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BRIEF COMMUNICATION

Newly Diagnosed Infection After Admission for Acute Heart Failure: From the KCHF Registry

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BACKGROUND: No studies have explored the association between newly diagnosed infections after admission and clinical outcomes in patients with acute heart failure. We aimed to explore the factors associated with newly diagnosed infection after admission for acute heart failure, and its association with in-hospital and post-discharge clinical outcomes.

METHODS AND RESULTS: Among 4056 patients enrolled in the Kyoto Congestive Heart Failure registry, 2399 patients without any obvious infectious disease upon admission were analyzed. The major in-hospital and post-discharge outcome measures were all-cause deaths. There were 215 patients (9.0%) with newly diagnosed infections during hospitalization, and 2184 patients (91.0%) without infection during hospitalization. The factors independently associated with a newly diagnosed infection were age ≥80 years, acute coronary syndrome, non-ambulatory status, hyponatremia, anemia, intubation, and patients who were not on loop diuretics as outpatients. The newly diagnosed infection group was associated with a higher incidence of in-hospital mortality (16.3% and 3.2%, $P<0.001$) and excess adjusted risk of in-hospital mortality (odds ratio, 6.07 [95% CI, 3.61–10.19], $P<0.001$) compared with the non-infection group. The newly diagnosed infection group was also associated with a higher 1-year incidence of post-discharge mortality (19.3% in the newly diagnosed infection group and 13.6% in the non-infection group, $P<0.001$) and excess adjusted risk of post-discharge mortality (hazard ratio, 1.49 [95% CI, 1.08–2.07], $P=0.02$) compared with the non-infection group.

CONCLUSIONS: Elderly patients with multiple comorbidities were associated with the development of newly diagnosed infections after admission for acute heart failure. Newly diagnosed infections after admission were associated with higher in-hospital and post-discharge mortality in patients with acute heart failure.

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Key Words: acute heart failure ■ heart failure ■ infections ■ mortality

Infection is a common precipitating factor for hospitalization and is associated with increased mortality in patients with heart failure (HF).[1] Patients admitted with decompensated HF and those with a concurrent infection are at a higher risk of in-hospital mortality.[2] In addition, newly developed infections after admission for acute HF (AHF) are often encountered in daily practice and are difficult to treat. However, it remains

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unclear as to which population is associated with the development of infections after admission for AHF. Thus, we aimed to define the factors associated with developing a newly diagnosed infection after admission for AHF, and to investigate their association with in-hospital and post-discharge clinical outcomes in patients with AHF.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design, Setting, and Population

The KCHF (Kyoto Congestive Heart Failure) registry is a prospective multicenter cohort study for AHF between October 2014 and March 2016 across 19 secondary and tertiary hospitals in Japan.[3] We enrolled consecutive patients with AHF who were admitted to the participating centers and who underwent HF-specific treatment involving intravenous drugs administered within 24 hours of admission.

Among the 4056 patients enrolled in the KCHF registry, we excluded the following cases upon admission: 197 patients with obvious infectious diseases, 197 patients with fever (body temperature ≥37.5 °C), and 1263 patients with CRP (C-reactive protein) levels >10 mg/L.[4] We divided the study population into 2 groups according to the presence or absence of newly diagnosed infections after admission (Figure S1).

Ethics

The investigation conformed to the principles outlined in the Declaration of Helsinki. The study protocol was approved by the respective ethical committees of Kyoto University Hospital (local identifier: E2311) and of each participating hospital. Written informed consent was waived by the institutional review boards of Kyoto University Hospital and each participating center, because the study met the conditions outlined in the Japanese ethical guidelines for medical and health research involving human subjects.[5]

Definitions

Infection was defined by the evaluating clinicians when there were suspected and documented sources of infection, accompanied by deteriorating symptoms and signs (eg, pyrexia, tachycardia, hypotension, tachypnea, and confusion), and laboratory indices (eg, elevated inflammatory markers, with microbiological, serological, and/or imaging evidence), resulting in treatment with antimicrobial therapy.[5] The sources included the following[5]: respiratory tract, urinary tract (eg, cystitis and pyelonephritis), biliary/gastrointestinal, soft-tissue (eg, cellulitis, gangrene, and necrotizing fasciitis), catheter-related infections, and others. Other definitions for the baseline factors and data collection are provided in Data S1.

In-hospital outcome measures included all-cause, cardiovascular, and non-cardiovascular deaths. Post-discharge outcome measures included all-cause, cardiovascular and non-cardiovascular deaths, and HF hospitalization (Data S1).

Statistical Analysis

Categorical variables were expressed as numbers and percentages and were compared using the χ^2 test or Fisher exact test. Continuous variables were expressed as mean and SD or median with interquartile range (IQR), and were compared using Student *t* test or Wilcoxon rank sum test based on their distribution. To determine the factors associated with developing a newly diagnosed infection after admission, we created a multivariable logistic regression model. We examined all clinical and laboratory categorical variables using univariate analysis (Table S1). We subsequently included all factors with $P<0.10$ using a multivariate model. For sensitivity analysis, we used the continuous variables. We developed a multivariable logistic regression model to explore the risk of developing a newly diagnosed infection on in-hospital mortality and selected 19 risk-adjusting variables according to the clinical relevance and relations to outcomes consistent with previous studies[6] (Table S1). For sensitivity analysis, we used continuous variables such as age, body mass index, heart rate, systolic blood pressure, left ventricular ejection fraction, estimated glomerular filtration rate, and albumin, sodium, and hemoglobin levels in the model. The results were expressed as odds ratios (ORs) and 95% CIs. Moreover, we regarded the date of discharge as "time zero" for clinical follow-up after discharge. The cumulative incidences of all-cause, cardiovascular, and non-cardiovascular deaths after discharge were estimated using the Kaplan–Meier method, with intergroup differences assessed by the log-rank test. The cumulative incidence of HF hospitalization after discharge was estimated using the Gray method, accounting for the competing risk of all-cause death. We used the multivariable Cox proportional hazard model to evaluate the risk of developing a newly diagnosed infection relative to non-infection for all-cause, cardiovascular, and non-cardiovascular deaths after discharge using 21 risk-adjusting variables that were based on the clinical relevance and relations to outcomes consistent with previous studies[6] (Table S2). Continuous variables were dichotomized using clinically meaningful reference values or median values. To account for the competing risk of all-cause death,

the risk of HF hospitalization was described using the Fine-Gray subdistribution hazard model. For sensitivity analysis, we used the aforementioned continuous variables. The results were expressed as hazard ratios (HRs) and 95% CIs. We also evaluated the interactions between the subgroup factors (age, diabetes, left ventricular ejection fraction, white blood cell, CRP, estimated glomerular filtration rate, and serum sodium, albumin, and hemoglobin levels), and the effects of newly diagnosed infection relative to non-infection on all-cause death after discharge. All statistical analyses were conducted by 2 physicians (Y.S. and T.K.) and a statistician (T.M.) using JMP Pro software (version 15; SAS Corp., Cary, NC, USA) and EZR.[7] All reported *P* values were 2-tailed, while statistical significance was set to $P<0.05$.

RESULTS

Patient Characteristics

In 2399 enrolled patients, the mean age was 77.1±12.3 years, of whom 47.1% were women (Table S1). After admission, 215 patients (9.0%) developed newly diagnosed infections (Figure S1). The sources of infection were the respiratory tract (48%), followed by the urinary tract (34%), biliary/gastrointestinal tract (6%), catheter related (4%), and soft tissues (3%) (Figure S2).

Compared with patients without infection, those with a newly diagnosed infection were older, had lower serum albumin, sodium, and hemoglobin levels, but had higher white blood cell and CRP levels. The causative agent was found to be associated with acute coronary syndrome. Patients with a newly diagnosed infection had a higher prevalence of cognitive dysfunction, intubation, and treatment with inotropes. They also had fewer prescriptions for β-blockers and loop diuretics at admission (Table S1).

