

Serum and Urine Osmolality as Predictors of Adequate Diuresis in Acute Decompensated Heart Failure: A Prospective Cohort Study

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Keywords

Heart failure · Diuresis · Serum osmolality · Urine osmolality

Abstract

Background: Determination of adequacy of decongestion remains a significant challenge in the management of acute heart failure (AHF). **Methods:** This is a prospective single center cohort study of patients (>18 years old) admitted for AHF on intravenous diuretics, with BNP >100 pg/mL or echocardiographic findings of reduced ejection fraction or diastolic dysfunction, and at least 1 clinical sign of volume overload. Patients with eGFR ≤45 mL/min or on dialysis, and with exposure to contrast dye or nephrotoxins were excluded. Serum and spot urine osmolality were obtained in the early morning simultaneously daily for 5 days or until discharge. Receiver operating characteristic curves were used to analyze the optimal cutoffs for the osmolality values in the prediction of heart failure (HF) readmissions. **Results:** Of the total 100 patients, 62% were male and 59% were Black American. The mean age was 64.41 ± 12.53 and 34% had preserved ejection fraction. Patients with 30-day readmission had higher serum osmolality (mOsm/kg) on admission (305 [299–310] vs. 298 [294–303]; $p = 0.044$) and had higher drop

in serum osmolality between admission and discharge (−7.5 [−9.0, −1.25] vs. −1.0 [−4.0, 4.0]; $p = 0.044$). Serum osmolality on admission of >299 mOsm/kg (sensitivity: 83%, specificity: 61%) and drop in serum osmolality between admission and discharge of >2 mOsm/kg (sensitivity: 83%, specificity: 65%) was associated with 30-day HF readmissions. No patients discharged with urine osmolality more than 500 mOsm/kg had 30-day readmissions, but this was not statistically significant, $p = 0.334$. **Conclusion:** Measurement of serum osmolality and urine osmolality may have some utility in AHF, but interpretation should consider baseline values and dynamic changes to account for individual differences in sodium and water handling.

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Published by S. Karger AG, Basel

Introduction

Heart failure (HF) is a major cause of morbidity and mortality in the USA with over 6 million adults affected and up to 13.4% of deaths annually [1]. The overall burden to patients and the healthcare system also extends to the hospitalizations costs as well as readmissions [2]. Determination of euvolemia or adequate decongestion dur-

ing HF hospitalizations has remained a challenge for clinicians together with balancing the risks of hypotension, electrolyte imbalances, and renal function [3]. In the DOSE-AHF (Diuretic Strategies in Patients with Acute Decompensated Heart Failure) study, only 15% of patients achieved freedom from congestion after 72 h of diuretics [4]. Inadequate decongestion in turn leads to poor outcomes with higher mortality risks and HF hospitalizations [5, 6]. Efforts have been directed towards determination of biomarkers which are easy to measure that can assist in determination of decongestion in the setting of acute HF [7]. The use of natriuretic peptides as well as level of hemoconcentration have been explored as surrogate markers of decongestion in HF management [8, 9] with inherent limitations [7]. Neurohormonal dysregulation predominantly driven by activation of the renin angiotensin-aldosterone system with arginine vasopressin (AVP) as well as the sympathetic nervous system drives the vicious cycle of organ dysfunction and congestion in HF [10]. AVP release is typically triggered by increased plasma osmolality but occurs even with low plasma osmolality and hyponatremia in HF leading to water retention [11], potentially reflecting a heightened state of neurohormonal activation. This water balance reflected by the actions of vasopressin can be easily evaluated by measuring serum or plasma osmolality directly or using components found in a basic metabolic panel (BMP) including serum sodium, blood urea nitrogen, and glucose levels [12]. While plasma osmolality has been associated with poor prognosis in HF patients, its' utility in HF management has not been previously evaluated [13, 14]. This study explored whether serum and or urine osmolality could be utilized as predictors of adequate diuresis in patients hospitalized with acute HF in association with 30- and 60-day HF readmission rates.

