ORIGINAL ARTICLE

Acute kidney injury: a clinical issue in hospitalized patients with heart failure with mid-range ejection fraction

Radu I. Lala[1,2], Diana Lungeanu[3], Maria Puschita[1], Adina Pop-Moldovan[2], Dan Darabantiu[1,2]

1 Department of Cardiology, "Vasile Goldiş" West University of Arad, Arad, Romania
2 Department of Cardiology, Arad County Emergency Clinical Hospital, Arad, Romania
3 Department of Functional Sciences, Centre for Modeling Biological Processes and Data Analysis, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania

KEY WORDS

cardiorenal syndrome, heart failure, prognosis, renal insufficiency, ventricular ejection fraction

ABSTRACT

INTRODUCTION Acute kidney injury (AKI) during hospitalization is associated with increased mortality in patients with acute heart failure (AHF). In 2016, the European Society of Cardiology introduced the category of heart failure (HF) with mid-range ventricular ejection fraction (HFmrEF) as a distinct category from HF with preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF).

OBJECTIVES The aim of this study was to evaluate in-hospital mortality risk associated with AKI in patients with AHF, with a focus on the HFmrEF group.

PATIENTS AND METHODS A total of 365 health records of patients with a primary diagnosis of acute decompensated heart failure (ADHF) were reviewed. AKI was defined according to Acute Kidney Injury Network criteria. HF was diagnosed based on Framingham criteria. Patients with ADHF were evaluated as 3 separate groups, based on ventricular ejection fraction: HFpEF (≥50%), HFmrEF (40%–49%), and HFrEF (<40%). Risk and survival analyses were conducted on de-identified data.

RESULTS The AKI-associated in-hospital mortality odds ratios for HFmrEF and HFrEF groups were 4.55 (95% CI, 1.46–14.18) and 2.59 (95% CI, 1.05–6.41), respectively, with a highly significant difference between the groups ($P = 0.002$; Mantel–Haenszel test). The hazard ratios in the Cox proportional hazards model were 4.79 (95% CI, 1.54–14.96) and 2.94 (95% CI, 1.27–6.80) for HFmrEF and HFrEF groups, respectively.

CONCLUSIONS AKI was associated with a higher risk of mortality in patients with HFmrEF when compared with those with HFrEF, suggesting a stronger prognostic impact of AKI in patients with HFmrEF.

INTRODUCTION Cardiorenal syndrome (CRS) is a complex pathophysiologic disorder that describes the hemodynamic and neurohormonal interaction between the heart and kidney, whereby acute dysfunction in one organ leads to acute dysfunction in the other.[1] Acute kidney injury (AKI) is recognized to be an independent predictor of poor short- and long-term outcome in patients with acute decompensated heart failure (ADHF) due to fluid overload or low output,[2] although an aggressive decongestive therapy has been identified as having a positive effect on survival.[3] Renal function worsening has also been well described for patients with acute heart failure (AHF) admitted to intensive care units,[4] as its recognition is important not only for its clinical implications but also for the appropriate management of the patient.

On the other hand, epidemiological data are scarce when it comes to the incidence and outcome of AKI among hospitalized AHF patients classified according to their left ventricular ejection fraction (EF). In 2013, the American College of Cardiology Foundation/American Heart Association (ACC/AHA) introduced heart failure (HF) with borderline EF (range, 40% to 50%) as a subcategory of HF with preserved EF.[5] In 2016, the European Society of Cardiology (ESC) went further and classified HF with mid-range EF (HFmrEF) as a distinct category in their guidelines.[6] While the importance of comparing comorbidities and assessing risks for HFmrEF patients

Correspondence to:
Diana Lungeanu, PhD,
"Victor Babeş" University of Medicine and Pharmacy, P-ta Eftimie Murgu 2, 300041-Timişoara, Romania, phone: +40 256 490288,
email: dlungeanu@umft.ro
Received: August 17, 2018.
Revision accepted: October 31, 2018.
Published online: November 8, 2018.
Conflict of interest: none declared.
Pol Arch Intern Med. 2018; 128 (12): 746-754
doi:10.20452/pamw.4369

is acknowledged,[7-10] specific evidence and data on its subsequent application in everyday clinical practice are still limited.

This study aimed at evaluating the mortality prognosis of AKI in hospitalized patients with ADHF grouped according to their EF, with a focus on the HFmrEF condition.

PATIENTS AND METHODS

Study design and population A retrospective cross-sectional study on routinely collected medical data was conducted, including 365 consecutive patients admitted to the Cardiology Unit of Arad Emergency Clinical County Hospital, between July 2012 and December 2016, with a primary diagnosis of ADHF. Collected data were de-identified before conducting the statistical analysis and no written informed consent was needed for this secondary use of medical data. Included health records were reviewed and HF was diagnosed based on Framingham criteria.

The primary focus was on AKI among patients with HFmrEF, so we decided to estimate the necessary sample size for this group, and it resulted in a total of 142 patients (for hazard ratio [HR], 2; proportion of AKI-exposed patients, 0.3; baseline event rate, 0.06; average planned length of in-hospital follow-up, 21 days; median survival time, 11 days; censoring rate, 0.05; $\alpha = 0.05$; and $\beta = 0.2$). All consecutive patients who met the criterion for ADHF diagnosis were included (starting with December 2016 and going backwards in medical records archives). The only exclusion criteria were prior renal replacement therapy and active cancer. ADHF patients were evaluated as 3 separate groups, based on their left ventricular EF and according to the 2016 ESC guidelines on HF[6]: HFpEF (≥50%), HFmrEF (40%–49%), and HFrEF (≤40%). Overall data accrual stopped when the planned number for the HFmrEF group was attained. For each patient, data from medical records referring to the current episode of care were collected (ie, from hospital admission to discharge or death), including age, sex, New York Heart Association class, comorbidities, electrocardiographic parameters, laboratory data, and EF measured by cardiac ultrasonography (Simpson biplane method) were recorded.