Factors Associated With Newly Diagnosed Infection After Admission

In the multivariable logistic regression analysis, factors independently associated with newly diagnosed infection after admission were age ≥80 years (adjusted OR, 1.56 [95% CI, 1.11–2.19], $P=0.01$), acute coronary syndrome (adjusted OR, 2.97 [95% CI, 1.81–4.88], $P<0.001$), non-ambulatory status (adjusted OR, 1.61 [95% CI, 1.10–2.37], $P=0.02$), serum sodium <135 mEq/L (adjusted OR, 1.70 [95% CI, 1.11–2.61], $P=0.02$), anemia (adjusted OR, 1.82 [95% CI, 1.28–2.58], $P<0.001$), intubation (adjusted OR, 6.54 [95% CI, 3.18–13.44], $P<0.001$), and patients who were not on loop diuretics as outpatients (adjusted OR, 1.58 [95% CI, 1.12–2.22], $P=0.009$) (Table 1). In the analysis of continuous variables, the trends were mostly consistent with the main analysis, except for hemoglobin, which became insignificant (per mg/dL decrease, adjusted OR, 1.08 [95% CI, 0.999–1.16], $P=0.054$), and CRP, which became significant (per mg/L increase, adjusted OR, 1.07 [95% CI, 1.01–1.13], $P=0.02$) (Table S3).

In-Hospital Outcomes

The incidence of in-hospital all-cause death was significantly higher in the newly diagnosed infection group than in the non-infection group (16.3% and 3.2%,

Table 1. Factors Associated With Newly Diagnosed Infection by Logistic Regression Analysis

Variables	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age ≥80 y	1.64 (1.23–2.19)	<0.001	1.56 (1.11–2.19)	0.01
Associated with ACS	3.42 (2.21–5.28)	<0.001	2.97 (1.81–4.88)	<0.001
Absence of atrial fibrillation or flutter	1.34 (0.998–1.79)	0.052	1.09 (0.78–1.51)	0.63
Cognitive dysfunction	1.78 (1.28–2.48)	<0.001	1.28 (0.86–1.91)	0.23
Non-ambulatory status	1.79 (1.30–2.47)	<0.001	1.61 (1.10–2.37)	0.02
Systolic BP <90 mm Hg	2.08 (1.07–4.04)	0.03	1.43 (0.64–3.18)	0.38
Albumin <30 g/L	1.62 (1.03–2.55)	0.04	1.18 (0.71–1.93)	0.52
Sodium <135 mEq/L	1.86 (1.24–2.78)	0.003	1.70 (1.11–2.61)	0.02
Anemia	1.58 (1.16–2.15)	0.004	1.82 (1.28–2.58)	<0.001
WBC>median value	1.36 (1.03–1.81)	0.03	1.16 (0.84–1.61)	0.37
CRP>3 mg/L	1.31 (0.99–1.73)	0.06	1.25 (0.92–1.69)	0.16
Intubation	8.37 (4.53–15.47)	<0.001	6.54 (3.18–13.44)	<0.001
Inotropes	2.93 (1.71–5.04)	<0.001	1.38 (0.69–2.77)	0.37
Patients who were not on β-blockers as an outpatient	1.58 (1.17–2.13)	0.003	1.23 (0.88–1.73)	0.22
Patients who were not on loop diuretics as an outpatient	1.63 (1.22–2.18)	<0.001	1.58 (1.12–2.22)	0.009

ACS indicates acute coronary syndrome; BP, blood pressure; CRP, C-reactive protein; OR, odds ratio; and WBC, white blood cell.

Table 2. In-Hospital Outcomes

Variables	Newly diagnosed infection N of patients with event/N of patients at risk (incidence [%])	Non-infection N of patients with event/N of patients at risk (incidence [%])	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
All-cause death	35/215 (16.3)	69/2184 (3.2)	5.96 (3.86–9.20)	<0.001	6.07 (3.61–10.19)	<0.001
Cardiovascular death	25/215 (11.6)	60/2184 (2.7)	4.66 (2.85–7.60)	<0.001	4.25 (2.36–7.65)	<0.001
Non-cardiovascular death	10/215 (4.7)	9/2184 (0.4)	11.79 (4.74–29.34)	<0.001	17.18 (5.79–50.97)	<0.001

OR indicates risk of newly diagnosed infection relative to non-infection for all-cause death, cardiovascular death, and non-cardiovascular death during the index hospitalization.

Risk-adjusting variables selected for the multivariable logistic regression model: age ≥80 y, sex, BMI ≤22 kg/m^2, cause of HF hospitalization associated with ACS, previous HF hospitalization, hypertension, diabetes, atrial fibrillation or flutter, previous myocardial infarction, previous stroke, chronic lung disease, ambulatory status, systolic blood pressure <90 mm Hg, heart rate <60 beats/min, LVEF <40% on echocardiography, eGFR <30 mL/min per 1.73 m^2, serum albumin <30 g/L, serum sodium <135 mEq/L, and anemia.

ACS indicates acute coronary syndrome; BMI, body mass index; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; and OR, odds ratio.

adjusted OR, 6.07 [95% CI, 3.61–10.19], *P*<0.001) (Table 2). The excess risk of newly diagnosed infection relative to non-infection was consistently observed in both cardiovascular and non-cardiovascular deaths (Table 2). The results of the sensitivity analysis were consistent with those of the main analysis (Table S4).

Outcomes After Discharge

In the study population, 2115 and 180 patients in the non-infection and newly diagnosed infection groups, respectively, were discharged alive. Characteristics of patients who were discharged alive were consistent with those of the entire study population (Table S2). The median follow-up duration was 475 (IQR, 362–653) days, with a 93.8% follow-up rate at 1 year. The cumulative 1-year incidence of all-cause death was significantly higher in the newly diagnosed infection group than in the non-infection group (19.3% versus 13.6%, *P*<0.001; adjusted HR, 1.49 [95% CI, 1.08–2.07], *P*=0.02) (Figure A). The excess risk of newly diagnosed infection relative to non-infection was consistently observed for cardiovascular death, but not for non-cardiovascular death (Figure [B and C]). Furthermore, the cumulative 1-year incidence of HF hospitalization did not differ between the newly diagnosed infection and non-infection groups (22.0% and 24.7%, *P*=0.40; adjusted HR, 0.82 [95% CI, 0.58–1.16], *P*=0.26) (Figure [D]). The results of the sensitivity analysis were consistent with those of the main analysis (Table S5). In the subgroup analysis, there were no significant interactions between the subgroup factors and the effect of newly diagnosed infection after admission compared with non-infection for all-cause death after discharge (Figure S3).

