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ORIGINAL ARTICLE

Association of congestion with worsening renal function in acute decompensated heart failure according to age

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Abstract

Aims Acute decompensated heart failure (ADHF) is a frequent cause of hospitalization for patients with heart disease, and ADHF patients are at high risk of heart failure (HF) re-hospitalization. Residual congestion at discharge is also a strong predictor of poor outcomes and re-hospitalization for ADHF patients. However, the impact of residual congestion at discharge on worsening renal function (WRF) in both high-aged and older patients remains uncertain because previous studies of WRF in ADHF patients were conducted for older patients. We therefore designed and conducted a retrospective, population-based study using the Kobe University Heart Failure Registry in Awaji Medical Center (KUNIUMI) Registry to investigate the association of residual congestion at discharge with WRF in ADHF patients according to age.

Methods and results We studied 966 hospitalized ADHF patients with a mean age of 80.2 ± 11.4 years from among 1971 listed in the KUNIUMI Registry. WRF was defined as an increase of ≥0.3 mg/dL in the serum creatinine level during the hospital stay compared with the value on admission. The primary endpoint was defined as cardiovascular death or HF re-hospitalization after discharge over a mean follow-up period of 2.0 ± 0.1 years. The primary endpoint was recorded for 369 patients (38.2%). As expected, patients with both WRF and residual congestion at discharge had significantly less favourable outcomes compared with those without one of them, and patients without either of these two characteristics had the most favourable outcomes, whereas those with residual congestion and with WRF had the least favourable outcomes. Moreover, WRF was significantly associated with worse outcomes for high-aged patients ≥80 years old, but not for those <80 years old if decongested. Multivariable Cox regression analysis showed that both residual congestion at discharge and WRF were the independent predictors of outcomes for high-aged patients, but residual congestion at discharge, not WRF, was the independent predictor of outcomes for older patients.

Conclusions Association of residual congestion at discharge with WRF for hospitalized ADHF patients can differ according to age. Our findings showed the importance of WRF and residual congestion at discharge for high-aged ADHF patients and of aggressive diuresis to alleviate congestion for older ADHF patients for better management of such patients in a rapidly ageing society.

Keywords Acute decompensated heart failure; Congestion; Worsening renal function; High-aged

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Introduction

Acute decompensated heart failure (ADHF) is a frequent cause of hospitalization for patients with heart disease, and ADHF patients are at high risk of heart failure (HF) of up to 30% at 3 months[1] requiring re-hospitalization and have worse short-term and long-term survival with mortality as high as 46% at 1 year.[2,3] Excessive fluid removal for decongestion can lead to acute decline in kidney function of patients with ADHF during hospitalization, known as worsening renal function (WRF), and constitutes an adverse prognostic factor for such patients.[4–6] WRF developed in 23% of hospitalized ADHF patients, who had 1.62 times higher odds of dying at 6 months, as well as longer hospital stay and higher re-admission rates.[7] Furthermore, the prevalence of WRF and the impact of prognosis on WRF were similar in chronic HF patients.[7] Other predictors of developing WRF are baseline impaired renal function, low left ventricular (LV) ejection fraction (LVEF), and older age.[3,8] In addition, residual congestion at discharge is a strong predictor of poor outcomes and re-admission for ADHF patients.[9–11] Nevertheless, numerous ADHF patients are discharged with residual congestion.[12–15] Both WRF and residual congestion at discharge were associated with poor outcomes for ADHF patients, but the impact of residual congestion at discharge on WRF in both high-aged and older ADHF patients remains uncertain because most of the previous studies of WRF in ADHF patients regarding WRF were conducted for older patients with a mean age of 65–75 years.[16]

Therefore, we designed and conducted a retrospective, population-based study using the Kobe University Heart Failure Registry for the Awaji Medical Center (KUNIUMI) Registry acute cohort in order to investigate the association of residual congestion at discharge with WRF for ADHF patients according to age.

Methods

Study design

This study is part of the KUNIUMI Registry acute cohort, which was previously described in detail.[17] Briefly, the KUNIUMI Registry acute cohort is a population-based registry of acute HF in Awaji Island, one of the largest islands in Japan. Awaji Island is home to one of the oldest populations in Japan, with 34.2% of the population 65 years old or older in 2015. In addition, there is a characteristically low migration rate with a relatively stable population, so the more consistent incidence rates and follow-up data in this study can be compared with previous registry data. This study was approved by the ethics committee of Awaji Medical Center (No. 20-11) and was conducted in accordance with the Declaration of Helsinki.

