IJSCIA

International Journal of Scientific Advances
ISSN: 2708-7972
Volume: 5 | Issue: 3 | May – Jun 2024 Available Online: www.ijscia.com
DOI: 10.51542/ijscia.v5i3.20

The Role of Urine Na+ Levels as A Predictor of Diuresis Response, Length of Stay, Rehospitalization And Death Due to Cardiovascular Disease In 30 Days Post Treatment in Acute Heart Failure Patients

I Gede Bagus Bhaskara Wijaksana*, I Nyoman Wiryawan, and Luh Oliva Saraswati Suastika

Department of Cardiology and Vascular Medicine, Faculty of Medicine Udayana University
Prof. Dr. I.G.N.G. Ngoerah Hospital, Denpasar, Bali, Indonesia

E-mail: bhazkarawijaksana@gmail.com; dr_wiryawan@yahoo.com; oliva_saraswati@unud.ac.id

ABSTRACT

Background: The incidence of rehospitalization and death due to cardiovascular disease in acute heart failure (AHF) is relatively high. The spot urine Na+ value 6 and 48 hours after loop diuretic still does not have a clear role as a predictor of diuresis response, length of stay, rehospitalization as well as the composite of rehospitalization events and death due to cardiovascular disease within 30 days. ***Objective:*** To determine whether spot urinary Na+ 6 hours and 48 hours after loop diuretic is a predictor of diuresis response, length of stay, rehospitalization as well as a composite of events within 30 days. ***Methods:*** This study is a prospective cohort of AHF patients treated in February-March 2024. The independent variable is the spot urine Na+ value 6 and 48 hours after loop diuretic. Outcomes consist of diuresis response, length of stay, rehospitalization as well as a composite of rehospitalization and death due to cardiovascular disease within 30 days. ***Results:*** A total of 72 AHF patients were included in the study. Rehospitalization events occurred in 20.8% of cases while composite events occurred in 22.2%. The cut point value for spot urinary Na+ 6 hours after loop diuretic in this study was 62.3 mmol/L. 6-hour spot urine Na+ was a predictor of poor diuresis response with adjusted OR 3.67 (95% CI 1.12-11.8; $p < 0.03$). Regression analysis showed that 6-hour spot urine Na+ was not a predictor of length of stay (β coefficient: -0,023 95% CI -0,054 – 0,008; $p = 0.138$). 6-hour spot urine Na+ was a predictor of rehospitalization with adjusted HR 3.53 (95% CI 1.11-11.18; $p = 0.032$). The 6-hour spot urine Na+ value was a composite predictor of 30-day events with HR 4.89 (95% CI 1.58-15.11; $p = 0.006$). No association was found between 48-hour spot urine Na+ values with diuresis response, length of stay, rehospitalization and events within 30 days. ***Conclusion:*** Spot urine Na+ value 6 hours after loop diuretic is a predictor of diuresis response, rehospitalization and composite events within 30 days. The 6-hour urine Na+ spot value is not a predictor of length of stay. The 48-hour urine Na+ spot value is not a predictor of diuresis response, length of stay, rehospitalization or composite events within 30 days.

Keywords: Spot urine Na+ ; diuresis response; length of stay; acute heart failure; rehospitalization; death from cardiovascular disease

INTRODUCTION

Acute heart failure (AHF) is still associated with a high risk of mortality and rehospitalization. AHF is associated with a mortality risk of 4-10% within 60-90 days post-treatment to 25-30% within 1 year [1]. It is estimated that 25% of patients who experience rehospitalization due to heart failure occur within 30 days post-treatment and within this period the mortality rate can reach 10% [2]. In addition to mortality and rehospitalization, length of stay is also one of the main problems in AHF patients. Prolonged length of stay in AHF patients has been associated with worse outcomes. Reynolds et al. showed that in acute heart failure patients, a length of stay of 5-10 days was associated with a 17% increased risk of readmission and a 52% increased risk of 30-day mortality compared to a length of stay of 3-4 days [3].

Adequate diuresis therapy is one of the main treatments in achieving the main target of managing acute heart failure (AHF). Currently, the European Society of Cardiology (ESC) guideline on heart failure in 2021 recommends diuresis using loop diuretics as the first-choice therapy [4]. Effective management of congestion in AHF hospitalization has been associated with reduced in-hospital mortality, survival, and rehospitalization rates [5]. Matsue et al. in the REALITY-AHF (Registry Focused on Very Early Presentation and Treatment in Emergency Department of Acute Heart Failure) observational cohort showed that patients who received loop diuretic therapy early (< 60 minutes) were associated with lower in-hospital mortality (2.3% vs 6.0%; $p = 0.002$) compared to patients who received loop diuretics later [6].

Impaired Na+ homeostasis is one of the key pathophysiology in AHF where there is dysregulation of Na+ homeostasis resulting in a positive Na+ balance in the body. In heart failure there is neurohormonal dysregulation and hemodynamic disturbances that cause the inability of the kidneys to regulate Na+ excretion. The imbalance of Na+ absorption and excretion results in a positive Na+ balance that can cause fluid transudation into interstitial tissue and ultimately lead to a clinical picture of congestion. The natriuresis response can describe the degree of neurohormal and hemodynamic disturbances in heart failure conditions [7].

Urinary Na+ has the potential to evaluate diuresis efficacy and predict outcomes in AHF patients. However, there are currently no definitive recommendations regarding the timing of the examination and the most ideal cutoff point of urine Na+. In addition, data on natriuresis response in Indonesia is still scarce. In this study, the researchers wanted to determine the correlation of spot examination of urine Na+ with diuresis response and its potential as a predictor of length of stay and rehospitalization and death from cardiovascular disease within 30 days. If the hypothesis in this study is proven, spot examination of urine Na+ can be routinely performed in AHF patients as a guideline for diuresis in relation to being a predictor of length of stay and rehospitalization and death from cardiovascular disease within 30 days.

METHOD

This study was an analytic observational study with a prospective cohort design. The study started with the assessment of urine Na+ levels 6 hours and 48 hours post loop diuretic. Follow-up evaluation of diuresis response within 72 hours, length of stay, and rehospitalization and composite of rehospitalization and/or death within 30 days post-treatment.

The study was conducted from January 2024 to May 2024. The study was conducted at Prof. dr. I.G.N.G. Ngoerah, Denpasar, Bali. Examination of urine Na+ spot levels 6 hours post loop diuretic was carried out in the emergency department and then 48 hours urine Na+ spot levels were examined in the treatment room. Blood samples were sent and examined at the Clinical Pathology Laboratory of Prof. dr. I.G.N.G Ngoerah Hospital.

The target population was all patients with AHF who received loop diuretic therapy and were hospitalized. AHF was defined as a worsening of the signs and symptoms of heart failure leading to a cardiac polyclinic visit, emergency department visit or even hospitalization. This includes de novo heart failure and acute decompensated heart failure. Diagnosis of AHF is based on patient assessment in the medical record at the time of treatment.

Inclusion criteria: AHF patients aged ≥ 18 years and receiving intravenous loop diuretic therapy. Exclusion criteria: a) AHF patients with cardiogenic shock; b) AHF patients with cardiac tamponade, pulmonary embolism and mechanical causes; c) Patients with stage V chronic renal failure (eGFR < 15 ml/min/1.73 m2) or required hemodialysis treatment; d) AHF patients who were pregnant or breastfeeding; e) AHF patients with comorbid malignancies; AHF patients who were referred from other health facilities after receiving treatment for > 24 hours; and f) AHF patients who refused to participate in the study. Drop out criteria: a) AHF patients who experienced mortality during the first in-hospital mortality; b) AHF patients who experienced loss to follow up, including patients who could not be contacted again by researchers for various reasons during the 30-day post-treatment observation period (moving domicile, refusing further follow-up, and so on).

RESEARCH PROCEDURE

(1) The researcher submitted a research ethics eligibility application to the Ethics Commission of the Faculty of Medicine, Udayana University / Prof. dr. I.G.N.G. Ngoerah Hospital

(2) AHF patients who underwent hospitalization at Prof. dr. I.G.N.G. Ngoerah Hospital who met the inclusion criteria and were not included in the exclusion criteria were asked for consent to participate in the study through filling out informed consent before being included in the study.

(3) AHF patients who underwent hospitalization at Prof. dr. I.G.N.G. Ngoerah Hospital who met the inclusion criteria, were not included in the exclusion criteria and were willing to participate in the study after filling out informed consent were included in the study. All research samples received heart failure therapy according to AHF guidelines based on the European Society of Cardiology.

(4) Patients had spot Na+ urine collected within 6 hours and 48 hours of the first furosemide dose. Urine samples were obtained via urinary catheter/directly in patients who did not use a urinary catheter after 6 and 48 hours of the first loop diuretic dose. Samples were then stored in 20cc urine vials and immediately sent to the clinical pathology laboratory for analysis.

(5) Calculation of diuresis response using net urine output in 72 hours Where the diuresis response is calculated as net urine output in 72 hours divided by the total dose of loop diuretic equivalent iv/40 mg. Net urine output is calculated based on the cumulative amount of urine for 72 hours without insensible water loss (IWL in milliliters (mL) minus the cumulative amount of incoming fluid in milliliters (mL).

(6) Patients were then followed up for 30 days using text messages or telephone calls to monitor rehospitalization and death from cardiovascular disease. Data on the cause of rehospitalization and/or death from cardiovascular disease were collected from the medical records at the hospital where the patient was treated or from the medical summary at discharge. If the patient

died at home, cardiovascular disease deaths were identified through in-depth interviews with family members with first-degree consanguinity regarding the chronology of death of the sample and evidenced by a death certificate issued by the civil registry office.

(7) Patients who experience rehospitalization and/or death due to cardiovascular disease will have the time between hospital discharge (when the patient was first included in the study) and subsequent hospitalization or death recorded in days.

The data collected in each group will then be analyzed with the SPSS version 26 program which includes descriptive analysis, Receiver Operating Characteristic curve analysis, mean comparison test with independent t-test if the data varies normally or Mann Whitney test if the data is not normally distributed.

Comparison test of proportions by cross tabulation and Chi-Square statistical test. Linear regression analysis with association expressed as Coefficient ß. Conclusions were based on 95% confidence intervals with p values at an alpha cut-off of 0.05. Survival analysis was performed with Kaplan-Meier Curve and Cox regression test. The confidence level in this study was 95%. Ho is rejected if the p value <0.05

RESULT

ROC curve analysis and depiction were used to obtain the best 6-hour and 48-hour post-administration loop diuretic spot Na+ cut-off values as a composite predictor of 30-day cardiovascular disease-related rehospitalization and/or death in AHF patients (Figure 1). Based on this analysis, the best 6-hour urine Na+ spot cut-off value as a composite predictor of the incidence of rehospitalization and/or death from cardiovascular disease within 30 days in AHF patients was 62.3 mmol/L with a sensitivity of 56.3% and a specificity of 78.5% and an AUC value of 0.26; 95% CI 0.12-0.41 p = 0.005.