DISCUSSION

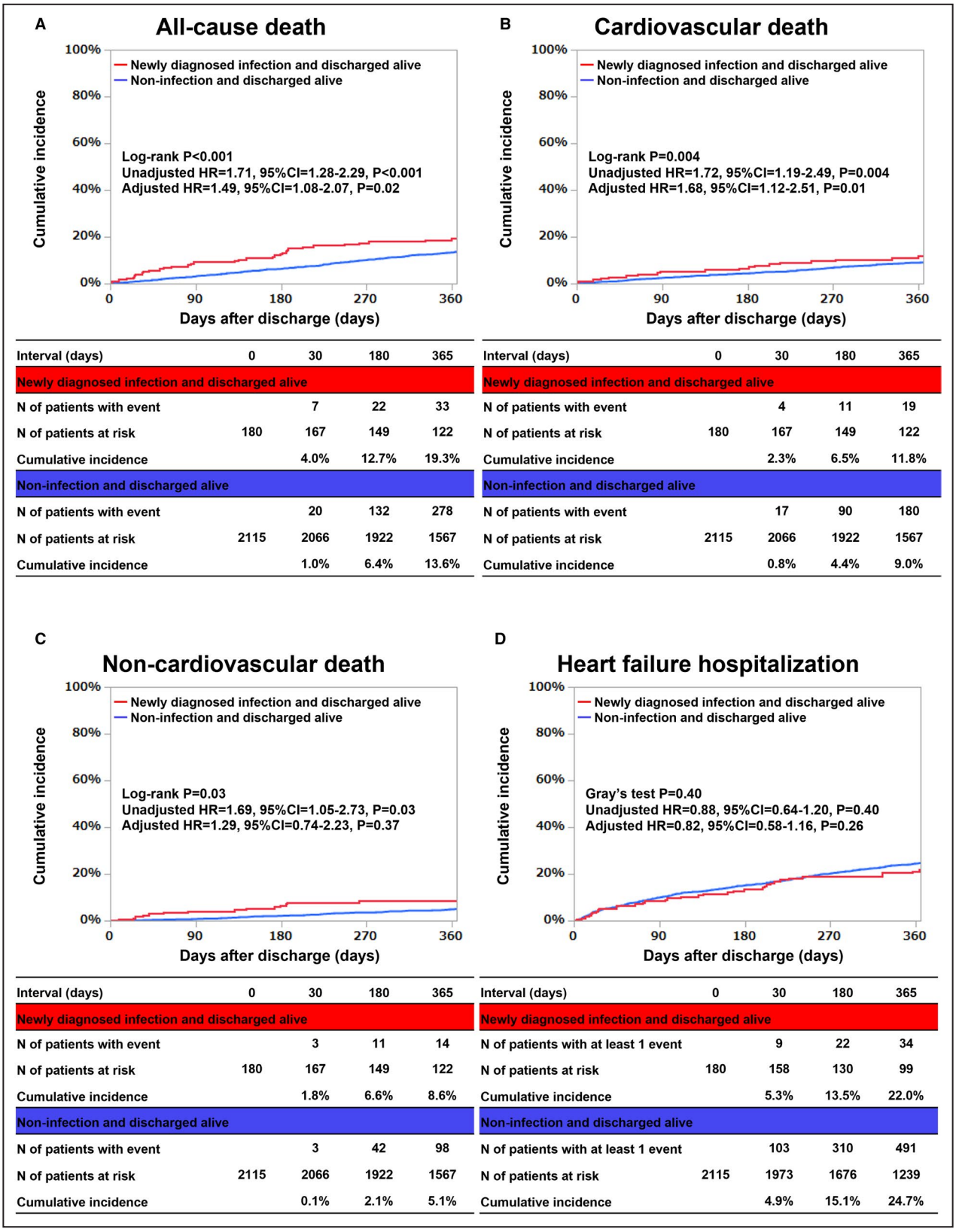
The main findings of this study are as follows: (1) patients who were elderly, intubated, non-ambulatory, diagnosed with acute coronary syndrome and other comorbidities, and not on a loop diuretic prescription were associated with newly diagnosed infections after admission; and (2) patients with newly diagnosed infection after admission had a significantly higher risk of in-hospital and post-discharge mortality than those who did not develop any infection.

Factors Associated With Newly Diagnosed Infection After Admission

Our study is the first to define independent factors associated with patients with AHF who developed a newly diagnosed infection after admission. We found that a wide range of patient factors were associated with newly diagnosed infections after admission. Elderly age is a risk marker for many adverse clinical events; furthermore, it is not surprising that intubation is independently associated with infection, when ventilator-associated pneumonia is the most frequent intensive care unit–related infection in patients requiring intubation.[8] Acute coronary syndrome was more than twice as common in patients with newly diagnosed infection as in those without infection, in line

Figure. Kaplan–Meier curves for outcomes after discharge.

A, All-cause death, (**B**) cardiovascular death, (**C**) non-cardiovascular death, and (**D**) HF hospitalization. Main outcome measure was all-cause death. Risk-adjusting variables selected for the Cox proportional hazard model and Fine–Gray subdistribution hazard model: age ≥80 y, sex, body mass index ≤22 kg/m^2, cause of HF hospitalization associated with ACS, previous HF hospitalization, hypertension, diabetes, atrial fibrillation or flutter, previous myocardial infarction, previous stroke, chronic lung disease, ambulatory status, systolic blood pressure <90 mm Hg, heart rate <60 beats/min, LVEF <40% on echocardiography, eGFR <30 mL/min per 1.73 m^2, serum albumin <30 g/L, serum sodium <135 mEq/L, anemia, prescription of ACEIs or ARBs at discharge, and prescription of β-blockers at discharge. ACEIs indicates angiotensin-converting enzyme inhibitors; ACS, acute coronary syndrome; ARBs, angiotensin II receptor blockers; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; and N, number.



Interval (days)	0	30	180	365
Newly diagnosed infection and discharged alive				
N of patients with event		7	22	33
N of patients at risk	180	167	149	122
Cumulative incidence		4.0%	12.7%	19.3%
Non-infection and discharged alive				
N of patients with event		20	132	278
N of patients at risk	2115	2066	1922	1567
Cumulative incidence		1.0%	6.4%	13.6%

Interval (days)	0	30	180	365
Newly diagnosed infection and discharged alive				
N of patients with event		4	11	19
N of patients at risk	180	167	149	122
Cumulative incidence		2.3%	6.5%	11.8%
Non-infection and discharged alive				
N of patients with event		17	90	180
N of patients at risk	2115	2066	1922	1567
Cumulative incidence		0.8%	4.4%	9.0%

Interval (days)	0	30	180	365
Newly diagnosed infection and discharged alive				
N of patients with event		3	11	14
N of patients at risk	180	167	149	122
Cumulative incidence		1.8%	6.6%	8.6%
Non-infection and discharged alive				
N of patients with event		3	42	98
N of patients at risk	2115	2066	1922	1567
Cumulative incidence		0.1%	2.1%	5.1%

Interval (days)	0	30	180	365
Newly diagnosed infection and discharged alive				
N of patients with at least 1 event		9	22	34
N of patients at risk	180	158	130	99
Cumulative incidence		5.3%	13.5%	22.0%
Non-infection and discharged alive				
N of patients with at least 1 event		103	310	491
N of patients at risk	2115	1973	1676	1239
Cumulative incidence		4.9%	15.1%	24.7%

with a study by Liu et al.[9] Aging,[10] hyponatremia,[11] and anemia[12] are associated with frailty. Anemia is frequently associated with non-cardiovascular death in patients with HF.[13] The non-ambulatory state may also be related to frailty. These patients have been reported to be at a high risk of developing infections and having triggers for

HF. However, a precise cause–effect relationship was not determined in the present study. Nonetheless, our study highlighted the groups susceptible to infection during hospitalization. There is no evidence that loop diuretics play a protective role against infections. Diuretics are used as clinically needed for decongestion. In addition, β-blockers were used less frequently in patients with newly diagnosed infections. The use of these drugs before hospitalization may be negatively associated with a new onset of infection, probably because the intolerance of loop diuretics was caused by a poor baseline status. We need to cautiously treat elderly patients, those with poor baseline status, or those who require these medications but are intolerant to them, even if they do not present with an infection at admission.

In the present study, we excluded patients with suspected signs of infectious disease, such as fever and high CRP (>10 mg/L) levels at admission.[4] Nonetheless, white blood cell and CRP levels were elevated in patients with newly diagnosed infections compared with those without infection. There may be 2 possible explanations for this; first, infections such as an unrecognized aspiration and urinary tract infection were masked and smoldering at admission, and only became evident afterwards, which would not be classified as nosocomial infections. This finding may be more frequently observed in older patients. Second, patients with higher white blood cell and CRP levels have chronic inflammation caused by immune cell dysregulation, cell senescence, disrupted mitochondria, and obesity, all of which cause increased susceptibility to infection.[10] However, since there was no difference in the body mass index between patients with and without newly diagnosed infections, obesity may not be the underlying mechanism in the present study. Moreover, data regarding when the infections developed are lacking in this study; thus, we did not use the term nosocomial infection; instead, we used newly diagnosed infection after admission.

