

# Plasma osmolality predicts mortality in patients with heart failure with reduced ejection fraction

Hakkı Kaya<sup>1</sup>, Oğuzhan Yücel<sup>2</sup>, Meltem Refiker Ege<sup>3</sup>, Ali Zorlu<sup>1</sup>, Hasan Yücel<sup>1</sup>, Hakan Güneş<sup>4</sup>, Ahmet Ekmekçi<sup>5</sup>, Mehmet Birhan Yılmaz<sup>1</sup>

<sup>1</sup>Cumhuriyet University, Sivas, Turkey

<sup>2</sup>Samsun Training and Research Hospital, Samsun, Turkey

<sup>3</sup>Koru Hospital, Ankara, Turkey

<sup>4</sup>Sivas Numune Hospital, Sivas, Turkey

<sup>5</sup>Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, Istanbul, Turkey

## Abstract

**Background:** Heart failure (HF) is a fatal disease. Plasma osmolality with individual impacts of sodium, blood urea nitrogen (BUN), and glucose has not been studied prognostically in patients with HF.

**Aim:** This study aims to investigate the impact of serum osmolality on clinical endpoints in HF patients.

**Methods:** A total of 509 patients (383 males, 126 females) with HF with reduced ejection fraction in three HF centres were retrospectively analysed between January 2007 and December 2013. Follow-up data were completed for 496 patients. Plasma osmolality was calculated as  $(2 \times \text{Na}) + (\text{BUN}/2.8) + (\text{Glucose}/18)$ . Quartiles of plasma osmolality were produced, and the possible relationship between plasma osmolality and cardiovascular mortality was investigated.

**Results:** The mean follow-up was  $25 \pm 22$  months. The mean age was  $56.5 \pm 17.3$  years with a mean EF of  $26 \pm 8\%$ . The mean levels of plasma osmolality were as follows in the quartiles: 1<sup>st</sup> % =  $280 \pm 6$ , 2<sup>nd</sup> % =  $288 \pm 1$ , 3<sup>rd</sup> % =  $293 \pm 2$  (95% confidence interval [CI] 292.72–293.3), and 4<sup>th</sup> % =  $301 \pm 5$  mOsm/kg. The EF and B-type natriuretic peptide levels were similar in the four quartiles. Univariate and multivariate analyses in the Cox proportional hazard model revealed a significantly higher rate of mortality in the patients with hypo-osmolality. The Kaplan-Meier plot showed graded mortality curves with the 1<sup>st</sup> quartile having the worst prognosis, followed by the 4<sup>th</sup> quartile and the 2<sup>nd</sup> quartile, while the 3<sup>rd</sup> quartile was shown to have the best prognosis.

**Conclusions:** Our study results suggest that normal plasma osmolality is between 275 and 295 mOsm/kg. However, being close to the upper limit of normal range (292–293 mOsm/kg) seems to be the optimal plasma osmolality level in terms of cardiovascular prognosis in patients with HF.

**Key words:** heart failure, osmolality, mortality

Kardiol Pol 2017; 75, 4: 316–322

## INTRODUCTION

Chronic heart failure (HF) is a complex clinical syndrome resulting from any structural or functional cardiac disorders that impair the systolic ability of the ventricle. Despite available therapies, the rates of hospitalisation and death from HF still remain unacceptably high [1]. Risk stratification of patients with HF is critical. While B-type natriuretic peptide (BNP) has its primary implication in guiding HF treatment, it is also

a relevant marker for the prediction of mortality in HF patients [2]. On the other hand, the routine measurement of BNP is costly and it is not routinely performed in clinical practice.

The plasma osmolality, which is a useful marker of hydration status, is carefully managed by the body, measuring the fluid and electrolyte balance of the body [3]. The plasma glucose, blood urea nitrogen (BUN), and sodium are the main components of plasma osmolality. In HF patients, recognition

### Address for correspondence:

Hakkı Kaya, MD, Assist. Prof., Department of Cardiology, Cumhuriyet University, Sivas, Turkey, e-mail: drhakkikaya84@gmail.com

Received: 26.07.2016

Accepted: 17.10.2016

Available as AoP: 07.12.2016

Kardiologia Polska Copyright © Polskie Towarzystwo Kardiologiczne 2017

of the predictors of poor outcome is of utmost importance because this may help the physician to decide on the most appropriate therapy.

To the best of our knowledge, there is no study investigating the prognostic value of plasma osmolality with individual impacts of sodium, BUN, and glucose in patients with HF. In this study, therefore, we aimed to investigate the impact of serum osmolality on clinical endpoints in HF patients.

## METHODS

A total of 509 patients with HF with reduced ejection fraction (HFrEF) in three HF centres were retrospectively analysed between January 2007 and December 2013. Patients older than 18 years with an EF of  $\leq 35\%$  and BNP level of  $> 35$  pg/mL were included in the study. Pregnant women, patients with acute myocardial ischaemia within the past 30 days, acute myocarditis, cancer and/or a life expectancy of less than one year, and those with missing results for sodium, plasma glucose, BUN, or BNP within the first 8 h of admission were excluded.