AKI was evaluated based on Acute Kidney Injury Network (AKIN) criteria,[11] defined as an abrupt increase in serum creatinine levels (0.3 mg/dl within 48 h) and a percentage increase in serum creatinine levels of 50% or higher (1.5-fold increase from baseline). The AKIN criteria were chosen owing to their higher sensitivity in identifying patients with AKI compared with the RIFLE criteria, based on a meta-analysis of Xiong et al,[12] and their higher specificity for predicting primary outcomes at 30 days in ADHF patients, thus resulting in better positive predictive values in the short term.[13] Furthermore, due to the small number of patients with more than a 2-fold increase in serum creatinine levels from baseline (ie, describing greater renal injury), we agreed to focus on AKI diagnosis itself rather than to grade the condition.

Admission creatinine level was taken as the baseline. Each EF group was further divided into subgroups based on the presence of AKI. Comparisons were made between the resulting groups.

For AKI patients, the CRS was considered as type 1 in those with unknown kidney disease, type 2 in those with known chronic heart failure, and type 4 in those with known chronic kidney disease.[12] Information on medication at admission and during hospitalization was obtained from data sheets, and medication use was evaluated as risk factors for AKI development: angiotensin-converting enzyme inhibitors / adrenergic angiotensin receptor blockers, spironolactone, and furosemide, including a cumulative diuretic dose.

Data analysis Descriptive statistics included the observed frequency counts (percentage) for categorical variables and median (interquartile range) for numerical variables. Categorical variables were compared with the χ^2 test (either asymptotic or Monte Carlo simulation with 10 000 replicates) or the Fisher exact test. For a stratified analysis of categorical variables, the Mantel–Haenszel test was employed. Odds ratios (ORs) were used as risk estimates. The distribution of numerical variables across multiple groups was compared with the Kruskal–Wallis test.

Survival analysis was conducted to investigate the AKI-associated death among the 3 EF ranges, observing the Kaplan–Meier curves and applying the log-rank test. For survival time, the mean and standard error were used as descriptive statistics. To calculate the HRs, the Cox proportional hazards model was used, starting with crude models and further controlling for possible confounders related to age and sex, or associated comorbidities significant in a univariate analysis (the latter finally discarded in the analysis). The proportional hazards assumptions were evaluated using both graphic and goodness-of-fit approaches (ie, both log-log plots and correlation testing for the Schoenfeld residuals to ranked failure times). The regression models were compared using likelihood ratio statistic and the χ^2 test.

All reported probability values were 2-tailed, and the significance levels of 0.05 and 0.01 were assumed as denoting significant and highly significant results, respectively. Statistical analysis was conducted with SPSS v.20 and R v.3.2.3 software packages (https://www.r-project.org/; including "survival" and "powerSurvEpi" packages).

Ethical standards The study was approved by the Committee for Medical Research Ethics of Arad County Emergency Clinical Hospital. Patients were not required to give informed consent, because the analysis was conducted

TABLE 1 Baseline characteristics, physical signs, and laboratory results at admission for the 3 groups of hospitalized patients with heart failure (n = 365) and their respective subgroups according to the presence of acute kidney injury

Variable	HFpEF (n = 66)		HFmrEF (n = 142)		HFrEF (n = 157)		*P* value
	No AKI (n = 50)	AKI (n = 16)	No AKI (n = 105)	AKI (n = 37)	No AKI (n = 111)	AKI (n = 46)	
Age, y, median (IQR)	69.5 (62–76)	73 (61.5–78)	68 (61–77)	69 (60–77)	69 (62–73)	72 (65–76)	0.65
Female sex, n (%)	30 (60.0)	9 (56.2)	38 (36.9)	23 (62.2)	42 (37.8)	16 (34.8)	0.005
Hospitalization, d, median (IQR)	8 (7–12)	9 (7–15)	8 (5–13)	8 (6–14)	11 (6.5–15)	8 (5–14)	0.06
Death, n (%)	2 (4.0)	1 (6.7)	6 (5.7)	8 (21.6)	12 (10.8)	11 (23.9)	0.003
CKD, n (%)	17 (34.0)	8 (50.0)	33 (31.4)	24 (64.9)	45 (40.5)	27 (58.7)	0.001
Hypertension, n (%)	31 (62.0)	13 (81.2)	72 (68.6)	28 (75.7)	74 (66.7)	23 (50.0)	0.10
COPD, n (%)	8 (16.0)	6 (37.5)	10 (9.5)	6 (16.2)	15 (13.5)	2 (4.3)	0.02
Diabetes, n (%)	18 (36.0)	2 (12.5)	27 (25.7)	13 (35.1)	42 (37.8)	18 (39.1)	0.17
Ischemic HD, n (%)	18 (36.0)	5 (31.2)	55 (52.4)	21 (56.8)	58 (52.3)	19 (41.3)	0.14
Idiopathic HD, n (%)	4 (8.0)	–	10 (9.5)	7 (18.9)	12 (10.8)	2 (4.3)	0.21
Valvular HD, n (%)	22 (44.0)	5 (31.2)	41 (39.0)	14 (37.8)	61 (55.0)	29 (63.0)	0.02
Atrial fibrillation, n (%)	28 (56.0)	6 (37.5)	44 (41.9)	18 (48.6)	56 (50.5)	24 (52.2)	0.53
NYHA class at admission, n (%)							
I	1 (2.0)	–	–	–	–	–	<0.001
II	9 (18.0)	2 (12.5)	–	–	15 (13.5)	6 (13.0)	
III	28 (56.0)	11 (68.8)	52 (49.5)	17 (45.9)	28 (25.2)	17 (37.0)	
IV	12 (24.0)	3 (18.8)	53 (50.5)	20 (54.1)	68 (61.3)	23 (50.0)	
CRS type (8.8% missing), n (%)							
1	–	3 (18.75)	–	10 (27.03)	–	12 (26.09)	0.78
2	–	5 (31.25)	–	20 (54.05)	–	21 (45.65)	
4	–	2 (12.5)	–	7 (18.92)	–	13 (28.26)	

