ORIGINAL ARTICLE

# Acidic urine as a novel risk factor for diuretic resistance and worse in-hospital prognosis in patients with acute heart failure

Tomasz Imiela[1], Anna M. Imiela[2], Grzegorz Karczmarewicz[1], Andrzej Budaj[1]

1 Department of Cardiology, Center of Postgraduate Medical Education, Grochowski Hospital, Warsaw, Poland
2 Department of Hypertension, National Institute of Cardiology, Warsaw, Poland

**KEY WORDS**

diuretic resistance, heart failure, urine pH

**EDITORIAL**

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**ABSTRACT**

**INTRODUCTION** Loop diuretic resistance (LDR) is a risk factor for poor prognosis in patients with acute heart failure (AHF). Acidic urine (pH <6) might be associated with diminished effect of diuretics and worse in-hospital course in this patient population.

**OBJECTIVES** The aim of the study was to assess the influence of acidic urine on in-hospital prognosis and diuretic efficacy in patients with AHF.

**PATIENTS AND METHODS** This was a retrospective analysis of hospitalizations due to AHF in patients with ejection fraction of 50% or less. Analyzed end points were: in-hospital death and composite end point (death, myocardial infarction, stroke, unplanned revascularization, or catecholamine infusion). Diuretic efficacy was assessed as diuresis per intravenous furosemide dose equivalent. Receiver operating characteristic curve analysis for in-hospital death was used to set a cutoff value for diuretic resistance. Logistic regression analysis was used to select independent risk factors for the occurrence of in-hospital death, composite end point, and LDR.

**RESULTS** A total of 373 hospitalizations (300 patients) were analyzed. Urine pH of less than 6 on admission was present in 158 cases (42.1%). In-hospital mortality was 7.5% in cases with nonacidic urine as compared with 15% of those with acidic urine ($P = 0.03$). Composite end point occurred in 10% of patients with nonacidic urine as compared with 31% of those with acidic urine ($P < 0.001$). Acidic urine was found to be an independent risk factor for the composite end point. The threshold for LDR was set at 691.45 ml of diuresis/40 mg of intravenous furosemide. Low urine pH was found to be an independent risk factor for LDR.

**CONCLUSIONS** Low urine pH might be a useful marker identifying patients at high risk for LDR and adverse in-hospital outcome.

Correspondence to:
Tomasz Imiela, MD, PhD, Department of Cardiology, Center of Postgraduate Medical Education, Grochowski Hospital, ul. Grenadierów 51/59, 04-073 Warszawa, Poland, phone: +48 22 515 26 60, email: tomasz.imiela1@gmail.com
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**INTRODUCTION** In the past several years, it has become evident that heart failure (HF) remains a major health problem with high mortality. Chronic HF is disturbed by frequent episodes of exacerbations, leading to episodes of acute heart failure (AHF) resulting mainly from congestion.[1] Implementation of guidelines into the clinical practice has led to a significant reduction of morbidity and rehospitalization rate in this population.[2] Preventing rehospitalizations still presents an important challenge for physicians and patients.[3] Increasing symptoms of congestion are the main reason for frequent rehospitalization.[4] Given the pivotal role of congestion in AHF, diuretics are the cornerstone of HF therapy.[5] Loop diuretics (LDs) are the most common drugs used to alleviate signs and symptoms of fluid overload.[1]

There is accumulating evidence showing a cross talk between the heart and the kidneys in AHF. The kidney is a major regulatory organ responsible not only for diuresis but also contributing to several maladaptive processes.[6] Data obtained in randomized controlled trials have shown that drugs regulating kidney function, such as renin–angiotensin system blockers, mineralocorticoid receptor antagonists, as well as sodium-glucose

## WHAT'S NEW?

In a retrospective analysis, acidic urine (pH <6) was related to worse in-hospital outcomes (death, myocardial infarction, stroke, unplanned revascularization, catecholamine infusion) and diuretic resistance in 373 consecutive hospitalizations in patients with acute heart failure. Acidic urine might be a useful marker to timely select patients at high risk for diuretic resistance and adverse in-hospital outcome.

transport protein 2 inhibitors, reduce morbidity and mortality in patients with AHF. Despite using several renal biomarkers, such as cystatin C, albuminuria, or estimated glomerular filtration rate, there is a paucity of prognostic indicators of worsening kidney function and higher cardiovascular risk. Acidic urine has been suggested to be a predictor of chronic kidney disease; however, there are sparse data demonstrating the role of low urine pH in AHF.[7,8]

