.538-3.745	<0.001	1.934	1.170-3.198	0.010
Hemoglobin (per 1.0 g/dl increase)	1.000	0.989-1.011	0.969	1.011	0.970-1.053	0.603
BUN (per 1.0 mg/dl increase)	1.012	1.006-1.018	<0.001	1.005	0.998-1.011	0.175
CRP (per 1.0 mg/dl increase)	1.050	1.022-1.079	<0.001	1.023	0.993-1.054	0.127
Prescribed hemodialysis (yes)	1.837	1.021-3.304	0.042	1.530	0.780-3.003	0.216
LVEF (>40%)	1.425	1.149-1.767	0.001	1.441	1.125-1.847	0.004
PNI						
Normal (high-PNI)	1.000					1.000
Mild (middle-PNI)	1.674	1.111-2.523	0.014	1.395	0.909-2.139	0.127
Severe (low-PNI)	2.220	1.513-3.256	<0.001	1.865	1.224-2.841	0.004

BUN = blood urea nitrogen; CI = confidence interval; CRP = C-reactive protein; LVEF = left ventricular ejection fraction measured by echocardiography; OR = odds ratio; PNI = prognostic nutritional index; SBP = systolic blood pressure.

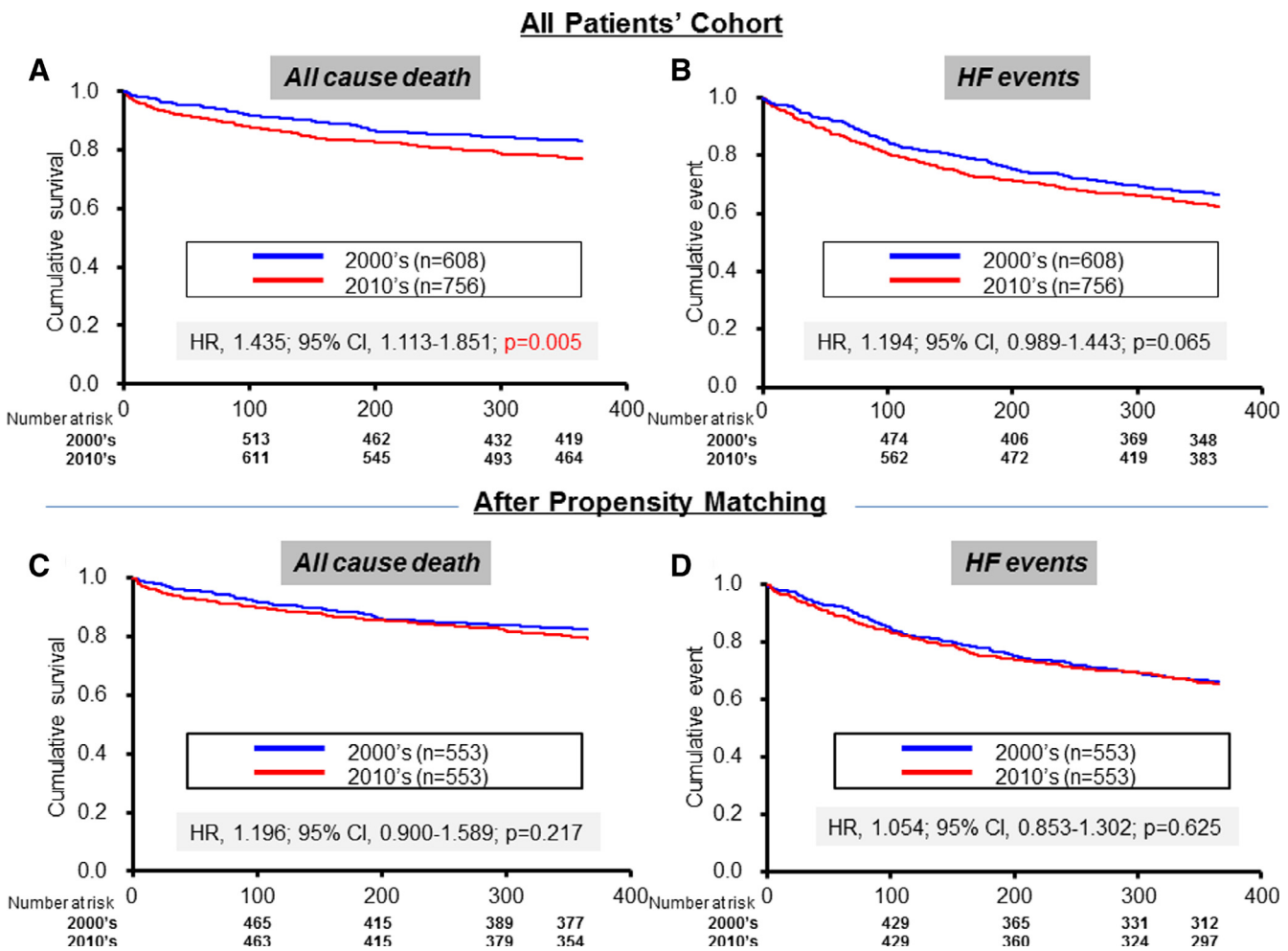

Figure 2. Kaplan-Meier survival curves for the years of admission before and after propensity matching. *(A)* Kaplan-Meier survival curves showing that the prognosis, including all-cause death, was significantly poorer in the 2010s group than in the 2000s group (p = 0.005). *(B)* Kaplan-Meier survival curves showing that prognosis, including HF events, tended to be poorer in the 2010s group than in the 2000s group (p = 0.065). *(C)* Kaplan-Meier survival curves showing that prognosis, including all-cause death, of the 2010s and 2000s groups did not statistically differ (p = 0.217) following propensity matching. *(D)* Kaplan-Meier survival curves showing that prognosis, including HF events, in the 2010s and 2000s groups did not statistically differ (p = 0.625).

managing AHF during the next decade. AHF is heterogeneous; therefore, we included overweight, young male patients and severely thin female patients. Therefore, we reported the "obesity paradox" as an outcome of severely decompensated AHF patients.[22] Body mass index did not correlate with nutrition status in AHF.