Data about patients and current medication were obtained from the records of hospitals. Within 8 h of admission, blood samples were collected using a needle and syringe and transferred to collection tubes, which were immediately inverted several times. The samples were then analysed. The equation for serum osmolality involved the sum of multiples of serum sodium, glucose, and BUN. It was calculated as  $(2 \times \text{Na}) + (\text{BUN}/2.8) + (\text{Glucose}/18)$ . The osmolality was assessed in miliosmoles per kilogram. Normal plasma osmolality was defined as being between 275 and 295 mOsm/kg [4]. The patients were stratified by quartiles of admission osmolality with low osmolality (the first quartile) and high osmolality (the fourth quartile). The mortality in four patient groups was defined as hypo-osmolar, normo-hypo-osmolar, normo-hyperosmolar, and hyperosmolar based on the plasma osmolality. The clinical outcomes were compared between those groups. Other laboratory results, clinical characteristics, cardiovascular (CV) risk factors, comorbidities, and medications were recorded.

Following the index visit, CV death-related outcomes during follow-up were assessed by an independent investigator, who gathered and reviewed the hospital's medical records and made necessary phone calls for collecting data. The follow-up data were complete in 496 patients for CV death.

In addition, CV death was defined as death due to acute coronary syndrome (ACS), sudden death, HF, or stroke. Hypertension was defined as a blood pressure of  $> 140/90$  mm Hg on more than two occasions during office measurements or being on anti-hypertensive treatment. Diabetes mellitus was defined as a fasting blood glucose of  $\geq 126$  mg/dL or being on anti-diabetic treatment. Coronary artery disease (CAD) was defined as a previous clinical history of CAD or a documented coronary stenosis of  $> 50\%$ . Functional classification was made according to the New York Heart Association functional

classification, which provides a simple way of classifying the extent of HF [5].

Echocardiographic measurements were obtained in accordance with the recommendations of the American Society of Echocardiography. The wall thickness and chamber sizes were measured on transthoracic echocardiograms. The left ventricular EF (LVEF) was measured using the Simpson 2S biplane method [6].

Written, informed consent was obtained from each patient. The study protocol was approved by the local Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki for Human Research.

## Statistical analysis

Statistical analysis was performed using SPSS version 14.0 software (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to verify the normality of the distribution of continuous variables. Abnormally distributed continuous variables were expressed in mean  $\pm$  standard deviation (SD) or median (min–max), while categorical variables were presented as percentages. The  $\chi^2$  or Fisher's exact tests were used for the intergroup analysis. Independent t-test was used for normally distributed continuous variables, while the Mann-Whitney U test was applied for abnormally distributed variables. Univariate analysis was done to quantify the association of variables with mortality. Significant variables in the univariate analysis and other potential confounders were included in the multivariate Cox proportional hazard model with the forward stepwise method to determine the independent prognostic factors for mortality. The Kaplan-Meier curves were used to display the mortality in four patient groups. A p value of 0.05 was considered statistically significant.

## RESULTS

The mean follow-up was  $25 \pm 22$  months (up to 111 months). Baseline characteristics including CV risk factors, medications used, and laboratory findings are shown in Table 1. The mean age of the study population was  $56 \pm 17$  years. Of 496 patients, 378 were males and 118 patients were females. The mean EF was  $26 \pm 8\%$ . The median level of BNP was 240 pg/mL.

The mean levels of plasma osmolality were classified in quartiles: mean osmolality in the 1<sup>st</sup> quartile  $280 \pm 6.2$  mOsm/kg, in the 2<sup>nd</sup> quartile  $288 \pm 1$  mOsm/kg, in the 3<sup>rd</sup> quartile  $293 \pm 2$  mOsm/kg, and in the 4<sup>th</sup> quartile  $301 \pm 5$  mOsm/kg. The 1<sup>st</sup> quartile was also defined as the hypo-osmolar group ( $n = 124$ ), the 2<sup>nd</sup> and 3<sup>rd</sup> quartiles were defined as normo-osmolar groups ( $n = 248$ ), and the 4<sup>th</sup> quartile was defined as the hyper-osmolar group ( $n = 124$ ). The EF and BNP levels were similar in the four subgroups. The mean age, systolic blood pressure, fasting glucose levels, BUN, creatinine, sodium, and triglyceride levels were significantly different among the four quartiles of osmolality. The patients in the 4<sup>th</sup> quartile were older with higher creatinine levels than the other quartiles of osmolality.