Pursuing complete decongestion with the use of LD is the mainstay of the treatment of AHF.[9] Acquired data indicate that poor response to treatment with LD (loop diuretic resistance [LDR]) may be an independent prognostic factor in AHF.[10,11] The development of LDR is a multifactorial process, difficult to quantify in the clinical setting. Loop diuretic resistance, defined as decreased diuresis relative to the dose of LD, accounts for approximately 35% of hospitalized patients with AHF and is an independent risk factor for in-hospital mortality.[12]

There are no rational evidence-based treatment approaches to patients with AHF and numerous treatment modalities have so far failed to achieve considerable success in that population.[13,14] Treatment of LDR continues to pose a major clinical dilemma, not covered by official guidelines.

For this study, we sought to assess whether urine pH of less than 6 is related to worse outcomes and LDR in AHF hospitalizations.

**PATIENTS AND METHODS** The present study was a single-center retrospective analysis of all consecutive hospitalizations due to AHF from year 2015 to 2017 in the Cardiology Department of the Center of Postgraduate Medical Education, Grochowski Hospital, Warsaw, Poland. This study was approved by the institutional Ethics Committee (approval no. 88/PB/2018) and all procedures in the study were in accordance with the 1964 Declaration of Helsinki.

Hospitalizations of patients were included in the analysis if the following criteria were met: left ventricular ejection fraction (EF) of 50% or less, signs of congestion, age 18 years or older, urinalysis performed within the first 48 hours from admission. As detailed echocardiogram records for some cases in our database were not available, we decided to include only patients with mid-range or reduced EF (diastolic dysfunction might not be assessed in every case). Congestion was defined as lung congestion / pleural fluid on chest X-ray and / or clinical symptoms: edema, ascites, elevated jugular venous pressure. We followed the European Society of Cardiology HF guidelines for the diagnosis of AHF.[15] The following factors presented on admission were defined as exclusion criteria: acute coronary syndrome or pulmonary embolism, hypotension with systolic blood pressure of less than 90 mm Hg or mean arterial blood pressure of less than 65 mm Hg or requiring inotropic agents during the first 24 hours after admission, impaired renal function defined as estimated glomerular filtration rate of less than 15 ml/min/1.73 $m^2$ on admission, liver cirrhosis, liver failure. The records of all ward admissions were screened by the first author, afterwards, the first, second, or third author reviewed the available documentation for inclusion and exclusion criteria. The flow chart of patients evaluated and included in the study is presented in **FIGURE 1**.

A detailed history concerning major cardiovascular risk factors and characteristics of pharmacological treatment were obtained. Multimorbidity was quantified with the use of Charlson Comorbidity Index (CCI).[16] Standard laboratory evaluations, blood pressure monitoring, urine samples, echocardiography, and chest X-ray were effectively measured in all patients. Diuretic efficacy was assessed as diuresis in relation to 40 mg of administered intravenous furosemide during the first 4 days of hospital stay.

**pH test and outcomes assessment** Urine pH was assessed within the first 24 hours after admission using a dipstick spot test (Mission Urinalysis Reagent Strips, ACON Laboratories Inc, San Diego, United States). Acidic urine was defined as urine pH of less than 6.

Analyzed end points were in-hospital death and composite end point (CEP): in-hospital death, myocardial infarction, stroke, unplanned revascularization, or need for the initiation of catecholamine therapy. Composite end point included the events registered during the index hospitalization. Adrenaline, noradrenaline, dopamine, and dobutamine were considered catecholamines for the current study (included patients did not receive other vasopressors).

**Statistical analysis** The normality of variables distribution was checked with the Shapiro–Wilk test. Continuous variables with normal distribution were compared using the *t* test for independent variables (with the assumption of the equality of variances, which was also tested). Continuous variables with abnormal distribution were compared using the Mann–Whitney test, while categorical variables were compared using the $\chi^2$ test. We used logistic regression analysis to assess the independent risk factors for in-hospital death, the occurrence of CEP and to assess the risk factors for diuretic resistance, with variables significant in univariable