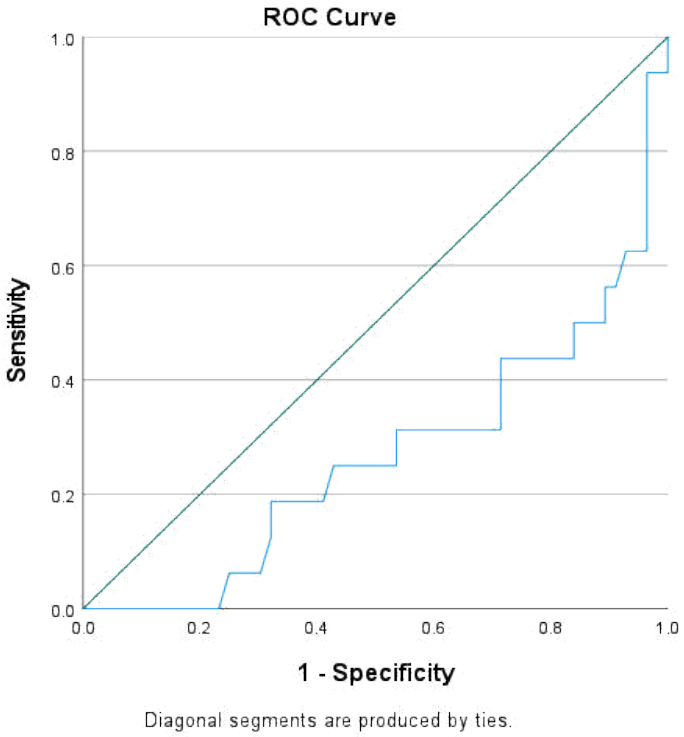


FIGURE 1: ROC Curve, Sensitivity and Specificity Values of Spot Na+ Urine 6 hours post loop diuretic administration as a Composite Predictor of Rehospitalization Events and/or death due to cardiovascular disease within 30 days.

Furthermore, subjects with 6-hour post-loop diuretic urine Na+ spot values < 62.3 mmol/L were classified as low 6-hour post-loop diuretic urine Na+ spot values and subjects with values ≥ 62.3 mmol/L were considered as normal/high 6-hour post-loop diuretic urine Na+ spot values.

The results of descriptive analysis of the study population based on spot values of urine Na+ 6 hours and 48 hours after the administration of loop diuretics are shown in Table 1 and Table 2.

TABLE 1: Demographic and clinical characteristics of study subjects based on urinary Na^+ spot levels 6 hours and 48 hours post loop diuretic administration.

Variables	Spot Na values⁺ 6-hour urine		p	Spot Na values⁺ 48-hour urine		p
	Low	Normal. High		Low	Normal. High	
Number of subjects, n (%)	20 (27,8)	52 (72,2)		32 (44,4)	40 (55,6)	
Gender						
Male, n (%)	15 (75,0)	35 (67,3)	0,526[b]	22 (68,8)	28 (70,0)	0,909[b]
Female, n (%)	5 (25,0)	17 (32,7)		10 (31,3)	12 (30,0)	
Age, years, mean±SB	58,4 ± 13,3	55,9 ± 14,5	0,512[a]	53,5 ± 14,3	59,1 ± 13,6	0,097[a]
AHF Profile						
ADHF, n (%)	16 (27,6)	42 (72,4)	0,941[b]	21 (36,2)	37 (63,8)	0,004[b,d]
Acute Pulmonary Oedema, n (%)	4 (28,6)	10 (71,4)		11 (78,6)	3 (21,4)	
Rw Rehospitalization 12 months						
Rehospitalization > 1 time	8 (40,0)	23 (44,2)	0,745[b]	10 (31,3)	21 (52,5)	0,070[b,]
Rehospitalization ≤ 1 time	12 (60,0)	29 (55,8)		22 (68,8)	19 (47,5)	
Risk factors and comorbidities						
Smoking,						
Yes, n (%)	10 (50,0)	22 (42,3)	0,556[b]	15 (46,9)	17 (42,5)	0,710[b]
No, n (%)	10 (50,0)	30 (57,7)		17 (53,1)	23 (75,5)	
Hypertension,						
Yes, n (%)	13 (65,0)	25 (48,1)	0,198[b]	16 (50,0)	22 (55,0)	0,673[b]
No, n (%)	7 (35,0)	27 (51,19)		16 (50,0)	18 (45,0)	
Diabetes mellitus,						
Yes, n (%)	8 (40,0)	14 (26,9)s	0,281[b]	10 (31,3)	12 (30,0)	0,909[b]
No, n (%)	12 (60,0)	38 (73,1)		22 (68,8)	28 (70,0)	
CHD,						
Yes, n (%)	10 (50,0)	23 (44,2)	0,660[b]	13 (40,6)	20 (50,0)	0,428[b]
No, n (%)	10 (50,0)	29 (55,8)		19 (59,4)	20 (50,0)	
COPD,						
Yes, n (%)	2 (10,0)	5 (9,6)	0,961[b]	2 (6,3)	5 (12,5)	0,374[b]
No, n (%)	18 (90,0)	47 (90,4)		30 (93,8)	35 (87,5)	
Routine use of Loop diuretics						
Yes, n (%)	11 (55,0)	37 (71,2)	0,193[b]	15 (46,9)	33 (82,5)	**0,001[b,d]**
No, n (%)	9 (45,0)	15 (28,8)		17 (53,1)	7 (17,5)	
Loop diuretic dose 48-hour median IQR	80 (0-240)	40 (0-160)	0,156[c,]	40 (0-120)	40 (0-240)	0,348[c]
Non-furosemide diuretic treatment						
Yes, n (%)	1 (5,0)	1 (1,9)	0,477[b]	25 (78,1)	34 (85,0)	0,451[b]
No, n (%)	19 (9,5)	51 (98,1)		7 (21,9)	6 (15,0)	
Furosemide dosage						
High, n (%)	7 (22,6)	24 (77,4)	0,393[b]	20 (64,5)	11 (35,5)	**0,003[b,d]**
Low, n (%)	13 (31,7)	28 (68,3)		12 (29,3)	29 (70,7)	
Pre discharge heart failure therapy						
Furosemide						
Yes n (%)	18 (90,0)	49 (94,2)	0,527[b]	29 (90,6)	38 (95,0)	0,486[b]
No n (%)	2 (10,0)	8 (5,3)		3 (9,4)	2 (5,0)	
ACEi/ARB/ARNI						
Yes n (%)	20 (100,0)	47 (90,4)	0,151[b]	31 (96,9)	36 (90,0)	0,373[b]
No n (%)	0 (0,0)	5 (9,6)		1 (3,1)	4 (10,0)	
Beta blockers						
Yes n (%)	20 (100,0)	46 (88,5)	0,113[b]	28 (87,5)	38 (95,0)	0,395[b]
No n (%)	0 (0,0)	6 (11,5)		4 (12,5)	2 (5,0)	

Variables	Spot Na values+ 6-hour urine		p	Spot Na values+ 48-hour urine		p
	Low	Normal. High		Low	Normal. High	
MRA						
Yes n (%)	15 (75,0)	43 (82,7)	0,460[b]	24 (75,0)	34 (85,0)	0,287[b]
No n (%)	5 (25,0)	9 (17,3)		8 (25,0)	6 (15,0)	
Digitalis						
Yes n (%)	1 (5,0)	9 (17,3)	0,176[b]	4 (12,5)	6 (15,0)	0,761[b]
No n (%)	19 (95,0)	43 (82,7)		28 (87,5)	34 (85,0)	
Thiazide Diuretic						
Yes n (%)	1 (5,0)	1 (1,9)	0,477[b]	2 (6,3)	0 (0,0)	0,109[b]
No n (%)	19 (9,5)	51 (98,1)		30 (93,8)	40 (100,0)	
If-channel blocker						
Yes n (%)	1 (5,0)	5 (9,6)	0,526[b]	1 (3,1)	5 (12,5)	0,153[b]
No n (%)	19 (95,0)	47 (90,4)		31 (96,9)	35 (87,5)	
SGLT2i						
Yes n (%)	0 (0,0)	4 (7,7)	0,202[b]	2 (6,3)	2 (5,0)	0,818[b]
No n (%)	20 (100)	48 (92,3)		30 (94,8)	38 (95,0)	
Clinical parameters						
Respiration rate increases	5 (25,0)	23 (44,2)	0,134[b,]	12 (37,5)	16 (40,0)	0,829[b]
Normal respiration rate	15 (75,0)	29 (55,8)		20 (62,5)	24 (60,0)	
Low initial inlet SBP	3 (15,0)	14 (26,9)	0,286[b]	7 (21,9)	10 (25,0)	0,756[b]
Normal initial admission SBP	17 (85,0)	38 (73,1)		25 (78,1)	30 (75,0)	
Functional class						
FC III/IV	6 (30,0)	23 (44,2)	0,270[b]	11 (34,4)	18 (45,0)	0,361[b]
FC I/II	14 (70,0)	29 (55,8)		21 (65,6)	22 (55,0)	

[a]Independent T test,[b] Chi Square test,[c] Mann U Whitney test,[d] Statistically significant.
ACEi, ACE-inhibitor; ARB, Angiotensin Receptor Blocker; ARNI, Angiotensin Receptor Neprilysin Inhibitor; FC, Functional class; AHF, acute heart failure; MRA, mineralocorticoid receptor antagonist; CHD, Coronary Heart Disease; SGLT2-i, SGLT2 inhibitor; SBP, Systolic blood pressure.

TABLE 2: Laboratory and echocardiographic characteristics of study subjects based on urinary Na^+ spot levels 6 hours and 48 hours post loop diuretic administration.

Variables	Spot Na values+ 6-hour urine		p	Spot Na values+ 48-hour urine		p
	Low	Normal. High		Low	Normal. High	
eGFR, (mL/min/1.73 m2), rerate ± SB	52,9 ± 28,5	59,2 ± 26,0	0,387[a]	63,2 ± 26,4	52,9 ± 27,7	0,120[a]
Decreased (< 60 mL/min/1.73 m2)	20 (100)	51 (98,1)	0,532[b]	22 (68,8)	36 (90,0)	0,024[b]
No Decrease (≥ 60 mL/min/1.73 m2)	0 (0,0)	1 (1,9)		10 (31,3)	4 (10,0)	
Na, mmol/L, rerate ±SD	133 ± 7,7	137,2 ± 7,7	**0,006[a,d]**	135,5 ± 6,6	136,4 ± 5,4	0,158[a]
Hyponatremia	10 (50,0)	13 (25,0)	**0,042[b,d]**	13 (40,6)	10 (25,0)	
No Hyponatremia	10 (50,0)	39 (75,0)		19 (59,4)	30 (75,0)	
Average Hb ± SD	12,3 ± 2,8	12,4 ± 2,0	0,704[a]	12,9 ± 2,1	11,9 ±2,32	0,561[a]
Anaemia (Hb < 10g/dl)	6 (30,0)	7 (13,5)	0,102[b]	4 (12,5)	9 (22,5)	0,273[b]
No Anaemia (Hb > 10g/dl)	14 (70,0)	45 (86,5)		28 (87,5)	31 (77,5)	
Hypoalbuminemia						
Albumin ≤ 2.5 g/dl	1 (50,0)	1 (50,0)	0,477[b]	0 (0,0)	2 (5,0)	0,200[b]
Albumin > 2.5 g/dl	19 (95,0)	51 (98,1)		32 (100,0)	38 (95,0)	
Echocardiography						
LVEF, %, median	38,5 (19,0-65,3)	34,5 (14,0-69,0)	0,262[c]	41,5 (14,0-65,3)	33,5 (17,2-69,0)	0,062[c]
Reduced LVEF	11 (55,0)	29 (55,8)	0,359[b]	14 (43,8)	26 (65,0)	0,071[b]
Non-Reduced LVEF	9 (45,0)	23 (44,2)		18 (56,3)	14 (35,0)	
Average E/e' Average ± SD	15,2 ± 3,22	15,7 ± 3,18	0,442[b]	16,4 ± 2,4	14,8 ± 3,5	0,322[b]
ePCWP, mmHg, Average ± SD	20,6 ± 4,0	21,4 ± 3,9	0,447[b]	22,2 ± 3,0	20,2 ± 4,3	0,011[b]

[a]Independent T test,[b] Chi Square test,[c] Mann U Whitney test,[d] Statistically significant.
eGFR, Estimated Glomerular Filtration Rate, LVEF: Left Ventricular Ejection Fraction, Na+: Sodium.