**Table 1.** Baseline characteristics of study patients and laboratory findings and medications

Variable	Hypo-osmolar (n = 124)	Normo-osmolar (n = 248)		Hyper-osmolar (n = 124)	P
		Normo-hypo- osmolar (n = 124)	Normo-hyper- osmolar (n = 124)		
<b>Baseline characteristics</b>					
Mean age [years]	57 ± 17	53 ± 17	55 ± 17	61 ± 17	0.003
Male/Female	91/33	90/34	97/27	100/24	0.381
Hypertension	75 (61%)	59 (48%)	63 (51%)	78 (63%)	0.041
Diabetes mellitus	19 (15%)	26 (21%)	29 (23%)	40 (32%)	0.015
Coronary artery disease	106 (85%)	93 (75%)	107 (89%)	78 (63%)	0.045
Disease duration [months]	27 ± 26	20 ± 18	33 ± 41	27 ± 29	0.223
Heart rate [bpm]	75 ± 31	82 ± 25	82 ± 26	77 ± 31	0.328
Systolic blood pressure [mm Hg]	109 ± 23	116 ± 20	122 ± 26	120 ± 26	0.011
Diastolic blood pressure [mm Hg]	73 ± 13	76 ± 14	78 ± 14	79 ± 14	0.057
NYHA class 3–4	26 (21%)	20 (16%)	31 (25%)	17 (14%)	0.105
Atrial fibrillation	33 (27%)	17 (14%)	23 (19%)	32 (26%)	0.035
LVEF [%]	25 ± 8	27 ± 8	26 ± 8	27 ± 9	0.382
<b>Primary end point</b>					
Cardiovascular mortality	63 (51%)	36 (29%)	28 (23%)	47 (38%)	< 0.001
<b>Laboratory findings</b>					
Osmolality	280.1 ± 6.1	288.5 ± 1.4	293.2 ± 1.6	301.2 ± 5.4	< 0.001
Fasting glucose [mg/dL]	109 ± 17	117 ± 46	118 ± 45	138 ± 77	< 0.001
Blood urea nitrogen [mg/dL]	23 ± 12	20 ± 9	26 ± 17	34 ± 22	< 0.001
Creatinine [mg/dL]	1.05 ± 0.4	1.04 ± 0.5	1.16 ± 0.4	1.43 ± 0.7	< 0.001
Sodium [mEq/L]	133 ± 4	137 ± 2	139 ± 3	141 ± 4	< 0.001
Potassium [mEq/L]	4.4 ± 0.6	4.5 ± 0.5	4.5 ± 0.5	4.7 ± 0.7	0.008
Haemoglobin [g/dL]	13.1 ± 2	13.5 ± 2	13.5 ± 2	13.8 ± 2	0.068
B-type natriuretic peptide > 240 pg/mL	32 (55%)	28 (34%)	24 (29%)	17 (28%)	0.005
Total cholesterol [mg/dL]	149 ± 49	169 ± 51	173 ± 47	162 ± 46	0.001
HDL cholesterol [mg/dL]	33 ± 13	38 ± 12	38 ± 11	36 ± 11	0.009
LDL cholesterol [mg/dL]	96 ± 36	107 ± 43	105 ± 37	99 ± 33	0.066
Triglyceride [mg/dL]	108 ± 65	123 ± 73	146 ± 86	135 ± 87	0.002
Alanine aminotransferase [IU/L]	71 ± 151	28 ± 21	38 ± 85	36 ± 36	0.155
Aspartate aminotransferase [IU/L]	60 ± 114	29 ± 17	35 ± 86	32 ± 19	0.007
<b>Medication</b>					
Antiplatelet agents	62 (50%)	67 (54%)	67 (54%)	67 (54%)	0.895
Beta-blockers	76 (61%)	91 (73%)	81 (65%)	114 (92%)	< 0.001
ACE inhibitor/ARB	77 (62%)	94 (76%)	100 (81%)	101 (82%)	0.001
Digoxin	65 (52%)	56 (45%)	59 (48%)	59 (48%)	0.710
Diuretics	78 (63%)	78 (63%)	71 (57%)	80 (65%)	0.895
Mineralocorticoid receptor antagonist	79 (64%)	82 (66%)	83 (67%)	85 (69%)	0.879

ACE — angiotensin-converting enzyme; ARB — angiotensin receptor blocker; HDL — high-density lipoprotein; LDL — low-density lipoprotein; LVEF — left ventricular ejection fraction; NYHA — New York Heart Association