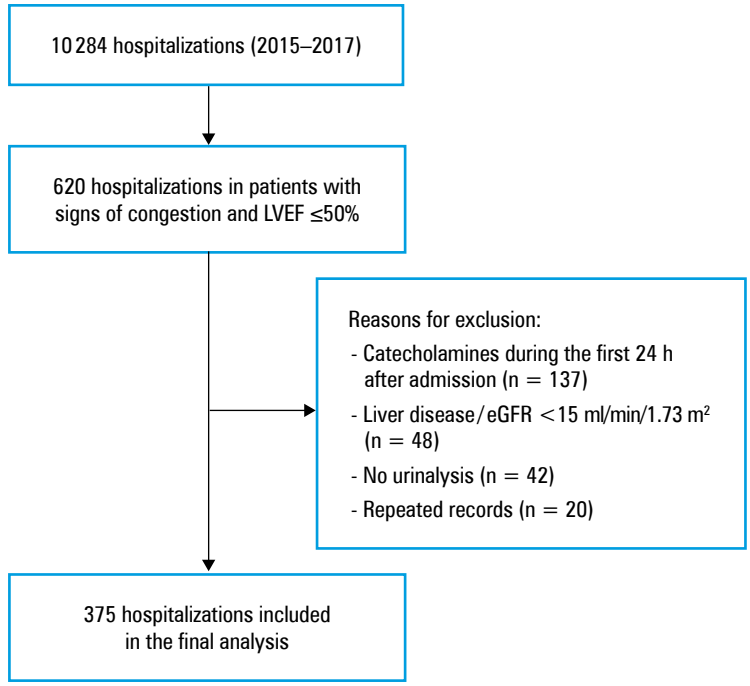



**FIGURE 1** Flow chart of patients evaluated and included in the study
Abbreviations: eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction

analysis included to the regression model. To determine the cutoff value for diuretic resistance, a receiver operating characteristic curve for diuretic efficacy and the risk of in-hospital death was constructed. A cutoff value was determined as a point with the highest sum of sensitivity and specificity. A *P* value of less than 0.05 was regarded statistically significant. The bootstrap method was used to assess 95% CI for sensitivity and specificity. All the analyses were performed with STATISTICA, version 11 (StatSoft Inc, Tulsa, Oklahoma, United States) and using R statistical software, version 10.0 (R Foundation for Statistical Computing, Vienna, Austria).

**RESULTS** Hospitalizations (n = 373) of 300 patients diagnosed with HF were recorded. The median (interquartile range [IQR]) age of the 158 inpatients with pH of less than 6 was 71 (63–82) years as compared with 74 (65–83) years in 215 patients with pH of 6 or greater. About 70% of patients in the later group were male. There were no differences between the groups in terms of age and sex. Most of the patients had numerous comorbidities, with a median CCI score of 3. Coronary artery disease (CAD) was the cause of HF in 64.6% of cases. There were no differences in terms of CAD, hypertension, or COPD / asthma; however, patients with acidic urine were significantly more often diagnosed with pneumonia (TABLE 1).

The median (IQR) length of hospitalization was 15 (11–23) days and the most common reasons for AHF were infection (29.2%), arrythmia (27.9%), and inadequate pharmacotherapy (27.6%). The median (IQR) EF was 28% (20%–38%). Urine pH of less than 6 was present in 158 cases (42.1%). Clinical characteristics of the study cohort are presented in TABLE 1.

In terms of biochemical characteristics, patients with acidic urine were characterized by significantly higher N-terminal pro–B-type natriuretic peptide (NT-proBNP), potassium, and hemoglobin plasma levels comparing with patients with urine pH of 6 or greater. Moreover, inflammatory markers, such as C-reactive protein and total white blood cell count, were also increased in the group with acidic urine (TABLE 1).

In-hospital mortality was 7.5% in patients with nonacidic urine as compared with 15% in those with acidic urine ($P = 0.03$). The composite end point occurred in 10% of patients with nonacidic urine as compared with 31% of those with acidic urine ($P < 0.001$) (TABLE 2).

The multivariable logistic regression model showed that older age, lower systolic blood pressure, lower EF, NYHA class IV on admission, diagnosis of pneumonia, lower serum sodium, and lower diuretic efficacy were the independent risk factors for in-hospital death (TABLE 3).

In logistic regression analysis, the independent risk factors for CEP were: lower urine pH, lower systolic blood pressure, lower EF, NYHA class IV on admission, diagnosis of pneumonia, and lower diuretic efficacy (TABLE 4).

A receiver operating characteristic curve for diuretic efficacy and risk for in-hospital death was constructed (FIGURE 2). The cutoff value for LDR was set at 691.45 ml/40 mg of intravenous furosemide, with the area under the curve of 84.2%; sensitivity of 79.5% (95% CI, 66.6–92.3) and specificity of 77% (95% CI, 72.2–81.9).

