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ARTICLE

Prognostic factors for one-year mortality in patients with acute heart failure with and without chronic kidney disease: differential impact of beta-blocker and diuretic treatments

Kenichi Matsushita[1] · Toshinori Minamishima[1] · Konomi Sakata[1] · Toru Satoh[1] · Hideaki Yoshino[1]

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Abstract

The pathophysiology and treatment of acute decompensated heart failure (HF) in the presence of chronic kidney disease (CKD) remain ill defined. Here we compared the prognostic factors for 1-year mortality in patients with acute HF with and without CKD. We retrospectively studied 392 consecutive patients with acute decompensated HF. CKD as a comorbidity in these patients was defined by an estimated glomerular filtration rate of <60 mL/min/1.73 m^2. Potential risk factors for 1-year mortality were selected by univariate analyses; then multivariate Cox regression analysis with forward selection (likelihood ratio) was performed to identify significant factors. Across the study cohort, 65% of patients had CKD, and the 1-year mortality rate was 9.2%. In the HF with CKD group, older age, lower systolic blood pressure at admission, discharge medications without beta-blockers, and discharge medications without diuretics were independent risk factors for 1-year mortality. In contrast, coexisting chronic obstructive pulmonary disease and higher C-reactive protein levels were independent risk factors for 1-year mortality in the HF without CKD group. Kaplan–Meier survival curves showed that discharge medications with no beta-blockers or diuretics correlated with significantly lower survival rates in patients with CKD ($P < 0.001$ in both groups, log-rank test), but not in patients without CKD ($P = 0.822$ and $P = 0.374$, respectively, log-rank test). Thus, there were significant differences in the prognostic factors for 1-year mortality between acute HF patients with and without CKD including beta-blocker and diuretic treatments. These findings suggest that patients with HF might benefit from individualized therapies.

Keywords cardiorenal syndrome · chronic kidney disease · heart failure · individualized treatment

Introduction

Heart failure (HF) is a highly heterogeneous clinical syndrome that remains to be adequately classified based on pathophysiological mechanisms. In this regard, comorbid chronic kidney disease (CKD) in patients with HF is of note, and the adverse interplay between the heart and kidney, wherein dysfunction of one organ initiates and perpetuates disease in the other, is known as cardiorenal syndrome [1]. Bidirectional crosstalk between these organs causes pathological changes in both, potentially creating a vicious cycle [1–5], while multifactorial pathways implicated in both HF and CKD further complicate the clinical features of patients presenting with acute decompensated HF and concomitant CKD. Importantly, the prevalence of concomitant CKD in patients with HF is high [6, 7]. Despite this, randomized controlled trials for cardiovascular disease frequently exclude patients with CKD [8], and the treatment strategies for acute decompensated HF in the presence of CKD remain poorly defined. There are some indications that coexisting CKD often complicates the treatment course of acute decompensated HF [9], and that the management of such patients continues to be challenging [10], frequently resulting in undertreatment [11]. Thus, assessing the clinical characteristics of HF with CKD and the effects of treatments is an important area of investigation from the viewpoint of personalized medicine. Accordingly, the present study compared prognostic factors for 1-year mortality in patients with acute decompensated HF with and without CKD.

✉ Kenichi Matsushita
kenichi-matsushita@umin.ac.jp

[1] Division of Cardiology, Second Department of Internal Medicine, Kyorin University School of Medicine, Tokyo, Japan

Methods

We retrospectively studied patients who were admitted to Kyorin University Hospital for acute decompensated HF from March 2009 to August 2013. Patients with acute coronary syndrome or hemodialysis were excluded from the study, as were patients without data on age, serum creatinine, or discharge medications. The estimated glomerular filtration rate (eGFR; mL/min/1.73 m^2) was calculated using the Japanese GFR equation based on serum creatinine as follows:[12]

In males: $eGFR = 194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$

In females: $eGFR = 194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739$

CKD was defined by an eGFR of <60 mL/min/1.73 m^2.