The effect of control variables on independent variables with categorical scales (gender, risk factors/comorbidities, history of loop diuretic use, non-loop diuretic use, predischarge heart failure therapy, respiratory rate classification, systolic blood pressure classification, functional class, eGFR value classification, hyponatremia, hypoalbuminemia, and anemia) was tested for significance with the Chi square test. The variable is said to be meaningful if the p value <0.05.

The diuresis response was grouped into less diuresis response and sufficient diuresis response based on the median diuresis response value of 682.5 ml/40 mg furosemide. Subjects with a response of <682.5 ml/40 mg furosemide were categorized as a poor diuresis response group, while subjects with a diuresis response of ≥682.5 ml/40 mg furosemide were categorized as a moderate diuresis response group. Analysis of the distribution of diuresis response based on the characteristics of the study subjects can be seen in Table 3.

TABLE 3: Distribution of diuresis response based on the characteristics of the study subjects.

Variables	Diuresis Response		p
	Less	Simply	
Number of subjects n (%)	36 (50)	36 (50)	
Age, years, mean ± SB	58,0 ± 14,6	55,1 ± 13,6	0,385[a]
Gender			
Male, n (%)	24 (48,0)	26 (52,0)	0,360[b]
Female, n (%)	8 (36,4)	14 (63,6)	
AHF Profile			
ADHF, n (%)	25 (43,1)	33 (56,9)	0,641[b]
Acute Pulmonary Oedema, n (%)	7 (50)	7 (50)	
Rw Rehospitalization 12 months			
Rehospitalization > 1 time	16 (51,6)	15 (48,6)	0,287[b]
Rehospitalization ≤ 1 time	16 (39,0)	25 (61,0)	
Risk factors and comorbidities			
Smoking,			
Yes, n (%)	16 (50,0)	16 (50,0)	0,396[b]
No, n (%)	16 (40,0)	24 (60,0)	
Hypertension,			
Yes, n (%)	15 (39,5)	23 (60,5)	0,370[b]
No, n (%)	17 (50,0)	17 (50,0)	
Diabetes mellitus,			
Yes, n (%)	14 (63,6)	8 (36,4)	**0,030[b,d]**
No, n (%)	18 (36,0)	32 (64,0)	
CHD			
Yes, n (%)	15 (45,5)	18 (54,5)	0,874[b]
No, n (%)	17 (43,6)	22 (56,4)	
COPD,			
Yes, n (%)	15 (45,5)	19 (52,6)	0,493[b]
No, n (%)	17 (43,6)	21 (58,4)	
Laboratory and echocardiography			
eGFR, (mL/min/1.73 m2), mean ± SB	57,1 ± 27,5	57,7 ± 27,7	0,937[a]
Decreased (< 60 mL/min/1.73 m2)	25 (43,1)	33 (56,9)	0,641[b]
Not declining (≥ 60mL/min/1.73m2)	7 (50,0)	7 (50,0)	
Na, mmol/L, mean ±SB	135,1 ± 6,9	136, ± 5,1	**0,230[a,d]**
Hyponatremia	12 (52,2)	11 (47,8)	0,366[b]
No Hyponatremia	20 (40,8)	29 (59,2)	
Hb level (g/dl) mean ±SB	22,5 ± 2,1	12,2 ± 2,3	0,588[a]
Anemia (Hb < 10g/dl)	6 (46,2)	7 (53,8)	0,891[b]
No Anemia (Hb > 10g/dl)	26 (44,1)	33 (55,9)	
Hypoalbumin			
Albumin < 2.5 g/dl	1 (50)	1 (50)	0,873[b,]
Albumin > 2.5 g/dl	31 (44,3)	39 (55,7)	
Echocardiographic Parameters			
LVEF, %, median			0,467[c]
Reduced LVEF	19 (47,5)	21 (52,5)	0,560[b]
Non-Reduced LVEF	13 (40,6)	19(59,4)	

Variables	Diuresis Response		p
	Less	Simply	
Diuretic Therapy			
Routine use of Furosemide			
Yes, n (%)	21 (43,8)	27 (56,3)	0,867 [b]
No, n (%)	11 (45,8)	13 (54,2)	
Diuretic 48-hour loop dose, mg, median IQR,	40 (0-160)	40 (0-240)	0,729[c]
Furosemide dose IQR treatment	357,5 (60-1440)	320 (60-1410)	0,486
Furosemide dosage			
High, n (%)	22 (53,7)	19 (46,3)	**0,070[b]**
Low, n (%)	10 (32,3)	21 (67,7)	
Non-loop diuretics			
Yes, n (%)	27 (45,8)	32 (54,2)	0,632[b]
No, n (%)	5 (38,5)	8 (61,5)	
Total 72-hour urine, ml, mean ± S.D.	7814,5 ± 3602 ,5	10080 ± 5455,2	
Net urine output, ml, mean ± S.D.	4142,2 ± 2634,5	8983,5 ± 7477,8	
Net urine output per 40 mg furosemide iv, ml/40 mg, mean ± S.D.	439,7 ± 167,6	983,2 ± 44,1	

[a]Independent T test,[b] Chi Square test,[c] Mann U Whitney test,[d] Statistically significant.
ACEi, ACE-inhibitor; ARB, Angiotensin Receptor Blocker; ARNI, Angiotensin Receptor Neprilysin Inhibitor; FC, Functional class; AHF, acute heart failure; MRA, mineralocorticoid receptor antagonist; CHD, Coronary Heart Disease; SGLT2-i, SGLT2 inhibitor; SBP, Systolic blood pressure,
eGFR, Estimated Glomerular Filtration Rate, LVEF: Left Ventricular Ejection Fraction, Na+: Sodium.

The furosemide dose variable is the total furosemide dose that has been administered during 72 hours of treatment and is a numerical variable. A receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off point of furosemide dose on diuresis response outcomes. From the results of this analysis, the best cut-off point for furosemide dose was 307.5 mg with an area under the curve (AUC) value of 0.653 (95% CI 0.523-0.784; p = 0.025). Furthermore, research subjects with furosemide dose > 307.5 mg were classified into high furosemide dose and subjects with furosemide dose ≤ 307.5 mg were classified as low furosemide dose.

The results of bivariate analysis between groups shown in Table 3, showed variables that were significantly different from the diuresis response, including serum Na^+ values, type 2 DM and furosemide dose during treatment had a P value <0.25 so that they were included in the multivariate analysis.

Although the furosemide dose variable had a significant p value, it was not included in the further multivariate analysis because it is one of the components of the diuresis response calculation.

Differences in length of stay based on 6-hour and 48-hour urine Na^+ spot values after loop diuretic administration and confounding variables are shown in Table 4. The distribution of length of stay based on 6- and 48-hour urine Na^+ spot values was not found to be normal, so the Mann-Whitney Test was used to determine the significance of the difference in medians. There was a significant difference in the median length of stay of subjects with a low 6-hour post-loop diuretic urine Na^+ spot value compared to subjects with a normal/high 6-hour urine Na^+ spot value. There was no significant difference in the median length of stay of patients with low 48-hour urine spot Na^+ values post loop diuretic administration compared to patients with normal/high 48-hour urine spot Na^+ values. Analysis of confounding variables found no difference in median length of stay.

TABLE 4: Differences in Length of Stay based on spot Na+ urine values 6 hours and 48 hours post loop diuretic administration and subject characteristics.

Variables	Median (days)	p
Total subjects	5 (3-21)	
Spot Na urine 6 hours		
Spot low 6-hour urine Na	6 (4-21)	**0,024[c,d]**
Spot na normal/high 6-hour urine	5 (3-15)	
Spot Na urine 48 hours		
Spot low 48-hour urine Na	5 (3-16)	0,165
Spot Na urine 48 hours normal/increased	5,5 (3-21)	
Age, years,		
Age above median	5 (3-21)	0,534[c]
Below median age	5 (3-16)	

Variables	Median (days)	p
Gender		
Male, n (%)	5 (3-15)	0,322[c]
Female, n (%)	5 (3-21)	
AHF Profile		
ADHF, n (%)		
Acute Pulmonary Oedema, n (%)	5 (3-6)	137[b]
Risk factors and comorbidities	5 (3-21)	
Smoking,		
Yes, n (%)	5 (3-16)	0,890[c]
No, n (%)	5 (3-21)	
Hypertension,		
Yes, n (%)	5 (3-16)	0,945[c]
No, n (%)	5 (3-21)	
Diabetes mellitus,		
Yes, n (%)	3 (3-16)	0,550[c]
No, n (%)	5 (3-21)	
CHD		
Yes, n (%)	5 (3-16)	0,765[c]
No, n (%)	5 (3-21)	
COPD,		
Yes, n (%)	4 (3-15)	0,5483[c]
No, n (%)	5 (3-21)	
Routine use of Furosemide		
Yes, n (%)	5 (3-21)	0,719 [c]
No, n (%)	5 (3-16)	
Clinical parameters		
RR increased	5 (3-15)	0,609[c]
Normal RR	5 (3-21)	
SBP, mmHg, median		
Low initial inlet SBP	5 (3-8)	0,968[c]
Normal initial admission SBP	5 (3-21)	
Functional class		
FC III/IV	5 (3-21)	0,699[c]
FC I/II	5 (3-16)	
Everest score		
Normal 1	5 (3-21)	0,841[c]
Abnormal > 2	5 (3-16)	
Pre discharge heart failure therapy		
Furosemide		
Yes n (%)	5 (3-16)	0,715[c]
No n (%)	5 (5-21)	
ACEi/ARB/ARNI		
Yes n (%)	5 (3-21)	0,830[c]
No n (%)	6 (3-7)	
Beta blockers		
Yes n (%)	5 (3-21)	0,570[c]
No n (%)	5 (3-7)	
MRA		
Yes n (%)	5 (3-16)	0,572[c]
No n (%)	5 (3-21)	
Digitalis		
Yes n (%)	5 (3-16)	0,803[c]
No n (%)	5 (3-12)	
Non-Loop Diuretics		
Yes n (%)	5 (3-16)	0,693[c]
No n (%)	5 (5-21)	
If-channel blocker		
Yes n (%)	5,5 (3-9)	0,626[c]
No n (%)	5 (3-21)	

Variables	Median (days)	p
SGLT2i		
Yes n (%)	7,5 (4-9)	0,205[c]
No n (%)	5 (3-21)	
Laboratory and echocardiography		
eGFR		
Declining (< 60 mL/min/1.73 m2)	5 (3-21)	0,994[c]
Not declining (≥ 60 mL/min/1.73 m2)	7 (50,0)	
Na^+ serum		
Hyponatremia	5 (3-21)	0,196[c]
No Hyponatremia	5 (3-15)	
Hb levels		
Anemia (Hb < 10g/dl)	5 (3-21)	0,817[c]
No Anemia (Hb > 10g/dl)	5 (3-15)	
Hypoalbumin		
Albumin < 2.5 g/dl	5 (3-16)	0,200[c,]
Albumin > 2.5 g/dl	5 (3-21)	
Echocardiographic Parameters		
LVEF		
Reduced LVEF	5 (3-21)	0,716[c]
Non-Reduced LVEF	5 (3-16)	

[a]Independent T test,[b] Chi Square test,[c] Mann U Whitney test,[d] Statistically significant.
ACEi, ACE-inhibitor; ARB, Angiotensin Receptor Blocker; ARNI, Angiotensin Receptor Neprilysin Inhibitor; FC, Functional class; AHF, acute heart failure; MRA, mineralocorticoid receptor antagonist; CHD, Coronary Heart Disease; SGLT2-i, SGLT2 inhibitor; SBP, Systolic blood pressure,
eGFR, Estimated Glomerular Filtration Rate, LVEF: Left Ventricular Ejection Fraction, Na+: Sodium.

