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Predictors of Long-Term Mortality and Frequent Re-Hospitalization in Patients with Acute Decompensated Heart Failure and Kidney Dysfunction Treated with Renin-Angiotensin System Blockers

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Background: Assessment of risk for all-cause mortality and re-hospitalization is an important task during discharge of acute heart failure (AHF) patients, as they warrant different management strategies. Treatment with optimal medical therapy may change predictors for these 2 end-points in AHF patients with renal dysfunction. The aim of this study was to evaluate the predictors for long-term outcome in AHF patients with kidney dysfunction who were discharged on optimal medical therapy.

Material/Methods: The study was conducted retrospectively. The study group consisted of 225 AHF patients with moderate-to-severe kidney dysfunction, who were hospitalized at Kocaeli University Hospital Cardiology Clinic and who were prescribed beta-blockers and ACE-inhibitors or angiotensin II receptor blockers at discharge. Clinical, echocardiographic, and biochemical predictors of the composite of total mortality and frequent re-hospitalization (≥ 3 hospitalizations during the follow-up) were assessed using Cox regression and the predictors for each end-point were assessed by competing risk regression analysis.

Results: Incidence of all-cause mortality was 45.3% and frequent readmissions were 49.8% in a median follow-up of 54 months. The associates of the composite end-point were age, NYHA class, respiration rate on admission, eGFR, hypoalbuminemia, mitral valve E/E' ratio, and ejection fraction. In competing risk regression analysis, right-sided HF, hypoalbuminemia, age, and uric acid appeared as independent associates of all-cause mortality, whereas NYHA class, NT-proBNP, mitral valve E/E' ratio, and uric acid were predictors for re-hospitalization.

Conclusions: Predictors for all-cause mortality in AHF with kidney dysfunction treated with optimal therapy are mainly related to advanced HF with right-sided dysfunction, whereas frequent re-hospitalization is associated with volume overload manifested by increased mitral E/E' ratio and NT-proBNP levels.

MeSH Keywords: **Heart Failure • Prognosis • Renal Insufficiency • Risk Assessment**

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Background

Renal dysfunction is a frequent co-morbidity in acute decompensated heart failure (ADHF) and is independently associated with poor prognosis [1,2]. ADHF patients with moderate-to-severe renal dysfunction are older and have a higher prevalence of diabetes, anemia, history of hypertension, myocardial infarction, and hospitalization for heart failure (HF) than those with normal or mildly impaired renal function [3]. Numerous studies show that optimal medical therapy, including renin-angiotensin system (RAS) blockers, restores adverse outcome in HF patients with renal dysfunction [4–6].

Prediction of outcome is an important aspect of HF management [7]. Use of optimal medical therapy may decrease the number of re-hospitalizations and alter types of prognostic predictors of all-cause mortality in ADHF patients with renal dysfunction. Understanding the predictors of these 2 end-points is important in order to select further management strategies that can help to reduce the risk burden for individual patients. Both of these clinical outcomes are competitive end-points, and the occurrence of one precludes the occurrence of the other.

The aim of this study was to investigate the predictors of long-term clinical outcome in optimally treated ADHF patients with renal dysfunction, using competing risk regression model and all-cause mortality and frequent hospitalization as competing events.

Material and Methods

The study was conducted retrospectively and the study group consisted of consecutive patients admitted to Kocaeli University Cardiology Clinic due to acute decompensation of systolic HF from 2003 to 2014. Clinical features on admission and prescriptions at discharge were recorded from patient files in 2016. The inclusion criteria were hospitalization because of ADHF with a left ventricular ejection fraction (LVEF) 40%, ages 18–90 years, moderate-to-severe renal dysfunction at discharge, at least 1 hospitalization because of heart failure before, and being on optimal medical therapy at discharge and follow-up. Being on optimal medical therapy was defined as prescription of beta-blockers and ACE-inhibitors or angiotensin receptor blockers at discharge. Exclusion criteria were acute coronary syndrome in the preceding 6 months, clinically significant valvular heart disease, planned cardiovascular surgery, requirement of dialysis, known malignancies, use of only 1 guideline-directed medical therapy agent, and unknown follow-up status.