Data are presented as median (IQR), with the Kruskal–Wallis test applied to compare distributions across the 6 groups of AKI-EF combination, or as number (percentage) of patients, with the χ^2 test (either asymptotic or Monte-Carlo simulation with 10 000 samples) applied to investigate the significance of observed differences in proportions. $P < 0.05$ and $P < 0.01$ were considered significant and highly significant, respectively.

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRS, cardiorenal syndrome; EF, ejection fraction; HD, heart disease; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IQR, interquartile range; NYHA, New York Heart Association

retrospectively on de-identified medical data and each patient had agreed to treatment by written consent.

RESULTS **Baseline characteristics** The mean (SD) age of the study population was 68.56 (10.59) years, of which 44% were female. Of the total 365 patients, 66 (18.1%), 142 (38.9%), and 157 (43%) had HFpEF, HFmrEF, and HFrEF, respectively. AKI was diagnosed in 99 patients with ADHF (27.1%): 16 patients with HFpEF (4.4%), 37 patients with HFmrEF (10.1%), and 46 patients with HFrEF (12.6%). AKI patients in the HFmrEF group showed a higher prevalence of chronic kidney disease (CKD) than AKI patients in the HFrEF and HFpEF groups (64.9% vs 58.7% and 50%, respectively; $P = 0.001$). Chronic obstructive pulmonary disease was frequent in AKI patients with HFpEF, and valvular heart disease, in AKI patients with HFrEF. The detailed baseline characteristics are presented in TABLE 1.

The HFrEF-AKI group also had the worst kidney function, expressed as glomerular filtration rate ($P < 0.001$). There were no significant differences regarding the medication use between the AKI subgroups. The results of medical investigations and the medication use prior to and during the current episode of care are shown in TABLE 2.

For exploratory purposes, in TABLES 1 and 2, the statistical tests were first conducted across the 6 groups of AKI-EF combinations (a comparison of AKI vs non–AKI groups for each EF category would have unnecessarily inflated the risk of type 1 statistical error). When the test across the 6 groups was statistically significant, further testing was carried out for each AKI/non–AKI condition across the 3 EF groups.

Acute kidney injury and in-hospital mortality risk A total of 40 in-hospital deaths (10.96%) were recorded. The risk analysis for AKI-associated mortality in the 3 EF groups is shown in TABLE 3. There was no association in the HFpEF group, while the ORs for the other 2 groups were high and significant. The risk in the HFmrEF group was higher (with a significant difference between the 2 EF categories, as demonstrated by the Mantel–Haenszel test).

TABLE 2 Medical investigations, laboratory results, and medication for the 3 groups of hospitalized patients heart failure (n = 365) and their respective subgroups according to the presence of acute kidney injury (continued on the next page)