Newly Diagnosed Infection After Admission and Clinical Outcomes in Patients With AHF

No previous studies have investigated the impact of newly diagnosed infections after admission on clinical outcomes in patients with AHF. Fonarow et al have reported that respiratory infection was the most common precipitating factor of HF admission; furthermore, those with infection were at a higher risk of in-hospital mortality, but not for post-discharge mortality.[2] In contrast, our study demonstrated that 9.0% of the patients with AHF without infection at admission had developed an infection after admission, and had shown a higher in-hospital and post-discharge mortality risk.

The worse in-hospital outcome associated with newly diagnosed infection after admission may reflect a vicious interaction between HF and infection. Preexisting HF is a risk factor for the development of respiratory infections.[14] In addition, respiratory infections have been demonstrated to trigger and exacerbate cardiac events.[15] Therefore, the cause–effect relationship between HF and respiratory infections may be bidirectional. Acute systemic inflammation in response to infection can depress myocardial function and cause cardiac arrhythmia, myocardial ischemia, hypoxemia, and sympathetic activation.[15]

In contrast to a previous study, the incidence of all-cause death and cardiovascular death after discharge was significantly higher in patients with a newly diagnosed infection than in those without an infection. Worsening of renal function and HF during hospitalization may have an influence on clinical outcomes. In addition, the distinctly worse outcome in patients with newly diagnosed infections was related to the disproportionate increase in non-cardiovascular deaths compared with cardiovascular deaths, which reinforced the significantly higher overall mortality in patients with newly diagnosed infection. Although the worse outcome of patients with newly diagnosed infection was largely influenced by a poor baseline status, we confirmed that there were no interactions between baseline factors and the effect of newly diagnosed infection for all-cause mortality. In our study, we did not find an unfavorable association between newly diagnosed infection and HF hospitalization after discharge. The higher post-discharge mortality in patients with newly diagnosed infections could overrun HF exacerbation in the more fragile subpopulation, thereby abolishing differences with patients without infection.

Further research on the association between the diagnosis of infection post-admission and prognosis after discharge is necessary. In addition, additional information is needed to design preventive and therapeutic strategies specifically directed toward these infections.

Limitations

The present study has several limitations. First, the observational nature of the study design could have introduced confounding factors and selection bias. Second, we did not have data on the onset of symptoms related to the new infection and its day of diagnosis. There may have been infections that were not detected at admission, even after excluding those with an obvious infectious disease, fever, and high CRP levels. Finally, we did not have data on post-diagnosis treatment of infection and the direct trigger of the infection, such as central venous catheters and indwelling catheters.

CONCLUSIONS

Elderly patients with multiple comorbidities were associated with the development of newly diagnosed

infections after admission for AHF. Moreover, newly diagnosed infections after admission were associated with higher in-hospital and post-discharge mortality among patients with AHF.

ARTICLE INFORMATION

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Disclosures

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Supplementary Material

Appendix. KCHF Study Investigators
Data S1. Supplemental Methods
Tables S1–S5
Figures S1-S3
References 16–18

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SUPPLEMENTAL MATERIAL

APPENDIX

KCHF study investigators

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Data S1. Supplemental Methods

Definitions

The definitions of the baseline factors in Kyoto Congestive Heart Failure (KCHF) registry were according to the previous reports[3,16]. Anemia was defined using the World Health Organization criteria (hemoglobin <12.0 g/dL in women and <13.0 g/dL in men). Heart failure (HF) was classified based on left ventricular ejection fraction (LVEF) as heart failure with preserved LVEF (HFpEF) with LVEF ≥50%, heart failure with mid-range LVEF (HFmrEF) with LVEF 40%-49%, and heart failure with reduced LVEF (HFrEF) with LVEF <40%. High C-reactive protein (CRP) levels was defined as CRP >3 mg/L according to the previously reported cut-off values[4]. Worsening HF during hospitalization was defined as additional intravenous drug treatment for HF, hemodialysis, or mechanical circulatory or respiratory support, occurring >24 h after therapy initiation[17]. Worsening renal function was defined as >0.3 mg/dL increase in serum creatinine during the index hospitalization[18].

Death was regarded as cardiovascular in origin unless obvious non-cardiovascular causes could be identified. Cardiovascular death included death related to HF, acute myocardial infarction, fatal ventricular arrhythmia, sudden cardiac death, other cardiac death, stroke, intracranial hemorrhage, and other vascular death[3,16].

Sudden cardiac death was defined as unexplained death of a previously stable patient, including fatal ventricular arrhythmia, and cardiac arrest. Non-cardiovascular death included death related to malignancy, infections, renal failure, liver failure, respiratory failure, bleeding, and other causes. HF hospitalization was defined as hospitalization due to worsening of HF requiring intravenous drug therapy[3,16]. Outcome events were adjudicated by a clinical event committee.

Data collection at follow-up

The attending physicians or research assistants at each participating hospital collected data regarding clinical events that occurred during follow-up from the hospital charts or by contacting patients, their relatives, or their referring physicians with their consent. One-year clinical follow-up data with an allowance of 1-month were collected in October 2017.

Clinical event committee

Mitsuaki Kawato, Nishi Kobe Medical Center

Mamoru Toyofuku, Japanese Red Cross Wakayama Medical Center

Table S1. Patient characteristics in the entire study population.

Variables	Entire study population (N=2399)	Newly diagnosed infection (N=215)	Non-infection (N=2184)	P value	Total N
Clinical Characteristic					
Age, years	77.1 ± 12.3	80.0 ± 11.6	76.8 ± 12.3	<0.001	2399
Age ≥80 years*	1195 (49.8)	131 (60.9)	1064 (48.7)	<0.001	2399
Women*	1131 (47.1)	104 (48.4)	1027 (47.0)	0.71	2399
BMI, kg/m^2	23.0 ± 4.4	22.6 ± 4.1	23.0 ± 4.4	0.22	2297
BMI ≤22 kg/m^2*	1025 (44.6)	97 (48.7)	928 (44.2)	0.22	2297
Etiology				<0.001	2399
Associated with ACS*	129 (5.4)	30 (14.0)	99 (4.5)		2399
CAD not associated with ACS	633 (26.4)	56 (26.0)	577 (26.4)		2399
Hypertensive heart disease	580 (24.2)	52 (24.2)	528 (24.2)		2399
Valvular heart disease	466 (19.4)	35 (16.3)	431 (19.7)		2399
Cardiomyopathy	401 (16.7)	21 (9.8)	380 (17.4)		2399
Arrhythmia-related	124 (5.2)	11 (5.1)	113 (5.2)		2399
Others	66 (2.8)	10 (4.7)	56 (2.6)		2399
Medical history					
Prior hospitalization due to HF*	868 (36.8)	72 (34.0)	796 (37.1)	0.37	2358
Hypertension*	1706 (71.1)	162 (75.3)	1544 (70.7)	0.15	2399
Diabetes*	857 (35.7)	76 (35.3)	781 (35.8)	0.90	2399
Dyslipidemia	923 (38.5)	81 (37.7)	842 (38.6)	0.80	2399
Atrial fibrillation or flutter*	998 (41.6)	76 (35.3)	922 (42.2)	0.051	2399
Previous myocardial infarction*	534 (22.3)	51 (23.7)	483 (22.1)	0.59	2399
Previous PCI or CABG	597 (24.9)	58 (27.0)	539 (24.7)	0.46	2399
Prior device implantation				0.53	2399
Pacemaker	143 (6.0)	13 (6.0)	130 (6.0)		
ICD	45 (1.9)	3 (1.4)	42 (1.9)		
CRTP/CRTD	58 (2.4)	2 (0.9)	56 (2.6)		
Previous stroke*	347 (14.5)	32 (14.9)	315 (14.4)	0.85	2399
Current smoking	299 (12.7)	22 (10.4)	277 (12.9)	0.29	2360
Chronic kidney disease	1009 (42.1)	92 (42.8)	917 (42.0)	0.82	2399
Chronic lung disease*	266 (11.1)	31 (14.4)	235 (10.8)	0.10	2399