Study population and eligibility criteria

A total of 1971 consecutive hospitalized ADHF patients who met the Framingham criteria[18] and residing on Awaji Island between April 2013 and March 2020 were retrospectively enrolled in this study (*Figure 1*). From among 1971 consecutive hospitalized ADHF patients, we excluded 471 with recurrent HF hospitalization, 90 with in-hospital death, 65 with transition to haemodialysis, 350 with insufficient date, and 29 with inaccessible follow-up. The final enrolment thus consisted of 966 first-time hospitalized ADHF patients. In-hospital care and post-discharge care for HF were based on the procedures used by the attending physicians, including senior cardiologists. Echocardiography was performed with commercially available ultrasound systems, and standard echocardiographic measurements were obtained in accordance with the current guidelines of the European Association of Cardiovascular Imaging.[19]

Definition of WRF

WRF was defined as an increase of $\geq$0.3 mg/dL in the serum creatinine level during the hospital stay compared with the value on admission.[4,6,20,21]

Definition of residual decongestion at discharge

The presence or absence of residual congestion was determined at the time of discharge by several senior cardiologists, and its presence was based on physical examination findings such as orthopnoea, pulmonary rales and peripheral oedema,[11] a reduction in B-type natriuretic peptide (BNP) of $<$30% compared with the value at admission,[22] and the presence of pleural effusions detected on chest X-rays.[23]

Definition of primary endpoint

The primary endpoint was defined as cardiovascular events, namely, cardiovascular death and re-hospitalization for HF after discharge over a mean follow-up period of 2.0 ± 0.1 years.

Statistical analysis

Continuous variables were expressed as mean values with their standard deviations for normally distributed data and as medians with their interquartile range for non-normally distributed data. Categorical variables were expressed as

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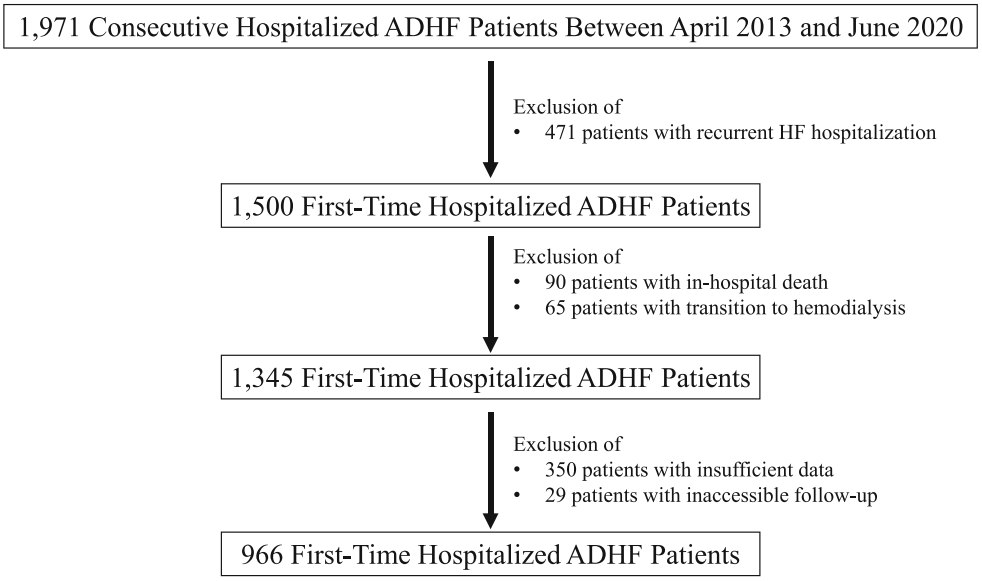
Figure 1 Flowchart of patients recruited for this study. ADHF, acute decompensated heart failure; HF, heart failure.



frequencies and percentages. The parameters of the two subgroups were compared using Student's t-test or the Mann–Whitney *U* test depending on data distribution. Proportional differences were evaluated using Fisher's exact test. Survival curves of freedom from all-cause death and HF re-hospitalization were determined with the Kaplan–Meier method, and cumulative event rates were compared by using the log-rank test. The associations of parameters with cardiovascular death were identified by means of a Cox proportional hazards model for univariate and multivariate analyses. Variables with a univariate value of $P < 0.05$ were incorporated into the stepwise selection. For all steps, a P value of <0.05 was considered statistically significant. All analyses were performed using a commercially available software (MedCalc software version 19.0.7; MedCalc Software, Mariakerke, Belgium).

Results

Patient characteristics

The baseline characteristics of the 966 ADHF patients are summarized in *Table 1*. Their mean age was 80.2 ± 11.4 years, and 520 patients (53.8%) were male. Of these patients, 38 (3.9%) were New York Heart Association class II, 202 (20.9%) class III, and 725 (75.1%) class IV. In accordance with the universal definition and classification of HF,[24] 312 patients (32.3%) were diagnosed with HF with reduced ejection fraction, 189 (19.6%) with HF with mildly reduced ejection fraction, and 462 (47.8%) with HF with preserved ejection fraction, and the HF phenotype of three (0.3%) was unknown. The percentage distribution of doses of guideline recommended cardioprotective drugs for patients with HFrEF[25] is shown in *Table S1*.

Prognostic impact of residual congestion on ADHF patients

Residual congestion at discharge was detected in 468 patients (48.4%). A comparison of baseline clinical characteristics of patients with and without residual congestion at discharge is shown in *Table 2A*.

The primary endpoint was recorded for 369 patients (38.2%). As expected, patients with residual congestion at discharge had significantly less favourable outcomes compared with those without it, as shown in *Figure 2A* [hazard ratio (HR), 2.34; 95% confidence interval (CI), 1.90–2.89; $P < 0.01$].

