ORIGINAL ARTICLE

Fractional excretion of sodium and 1-year cardiovascular mortality in acute decompensated heart failure, is there any relationship?

Seyed Hossein Sharoubandi[1], Maryam Moshkani Farahani[1], Arezoo Khosravi[1], Najmeh Rabanipour[2]

[1]Atherosclerosis Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran, [2]Department of Biostatistics and Epidemiology, School of Health, Isfahan University of Medical Science, Isfahan, Iran

Background: Renal impairment (RI), the most common comorbidity in acute decompensated heart failure (ADHF) patients, leads to cardiorenal syndrome. Fractional excretion of sodium (FENa), an indicator of sodium handling by the kidney, is widely used to assess natriuresis, the underlying treatment of ADHF. The aim of this study was to investigate the association of FENa with RI and 1-year cardiovascular mortality. **Materials and Methods:** This prospective study was implemented in the Persian Registry of Cardiovascular Disease/Heart Failure study context. Any individuals over 18 years suffering from ADHF admitted to the emergency department were eligible to be recruited in our study. We excluded the patients with previously untreated chronic comorbidities, who died during hospitalization, and without follow-up and other etiologies rather than cardiovascular diseases since discharge. Baseline demographic and clinical data gathered. RI was defined as a 0.3 mg/dL rise of creatinine during admission. The primary and secondary clinical outcomes were RI and cardiovascular mortality, respectively. **Results:** During the study period, 158 patients were recruited, with 103 (65.1%) developing RI and 25.68% of the population expired. Higher blood pressure, overall furosemide dose, as well as lower FENa, and serum creatinine on admission were prevalent among patients who developed RI. Greater serum sodium levels on admission and discharge, a lack of a history of ischemic heart disease, and hyponatremic status during admission were associated with a higher mortality rate. The Pearson correlations demonstrate the significant association of FENa with creatinine alterations (P = 0.001, r = −0.47). The linear regression analysis demonstrates the significant association of FENa with creatinine alteration during admission (B = −1.43, 95% confidence interval [CI] [− 1.86, −1.002], P = 0.001). Multiple logistic regression demonstrates no significant association of prediction of FENa with creatinine alterations (odds ratio [OR] =0.33, 95% CI [0.09–1.19], P = 0.091). The logistic regression analysis revealed no association between FENa and 1-year mortality (OR = 0.85, 95% CI (0.26–2.75), P = 0.79). **Conclusion:** A lower FENa on admission indirectly predicts the development of RI in patients with ADHF. Meanwhile, FENa is unable to predict 1-year cardiovascular mortality.

Key words: Fractional excretion of sodium, heart failure, mortality, renal impairment

How to cite this article: Sharoubandi SH, Farahani MM, Khosravi A, Rabanipour N. Fractional excretion of sodium and 1-year cardiovascular mortality in acute decompensated heart failure, is there any relationship? J Res Med Sci 2025;30:41.

INTRODUCTION

Heart failure (HF) is a syndrome of the inappropriate ability of the heart to respond to the body's metabolic needs due to functional and structural defects, which causes a high mortality rate and heavy economic burden annually.[1,2]

Renal impairment (RI), defined by a 0.3 mg/dL (26.5 mmol/L) rise in serum creatinine, is the most common and confounding comorbidity seen in the setting of HF. Furthermore, RI is a component of different types of cardiorenal syndromes (CRSs). Recent literature revealed that 25% of admitted patients with acute decompensated HF (ADHF) suffered from type 1 of CRS and pointed toward worse outcomes.[3,4]

Aggressive diuresis, the underlying treatment of ADHF, plays a crucial role in RI by inducing sodium

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jrms

DOI: 10.4103/jrms.jrms_153_23

Address for correspondence: Dr. Seyed Hossein Sharoubandi, Atherosclerosis Research Center, Baqiyatallah University of Medical Sciences, Vanak Square, Mollasadra Street, Tehran, Iran.
E-mail: hsharoo. 1975@gmail.com

Submitted: 09-Mar-2023; **Revised:** 04-Nov-2023; **Accepted:** 03-Apr-2024; **Published:** 30-Aug-2025

depletion and subsequent volume loss. On the other hand, the activation of mechanisms, including renin–angiotensin–aldosterone system (RAAS), sympathetic nervous system (SNS), and antidiuretic hormone, due to left ventricular dysfunction causes volume overload by inducing sodium resorption and subsequent RI.[5,6]

At first, in 1976, Espinel showed fractional excretion of sodium (FENa) to be beneficial in differentiating prerenal and intrinsic acute kidney injury (AKI).[7] FENa is widely used in studies due to being an indicator of sodium handling by kidneys.[8] However, FENa performance in diagnosing AKI has been inconsistent in the various studies due to multiple reported confounders. Although concurrent use of diuretics is an important confounder, previous studies revealed different cutoffs for diuretic resistance based on the studied population as an important prognostic factor for in-hospital and short-term mortality in patients with ADHF.[6,9-13]

RI, the principal prognostic mortality factor, makes it the target in the comorbidities treatment of ADHF patients. Meanwhile, the mentioned pathophysiologic pathways lead to RI by changes in sodium serum level and make FENa an objective origin, an economically inexpensive, and wildly available instrument for detecting RI. Thus, this study aims to evaluate if FENa significantly predicts RI and 1-year cardiovascular mortality in patients with ADHF.