Variable	HFpEF (n = 66)		HFmrEF (n = 142)			HFrEF (n = 157)	*P* value
	No AKI (n = 50)	AKI (n = 16)	No AKI (n = 105)	No AKI (n = 50)	AKI (n = 16)	No AKI (n = 105)	
Systolic BP, mm Hg, median (IQR)[a]	140 (120–155)	160 (125–165)	140 (120–170)	160 (130–185)	140 (120–165)	145 (120–170)	0.09
Diastolic BP, mm Hg, median (IQR)[a]	80 (60–90)	90 (80–100)	80 (75–100)	95 (80–112.5)	80 (70–100)	80 (70–107.5)	0.05
Heart rate, bpm, median (IQR)[a]	85 (72–103)	96 (82.5–100)	92 (80–116)	100 (90–105)	90 (80–108)	100 (86.5–120)	0.08
QRS complex, ms, median (IQR)[b]	98 (89.5–118.5)	99 (88.5–115)	105 (98–120)	106 (96.5–120)	120.5 (94–138)	110 (96–136)	0.001 (no AKI) 0.24 (AKI)
EF, %, median (IQR)[a]	50 (50–56)	50.5 (50–56.5)	43 (40–45)	43 (40–45)	28 (25–31.5)	30 (25–35)	NA
Creatinine at admission, mg/dl, median (IQR)[b]	1.07 (0.78–1.25)	1.04 (0.9–1.5)	1.0 (0.9–1.2)	1.30 (1.0–2.1)	1.15 (0.9–1.46)	1.31 (0.96–1.85)	0.04 (no AKI) 0.25 (AKI)
Creatinine at 48 hours, mg/dl, median (IQR)[b]	1.04 (0.8–1.25)	1.44 (1.25–1.83)	1.0 (0.9–1.2)	1.53 (1.27–2.47)	1.11 (0.9–1.44)	1.55 (1.25–2.39)	0.02 (no AKI) 0.79 (AKI)
Creatinine, mg/dl, median (IQR)[b,c]	0.02 (–0.06 to 0.1)	0.47 (0.31–0.56)	0 (–0.1 to 0.1)	0.37 (0.3–0.36)	0 (–0.15 to 0.13)	0.41 (0.33–0.54)	0.88 (no AKI) 0.73 (AKI)
Urea, mg/dl, median (IQR)[b]	43 (30–59)	44 (30–66)	5 (32–385)	191 (88–1198)	50 (35–71)	57 (40–86)	0.02 (no AKI) 0.07 (AKI)
Na (45% missing), mmol/l, median (IQR)[b]	140 (137–142)	140 (136.5–146.5)	137 (135–140)	137 (135–141)	137 (132.5–140)	140.5 (136–143)	0.03 (no AKI) 0.41 (AKI)
K (36% missing), mmol/l, median (IQR)[b]	4.2 (3.65–4.6)	4.1 (3.55–4.3)	4 (3.6–4.5)	4 (3.7–4.8)	4 (3.55–4.6)	4.45 (3.8–4.8)	0.73 (no AKI) 0.29 (AKI)
Glycemia (16.4% missing), mg/dl, median (IQR)[b]	113.5 (100–157)	99.5 (94.5–145)	110.5 (91–136.5)	160 (108–251.5)	120 (94–168)	138 (95–189)	0.29 (no AKI) 0.10 (AKI)
GFR, ml/min/1.73 m^2, median (IQR)[b]	71 (47–90)	48 (42.5–76)	73 (56–89)	45 (27–63)	58 (45–84.5)	41.5 (23–54)	0.03 (no AKI) 0.10 (AKI)
Hemoglobin (34.5% missing), g/dl, median (IQR)[a]	13.15 (11.9–14.7)	13 (11.85–14.7)	13.4 (11.3–14.1)	11.65 (10–14.5)	13.1 (11.65–14.15)	13 (11.35–15)	0.62
ACEI prev. (8.8% missing), n (%)	12 (24)	2 (12.5)	15 (14.3)	6 (16.2)	36 (32.4)	12 (26.1)	0.002
ACEI hosp. (8.8% missing), n (%)	13 (26)	2 (12.5)	56 (53.3)	21 (56.8)	49 (44.1)	20 (43.5)	0.24
ARB prev. (8.8% missing), n (%)	1 (2)	1 (6.25)	3 (2.9)	4 (10.8)	1 (0.9)	1 (2.2)	0.08

TABLE 2 Medical investigations, laboratory results, and medication for the 3 groups of hospitalized patients heart failure (n = 365) and their respective subgroups according to the presence of acute kidney injury (continued on the next page)

Variable	HFpEF (n = 66)		HFmrEF (n = 142)		HFrEF (n = 157)		*P* value
	No AKI (n = 50)	AKI (n = 16)	No AKI (n = 105)	No AKI (n = 50)	AKI (n = 16)	No AKI (n = 105)	
ARB hosp. (8.8% missing), n (%)	3 (6)	1 (6.25)	4 (3.8)	1 (2.7)	12 (10.8)	0	0.07
MRA hosp. (8.8% missing), mg, median (IQR)[b]	0 (0–37.5)	0 (0–50)	0 (0–50)	0 (0–0)	25 (0–50)	0 (0–25)	0.13 (no AKI) 0.49 (AKI)
Furosemide hosp. (8.8% missing), mg, median (IQR)[b]	40 (0–40)	40 (0–60)	40 (40–40)	40 (40–60)	40 (40–60)	40 (0–60)	0.04 (no AKI) 0.72 (AKI)
NYHA class at discharge, n (%)							
I	1 (2.0)	–	1 (1.0)	–	–	–	<0.001
II	26 (52.0)	6 (37.5)	44 (41.9)	8 (21.6)	21 (18.9)	6 (13.0)	
III	21 (42.0)	8 (50.0)	51 (48.6)	18 (48.6)	72 (64.9)	32 (69.6)	
IV	2 (4.0)	2 (12.5)	9 (8.6)	11 (29.7)	18 (16.2)	8 (17.4)	

Data are presented as median (IQR)[a,b] or as number (percentage)[d]. $P < 0.05$ and $P < 0.01$ were considered significant and highly significant, respectively.

a The Kruskal–Wallis test was applied to compare distributions across the 6 groups of AKI-EF combination.

b The Kruskal–Wallis test was applied to compare distributions across the 3 EF groups for no-AKI and AKI subgroups, respectively (*P* values are specified for the 2 subgroups)

c Difference between serum creatinine levels at admission and at 48 hours since admission.

d The χ^2 test (asymptotic or Monte-Carlo simulation with 10 000 samples) was applied to investigate the significance of observed differences in proportions between the 6 groups of AKI-EF combination.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; EF, ejection fraction; GFR, glomerular filtration rate; K, potassium; hosp., diagnosed or prescribed during hospital stay, during the current episode of care; MRA, mineralocorticoid antagonist; Na, sodium; NA, not applicable; prev., previously diagnosed or prescribed, before the current episode of care; others, see **TABLE 1**

TABLE 3 Analysis of the risk for in-hospital mortality for heart failure with preserved, mid-range, and reduced ejection fraction associated with acute kidney injury

HF group	AKI		Deaths, n (%)[a]	*P* value; Fisher exact test (2-sided)	OR (95% CI)	Mantel–Haenszel test for conditional independence of HF groups[b]
HFpEF (n = 66)	No	50	2 (4)	1	1.60 (0.14–18.91)	–
	Yes	16	1 (6.2)			
HFmrEF (n = 142)	No	105	6 (5.7)	0.01	4.55 (1.46–14.18)	$\chi^2 = 10.063$ (df = 1) $P = 0.002$
	Yes	37	8 (21.6)			
HFrEF (n = 157)	No	111	12 (10.8)	0.047	2.593 (1.05–6.41)	
	Yes	46	11 (23.9)			

a Fisher exact test was applied to investigate the significance of observed differences in proportions.

b Two subgroups were compared: HFmrEF and HFrEF.