Linear regression analysis was performed to assess the correlation between 6-hour and 48-hour urine Na^+ spot values and length of stay. The 6-hour and 48-hour post-loop diuretic spot Na^+ values were not found to be significantly associated with length of stay (Table 5).

Table 5: Linear regression analysis of length of stay based on spot Na+ urine values 6 hours and 48 hours post loop diuretic administration.

Variables	Coefficient b	95% CI	p
Spot Na^+ 6-hour urine	-0,023	-0,54-0,008	0,138
Spot Na^+ 48-hour urine	0,012	0,012-0,036	0,326

The distribution of the incidence of rehospitalization and the composite of rehospitalization and/or death based on demographic and clinical characteristics as well as heart failure therapy of the study subjects can be listed in table 6 and Table 7.

TABLE 6: Distribution of the incidence of rehospitalization and composite of rehospitalization and/or death based on demographic and clinical characteristics of study subjects.

Variables	Rehospitalization		p	Rehospitalization and/or Mortality Composite		p
	Yes	No		Yes	No	
Number of subjects	15	57		16	56	
Gender						
Male, n (%)	12 (24,0)	38 (76,0)	0,319[b]	13 (26,0)	37 (74,0)	0,245[b]
Female, n (%)	3 (13,6)	19 (86,4)		3 (13,6)	19 (86,4)	
Age, years, mean±SB	64,7 ± 14,5	54,4 ± 13,3	**0,011**[a,d]	64,3 ± 14,1	54,4 ± 13,4	**0,120**[a,d]
AHF Profile						
ADHF, n (%)	12 (20,7)	46 (79,3)	0,951[b]	13 (22,4)	45 (77,6)	0,937[b]
Acute Pulmonary Oedema, n (%)	3 (21,4)	11 (78,6)		3 (21,4)	11 (78,6)	
Rehospitalization 12 months						
Rehospitalization > 1 time	7 (17,1)	34 (82,9)	0,366[b]	9 (29,0)	22 (71,0)	0,227[b]
Rehospitalization ≤ 1 time	8 (25,8)	23 (74,2)		7 (17,1)	34 (82,9)	

Variables	Rehospitalization		p	Rehospitalization and/or Mortality Composite		p
	Yes	No		Yes	No	
Risk factors and comorbidities						
Smoking,						
Yes, n (%)	7 (21,9)	25 (78,1)	0,846[b]	8 (25,0)	24 (75,0)	0,612[b]
No, n (%)	8 (20,0)	32 (80,0)		8 (20,0)	32 (80,0)	
Hypertension,	o					
Yes, n (%)	8 (18,6)	35 (81,4)	0,571[b]	8 (18,6)	35 (81,4)	0,369[b]
No, n (%)	7 (24,1)	22 (75,9)		8 (27,6)	21 (72,4)	
Diabetes mellitus,						
Yes, n (%)	7 (31,8)	15 (68,2)	**0,128[b]**	7 (31,8)	15 (68,2)	**0,194[b]**
No, n (%)	8 (16,0)	42 (84,0)		9 (18,0)	41 (82,0)	
CHD,						
Yes, n (%)	9 (27,3)	24 (72,7)	**0,216[b]**	10 (30,3)	23 (69,7)	**0,129[b]**
No, n (%)	6 (15,4)	33 (84,6)		6 (15,4)	33 (84,6)	
COPD,						
Yes, n (%)	2 (28,6)	5 (71,4)	0,596[b]	2 (28,6)	5 (71,4)	0,671[b]
No, n (%)	13 (20,0)	52 (80,0)		14 (21,5)	51 (78,5)	
Stroke,						
Yes, n (%)	0 (0)	2 (100)	0,462[b]	0 (0,0)	2 (100)	0,443[b]
No, n (%)	15 (21,4)	55 (78,6)		16 (22,9)	54 (77,1)	
Routine use of Furosemide						
Yes, n (%)	11 (22,9)	37 (77,1)	0,538[b]	12 (25,0)	36 (75,0)	0,423[b]
No, n (%)	4 (16,7)	20 (83,3)		4 (16,7)	20 (83,3)	
Furosemide dose 48 hours median IQR	60 (0-240)	40 (0-240)	0,890[b]	50 (0-240)	40 (0-240)	0,871[b]
Clinical parameters						
RR increased	4 (14,3)	24 (85,7)	0,275[b,]	5 (17,9)	23 (82,1)	0,4777[b]
Normal RR	11 (25,0)	31 (70,5)		11 (25,0)	33 (75,0)	
SBP, mmHg, median			0,583[c]			0,460[b]
Low initial inlet SBP	5 (29,4)	12 (70,6)	0,319[b]	5 (29,4)	12 (70,6)	0,415[b]
Normal initial admission SBP	10 (18,2)	45 (81,8)		11 (20,0)	44 (80,0)	
Functional class						
FC III/IV	5 (17,2)	24 (82,8)	0,538[b]	6 (20,7)	23 (79,3)	0,797[b]
FC I/II	10 (23,3)	33 (76,6)		10 (23,3)	33 (76,7)	
Everest score						
Normal 1	3 (10,3)	26 (89,7)	0,072[b]	3 (10,3)	26 (89,7)	**0,047[b,d]**
Abnormal > 2	12 (27,9)	31 (72,1)		13 (30,2)	30 (69,8)	
Pre discharge heart failure therapy						
Furosemide						
Yes n (%)	11 (22,9)	52 (82,5)	**0,062[b]**	12 (19,0)	51 (81,0)	**0,086[b]**
No n (%)	4 (16,7)	5 (83,3)		4 (44,4)	5 (55,6)	
ACEi/ARB/ARNI						
Yes n (%)	14 (20,9)	53 (79,1)	0,962[b]	15 (22,4)	52 (77,6)	0,901[b]
No n (%)	1 (20,0)	4 (80,0)		1 (20,0)	4 (80,0)	
Beta blockers						
Yes n (%)	12 (19,0)	51 (81,0)	0,324[b]	13 (20,6)	50 (79,4)	0,391[b]
No n (%)	3 (33,3)	6 (66,7)		3 (33,3)	6 (66,7)	
MRA						
Yes n (%)	11 (19,0)	47 (81,0)	0,427[b]	12 (20,7)	46 (79,3)	0,524[b]
No n (%)	4 (28,6)	10 (71,4)		4 (28,6)	10 (71,4)	
Digitalis						
Yes n (%)	3 (30,0)	7 (70,0)	0,442[b]	3 (30,0)	7 (70,0)	0,524[b]
No n (%)	12 (19,4)	50 (80,6)		13 (21,0)	49 (79,0)	
Non-Loop Diuretics						
Yes n (%)	1 (50,0)	1 (50,0)	0,303[b]	1 (50,0)	1 (50,0)	0,338[b]
No n (%)	14 (20,0)	56 (80,0)		15 (21,4)	55 (78,6)	

Variables	Rehospitalization		p	Rehospitalization and/or Mortality Composite		p
	Yes	No		Yes	No	
If-channel blocker						
Yes n (%)	0 (0,0)	6 (100)	0,431[b]	0 (0,0)	6 (100)	0,393[b]
No n (%)	15 (22,7)	51 (77,3)		16 (24,2)	50 (75,8)	
SGLT2i						
Yes n (%)	1 (25,0)	3 (75,0)	0,833[b]	1 (25,0)	3 (75,0)	0,891[b]
No n (%)	14 (20,6)	54 (79,4)		15 (22,1)	53 (77,9)	

[a]Independent T test,[b] Chi Square test,[c] Mann U Whitney test,[d] Statistically significant.
ACEi, ACE-inhibitor; ARB, Angiotensin Receptor Blocker; ARNI, Angiotensin Receptor Neprilysin Inhibitor; FC, Functional class; AHF, acute heart failure; IMT, body mass index; MRA, mineralocorticoid receptor antagonist; CHD, Coronary Heart Disease; SGLT2-i, SGLT2 inhibitor; SBP, Systolic blood pressure

Based on the results of bivariate analysis between groups as shown in Table 6 and Table 7, age, history of diabetes mellitus, history of coronary heart disease, history of furosemide uses at discharge, serum Na+ level, and EVEREST score were significantly different based on the incidence of rehospitalization. Other confounding variables with p value <0.25 or theoretically associated with rehospitalization were still included in the multivariate analysis to assess factors independently associated with the incidence of rehospitalization.

TABLE 7: Distribution of the incidence of rehospitalization and composite of rehospitalization and/or death by Laboratory and Echocardiographic characteristics.