**Table 2.** Univariate and multivariate analyses of mortality

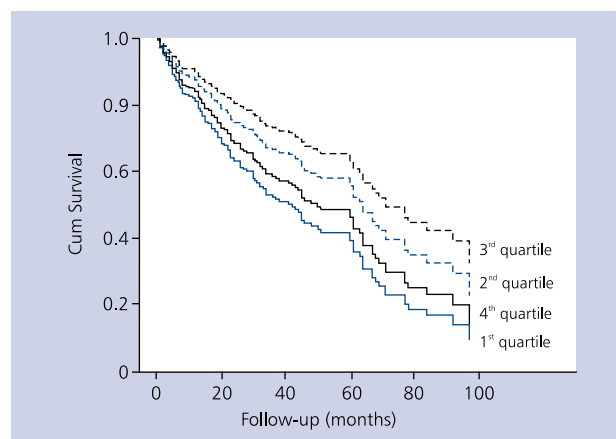
	Univariate			Multivariate		
	p	HR	95% CI	p	HR	95% CI
<b>Statistically significant variables</b>						
Hypo-osmolality	< 0.001	2.428	1.602–3.682	0.021	1.651	1.077–2.530
Normo-hyperosmolality	0.001	0.451	0.282–0.722			
Mean age [years]	< 0.001	1.026	1.015–1.038			
NYHA class 3–4	0.004	1.944	1.232–3.065			
Atrial fibrillation	0.001	2.050	1.323–3.178			
LVEF [%]	0.046	0.977	0.955–1.000			
Creatinine [mg/dL]	< 0.001	2.181	1.494–3.185			
Haemoglobin [g/dL]	0.002	0.856	0.775–0.945			
B-type natriuretic peptide > 240 pg/mL	< 0.001	6.367	3.602–11.257			
Total cholesterol [mg/dL]	< 0.001	0.990	0.986–0.995			
HDL cholesterol [mg/dL]	< 0.001	0.960	0.943–0.977			
Triglyceride [mg/dL]	< 0.001	0.990	0.987–0.994	0.007	1.002	1.001–1.004
Alanine aminotransferase [IU/L]	0.020	1.006	1.001–1.011			
Aspartate aminotransferase [IU/L]	0.016	1.013	1.002–1.023			
Beta-blockers usage	0.003	1.841	1.227–2.764			
<b>Variables which correlated with osmolality</b>						
Normo-hypo-osmolality	0.104	0.694	0.446–1.078			
Hyperosmolality	0.447	1.178	0.773–1.795			
Hypertension	0.155	1.312	0.903–1.907			
Diabetes mellitus	0.118	1.409	0.917–2.164			
Coronary artery disease	0.645	1.122	0.688–1.828			
Systolic blood pressure [mm Hg]	0.413	0.995	0.983–1.007			
Potassium [mEq/L]	0.821	1.036	0.761–1.412			
ACE inhibitor/ARB usage	0.744	1.073	0.702–1.639			

All the variables from Table 1 were examined and only those significant at a p < 0.05 level and those with a correlated osmolality are shown in univariate analysis. The multivariate Cox proportional hazard model with forward stepwise method included all univariate predictors and those with correlated osmolality level. ACE — angiotensin-converting enzyme; ARB — angiotensin receptor blocker; CI — confidence interval; HDL — high-density lipoprotein; LVEF — left ventricular ejection fraction; NYHA — New York Heart Association; OR — odds ratio

Univariate and multivariate predictors of mortality included into the Cox proportional hazard model are presented in Table 2. This model revealed a significantly higher rate of mortality in the patients with hypo-osmolality. The Kaplan-Meier plot yielded graded mortality curves with the 1<sup>st</sup> quartile having the worse prognosis, followed by the 4<sup>th</sup> and the 2<sup>nd</sup> quartiles, while the 3<sup>rd</sup> quartile was shown to have the best prognosis (Fig. 1).

**DISCUSSION**

The main finding of the present study is the association between the serum osmolality and mortality in hospitalised patients with HFrEF. Admission osmolality in the lowest quartile was highly and independently predictive of mortality in this patient population.



**Figure 1.** Kaplan-Meier curves for cardiovascular mortality

Although all the components of serum osmolality separately have a prognostic value in patients with HF, reduced serum osmolality in this group can mainly be associated with hyponatraemia with euvolaemia or hyponatraemia with hypervolaemia coupling [7]. Hyponatraemia is defined as serum sodium concentration lower than 136 mmol/L. It is the most common electrolyte disorder in the clinical setting in hospitalised HF patients [8]. Many patients with HF have reduced sodium levels due to neurohormonal activation or the effects of medications [9]. Chronic activation of the renin–angiotensin–aldosterone system with the stimulation of sympathetic nervous system as a response to inadequate tissue perfusion stimulates water and sodium retention. To increase the intravascular volume, arginine vasopressin is released as a response to low cardiac output. Arginine vasopressin plays a key role in the development of hyponatraemia in HF [10, 11]. A number of clinical studies have confirmed the association of hyponatraemia with increased morbidity and mortality in hospitalised patients with HF [12–15]. In our study, serum sodium levels were significantly different among the four osmolality quartile groups with lower values in the hypo-osmolar group.

Another component of serum osmolality is the serum glucose level. Hypo-osmolality due to hypoglycaemia may have deleterious effects on survival in patients with HF. Although high glucose levels are well-known to increase the risk of HF irrespective of other traditional risk factors and ischaemia [16], low glucose levels are found to be associated with a higher risk of in-hospital mortality [17]. Hypoglycaemia during the course of congestive HF may result from reduced hepatic glucose output by poor diet, poor glucose absorption, and impaired hepatic glycogenolysis and gluconeogenesis [18]. Chronic, passive, long-standing congestion of the liver is a common feature and hypoglycaemia secondary to hepatic dysfunction arising from chronic passive congestion of the liver is not uncommon. Recognition and treatment of hypoglycaemia are obviously of utmost importance during the course of congestive HF. In most cases, the improvement of HF necessitates the correction of hypoglycaemia [19]. In our study, hypo-osmolar patients who had worse prognosis had statistically significant lower glucose levels.