The major findings of the present study were the length of hospital stay (LOHS) of AHF patients in the 2010s group was shorter than those in the 2000s group, even after propensity score matching according to baseline characteristics. The LOHS after AHF in Japan is over 20 days due to Japan's socialized medical system, which was much longer than in any Western and Asian countries.[23,24] The present study suggests that LOHS was decreasing, even though patient condition was becoming more severe; however, this was still longer than other reports from the 2000s.[12,13,23,24] Changes in the approach toward a socialized medical system was one of the main reasons. Changes in management of AHF from the 2010s, such as the introduction of tolvaptan and the use of NPPV, may have also contributed to reducing LOHS for AHF patients.[25,26] A prolonged hospital stay due to detailed investigation of etiology, attempted slow rehabilitation, and adjusting medication dosage is associated with a decrease in activities of daily living in older, frail, and malnourished AHF patients. Management practices to maintain daily living activities by shortening hospitalization should be considered in the next "HF pandemic" era.

There are available data from nationwide cohort studies in Denmark, the United States, and the National Inpatient Sample.[27–29] The results show that in-hospital mortality decreased during their study periods. Furthermore, the HF-related admission and in-hospital mortality rates showed the greatest improvement after 2005, according to the 2005 ACC/AHA HF guidelines.[29] However, long-term prognosis was not evaluated in these nationwide cohorts. Shiraishi et al[17] reported using Japanese AHF registries that long-term prognosis, including 365-day mortality and 365-day readmission due to HF, remained unchanged from 2007 to 2015. Our findings suggest that long-term prognosis of patients with severe AHF requiring ICU admission is now becoming poorer due to differences in some baseline factors

Table 5
Characteristics of the patients according to the year of admission after propensity matching