Prognostic impact of WRF on ADHF patients

WRF was diagnosed in 320 patients (33.1%) during the mean hospital stay of 23.9 ± 18.7 days, and the mean time to onset of WRF was 12.7 ± 11.1 days. A comparison of baseline characteristics of patients with and without WRF is shown in *Table 2B*. Similarly, patients with WRF had significantly less favourable outcomes compared with those without, as shown in *Figure 2B* (HR, 1.60; 95% CI, 1.27–2.00; $P < 0.01$).

Next, the patients were subdivided into four groups, based on the presence or absence of residual congestion at discharge and WRF during hospitalization (*Figure 3*). Patients without either residual congestion at discharge or WRF had

Table 1 Baseline characteristics of patients

	Overall patients (N = 966)	High-aged patients (≥80 years) (N = 609)	Older patients (<80 years) (N = 357)	P value (high-aged vs. older)
Clinical characteristics				
Age, years	80.2 ± 11.4	87.2 ± 4.5	68.4 ± 9.8	<0.01
Gender (male), *n* (%)	520 (53.8)	278 (45.6)	242 (67.8)	<0.01
Body mass index, kg/m^2	21.2 ± 4.4	20.4 ± 3.7	22.6 ± 5.1	<0.01
NYHA class, *n* (%)				
II	38 (3.9)	22 (3.6)	16 (4.5)	0.50
III	202 (20.9)	124 (20.4)	78 (21.8)	0.57
IV	725 (75.1)	463 (76.0)	262 (73.4)	0.40
HF classification, n (%)				
HFrEF	312 (32.3)	151 (24.5)	161 (45.1)	<0.01
HFmrEF	189 (19.6)	127 (20.9)	62 (17.4)	0.18
HFpEF	462 (47.8)	328 (53.9)	134 (37.5)	<0.01
Unknown	3 (0.3)	3 (0.5)	0 (0)	0.19
Haemodynamics on admission				
Systolic blood pressure, mmHg	144 ± 32	145 ± 31	143 ± 34	0.58
Systolic blood pressure < 90 mmHg, *n* (%)	27 (2.8)	16 (2.6)	11 (3.1)	0.58
Heart rate, beats/min	94 ± 29	89 ± 32	103 ± 26	<0.01
Cardiogenic shock, n (%)	20 (2.1)	12 (2.0)	8 (2.2)	0.90
Co-morbidities, *n* (%)				
Hypertension	623 (64.6)	404 (66.3)	219 (61.3)	0.13
Diabetes mellitus	267 (27.8)	129 (21.2)	138 (38.7)	<0.01
Atrial fibrillation	517 (53.5)	347 (57.0)	170 (47.6)	<0.01
Ischaemic heart disease	260 (26.9)	144 (23.6)	116 (32.5)	<0.01
Valvular disease	256 (26.5)	197 (32.2)	59 (16.5)	<0.01
Lung disease	162 (16.8)	106 (17.4)	56 (15.7)	0.50
Prior history of heart failure	69 (7.1)	38 (6.2)	31 (8.7)	0.16
Blood examination at discharge				
Haemoglobin, mg/dL	11.6 ± 2.2	11.1 ± 1.8	12.5 ± 2.4	<0.01
Albumin, mg/dL	3.1 ± 0.5	3.0 ± 0.5	3.2 ± 0.5	<0.01
Blood urea nitrogen, mg/dL	26.7 ± 16.3	28.7 ± 17.8	23.2 ± 12.7	<0.01
Creatinine, mg/dL	1.3 ± 1.0	1.3 ± 0.9	1.3 ± 1.2	0.37
eGFR, mL/min/1.73 m^2	49.3 ± 23.3	45.9 ± 22.1	55.2 ± 24.2	<0.01
Brain natriuretic peptide, pg/mL	271 (249–295)	285 (263–309)	243 (202–297)	0.53
Treatments at discharge, *n* (%)				
ACE-Is/ARBs	697 (72.4)	427 (70.1)	270 (75.6)	0.05
β-Blockers	744 (77.3)	438 (71.9)	306 (85.7)	<0.01
MRAs	451 (46.9)	265 (43.5)	186 (52.1)	0.01
Loop diuretics	757 (78.6)	501 (82.3)	256 (71.7)	<0.01
	24.8 ± 18.0	25.6 ± 20.2	24.3 ± 16.7	0.35
Dose of loop diuretics, mg				
Tolvaptan	228 (23.7)	162 (26.6)	66 (18.5)	<0.01
Echocardiographic data				
LVEF, %	47.0 ± 13.7	49.5 ± 12.9	42.7 ± 13.9	<0.01
Left atrial diameter, mm	43.6 ± 8.3	43.5 ± 8.2	43.9 ± 8.5	0.46
Residual congestion at discharge, *n* (%)	468 (48.4)	339 (55.7)	129 (36.1)	<0.01
Worsening renal function, *n* (%)	320 (33.1)	219 (36.0)	101 (28.2)	0.02

ACE-Is, angiotensin converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; BMI, body mass index; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly-reduced ejection fraction; HFrEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; MRAs, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; sBP, systolic blood pressure.
Data are mean ± SD for normally distributed data and median and interquartile range for non-normally distributed data, or *n* (%).

the most favourable outcomes, whereas those with both had the least favourable outcomes.