Variables	Rehospitalization		p	Rehospitalization and/or Mortality Composite		p
	Yes	No		Yes	No	
eGFR, (mL/min/1.73 m2), mean ± SB	50,1 ± 27,9	59,4 ± 27,2	0,256[a]	53,0 ± 29,3	58,7 ± 27,0	0,464[a]
Decreased (< 60 mL/min/1.73 m2)	12 (20,7)	46 (79,3)	0,951[b]	12 (20,7)	46 (79,3)	
Not declining (≥ 60 mL/min/1.73 m2)	3 (21,4)	11 (78,6)		4 (28,6)	10 (71,4)	
Na, mmol/L, mean ±SB	132,0 ± 7,57	137,0 ± 5,05	**0,003[a,d]**	132,5 ± 7,5	137,0 ± 5,0	**0,007[a,d]**
Hyponatremia	7 (304)	16 (69,6)	0,816[b]	7 (30,4)	16 (69,6)	0,251
No Hyponatremia	8 (16,3)	41 (83,7)		9 (18,4)	40 (81,6)	
Hb level (g/dl) mean ±SB	12,0 ± 1,8	12,5 ± 2,3	0,511[a]	12,1 ± 1,7	12,4 ± 2,41	0,560[a]
Anemia (Hb < 10g/dl)	4 (30,8)	9 (69,2)	0,331[b]	4 (30,8)	9 (69,2)	0,413[b]
No Anemia (Hb > 10g/dl)	11 (18,6)	48 (81,4)		12 (20,3)	47 (79,7)	
Hypoalbumin						
Albumin < 2.5 g/dl	0 (0,0)	2 (100)	0,462[b]	0 (0,0)	2 (100)	0,443[b]
Albumin > 2.5 g/dl	15 (21,4)	55 (78,6)		16 (22,9)	54 (77,1)	
Echocardiographic Parameters						
LVEF, %, median	38,0 (19-69)	36,9 (14-68)	0,252[c]	37,5 (19-69)	37,0 (14-68)	0,397[c]
Reduced EF n (%)	8 (20,0)	32 (80,0)	0,338[b]	9 (22,5)	31 (77,5)	0,279[b]
Non-Reduced EF n (%)	7 (21,9)	25 (78,1)		7 (21,9)	25 (78,1)	
Average E/e' mean ± SB	16,5 ± 4,7	15,2 ±2,61	0,179[a]	16,3 ± 4,6	15,3 ± 2,6	0,240[a]
ePCWP, mmHg, mean±SEM	22,4 ± 5,9	20,8 ± 3,2	0,179[a]	22,2 ± 5,7	20,8 ± 3,2	0,240[a]

[a]Independent T test,[b] Chi Square test,[c] Mann U Whitney test,[d] Statistically significant.
BUN, Blood Urea Nitrogen; Cl, Chloride; eGFR, estimated glomerular filtration rate, LVEF: Left Ventricle Ejection Fraction.

In bivariate analysis between groups of confounding variables and the composite of rehospitalization and/or death showed that age, history of diabetes mellitus, history of coronary heart disease, history of furosemide uses at discharge, serum Na^+ level, and EVEREST score, were significantly different with a p value <0.25.

Other confounding variables theoretically associated with rehospitalization were still included in the multivariate analysis to determine factors independently associated with the composite of rehospitalization and/or death.

Table 8 shows the comparison of the proportion of diuresis response based on 6-hour and 48-hour post loop diuretic urine Na^+ spot values. The risk of diuresis response is less increased more than 3 times in the group with lower 6-hour post loop diuretic urine Na^+ levels compared to the group with normal/high 6-hour post loop diuretic urine Na^+ levels.

Next, multivariate logistic regression analysis was performed to control for confounding variables that have the potential to influence the relationship between the independent variable (6-hour post loop diuretic urine Na spot level) and the dependent variable (diuresis response). Multivariate analysis was performed using the logistic regression test with the backward method (Table 9).

TABLE 8: Cross tabulation of proportion of diuresis response based on spot urine Na values 6 hours and 48 hours post loop diuretic administration.

Variables	Diuresis response		Unadjusted OR	95% CI	p
	Less	Simply			
Spot Na^+ 6-hour urine					
Low	13 (65,0)	7 (35,0)	3,50	1,18-10,35	**0,023[a]**
Normal/Increased	18 (34,6)	34 (65,4)			
Spot Na^+ 48-hour urine					
Low	15 (46,9)	17 (53,1)	0,75	0,29-1,93	0,559
Normal/Increased	16 (40,0)	24 (60,0)			

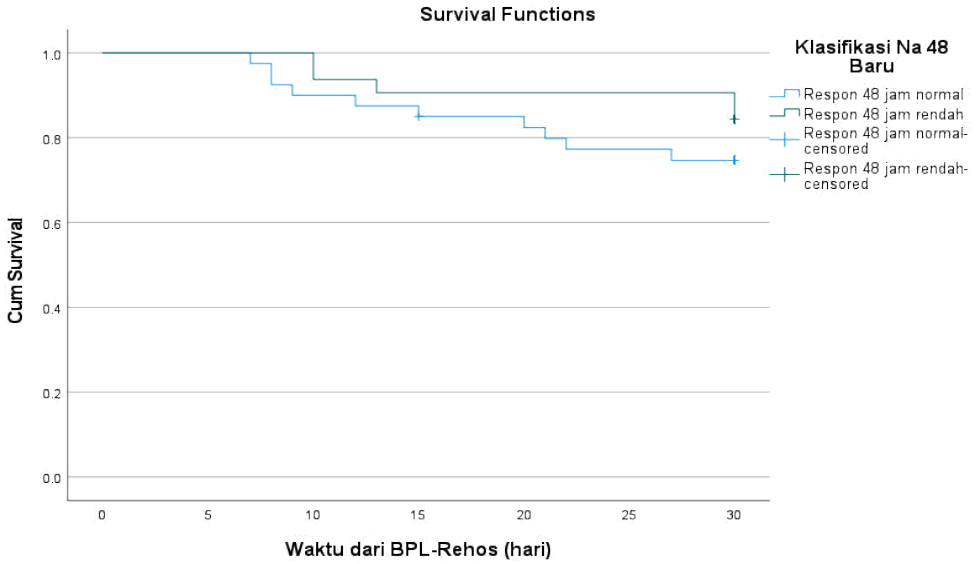
[a]Statistically significant.

TABLE 9: Multivariate logistic regression analysis of independent predictors of diuresis response in AHF.

Variables	Adjusted OR	95% CI	p
Age	1,01	0,97-1,05	0,678
Gender (male)	1,39	0,45-4,32	0,46
History of DM	1,23	0,45-94,79	0,71
Use of Furosemide within 30 days	1,03	0,35-3,04	0,55
Use of other diuretics	1,55	0,41-5,98	0,52
Hyponatremia	0,74	0,23-2,34	0,61
Hypoalbuminemia	0,93	0,36-23,9	0,96
eGFR Classification	0,85	0,23-3,40	0,85
Spot Na value$^+$ 6-hour urine	**3,67**	**1,12-11,8**	**0,03[a]**

[a]Adjusted HR based on 6-hour post-loop diuretic urine Na+ spot levels, and confounding variables.
DM, diabetes mellitus, HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate.

Survival analysis was performed to assess the interaction of 6-hour and 48-hour urine spot Na^+ values post loop diuretic administration as a predictor of rehospitalization. The analysis was first performed by assessing the proportional hazard (PH) assumption with Kaplan Meier curves on the independent variable (spot Na^+ level of urine 6 hours and 48 hours post-administration of loop diuretics) as attached in Figure 2.



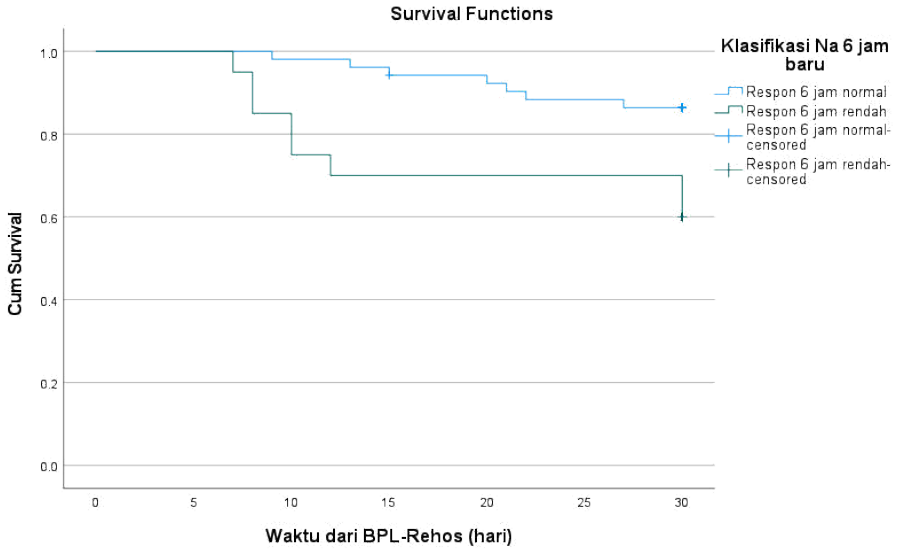


FIGURE 2: Kaplan-Meier survival curves of rehospitalization based on (A) urine Na^+ spot levels 6 hours post loop diuretic administration and (B) urine Na^+ spot levels 48 hours post loop diuretic administration.

Based on Table 10, subjects with lower 6-hour urine spot Na^+ values post loop diuretic administration had a lower 30-day survival rate for rehospitalization events compared to patients with normal/higher 6-hour urine spot Na^+ values (60.0% versus 86.5% log rank test p = 0.008). In contrast, there was no significant difference in 30-day survival rate in patients with low post-loop diuretic 48-hour urine spot Na^+ levels compared with patients with normal/high 48-hour urine spot Na^+ levels.

TABLE 10: Mean Survival Time and 30-Day Survival Rate based on 6-hour and 48-hour post-loop diuretic urine Na+ spot values.

Variables	Mean Survival Time (days)	95% CI	30-Day Survival Rate (%)	p
Spot Na^+ 6-hour urine				
Spot Na^+ low 6-hour urine	23,75	19,2-28,2	60,0	**0,008**
Spot Na^+ normal/high 6-hour urine	28,37	27,1-29,6	86,5	
Spot Na^+ 48-hour urine				
Spot Na^+ low 48-hour urine	28,21	26,06-30,37	84,4	0,290
Spot Na^+ normal/increased 48-hour urine	26,20	23,91-28,49	75,0	

[a]statistically significant.

Based on the Cox Regression test, 6-hour urine spot Na^+ levels after loop diuretic administration were significantly associated with the incidence of rehospitalization within 30 days in AHF patients. Patients with low urine spot Na^+ values 6 hours post loop diuretic administration had an almost 4 times higher risk of rehospitalization within 30 days (unadjusted HR 3.59; 95% CIKS 1.30-9.91, p = 0.014). Based on multivariate analysis, the spot Na^+ value of urine 6 hours post loop diuretic administration proved to be an independent predictor of rehospitalization within 30 days in AHF patients (Table 11). Another variable that was shown to be a predictor that increased the incidence of rehospitalization within 30 days in AHF patients was age.

TABLE 11: Multivariate analysis of cox regression of spot Na^+ urine values 6 hours post loop diuretic as a predictor of the incidence of rehospitalization within 30 days.

Variables	[a]Adjusted HR	95% CI	p
Age	**1,06**	**1,01-1,11**	**0,011**
DM	1,35	0,40-4,58	0,621
CHD	1,05	0,31-3,48	0,930
EVEREST Score	3,17	0,79-12,67	0,102
LVEF Classification	1,44	0,41-4,97	0,560
Hyponatremia	1,98	0,48-8,44	0,343
Low 6-hour urine Na^+ spot levels	**3,53**	**1,11-11,18**	**0,032**

[a]Adjusted HR based on 6-hour post-loop diuretic urine Na+ spot levels, and confounding variables.
HT, Hypertension; HR, Hazard Ratio; CI, Confidence Interval, LVEF, left ventricular ejection fraction.

Analysis of the role of spot urinary Na+ values 6 hours and 48 hours post loop diuretic administration as a composite predictor of rehospitalization and/or death within 30 days in AHF patients began with an assessment of the PH assumption with Kaplan Meier curves.