Taking into account the presence of LDR defined as diuresis below 691.45 ml/40 mg

**TABLE 1** Baseline clinical characteristics of patients with pH of less than 6 and of 6 or greater

| Clinical features | All (n = 373) | pH <6 (n = 158) | pH ≥6 (n = 215) | *P* value |
|---|---|---|---|---|
| Age, y | 73 (64–83) | 71 (63–82) | 74 (65–83) | 0.19 |
| Male sex, n (%) | 261 (71) | 114 (72) | 151 (70) | 0.73 |
| SBP, mm Hg | 120 (110–140) | 125 (110–140) | 120 (110–140) | 0.22 |
| DBP, mm Hg | 75 (70–85) | 75 (65.5–90) | 75 (70–80) | 0.73 |
| HR, bpm | 80 (72–100) | 90 (75–112.5) | 80 (70.75–95) | 0.001 |
| LVEF, % | 28 (20–38) | 26 (20–35) | 30 (20–39) | 0.33 |
| LVEF <40%, n (%) | 285 (76) | 124 (78) | 161 (75) | 0.4 |
| NYHA | 3 (3–4) | 3 (3–4) | 3 (3–3.25) | 0.002 |
| CCI | 3 (2–4) | 3 (2–4) | 3 (2–4) | 0.63 |
| Pneumonia diagnosis, n (%) | 134 (36) | 73 (46) | 61 (28) | <0.001 |
| Medical history, n (%) | | | | |
| CAD | 267 (72) | 107 (68) | 160 (74) | 0.24 |
| PCI | 183 (49) | 73 (46) | 110 (51) | 0.35 |
| CABG | 66 (18) | 27 (17) | 39 (18) | >0.99 |
| Hypertension | 273 (73) | 120 (76) | 153 (71) | 0.34 |
| COPD/asthma | 73 (20) | 32 (20) | 41 (19) | 0.9 |
| Atrial fibrillation | 278 (75) | 115 (73) | 163 (76) | 0.3 |
| Chronic kidney disease | 214 (57) | 90 (57) | 124 (58) | 0.91 |
| Cause of HF, n (%) | | | | |
| CAD | 241 (65) | 99 (63) | 142 (66) | 0.35 |
| Dilated cardiomyopathy | 34 (9) | 10 (6) | 24 (11) | 0.09 |
| Myocarditis | 6 (2) | 2 (1) | 4 (2) | 0.41 |
| Toxic | 11 (3) | 7 (4) | 4 (2) | 0.12 |
| Arrhythmia | 21 (6) | 7 (4) | 14 (7) | 0.41 |
| Valvular heart disease | 23 (6) | 13 (8) | 10 (5) | 0.07 |
| Other/unknown | 37 (10) | 20 (13) | 17 (8) | 0.08 |
| Biochemical characteristics | | | | |
| NT-proBNP (n = 276), pg/ml | 5918 (3041–11 959) | 8228 (3550–15 536) | 4999 (2422–9098) | 0.003 |
| Creatinine, mg/dl | 1.3 (1.0–1.7) | 1.4 (1.02–1.78) | 1.3 (1.00–1.65) | 0.21 |
| eGFR, ml/min/1.73 $m^2$ | 50.8 (34.5–69.3) | 49.9 (32.7–66.6) | 52.0 (35.6–70.6) | 0.83 |
| WBC, K/μl | 8.5 (6.9–10.6) | 9.1 (7.0–11.4) | 8.1 (6.8–10.2) | 0.046 |
| CRP, mg/dl | 10.3 (4.2–24.2) | 14.7 (5.0–28.8) | 8.3 (3.9–22) | 0.02 |
| Hemoglobin, g/dl | 12.9 (11.6–14.3) | 13.3 (11.7–14.4) | 12.6 (11.4–14.1) | 0.03 |
| $K^+$, mmol/l | 4.4 (4.1–4.9) | 4.6 (4.2–5) | 4.4 (4.1–4.7) | 0.02 |
| $Na^+$, mmol/l | 138 (134–140) | 138 (135–140) | 138 (133–140) | 0.33 |
| TnT, ng/l | 34.2 (21.7–51.9) | 37.5 (24.4–58.7) | 32.1 (20.9–48.9) | 0.1 |
| Medications before admission, n (%) | | | | |
| ACEI or ARB | 269 (72) | 112 (71) | 157 (73) | 0.64 |
| β-Blockers | 341 (91) | 143 (91) | 198 (92) | 0.85 |
| MRA | 199 (53) | 76 (48) | 123 (57) | 0.08 |
| Loop diuretics | 257 (69) | 103 (65) | 154 (72) | 0.31 |
| Digoxin | 54 (14) | 21 (13) | 33 (15) | 0.6 |
| Antibiotics during hospitalization, n (%) | | | | |
| β-Lactams | 144 (39) | 79 (50) | 65 (30) | <0.001 |
| Macrolides | 11 (3) | 7 (4) | 4 (2) | 0.17 |
| Quinolones | 79 (21) | 46 (29) | 33 (15) | 0.002 |

Data are presented as median (interquartile range) unless otherwise indicated.