In addition, renal dysfunction, a common finding in HF, has emerged as one of the most potent indicators in these patients [20]. Patients with renal dysfunction during HF hospitalisation have higher in-hospital mortality rates, longer length of stay, and increased long-term mortality rates [21–23]. Urea also plays a basic and direct role in the fluid and sodium homeostasis, which is regulated by the neurohormonal system [24]. Increased BUN levels may indicate adrenergic activation, activation of the renin–angiotensin–aldosterone system, and increased vasopressin levels [25–27]. Although high BUN

levels in HF patients predict a higher in hospital-mortality, low osmolality not due to high BUN levels can be a marker of worse prognosis. Low levels of BUN are less common in HF patients; however, they may be caused by malabsorption or abnormal liver functions due to congestion or low muscle mass related with advanced disease.

The main advantages of using serum osmolality in clinical practice include the utilisation of standardised and objective analytic procedures without any requirement for additional and nutritional data [28]. In addition, serum samples contain numerous substances (i.e. chloride, potassium, and bicarbonate), which constitute 95% of total osmolality. Although they are found in small amounts, proteins also affect total serum osmolality. Furthermore, there are individual differences in serum protein concentrations. Serum osmolality is primarily done to investigate hyponatraemia. Serum sodium levels can be low when the presence of water in the blood decreases due to the presence of increased protein or lipids [29, 30]. On the other hand, all osmolality calculations were made according to a single fasting blood sample. Many equations have been used to calculate osmolality, but which serum osmolality equation best predicts serum osmolality is unclear. Osmolality is dynamic and can fluctuate as the body responds to and corrects temporary water imbalances. Osmolality results are not diagnostic, while they only suggest that a person has an imbalance. Lastly, further investigations are needed to confirm our results.

Despite the limitations of the study, our results suggest that the serum osmolality of HF patients on admission to hospital is a good prognostic marker. In our study, all the components of serum osmolality (i.e. glucose, BUN, sodium levels) were significantly different among the four osmolality quartiles with lower levels in the first quartile showing worse prognosis. In our study, serum osmolality was found to predict prognosis independently of EF, functional capacity, and BNP levels. It is well-known that functional capacity is a powerful determinant of outcomes, and it is an important prognostic marker in routine clinical use. Also, BNP levels predict the functional capacity in HF patients [31]. Unlike BNP levels, serum osmolality can predict the prognosis independently of the functional status.

## CONCLUSIONS

In conclusion, our study results suggest that normal plasma osmolality is between 275 and 295 mOsm/kg. However, being close to the upper limit of normal range (292–293 mOsm/kg) seems to be the optimal plasma osmolality level in terms of CV prognosis in patients with HF. We believe that osmolality is a feasible and cost-effective predictor of mortality in patients with HF. However, further studies are needed both to establish a conclusion and to elucidate the exact role of osmolality in guiding HF therapy.