Prognostic impact of WRF on ADHF patients by age

Because the mean age in this study was 80.2 ± 11.4 years, patients were divided into two groups, a high-aged group aged ≥80 years and an older group aged <80 years (*Table 1*). In addition, patients in the high-aged group had significantly less favourable outcomes than those in the older group as shown in *Figure S1* (HR, 1.78; 95% CI, 1.44–2.19; $P < 0.01$).

Tables 3 and 4 shows the results of univariable and multivariable Cox regression analyses for predicting the primary endpoint for high-aged and older patients. The findings of multivariable Cox regression analysis for high-aged patients

Table 2A Baseline characteristics of patients with and without residual congestion at discharge

	Patients *with* residual congestion at discharge (N = 468)	Patients *without* residual congestion at discharge (N = 498)	P value
Clinical characteristics			
Age, years	83.0 ± 9.4	77.7 ± 12.6	<0.01
Gender (female), *n* (%)	234 (50.0)	212 (42.6)	0.02
Body mass index, kg/m^2	21.3 ± 4.5	21.1 ± 4.4	0.49
NYHA class, *n* (%)			
II	14 (3.0)	24 (4.8)	0.14
III	98 (20.9)	104 (21.0)	0.99
IV	356 (76.1)	369 (74.1)	0.51
HF classification			
HFrEF	132 (28.2)	180 (36.1)	0.01
HFmrEF	95 (20.3)	94 (18.9)	0.57
HFpEF	239 (51.1)	223 (44.8)	0.05
Unknown	2(0.4)	1 (0.2)	0.53
Co-morbidities, *n* (%)			
Hypertension	313 (66.9)	310 (62.2)	0.14
Diabetes mellitus	118 (25.2)	149 (30.0)	0.09
Atrial fibrillation	266 (56.8)	251 (50.4)	0.05
Ischaemic heart disease	130 (27.8)	130 (26.1)	0.56
Valvular disease	142 (30.3)	114 (22.3)	0.01
Lung disease	84 (17.9)	78 (15.7)	0.35
Blood examination at discharge			
Haemoglobin, mg/dL	11.1 ± 1.9	12.1 ± 2.2	<0.01
Albumin, mg/dL	3.0 ± 0.5	3.2 ± 0.5	<0.01
Blood urea nitrogen, mg/dL	28.3 ± 18.8	25.2 ± 13.5	<0.01
Creatinine, mg/dL	1.4 ± 1.1	1.2 ± 1.0	0.03
eGFR, mL/min/1.73 m^2	46.5 ± 24.2	52.0 ± 22.2	<0.01
Brain natriuretic peptide, pg/mL	332 (301–370)	217 (194–245)	<0.01
Medications at discharge, *n* (%)			
ACE-Is/ARBs	333 (71.2)	364 (73.1)	0.54
β-Blockers	352 (75.2)	392 (78.7)	0.22
MRAs	206 (44.0)	245 (49.2)	0.11
Loop diuretics	385 (82.2)	372 (74.7)	<0.01
Tolvaptan	132 (28.2)	96 (19.2)	<0.01
Echocardiographic data			
LVEF, %	48.3 ± 13.4	45.7 ± 13.8	<0.01
Left atrial diameter, mm	43.9 ± 8.3	43.4 ± 8.3	0.34

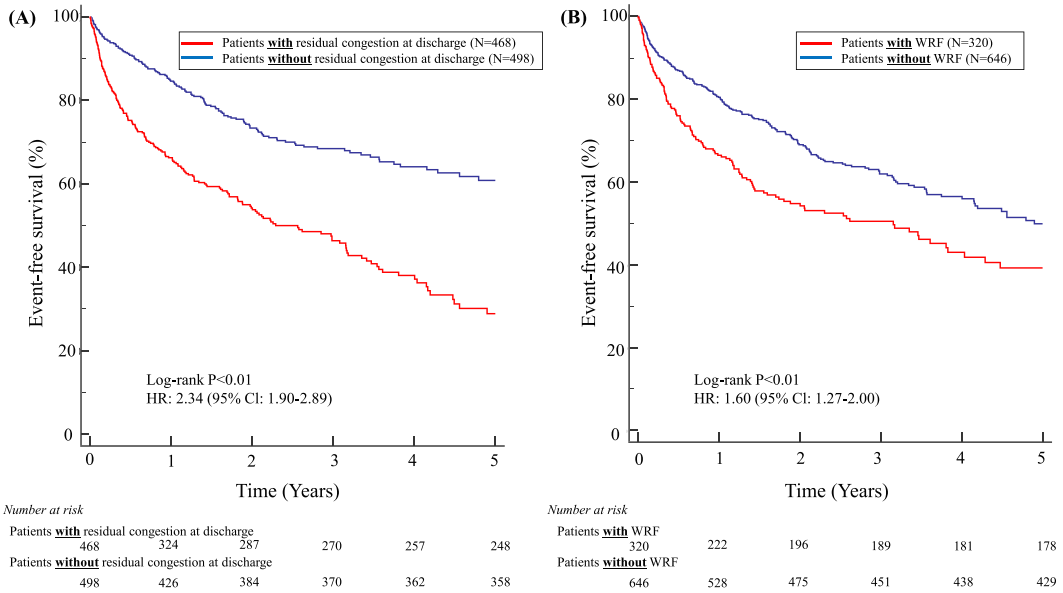
showed that both residual congestion at discharge and WRF were independent predictors of the primary endpoint (residual congestion at discharge; HR, 2.02; 95% CI, 1.34–3.05; $P < 0.01$, WRF; HR, 1.70; 95% CI, 1.15–2.50; $P = 0.01$). On the other hand, the findings of multivariable Cox regression analyses for predicting the primary endpoint for older patients showed that residual congestion at discharge was the independent predictor of the primary endpoint (HR, 2.01; 95% CI, 1.07–3.80; $P = 0.03$), but WRF was not. *Table S2* shows the results of univariable and multivariable Cox regression analyses for predicting the primary endpoint for all patients.