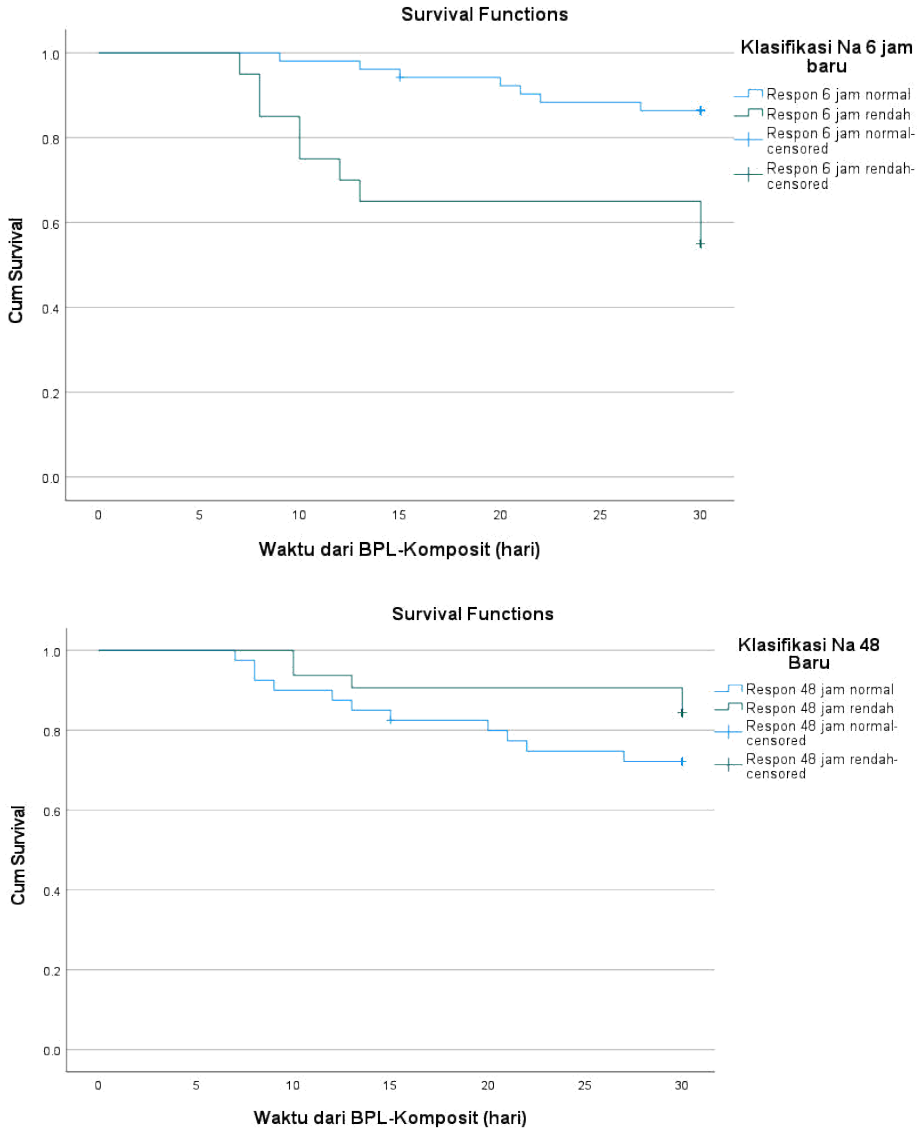


FIGURE 3: Kaplan-Meier survival curves of the composite event of rehospitalization and death from cardiovascular disease within 30 days based on urinary Na+ spot levels 6 hours post loop diuretic administration and (B) urinary Na+ spot levels 48 hours post loop diuretic administration.

The results of the survival analysis showed that subjects with low 6-hour post-loop diuretic spot Na^+ values had a significantly lower 30-day survival rate for the composite of rehospitalization and/or death than subjects with normal/higher 6-hour post-loop diuretic spot Na^+ values (55.0% versus 86.5%; log rank test 0.002). There was no significant difference in 30-day survival rate for the composite of rehospitalization and/or death from cardiovascular disease based on spot Na^+ values 48 hours post loop diuretic administration (Table 12).

TABLE 12: Mean Survival Time and 30-Day Survival Rate based on 6-hour and 48-hour post-loop diuretic urine Na+ spot values.

Variables	Mean Survival Time (days)	95% CI	30-Day Survival Rate (%)	p
Spot Na^+ 6-hour urine				
Spot Na^+ low 6-hour urine	**22,90**	**18,36-27,43**	**55,0**	**0,002**
Spot Na^+ normal/high 6-hour urine	28,39	27,15-29,63	86,5	
Spot Na^+ 48-hour urine				
Spot Na^+ low 48-hour urine	28,21	26,06-30,37	84,4	0,198
Spot Na^+ urine 48 hours normal/increased	25,77	23,41-28,14	72,5	

[a]Statistical significant.

Based on the Cox Regression test, the spot value of urine Na^+ 6 hours after loop diuretic administration was a significant predictor of the incidence of rehospitalization within 30 days in AHF patients. Subjects with lower 6-hour urine spot Na^+ values post loop diuretic administration had 4 times higher risk of experiencing a composite event of rehospitalization and/or death within 30 days (Unadjusted HR 4.21;95%CI 1.56-11.33 p = 0.004). Table 13 shows that a low 6-hour post-loop diuretic urine spot Na^+ level was an independent predictor of the composite event of rehospitalization and/or death within 30 days in AHF patients (adjusted HR 4.89; 95% CI 1.58-15.11; p = 0.006). Other variables that proved to be independent significant predictors of the composite of rehospitalization and/or mortality were age.

TABLE 13: Multivariate analysis of cox regression of spot Na^+ urine values 6 hours post loop diuretic as a predictor of the incidence of composite event of rehospitalization and cardiovascular mortality within 30 days.

Variables	[a]Adjusted HR	95% CI	p
Age	**1,06**	**1,01-1,11**	**0,012**
DM	1,09	0,32-3,66	0,890
CHD	1,43	0,44-4,67	0,545
EVEREST Score	4,12	0,83-13,19	0,089
LVEF Classification	3,31	0,49-5,75	0,406
Hyponatremia	1,65	0,41-6,68	0,477
Low 6-hour urine Na^+ spot levels	**4,89**	**1,58-15,11**	**0,006**

[a]Adjusted HR based on 6-hour post-loop diuretic urine Na+ spot levels, and confounding variables.
HT, Hypertension; HR, Hazard Ratio; CI, Confidence Interval, LVEF, left ventricular ejection fraction.

DISCUSSION

The primary goals of therapy in AHF patients are safe and effective early decongestion and prevention of rehospitalization/mortality. Ineffective decongestion and residual congestion have been associated with repeated episodes of rehospitalization. Until now, the use of loop diuretics is still the first choice of decongestion therapy for AHF patients. However, there is no consensus to guide decongestion therapy. The currently routinely used parameters of urine production and weight change do not correlate well and are difficult to evaluate accurately. A method of monitoring diuresis response that is accurate, simple, and has a good association with cardiovascular outcomes is needed.

This study evaluated 6-hour and 48-hour urine spot Na^+ values post loop diuretic administration as predictors of diuresis response within 72 hours of treatment. The prognostic impact of 6-hour and 48-hour spot Na^+ urine based on length of stay, incidence of rehospitalization and composite of rehospitalization and/or death from cardiovascular disease within 30 days was also evaluated in this study.

This study involved 72 AHF patients who were treated at Prof. Dr. I.G.N.G. Ngoerah who were taken based on the inclusion and exclusion criteria that have been set. Based on the spot value of urine Na^+ 6 hours post loop diuretic administration, as many as 20 subjects (27.8%) subjects had a low spot value of urine Na^+ 6 hours post loop diuretic and as many as 52 (72.2%) the rest had a normal / high spot value of urine Na^+ 6 hours post loop diuretic. Similar results were obtained by Luk et al., (2018), Brinkley et al., (2018), and Galluzzo et al., (2019) with the value of the proportion of each subject with low initial diuresis phase spot Na^+ Urine values as much as 30.1%, 33.5%, and 35.0%, respectively These results are not much different from the data obtained from this study [8–10]. ROC analysis showed a value of < 62.3 mmol/L as the optimal cut off value in predicting rehospitalization and composite outcomes of rehospitalization and/or death from heart disease. This value is higher than the cutoff point obtained by Luk et al. (2018) who obtained a cutoff point of < 60 mmol/L [8]. While Brinkley et al (2018) found a spot value of urinary Na^+ < 65 mmo/L as the optimal cutoff point value in predicting outcomes [9]. Lower values were obtained by Doering et al, (2017) who found a spot Na^+ urine cut off value < 50 mmol/L correlated with a higher incidence of readmissions [11]. This variation in values may be explained by differences in sampling time in each study.

During heart failure treatment, the spot value of urine Na^+ is dynamic and is influenced by changes in clinical conditions. Biegus et al, (2021) divide the natriuresis response based on the phase of heart failure treatment, namely the early / active decongestive phase where the patient is still experiencing gross fluid overload (from the time the patient enters treatment until day 2) and the stabilization phase where the patient has experienced euvolemic conditions [12]. Biegus et al, (2019) shows the trend of increasing the average value of Na+ urine spots 6 hours from baseline and decrease in the average value of Na+ urine spots in 24 and 48 hours. The same thing was found in this study where there was a decrease in the average value of the Na+ urine spot level 6 hours 84.1 ± 26.3 mmol/L to 70.38 ± 34.3 mmol/L on the average Na+ urine spot 48 hours. [13].

There was a difference in prehospitalization furosemide dose between low and high 6-hour and 48-hour urine spot Na^+ values where the median furosemide dose tended to be higher in the group with lower urine spot Na^+ values.

Similar findings were obtained by Damman et al, (2020) who showed significant differences in the dose of loop diuretics before treatment between patients with different 6-hour urine Na^+ tertiles. Long-term administration of loop diuretics and dose escalation has been associated with changes in the distal convoluted tubule. The distal convoluted tubule has increased Na^+ absorption as a form of compensation for loop diuretic exposure to the ascending renal tubule [14].

There was no significant difference in the mean eGFR values between the spot Na^+ urine 6 hours and 48 hours post loop diuretic administration groups. The proportion test based on eGFR values < 60 ml/min/1.73 m2 also showed no significant difference between the 6-hour and 48-hour spot Na^+ urine groups. Similar findings were obtained by Doering et al. (2017) which showed no difference in the eGFR value of subjects with urine Na+ spot values < 50 meq/L compared to subjects with higher urine Na^+ spot values ($p = 0.361$) [11]. Similar results were also found by Galluzzo et al., (2020) who found no difference in eGFR values based on the spot value of urine Na^+ ($p = 0.72$) [10]. In contrast, Damman et al. (2020) showed a significant difference in eGFR values based on the classification of 6-hour urine sodium tertiles ($p < 0.001$) [15]. This finding can be explained by the existence of two different mechanisms of renal dysfunction in heart failure, namely impaired glomerular filtration and impaired natriuresis response [5]. Dysregulation of natriuresis not only involves decreased flow at the renal glomerulus, but also involves other segments such as the proximal tubule, loop of henle, macula densa and distal convoluted tubule [16].