METHODS

Study design

Briefly, the Persian Registry of Cardiovascular Disease/HF (PROVE/HF) study is a registry of HF patients' data based on the International Classification of Disease, 10th revision from 18 distinct cardiac centers, Isfahan Province, Iran, launched in March 2015.[14] The data were gathered continuously through a questionnaire containing 27 parts comprising demographic, underlying, and comorbid diseases leading to HF, past medical history, preadmission medication usage, and any medical treatment implemented during hospitalization from medical records of hospital archives by trained data collectors. The study was conducted under the Declaration of Helsinki, and written informed consent was obtained before enrollment. This study was approved by the research ethics committee, with ethical code # IR.BMSU.REC.1399.534 (Clinical trial number: 99000679).

Data collection, definitions, and outcomes

This prospective single-center cohort study was implemented in the PROVE/HF study context. From April 2020 to March 2022, any individuals aged over 18 years suffering from ADHF, regardless of the disease onset, admitted to the emergency department were eligible to be recruited in our study. We excluded the patients with previously untreated chronic comorbidities, including malignancies, severe infections, liver disease, current corticosteroid-or chemotherapeutic-based agents, and those who died during hospitalization or without follow-up, and other etiologies rather than cardiovascular diseases (CVDs) since discharge.

Consecutive patients who fulfilled our inclusion criteria were recruited for the study. The information, including demographic data, clinical data, laboratory outcomes, and medications, was gathered during the follow-up period (1st year and annually). The age, gender, height, weight, smoking habits, and history of ischemic heart diseases (IHDs), diabetes mellitus (DM), hypertension, and kidney diseases were gathered. Moreover, data on preadmission medication, including beta-blockers (BBs), angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), diuretics, and mineralocorticoid receptor antagonists (MRAs), were asked. Furthermore, the patients were divided into two groups: patients with ischemic cardiomyopathy (ICMP) and patients with non-ICMP (NICMP). For the ICMP group, patients with a history of previous myocardial infarction documented by the finding of an abnormal Q wave on electrocardiography, elevated cardiac enzyme levels on laboratory testing during hospitalization for acute coronary syndrome, and localized akinesia on echocardiography, with evidence of obstructive coronary disease on angiography, were included. In the NICMP group, the exclusion of myocardial ischemia was done by coronary angiography or computed tomography angiography. The heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and left ventricular ejection fraction were also assessed since admission. FENa was calculated by dividing the sodium clearance over creatinine clearance, using the same blood and urine spot samples drawn on admission before giving furosemide. All patients were on loop diuretic therapy and evaluated daily by an expert physician about the appropriate dose and route of administration of loop diuretics. The oral form of diuretic was considered equivalent to a half dose of the intravenous form.[15] Body mass index was calculated by division of weight (in kilograms) over height (in squared meters) (kg/m^2). Regardless of the etiology, RI was defined as the primary clinical outcome of the study. Short-term mortality (1 year) because of CVD was defined as the secondary clinical outcome of the study.

Statistical analysis

Continuous and categorical data were reported as mean ± standard deviation and frequency (percentage), respectively. The normality of continuous data was evaluated using the Kolmogorov–Smirnov test and the Q-Q plot. In the current study, FENa was considered a predictor for two

dependent variables, i.e., creatinine changes (evaluated both quantitively as well as ≥0.3 and <0.3) and mortality after 1-year follow-up. Basic and clinical characteristics of the study participants, both continuous and categorical, were analyzed using independent samples *t*-tests and chi-squared tests, respectively, to compare the categories of creatinine rise and mortality. The association between FENa and creatinine changes was evaluated by Pearson correlation (bivariate association) and linear regression analysis. We used simple and multiple linear regression analysis. In multiple linear regression, we adjusted the effects of potential confounders for the association between FENa and values of change in creatinine. The linear regression was reported as regression coefficient (B) and 95% confidence interval (CI) for B. We also used logistic regression to predict creatinine changes, categories (≥0.3 and <0.3), and mortality by FENa. Both simple and multiple logistic regression were used, and adjustment was made for potential confounders in multiple regression. The results of logistic regression were reported as odds ratio (OR) and 95% CI for OR. Decision levels (cutoffs) to dichotomize interval variables were determined by ROC curves. All statistical analyses were performed using SPSS software version 26 (IBM Corp., Armonk, N.Y., USA). $P < 0.05$ was considered significant, and <0.1 was marginally significant.