Next, we investigated the association of WRF with primary endpoint for ADHF patients without residual congestion at discharge. In the high-aged group, patients with WRF had significantly less favourable outcomes compared with those without it (HR, 1.74; 95% CI, 1.10–2.77; $P = 0.02$; *Figure 4A*). In the older group without residual congestion at discharge, however, the outcomes for patients with WRF were similar to those for patients without it (HR, 1.45; 95% CI, 0.78–2.69; $P = 0.24$; *Figure 4B*).

Discussion

The findings of this study demonstrate that the presence of WRF and residual congestion at discharge is an independent predictor of less favourable long-term outcomes after hospital discharge for ADHF patients. In addition, WRF was found to be significantly associated with less favourable outcomes for high-aged patients ≥80 years old, but not for older patients <80 years old if the latter are decongested. Multivariable Cox regression analysis showed that both residual congestion at discharge and WRF are independent predictors of long-term outcomes for high-aged patients, but residual congestion at discharge, not WRF, was the independent predictor of long-term outcomes for older patients.

Figure 2 (A) Kaplan–Meier curve representing the primary endpoint, showing that patients with residual congestion at discharge had significantly less favourable outcomes than those without it. (B) Kaplan–Meier curve indicating the primary endpoint, showing that patients with worsening renal function (WRF) had significantly unfavourable outcomes compared with those without.



WRF in ADHF patients

ADHF is the prognostic relevant cause of hospitalization worldwide. It is associated with high in-hospital and post-discharge mortality and re-hospitalization rates. Cardiac and kidney dysfunction is a common finding in ADHF patients,[26] and primary disorder of one of these two organs often results in secondary dysfunction of or injury to the other, representing the pathophysiological basis of the so-called cardio-renal syndrome.[26] WRF occurs frequently among hospitalized HF patients and is associated with significantly worse outcomes.[4–6] The incidence of WRF in HF patients was reported to be 23% and was found to be associated with unfavourable outcomes.[16] Gottlieb *et al*. demonstrated that any detectable increase in serum creatinine, regardless of peak creatinine values, was associated with increased mortality and prolonged hospital stay for hospitalized HF patients.[27] Lazaros *et al*. found that WRF emerged as a powerful independent predictor of 1-year mortality for 447 patients with acute myocardial infarction, independently from baseline renal function levels.[28] Its multiple pathways play a role in the aetiology of WRF in HF, including renal congestion, restricted cardiac output, neurohormonal activation, and immunological feedback pathways, whereas intrinsic chronic kidney disease is related to shared risk factors.[29] Congestion in hospitalized ADHF patients results in increased cardiac filling pressures, so decongestion is the most important for in-hospital care of ADHF patients. Guidelines strongly recommend the use of loop diuretics for decongestion,[30] but it is estimated that this use commonly results in a reduction in the glomerular filtration rate so that aggressive guideline-directed medical therapy may result in WRF, thus presenting attending physicians with a dilemma.

Residual congestion in ADHF patients

Residual congestion at discharge is a strong predictor of poor outcomes and re-admission for ADHF patients,[9–11] and our findings were thus consistent with those of previous studies. Nevertheless, it has been reported that many ADHF patients are discharged with residual congestion.[12–15] Felker *et al*. reported that only 15% of ADHF patients were assessed by their attending physician to be euvolemic after decongestive therapy.[15] Furthermore, outcomes remain poor even for ADHF patients with limited clinical signs or symptoms of congestion at discharge.[31] Residual congestion at discharge was also found to be associated with WRF in ADHF patients, and both have been consistently shown to be among the most important prognostic variables.[9–11] We were able to demonstrate that both residual congestion at discharge and WRF were associated with poor outcomes for ADHF patients, and that ADHF patients with residual congestion at discharge and with WRF had the worst outcomes. Metra *et al*. reported that WRF alone had no prognostic value for 599 consecutive ADHF patients with a mean age of 69.1 ± 10.8 years, but that patients with WRF and residual congestion at discharge had an increased risk of death or re-hospitalization, and that the