A past history of HF, hypertension, dyslipidemia, diabetes mellitus, or chronic obstructive pulmonary disease was determined from interviews with the patient or their family based on previous health checks, diagnoses made by family doctors, or a combination thereof. Left ventricular ejection fraction (LVEF) was determined using the modified biplane Simpson's method [13]. The peak velocities of early (E) and late (A) mitral flow, and the deceleration time of the E wave (DT) were measured using pulsed-wave Doppler sampling from the tip of the mitral valve leaflets. Pulsed-wave tissue Doppler imaging was applied to the apical four-chamber view to determine early (E′) and late (A′) velocities. The peak early diastolic myocardial velocities at both the septal and lateral annuli were measured and averaged to calculate mean early velocity (E′). We did not measure the peak velocities of E and A, DT, or the E/E′ ratio if the patient had undergone mitral valve replacement or repair.

This study was approved by the institutional ethics review board of Kyorin University School of Medicine.

Continuous data were assessed for normality using the Shapiro–Wilk test. Normally distributed continuous variables are presented as the mean ± SD and were compared between HF patients with and without CKD using the unpaired *t*-test or Welch test depending on the results of Levene's test for homoscedasticity. Continuous variables that were not normally distributed are presented as the median with interquartile range and were compared between groups using the Mann–Whitney test. Categorical data are presented as percentages and were compared using either the Chi-squared test if <20% of expected counts were <5 or Fisher's exact test if ≥20% of expected counts were <5. Kaplan–Meier survival curves and log-rank tests were used to compare 1-year all-cause mortality between groups. Potential risk factors for 1-year mortality were selected by univariate analyses. Variables with $P < 0.10$ in the univariate analyses were then used in multivariate Cox regression analyses with forward selection based on likelihood ratio statistics to identify significant factors. All statistical analyses were performed using SPSS version 22 (IBM Japan, Tokyo, Japan). $P < 0.05$ was considered significant.

Results

Of the 487 consecutive patients screened, excluding 95 who met the exclusion criteria, 392 were enrolled in this study. Table 1 details the clinical characteristics of study participants, of whom 254 patients (65%) had HF with CKD and 138 patients (35%) had HF without CKD. There were no significant differences between HF patients with and without CKD with respect to LVEF, E/E′ ratio, systolic blood pressure, heart rate, proportion of men, body mass index, prevalence of diabetes mellitus, glycosylated hemoglobin, rates of pretreatment with renin–angiotensin–aldosterone system inhibitors (RAASI) and beta-blockers, and discharge prescription rates of RAASI, beta-blockers, calcium channel blockers, and diuretics. Regarding LVEF, we further divided the population into those with LVEF ≥ 50% and those with LVEF < 50%. The rate of HF with LVEF ≥ 50% did not differ significantly between HF patients with and without CKD (45% vs. 43%, respectively; $P = 0.766$). HF patients with CKD had significantly higher age, rates of atrial fibrillation or flutter, and rates of history of HF and hypertension than those without CKD. In addition, serum potassium, C-reactive protein (CRP), and plasma B-type natriuretic peptide (BNP) concentrations at the time of admission, and rates of pretreatment with calcium channel blockers and diuretics were significantly higher in HF patients with than without CKD. Conversely, eGFR and hemoglobin were significantly lower in HF patients with CKD compared to those without CKD (Table 1).

For the entire study cohort, 1-year mortality was 9.2%. As shown in Fig. 1, a trend towards higher 1-year mortality was observed in HF patients with CKD compared to those without CKD, although this difference did not reach statistical significance (log-rank, $P = 0.148$).

In HF patients with CKD, univariate Cox regression analyses identified age ($P = 0.005$), systolic blood pressure at admission ($P = 0.014$), heart rate at admission ($P = 0.022$), eGFR ($P = 0.016$), plasma BNP ($P = 0.063$), pretreatment with diuretics ($P = 0.014$), discharge medications without RAASI ($P = 0.006$), discharge medications without beta-blockers ($P < 0.001$), discharge medications without calcium channel blockers ($P = 0.017$), and discharge medications without diuretics ($P < 0.001$) as potential risk factors for 1-year mortality (Table 2). Subsequent multivariate Cox regression analysis with forward selection based on likelihood ratio statistics for variables with $P < 0.10$ in the univariate analyses revealed older age (hazard ratio [HR] 1.070; 95% confidence interval [CI] 1.013–1.131;