COPD	158 (6.6)	17 (7.9)	141 (6.5)	0.41	2399
Malignancy	340 (14.2)	30 (14.0)	310 (14.2)	0.92	2399
Cognitive dysfunction	384 (16.0)	52 (24.2)	332 (15.2)	<0.001	2399
Daily life activities				0.001	2379
Ambulatory*	1957 (82.3)	157 (73.4)	1800 (83.1)		
Use of wheelchair	349 (14.7)	49 (22.9)	300 (13.9)		
Bedridden	73 (3.1)	8 (3.7)	65 (3.0)		
Vital signs at presentation					
Temperature, ℃	36.4 ± 0.5	36.4 ± 0.5	36.4 ± 0.5	0.84	2275
Heart rate, beats/min	95.1 ± 27.8	96.2 ± 28.4	95.0 ± 27.7	0.51	2386
Heart rate <60 beats/min*	176 (7.4)	19 (8.8)	157 (7.2)	0.39	2386
Systolic BP, mmHg	149.6 ± 35.8	148.3 ± 37.2	149.7 ± 35.6	0.58	2388
Systolic BP <90 mm Hg*	66 (2.8)	11 (5.1)	55 (2.5)	0.03	2391
Rhythms at presentation				0.12	2399
Sinus Rhythm	1320 (55.0)	129 (60.0)	1191 (54.5)		
Atrial fibrillation or flutter	878 (36.6)	65 (30.2)	813 (37.2)		
Others	201 (8.4)	21 (9.8)	180 (8.2)		
NYHA functional class III or IV	2064 (86.4)	191 (89.3)	1873 (86.1)	0.20	2389
Echocardiography					
LVEF, %	45.4 ± 16.3	46.5 ± 16.6	45.3 ± 16.2	0.35	2328
LVEF classification				0.81	2388
HFrEF (LVEF <40%)*	964 (40.4)	84 (39.1)	880 (40.5)		
HFmrEF (LVEF 40%-49%)	430 (18.0)	37 (17.2)	393 (18.1)		
HFpEF (LVEF ≥50%)	994 (41.6)	94 (43.7)	900 (41.4)		
Laboratory findings on admission					
BNP, pg/mL	703.5 (405.6-1215.4)	702.7 (426.5-1195.5)	703.9 (404.6-1216.7)	0.90	2135
Serum creatinine, mg/dL	1.07 (0.82-1.55)	1.11 (0.81-1.68)	1.06 (0.82-1.53)	0.54	2395
eGFR, mL/min/1.73m^2	46.9 ± 23.2	45.6 ± 23.9	47.0 ± 23.1	0.38	2395
eGFR <30 mL/min/1.73m^2*	597 (24.9)	63 (29.3)	534 (24.5)	0.12	2395
Albumin, g/L	36.0 ± 4.5	34.9 ± 4.7	36.1 ± 4.5	<0.001	2321
Albumin <30 g/L*	180 (7.8)	24 (11.4)	156 (7.4)	0.04	2321
Sodium, mEq/L	139.6 ± 4.0	138.7 ± 5.0	139.7 ± 3.9	0.001	2389
Sodium <135 mEq/L*	219 (9.2)	32 (14.9)	187 (8.6)	0.002	2389

Hemoglobin, g/dL	11.8 ± 2.4	11.4 ± 2.5	11.8 ± 2.3	0.02	2394
Anemia*	1482 (61.9)	153 (71.2)	1329 (61.0)	0.003	2394
WBC, $\times 10^9$/L	7.36 ± 3.18	8.23 ± 3.83	7.28 ± 3.10	<0.001	2394
WBC > median value (6.70×10^9/L)	1168 (48.8)	120 (55.8)	1048 (48.1)	0.03	2394
CRP, mg/L	2.6 (1.1-5.0)	3.0 (1.5-6.0)	2.5 (1.1-5.0)	0.01	2305
CRP >3 mg/L	955 (41.4)	101 (47.4)	854 (40.8)	0.06	2305
Management on admission					
Respiratory management				<0.001	2399
None	743 (31.0)	44 (20.5)	699 (32.0)		
Oxygen inhalation	1296 (54.0)	126 (58.6)	1170 (53.6)		
NPPV	316 (13.2)	26 (12.1)	290 (13.3)		
Intubation	44 (1.8)	19 (8.8)	25 (1.1)		
Inotropes	84 (3.5)	18 (8.4)	66 (3.0)	<0.001	2399
Medication prior to admission					
ACEIs/ARBs	1142 (47.6)	98 (45.6)	1044 (47.8)	0.53	2399
β-blockers	990 (41.3)	68(31.6)	922 (42.2)	0.003	2399
MRAs	440 (18.3)	34 (15.8)	406 (18.6)	0.32	2399
Loop diuretics	1165 (48.6)	81 (37.7)	1084 (49.6)	<0.001	2399

Values are number (%) or mean ± standard deviation, or median (interquartile range). P values were calculated using the chi square test or Fisher's exact tests for categorical variables, and the Student's t test or Wilcoxon rank sum test for continuous variables.

* Risk-adjusting variables selected for the multivariable logistic regression models for in-hospital outcomes.

Renal dysfunction was defined as eGFR <30 mL/min/1.73 m^2. HF was classified according to LVEF as reduced LVEF (<40%) (HFrEF), mid-range LVEF (40-49%) (HFmrEF), or with preserved LVEF (≥50%) (HFpEF). Anemia was defined using the World Health Organization criteria (hemoglobin <12.0 g/dL in women and <13.0 g/dL in men).

ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB,

angiotensin II receptor blocker; BMI, body mass index; BNP, brain-type natriuretic peptide; BP, blood pressure; CABG, coronary artery bypass grafting; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NPPV, noninvasive positive pressure ventilation; NT-pro BNP, N-terminal-pro brain-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; WBC, white blood cell.

Table S2. Patient characteristics of the patients who were discharged alive.