Methods

This was a prospective cohort single center study which included patients admitted for acute HF regardless of ejection fraction. Inclusion criteria were age ≥ 18 years, admission diagnosis of AHF with at least serum B-type natriuretic peptide level ≥ 100 pg/mL or echocardiographic evidence of reduced ejection fraction or diastolic dysfunction combined with at least 1 clinical sign of volume overload including rales or crackles, elevated jugular venous pressure or peripheral edema. Patients enrolled needed to be on IV diuretic therapy as part of inpatient treatment of AHF. Exclusion criteria included patients with eGFR ≤ 45 mL/min or on dialysis, exposure to contrast dye during the index admission (e.g., cardiac catheterization), gastrointestinal bleed during admission and exposure to any known nephrotoxins. Upon identifying candidates that fit the above criteria, informed consent was obtained. Serum

Table 1. Demographic and clinical profile of patients

	Total n = 100
Age (mean \pm SD), years	64.41 \pm 12.53
Female gender, n (%)	38 (38)
Ethnicity, n	
Black American	59
White American	3
Hispanic	11
Asian/other	27
Comorbidities	
BMI (mean \pm SD)	34.40 \pm 11.20
Hypertension	86
Diabetes	43
Coronary artery disease	39
ICD/CRT use	23
HFrEF ($>50\%$)	34
Clinical/lab parameters	
Baseline serum creatinine	1.05 \pm 0.35
Creatinine on admission	1.19 \pm 0.38
Ejection fraction	35.84 \pm 18.14
BNP, median (IQR), pg/mL	905 (415–1,786)
Serum osmolality admission, mOsm/kg	298 (294–303)
Serum osmolality discharge, mOsm/kg	297 (292–303)
Urine osmolality admission, mOsm/kg	361 (310–444)
Urine osmolality discharge, mOsm/kg	413 (350–500)
Serum Na admission, meq/L	139 (137–141)
Serum Na discharge, meq/L	139 (137–140)
Serum chloride admission, meq/L	105 (102–108)
Serum chloride on discharge, meq/L	101 (97–104)
Hematocrit on admission, %	37 (31–41)
Hematocrit on discharge, %	37 (33–42)
Medications	
Beta blockers	80
ACEI/ARB	57
MRA	16
Nitrates	26
Hydralazine	26
ARNI	13
Median length of stay, days (IQR)	5 (4–7)

HFrEF, heart failure with preserved ejection fraction.

osmolality and spot urine osmolality (mOsm/kg) measurements were obtained daily in the early morning for 5 days or until the patient was discharged. Both serum and serum osmolality were collected simultaneously in the early morning daily before medications including diuretics were given for the day. Demographic and clinical parameters were also obtained and recorded.

Statistical Analysis

Categorical variables were presented using frequencies and percentages. Distribution of continuous variables was determined. Normally distributed continuous variables were presented as mean and standard deviation, while skewed variables were presented as

Table 2. Comparison between laboratory parameters based on readmission status

Variable: median (IQR)	30-day readmissions (n = 6)	No readmissions (n = 91)	p value
Serum osmolality on admission, mOsm/kg	305 (299–310)	298 (294–303)	0.044
Serum osmolality on discharge, mOsm/kg	297 (288–310)	297 (292–303)	0.922
Serum osmolality difference (discharge-admission), mOsm/kg	–7.5 (–9.0 to –1.25)	–1.0 (–4.0 to 4.0)	0.044
Urine osmolality on admission, mOsm/kg	355 (295–372)	360 (313–453)	0.414
Urine osmolality on discharge, mOsm/kg	398 (328–444)	414 (353–507)	0.441
Urine osmolality difference (discharge-admission), mOsm/kg	63 (–41 to 136)	36 (0–128)	0.922
Urine to serum osmolality ratio admission	1.17 (0.96–1.23)	1.22 (1.04–1.49)	0.288
Urine to serum osmolality ratio discharge	1.34 (1.10–1.45)	1.44 (1.16–1.66)	0.393
Serum Na on admission	142 (137–143)	139 (137–141)	
Serum Na on discharge	138 (137–142)	142 (137–143)	
Hematocrit on admission	36 (30–43)	37 (31–41)	
Hematocrit on discharge	36 (29–45)	37 (33–42)	
Serum creatinine on admission	1.44 (1.05–1.60)	1.13 (0.90–1.34)	0.31
Serum creatinine on discharge	1.50 (1.20–1.58)	1.20 (0.94–1.48)	0.36
BNP on admission	1,910 (341–3,270)	858 (412–1,762)	0.37