Table 1 Patient characteristics

Variable	All patients ($n = 392$)	HF with CKD ($n = 254$)	HF without CKD ($n = 138$)	P value	Missing data for all patients (HF with CKD, HF without CKD)
Age, years	79 (69–84)	80 (72–84)*	75 (59–81)	<0.001	0
Male, %	62	65	57	0.085	0
BMI, kg/m^2	22.8 ± 4.2	22.7 ± 3.9	23.0 ± 4.6	0.569	27 (16, 11)
Af/AFL, %	43	47*	36	0.043	0
History of HF, %	26	31*	16	0.001	20 (17, 3)
History of HTN, %	65	72*	51	< 0.001	1 (1, 0)
History of DL, %	34	34	36	0.743	0
History of DM, %	34	36	30	0.249	0
History of COPD, %	6	8	4	0.228	2 (1, 1)
Smoking, %	43	42	45	0.529	8 (6, 2)
Systolic BP, mmHg	130 (115-152)	130 (116–157)	130 (112–150)	0.446	0
Heart rate, bpm	95 ± 28	94 ± 28	96 ± 28	0.375	2 (1, 1)
eGFR, mL/min/1.73 m^2	50.8 (32.9-68.4)	38.9 (26.2–49.6)*	73.5 (65.3–90.1)	< 0.001	0
WBC, number/μL	7794 ± 3374	8009 ± 3639	7395 ± 2788	0.063	1 (0, 1)
Hemoglobin, g/dL	12.0 ± 2.5	11.7 ± 2.4*	12.6 ± 2.5	0.001	1 (1, 0)
Na, mEq/L	139 ± 5	139 ± 4	139 ± 5	0.711	1 (1, 0)
K, mEq/L	4.3 ± 0.6	4.4 ± 0.6*	4.1 ± 0.5	< 0.001	1 (1, 0)
BS, mg/dL	136 (106–186)	140 (108–185)	132 (105–190)	0.745	100 (69, 31)
HbA1c, %	5.8 (5.4–6.5)	5.9 (5.5–6.6)	5.7 (5.3–6.3)	0.113	132 (90, 42)
CRP, mg/dL	0.7 (0.2–2.2)	0.8 (0.2–2.6)*	0.4 (0.1–1.8)	0.009	30 (21, 9)
BNP, pg/mL	695 (370–1265)	830 (423–1380)*	487 (253–1006)	< 0.001	14 (8, 6)
LVEF, %	47 ± 15	47 ± 15	46 ± 15	0.860	67 (47, 20)
LAD, mm	43 ± 8	44 ± 8	43 ± 7	0.220	49 (32, 17)
E/E′	14.2 ± 5.7	14.5 ± 5.7	13.7 ± 5.8	0.287	152 (106, 46)
E/A	0.9 (0.6–1.6)	1.0 (0.7–1.6)	0.8 (0.6–1.5)	0.281	189[a] (133, 56)
DT, ms	176 (140–235)	175 (145–233)	180 (131–238)	0.854	173 (112, 61)
Pretreatment					
RAASI, %	43	46	39	0.178	23 (20, 3)
Beta-blockers, %	35	38	31	0.201	21 (18, 3)
CCB, %	32	36*	25	0.038	21 (18, 3)
Diuretics, %	49	55*	38	0.001	21 (18, 3)
Discharge medication					
RAASI, %	61	58	67	0.103	0
Beta-blockers, %	74	73	76	0.537	0
CCB, %	33	32	34	0.721	0
Diuretics, %	79	80	76	0.377	0

Af/AFL atrial fibrillation/flutter, *BMI* body mass index, *BNP* plasma B-type natriuretic peptide, *BP* blood pressure, *BS* admission blood glucose level, *CCB* calcium channel blockers, *CKD* chronic kidney disease, *COPD* chronic obstructive pulmonary disease, *CRP* C-reactive protein, *DL* dyslipidemia, *DM* diabetes mellitus, *DT* deceleration time, *E/A* early to late transmitral flow velocity, *E/E′* the ratio of early transmitral velocity to tissue Doppler mitral annular early diastolic velocity, *eGFR* estimated glomerular filtration rate, *HbA1c* glycosylated hemoglobin, *HF* heart failure, *HTN* hypertension, *K* serum potassium, *LAD* left atrial diameter, *LVEF* left ventricular ejection fraction, *Na* serum sodium, *RAASI* renin–angiotensin–aldosterone system inhibitors, *WBC* white blood cell

Data are given as the mean ± SD, as the median (quartiles 1–3), or as percentages