SI conversion factors: to convert creatinine to μmol/l, multiply by 88.4; WBC to $\times 10^9$/l, by 1; CRP to mg/l, by 10; hemoglobin to g/l, by 10.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DBP, diastolic blood pressure on admission; eGFR, estimated glomerular filtration rate based on serum creatinine concentration (Chronic Kidney Disease Epidemiology Collaboration formula); HR, heart rate; K, serum potassium concentration; MRA, mineralocorticoid receptor blocker; Na, serum sodium concentration; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association classification; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TnT, high-sensitivity cardiac troponin T; WBC, white blood cell count; others, see **FIGURE 1**

**TABLE 2** Clinical end points in patients with pH of less than 6 and of 6 or greater

| End points | pH <6 (n = 158) | pH ≥6 (n = 215) | *P* value |
|---|---|---|---|
| Death | 23 (15) | 16 (7.5) | 0.03 |
| MI | 4 (2.6) | 1 (0.47) | 0.17 |
| Stroke[a] | 2 (1.3) | 0 (0) | 0.72 |
| Unplanned revascularization | 8 (5.1) | 2 (0.93) | 0.02 |
| Catecholamine usage | 38 (24) | 18 (8.4) | <0.001 |
| CEP | 49 (31) | 22 (10) | <0.001 |

Data are presented as number (percentage) of patients.

a Both cases of stroke were of ischemic etiology.

Abbreviations: CEP, composite end point; MI, myocardial infarction

**TABLE 3** Independent risk factors for in-hospital death in logistic regression analysis

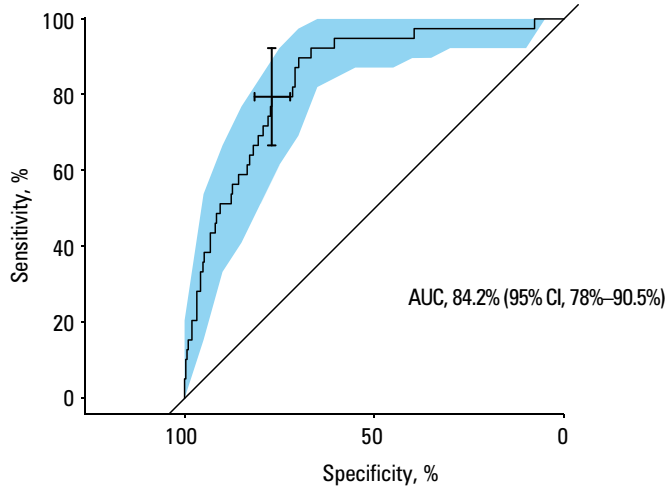
| Variable | Odds ratio for death (95% CI) | *P* value |
|---|---|---|
| Age, y | 1.062 (1.021–1.104) | 0.01 |
| SBP, mm Hg | 0.98 (0.961–0.996) | 0.03 |
| LVEF, % | 0.942 (0.906–0.979) | 0.007 |
| NYHA class IV on admission | 2.46 (1.123–5.387) | 0.04 |
| Pneumonia diagnosis | 3.065 (1.269–7.404) | 0.01 |
| $Na^+$, mmol/l | 0.914 (0.845–0.998) | 0.01 |
| Diuresis/furosemide iv, 1 ml/40 mg | 1.003 (1.002–1.004) | <0.001 |

Abbreviations: iv, intravenous; others, see **FIGURE 1** and **TABLE 1**

**TABLE 4** Independent risk factors for composite end point (in-hospital death, myocardial infarction, stroke, unplanned revascularization, or catecholamine infusion) in logistic regression analysis

| Variable | Odds ratio for CEP (95% CI) | *P* value |
|---|---|---|
| Urine pH | 0.262 (0.145–0.471) | <0.001 |
| SBP, mm Hg | 0.97 (0.952–0.99) | 0.001 |
| LVEF, % | 0.961 (0.924–0.999) | 0.02 |
| NYHA class IV on admission | 3.819 (1.923–7.584) | <0.001 |
| Pneumonia diagnosis | 2.915 (1.497–5.677) | 0.002 |
| Diuresis/furosemide iv, 1 ml/40 mg | 1.003 (1.002–1.004) | <0.001 |

Abbreviations: see **FIGURE 1** and **TABLES 1**, **2**, and **3**




furosemide, the groups did not differ in terms of age, sex, diagnosis of pneumonia, CAD, hypertension, and asthma/COPD. The group with LDR was characterized by significantly lower urine pH, left ventricular EF, higher plasma NT-proBNP, creatinine, C-reactive protein, lower sodium, troponin T, less frequent usage of angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists and β-blockers (**TABLE 5**).