RESULTS

During the study period, 158 patients were recruited into the study. The mean age was 70.01 ± 12.64 years, and 62.5% were male. Among them, 103 patients had <0.3 mg/dL creatinine alterations during their admission, forming 65.1% of the enrolled population. Table 1 represents the baseline, clinical, and laboratory characteristics of the patients based on developing RI. Patients who developed RI during their admission had higher SBP, and DBP, received a higher overall dose of furosemide during their admission, had lower serum creatinine on admission, and had a lower rate of annual administrations, and FENa [Table 1].

Table 2 demonstrates the correlation of the FENa with creatinine alterations during admission. The analysis of Pearson correlations demonstrates the significant association of FENa with creatinine alterations ($P = 0.001$, $r = 0.-47$). The analysis of linear regression demonstrates the significant association of FENa with creatinine alteration during admission ($B = -1.44$, 95% CI (−1.879, −1.020), $P = 0.001$). Meanwhile, the multivariable regression analysis demonstrated the same result after adjusting based on the annual admission rate, history of taking BBs, ICMP, and DM [$B = -1.43$, 95% CI (−1.86, −1.002), $P = 0.001$, Tables 2 and 3].

Table 4 demonstrates the crude and adjusted OR and 95% CI for developing RI based on the FENa. In terms of the association of FENa with the prediction of creatinine alteration and subsequent development RI, no significant difference was observed with a marginally significant *P* value (OR = 0.27, 95% CI [0.072–1.036], $P = 0.056$). Furthermore, multiple linear regression demonstrated the same result following adjusting the potential confounder [OR = 0.33, 95% CI (0.09-1.19), $P = 0.091$, Table 4].

A ROC curve was used to establish a cutoff level of FENa for predicting creatinine alteration, from which no significant cutoff value was obtained [$P = 0.19$, Figure 1].

Table 5 demonstrates the patients' baseline, clinical, and laboratory characteristics based on 1-year mortality. During the study period, 25.68% of the population expired with a mean age of 64.19 ± 14.53 and a predominance of the male gender (74.5%). A higher mortality rate was associated with greater serum sodium levels on admission and discharge. The patients who developed hyponatremia during admission had higher rates of 1-year mortality ($P = 0.02$), while the patients with a previous history of IHD had lower mortality (*P* value < 0.001). The expired patients were incomparable in terms of having a history of HTN, DM, stroke, CKD, and anemia [$P > 0.05$, Table 5].

Table 6 demonstrates the crude and adjusted OR and 95% CI of 1-year mortality based on the FENa. No association between FENa and 1-year mortality was observed even after adjusting for potential confounders, i.e., ICMP and hyponatremia [OR = 0.85, 95% CI (0.26–2.75), $P = 0.79$, Table 6]. A ROC curve was used to establish a cutoff level of FENa for predicting 1-year mortality following discharge, from which no significant cutoff value was obtained [$P = 0.75$, Figure 2].

DISCUSSION

In this prospective study, we aimed to investigate the association of FENa on admission with developing RI, the most common comorbidity and mortality factor, and 1-year cardiovascular mortality. There were two primary findings in this study; first, moderate negative linear association between FENa and creatinine alterations during admission. However, the result of our study suggests that despite the observed association, FENa is not an independent predictor of RI. Second, there was no association between FENa and 1-year cardiovascular mortality.

FENa, the reflection of sodium handling by the kidneys, is influenced by endo- and exogenous factors, including salt diet, hypoperfusion, venous congestion, hyponatremia, activation of neurohormonal mechanisms, and diuretics. This study demonstrated that a lower FENa on admission is associated with RI. However, FENa is not an independent

Table 1: Baseline and clinical characteristics of the study population based on creatinine alterations*