Variable	Year of admission		p Value
	2000s (2000 to 2009, n = 553)	2010s (2010 to 2017, n = 553)	
Age (years old)	74 (65-81)	74 (66-81)	0.935
Men	361 (65.3%)	371 (67.1%)	0.567
BMI (kg/m^2)	22.2 (20.3-24.8)	22.9 (20.3-25.4)	0.070
Readmission	182 (32.9%)	196 (35.4%)	0.410
Social vulnerable	238 (43.0%)	244 (44.1%)	0.584
Ischemia	228 (41.2%)	232 (42.0%)	0.855
Prescribed hemodialysis	16 (2.9%)	24 (4.3%)	0.259
CKD	278 (50.3%)	288 (52.1%)	0.588
Systolic blood pressure	160 (130-182)	161 (132-188)	0.576
LVEF (%)	35 (24-47)	35 (25-46)	0.662
Orthopnea	454 (82.1%)	442 (79.9%)	0.399
Total bilirubin (mg/dl)	0.6 (0.4-0.8)	0.6 (0.4-0.9)	0.886
Sodium (mmol/L)	140 (137-142)	140 (137-142)	0.686
Potassium (mmol/L)	4.2 (3.9-4.7)	4.3 (3.9-4.7)	0.696
Hemoglobin (g/dl)	12.4 (10.7-14.3)	12.4 (10.6-14.1)	0.828
BUN (mg/dl)	22.7 (17.6-32.6)	23.7 (17.4-34.1)	0.473
Creatinine (g/dl)	1.18 (0.93-1.74)	1.16 (0.85-1.78)	0.351
CRP (mg/dl)	0.57 (0.21-2.01)	0.54 (0.18-1.91)	0.287
BNP (pg/ml)	835 (404-1,405)	843 (475-1,521)	0.305
PNI	44.4 (39.8-48.0)	43.3 (38.7-49.0)	0.576
CONUT score	3 (1-4)	3 (1-5)	0.492
ICU hospitalization (days)	5 (4-8)	3 (3-5)	<0.001
Total hospitalization (days)	31 (20-54)	22 (15-38)	<0.001
In-hospital mortality	49 (8.9%)	51 (9.2%)	0.917

BMI = body mass index; BNP = brain natriuretic peptide; BUN = blood urea nitrogen; CKD = chronic kidney disease; CONUT = controlling nutritional status; CRP = C-reactive protein; ICU = intensive-care unit; LVEF = left ventricular ejection fraction measured by echocardiography; PNI = prognostic nutritional index.

The p values between the 2000s and the 2010s groups were determined using the Mann-Whitney U test or the chi-square test. All numerical data are expressed as the median (25% to 75% interquartile range).

associated with aging. Focusing on aging-associated issues such as malnutrition, frailty, social determinants, internal medicine, and outpatient management may lead to improved prognosis of HF in the next pandemic era.

The present study has several limitations. First, it was a retrospective study performed at a single center. It is therefore possible that unmeasured variables or missing data affected the results and the definition of risk and interpretation/appreciation of risk factors may differ between the early 2000s and late 2010s. Second, our study population was limited to patients admitted to the ICU. In our institute, patients are treated in a "closed ICU," in which all physicians are cardiologists. Thus, the majority of patients with severely decompensated AHF were admitted to the ICU. However, increasing competition for ICU beds (limited number of available ICU beds) may force physicians to admit more severe cases to general wards in some cases. The best strategy for presenting our data to the broader medical society would be to include all patients with AHF admitted to the emergency department in our analysis. However, no data were available regarding all patients with AHF admitted to the emergency department before 2009. This may be 1 major limitation of our study. Third, although the percentage of patients receiving statin therapy during the ICU stay is shown in the results, the exact percentage of admission is not stated. It may be important to know the actual number of patients on lipid-lowering therapy and whether this affects the way nutrition status is calculated. Fourth, although the use of IABP did not significantly reduce 30-day mortality in patients with cardiogenic shock complicating acute myocardial infarction,[30] IABP is useful as it improved therapy in our described patient population. Although treatment with Impella may be the best strategy for patients with severe HF, it was not used in our institution. Finally, the lag time between measuring serum albumin, lymphocyte count, and total-cholesterol upon admission time may have affected the results. Blood samples were collected within 30 minutes of patients admitted after May 2011. In the remaining patients, serum albumin levels were evaluated within 24 hours. Lymphocyte counts and total-cholesterol levels were evaluated using the first sample collected during hospitalization (3 [2 to 7] days).

In conclusion, AHF patients admitted to the ICU in the 2010s were categorized into 2 patient groups: aging patients (≥75 years) with a preserved LVEF (>40%) and malnutrition, and patients with a low SBP (<100 mm Hg) whose management utilized IABP. AHF patients admitted during the 2010s had poor long-term prognosis despite improved treatment strategies. The difference in the severity among eras may have been a key factor affecting long-term prognosis. The condition of AHF patients who require intensive care clearly became more critical year by year.