Logistic regression analysis identified the following independent risk factors for LDR: acidic urine pH, lower serum sodium level, higher NT-proBNP concentration, higher ambulatory dose of LD, higher CCI (**TABLE 6**).

**DISCUSSION** We present noteworthy findings from our study. First, patients with AHF, EF of 50% or less, and pH of less than 6 on admission were characterized by higher in-hospital mortality and CEP (death, myocardial infarction, stroke, unplanned revascularization, usage of catecholamine) in univariable analysis and CEP in multivariable analysis. So far, the importance of urine pH in patients with HF was analyzed in one study. Otaki et al[8] revealed that urine pH of less than 6 on admission in patients with AHF was related to higher mortality in long-term 556-day follow-up. The assessment of the prognosis in patients with HF with mid-range and reduced EF is a matter of interest. Rahimi et al[17] showed mortality risk factors such as: age, sex, kidney function, sodium concentration, diabetes mellitus type 2, EF, NYHA class. In our study the risk factors of higher in-hospital mortality in multivariable analysis were: age, systolic blood pressure, EF, NYHA class, pulmonary infection, hyponatremia, and lower diuretic efficacy. We observed that pH of less than 6 was related to higher risk of in-hospital death (in univariable analysis).

Secondly, in our study, we observed that patients with pH of less than 6 on admission were given catecholamine infusion more often as compared with those with pH of at least 6 (24% vs 8.4%). Catecholamine infusion (dobutamine, dopamine, noradrenaline) is reserved mainly for patients with hypotension and organ hypoperfusion.[15] The need for catecholamine administration during hospitalization is considered to be an important risk factor of poor prognosis in patients with AHF.[18,19] In the AHEAD registry, in 4153 patients with AHF (with mean EF of 37%), the need for catecholamine infusion was found to be one of the most powerful predictors of in-hospital death.[20,21] The role of urine pH or diuretic dosing was not taken into account in the aforementioned registry. Prolonged hypotension has

**FIGURE 2** Receiver operating characteristic curves for diuretic efficacy and risk for in-hospital death. The cutoff value for diuretic resistance was set at 691.45 ml/40 mg of intravenous furosemide.
Abbreviations: AUC, area under the curve