Hyponatremia is one of the most common electrolyte abnormalities in AHF. Galluzzo et al., (2020) showed that patients with lower urinary spot Na^+ values had lower serum sodium levels ($p = 0.004$) [10]. Similar results were obtained by Luk et al., (2018) which showed a significant difference in serum Na^+ levels between groups of patients with urine Na^+ spot values < 60 mmol/L and ≥ 60 mmol/L ($p = 0.002$) [8]. Similar results were obtained in this study. Patients with 6-hour post-loop diuretic urine spot Na+ values had lower mean serum Na^+ than patients with higher 6-hour urine spot Na^+ values (133 ± 7.7 mmol/L vs 137.2 ± 7.7 mmol/L; $p = 0.006$). Hyponatremia, especially dilutional hyponatremia is a common finding in advanced heart failure cases and is a marker of decreased renal perfusion and severe congestion. Low serum Na^+ concentration is associated with high neurohormonal activation and lower eGFR values [7].

The classification of diuresis response in this study was taken based on the median value of 72-hour net urine output per 40 mg furosemide iv dose with a value of 682.5 ml/40 mg furosemide (81.6-1553.4ml/40 mg furosemide dose). Testani et al (2014) also divided the diuresis response based on net urine output/40 mg furosemide. In this study, the median net urine output was 480 ml/40 mg furosemide (interquartile range 195-1024 ml/40 mg furosemide). This difference may be explained by differences in the timing of cumulative net urine output measurements [17].

Rehospitalization occurred in 15 (20.8%) subjects and the composite of rehospitalization and/or death due to cardiovascular disease occurred in 16 (22.2%) subjects out of a total of 72 subjects who were observed for 30 days post-hospitalization.

In this study, the 6-hour post-loop diuretic urine spot Na^+ value was shown to be significantly associated with diuresis response in AHF patients receiving loop diuretic therapy. Patients with lower 6-hour post-loop diuretic urine spot Na^+ values had a 3.6 times higher risk of poor diuresis response than patients with higher 6-hour urine spot Na^+ values. This association was independent of confounding factors.

The first observational study to evaluate spot urine Na^+ as a marker of diuresis response was conducted by Singh et al., (2014) which showed spot urine Na + values < 50 mmol / L in 3-24 hours after loop diuretic administration was associated with lower urine output, net fluid output and weight loss [18]. Similar results were obtained by Galluzzo et al (2020) who showed that AHF subjects with urine Na+ spot values < 50 mmol/L showed lower 24-hour urinary output and 48-hour weight loss [19]. In addition, Brinkley et al (2018), in their study involving 176 AHF patients with volume overload showed that subjects with a lower first post-urine spot Na+ value post loop diuretic administration were significantly associated with lower urine output ($p = 0.02$) [9]. Finally, a post hoc analysis from the Renal Optimization Strategies Evaluation in Acute Heart Failure (ROSE-AHF) showed that patients with urinary spot Na^+ values < 60 mmol/L were associated with lower weight loss than patients with urinary spot Na+ values > 60 mmol/L [20]

The process of natriuresis described by urinary Na excretion$^+$ directly reflects the mechanism of action of loop diuretics. The natriuresis effect starts at 1.5-2 hours post diuretic administration and reaches its peak within 6 hours. In general, weight loss and natriuresis occur gradually and progressively as the loop diuretic is administered. Most natriuresis occurs on the first day of diuretic administration and begins to decrease by the third day [21]. Examination of natriuresis can be done by measuring Na+ levels in urine over 24 hours, 6 hours or spot samples of urine Na+. Compared to urine collection, urine spot sample examination is simpler and easier to obtain. Spot Na^+ urine has been correlated with the value of total Na^+ excretion for 24 hours. Rhee et al in their study showed a strong correlation between the estimated urinary Na^+ excretion for 24 hours based on the calculation of spot urinary Na^+ and the measured urinary Na^+ value [22].

This study strengthens the association between the degree of natriuresis described by urinary Na^+ spot values.

Until now, several studies have shown the association between spot Na^+ values and diuresis response but there are differences in sampling time and examination cut off values (<50 mmol/L to <89 mmol/L). In the previous studies that have been conducted, spot examination of urine Na^+ was taken in the range of 2 hours to 72 hours. The 6-hour sampling in this study was made based on the physiological response of natriuresis after loop diuretic administration where the maximum natriuresis response occurs within 6 hours after the first dose of loop diuretic and describes the early natriuretic response in AHF patients who receive loop diuretic therapy [13].

In this study, there was no significant relationship between the 48-hour urine Na^+ spot value after loop diuretic administration and the 72-hour diuresis response. Several studies have assessed the relationship between 48-hour urine Na^+ spot values and diuresis response. Biegus et al. (2019) showed that a decrease/no increase in urinary Na^+ values within 48 hours from baseline values was associated with lower weight loss during treatment in AHF patients. Meanwhile, a study by Galluzzo et al. showed that 24-hour urinary Na^+ levels post loop diuretic administration were not associated with urinary output [13]. The findings in this study may be explained by the reduced ability of spot urinary Na^+ as a biomarker after 24 hours of loop diuretic administration. Natriuresis begins to decrease after the first day, as high urine output changes to hypotonic urine in AHF patients and reduced Na^+ secretion as decongestion occurs.

In this study, there was a significant difference in the median length of stay between subjects with low 6-hour post-loop diuretic urine Na+ spot values compared to subjects with high urine Na+ spot values (median 6 days compared to 5 days, p = 0.024). There was no significant difference in median days between patients with 48-hour post-loop diuretic urine spot Na+ values. Linear regression analysis showed no significant association of 6- and 48-hours post loop diuretic spot Na^+ values with length of stay, with b coefficients of -0,023 (p = 0.138) and 0,012 (p = 0.326), respectively.

Several studies have shown a correlation between natriuresis and length of stay in patients with ADHF. In a study involving 103 patients with ADHF, it was shown that patients with spot Na urine admission values ≤ 60 mmol/L had a longer length of stay (11 vs 6 days, P < 0.006) than patients with spot Na urine > 60 mmol/L [8]. Similar results were obtained by Cunningham et al. which showed that patients with spot Na + ≤ 60 mmol / L values were associated with a longer length of stay (7 days vs. 5 days, P < 0.001) compared to patients with spot Na + > 60 mmol / L values [23]. Meanwhile, Damman et al. (2020) found no significant difference in length of stay between 6-hour urine Na^+ tertiles in AHF patients (p = 0.21) [15].

The results of this study showed a difference in median days between patients with 6-hour urine Na+ spot values, but after regression analysis no strong association was found. This may be explained by other factors that influence length of stay. Wright et al. (2003) showed that in addition to signs of congestion, duration of intravenous diuretic administration, and worsening renal function, the presence of pulmonary problems (OR 3.8) and social factors (OR 6.8) also play a role as factors that prolong the length of stay [24].

In this study, the spot Na^+ value of urine 6 hours post loop diuretic administration was significantly associated with rehospitalization and the composite of rehospitalization and/or death from cardiovascular disease within 30 days in AHF patients receiving loop diuretic therapy. Patients with low 6-hour post-loop diuretic urine spot Na^+ values were at 3.5 times higher risk of rehospitalization and 4.9 times higher risk of composite rehospitalization and/or death from cardiovascular disease within 30 days. This association was independent of confounding factors.

These results further strengthen the findings of previous studies that have found associations between natriuresis response and outcomes of rehospitalization and/or cardiovascular death. Poor natriuresis response is associated with short- and long-term outcomes in AHF patients. Brinkley et al. showed that 24.3% of AHF patients with high urine spot Na^+ values and 58.9% of AHF patients with low urine spot Na^+ values were associated with rehospitalization within 30 days [9]. Similar results were obtained by Doering et al. who showed a higher 30-day rehospitalization rate in AHF patients with lower urine Na+ spot values (28% vs. 13%, p = 0.03) compared to higher urine Na^+ spot values [11]. In a retrospective ROSE-AHF study conducted by Hodson et al, (2019) it was shown that around 30% of patients experienced a low diuresis response within 24 hours [20]. This low natriuresis response was associated with an increased risk of all-cause mortality in the last 6 months, (HR 2.02, 95% CI 1.17-3.46). Finally, Biegus et al. showed a higher readmission rate at 1-year follow-up of AHF patients with spot urine Na+ values < 60 mmol/L compared to spot urine Na+ values > 60 mmol/L (OR 3.2 95% CI 1.6-6.2, P < 0.01) [12].

Several mechanisms may explain the association between urinary spot Na^+ values and worse outcomes in AHF patients. First, urinary spot Na^+ values may represent renal hypoperfusion. Hypoperfusion is common in AHF and is associated with worse outcomes [24]. This in turn activates the glomerulotubular and tubuloglomerular feedback mechanisms, both of which lead to an increase in Na+ uptake in the proximal tubule and ultimately a decrease in natriuresis [25]. Second, decreased urinary Na^+ levels may represent increased neurohormonal activity that has been associated with worse clinical outcomes in AHF patients. Honda et al. (2018) in their study involving 669 AHF patients, showed patients with lower urinary Na^+ values had higher renin (p < 0.001) and plasma aldosterone (p < 0.001) activities [26]. Third, the spot value of urine Na^+ may reflect a decreased response to diuretics.

Finally, the spot Na value$^+$ may reflect the process of worsening renal function which has been associated with poor prognosis in AHF.

There was no association between the spot Na^+ value of 48-hour urine after loop diuretic administration with the incidence of rehospitalization and a composite of the incidence of rehospitalization and/or death from cardiovascular disease within 30 days in AHF patients. Biegus et al. (2021) showed 48-hour spot urine Na^+ values had prognostic significance for rehospitalization with an HR of 0.97 (0.81-0.91) $p < 0.005$ for each 10 mmol/L increase in spot urine Na^+[12] . In addition, Biegus et al. (2019) also showed that no increase in spot urinary Na^+ values within 48 hours post loop diuretic administration compared to baseline values was independently associated with mortality at 1 year [13]. The decrease in 48-hour urine spot Na^+ values as a predictor of outcomes in AHF patients can be expected to occur due to decreased natriuresis during treatment [19].

The decrease in natriuresis can be explained by firstly, the clinician's tendency to reduce the diuretic dose after seeing the diuresis response within 24 hours post-treatment. Second, neurohormonal activation and increased Na^+ reabsorption in nephron segments other than the loop of henle may increase Na^+ avidity. Third, the post diuretic Na^+ retention condition where high Na^+ excretion after the first dose of loop diuretic is followed by a period of low Na^+ excretion may further reduce natriuresis. Finally, after 24 hours of initiation of loop diuretic therapy, the urine produced tends to be hypotonic with a higher amount of free water. This can lead to dilution of Na^+ concentrations which will be difficult to detect in spot urine Na^+ [19]. Verbrugge et al. (2014) showed that urinary Na^+ secretion during decongestion therapy in AHF patients decreased significantly after the first 24-hour interval ($P < 0.001$) and began to level off after 24 hours ($P = 0.579$) [27].

The results of this study provide additional value regarding information on the prognostic role of 6-hour urine spot Na^+ values in relation to the risk of rehospitalization and the composite of rehospitalization and/or short-term cardiovascular mortality after AHF. In addition, this study provides information on the decreasing role of spot urinary Na^+ as a predictor of cardiovascular outcomes within 48 hours post loop diuretic administration. In this study, only 1 subject experienced death within 30 days of discharge after AHF, so it can be assumed that the composite data of rehospitalization and/or death better describes the risk of rehospitalization. Therefore, the data in this study cannot provide information on the role of spot urine Na+ as a predictor of cardiovascular outcomes.