median and interquartile ranges. Due to the nature of distribution, Wilcoxon signed-rank tests were used to determine whether there were significant differences in serum and urine osmolality within the cohort on admission and on discharge. Patients with 30-day readmissions and 60-day HF readmissions were analyzed and compared to those who were not readmitted in terms of their serum and urine osmolality. Mann Whitney U test was used to determine differences in serum and urine osmolality and the ratios between those who were readmitted versus those who were not. Receiver operating characteristic curve and AUC were used to analyze the optimal cutoff for the different serum and urine osmolality variables in the prediction of readmissions. In this study, AUC 0.9–1 was defined as excellent accuracy: 0.9–1 = excellent; 0.8–0.9 = good; 0.7–0.8 = fair; 0.6–0.7 = poor; 0.5–0.6 = fail [15]. When the AUC is >0.7, Youden's index was calculated to identify the cutoff value that maximizes the sensitivity and specificity of each predictor. Sensitivities and specificities were obtained, and 95% confidence intervals were presented when appropriate. A *p* value of <0.05 was considered statistically significant. Analysis was done using IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY, USA: IBM Corp.

Results

A total of 100 patients hospitalized for AHF were included in the analysis. Majority of patients were males (62%) and Black Americans (59%). Others including Asians were at 27% and Hispanics at 11%, while only 3% were Caucasian. The mean age was 64.41 ± 12.53 and 43% of patients had diabetes while 86% had hypertension. About 39% of patients had known coronary artery disease. About 34% of patients had HF with preserved ejection fraction. Please see Table 1 for other demographic and clinical information.

The inpatient mortality rate was 3%. There was a 6% 30-day and 16% 60-day readmission rate for HF. There was a significantly higher urine osmolality on the day of discharge compared to the first urine osmolality value on admission (437.16 vs. 385.77 mOsm/kg), *p* < 0.001, but there were no significant differences between serum osmolality values on admission and discharge, *p* = 0.591.

Patients with 30-day readmissions had significantly higher serum osmolality 305 (299–310) mOsm/kg versus 298 (294–303) mOsm/kg on admission *p* = 0.044 (see Table 2). Only 9 patients in our sample had hyponatremia on admission (serum Na levels <135 meq/L). The lowest quartile for serum osmolality was <294 mOsm/kg and highest quartile was >303 mOsm/kg. Only 1 patient had serum osmolality less than the normal on admission (275–295 mOsm/kg). BNP values were not significantly different across serum osmolality quartiles, *p* = 0.426. On univariate analysis, 5 of the 6 patients with 30-day readmissions had admission serum osmolality >300 mOsm/kg, *p* = 0.047. There was also a significantly higher serum osmolality difference between discharge and admission, with a higher drop in serum osmolality on discharge among patients who were readmitted –7.5 (–9.0 to –1.25) versus –1.0 (–4.0 to 4.0), *p* = 0.044. No patients discharged with urine osmolality more than 500 mOsm/kg had 30-day readmissions but this was not statistically significant, *p* = 0.334, furthermore, only 2 patients with urine osmolality >500 mOsm/kg had 60-day readmissions compared to those with urine osmolality <500 mOsm/kg (8% vs. 19%) although this was also not statistically significant, *p* = 0.227. Of the serum and urine osmolality variables, only