*$P < 0.05$ for comparison between HF patients with and without CKD

[a]The number of missing data includes the unmeasured cases because of Af/AFL

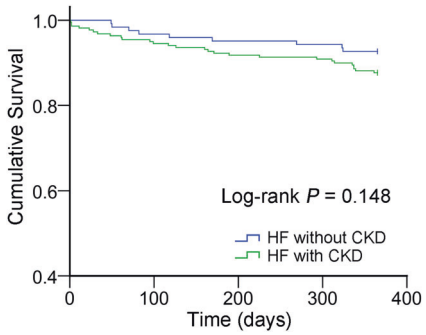

Fig. 1 Kaplan–Meier curves depicting 1-year survival of patients with acute decompensated HF with and without CKD. *CKD* chronic kidney disease, *HF* heart failure

$P = 0.016$), lower systolic blood pressure at admission (HR 0.979; 95% CI 0.963–0.996; $P = 0.015$), discharge medications without beta-blockers (HR 2.913; 95% CI 1.277–6.642; $P = 0.011$), and discharge medications without diuretics (HR 4.414; 95% CI 1.946–10.010; $P < 0.001$) to be significant risk factors for 1-year mortality (Table 3).

On the other hand, for HF patients without CKD, univariate Cox regression analyses identified age ($P = 0.050$), comorbid atrial fibrillation or flutter ($P = 0.080$), coexisting chronic obstructive pulmonary disease ($P < 0.001$), serum potassium value at admission ($P = 0.065$), and C-reactive protein levels at admission ($P = 0.002$) as potential risk factors for 1-year mortality (Table 2). Subsequent multivariate Cox regression analysis with forward selection (likelihood ratio) for variables with $P < 0.10$ by univariate analyses confirmed coexisting chronic obstructive pulmonary disease (HR 10.635; 95% CI 2.619–43.181; $P = 0.001$) and higher C-reactive protein levels at admission (HR 1.161; 95% CI 1.050–1.284; $P = 0.004$) as the significant risk factors for 1-year mortality among HF patients without CKD (Table 4).

With regard to discharge medications, the prognostic impacts of beta-blockers and diuretics on 1-year mortality differed significantly between HF patients with and without CKD. As shown in Fig. 2A and B, beta-blockers as discharge medications correlated with significantly lower mortality in HF patients with CKD ($P < 0.001$, log-rank test), but not in those without CKD ($P = 0.822$, log-rank test). Similarly, discharging HF patients with diuretic medications correlated with significantly lower mortality in those with CKD ($P < 0.001$, log-rank test; Fig. 2C), but not in those without CKD ($P = 0.374$, log-rank test; Fig. 2D).

Discussion

The present study confirmed that CKD is common in patients with acute decompensated HF and revealed significant differences in the risk factors for and prognostic impacts of discharge medications on 1-year mortality between HF patients with and without CKD. These findings suggest distinct underlying pathophysiologies at work in acute decompensated HF and the possible need for different therapeutic approaches between these patient groups.

Sympathetic overactivity is commonly seen in CKD, where it is an important contributor to increasing the risk of cardiovascular events as well as renal disease progression [14]. Converse et al. [15] demonstrated that damaged kidney led to sympathetic overactivity in that the rate of postganglionic sympathetic-nerve discharge to the blood vessels was significantly higher in hemodialysis patients who had not undergone nephrectomy than in normal controls, while hemodialysis patients who had undergone bilateral nephrectomy showed normal rates of sympathetic-nerve discharge. In addition, Salplachta et al. [16] reported that beta-blockers ameliorated cyclosporine-induced nephropathy in rats, suggesting that the sympathetic nervous system also plays a role in the progression of nephropathy, while DiBona et al. [17] showed that beta-blocker treatment improved the ability to excrete sodium loads in an experimental rat model of HF. These data imply that HF patients with CKD might benefit from beta-blocker treatment. Nevertheless, beta-blockers are underutilized in CKD, possibly because of concerns about metabolic disturbances, worsening renal function, and hemodynamic abnormalities [18]. Indeed, the relationship among beta-blockers, HF, and renal dysfunction seems complex and remains contentious in real-world clinical practice. In elderly patients with reduced LVEF after myocardial infarction, Shlipak et al. [19] associated beta-blocker therapy with greater benefit for patients with than without renal dysfunction, while Ghali et al. [20] reported a similar finding in systolic HF patients. On the other hand, some studies found no significant interactions between renal function and beta-blocker therapy with respect to clinical outcome [21, 22]. These discrepancies could reflect differences in patient background and disease conditions, and careful interpretation of each study is needed to investigate relevant links. The present study demonstrated an association between beta-blocker use and improved 1-year mortality in HF patients with CKD, but not in those without CKD, prompting the need for further prospective randomized trials to confirm the beneficial effects of beta-blockers in these patient groups.