Table 2B Baseline characteristics of patients with and without WRF

	Patients *with* WRF (N = 320)	Patients *without* WRF (N = 646)	*P* value
Clinical characteristics			
Age, years	80.9 ± 11.0	79.9 ± 11.7	0.21
Gender (male), *n* (%)	188 (58.8)	332 (51.4)	0.03
Body mass index, kg/m^2	21.1 ± 4.4	21.2 ± 4.4	0.71
NYHA class, *n* (%)			
II	7 (2.2)	31 (4.8)	0.05
III	59 (18.4)	143 (22.1)	0.18
IV	254 (79.3)	471 (72.9)	0.03
HF classification			
HFrEF	103 (32.2)	209 (32.4)	0.96
HFmrEF	66 (20.6)	123 (19.0)	0.56
HFpEF	150 (46.9)	312 (48.3)	0.68
Unknown	1 (0.3)	2(0.3)	0.99
Co-morbidities, *n* (%)			
Hypertension	225 (70.3)	398 (61.6)	0.01
Diabetes mellitus	103 (32.2)	164 (25.4)	0.02
Atrial fibrillation	169 (52.8)	348 (53.9)	0.76
Ischaemic heart disease	105 (32.8)	155 (24.0)	<0.01
Valvular disease	85 (26.6)	171 (26.5)	0.98
Lung disease	41 (12.8)	121 (18.7)	0.02
Blood examination at discharge			
Haemoglobin, mg/dL	11.0 ± 2.0	11.9 ± 2.1	<0.01
Albumin, mg/dL	3.0 ± 0.5	3.1 ± 0.5	<0.01
Blood urea nitrogen, mg/dL	34.4 ± 20.1	22.8 ± 12.5	<0.01
Creatinine, mg/dL	1.8 ± 1.4	1.0 ± 0.6	<0.01
eGFR, mL/min/1.73m^2	37.0 ± 20.3	55.5 ± 22.3	<0.01
Brain natriuretic peptide, pg/mL	314 (261–350)	263 (232–286)	<0.01
Medications at discharge, *n* (%)			
ACE-Is/ARBs	220 (68.8)	477 (73.8)	0.12
β-Blockers	252 (78.8)	492 (76.2)	0.30
MRAs	151 (47.2)	300 (46.4)	0.80
Loop diuretics	267 (83.4)	490 (75.9)	<0.01
Tolvaptan	97 (30.3)	131 (20.3)	<0.01
Echocardiographic data			
LVEF, %	47.1 ± 13.4	46.9 ± 13.8	0.86
Left atrial diameter, mm	43.9 ± 8.1	43.5 ± 8.4	0.51

Data are mean ± SD for normally distributed data and median and interquartile range for non-normally distributed data, or *n* (%). All abbreviation as in *Table* 1.

presence of WRF and residual congestion at discharge was an independent predictor of outcomes, either mortality alone or mortality and HF re-hospitalization.[9]

Prognostic impact of WRF by age

The precise mechanism of the difference of prognostic impact of WRF by age is uncertain. However, one possible reason is the difference of renal functional reserve that represents the capacity of the kidney to increase glomerular filtration rate in response to certain physiological or pathological stimuli or conditions between high-aged ADHF patients and older patients. The renal functional reserve linearly deteriorates in accordance with the decrease of functioning nephron mass.[32] According to these findings, renal functional reserve of high-aged ADHF patients might be lower than older ADHF patients, though not estimated in this study.

Clinical perspectives

WRF in ADHF patients has been long recognized as a risk factor for adverse outcomes. However, most of the studies of this risk factor for ADHF patients were of patients with a mean age of 65–75,[16] so the difference between the impact of WRF on high-aged and older ADHF patients remains uncertain. The mean age of the subjects in our study was 80.2 ± 11.4 years old, which enabled us to compare the impact of WRF on outcomes for high-aged (≥80 years old) and older (<80 years old) ADHF patients. We were able to show that WRF was significantly associated with poor outcomes for the former, but not for the latter group of ADHF patients without residual congestion. Our findings demonstrate the importance of both avoiding WRF and decongestion for high-aged ADHF patients, whereas WRF was not a serious concern for older ADHF patients as long as they were decongested. The prevalence of HF has increased among elderly people in the current era of an HF

Figure 3 Kaplan–Meier curve representing the primary endpoint, showing that patients without residual congestion at discharge and without worsening renal function (WRF) had the most favourable outcomes, whereas those with residual congestion at discharge and with WRF had the least favourable outcomes.