**TABLE 5** Clinical characteristics of patients with and without diuretic resistance

| Clinical features | Loop diuretic resistance[a] (n = 127) | No loop diuretic resistance (n = 245) | *P* value |
|---|---|---|---|
| Urine pH | 5.8 (0.7) | 6.0 (0.8) | 0.02 |
| Age, y | 71 (63.5–82) | 74 (65–83) | 0.2 |
| Male sex, n (%) | 88 (69) | 176 (72) | 0.7 |
| SBP, mm Hg | 120 (110–130) | 125 (110–140) | 0.01 |
| DBP, mm Hg | 70 (65–80) | 80 (70–85) | 0.2 |
| HR, bpm | 82 (74–102.5) | 80 (72–100) | 0.2 |
| LVEF, % | 25 (17.6–34.5) | 30 (20.5–40) | 0.003 |
| LVEF <40%, n (%) | 103 (81) | 182 (74) | 0.06 |
| NYHA | 3 (3–4) | 3 (3–4) | 0.02 |
| CCI | 3 (2–5) | 3 (2–4) | 0.05 |
| Pneumonia diagnosis, n (%) | 51 (40) | 81 (33) | 0.2 |
| Medical history, n (%) | | | |
| CAD | 93 (73) | 174 (71) | 0.6 |
| PCI | 69 (54) | 113 (46) | 0.1 |
| CABG | 22 (17) | 44 (18) | 0.8 |
| Hypertension | 91 (72) | 181 (74) | 0.7 |
| COPD/asthma | 23 (18) | 49 (20) | 0.5 |
| Atrial fibrillation | 96 (76) | 182 (74) | 0.55 |
| Chronic kidney disease | 82 (65) | 132 (54) | 0.03 |
| Biochemical characteristics | | | |
| NT-proBNP, pg/ml | 6624 (2392–15 089) | 5702 (3091–10 767) | 0.06 |
| Creatinine, mg/dl | 1.5 (1.1–1.9) | 1.2 (1.0–1.6) | <0.001 |
| eGFR, ml/min/1.73 m$^2$ | 44.2 (29.4–61.4) | 53.8 (37.2–72.8) | 0.006 |
| WBC, K/μl | 8.6 (7–11) | 8.4 (6.8–10.5) | 0.6 |
| CRP, mg/dl | 11.1 (4.4–24.5) | 9.2 (3.85–24.7) | 0.05 |
| Hemoglobin, g/dl | 12.8 (11.6–14.3) | 12.9 (11.5–14.3) | 0.62 |
| $K^+$, mmol/l | 4.5 (4–4.9) | 4.4 (4.1–4.9) | 0.64 |
| $Na^+$, mmol/l | 137 (131–140) | 138 (135–140) | 0.007 |
| TnT, ng/l | 40.5 (24.7–60.3) | 32.1 (21.1–47.8) | 0.03 |
| Medications before admission, n (%) | | | |
| ACEI or ARB | 77 (61) | 191 (78) | <0.001 |
| β-Blockers | 109 (86) | 230 (94) | 0.01 |
| MRA | 66 (52) | 132 (54) | 0.82 |
| Loop diuretics | 96 (76) | 161 (66) | 0.04 |
| Ambulatory dose of LD (converted to oral furosemide), mg, mean (SD) | 135 (149) | 58 (74) | <0.001 |
| Digoxin | 19 (15) | 35 (14) | 0.82 |
| Antibiotics during hospitalization, n (%) | | | |
| β-Lactams | 53 (42) | 91 (37) | 0.32 |
| Macrolides | 6 (5) | 5 (2) | 0.19 |
| Quinolones | 37 (29) | 42 (17) | 0.009 |

Data are presented as median (interquartile range) unless otherwise indicated.

SI conversion factors: see **TABLE 1**

a Loop diuretic resistance was defined as diuresis <691.45 ml/40 mg of intravenous furosemide during the first 4 days of hospitalization.

Abbreviations: LD, loop diuretics; see **FIGURE 1** and **TABLE 1**

been indicated to disrupt renal perfusion and enhance sodium reabsorption in the proximal tubule.[22] Despite the fact that catecholamine usage might influence urine pH, in our study, the urinary pH was tested on hospital admission so that catecholamine usage would not affect pH value.

Low pH may be both the cause and the effect--marker of poor prognosis in HF patients. Acidic urine can be a part of systemic acidosis which can have a negative impact on patients with AHF.[23,24] However, urine acidosis may also accompany systemic alkalosis in patients treated with LD.[25] It is well documented that low urinary pH is a risk factor of chronic kidney injury.[7,26] pH value is mainly influenced by tubules but chronic kidney injury is evaluated by glomerular function (estimated glomerular filtration rate, proteinuria).[27] However, selective evaluation of nephron tubule function remains a great difficulty. There are no routinely used biomarkers to assess the function of different parts of the nephron (except of the glomerulus). Nevertheless, it seems that low urinary pH could be alone a useful predictor of poor prognosis in patients with AHF.

Loop diuretic resistance can be defined either descriptively as the persistence of congestion despite providing adequate decongestive treatment, or quantitatively, as low natriuresis / urine output / net fluid loss / weight loss / fractional sodium excretion per diuretic dose administered.[9] Each of the mentioned methods was found to add prognostic information in patients with HF.[9] As natriuresis is not routinely measured in clinical practice at our site, we used low diuresis per diuretic dose as a marker of LDR in this study. In the study which included 5268 patients with AHF from the ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) trial, LDR was defined as low diuresis per 40 mg intravenous furosemide, similarly to our study.[10] Patients with diuretic efficacy below the median in the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial experienced nearly 3-fold higher risk of death compared with those with diuretic efficacy above the median, despite adjustment for baseline and in-hospital characteristics (hazard ratio, 2.86; 95% CI, 1.53–5.36).[28]

Loop diuretic resistance can be also defined as the attenuation of the maximal diuretic efficacy that ultimately limits sodium and chloride excretion and is a well-characterized phenomenon of diuretic use.[29] Loop diuretic resistance can be associated with renal impairment, mortality, and increased risk of rehospitalization after HF.[30] It is well documented that several factors can contribute to LDR such as tubular remodeling, drug pharmacokinetics and pharmacodynamics, and the braking phenomenon.[29] Unbound LDs have to reach the urinary lumen of the thick ascending limb and bind to the site of chloride entry to inhibit $Na^+K^+2Cl^-$. Diet and HF can prolong the time to peak concentration and peak drug