In multivariate analysis, age was found to be one of the other factors affecting rehospitalization and the composite of rehospitalization and/or death.

The prevalence of heart failure increases with age, where the prevalence increases by 1% from 45-55 years of age and reaches almost 10% in patients aged 80 years [28]. Elbadawi et al. (2021) showed that patients aged 55-64 (OR 1.6; 95% CI 0.83-0.91) years and > 75 (OR 2.54; 95% CI 2.44 - 2.64) years had a higher risk of AHF rehospitalization than patients aged 18-34 years [29]. The increased rehospitalization in older age may be explained by the increase in comorbidities with age.

The limitation of this study is that it did not examine other residual confounding that could affect the outcomes of rehospitalization and the composite of rehospitalization and/or death. This study did not examine NT-proBNP and troponin, which are known to affect outcomes based on literature review. The limited scope of examination availability and health insurance coverage were the reasons for not examining these parameters. $^+$In addition, in this study, the Na intake variable could not be fully controlled, given the high variation of intake in each patient. All subjects had been given a low-salt diet according to the protocol in AHF therapy, but Na^+ intake outside the diet provided by the hospital could not be fully controlled. Finally, this study reflects a population of AHF patients at a tertiary referral center with higher disease severity and the application of a large number of exclusion criteria, which may affect the generalizability of the study.

CONCLUSION

(1) Urinary Na^+ spot levels 6 hours post loop diuretic is an independent predictor of diuresis response within 72 hours, incidence of rehospitalization and the composite of rehospitalization and/or death from cardiovascular disease within 30 days post treatment in patients with acute heart failure.
(2) 6-hour post-loop diuretic urine Na^+ spot levels is not an independent predictor of length of stay in acute heart failure patients.
(3) Urinary Na^+ spot level 48 hours post loop diuretic is not an independent predictor of diuresis response within 72 hours, length of stay, incidence of rehospitalization and composite of rehospitalization and/or death from cardiovascular disease within 30 days post treatment in patients with acute heart failure.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest related to the publication of this research article.

FUNDING

This research did not receive funding from the government or other private sectors.

ETHICS IN RESEARCH

This research received approval from the research ethics committee of Prof. Dr. IGNG Ngoerah Hospital/Faculty of Medicine, Udayana University.

REFERENCES

[1] Arrigo M, Jessup M, Mullens W, Reza N, Shah AM, Sliwa K, et al. Acute heart failure. Nat Rev Dis Primers 2020;6:16. https://doi.org/10.1038/s41572-020-0151-7.

[2] Greene SJ, Fonarow GC, Vaduganathan M, Khan SS, Butler J, Gheorghiade M. The vulnerable phase after hospitalization for heart failure. Nat Rev Cardiol 2015;12:220–9. https://doi.org/10.1038/nrcardio.2015.14.

[3] Reynolds K, Butler MG, Kimes TM, Rosales AG, Chan W, Nichols GA. Relation of Acute Heart Failure Hospital Length of Stay to Subsequent Readmission and All-Cause Mortality. Am J Cardiol 2015;116:400–5. https://doi.org/10.1016/j.amjcard.2015.04.052.

[4] McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42:3599–726. https://doi.org/10.1093/eurheartj/ehab368.

[5] Tersalvi G, Dauw J, Gasperetti A, Winterton D, Cioffi GM, Scopigni F, et al. The value of urinary sodium assessment in acute heart failure. Eur Heart J Acute Cardiovasc Care 2021;10:216–23. https://doi.org/10.1093/ehjacc/zuaa006.

[6] Matsue Y, Damman K, Voors AA, Kagiyama N, Yamaguchi T, Kuroda S, et al. Time-to-Furosemide Treatment and Mortality in Patients Hospitalized with Acute Heart Failure. J Am Coll Cardiol 2017;69:3042–51. https://doi.org/10.1016/j.jacc.2017.04.042.

[7] Nijst P, Verbrugge FH, Grieten L, Dupont M, Steels P, Tang WHW, et al. The Pathophysiological Role of Interstitial Sodium in Heart Failure. J Am Coll Cardiol 2015;65:378–88. https://doi.org/10.1016/j.jacc.2014.11.025.

[8] Luk A, Groarke JD, Desai AS, Mahmood SS, Gopal DM, Joyce E, et al. First spot urine sodium after initial diuretic identifies patients at high risk for adverse outcome after heart failure hospitalization. Am Heart J 2018;203:95–100. https://doi.org/10.1016/j.ahj.2018.01.013.

[9] Brinkley DM, Burpee LJ, Chaudhry S-P, Smallwood JA, Lindenfeld J, Lakdawala NK, et al. Spot Urine Sodium as Triage for Effective Diuretic Infusion in an Ambulatory Heart Failure Unit. J Card Fail 2018;24:349–54. https://doi.org/10.1016/j.cardfail.2018.01.009.

[10] Galluzzo A, Frea S, Boretto P, Pidello S, Volpe A, Canavosio FG, et al. Spot urinary sodium in acute decompensation of advanced heart failure and dilutional hyponatremia: insights from DRAIN trial. Clinical Research in Cardiology 2020;109:1251–9. https://doi.org/10.1007/s00392-020-01617-w.

[11] Doering A, Jenkins CA, Storrow AB, Lindenfeld J, Fermann GJ, Miller KF, et al. Markers of diuretic resistance in emergency department patients with acute heart failure. Int J Emerg Med 2017;10:17. https://doi.org/10.1186/s12245-017-0143-x.

[12] Biegus J, Zymliński R, Testani J, Marciniak D, Zdanowicz A, Jankowska EA, et al. Renal profiling based on estimated glomerular filtration rate and spot urine sodium identifies high-risk acute heart failure patients. Eur J Heart Fail 2021;23:729–39. https://doi.org/10.1002/ejhf.2053.

[13] Biegus J, Zymliński R, Sokolski M, Todd J, Cotter G, Metra M, et al. Serial assessment of spot urine sodium predicts effectiveness of decongestion and outcome in patients with acute heart failure. Eur J Heart Fail 2019;21:624–33. https://doi.org/10.1002/ejhf.1428.

[14] 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. Journal of the American Society of Nephrology 2017;28:3414–24. https://doi.org/10.1681/ASN.2016111178.

[15] Damman K, Ter Maaten JM, Coster JE, Krikken JA, van Deursen VM, Krijnen HK, et al. Clinical importance of urinary sodium excretion in acute heart failure. Eur J Heart Fail 2020;22:1438–47. https://doi.org/10.1002/ejhf.1753.

[16] Eaton D. Regulation of Sodium.Vanders Renal Physiology. McGraw-Hill Education, Chapter 7 2013;1:345–66.

[17] Testani, J. M., Brisco, M. A., Turner, J. M., Spatz, E. S., Bellumkonda, L., Parikh, C. R., & Tang, W. H. (2014). Loop diuretik efficiency a metric of diuretic responsiveness.

[18] Singh, D., Shrestha, K., Testani, J. M., Verbrugge, F. H., Dupont, M., Mullens, W., & Tang, W. H. W. (2014). Insufficient natriuretic response to continuous intravenous loop diuretik is associated with poor long-term outcomes in acute decompensated heart failure. Journal of Cardiac Failure, 20(6), 392–399. https://doi.org/10.1016/j.cardfail.2014.03.006

[19] Galluzzo A, Frea S, Boretto P, Pidello S, Volpe A, Canavosio FG, Golzio PG, Bergerone S, De Ferrari GM. (2020). Spot urinary sodium in acute decompensation of advanced heart

failure and dilutional hyponatremia: insights from DRAIN trial. Clin Res Cardiol. 2020 Oct;109(10):1251-1259.
doi: 10.1007/s00392-020-01617-w. Epub 2020 Mar 6. Erratum in: Clin Res Cardiol. 2020 Apr 8; PMID: 32144493.

[20] Hodson, D. Z., Griffin, M., Mahoney, D., Raghavendra, P., Ahmad, T., Turner, J., Wilson, F. P., Tang, W. H. W., Rao, V. S., Collins, S. P., Mullens, W., & Testani, J. M. (2019). Natriuretic Response Is Highly Variabel and Associated With 6-Month Survival: Insights From the ROSE-AHF Trial. JACC: Heart Failure, 7(5), 383–391.
https://doi.org/10.1016/j.jchf.2019.01.007

[22] Wilcox CS, Testani JM, Pitt B. Pathophysiology of Diuretic Resistance and Its Implications for the Management of Chronic Heart Failure. Hypertension 2020;76:1045–54.
https://doi.org/10.1161/HYPERTENSIONAHA.120.15205.

[23] Cunningham dkk. (2019). Lower urine sodium predicts longer length of stay in acute heart failure patients: Insights from the ROSE AHF trial. Clinical Cardiology. 2020;43:43–49.

[24] Wright SP dkk., (2003). Factors influencing the length of hospital stay of patients with heart failure. Eur J Heart Fail. 2003 Mar;5(2):201-9. doi:10.1016/s1388-9842(02)00201-5. PMID: 12644013.

[21] Rhee M-Y, Kim J-H, Shin S-J, Gu N, Nah D-Y, Hong K-S, et al. Estimation of 24-Hour Urinary Sodium Excretion Using Spot Urine Samples. Nutrients 2014;6:2360–75.
https://doi.org/10.3390/nu6062360.

[22] Ellison DH, Felker GM. Diuretic Treatment in Heart Failure. New England Journal of Medicine 2017;377:1964–75.
https://doi.org/10.1056/NEJMra1703100.

[23] Gupta R, Testani J, Collins S. Diuretic Resistance in Heart Failure. Curr Heart Fail Rep 2019;16:57–66.
https://doi.org/10.1007/s11897-019-0424-1.

[24] Nohria A, Tsang SW, Fang JC, Lewis EF, Jarcho JA, Mudge GH, et al. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. J Am Coll Cardiol 2003;41:1797–804.
https://doi.org/10.1016/S0735-1097(03)00309-7.

[25] Mullens W, Verbrugge FH, Nijst P, Tang WHW. Renal sodium avidity in heart failure: from pathophysiology to treatment strategies. Eur Heart J 2017;38:1872–82.
https://doi.org/10.1093/eurheartj/ehx035.

[26] Honda S, Nagai T, Nishimura K, Nakai M, Honda Y, Nakano H, et al. Long-term prognostic significance of urinary sodium concentration in patients with acute heart failure. Int J Cardiol 2018;254:189–94.
https://doi.org/10.1016/j.ijcard.2017.08.053.

[27] Verbrugge FH, Dupont M, Steels P, Grieten L, Swennen Q, Tang WH, Mullens W. The kidney in congestive heart failure: 'are natriuresis, sodium, and diuretics really the good, the bad and the ugly?'. Eur J Heart Fail. 2014 Feb;16(2):133-42. doi: 10.1002/ejhf.35. Epub 2013 Dec 9. PMID: 24464967.

[28] Coats AJS. Ageing, demographics, and heart failure. Eur Heart J Suppl 2019;21:L4–7.
https://doi.org/10.1093/eurheartj/suz235.

[29] Elbadawi A, Dang A, Elgendy IY, Thakker R, Albaeni A, Omer MA, et al. Age-specific trends and outcomes of hospitalizations with acute heart failure in the United States. Int J Cardiol 2021;330:98–105.
https://doi.org/10.1016/j.ijcard.2021.02.031.