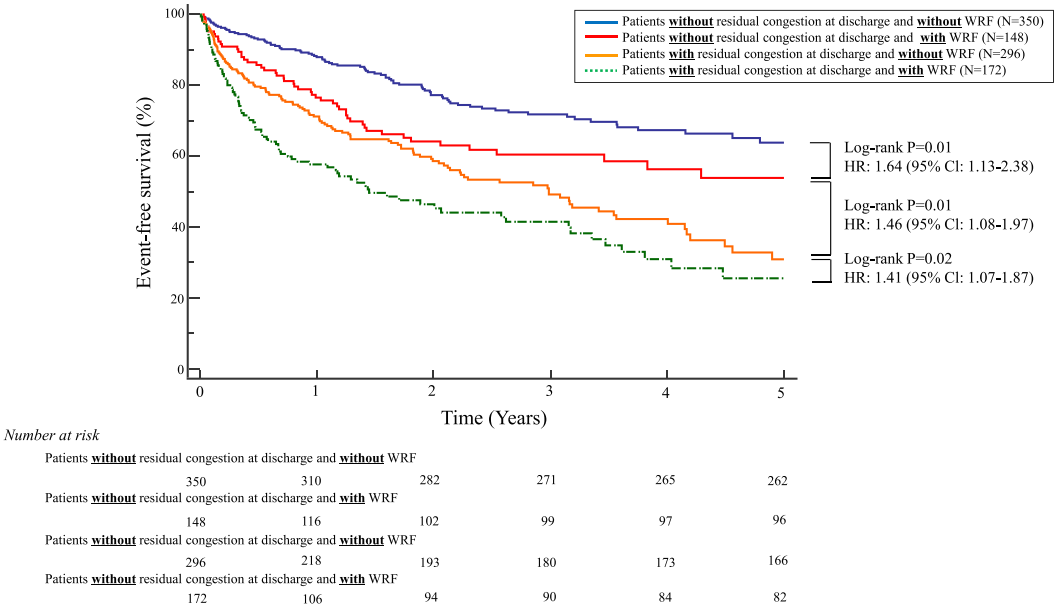


Table 3 Univariate and multivariate Cox proportional hazards analysis for predicting primary endpoint in high-aged patients

	Univariate			Multivariate		
Covariate	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	1.01	0.98–1.04	0.58			
Gender (male)	1.24	0.97–1.58	0.09	1.61	1.10–1.61	0.02
Body mass index	0.98	0.95–1.02	0.50			
NYHA class	1.25	0.98–1.60	0.08	1.90	1.17–3.06	0.01
Hypertension	1.31	1.01–1.72	0.05	1.66	1.08–2.57	0.02
Diabetes mellitus	1.08	0.81–1.45	0.60			
Atrial fibrillation	1.11	0.87–1.43	0.40			
Ischaemic heart disease	1.24	0.94–1.63	0.13			
Valvular disease	1.25	0.97–1.61	0.09			
LVEF	1.00	0.99–1.01	0.67			
Albumin	0.77	0.59–1.01	0.06			
Haemoglobin	0.88	0.82–0.94	<0.01			
Brain natriuretic peptide	1.01	1.00–1.01	<0.01			
Prescription of ACE-Is/ARBs	0.82	0.63–1.07	0.15			
Prescription of β-blockers	1.06	0.80–1.39	0.70			
Prescription of MRAs	1.04	0.81–1.33	0.75			
Prescription of loop diuretics	1.46	1.03–2.06	0.04			
Prescription of tolvaptan	1.77	1.34–2.34	<0.01	1.68	1.11–2.55	0.02
WRF	1.58	1.23–2.02	<0.01	1.70	1.15–2.50	0.01
Residual congestion at discharge	2.05	1.59–2.65	<0.01	2.02	1.34–3.05	<0.01

CI, confidential interval; HR, hazard ratio.
Other abbreviations as in *Table 1*.

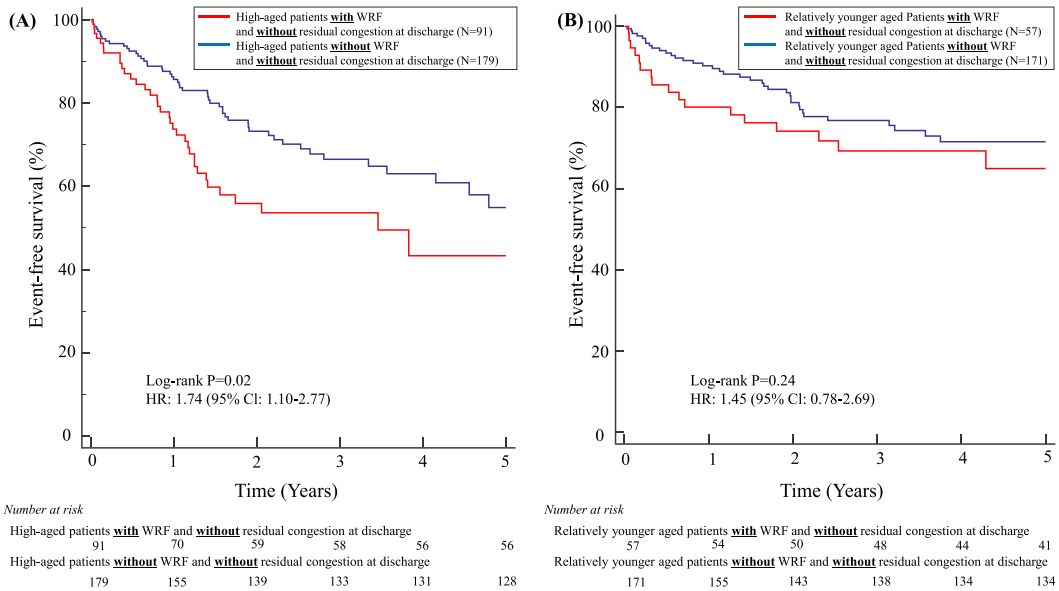
pandemic and also increases with age from around 1% for those aged <55 years old to >10% in those aged 70 years old or over.[30] High-aged ADHF patients ≥80 years old are not exceptional in an aging society, so age should be taken into consideration for the care of in-hospital ADHF patients. Given the pivotal role of congestion in HF, diuretics constitute a cornerstone of therapy for ADHF patients, and guidelines also include the use of loop diuretics to alleviate congestion as a class I recommendation.[30] Although the development of WRF by means of loop diuretics is a matter of concern for ADHF patients, our findings indicate that aggressive diuresis to alleviate congestion may be warranted to obtain a better prognosis for older ADHF patients.