Diuretics are indicated for the relief of symptoms due to volume overload in all HF patients irrespective of LVEF, although it is also suggested that such agents are used at the minimum possible dose to mitigate associated dehydration and subsequent deterioration in renal function [11, 23, 24]. Classically, a reduction in effective circulation fluid volume in HF is associated with reduced renal blood flow, which, along with inadequate perfusion pressure, can prompt renin

Table 2 Univariate Cox regression analysis of 1-year mortality in acute heart failure patients with and without chronic kidney disease

Variable	HF with CKD		HF without CKD	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.081 (1.023–1.141)	0.005	1.061 (1.000–1.127)	0.050
Male gender	1.062 (0.477–2.363)	0.883	0.934 (0.251–3.478)	0.919
BMI	0.988 (0.893–1.092)	0.807	0.857 (0.706–1.041)	0.120
Af/AFL	0.923 (0.432–1.971)	0.835	3.453 (0.863–13.808)	0.080
History of HF	1.902 (0.852–4.246)	0.117	0.778 (0.209–2.897)	0.986
History of HTN	0.557 (0.259–1.201)	0.136	0.571 (0.400–0.814)	0.708
History of DL	0.720 (0.315–1.645)	0.436	0.555 (0.115–2.671)	0.463
History of DM	1.104 (0.512–2.379)	0.800	0.305 (0.038–2.442)	0.263
History of COPD	1.608 (0.484–5.339)	0.438	12.604 (3.137–50.632)	<0.001
Smoking	1.522 (0.704–3.290)	0.286	0.944 (0.254–3.516)	0.932
Systolic BP	0.981 (0.967–0.996)	0.014	0.999 (0.978–1.020)	0.919
Heart rate	0.982 (0.967–0.997)	0.022	1.002 (0.978–1.026)	0.881
eGFR	0.967 (0.942–0.994)	0.016	1.018 (0.994–1.043)	0.134
WBC	1.000 (1.000–1.000)	0.563	1.000 (1.000–1.000)	0.777
Hemoglobin	0.955 (0.820–1.113)	0.558	0.903 (0.712–1.145)	0.398
Na	1.033 (0.942–1.133)	0.490	1.014 (0.877–1.172)	0.851
K	0.777 (0.419–1.443)	0.424	0.329 (0.101–1.071)	0.065
BS	1.000 (0.993–1.006)	0.922	0.996 (0.982–1.010)	0.579
HbA1c	0.921 (0.591–1.436)	0.717	0.563 (0.204–1.550)	0.266
CRP	1.037 (0.948–1.133)	0.430	1.154 (1.054–1.263)	0.002
BNP	1.000 (1.000–1.000)	0.063	1.000 (0.999–1.001)	0.846
LVEF	1.008 (0.978–1.039)	0.599	0.992 (0.941–1.045)	0.753
LAD	1.004 (0.958–1.053)	0.862	1.026 (0.938–1.123)	0.575
E/E′	0.998 (0.913–1.091)	0.962	1.108 (0.981–1.251)	0.100
E/A	0.865 (0.462–1.622)	0.652	1.382 (0.462–4.132)	0.563
DT	1.002 (0.997–1.007)	0.435	0.992 (0.978–1.005)	0.224
Pretreatment				
RAASI	1.944 (0.863–4.376)	0.108	2.336 (0.627–8.699)	0.206
Beta-blockers	1.265 (0.562–2.849)	0.570	1.835 (0.493–6.836)	0.365
CCB	1.074 (0.470–2.455)	0.865	1.622 (0.406–6.486)	0.494
Diuretics	3.419 (1.277–9.159)	0.014	2.259 (0.607–8.413)	0.224
Discharge medication				
RAASI	0.329 (0.148–0.733)	0.006	0.413 (0.111–1.540)	0.188
Beta-blockers	0.219 (0.102–0.472)	<0.001	1.198 (0.249–5.765)	0.822
CCB	0.231 (0.070–0.767)	0.017	1.443 (0.388–5.375)	0.584
Diuretics	0.190 (0.089–0.404)	<0.001	2.488 (0.311–19.894)	0.390