**Conflict of interest:** none declared

## References

- Gheorghiadu M, Zannad F, Sopko G, et al. International Working Group on Acute Heart Failure Syndromes. Acute heart failure syndromes: current state and framework for future research. *Circulation*. 2005; 112(25): 3958–3968, doi: [10.1161/CIRCULATIONAHA.105.590091](https://doi.org/10.1161/CIRCULATIONAHA.105.590091), indexed in Pubmed:16365214.
- Bhalla V, Willis S, Maisel A. B-type natriuretic peptide: the level and the drug? Partners in the diagnosis and management of congestive heart failure. *Congestive Heart Failure*. 2004; 10(s1): 3–27, doi: [10.1111/j.1527-5299.2004.03310.x](https://doi.org/10.1111/j.1527-5299.2004.03310.x).
- Earle LE, Sanders CA. The effect of changing serum osmolality on the release of antidiuretic hormone in certain patients with decompensated cirrhosis of the liver and low serum osmolality. *J Clin Invest*. 1959; 38(3): 545–550, doi: [10.1172/JCI103832](https://doi.org/10.1172/JCI103832), indexed in Pubmed: [13641405](https://pubmed.ncbi.nlm.nih.gov/13641405/).
- Fazekas AS, Funk GC, Klobassa DS, et al. Evaluation of 36 formulas for calculating plasma osmolality. *Intensive Care Med*. 2013; 39(2): 302–308, doi:[10.1007/s00134-012-2691-0](https://doi.org/10.1007/s00134-012-2691-0), indexed in Pubmed: [23081685](https://pubmed.ncbi.nlm.nih.gov/23081685/).
- The Criteria Committee of the New York Heart Association. Nomenclature and criteria for Diagnosis of the Heart and Great Vessels (9th edition). Boston: Little, Brown and Co. 1994: 253–256.
- Lang RM, Bierig M, Devereux RB, et al. Chamber Quantification Writing Group, American Society of Echocardiography's Guidelines and Standards Committee, European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005; 18(12): 1440–1463, doi:[10.1016/j.echo.2005.10.005](https://doi.org/10.1016/j.echo.2005.10.005), indexed in Pubmed: [16376782](https://pubmed.ncbi.nlm.nih.gov/16376782/).
- Oh M. Evaluation of renal function, water, electrolytes, and acid-base balance. In: McPherson RA, Pincus MR, eds. *Henry's Clinical Diagnosis and Management by Laboratory Methods*. 2011; Chapter 14: 169–192.
- Milionis HJ, Liamis GL, Elisaf MS. The hyponatremic patient: a systematic approach to laboratory diagnosis. *CMAJ*. 2002; 166(8): 1056–1062, indexed in Pubmed: [12002984](https://pubmed.ncbi.nlm.nih.gov/12002984/).
- Jao GT, Chiong JR. Hyponatremia in acute decompensated heart failure: mechanisms, prognosis, and treatment options. *Clin Cardiol*. 2010; 33(11): 666–671, doi: [10.1002/clc.20822](https://doi.org/10.1002/clc.20822), indexed in Pubmed: [21089110](https://pubmed.ncbi.nlm.nih.gov/21089110/).
- Hauptman PJ. Clinical challenge of hyponatremia in heart failure. *J Hosp Med*. 2012; 7 Suppl 4: S6–10, doi: [10.1002/jhm.1913](https://doi.org/10.1002/jhm.1913), indexed in Pubmed:[22489082](https://pubmed.ncbi.nlm.nih.gov/22489082/).
- Ghali JK, Tam SW. The critical link of hypervolemia and hyponatremia in heart failure and the potential role of arginine vasopressin antagonists. *J Card Fail*. 2010; 16(5): 419–431, doi: [10.1016/j.cardfail.2009.12.021](https://doi.org/10.1016/j.cardfail.2009.12.021), indexed in Pubmed: [20447579](https://pubmed.ncbi.nlm.nih.gov/20447579/).
- Gheorghiadu M, Abraham WT, Albert NM, et al. OPTIMIZE-HF Investigators and Coordinators. Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. *Eur Heart J*. 2007; 28(8): 980–988, doi: [10.1093/eurheartj/ehl542](https://doi.org/10.1093/eurheartj/ehl542), indexed in Pubmed: [17309900](https://pubmed.ncbi.nlm.nih.gov/17309900/).
- Kearney MT, Fox KAA, Lee AJ, et al. Predicting sudden death in patients with mild to moderate chronic heart failure. *Heart*. 2004; 90(10): 1137–1143, doi: [10.1136/hrt.2003.021733](https://doi.org/10.1136/hrt.2003.021733), indexed in Pubmed: [15367507](https://pubmed.ncbi.nlm.nih.gov/15367507/).
- Kodziszevska K, Leszek P, Korewicki J, et al. Old markers, new approach to assessment of risk in heart failure. *Kardiol Pol*. 2015; 73(6): 387–395, doi:[10.5603/KP.a2014.0245](https://doi.org/10.5603/KP.a2014.0245), indexed in Pubmed: [25563469](https://pubmed.ncbi.nlm.nih.gov/25563469/).
- Gromadziński L, Targoński R. Impact of clinical and echocardiographic parameters assessed during acute decompensation of chronic heart failure on 3-year survival. *Kardiol Pol*. 2006; 64(9): 951–956; discussion 957, indexed in Pubmed: [17054026](https://pubmed.ncbi.nlm.nih.gov/17054026/).