Variables	Discharged alive (N=2295)	Newly diagnosed infection and discharged alive (N=180)	Non-infection and discharged alive (N=2115)	P value	Total N
Clinical Characteristic					
Age, years	76.9 ± 12.3	79.9 ± 11.8	76.7 ± 12.3	<0.001	2295
Age ≥80 years†	1128 (49.2)	110 (61.1)	1018 (48.1)	<0.001	2295
Women†	1077 (46.9)	89 (49.4)	988 (46.7)	0.48	2295
BMI, kg/m^2	23.0 ± 4.4	22.6 ± 4.1	23.1 ± 4.4	0.22	2204
BMI ≤22 kg/m^2†	973 (44.1)	83 (50.0)	890 (43.7)	0.11	2204
Etiology				<0.001	2295
Associated with ACS†	115 (5.0)	23 (12.8)	92 (4.4)		
CAD not associated with ACS	607 (26.4)	46 (25.6)	561 (26.5)		
Hypertensive heart disease	567 (24.7)	49 (27.2)	518 (24.5)		
Valvular heart disease	431 (18.8)	26 (14.4)	405 (19.1)		
Cardiomyopathy	388 (16.9)	16 (8.9)	372 (17.6)		
Arrhythmia-related	122 (5.3)	10 (5.6)	112 (5.3)		
Others	65 (2.8)	10 (5.6)	55 (2.6)		
Medical history					
Prior hospitalization due to HF†	822 (36.4)	56 (31.5)	766 (36.9)	0.15	2256
Hypertension†	1643 (71.6)	137 (76.1)	1506 (71.2)	0.16	2295
Diabetes†	828 (36.1)	66 (36.7)	762 (36.0)	0.86	2295
Dyslipidemia	896 (39.0)	69 (38.3)	827 (39.1)	0.84	2295
Atrial fibrillation or flutter†	958 (41.7)	64 (35.6)	894 (42.3)	0.08	2295
Previous myocardial infarction†	513 (22.4)	41 (22.8)	472 (22.3)	0.89	2295
Previous PCI or CABG	577 (25.1)	47 (26.1)	530 (25.1)	0.75	2295
Prior device implantation				0.77	2295
Pacemaker	134 (5.8)	12 (6.7)	122 (5.8)		
ICD	43 (1.9)	3 (1.7)	40 (1.9)		
CRTP/CRTD	52 (2.3)	2 (1.1)	50 (2.4)		
Previous stroke†	323 (14.1)	28 (15.6)	295 (13.9)	0.55	2295
Current smoking	294 (13.0)	17 (9.6)	277 (13.3)	0.15	2259
Chronic kidney disease	964 (42.0)	76 (42.2)	888 (42.0)	0.95	2295

Chronic lung disease†	249 (10.9)	25 (13.9)	224 (10.6)	0.17	2295
COPD	150 (6.5)	13 (7.2)	137 (6.5)	0.70	2295
Malignancy	325 (14.2)	22 (12.2)	303 (14.3)	0.44	2295
Cognitive dysfunction	352 (15.3)	42 (23.3)	310 (14.7)	0.002	2295
Daily life activities				<0.001	2276
Ambulatory†	1892 (83.1)	130 (72.6)	1762 (84.0)		
Use of wheelchair	321 (14.1)	43 (24.0)	278 (13.3)		
Bedridden	63 (2.8)	6 (3.4)	57 (2.7)		
Vital signs at presentation					
Temperature, ℃	36.4 ± 0.5	36.4 ± 0.5	36.4 ± 0.5	0.41	2179
Heart rate, beats/min	95.1 ± 27.8	96.9 ± 28.6	94.9 ± 27.7	0.36	2283
Heart rate <60 beats/min†	172 (7.5)	16 (8.9)	156 (7.4)	0.47	2283
Systolic BP, mmHg	150.3 ± 35.6	151.4 ± 37.1	150.2 ± 35.4	0.67	2284
Systolic BP <90 mm Hg†	55 (2.4)	9 (5.0)	46 (2.2)	0.02	2287
Rhythms at presentation				0.26	2295
Sinus Rhythm	1255 (54.7)	105 (58.3)	1150 (54.4)		
Atrial fibrillation or flutter	850 (37.0)	57 (31.7)	793 (37.5)		
Others	190 (8.3)	18 (10.0)	172 (8.1)		
NYHA functional class III or IV	1965 (86.0)	158 (87.8)	1807 (85.8)	0.46	2286
Echocardiography					
LVEF, %	45.6 ± 16.2	47.1 ± 16.4	45.5 ± 16.2	0.21	2238
LVEF classification				0.41	2285
HFrEF (LVEF<40%)†	907 (39.7)	64 (35.6)	843 (40.1)		
HFmrEF (LVEF40%-49%)	413 (18.1)	32 (17.8)	381 (18.1)		
HFpEF (LVEF≥50%)	965 (42.2)	84 (46.7)	881 (41.9)		
Laboratory findings on admission					
BNP, pg/mL	695.7 (405.0-1194.1)	680.2 (416.9-1134.4)	698.4 (404.8-1208.1)	0.70	2040
Serum creatinine, mg/dL	1.06 (0.81-1.52)	1.05 (0.76-1.52)	1.06 (0.81-1.52)	0.61	2291
eGFR, mL/min/1.73m^2	47.4 ± 23.2	47.5 ± 24.7	47.4 ± 23.1	0.93	2291
eGFR <30 mL/min/1.73m^2†	551 (24.1)	45 (25.0)	506 (24.0)	0.76	2291
Albumin, g/L	36.0 ± 4.5	34.9 ± 4.8	36.1 ± 4.5	<0.001	2221
Albumin <30 g/L†	171 (7.7)	21 (11.9)	150 (7.3)	0.03	2221
Sodium, mEq/L	139.6 ± 3.9	139.0 ± 5.0	139.7 ± 3.8	0.03	2285

Sodium <135 mEq/L†	199 (8.7)	23 (12.8)	176 (8.4)	0.04	2285
Hemoglobin, g/dL	11.8 ± 2.4	11.4 ± 2.5	11.8 ± 2.3	0.03	2290
Anemia, (%)†	1411 (61.6)	129 (71.7)	1282 (60.8)	0.004	2290
WBC, $\times 10^9$/L	7.36 ± 3.17	8.23 ± 3.81	7.29 ± 3.10	<0.001	2290
CRP, mg/L	2.6 (1.1-5.0)	2.7 (1.3-6.0)	2.5 (1.1-5.0)	0.09	2205
CRP >3 mg/L	910 (41.3)	82 (45.8)	828 (40.9)	0.20	2205
Management on admission					
Respiratory management				<0.001	2295
None	720 (31.4)	38 (21.1)	682 (32.2)		
Oxygen inhalation	1229 (53.6)	102 (56.7)	1127 (53.3)		
NPPV	306 (13.3)	21 (11.7)	285 (13.5)		
Intubation	40 (1.7)	19 (10.6)	21 (1.0)		
Inotropes	74 (3.2)	16 (8.9)	58 (2.7)	<0.001	2295
Medication prior to admission					
ACEIs/ARBs	1093 (47.6)	80 (44.4)	1013 (47.9)	0.37	2295
β-blockers	966 (42.1)	59 (32.8)	907 (42.9)	0.008	2295
MRAs	414 (18.0)	29 (16.1)	385 (18.2)	0.48	2295
Loop diuretics	1107 (48.2)	63 (35.0)	1044 (49.4)	<0.001	2295
Medication at discharge					
ACEIs/ARBs†	1391 (60.6)	97 (53.9)	1294 (61.2)	0.055	2295
β-blockers†	1587 (69.2)	119 (66.1)	1468 (69.4)	0.36	2295
MRAs	1057 (46.1)	80 (44.4)	977 (46.2)	0.65	2295
Loop diuretics	1870 (81.5)	137 (76.1)	1733 (81.9)	0.053	2295
In-hospital events					
Worsening renal function	734 (32.5)	97 (53.9)	637 (30.7)	<0.001	2256
Worsening heart failure	320 (13.9)	54 (30.0)	266 (12.6)	<0.001	2295
Length of hospital stay (days)	15 (11-22)	23 (16-35)	15 (11-21)	<0.001	2295

Values are number (%) or mean ± standard deviation, or median (interquartile range). P values were calculated using the chi square test or Fisher's exact tests for categorical variables, and the Student's t test or Wilcoxon rank sum test for continuous variables.

† Risk-adjusting variables selected for the Cox proportional hazard models.

Renal dysfunction was defined as eGFR <30 mL/min/1.73 m^2. HF was classified according to LVEF as reduced LVEF (<40%) (HFrEF), mid-range LVEF (40-49%)

(HFmrEF), or with preserved LVEF (≥50%) (HFpEF). Anemia was defined using the World Health Organization criteria (hemoglobin <12.0 g/dL in women and <13.0 g/dL in men).

ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, brain-type natriuretic peptide; BP, blood pressure; CABG, coronary artery bypass grafting; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NPPV, noninvasive positive pressure ventilation; NT-pro BNP, N-terminal-pro brain-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; WBC, white blood cell.