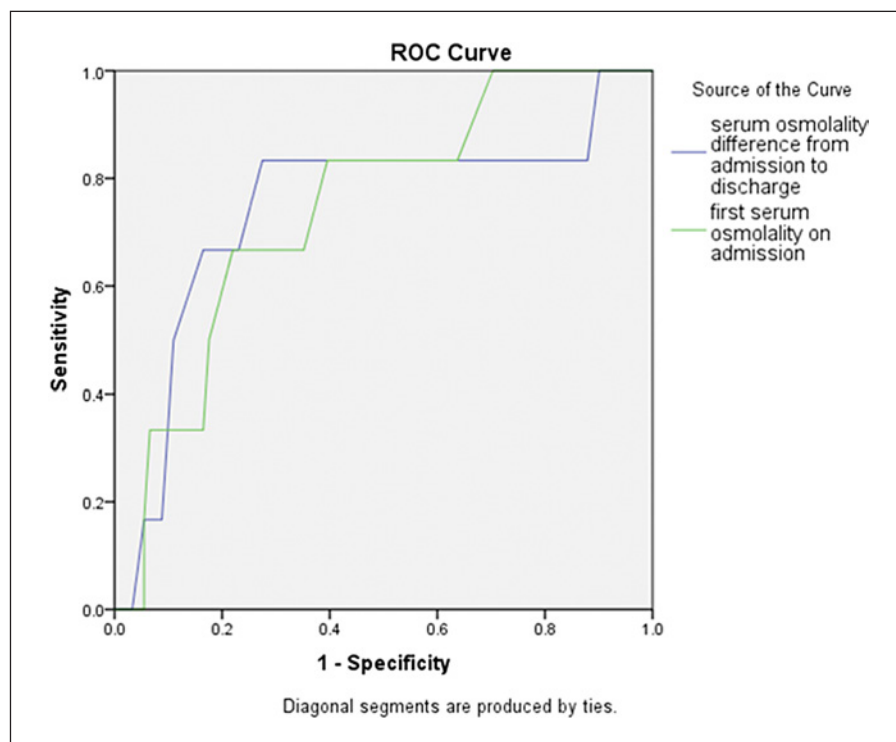


Fig. 1. ROC curves for prediction of 30-day readmissions. ROC, receiver operating characteristic.

first serum osmolality on admission (AUC 0.745 95% CI 0.563–0.927) and serum osmolality difference between admission and discharge (AUC 0.746 95% CI 0.507–0.986) were significantly predictive of 30-day HF readmissions (see Fig. 1). Utilizing the Youden index, first serum osmolality on admission of >299 had a sensitivity of 83% and a specificity of 61%, while a decrease in serum osmolality of >2 had a sensitivity of 83% and a specificity of 65% for 30-day readmissions.

Discussion

Plasma AVP is the main determinant of free-water excretion in humans. AVP release is highly sensitive to plasma osmolality, and it has been demonstrated that changes as low as 1% or less in plasma osmolality can trigger significant rise in AVP release [16]. AVP works via two mechanisms. By activating V1A receptors, it causes peripheral vasoconstriction and myocardial stimulation. Through the V2 receptors in the kidneys, AVP results in free-water retention [17]. By increasing free-water retention, and thereby decreasing urine flow, AVP also causes a proportional increase in urine osmolality. Since plasma AVP level is so closely linked to volume status, it is con-

ceivable that patients admitted for ADHF experience changes in their plasma and urine osmolality as they approach clinical euvolemia. Our study suggests that higher admission serum osmolality is associated with increased rates of 30-day readmission. This contrasts with other studies where a lower serum osmolality was associated with higher cardiovascular mortality [14]. In a post hoc analysis of the Effects of Oral Tolvaptan in Patients Hospitalized for Worsening Heart Failure (EVEREST) trial, Low discharge osmolality was also associated with a higher all-cause mortality, cardiovascular death, and HF hospitalizations [13]. We found that our sample patient population had predominantly higher serum osmolality levels ranges with the highest and lowest quartiles at >303 mOsm/kg and <294 mOsm/kg compared to previous studies [13, 14]. This can potentially be explained by differences in the amount of sodium in the diet, coupled with possible fluid restriction in the setting of HF may increase serum osmolality [18]. These patients with higher serum osmolality >300 on admission were also significantly associated with 30-day readmissions which is possible as higher serum osmolality levels triggers the release of AVP, which drives free-water retention leading to further congestion in these patients [19]. On the other hand, a study of over 2,000 patients actually found similar re-