Variables	Creatinine alterations		
	0.3 >Δ creatinine (*n*=103)	Δ creatinine >0.3 (*n*=55)	*P*
Length of hospital stay	6.23±4.56	6.24±4.79	0.99
SBP	120.01±23.80	132.69±23.67	0.002
DBP	76.11±16.22	85.19±22.24	0.003
HR	87.39±25.17	87.90±19.13	0.89
Overall furosemide dose	52±25.30	80±0	0.007
IV/IM furosemide dose	77.50±62.46	71.20±43.62	0.66
BUN	65.36±37.45	57.12±38.19	0.20
Serum sodium on admission	135.32±4.66	135.95±4.37	0.40
Serum creatinine on admission	1.71±1.32	1.30±0.53	0.005
Urinary creatinine on admission	152.33±81.46	147.76±79.56	0.73
Urinary sodium on admission	24.51±6.30	23.60±5.70	0.37
Serum sodium at discharge	138.47±4.01	137.91±4.53	0.42
Serum creatinine at discharge	1.31±0.59	1.92±0.70	<0.001
Urinary creatinine at discharge	159.91±86.22	164.16±83.65	0.76
Urinary sodium at discharge	28.29±8.65	29.29±7.97	0.47
Age	64.19±14.20	64.83±14.10	0.78
FENa	0.34±0.40	0.23±0.19	0.01
Gender			
Male	98 (76.6)	40 (72.7)	0.58
Female	30 (23.4)	15 (27.3)	
Mortality (1 year)			
No	99 (76.7)	37 (68.5)	0.24
Yes	30 (23.3)	17 (31.5)	
Rate of administration (<3 times a year)			
No	37 (28.5)	25 (45.5)	0.025
Yes	93 (71.5)	30 (54.5)	
Primary etiology			
HTN	2 (2)	0	0.24
IHD	56 (54.9)	19 (40.4)	
DCM	43 (42.2)	27 (57.4)	
Other	1 (1)	1 (2.1)	
Dyspnea classification			
1	1 (0.9)	1 (1.9)	0.87
2	6 (5.4)	4 (7.7)	
3	27 (24.3)	13 (25)	
4	77 (69.4)	34 (65.4)	
Smoking			
No	76 (69.1)	41 (83.7)	0.14
Yes	18 (16.4)	5 (10.2)	
ACE-I			
No	129 (99.2)	55 (100)	0.51
Yes	1 (0.8)	0	
ARB			
No	98 (75.4)	37 (67.3)	0.26
Yes	32 (24.6)	18 (32.7)	
BB			
No	60 (46.2)	34 (61.8)	0.051
Yes	70 (53.8)	21 (38.2)	
Loop diuretics			
No	44 (33.8)	18 (32.7)	0.88
Yes	86 (66.2)	37 (67.3)	
MRA			
No	102 (78.5)	38 (69.1)	0.17
Yes	28 (21.5)	17 (30.9)	

Contd...

Table 1: Contd...

Variables	Creatinine alterations		
	0.3 >Δ creatinine (*n*=103)	Δ creatinine >0.3 (*n*=55)	*P*
Anti-arrhythmic agents			
No	119 (91.5)	47 (85.5)	0.21
Yes	11 (8.5)	8 (14.5)	
ICMP			
No	82 (63.1)	27 (49.1)	0.08
Yes	48 (36.9)	28 (50.9)	
HT			
No	58 (44.6)	29 (52.7)	0.31
Yes	72 (55.4)	26 (47.3)	
DM			
No	83 (63.8)	42 (76.4)	0.096
Yes	47 (36.2)	13 (23.6)	
COPD			
No	101 (77.7)	40 (72.7)	0.47
Yes	29 (22.3)	15 (27.3)	
Anemia			
No	89 (68.5)	44 (80)	0.11
Yes	41 (31.5)	11 (20)	
CKD			
No	103 (79.2)	44 (80)	0.91
Yes	27 (20.8)	11 (20)	
Hyponatremia			
No	48 (43.2)	17 (30.9)	0.12
Hyponatremia	63 (56.8)	38 (69.1)	

**P* values were derived from independent *t*-test and χ^2 test. Data are represented as mean±SD or frequency (%). SD=Standard deviation; SBP=Systolic blood pressure; DBP=Diastolic blood pressure; HR=Heart rate; BUN=Blood urea nitrogen; IV/IM=Intravenously/intramuscularly; CKD=Chronic kidney disease; COPD=Chronic obstructive pulmonary disease; DM=Diabetes mellitus; ICMP=Ischemic cardiomyopathy; MRA=Mineralocorticoid receptor antagonists; ARB=Angiotensin receptor blocker; BB=Beta-blocker; IHD=Ischemic heart disease; HTN=Hypertension; FENa=Fractional excretion of sodium; ACE-I=Angiotensin-converting enzyme inhibitor; DCM=Dilated cardiomyopathy; HT=Hypothyroidism

Table 2: Correlations between creatinine change and fractional excretion of sodium

Variable	Pearson correlation	*P*
FENa	−0.47	<0.001

FENa=Fractional excretion of sodium

Table 3: Linear regression of creatinine alteraiton according to fractional excretion of sodium

Variable	Model (95% CI)	
	Univariate B	Multivariate B
FENa	−1.44 (−1.879–−1.02)	−1.43 (−1.86–−1.002)
P	<0.001	<0.001

Adjusted for 5 (rate of administration), 20.PDH (BB), IHD and DM. IHD=Ischemic heart disease; BB=Beta-blocker; CI=Confidence interval; FENa=Fractional excretion of sodium; DM=Diabetes mellitus; PDH=Past drug history

predictor of RI. Prior studies revealed that impaired kidney function, hyponatremia, hypoperfusion, systemic venous congestion, diuretic resistance, and highly active neurohormonal mechanisms are responsible for the development of RI.[5,6,8,16-20]