Table S3. Sensitivity analysis of factors associated with newly diagnosed infection by logistic regression analysis.

Variables	Unadjusted OR (95%CI)	P value	Adjusted OR (95%CI)	P value
Age (per year increase)	1.02 (1.01-1.04)	<0.001	1.02 (1.01-1.04)	0.003
Associated with ACS	3.42 (2.21-5.28)	<0.001	2.85 (1.73-4.71)	<0.001
Absence of atrial fibrillation or flutter	1.34 (0.998-1.79)	0.052	1.11 (0.80-1.55)	0.54
Cognitive dysfunction	1.78 (1.28-2.48)	<0.001	1.20 (0.80-1.79)	0.37
Non-ambulatory status	1.79 (1.30-2.47)	<0.001	1.53 (1.04-2.26)	0.03
Albumin (per g/L decrease)	1.06 (1.02-1.09)	<0.001	1.03 (0.996-1.07)	0.08
Sodium (per mEq/L decrease)	1.05 (1.02-1.09)	0.002	1.04 (1.01-1.08)	0.02
Hemoglobin (per g/dL decrease)	1.07 (1.01-1.14)	0.02	1.08 (0.999-1.16)	0.054
WBC (per 10^9/L increase)	1.08 (1.04-1.12)	<0.001	1.04 (0.99-1.09)	0.13
CRP (per mg/L increase)	1.07 (1.02-1.13)	0.006	1.07 (1.01-1.13)	0.02
Intubation	8.37 (4.53-15.47)	<0.001	6.26 (2.98-13.13)	<0.001
Inotropes	2.93 (1.71-5.04)	<0.001	1.54 (0.78-3.05)	0.21
Patients who were not on β-blockers as an outpatient	1.58 (1.17-2.13)	0.003	1.20 (0.85-1.68)	0.30
Patients who were not on loop diuretics as an outpatient	1.63 (1.22-2.18)	<0.001	1.54 (1.09-2.16)	0.01

ACS, acute coronary syndrome; CI, confidence interval; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; OR, odds ratio; WBC, white blood cell.

Table S4. Sensitivity analysis of in-hospital outcomes.

Variables	Adjusted OR (95% CI)	P value
All-cause death	7.06 (3.98-12.53)	<0.001
Cardiovascular death	5.31 (2.77-10.17)	<0.001
Non-cardiovascular death	13.27 (4.34-40.54)	<0.001

OR indicated risk of newly diagnosed infection relative to non-infection for all-cause death, cardiovascular death, and non-cardiovascular death during the index hospitalization.

Risk-adjusting variables selected for the multivariable logistic regression model: age, BMI, systolic blood pressure, heart rate, LVEF, eGFR, serum albumin, serum sodium, and hemoglobin as the continuous variable. sex, etiology of HF hospitalization associated with ACS, previous HF hospitalization, hypertension, diabetes, atrial fibrillation or flutter, previous myocardial infarction, previous stroke, chronic lung disease and ambulatory status as the categorical variable.

CI, confidence interval; OR, odds ratio

Table S5. Sensitivity analysis of outcomes after discharge.

Variables	Adjusted HR (95% CI)	P value
All-cause death	1.43 (1.03-1.99)	0.03
Cardiovascular death	1.63 (1.09-2.45)	0.02
Non-cardiovascular death	1.16 (0.66-2.02)	0.60
Heart failure hospitalization	0.77 (0.54-1.10)	0.15

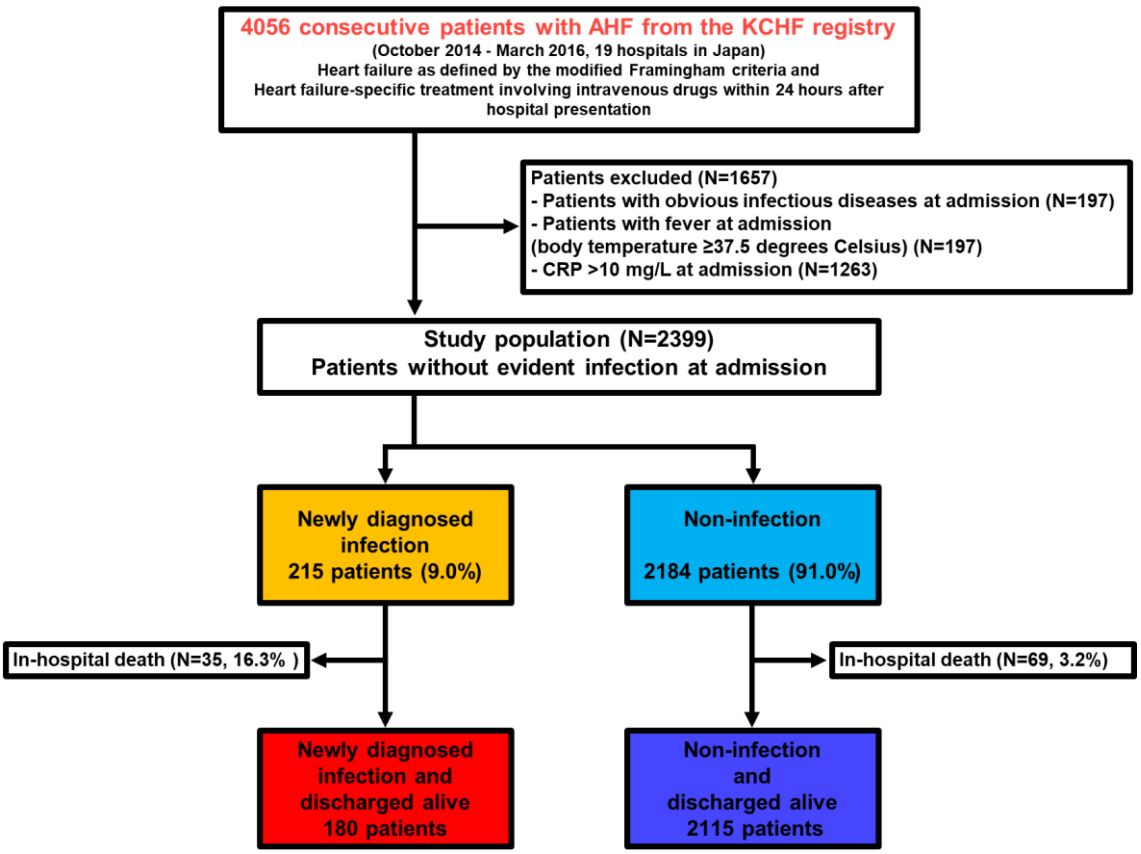
HR indicated risk of newly diagnosed infection relative to non-infection for all-cause death, cardiovascular death, non-cardiovascular death, and heart failure hospitalization after discharge.

Risk-adjusting variables selected for the multivariable Cox proportional hazard model and Fine-Gray sub-distribution hazard model: age, BMI, systolic blood pressure, heart rate, LVEF, eGFR, serum albumin, serum sodium, and hemoglobin as the continuous variable. sex, etiology of HF hospitalization associated with ACS, previous HF hospitalization, hypertension, diabetes, atrial fibrillation or flutter, previous myocardial infarction, previous stroke, chronic lung disease, ambulatory status, prescription of

angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) at discharge and prescription of β-blockers at discharge as the categorical variable.