sults with ours with a higher serum osmolality associated with poor outcomes of 1 year mortality and HF readmissions [20]. Potential explanations included the roles of comorbidities such as CKD and diabetes leading to higher levels of glucose, urea, and potassium all potentially affecting osmolality [20]. Excess AVP release in response to high osmotic stimuli on top of the already maladaptive neurohormonal system in HF can also lead to worse hemodynamic consequences and edema [20]. Variations in serum sodium ranges and osmolality in the context of HF should be interpreted with caution in the setting of dietary sodium intake; at the same time, differences in handling of sodium and fluid retention as salt-resistant individuals tend to store sodium without iso-osmolar water in the interstitial compartment as opposed to salt-sensitive patients [21]. On the other hand, our study did find that a drop in serum osmolality from admission to discharge was significantly associated with 30-day readmissions. This now points more to a state of persistent congestion as opposed to the group without readmissions where the change in serum osmolality was minimal. This characteristic lower serum osmolality on discharge was associated with more 30-day readmissions which was consistent with previous studies [13, 14]. Another explanation can be that high serum osmolalities can influence volume redistribution from the venous capacitance vessels heralding just the start of possible decongestion [20], which may be seen as a subsequent drop in serum osmolality. Measurement of serum osmolality trends on top of clinical assessment may potentially have therapeutic benefit to avoid prematurely discharging patients who may be simply just undergoing volume redistribution/plasma refill. These assumptions should be interpreted with caution as although we did see a decrease in serum Na from admission to discharge and median BNP was higher (but not statistically significant) in the readmission group 1,910 (341–3,270) versus 858 (412–1,762), $p = 0.37$, hematocrit was the same from admission and discharge 36 (30–43) versus 36 (29–45), $p = 0.91$ and other factors pertaining to serum osmolality such as glucose, blood urea nitrogen, and albumin to account for oncotic pressure and tendency for third spacing were not accounted for.

Limitations

There are several limitations to our study. The study is a single center analysis of patients admitted for AHF and utilizing serum and urine osmolality measurements in predicting HF readmissions. We only looked at HF readmissions as outcomes as this was the one closely related to osmolality measurements and volume status. ED visits

and observation status if they were not HF related were not considered. We had a lower overall rate of 30-day readmissions (6%) compared to the national average; this may likely be that the patients included were less sick, considering we excluded patients who got cardiac catheterization and patients with CKD stage 3B or worse. In addition, only 9 patients in our study had hyponatremia <135 meq/L, which may be an indicative of a less severe HF status. Although there were potentially clinically significant findings in that patients with high urine osmolality more than 500 on discharge were less likely to be admitted, this did not achieve statistical significance. We suspect that the study was underpowered to detect any statistically significant differences in this regard. Also, Black Americans and minorities such as Asians and Hispanics were better represented in this study with only 3% Caucasians. The baseline compliance to use of guideline-directed medical therapy was also low, and dietary habits were not taken into consideration. Changes in weight and urine output were not consistently monitored throughout the hospitalization and could not be included in the analysis. The findings may not be highly generalizable due to the findings above. However, our study provides evidence of feasibility that this approach of monitoring serum and urine osmolality may assist in the management of AHF in a challenging sample population such as ours in the poor socioeconomic stratum with multiple comorbidities and poor compliance to medical therapy. Use of osmolality values in combination with other biomarkers should be further investigated.

Conclusion

Measurement of serum osmolality and urine osmolality may have some utility in determination of decongestion in acute HF, but interpretation should take into consideration baseline values and dynamic changes to help account for individual differences sodium and water handling.

Statement of Ethics

This research project was reviewed and approved by the Institutional Review Board with IRB#5025 at Einstein Medical Center Philadelphia. Informed consent was obtained and documented for every single patient enrolled in this study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was supported by a grant to Dr. Kevin Bryan Lo and Dr. Janani Rangaswami from the Albert Einstein Society (AES) SEED grant.

Author Contributions

Kevin Bryan Lo, Grace Salacup, Jerald Pelayo, Prapaipan Putthapiban, Mario Naranjo-Tovar, and Janani Rangaswami were involved with the study conceptualization and design. Kevin Bryan

Lo, Grace Salacup, Jerald Pelayo, and Prapaipan Putthapiban were involved with patient enrollment, consent, labs, and data extraction. Data analysis and results were done by Kevin Bryan Lo, Sowmya Swamy, and Rasha Nakity. The first draft was done jointly by Kevin Bryan Lo, Sowmya Swamy, and Rasha Nakity with different versions edited and revised by Grace Salacup, Jerald Pelayo, Prapaipan Putthapiban, Mario Naranjo-Tovar, and Janani Rangaswami who also reviewed and approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in the main text. Further inquiries can be directed to the corresponding author.

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