Prior studies have revealed that baseline FENa before diuretic therapy may indicate the principal underlying pathophysiologic pathways, impairing kidney function, i.e., more than 3% indicating acute tubular necrosis and <1%

Table 4: Odds ratios of creatinine alteration according to fractional excretion of sodium*

Variable	Model OR (95% CI)	
	Univariate	Multivariate
FENa	0.27 (0.072–1.036)	0.33 (0.09–1.19)
P	0.056	0.091

*Results from binary logistic regression analysis. Adjusted for rate of administration, PDH (BB), ICMP, and DM. FENa=Fractional excretion of sodium; OR=Odds ratio; CI=Confidence interval; DM=Diabetes mellitus; ICMP=Ischemic cardiomyopathy; BB=Beta-blocker; PDH=Past drug history

indicating prerenal azotemia due to renal hypoperfusion, and subsequently, decreased estimated glomerular filtration rate (eGFR) in ADHF patients.[21] Hypoperfusion and further decreased eGFR cause less diuresis and natriuresis by the nonavailability of the diuretics to its urinary site of action and less sodium depletion leading to volume overload.[6] Systemic venous congestion also causes volume overload by a similar mechanism.[18] We could not assess systemic venous congestion due to not measuring the N-terminal pro-brain natriuretic peptide, an indicator of volume overload.

Natriuresis and diuresis result from the interplay among various endo- and exogenous factors among the most prominent neurohormonal mechanisms and diuretics and

Table 5: Baseline characteristics of the study population according to mortality (1 year)*

Variables	Mortality (1-year)		
	No (*n*=136)	Yes (*n*=47)	*P*
Length of hospital stay	6.19±4.60	-	-
SBP on admission	125.56±24.20	118.86±24.62	0.12
DBP on admission	79.69±18.93	76.79±17.36	0.38
HR on admission	87.05±23.03	89.55±25.18	0.55
Overall furosemide dose	56.67±25.35	-	-
IV/IM furosemide dose	77±57.38	52±17.89	0.34
BUN	64.96±39.40	57.44±32.91	0.27
Serum sodium on admission	134.87±4.55	137.27±4.18	0.003
Serum creatinine on admission	1.65±1.28	1.39±0.58	0.19
Urinary creatinine on admission	153.44±79.96	146.41±81.90	0.62
Urinary sodium on admission	24.48±6.29	23.43±5.64	0.33
Serum sodium at discharge	137.63±4.32	140±3.25	0.001
Serum creatinine at discharge	1.58±0.70	1.33±0.65	0.042
Urinary creatinine at discharge	166.58±83.20	147.25±90.64	0.20
Urinary sodium at discharge	29.10±8.56	27.5±7.98	0.28
Age	64.41±14.09	64.19±14.53	0.93
FeNa	0.31±0.37	0.27±0.26	0.44
Sex			
Male	102 (75.6)	35 (74.5)	0.88
Female	33 (24.4)	12 (25.5)	
Rate of administration			
No	44 (32.4)	18 (38.3)	0.46
Yes	92 (67.6)	29 (61.7)	
Primary etiology			
HTN	2 (1.8)	0	0.55
IHD	54 (48.2)	21 (58.3)	
DCM	54 (48.2)	15 (41.7)	
Other	2 (1.8)	0	
Dyspnea			
1	2 (1.7)	0	0.21
2	7 (5.8)	3 (7.1)	
3	25 (20.8)	15 (35.7)	
4	86 (71.7)	24 (57.1)	
Smoking			
No	89 (76.1)	27 (65.9)	0.20
Yes	28 (23.9)	14 (34.1)	
ACE-I			
No	135 (99.3)	47 (100)	0.56
Yes	1 (0.7)	0	
ARB			
No	100 (73.5)	34 (72.3)	0.87
Yes	36 (26.5)	13 (27.7)	
BB			
No	68 (50)	24 (51.1)	0.90
Yes	68 (50)	23 (48.9)	
Diuretics			
No	47 (34.6)	14 (29.8)	0.55
Yes	89 (65.4)	33 (70.2)	
Mineralocorticoid receptor antagonist			
No	102 (75)	36 (76.6)	0.83
Yes	34 (25)	11 (23.4)	
Anti-arrhythmic agents			
No	121 (89)	43 (91.5)	0.63
Yes	15 (11)	4 (8.5)	
IHD			
No	71 (52.2)	37 (78.7)	0.001
Yes	65 (47.8)	10 (21.3)	
HTN			
No	67 (49.3)	18 (38.3)	0.19
Yes	69 (50.7)	29 (61.7)	
DM			
No	94 (69.1)	29 (61.7)	0.35
Yes	42 (30.9)	18 (38.3)	
COPD			
No	106 (77.9)	33 (70.2)	0.28
Yes	30 (22.1)	14 (29.8)	
Anemia			
No	95 (69.9)	36 (76.6)	0.38
Yes	41 (30.1)	11 (23.4)	
CKD			
No	107 (78.7)	38 (80.9)	0.75
Yes	29 (21.3)	9 (19.1)	
ACE.ARB			
No	100 (73.5)	34 (72.3)	0.87
Yes	36 (26.5)	13 (27.7)	
RecodeSBP DBP			
HTN−	64 (47.1)	25 (53.2)	0.47
HTN+	72 (52.9)	22 (46.8)	
RecodeNa			
No	54 (44.6)	11 (25)	0.02
Hyponatremia	67 (55.4)	33 (75)	

Contd...