Biochemical analysis after stabilization of ADHF (latest biochemical analysis before discharge) and echocardiographic findings during hospital stay were examined. Estimated

glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [8]. Kidney dysfunction was established according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) K/DOQI guidelines [9]. Patients with an eGFR <60 mL/min/1.73 m² (moderately-to-severely decreased eGFR) were included in the study.

Factors associated with worse outcome are grouped as clinical, laboratory and echocardiographic variables. Clinical variables included respiration rate on admission, age, body mass index (at the time of euolemia after decongestive therapy), etiology of HF (ischemic or non-ischemic), right-sided HF (defined as presence of peripheral edema accompanied by jugular venous distension or hepatomegaly), and systolic blood pressure on admission. Echocardiographic variables used for prognostic evaluation were LVEF (measured by Simpson's method), mitral valve E/E' ratio, left atrial diameter, right ventricular outflow tract diameter, and pulmonary artery systolic pressure. Laboratory variables associated with worse prognosis were selected as eGFR, uric acid, albumin, transaminases, hemoglobin, C-reactive protein, NT-proBNP, and free-triiodothyronine (f-T3).

Follow-up of the patients was gathered from patient files, computerized data of health maintenance organizations, hospital visits, or telephone contact. In deceased patients, hospital recordings were reviewed when available, and for those who died outside the hospital, information was obtained from their relatives. The primary end-point of the study was the composite of all-cause mortality and frequent re-hospitalization, which was defined as hospitalization ≥ 3 times during the follow-up period. Secondary end-points were all-cause mortality and frequent re-hospitalization (whichever occurs first) as competing risks to each other.

Statistical analysis

All statistical analyses were performed using IBM SPSS for Windows version 20.0 (SPSS, Chicago, IL, USA) and Stata V.11 (Stata Corp LP, TX, USA). Kolmogorov-Smirnov tests were used to test the normality of data distribution. Continuous variables are expressed as mean \pm standard deviation, median (25th–75th percentiles), and categorical variables are expressed as counts (percentages). Factors predicting the composite end-point were evaluated using univariate analysis. Variables associated with each end-point were also assessed separately for 2 subgroups of patients: deceased vs. survivors and frequently re-hospitalized vs. not frequently hospitalized. The Pearson chi-squared test, the t test and, the Mann-Whitney U test were applied for categorical, parametrically, and non-parametrically continuous variables between subgroups, respectively. Pearson correlation analysis was used to find the correlation between

variables. As all of the covariates are clinically important determinants of outcome, all were included in the Cox proportional hazards regression model irrespective of their *P* values on univariate analysis. Variables showing an association with a *P* value <0.05 in the Cox regression model were included in competing risks regression analysis. When all-cause mortality and frequent hospitalization were used as competing events, the competing risks regression analysis were applied to investigate which of the handled covariates have significant influence on deaths. In competing risks regression analysis, NYHA class, right-sided HF, NT-proBNP, diastolic blood pressure, age, left ventricular ejection fraction, sodium, ALT, hypoalbuminemia, and mitral valve E/E' ratio were used to compare all-cause mortality and frequent re-hospitalization groups.

Additionally, uric acid was included in analysis, as it is an important prognostic biomarker in patients with kidney dysfunction.

Competing risk regression analysis

In the competing risks analysis, the cumulative incidence function is used to compare the risks of subgroups. This function estimates the probability of failing from cause *j* before a given time *t*. It is computed for a population or for a subgroup of interest [10]. The subdistribution hazard method is used to model the effects of covariates on the cumulative incidence functions [11]. In this approach, the subdistribution hazard gives the hazard of failing from a given cause in the presence of competing events, given that a subject has survived or has already died due to different causes [12,13].

The subdistribution hazard function is defined as

$$\bar{\lambda}_j(t|x) = \lim_{\Delta t \rightarrow 0} \frac{P(t \leq T < t + \Delta t, \epsilon = j | \{(T \geq t) \cup [(T \leq t) \cap (\epsilon \neq j)]\}, x)}{\Delta t}$$

This model links regression coefficients with the cumulative incidence function via the "hazard rate" obtained from the subdistribution function [14].