Af/AFL atrial fibrillation/flutter, *BMI* body mass index, *BNP* plasma B-type natriuretic peptide, *BP* blood pressure, *BS* admission blood glucose level, *CCB* calcium channel blockers, *CI* confidence interval, *CKD* chronic kidney disease, *COPD* chronic obstructive pulmonary disease, *CRP* C-reactive protein, *DL* dyslipidemia, *DM* diabetes mellitus, *DT* deceleration time, *E/A* early to late transmitral flow velocity, *E/E′* the ratio of early transmitral velocity to tissue Doppler mitral annular early diastolic velocity, *eGFR* estimated glomerular filtration rate, *HbA1c* glycosylated hemoglobin, *HF* heart failure, *HR* hazard ratio, *HTN* hypertension, *K* serum potassium, *LAD* left atrial diameter, *LVEF* left ventricular ejection fraction, *Na* serum sodium, *RAASI* renin–angiotensin–aldosterone system inhibitors, *WBC* white blood cell

release by the juxtaglomerular cells of the afferent arterioles, and subsequent activation of the renin–angiotensin system to induce sodium reabsorption, volume retention, afferent arteriolar constriction, decreased glomerular perfusion, and profibrotic neurohormone increases [4]. Such changes may worsen HF and establish a vicious cycle of effects. However, accumulating evidence now suggests that this classic theory of the association between HF and renal

blood flow is limited and that increased venous pressure seems to be more crucial [1]. For example, Mullens et al. [25] reported the prevalence of elevated intra-abdominal pressure in patients with acute decompensated HF and impaired renal function, showing that reduced intra-abdominal pressure was better correlated with improved renal function than any hemodynamic variable. Supporting this concept of venous congestion rather than arterial blood flow being an important mediator of cardiorenal syndrome, Nohria et al. [26] showed that only right arterial pressure correlated with baseline serum creatinine in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial. In addition, in monitoring hemodynamics using a pulmonary artery catheter in patients admitted with advanced decompensated HF and treated with intensive medical therapy, Mullens et al. [27] identified venous congestion as the most important hemodynamic factor driving worsening renal function. Damman et al. [28, 29] also reported central venous pressure as the most important predictor of worsening renal function and mortality in patients with cardiovascular disease, and further demonstrated that subtle changes in volume status by diuretic withdrawal and reinstitution are associated with increases and decreases of tubular dysfunction markers in stable HF, suggesting that diuretic therapy may favorably affect renal and tubular function in HF. Increasing evidence therefore supports the possibility of subsets of HF patients for whom continued diuretic therapy could be beneficial. The present study demonstrated an association between diuretic therapy and improved 1-year mortality in HF patients with CKD, but not in those without CKD. Further studies are needed to elucidate the

Table 3 Risk factors for 1-year mortality in acute heart failure patients with chronic kidney disease

Variable	HR (95% CI)	*P* value
Age	1.070 (1.013–1.131)	0.016
Systolic BP	0.979 (0.963–0.996)	0.015
Without beta-blockers at discharge	2.913 (1.277–6.642)	0.011
Without diuretics at discharge	4.414 (1.946–10.010)	<0.001

Multivariate Cox regression analysis with forward selection (likelihood ratio) was conducted in the acute heart failure with chronic kidney disease group. Significant risk factors were defined as $P < 0.05$

BP blood pressure, *CI* confidence interval, *HR* hazard ratio

Table 4 Risk factors for 1-year mortality in acute heart failure patients without chronic kidney disease

Variable	HR (95% CI)	*P* value
COPD	10.635 (2.619–43.181)	0.001
CRP	1.161 (1.050–1.284)	0.004

Multivariate Cox regression analysis with forward selection (likelihood ratio) was conducted in the acute heart failure without chronic kidney disease group. Significant risk factors were defined as $P < 0.05$

CI confidence interval, *COPD* chronic obstructive pulmonary disease, *CRP* C-reactive protein, *HR* hazard ratio