Table 5: Contd...

**P* values were derived from independent *t*-test and χ^2 test. Data are represented as mean±SD or frequency (%). SD=Standard deviation; SBP=Systolic blood pressure; DBP=Diastolic blood pressure; HR=Heart rate; BUN=Blood urea nitrogen; IV/IM=Intravenously/intramuscularly; CKD=Chronic kidney disease; COPD=Chronic obstructive pulmonary disease; DM=Diabetes mellitus; ICMP=Ischemic cardiomyopathy; MRA=Mineralocorticoid receptor antagonists; ARB=Angiotensin receptor blocker; BB=Beta-blocker; IHD=Ischemic heart disease; HTN=Hypertension; FENa=Fractional excretion of sodium; BB=Beta-blockers; ACE-I=Angiotensin-converting enzyme inhibitor; DCM=Dilated cardiomyopathy

Table 6: Odds ratios of mortality (1 year) according to fractional excretion of sodium*

Variable	Model OR (95% CI)	
	Univariate	Multivariate
FeNa	0.64 (0.21–1.98)	0.85 (0.26–2.75)
P	0.44	0.79

*Results from binary logistic regression analysis. Adjusted for IHD and recorded Na. IHD=Ischemic heart disease; OR=Odds ratio; CI=Confidence interval; FENa=Fractional excretion of sodium; Na=Sodium

may justify the lack of direct effect of diuretics on natriuresis and diuresis.[8,20] Loop diuretics, the most common diuretics used in ADHF patients, block the sodium resorption on the loop of Henle. Meanwhile, it does not affect the proximal tubule, a site that is recognized as having the highest sodium resorption.[13,22] Thus, decreased renal blood flow in this segment due to systemic venous congestion or hypoperfusion can lead to considerable sodium resorption

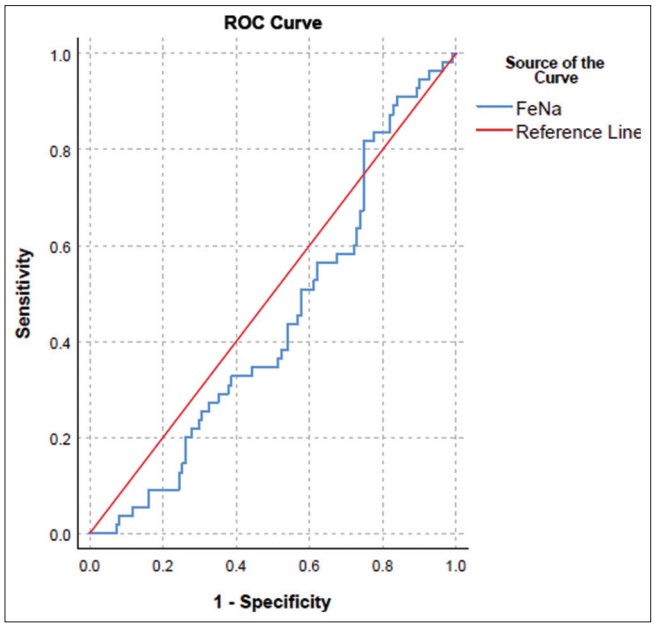

Figure 1: Receiver operating characteristic curve for fractional excretion of sodium and renal impairment. ROC = Receiver operating characteristic, FENa = Fractional excretion of sodium

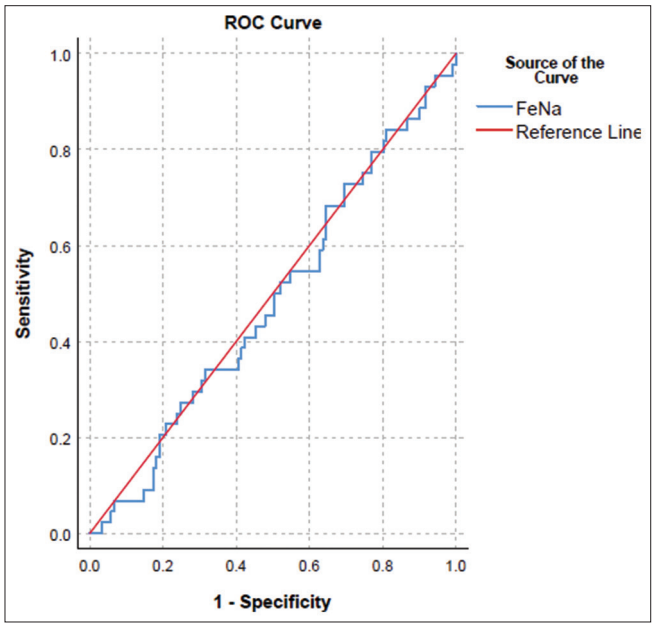

Figure 2: Receiver operating characteristic curve for fractional excretion of sodium and mortality (1 year). ROC = Receiver operating characteristic, FENa = Fractional excretion of sodium