Cumulative incidence curves were calculated treating death and re-hospitalization as competing events to each other over time. To further evaluate the accuracy of statistically significant parameters, the results were also included in a receiver operating characteristic (ROC) curve analysis. Cut-off values of the variables for predicting death and re-hospitalization were calculated. A two-sided *P* value <0.05 was considered statistically significant.

Results

The final study population consisted of 225 systolic HF patients (144 male, 65%) with a mean left ventricular ejection fraction

of 25±8% and a mean eGFR of 41±13 mL/min/1.73 m². All of them were using a RAS blocker at tolerated maximal dose during follow-up. The percentage of moderate kidney dysfunction was 81% (182 patients) and the percentage of severe kidney dysfunction was 19% (43 patients). Baseline characteristics of the study group are presented in Table 1.

Total number of all-cause mortalities was 102 (45.3%) and the percentage of patients with frequent readmissions was 49.8% (112 patients) in a median follow-up of 54 months (range 24-97 months). Sixty-four patients (63%) died after frequent re-hospitalizations; thus, a composite end-point occurred in a total of 150 patients (67%).

Univariate associates of the composite end-point are presented in Table 2. In Cox regression analysis, predictors of death were age, NT-proBNP, NYHA class, ALT, right-sided HF, mitral valve E/E' ratio, sodium, and left ventricular ejection fraction (Table 3).

In competing risk regression analysis, right-sided HF (*p*=0.009), hypoalbuminemia (0.009), age (*p*=0.015), and uric acid (*p*=0.023) were independent associates of mortality, whereas NT-proBNP (*p*<0.001), NYHA class III/IV functional capacity (*p*=0.003), uric acid (*p*=0.020), and mitral valve E/E' ratio (*p*=0.040) were independent predictors for frequent hospitalization (Table 4). The estimates of cumulative incidence functions for re-hospitalization and death for NYHA class III/IV and right-sided HF are given in Figure 1.

To evaluate the accuracy of the parameters showing an independent association with all-cause mortality and re-hospitalization, the results were included in a receiver operating characteristic (ROC) curve analysis. Cut-off values of the variables for predicting death were: age >72 years, albumin <3.1 mg/dl, uric acid >5.8 pg/mL, NT-proBNP >1160 pg/mL, and mitral valve E/E' ratio >12.7. Cut-off values of the variables for predicting re-hospitalization were: age >70 years, albumin <3.0 mg/dl, uric acid >8.8 pg/mL, NT-proBNP >2630 pg/mL, and mitral valve E/E' ratio >17.2 (Table 5).

Discussion

Results of this study showed a high rate of mortality in ADHF patients with kidney dysfunction (42% in patients with moderate and 61% with severe kidney dysfunction in a median 54-month follow-up), despite being on RAS- and beta-blockers. Nevertheless, the rates were lower than the study by Löfman et al. [15], who reported a 5-year cumulative probability of death above 60% in those with moderate kidney dysfunction and above 80% in patients with severe kidney dysfunction. Rate of re-hospitalization was also high: 86% of all the patients were re-hospitalized during the study period,

Table 1. Baseline characteristics of the study group.