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Disclosuress

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1. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, Murabito JM, Vasan RS, Benjamin EJ, Levy D. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation* 2002;106:3068–3072.
2. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, Nodari S, Lam CS, Sato N, Shah AN, Gheorghiade M. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol* 2014;63:1123–1133.
3. Sakata Y, Shimokawa H. Epidemiology of heart failure in Asia. *Circ J* 2013;77:2209–2217.
4. Shimokawa H, Miura M, Nochioka K, Sakata Y. Heart failure as a general pandemic in Asia. *Eur J Heart Fail* 2015;17:884–892.
5. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;37:2129–2200.
6. Onodera T, Goseki N, Kosaki G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. *Nihon Geka Gakkai Zasshi* 1984;85:1001–1005.
7. Ignacio de Ulibarri J, Gonzalez-Madrono A, de Villar NG, Gonzalez P, Gonzalez B, Mancha A, Rodriguez F, Fernandez G. CONUT: a tool for controlling nutritional status. First validation in a hospital population. *Nutr Hosp* 2005;20:38–45.
8. Sakata Y, Miyata S, Nochioka K, Miura M, Takada T, Tadaki S, Takahashi J, Shimokawa H. Gender differences in clinical characteristics, treatment and long-term outcome in patients with stage C/D heart failure in Japan. Report from the CHART-2 study. *Circ J* 2014;78:428–435.
9. Sato N, Kajimoto K, Keida T, Mizuno M, Minami Y, Yumino D, Asai K, Murai K, Muanakata R, Aokage T, Sakata Y, Mizuno K, Takano T, TEND Investigators. Clinical features and outcome in hospitalized heart failure in Japan (from the ATTEND Registry). *Circ J* 2013;77:944–951.
10. Tsuchihashi-Makaya M, Hamaguchi S, Kinugawa S, Yokota T, Goto D, Yokoshiki H, Kato N, Takeshita A, Tsutsui H, JCARE-CARD Investigators. Characteristics and outcomes of hospitalized patients with heart failure and reduced vs preserved ejection fraction. Report from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). *Circ J* 2009;73:1893–1900.
11. Atherton JJ, Hayward CS, Wan Ahmad WA, Kwok B, Jorge J, Hernandez AF, Liang L, Kociol RD, Krum H, ADHERE International −Asia Pacific Scientific Advisory Committee. Patient characteristics from a regional multicenter database of acute decompensated heart failure in Asia Pacific (ADHERE International-Asia Pacific). *J Card Fail* 2012;18:82–88.
12. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, Hochadel M, Komajda M, Lassus J, Lopez-Sendon JL, Ponikowski P, Tavazzi L, EuroHeart Survey Investigators, Heart Failure Association, European Society of Cardiology. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. *Eur Heart J* 2006;27:2725–2736.
13. Adams KF Jr., Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, Berkowitz RL, Galvao M, Horton DP, ADHERE Scientific Advisory Committee and Investigators. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J* 2005;149:209–216.
14. Shiraishi Y, Kohsaka S, Abe T, Mizuno A, Goda A, Izumi Y, Yagawa M, Akita K, Sawano M, Inohara T, Takei M, Kohno T, Higuchi S, Yamazoe M, Mahara K, Fukuda K, Yoshikawa T, West Tokyo Heart Failure Registry Investigator. Validation of the get with the guideline-heart failure risk score in Japanese patients and the potential improvement of its discrimination ability by the inclusion of B-type natriuretic peptide level. *Am Heart J* 2016;171:33–39.
15. Sato N, Kajimoto K, Asai K, Mizuno M, Minami Y, Nagashima M, Murai K, Muanakata R, Yumino D, Meguro T, Kawana M, Nejima J, Satoh T, Mizuno K, Tanaka K, Kasanuki H, Takano T, ATTEND Investigators. Acute decompensated heart failure syndromes (ATTEND) registry. A prospective observational multicenter cohort study: rationale, design, and preliminary data. *Am Heart J* 2010;159. 949−955.e1.
16. Matsue Y, Damman K, Voors AA, Kagiyama N, Yamaguchi T, Kuroda S, Okumura T, Kida K, Mizuno A, Oishi S, Inuzuka Y, Akiyama E, Matsukawa R, Kato K, Suzuki S, Naruke T, Yoshioka K, Miyoshi T, Baba Y, Yamamoto M, Murai K, Mizutani K, Yoshida K, Kitai T. Time-to-furosemide treatment and mortality in patients hospitalized with acute heart failure. *J Am Coll Cardiol* 2017;69:3042–3051.