**TABLE 6** Risk factors for loop diuretic resistance in logistic regression analysis

| Variable | Odds ratio for CEP (95% CI) | *P* value |
|---|---|---|
| Urine pH | 0.607 (0.41–0.899) | 0.046 |
| $Na^+$, mmol/l | 0.923 (0.87–0.979) | 0.001 |
| NT-proBNP, 1000 pg/ml | 1.055 (1.018–1.093) | 0.003 |
| Ambulatory dose of LD (converted to oral furosemide) | 1.01 (1.006–1.014) | <0.001 |
| CCI, point | 1.35 (1.132–1.61) | 0.006 |

Abbreviations: see TABLES 1, 2, and 5

levels.[31] Taking into account the fact that LDs are 95% protein bound, hypoalbuminemia increases the volume of distribution and reduces the availability of LD for facilitated diffusion. Uremic toxins and nonsteroidal anti-inflammatory drugs can also inhibit drug transport across proximal tubular epithelial cells.[29] Chronic kidney disease can also reduce the excretion of a diuretic into the tubular lumen. Diuretic-induced sodium excretion is reduced in chronic kidney disease by the reduced filter load of sodium. Moreover, the administration of effective doses multiple times per day can circumvent the above constraints.[32,33] Heart failure reduces the peak effect of the drug, which may be caused by increased proximal reabsorption of sodium (for example resulting from the activation of the renin-angiotensin-aldosterone system) or increased expression of $Na^+K^+2Cl^-$. Recent data show that hypochloremia plays an important role in neurohormonal activation in patients with HF on high-dose LD, which can contribute to LDR in these subjects.[34]

The correlation between low urine pH and the presence of LDR has never been studied before. The potential causal relationship between urine pH and diuretic efficacy remains to be evaluated. Acid-base and electrolyte disturbances may play a pivotal role in the development of LDR.[35] Hyponatremia was found to be a marker for LDR in the ASCEND-HF trial.[10] Urine acidosis might be a marker of increased chloride excretion in HF patients, leading to hypochloremia and worse long-term outcomes.[36,37] It was proposed that acidic urine may also lower diuretic potency of thiazide diuretics.[38] Distal tubular hypertrophy, one of the possible LDR mechanisms, might be triggered by hypokalemia and metabolic alkalosis (probably accompanied by low urine pH).[39,40]

Our intention was to assess the prognostic value of urine pH as a simple spot test usually available quickly after admission. Our findings might be relevant for HF experts, but the implications are mainly for patients treated for AHF in the emergency department and for healthcare providers such as internists, cardiologist, and general practitioners. It remains to be determined if patients with low urine pH might benefit from some form of therapy, for example the administration of diuretics (like acetazolamide) that may increase urine pH.[23] Moreover, the observation of urine pH in patients treated with high-dose LD / with developed LDR might pose a great opportunity to select patients at higher risk of cardiovascular death in daily practice.

There is a need to conduct more studies in the area of cardiorenal medicine and to create guidelines and optimal clinical practice models to improve the quality of treatment of patients diagnosed with AHF and LDR.

**Limitations** Our study has several limitations. Blood gas analyses were not taken routinely from every patient and thus were not included in the analysis. We did not collect data on urine osmolality or urine electrolytes. Patients were treated with different drugs such as renin-angiotensin--aldosterone blockers and β-blockers, which could affect urine pH. Despite the fact that patients were subjected to a low-sodium diet, we cannot exclude the impact of diet on urine pH.

Mortality and occurrence of CEP in our group were higher than in other available studies. Our study included an unselected group of older patients with AHF (mean age >70 years). Overall in-hospital mortality was high (10.6%) but similar to that observed in the AHEAD registry.[21]

**Conclusions** This is the first study to demonstrate that acidic urine might be a risk factor of poor in-hospital outcomes in patients with AHF and EF of 50% or less. Low urine pH might also be a risk factor for LDR in this patient population. More studies are needed to provide adequate explanation to our observations.

## ARTICLE INFORMATION

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**CONTRIBUTION STATEMENT** TI and AB conceived the concept of the study and are responsible for the study design; they also supervised data collection. AI, GK, TI were responsible for the data collection. AI wrote the first draft of the article. AB and TI obtained the funding. All authors contributed substantially to interpretation of data and critical revision of the article for important intellectual content.

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