	Total study group (n = 225)	
Clinical characteristics		
Age (y)	68.10±9.05	
Male (%)	144	(64)
Body mass index (kg/m ²)	27±4	
NHYA class III/IV (%)	220 (89)/25 (11)	
Ischemic etiology (%)	163	(72)
Diabetes (%)	108	(48)
Respiration rate on admission	26	(14-40)
Systolic blood pressure (mm Hg)	120.0	(110.0–140.0)
Diastolic blood pressure (mm Hg)	80.0	(70.0–80.0)
Right-sided heart failure (%)	127	(56)
Medications at discharge		
ACEI or ARB (%)	225	(100)
Beta-blocker (%)	225	(100)
Aldosterone antagonist (%)	105	(47)
Loop diuretics (%)	194	(86)
Digoxin (%)	36	(16)
Aspirin (%)	192	(85.3)
Statin (%)	135	(60)
Oral anticoagulants (%)	72	(32)
Laboratory variables		
eGFR (mL/min/1.73 m ²)	43.0	(32.0–50.5)
Albumin (g/dL)	3.5	(3.1–3.9)
Hemoglobin (g/dL)	12.0	(10.8–13.5)
ALT (IU/L)	23.0	(14.5-36.0)
AST (IU/L)	24.0	(19.0-43.0)
Sodium (mEq/L)	137.0	(13.0–141.0)
Uric acid (mg/dl)	8.1	(6.7–9.4)
C-reactive protein (mg/L)	1.1	(0.5–2.8)
Free-triiodothyronine (pg/mL)	2.4	(2.0–2.9)
NT-proBNP (pg/mL)	1170.0	(595.0–2550.0)
Echocardiographic variables		
Left ventricular ejection fraction	25.0	(20.0–30.0)
Mitral valve E/E' ratio	14.8	(10.9–19.0)
Left atrial diameter (mm)	47.0	(43.0–52.0)
Left ventricular end-diastolic diameter (mm)	62.0	(57.0–67.0)
Right ventricular outflow tract diameter (mm)	27.0	(24.0–31.0)
Pulmonary artery systolic pressure (mm Hg)	45.0	(35.0–55.0)

Table 2. Univariate associates of composite end-point.

	Patients with composite end-point (n=150)		Patients without composite end-point (n=75)		P
Clinical characteristics					
Age (y)	69.18±9.42		65.95±7.91		0.007
Male (%)	96	(64)	48	(64)	1.000
Body mass index (kg/m ²)	27.03±4.26		27.03±4.11		0.560
NHYA class III/IV	127 (84.7)/23 (15.3)		73 (97.3)/2 (2.7)		0.009
Ischemic etiology (%)	115	(76.7)	48	(54.3)	0.045
Diabetes (%)	69	(72)	39	(36)	0.396
Respiration rate on admission	25	(20–26)	26	(25–28)	<0.001
Systolic blood pressure (mm Hg)	130	(110–140)	120	(110–135)	0.342
Diastolic blood pressure (mm Hg)	80	(70–85)	70	(70–80)	0.155
Right-sided heart failure (%)	86	(57.3)	41	(54.7)	0.704
Medications at discharge					
Aldosterone antagonist (%)	60	(40)	45	(60)	0.005
Loop diuretics (%)	127	(85)	67	(89)	0.338
Digoxin (%)	24	(16)	12	(16)	1.000
Aspirin (%)	133	(89)	59	(79)	0.046
Statin (%)	90	(60)	45	(60)	1.000
Oral anticoagulants (%)	47	(31)	25	(33)	0.762
Laboratory variables					
eGFR (mL/min/1.73 m ²)	46.0	(37.0–53.0)	41.0	(31.8–49.3)	0.002
Albumin (g/dL)	3.7	(3.4–4.0)	3.3	(3.0–3.7)	<0.001
Hemoglobin (g/dL)	12.12±1.90		12.7	(11.0–14.4)	0.083
ALT (IU/L)	21.0	(14.0–31.0)	24.0	(15.0–41.0)	0.230
AST (IU/L)	23.0	(19.0–37.0)	24.5	(18.8–42.3)	0.463
Sodium (mEq/L)	137.0	(133.0–139.0)	138.0	(134.0–141.0)	0.487
Uric acid (mg/dl)	2.6	(2.1–3.0)	2.4	(1.9–2.9)	0.076
C-reactive protein (mg/L)	1.1	(0.5–2.5)	1.2	(0.5–2.9)	0.519
Free-triiodothyronine (pg/mL)	2.6	(2.1–3.0)	2.4	(1.9–2.9)	0.076
NT-proBNP (pg/mL)	1170.0	(609.0–2176.0)	1219.0	(589.0–2692.5)	0.375
Echocardiographic variables					
Left ventricular ejection fraction	30.0	(20.0–35.0)	20.0	(17.8–30.0)	0.001
Mitral valve E/E' ratio	12.3	(9.0–15.0)	15.6	(12.3–21.6)	<0.001
Left atrial diameter (mm)	46.0	(43.0–52.0)	47.0	(43.0–52.0)	0.941
Left ventricular end-diastolic diameter (mm)	46.0	(43.0–52.0)	47.0	(43.0–52.0)	0.060
Right ventricular outflow tract diameter (mm)	26.0	(25.0–30.0)	28.0	(24.0–31.0)	0.126
Pulmonary artery systolic pressure (mm Hg)	45.0	(30.0–55.0)	45.0	(35.0–55.0)	0.929

Table 3. Variables showing an independent association with the composite of all-cause mortality in Cox Proportional Hazard Analysis [HR (95% CI)].