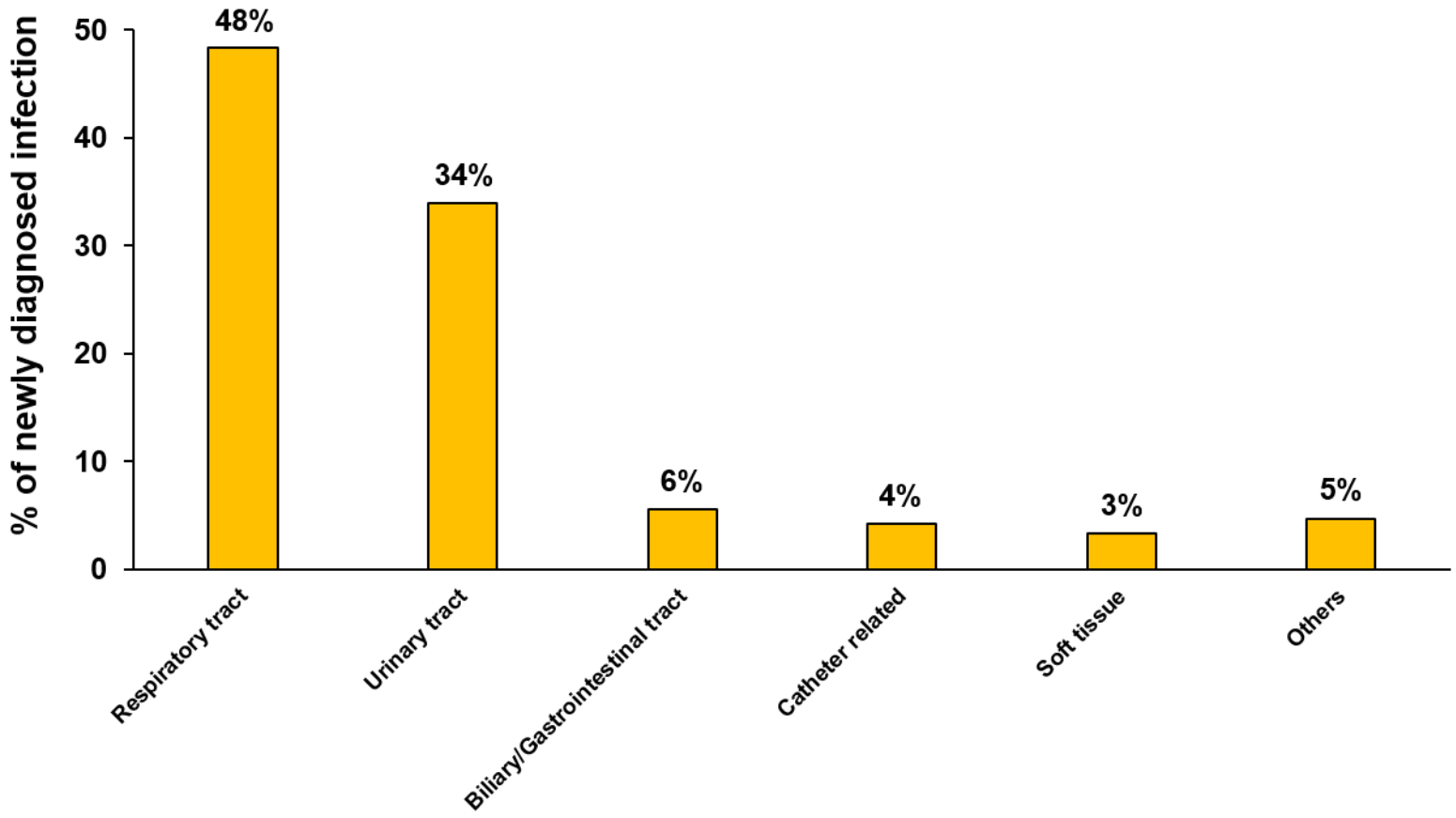
CI, confidence interval; HR, hazard ratio

Figure S1. Study flowchart



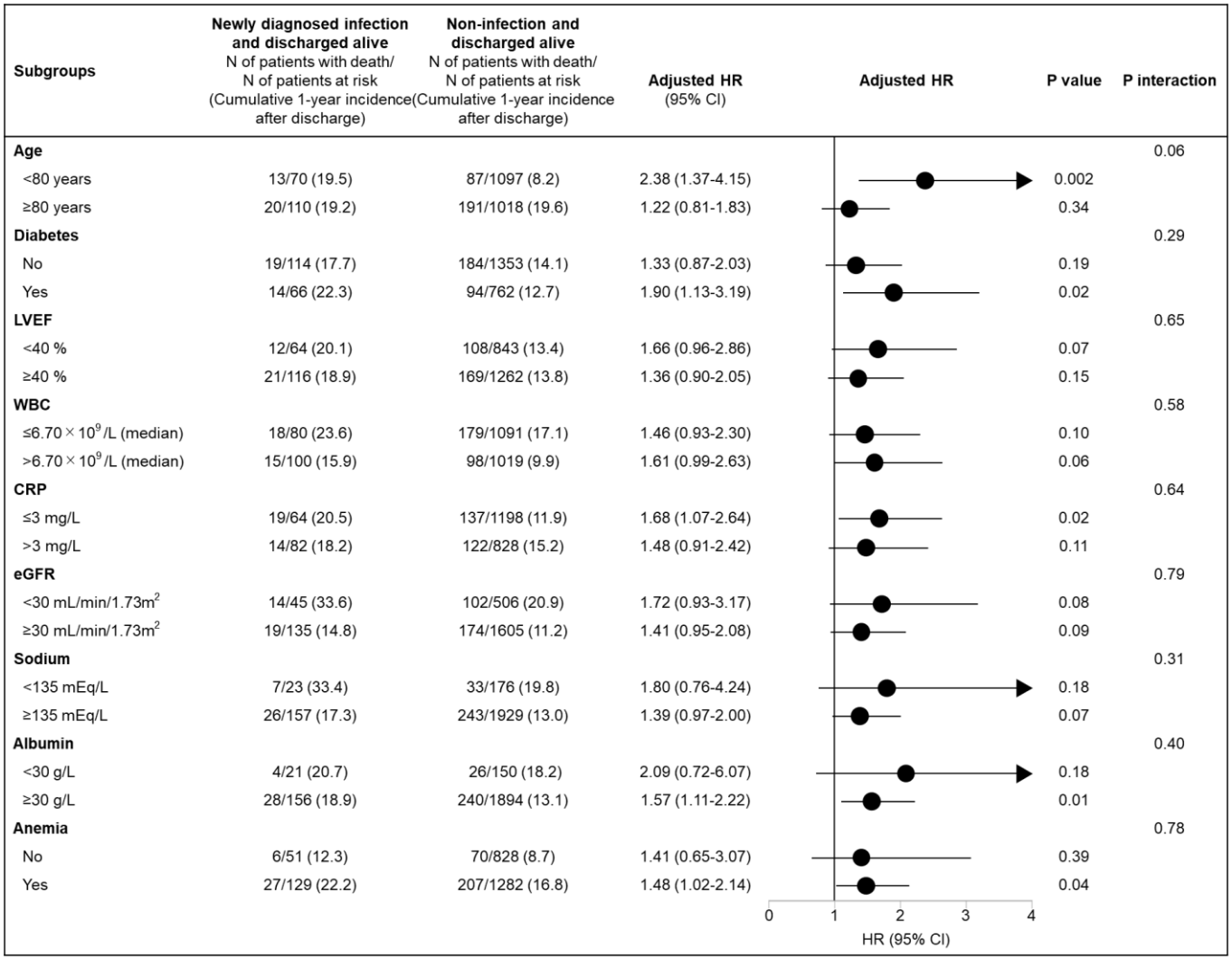
AHF, acute heart failure; CRP, C-reactive protein; KCHF, Kyoto Congestive Heart Failure

Figure S2. Classification of the sources of infection.



Others: bacteremia (N=5); infectious endocarditis (N=1), mediastinitis (N=2); shingles (N=1); suppurated thrombophlebitis (N=1)

Figure S3. Subgroup analyses.



Outcome measure in subgroup analysis was all-cause death.

CI, confidence interval; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; N, number; WBC, white blood cell.