$P < 0.01$ was considered highly significant.

Abbreviations: HF, heart failure; OR, odds ratio; others, see **TABLE 1**

Acute kidney injury–associated mortality hazard ratio for acute decompensated heart failure patients with mid-range ejection fraction The survival analysis of AKI-associated mortality for the 3 EF groups is presented in **TABLE 4**. It shows a highly significant shortening of the survival time for the AKI subgroups both in the HFmrEF and HFrEF groups. The overall median survival time was 45 days (95% CI, 15.47–74.53), although it could not be determined for each group due to the limited follow-up duration (ie, in-hospital episode of care). The survival curves for the 3 EF groups are shown in **FIGURE 1A–1C**.

The Cox proportional hazards regression analysis (**TABLE 5**) was conducted for the 2 EF groups that showed the association of AKI with a higher

TABLE 4 Survival analysis of mortality for heart failure with preserved, mid-range, and reduced ejection fraction associated with acute kidney injury

HF group	AKI	n	No. of events	Censored	Survival time, d, mean (SE)	Log-rank test
HFpEF (n = 66)	No	50	2	48	46.92 (3.91)	$\chi^2 = 0.043$ (df = 1)
	Yes	16	1	15	21.5 (2.48)	$P = 0.85$
HFmrEF (n = 142)	No	105	6	99	34 (2.13)	$\chi^2 = 8.928$ (df = 1)
	Yes	37	8	29	17.27 (1.41)	$P = 0.003$
HFrEF (n = 157)	No	111	12	99	32.63 (3.56)	$\chi^2 = 7.072$ (df = 1)
	Yes	46	11	35	19.13 (1.49)	$P = 0.008$

Overall comparison adjusted for the HF group: log-rank test, $\chi^2 = 14\,588$ (df = 1); $P < 0.001$ was considered highly significant.

Abbreviations: see TABLES 1 and 3

TABLE 5 Cox regression analysis of mortality for heart failure with mid-range and reduced ejection fraction associated with acute kidney injury

HF group	Model[a,b]	HR (95% CI)	–2LogL	LR significance[a]
HFmrEF	Model 1: Baseline AKI	4.79 (1.54–14.96)	108.639	0.003
	Model 1 adjusted for age and sex	4.299 (1.36–13.64)	105.943	0.26
HFrEF	Model 2: Baseline AKI	2.94 (1.27–6.80)	173.54	0.008
	Model 2 adjusted for age and sex	2.83 (1.17–6.83)	172.678	0.35

a Model 1 and Model 2 are the crude models to which possible confounders were subsequently added. Successive models were compared using the LR statistic and the χ^2 test.

b The proportional hazards assumptions were evaluated and were met.

$P < 0.001$ was considered highly significant.

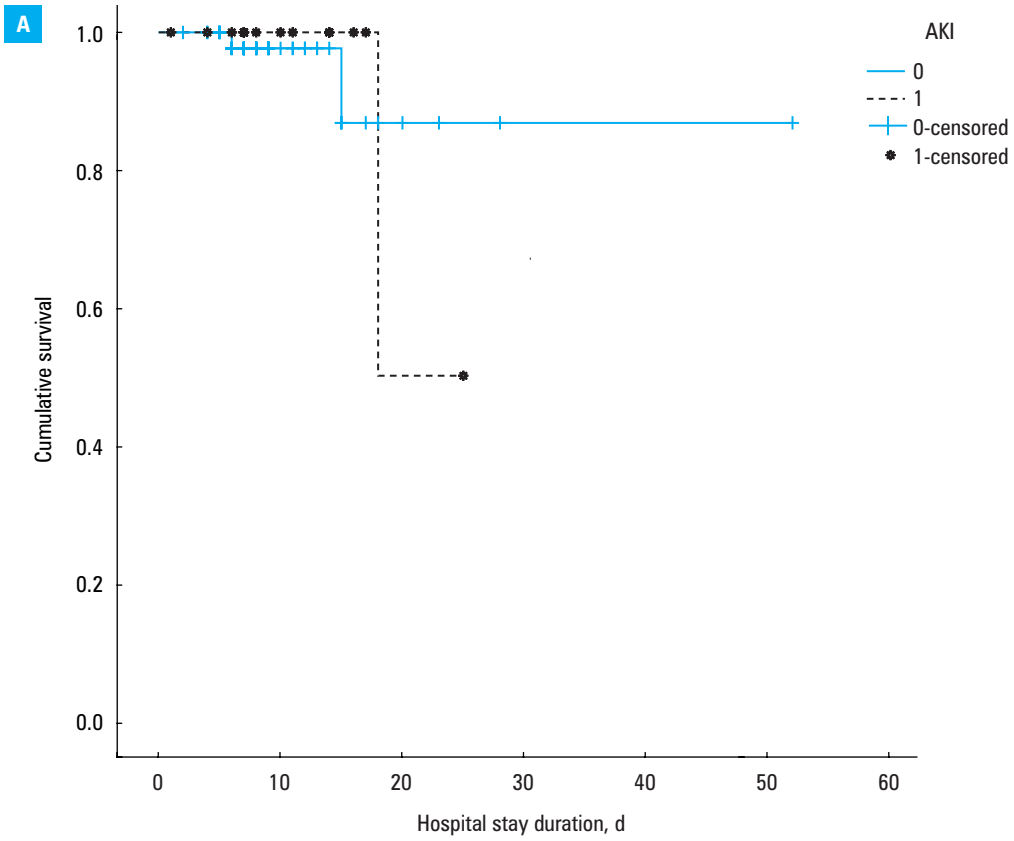
Abbreviations: HR, hazard ratio; LR, likelihood ratio; others, see TABLES 1 and 3