	Composite end-point
NHYA class III/IV (%)	3.189 (1.911–5.322) p<0.001
Right-sided heart failure (%)	0.538 (0.356–0.813) p=0.003
Sodium (mEq/L)	0.957 (0.925–0.991) p=0.014
NT-proBNP (pg/mL)	1.001 (1.000–1.001) p<0.001
ALT (IU/L)	1.001 (1.000–1.002) p=0.002
Left ventricular ejection fraction (%)	0.963 (0.935–0.993) p=0.015
Mitral valve E/E' ratio	1.051 (1.016–1.086) p=0.004
Age (years)	1.050 (1.026–1.075) p<0.001

and 58% of them had more than 1 hospitalization/year. The reported 1-year readmission rate in HF varies between 30% and 50% [16]. As the patients included in this study were at higher risk for volume overload, this rate of re-hospitalization was as expected.

The independent predictors for the composite of all-cause mortality and re-hospitalization in Cox regression analysis (age, NT-proBNP, NYHA class, ALT, right-sided HF, mitral valve E/E' ratio, sodium, and left ventricular ejection fraction) were separated in competing risk regression analysis when we evaluated which of the end-points would develop first in the follow-up period. Age and factors associated with right-sided HF (i.e., its clinical symptoms/signs and hypoalbuminemia) appeared as the more important determinants for all-cause mortality, whereas parameters associated with volume overload (i.e., NT-proBNP and mitral valve E/E' ratio) appeared to be the more important determinants for frequent re-hospitalization. Serum uric acid was an important determinant for both of these end-points.

Predictors of mortality and effect of renal dysfunction in ADHF have been investigated in many studies; however, outcome studies focusing specifically on the ADHF patients with kidney impairment are limited. These patients are older, have several co-morbidities, and often have longer duration of HF [1–3,16]. Kidney dysfunction may be secondary to venous congestion, low cardiac output, RAS stimulation, and sympathetic activation in HF. Several studies have shown that patients with

cardiovascular disease and kidney dysfunction receive fewer guideline-recommended treatments, partly due to lack of evidence from clinical trials and concerns about drug toxicity [17]. Our study was different from others in that we used the 2 main HF drugs (beta-blockers and RAS-inhibitors) in all patients. The outcome analysis in this selected group of patients showed that although predictors for 'composite end-point' remained nearly the same as in existing risk estimation systems, the competing risk regression analysis showed that right-sided-HF and the related biochemical marker hypoalbuminemia were the main determinants of poor survival in these patients [18,19].

Right-sided HF is a well-known predictor of cardiovascular outcome. A sub-study of the AF-CHF trial, which included patients with a high percentage of guideline-directed medical therapy, showed that among various signs of congestion, especially presence of peripheral edema, is independently associated with all-cause mortality and HF-related death [20]. In advanced HF with right-sided dysfunction, increased hydrostatic pressure in right heart cavities is transmitted to systemic veins and capillaries, leading to venous congestion and peripheral edema. Increased intra-abdominal pressure due to splanchnic venous and/or interstitial congestion results in transient or permanent renal and liver dysfunction. Liver dysfunction in advanced HF is characterized by elevated levels of transaminases, alkaline phosphatase, gamma-glutamyl transpeptidase, and total bilirubin, as well as hypoalbuminemia [21]. These changes may be transient and improve during the course of ADHF management, but may also become persistent in those with right-sided HF due to passive hepatic congestion.