- Schocken DD, Benjamin EJ, Fonarow GC, et al. American Heart Association Council on Epidemiology and Prevention, American Heart Association Council on Clinical Cardiology, American Heart Association Council on Cardiovascular Nursing, American Heart Association Council on High Blood Pressure Research, Quality of Care and Outcomes Research Interdisciplinary Working Group, Functional Genomics and Translational Biology Interdisciplinary Working Group. Prevention of heart failure: a scientific statement from the American Heart Association Councils on Epidemiology and Prevention, Clinical Cardiology, Cardiovascular Nursing, and High Blood Pressure Research; Quality of Care and Outcomes Research Interdisciplinary Working Group; and Functional Genomics and Translational Biology Interdisciplinary Working Group. *Circulation*. 2008; 117(19): 2544–2565, doi: [10.1161/CIRCULATIONAHA.107.188965](https://doi.org/10.1161/CIRCULATIONAHA.107.188965), indexed in Pubmed: [18391114](https://pubmed.ncbi.nlm.nih.gov/18391114/).
- Boucai L, Southern WN, Zonszein J. Hypoglycemia-associated mortality is not drug-associated but linked to comorbidities. *Am J Med*. 2011; 124(11): 1028–1035, doi: [10.1016/j.amjmed.2011.07.011](https://doi.org/10.1016/j.amjmed.2011.07.011), indexed in Pubmed: [22017781](https://pubmed.ncbi.nlm.nih.gov/22017781/).
- Mellinkoff SM, TUMULTY PA. Hepatic hypoglycemia; its occurrence in congestive heart failure. *N Engl J Med*. 1952; 247(20): 745–750, doi:[10.1056/NEJM195211132472001](https://doi.org/10.1056/NEJM195211132472001), indexed in Pubmed: [13002607](https://pubmed.ncbi.nlm.nih.gov/13002607/).
- Benzing G, Schubert W, Sug G, et al. Simultaneous hypoglycemia and acute congestive heart failure. *Circulation*. 1969; 40(2): 209–216, indexed in Pubmed: [4307751](https://pubmed.ncbi.nlm.nih.gov/4307751/).
- Bock JS, Gottlieb SS. Cardiorenal syndrome: new perspectives. *Circulation*. 2010; 121(23): 2592–2600, doi: [10.1161/CIRCULATIONAHA.109.886473](https://doi.org/10.1161/CIRCULATIONAHA.109.886473), indexed in Pubmed: [20547939](https://pubmed.ncbi.nlm.nih.gov/20547939/).
- Lanfer DE, Peterson EL, Campbell J, et al. Relation of worsened renal function during hospitalization for heart failure to long-term outcomes and rehospitalization. *Am J Cardiol*. 2011; 107(1): 74–78, doi: [10.1016/j.amjcard.2010.08.045](https://doi.org/10.1016/j.amjcard.2010.08.045), indexed in Pubmed: [21146690](https://pubmed.ncbi.nlm.nih.gov/21146690/).
- Balsam P, Tymiąńska A, Kapłon-Cieślicka A, et al. Predictors of one-year outcome in patients hospitalised for heart failure: results from the Polish part of the Heart Failure Pilot Survey of the European Society of Cardiology. *Kardiol Pol*. 2016; 74(1): 9–17, doi: [10.5603/KP.a2015.0112](https://doi.org/10.5603/KP.a2015.0112), indexed in Pubmed: [26101021](https://pubmed.ncbi.nlm.nih.gov/26101021/).
- Biegus J, Zymliński R, Szachniewicz J, et al. Clinical characteristics and predictors of in-hospital mortality in 270 consecutive patients hospitalised due to acute heart failure in a single cardiology centre during one year. *Kardiol Pol*. 2011; 69(10): 997–1005, indexed in Pubmed: [22006596](https://pubmed.ncbi.nlm.nih.gov/22006596/).
- Sands JM, Layton HE. The physiology of urinary concentration: an update. *Semin Nephrol*. 2009; 29(3): 178–195, doi:[10.1016/j.semnephrol.2009.03.008](https://doi.org/10.1016/j.semnephrol.2009.03.008), indexed in Pubmed: [19523568](https://pubmed.ncbi.nlm.nih.gov/19523568/).
- Conte G, Dal Canton A, Terribile M, et al. Renal handling of urea in subjects with persistent azotemia and normal renal function. *Kidney Int*. 1987; 32(5): 721–727, indexed in Pubmed: [3323600](https://pubmed.ncbi.nlm.nih.gov/3323600/).
- Schrier R. Vasopressin and aquaporin 2 in clinical disorders of water homeostasis. *Semin Nephrol*. 2008; 28(3): 289–296, doi:[10.1016/j.semnephrol.2008.03.009](https://doi.org/10.1016/j.semnephrol.2008.03.009).
- Kirtane AJ, Leder DM, Waikar SS, et al. TIMI Study Group. Serum blood urea nitrogen as an independent marker of subsequent mortality among patients with acute coronary syndromes and normal to mildly reduced glomerular filtration rates. *J Am Coll Cardiol*. 2005; 45(11): 1781–1786, doi:[10.1016/j.jacc.2005.02.068](https://doi.org/10.1016/j.jacc.2005.02.068), indexed in Pubmed: [15936606](https://pubmed.ncbi.nlm.nih.gov/15936606/).
- Cheuvront SN, Ely BR, Kenefick RW, et al. Biological variation and diagnostic accuracy of dehydration assessment markers. *Am J Clin Nutr*. 2010; 92(3): 565–573, doi: [10.3945/ajcn.2010.29490](https://doi.org/10.3945/ajcn.2010.29490), indexed in Pubmed: [20631205](https://pubmed.ncbi.nlm.nih.gov/20631205/).
- Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for water, potassium, sodium, chloride and sulfate. Washington, DC: National Academies Press : 269–423.
- Senay LC, Kok R. Effects of training and heat acclimatization on blood plasma contents of exercising men. *J Appl Physiol Respir Environ Exerc Physiol*. 1977; 43(4): 591–599, indexed in Pubmed: [908673](https://pubmed.ncbi.nlm.nih.gov/908673/).
- Krüger S, Graf J, Kunz D, et al. brain natriuretic peptide levels predict functional capacity in patients with chronic heart failure. *Journal of the American College of Cardiology*. 2002; 40(4): 718–722, doi: [10.1016/s0735-1097\(02\)02032-6](https://doi.org/10.1016/s0735-1097(02)02032-6).