and subsequent less sodium depletion.[21] However, aggressive natriuresis by loop diuretics may activate the RAAS by the direct inhibiting effect of loop diuretics on macula densa cells in the kidney and herald a decrease in effective intravascular volume, which leads to renin secretion and activation of RAAS, eventually.[23] RAAS affords more sodium resorption in the distal, and collecting tubule leads to sodium retention and diuretic resistance.[24] Meanwhile, ACE-Is/ARBs/MRAs, medications frequently used in the treatment of HF patients, antagonize the RAAS effect.[25] However, recent studies revealed no independent potency of these drugs, regardless of the cause, to the development of CRS in patients dependent on RAAS to maintain their GFR.[23,26,27]

BB therapy was found to be effective in treating HF by reducing HR, direct inhibitor of renin secretion, and SNS.[23,28] BB therapies had no effects in our study due to not being comparable in both groups.

Hyponatremia leads to diminished natriuresis and diuresis by lowering diuretics efficacy and diminished sodium delivery to distal tubule and secondary activation of RAAS and remained volume overload.[29] In this study, the impact of hyponatremia on RI was ruled out due to the lack of difference between the two groups. Meanwhile, hyponatremia was associated with mortality. However, our further analysis revealed no independent association of hyponatremia with mortality. In this regard, many studies reported a significant association of hyponatremia with higher short-and long-term mortality.[17,30]

Our study indicated that the lower FENa was associated with a higher mortality rate. However, the observed outcome was not significant. Short-term mortality was associated with hyponatremic status and NICMP. It may be explained by the volume overload status seen in hyponatremic patients, less diuretic efficacy, and the aggressive treatment and follow-up implemented following IHD. Although our study demonstrated no significant association of FENa with mortality, dead individuals had lower FENa on admission. The study conducted by Thabt confirmed our outcomes.[19]

The present study is limited by several factors, including the observational origin of the study, the low sample size, which led to not detecting accurate cutoff, both for developing RI and mortality, random urine spot for calculating FENa compared to 24-h urine sample, and lower period of follow-up patients. However, we calculated FENa from simultaneous blood and urine samples taken before giving furosemide to prevent the confounding effect of a loop diuretic.