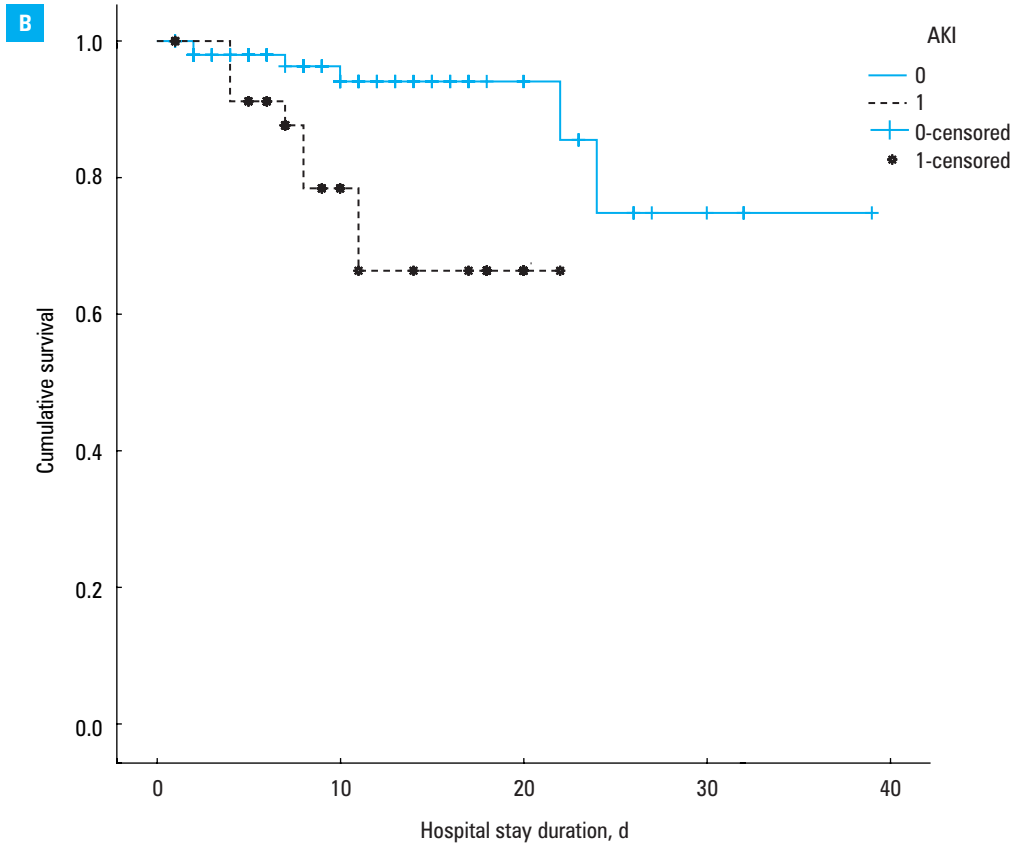
number of events and decreased survival time (log-rank test, $P < 0.05$): HFmrEF and HFrEF.