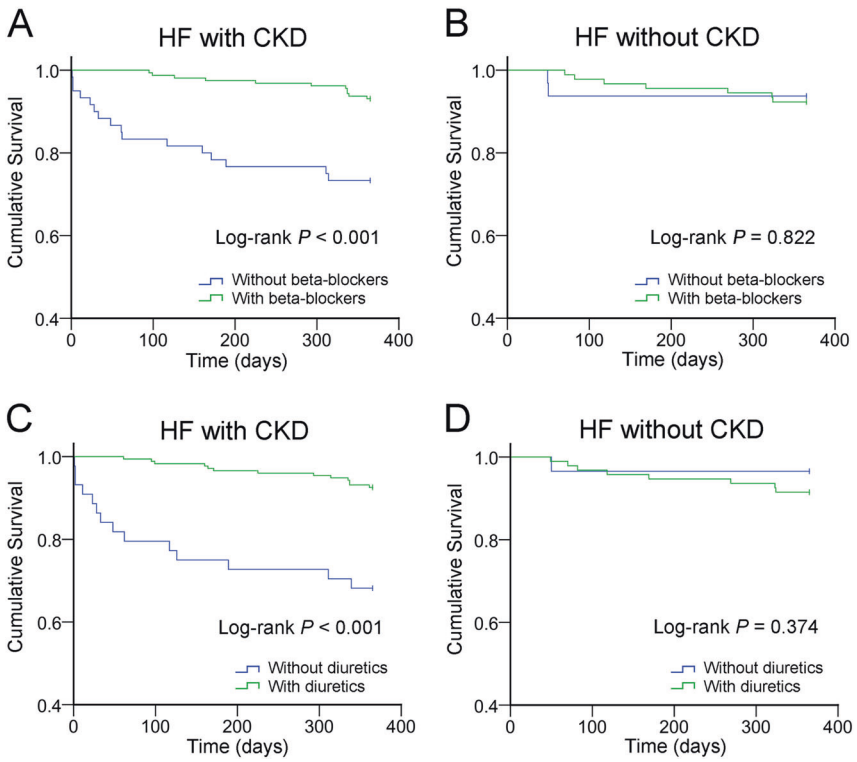

Fig. 2 Kaplan–Meier curves showing 1-year survival of HF patients with and without beta-blockers at discharge (**A**, **B**) and of HF patients with and without diuretics at discharge (**C**, **D**). **A**, **C** HF patients with CKD. **B**, **D** HF patients without CKD. *CKD* chronic kidney disease, *HF* heart failure

complex pathophysiological mechanisms related to the effects of diuretics in HF patients.

There are several limitations to the present study. First, this was a retrospective analysis with all the inherent problems of such a design in proving causality. Second, not all comorbid diseases and conditions associated with mortality could be evaluated, although we tried to include as many potential prognostic factors as possible. Certain risk or beneficial factors of prognosis were not recorded and analyzed, such as data on albuminuria/proteinuria, primary valvular disease, surgical procedure, and detailed treatment protocols including the name and dose of each drug. In addition, renal dysfunction has been reported as a risk factor [5] in previous studies, including the JCARE-CARD (Japanese Cardiac Registry of Heart Failure in Cardiology) [30], the KorHF (Korean Heart Failure) [31], and the Hong Kong Heart Failure [32] registries but was not shown in the present study, although a trend towards higher 1-year mortality was observed in HF patients with CKD compared to those without CKD. This might be due to differences in not only patient background and disease conditions, but also sample size. It is also possible that the number of patients was not sufficiently large to identify all possible risk factors. Nevertheless, the present study was of sufficient size to demonstrate that several prognostic factors such as age, systolic blood pressure at admission, discharge medications without beta-blockers, discharge medications without diuretics, coexisting chronic obstructive pulmonary disease, and C-reactive protein levels at admission differ significantly between HF patients with and without CKD.

In conclusion, the present study demonstrated significant differences in the prognostic factors for 1-year mortality between HF patients with and without CKD. In particular, discharge medications without beta-blockers correlated with significantly lower survival rates in HF patients with CKD, but not in those without CKD. Discharge medications with diuretics also correlated with a significant reduction in 1-year mortality only in HF patients with CKD. Elucidation of the pathophysiological mechanisms behind these findings could lead to more effective individualized therapeutic strategies for patients with HF.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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