Hypoalbuminemia, which is a marker for liver dysfunction, is common in patients with systolic HF, occurring in approximately one-third of patients [22]. It is attributed to hemodilution, malnutrition, renal dysfunction, chronic inflammation, advanced age, and frailty, and was associated with poor prognosis in several HF studies [23,24]. In our study, a serum albumin level <3.1 g/dL was significantly associated with all-cause mortality. Similar to the study of Horwich et al. [23], these relations were independent of body weight and body mass index, suggesting that the pathophysiological pathway in hypoalbuminemia is distinct from that in cardiac cachexia. A Pearson correlation analysis performed in our study revealed a significant correlation between CRP and albumin level ($r=0.15$; $p=0.024$), suggesting the effect of systemic inflammation, which might be particularly exaggerated in patients with right-sided HF and hepatic congestion. Indeed, recent evidence suggests that systemic inflammation may be a primary regulator of hepatic protein metabolism, and that intrinsic liver damage due to chronic hepatic congestion associated with a dynamic systemic inflammatory state contributes more to hypoalbuminemia than nutritional status [25].

Table 4. Independent associates of all-cause mortality and re-hospitalization in competing risk regression analysis (hazard risks and 95% CI).

	SHR	Std. Err	z	P> z	[95% Conf. Interval]	
					Upper	Lower
NHYA class III/IV						
Re-hospitalization (a)	3.2612	1.2932	2.98	0.003	1.4991	7.0944
Death (b)	0.2735	0.3113	-1.14	0.255	0.0294	2.5458
Right-sided heart failure						
Re-hospitalization (a)	1.0801	0.2673	0.31	0.756	0.6650	1.7544
Death (b)	0.3893	0.1403	-2.62	0.009	0.1921	0.7890
NT-proBNP						
Re-hospitalization (a)	1.0001	0.0001	5.67	<0.001	1.0001	1.0001
Death (b)	0.9999	0.0001	-1.49	0.137	0.9997	1.0000
Diastolic blood pressure						
Re-hospitalization (a)	0.9837	0.0083	-1.95	0.051	0.9676	1.0001
Death (b)	0.9932	0.0161	-0.42	0.674	0.9622	1.0252
Age						
Re-hospitalization (a)	1.0116	0.0117	0.99	0.320	0.9889	1.0349
Death (b)	1.0564	0.0238	2.43	0.015	1.0107	1.1041
Left ventricular ejection fraction						
Re-hospitalization (a)	0.9800	0.0158	-0.70	0.487	0.9586	1.0203
Death (b)	0.9923	0.0271	-0.28	0.778	0.9406	1.0469
Sodium						
Re-hospitalization (a)	1.0059	0.0210	0.28	0.777	0.9656	1.0480
Death (b)	0.9599	0.0264	-1.49	0.137	0.9095	1.0131
Alanine Aminotransferase						
Re-hospitalization (a)	1.0003	0.0005	0.46	0.644	0.9992	1.0013
Death (b)	1.0003	0.0004	0.72	0.470	0.9995	1.0011
Albumin						
Re-hospitalization (a)	0.7714	0.1615	-1.24	0.215	0.5118	1.1627
Death (b)	0.4087	0.1397	-2.62	0.009	0.2092	0.7985
Mitral valve E/E' ratio						
Re-hospitalization (a)	1.0394	0.0195	2.06	0.040	1.0019	1.0784
Death (b)	0.9794	0.0570	-0.36	0.721	0.8739	1.0977
Uric acid						
Re-hospitalization (a)	1.0958	0.0429	2.33	0.020	1.0148	1.1832
Death (b)	0.8095	0.0753	-2.27	0.023	0.6746	0.9713

(a) – “Deaths” were used as competing risks; (b) – “Re-hospitalization” were used as competing risks.