**Cite this article as:** Kaya H, Yücel O, Ege MR, et al. Plasma osmolality predicts mortality in patients with heart failure with reduced ejection fraction. *Kardiol Pol*. 2017; 75(4): 316–322, doi: [10.5603/KPa2016.0168](https://doi.org/10.5603/KPa2016.0168).

# Osmolalność osocza jako czynnik predykcyjny śmiertelności u chorych z niewydolnością serca i obniżoną frakcją wyrzutową

Hakkı Kaya<sup>1</sup>, Oğuzhan Yücel<sup>2</sup>, Meltem Refiker Ege<sup>3</sup>, Ali Zorlu<sup>1</sup>, Hasan Yücel<sup>1</sup>, Hakan Güneş<sup>4</sup>, Ahmet Ekmekçi<sup>5</sup>, Mehmet Birhan Yılmaz<sup>1</sup>

<sup>1</sup>Cumhuriyet University, Sivas, Turcja

<sup>2</sup>Samsun Training and Research Hospital, Samsun, Turcja

<sup>3</sup>Koru Hospital, Ankara, Turcja

<sup>4</sup>Sivas Numune Hospital, Sivas, Turcja

<sup>5</sup>Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, Istanbul, Turcja

## Streszczenie

**Wstęp:** Niewydolność serca (HF) jest chorobą śmiertelną. Nie prowadzono dotychczas prognostycznych badań nad osmolalnością osocza, wraz z indywidualnym wpływem na stężenie sodu, azotu mocznikowego we krwi (BUN) i glukozy, u chorych na HF.

**Cel:** Celem niniejszego badania była ocena wpływu osmolalności osocza na kliniczne punkty końcowe u chorych z HF.

**Metody:** Do badania włączono 509 pacjentów (383 mężczyzn, 126 kobiet) z HF i obniżoną frakcją wyrzutową z trzech ośrodków kardiologicznych, a ich dane analizowano retrospektywnie w okresie od stycznia 2007 r. do grudnia 2013 r. Kompletnie dane z obserwacji zebrano od 496 chorych. Osmolalność osocza obliczano wg wzoru:  $(2 \times \text{Na}) + (\text{BUN}/2,8) + (\text{glukoza}/18)$ . Dokonano podziału na grupy w zależności od kwartyli osmolalności osocza i analizowano możliwe zależności między osmolalnością osocza a śmiertelnością sercowo-naczyniową.

**Wyniki:** Okres obserwacji trwał średnio  $25 \pm 22$  miesiące. Średni wiek badanych wynosił  $56,5 \pm 17,3$  roku, a średnia frakcja wyrzutowa —  $26 \pm 8\%$ . Średnie poziomy osmolalności osocza miały następujące wartości w poszczególnych kwartylach: 1. kwartyl % =  $280 \pm 6$ , 2. kwartyl% =  $288 \pm 1$ , 3. kwartyl % =  $293 \pm 2$  (95% przedział ufności 292,72–293,3), 4. kwartyl % =  $301 \pm 5$  mOsm/kg. Wartości frakcji wyrzutowej i peptydu natriuretycznego typu B były podobne dla wszystkich kwartyli. Jedno- i wieloczynnikowe analizy w modelu proporcjonalnego hazardu Coxa wykazały istotnie wyższą śmiertelność u chorych z hiposmolalnością osocza. W analizie Kaplana-Meiera uzyskano krzywe proporcjonalnych wartości wskaźnika śmiertelności, przy czym najgorsze rokowanie wiązało się z 1. kwartylem osmolalności osocza, nieco lepsze było kolejno dla 4. i 2. kwartyli, a najlepsze rokowanie wiązało się z 3. kwartylem.

**Wnioski:** Wyniki badania sugerują, że prawidłowe wartości osmolalności osocza mieszczą się w zakresie od 275 do 295 mOsm/kg. Jednak wydaje się, że optymalne wartości tego parametru w odniesieniu do rokowania u chorych z HF są zbliżone do górnego zakresu wartości prawidłowych (292–293 mOsm/kg).

**Słowa kluczowe:** niewydolność serca, osmolalność, śmiertelność

Kardiologia 2017; 75, 4: 316–322

## Adres do korespondencji:

Hakkı Kaya, MD, Assist. Prof., Department of Cardiology, Cumhuriyet University, Sivas, Turkey, e-mail: drhakkikaya84@gmail.com

Praca wpłynęła: 26.07.2016 r.

Zaakceptowana do druku: 17.10.2016 r.

Data publikacji AoP: 07.12.2016 r.