In conclusion, our study demonstrated confirmatory evidence regarding the indirect association of low FENa with the development of RI during admission. We also provided evidence regarding the inability of FENa to predict short-term cardiovascular mortality.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Hoseinbor M, Vakhshoori M, Babak A, Givi M, Heidarpour M, Nikouei F, *et al.* Frequency of readmission in Iranian heart failure patients within six months after discharge and its association with guideline directed medical treatment. Drug Invention Today 2019;70:11.
2. Dickstein K, Vardas PE, Auricchio A, Daubert JC, Linde C, McMurray J, *et al.* 2010 focused update of ESC guidelines on device therapy in heart failure: An update of the 2008 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 ESC guidelines for cardiac and resynchronization therapy. Developed with the special contribution of the Heart Failure Association and the European Heart Rhythm Association. Europace 2010;12:1526-36.
3. Löfman I, Szummer K, Evans M, Carrero JJ, Lund LH, Jernberg T. Incidence of, associations with and prognostic impact of worsening renal function in heart failure with different ejection fraction categories. Am J Cardiol 2019;124:1575-83.
4. Ronco C, Bellasi A, Di Lullo L. Cardiorenal syndrome: An overview. Adv Chronic Kidney Dis 2018;25:382-90.
5. Eshaghian S, Horwich TB, Fonarow GC. Relation of loop diuretic dose to mortality in advanced heart failure. Am J Cardiol 2006;97:1759-64.
6. Kumar D, Bagarhatta R. Fractional excretion of sodium and its association with prognosis of decompensated heart failure patients. J Clin Diagn Res 2015;9:C01-3.
7. Espinel CH. The FENa test. Use in the differential diagnosis of acute renal failure. JAMA 1976;236:579-81.
8. Volpe M, Magri P, Rao MA, Cangianiello S, DeNicola L, Mele AF, *et al.* Intrarenal determinants of sodium retention in mild heart failure: Effects of angiotensin-converting enzyme inhibition. Hypertension 1997;30:168-76.
9. Gabrielsen A, Bie P, Holstein Rathlou NH, Christensen NJ, Warberg J, Dige Petersen H, *et al.* Neuroendocrine and renal effects of intravascular volume expansion in compensated heart failure. Am J Physiol Regul Integr Comp Physiol 2001;281:R459-67.
10. Fifer MA, Molina CR, Quiroz AC, Giles TD, Herrmann HC, De Scheerder IR, *et al.* Hemodynamic and renal effects of atrial natriuretic peptide in congestive heart failure. Am J Cardiol 1990;65:211-6.
11. Dormans TP, Gerlag PG. Combination of high-dose furosemide and hydrochlorothiazide in the treatment of refractory congestive heart failure. Eur Heart J 1996;17:1867-74.
12. Kono H, Kitai T, Kim K, Kobori A, Ehara N, Kinoshita M, *et al.* Fractional excretion of sodium after the treatment of acute decompensated heart failure predicts the prognosis. J Am Coll Cardiol 2019;73:1002.
13. Alattar FT, Imran N, Debari VA, Mallah KN, Shamoon FE. Fractional excretion of sodium predicts worsening renal function in acute decompensated heart failure. Exp Clin Cardiol 2010;15:e65-9.
14. Givi M, Heshmat Ghahdarijani K, Garakyaraghi M, Yadegarfar G, Vakhshoori M, Heidarpour M, *et al.* Design and methodology of heart failure registry: Results of the Persian registry of cardiovascular disease. ARYA Atheroscler 2019;15:228-32.
15. Hammarlund MM, Paalzow LK, Odlind B. Pharmacokinetics of furosemide in man after intravenous and oral administration. Application of moment analysis. Eur J Clin Pharmacol 1984;26:197-207.
16. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, *et al.* Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol 2009;53:589-96.
17. Konishi M, Haraguchi G, Ohigashi H, Sasaoka T, Yoshikawa S, Inagaki H, *et al.* Progression of hyponatremia is associated with increased cardiac mortality in patients hospitalized for acute decompensated heart failure. J Card Fail 2012;18:620-5.
18. Guglin M, Rivero A, Matar F, Garcia M. Renal dysfunction in heart failure is due to congestion but not low output. Clin Cardiol 2011;34:113-6.
19. Thabt SS, Enany BE, Soliman KR. Fractional sodium excretion and its relation to in-hospital morbidity and mortality in patients admitted with decompensated heart failure. Egypt Heart J 2013;65:111-5.
20. Hasselblad V, Gattis Stough W, Shah MR, Lokhnygina Y, O'Connor CM, Califf RM, *et al.* Relation between dose of loop diuretics and outcomes in a heart failure population: Results of the ESCAPE trial. Eur J Heart Fail 2007;9:1064-9.
21. Ahmadi F, Torfi E, Afshani SM, Kazemi Mansourabad S, Hayati F. Can fractional excretion of sodium predict worsening of renal function, in-hospital mortality, and length of hospital stay in acute decompensated heart failure? ARYA Atheroscler 2021;17:1-5.
22. Palmer LG, Schnermann J. Integrated control of Na transport along the nephron. Clin J Am Soc Nephrol 2015;10:676-87.
23. Knight EL, Glynn RJ, McIntyre KM, Mogun H, Avorn J. Predictors of decreased renal function in patients with heart failure during angiotensin-converting enzyme inhibitor therapy: Results from the studies of left ventricular dysfunction (SOLVD). Am Heart J 1999;138:849-55.
24. Rao VS, Planavsky N, Hanberg JS, Ahmad T, Brisco Bacik MA, Wilson FP, *et al.* Compensatory distal reabsorption drives diuretic resistance in human heart failure. J Am Soc Nephrol 2017;28:3414-24.
25. Szady AD, Hill JA. Diuretics in heart failure: A critical appraisal of efficacy and tolerability. Drugs 2009;69:2451-61.
26. Mandal AK, Markert RJ, Saklayen MG, Mankus RA, Yokokawa K. Diuretics potentiate angiotensin converting enzyme inhibitor-induced acute renal failure. Clin Nephrol 1994;42:170-4.
27. Jolobe OM. Evaluation of renal function in elderly heart failure patients on ACE inhibitors. Postgrad Med J 1999;75:275-7.
28. Kotecha D, Gill SK, Flather MD, Holmes J, Packer M, Rosano G, *et al.* Impact of renal impairment on beta-blocker efficacy in patients with heart failure. J Am Coll Cardiol 2019;74:2893-904.
29. Krämer BK, Schweda F, Riegger GA. Diuretic treatment and diuretic resistance in heart failure. Am J Med 1999;106:90-6.
30. Callahan MA, Do HT, Caplan DW, Yoon Flannery K. Economic impact of hyponatremia in hospitalized patients: A retrospective cohort study. Postgrad Med 2009;121:186-91.