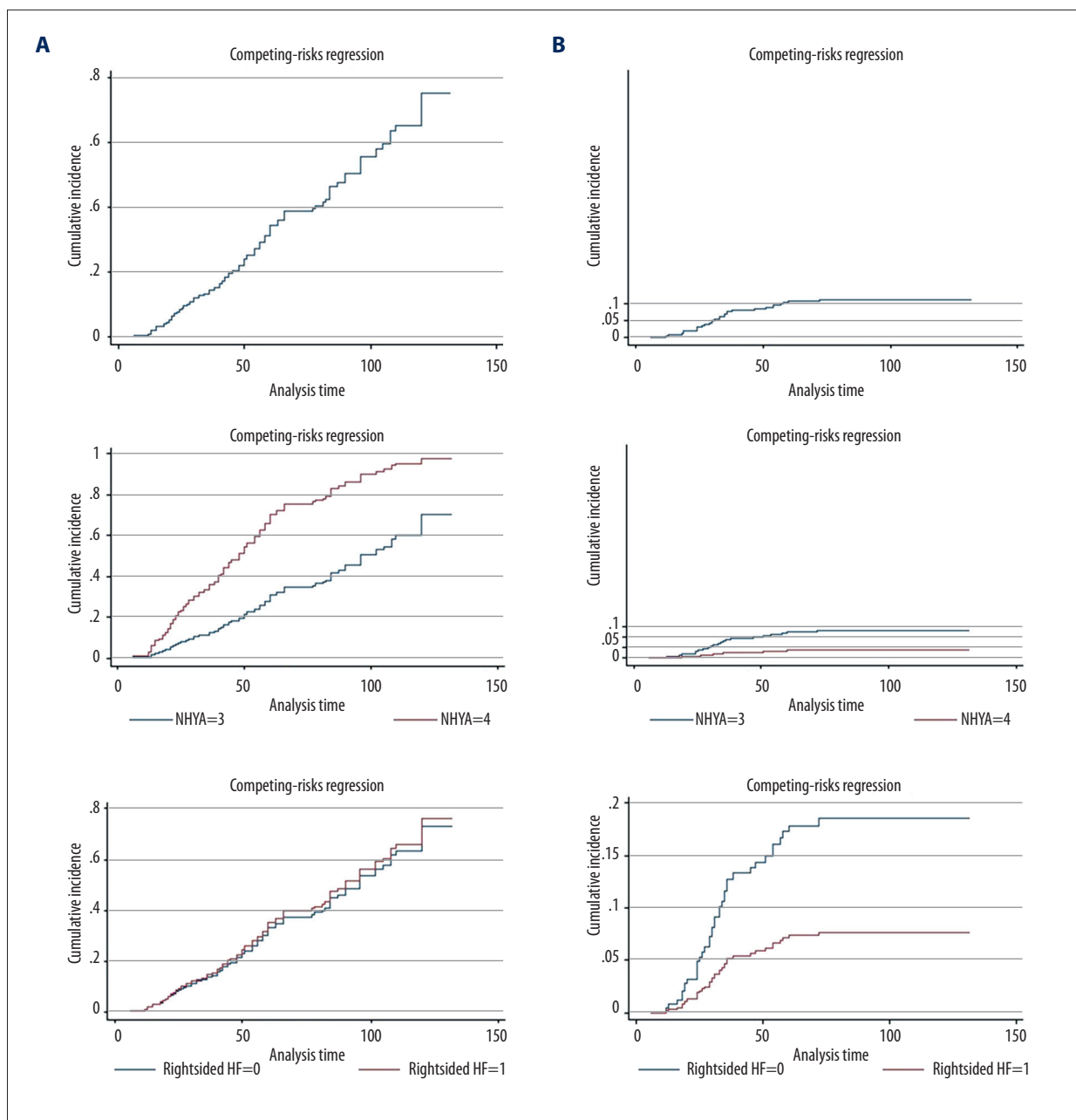


Figure 1. Cumulative Incidence Function for NYHA Class III/IV and right-sided heart failure frequent re-hospitalization and death [(A) “Deaths” were used as competing risks, (B) “Re-hospitalizations” were used as competing risks].

The predictors for re-hospitalization were different than the predictors for mortality. A NT-proBNP-level >2630 pg/dl and a mitral E/E' ratio >17.2 were significantly associated with recurrent hospitalization, whereas right-sided HF was no longer an independent determinant of re-hospitalization when mortality was used as the competing end-point. Results of this study are opposing the findings of Nunez et al. [26], who failed to show BNP as a predictor for readmissions due to ADHF, when death was used as a competing outcome. Discrepancies between the results of the 2 studies may be attributed to differences

between patient characteristics and variables used in the statistical models. The cut-off values found in our study were fairly similar to previously suggested cut-off levels in guidelines and suggest that congestion in these patients was not adequately relieved at the time of discharge. Current HF guidelines recommend measurement of natriuretic peptides before discharge to monitor therapy and congestion status [7,27]. Results of our study confirm this recommendation and suggest that re-consideration of congestion and its management will be important to prevent re-hospitalization in these patients.