Table 4 Univariate and multivariate cox proportional hazards analysis for predicting primary endpoint in older patients

	Univariate			Multivariate		
Covariate	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	1.05	1.02–1.07	<0.01			
Gender (male)	1.04	0.68–1.54	0.86			
Body mass index	0.97	0.93–1.01	0.13			
NYHA class	0.79	0.58–1.08	0.14	0.47	0.29–0.78	<0.01
Hypertension	1.87	1.24–2.84	<0.01			
Diabetes mellitus	1.61	1.10–2.34	0.01			
Atrial fibrillation	1.56	1.07–2.28	0.02			
Ischaemic heart disease	1.61	1.11–2.35	0.01			
Valvular disease	1.00	0.60–1.67	0.99			
LVEF	1.00	0.98–1.01	0.43			
Albumin	0.75	0.50–1.10	0.15			
Haemoglobin	0.82	0.75–0.89	<0.01	0.78	0.67–0.92	<0.01
Brain natriuretic peptide	1.01	1.00–1.01	<0.01			
Prescription of ACE-Is/ARBs	1.61	0.97–2.66	0.07	2.45	1.07–5.64	0.03
Prescription of β-blockers	1.23	0.67–2.24	0.50			
Prescription of MRAs	0.89	0.61–1.29	0.52			
Prescription of loop diuretics	1.93	1.20–3.12	<0.01			
Prescription of tolvaptan	2.49	1.64–3.77	<0.01	3.85	2.00–7.42	<0.01
WRF	1.35	0.91–2.01	0.13			
Residual congestion at discharge	2.35	1.62–3.41	<0.01	2.01	1.07–3.80	0.03

All abbreviations as in *Tables 1 and 3*.

Figure 4 *(*A) Kaplan–Meier curve representing the primary endpoint, showing that patients in the high-aged group without residual congestion at discharge but with worsening renal function (WRF) had significantly less favourable outcomes than those without WRF. (B*)* Kaplan–Meier curve representing the primary endpoint, showing that patients with WRF had outcomes similar to the outcomes of those without WRF in the older group without residual congestion at discharge.



Study limitations

This is a retrospective study so that some data were missing. Further prospective studies with fewer missing data are needed to validate our findings. Furthermore, there is currently no single established assessment of residual congestion at discharge so that several previous studies were referred.[11,22,23] Thus, evaluation of pulmonary oedema and pleural fluid using lung ultrasound or body weight was not part of this study. Finally, there is a relatively large proportion of patients being treated with tolvaptan (23.7%) in this study, which is not in line with international guidelines. However,

use of tolvaptan during hospitalization for ADHF patients who are resistant to other diuretics is recommended as class I of recommendation and level A of evidence in Japan.[25]

Conclusions

Associations of residual congestion at discharge with WRF in hospitalized ADHF patients can differ by age. Our findings showed the importance of WRF and residual congestion at discharge for high-aged ADHF patients and of aggressive diuresis to alleviate congestion for better management of older ADHF patients.

Conflict of interest

K.H. has received research funding from Daiichi Sankyo Company, Limited, Actelion Pharmaceuticals Japan, Terumo Corporation, Abbott Vascular Japan, Otsuka Pharmaceutical Company, Limited, Kowa Company, Limited, Takeda Pharmaceutical Company Limited, Nihon Medi-Physics Company Limited, Novartis Pharma Company Limited, Bayer Company Limited, Biotronic Japan Company Limited, FUJIFILM Toyama Chemical Company Limited, Medtronic Japan Company Limited, Sysmex Company Limited. H.T. is a consultant for AstraZeneca plc, Ono Pharmaceutical Company, Limited. Pfizer Inc, Otsuka Pharmaceutical Co., Ltd., and Novartis International AG. The remaining authors have no conflicts of interest to declare.

Funding

None declared.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Kaplan–Meier curve representing the primary endpoint, showing that patients in the high-aged group had significantly less favorable outcomes than those in the older group.

Table S1. Baseline characteristics of GDMT of HFrEF patients.

Table S2. Univariate and multivariate cox proportional hazards analysis for predicting primary endpoint in all patients.

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