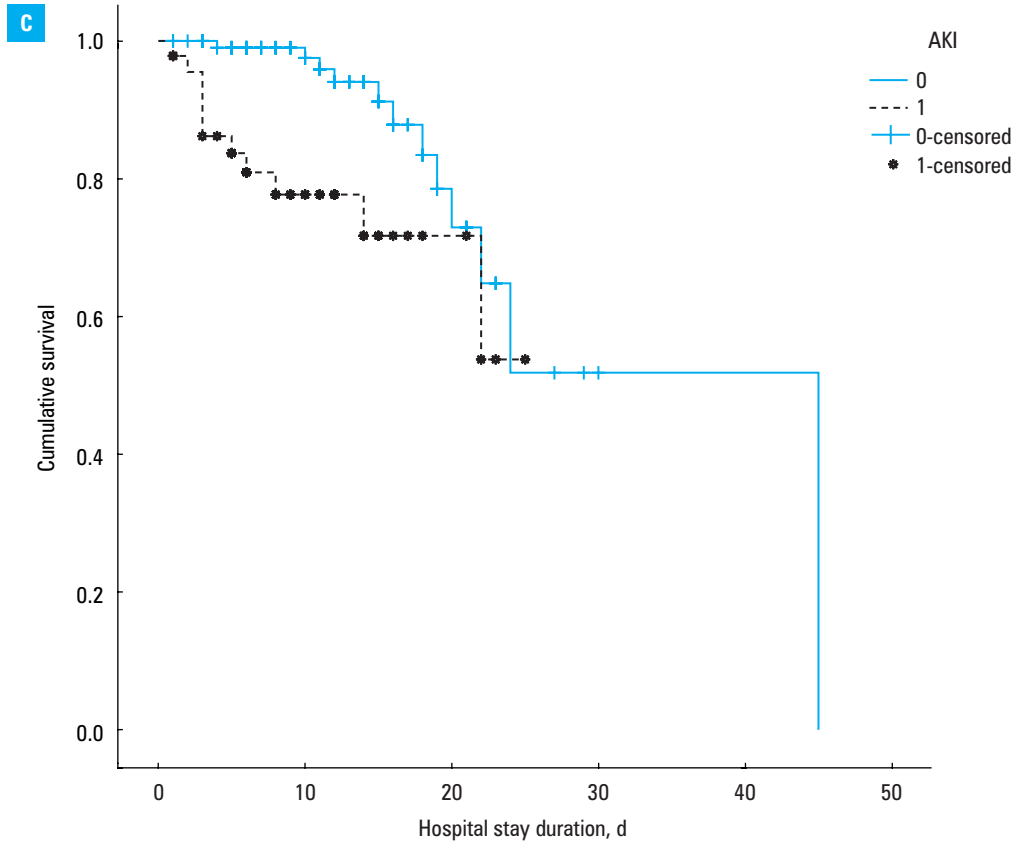
DISCUSSION **Acute kidney injury and in-hospital mortality risk** Though different classification criteria are being used in medical practice, comparing results across the studies is of great interest. Roy et al[13] considered and discussed the pros and cons of AKI definitions and rankings, with the ensuing consequences, concluding that the differences in terms of predictive abilities were only marginal. Therefore, we compared the results to other studies on ADHF patients, irrespective of their classification system, and found that AKI incidence at admission was similar[14-16]: 24%, 26%, and 29% for HFpEF, HFmrEF, and HFrEF, respectively. On the other hand, the overall proportion of HFpEF patients in this study was unusually small when compared to larger-size, registry-based studies.[17,18] We observed a higher proportion of acute worsening of renal function in patients with HFmrEF and pre-existing CKD. Zhou et al[19] already reported the pre-existing CKD as a risk factor for AKI in ADHF patients, and Yamigishi et al[20] demonstrated that a history of hypertension was a risk factor for AKI in ADHF patients. Considering that additional studies reported acute worsening of renal function during hospitalization,[18,21-23] we focused on the creatinine change within the first 48 hours from admission in order to minimize this possible issue and study patients at risk due to AHF. While the overall percentage of deaths was higher among HFrEF patients, the AKI-associated in-hospital mortality risk resulted in an almost twice higher OR for HFmrEF patients than for HFrEF patients. This suggests a stronger impact of AKI on the clinical evolution in the HFmrEF group. Though Kapoor et al[24] reported worsening renal failure as an independent risk factor for in-hospital mortality in patients with HF irrespective of EF, the present results partially confirm previously reported risk values for in-hospital mortality associated with AKI in AHF patients,[15,25-27] also bringing new information for each range of left ventricular EF.

Acute kidney injury–associated mortality hazard ratio for acute decompensated heart failure patients with mid-range ejection fraction Not surprisingly, AKI proved to be a highly significant discriminatory factor in the survival analysis for both HFmrEF and HFrEF patients. According to Nauta et al,[28] there is a high resemblance between HFmrEF and HFrEF with respect to ischemic etiology, biomarkers, and response to treatment. Ronco et al[29] showed that, in AHF, AKI might be a consequence of both backward failure (due to increased intra-abdominal and central venous

FIGURE 1
Kaplan–Meier curves for in-hospital mortality associated with acute kidney injury in hospitalized patients with heart failure with preserved ejection fraction (EF) (**A**), mid--range EF (**B**); and reduced EF (**C**)







pressure, thus indicating CRS type 2) and forward failure (low output state indicating CRS type 1), combined with neurohormonal activation, hypothalamic-pituitary stress reaction, and inflammation. The Cox regression analysis conducted in the present study provided evidence that an AKI-associated HR for HFmrEF was even higher than for HFrEF.

Strengths and limitations The main strength of this pilot study consists in evaluation of the AKI association with mortality risk in ADHF patients, while considering the 3 EF ranges according to recent ESC and ACC/AHA guidelines. An important limitation is the retrospective cross-sectional observational design, as it is unable to distinguish antecedent from consequent in clinical conditions and to calculate population-based rates, the latter shortcoming leading to a sample size discrepancy between the HFpEF and the other 2 EF groups. This difference might be explained by the fact that HFpEF patients had been earlier discharged from the emergency room after having received decongestive therapy, so no data were available in the reviewed medical records. Due to limited information in medical records, the differentiation between CRS type 2 and 4 was also challenging. An additional limitation is the retrospective design: the medical decision was based mainly on the clinical signs (ie, serum biomarkers not available for all cases) and the baseline AKI diagnosis was solely made at admission (ie, no reassessment during hospitalization and no severity grading).

Conclusions This pilot study provides novel insights into renal injury in the AHF setting, while considering the newly proposed classification for left ventricular EF. HFmrEF is an emerging category from the previously recognized HF classifications, and it seems to have distinct characteristics with serious survival impact on hospitalized patients. Though larger studies are needed to explore the mechanisms and strategies to distinguish the primary origin of kidney injury in these ADHF populations and develop evidence-based therapies, the present study proved that AKI is significantly associated with a higher risk of mortality in patients with HFmrEF when compared with those with HFrEF, thus implying a stronger impact of AKI on their outcome.