Table 5. ROC analysis of the variables having an independent association with all-cause mortality and re-hospitalization in competing risk regression analysis.

	Cut-off value	AUC	95% CI	P
Albumin				
All-cause mortality	≤3.1 g/dL	0.684	0.619–0.744	<0.001
Re-hospitalization	≤3.0 g/dL	0.614	0.547–0.678	0.006
Uric acid				
All-cause mortality	≥5.8 pg/mL	0.511	0.444–0.578	0.775
Re-hospitalization	>8.8 pg/mL	0.632	0.566–0.695	0.002
NT-proBNP				
All-cause mortality	≥1160 pg/mL	0.542	0.475–0.608	0.275
Re-hospitalization	>2630 pg/mL	0.701	0.636–0.760	<0.001
Mitral valve E/E' ratio				
All-cause mortality	>12.7 g/dL	0.662	0.596–0.724	<0.001
Re-hospitalization	>17.2 g/dL	0.724	0.660–0.781	<0.001
Age				
All-cause mortality	>72 years	0.642	0.576–0.705	<0.001
Re-hospitalization	>70 years	0.547	0.479–0.613	0.257

An interesting finding of our study was the independent association of uric acid with both end-points in competing risk regression analysis. The cut-off value for uric acid (>5.8 mg/dl) to predict death was within the normal limits of the test (2.0-7.0 mg/dl) and was considerably lower than in the AHEAD study [28], which showed that an increased uric acid level in ADHF (>8.4 mg/dL) is as an independent prognostic factor for increased long-term mortality. The discrepancy between these results may again result from different patient characteristics and management. Nevertheless, the cut-off value for predicting frequent re-hospitalization (>8.8 mg/dl) in our study was similar to that of previous studies. Hyperuricemia may result from undersecretion of uric acid due to impaired renal function, use of diuretics, or overproduction of uric acid related to xanthine oxidase activation and the subsequent inflammation pathway [29]. It plays a significant role in cardiorenal disease due to its intracellular effects. Several studies observed improved survival with allopurinol [30,31], but due to the lack of landmark randomized controlled trials, administration of this drug is left to the judgment of clinicians.

Limitations of the study

This was a retrospective study based on review of patient files. Follow-up of the patients was gathered from patient files, computerized data of health maintenance organizations, hospital

visits, or telephone contact. Patient files suspected to be inaccurate or incomplete were excluded from the study. There may be several other confounding factors despite adjustment for well-known risk factors in modeling many variables. Changes in biochemical variables, medications, and adjustments in dosages during follow-up could not be followed in detail. Follow-up was performed via telephone contact; therefore, exact cause of death (e.g., sudden, cardiac, non-cardiac) could not be estimated.

Conclusions

ADHF patients with kidney dysfunction have a high risk for death and re-hospitalization despite being treated with beta-blockers and RAS-inhibitors. Predictors for all-cause mortality are related mainly to advanced (right-sided) HF, whereas predictors for frequent re-hospitalization are related to volume overload. Both situations necessitate further management strategies to improve abdominal and systemic congestion. Possible current and future treatment alternatives include ultrafiltration or continuous ambulatory peritoneal dialysis, using vasodilators such as serelaxin, and removal of sodium with neprilysin inhibitors and oral sodium binders [31,32]. Future studies specifically targeting HF patients with kidney dysfunction may give further clues to improve survival in these patients.

Medical record review and study protocol were approved by the Kocaeli University Medical Institutional Review Board (KÜ GOKAEK 114) and patient consent was not required for this study.

Disclosure of conflict of interest

The authors have nothing to declare for this study.

Disclosure of financial conflict of interest

The authors have nothing to declare for this study.

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