17. Shiraishi Y, Kohsaka S, Sato N, Takano T, Kitai T, Yoshikawa T, Matsue Y. 9-year trend in the management of acute heart failure in Japan: a report from the National Consortium of Acute Heart Failure Registries. *J Am Heart Assoc* 2018;7:e008687.
18. Krack A, Sharma R, Figulla HR, Anker SD. The importance of the gastrointestinal system in the pathogenesis of heart failure. *Eur Heart J* 2005;26:2368–2374.
19. Iwakami N, Nagai T, Furukawa TA, Sugano Y, Honda S, Okada A, Asaumi Y, Aiba T, Noguchi T, Kusano K, Ogawa H, Yasuda S, Anzai T, NaDEF Investigators. Prognostic value of malnutrition assessed by Controlling Nutritional Status score for long-term mortality in patients with acute heart failure. *Int J cardiol* 2017;230:529–536.
20. Yokota J, Ogawa Y, Yamanaka S, Takahashi Y, Fujita H, Yamaguchi N, Onoue N, Ishizuka T, Shinozaki T, Kohzuki M. Cognitive dysfunction and malnutrition are independent predictor of dysphagia in patients with acute exacerbation of congestive heart failure. *PLoS One* 2016;11:e0167326.
21. Shirakabe A, Hata N, Kobayashi N, Okazaki H, Matsushita M, Shibata Y, Nishigoori S, Uchiyama S, Asai K, Shimizu W. The prognostic impact of malnutrition in patients with severely decompensated acute heart failure, as assessed using the Prognostic Nutritional Index (PNI) and Controlling Nutritional Status (CONUT) score. *Heart Vessels* 2018;33:134–144.
22. Matsushita M, Shirakabe A, Hata N, Shinada T, Kobayashi N, Tomita K, Tsurumi M, Okazaki H, Yamamoto Y, Asai K, Shimizu W. Association between the body mass index and the clinical findings in patients with acute heart failure: evaluation of the obesity paradox in patients with severely decompensated acute heart failure. *Heart Vessels* 2017;32:600–608.
23. Mentz RJ, Roessig L, Greenberg BH, Sato N, Shinagawa K, Yeo D, Kwok BW, Reyes EB, Krum H, Pieske B, Greene SJ, Ambrosy AP, Kelly JP, Zannad F, Pitt B, Lam CS. Heart failure clinical trials in East and Southeast Asia: understanding the importance and defining the next steps. *JACC Heart Fail* 2016;4:419–427.
24. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, Nodari S, Lam CSP, Sato N, Shah AN, Gheorghiade M. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol* 2014;63:1123–1133.
25. Shirakabe A, Hata N, Yamamoto M, Kobayashi N, Shinada T, Tomita K, Tsurumi M, Matsushita M, Okazaki H, Yamamoto Y, Yokoyama S, Asai K, Shimizu W. Immediate administration of tolvaptan prevents the exacerbation of acute kidney injury and improves the mid-term prognosis of patients with severely decompensated acute heart failure. *Circ J* 2014;78:911–921.
26. Shirakabe A, Hata N, Yokoyama S, Shinada T, Kobayashi N, Tomita K, Kitamura M, Nozaki A, Tokuyama H, Asai K, Mizuno K. Predicting the success of noninvasive positive pressure ventilation in emergency room for patients with acute heart failure. *J Cardiol* 2011;57:107–114.
27. Win TT, Davis HT, Laskey WK. Mortality among patients hospitalized with heart failure and diabetes mellitus: results from the

National Inpatient Sample 2000 to 2010. *Circ Heart Fail* 2016;9: e003023.
28. Schmidt M, Ulrichsen SP, Pedersen L, Botker HE, Sorensen HT. Thirty-year trends in heart failure hospitalization and mortality rates and the prognostic impact of co-morbidity: a Danish nationwide cohort study. *Eur J Heart Fail* 2016;18:490–499.
29. Akintoye E, Briasoulis A, Egbe A, Dunlay SM, Kushwaha S, Levine D, Afonso L, Mozaffarian D, Weinberger J. National trends in admission and in-hospital mortality of patients with heart failure in the United States (2001-2014). *J Am Heart Assoc* 2017;6:1–14.
30. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, Richardt G, Hennersdorf M, Empen K, Fuernau G, Desch S, Eitel I, Hambrecht R, Fuhrmann J, Bohm M, Ebelt H, Schneider S, Schuler G, Werdan K, IABP-SHOCK II Trial Investigators. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med* 2012;367:1287–1296.