ACKNOWLEDGMENTS This research did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONTRIBUTION STATEMENT Concept for the study and extraction of medical data: RIL, DD, MP, and AP-M. Data analysis and interpretation: RIL, DL, and DD. Writing the manuscript: RIL and DL. All authors contributed to drafting and revising the manuscript for intellectual content, approved the final version, and agreed to be accountable for all aspects of the work.

REFERENCES

1 Ronco C, Haapio M, House AA, et al. Cardiorenal syndrome. J Am Coll Cardiol. 2008; 52: 1527-1539.

2 Han SW, Ryu KH. Renal dysfunction in acute heart failure. Korean Circ J. 2011; 41: 565-574.

3 Testani JM, Chen J, McCauley BD, et al. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. Circulation. 2010; 122: 265-272.

4 Hoste EAJ, Clermont G, Kersten A, et al. RIFLE criteria for acute kidney injury is associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care. 2006; 10: R73.

5 Yancy CW, Jessup M, Bozkurt B, et al. ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013; 62: e147-e239.

6 Ponikowski P, Voors AA, Anker SD, et al; Authors/Task Force Members; Document Reviewers. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016; 18: 891-975.

7 Hsu JJ, Ziaeian B, Fonarow GC. Heart failure with mid-range (borderline) ejection fraction: clinical implications and future directions. JACC Heart Fail. 2016; 5: 763-771.

8 Lam CSP, Teng THK. Understanding heart failure with mid-range ejection fraction. JACC Heart Fail. 2016; 4: 473-476.

9 Lund LH. Heart failure with "mid-range" ejection fraction – new opportunities. J Card Fail. 2016; 22: 769-770.

10 Pérez-Calvo JI, Josa-Laorden C, Rubio-Gracia J, Giménez-López I. Comorbidities in heart failure with mid-range ejection fraction. Eur J Intern Med. 2017; 41: e27-e28.

11 Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2006; 11: R31.

12 Xiong J, Tang X, Hu Z, et al. The RIFLE versus AKIN classification for incidence and mortality of acute kidney injury in critical ill patients: a meta-analysis. Sci Rep. 2015; 5: 17917.

13 Roy AK, Mc Gorrian C, Treacy C, et al. A comparison of traditional and novel definitions (RIFLE, AKIN, and KDIGO) of acute kidney injury for the prediction of outcomes in acute decompensated heart failure. Cardiorenal Med. 2013; 3: 26-37.

14 Di Lullo L, Bellasi A, Barbera V, et al. Pathophysiology of the cardio-renal syndromes types 1-5: an uptodate. Indian Heart J. 2017; 69: 255-265.

15 Hata N, Yokoyama S, Shinada T, et al. Acute kidney injury and outcomes in acute decompensated heart failure: evaluation of the RIFLE criteria in an acutely ill heart failure population. Eur J Heart Fail. 2010; 12: 32-37.

16 Shirakabe A, Hata N, Kobayashi N, et al. Prognostic impact of acute kidney injury in patients with acute decompensated heart failure. Circ J. 2013; 77: 687-696.

17 Löfman I, Szummer K, Dahlström U, et al. Associations with and prognostic impact of chronic kidney disease in heart failure with preserved, mid-range, and reduced ejection fraction. Eur J Heart Fail. 2017; 19: 1606-1614.

18 Lazzeri C, Valente S, Tarquini R, Gensini GF. Cardiorenal syndrome caused by heart failure with preserved ejection fraction. Int J Nephrol. 2011; 2011: 634903.

19 Zhou Q, Zhao C, Xie D, et al. Acute and acute-on-chronic kidney injury of patients with decompensated heart failure: impact on outcomes. BMC Nephrol. 2012; 13: 51.

20 Yamagishi T, Matsushita K, Minamishima T, et al. Comparison of risk factors for acute worsening renal function in heart failure patients with and without preserved ejection fraction. Eur J Intern Med. 2015; 26: 599-602.

21 Palazzuoli A, Ruocco G, Ronco C, McCullough PA. Loop diuretics in acute heart failure: beyond the decongestive relief for the kidney. Crit Care. 2015; 19: 296.

22 Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med. 2014; 370: 1383-1392.

23 Solomon SD, Zile M, Pieske B, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet. 2012; 380: 1387-1395.

24 Kapoor JR, Kapoor R, Ju C, et al. Precipitating clinical factors, heart failure characterization, and outcomes in patients hospitalized with heart failure with reduced, borderline, and preserved ejection fraction. JACC Heart Fail. 2016; 4: 464-472.

25 Vandenberghe W, Gevaert S, Kellum JA. Acute kidney injury in cardiorenal syndrome type 1 patients: a systematic review and meta-analysis. Cardiorenal Med. 2016; 6: 116-128.

26 Metra M, Davison B, Bettari L, et al. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. Circ Heart Fail. 2012; 5: 54-62.

27 Yamada T, Morita T, Furukawa Y, et al. Moderate to severe acute kidney injury has a long-term prognostic significance in cardiovascular and renal outcomes in acute heart failure patients with reduced but not preserved ejection fraction. Eur Heart J. 2013; 34 (suppl 1): P1532.

28 Nauta JF, Hummel YM, van Melle JP, et al. What have we learned about heart failure with mid-range ejection fraction one year after its introduction? Eur J Heart Fail. 2017; 19: 1569-1573.

29 Ronco C, Cicoira M, McCullough PA. Cardiorenal syndrome type 1: pathophysiological crosstalk leading to combined heart and kidney dysfunction in the setting of acutely decompensated heart failure. J Am Coll Cardiol. 2012; 60: 1031-1042.