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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

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

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## 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 × Na) + (BUN/2.8) + (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 ± 22 months. The mean age was 56.5 ± 17.3 years with a mean EF of 26 ± 8%. The mean levels of plasma osmolality were as follows in the quartiles: 1st % = 280 ± 6, 2nd % = 288 ± 1, 3rd % = 293 ± 2 (95% confidence interval [CI] 292.72–293.3), and 4th % = 301 ± 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 1st quartile having the worst prognosis, followed by the 4th quartile and the 2nd quartile, while the 3rd 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

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## 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

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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 ≤ 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 × Na) + (BUN/2.8) + (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 ≥ 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 ± 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 ± 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 ± 17 years. Of 496 patients, 378 were males and 118 patients were females. The mean EF was 26 ± 8%. The median level of BNP was 240 pg/mL.

The mean levels of plasma osmolality were classified in quartiles: mean osmolality in the 1st quartile 280 ± 6.2 mOsm/kg, in the 2nd quartile 288 ± 1 mOsm/kg, in the 3rd quartile 293 ± 2 mOsm/kg, and in the 4th quartile 301 ± 5 mOsm/kg. The 1st quartile was also defined as the hypo-osmolar group (n = 124), the 2nd and 3rd quartiles were defined as normo-osmolar groups (n = 248), and the 4th 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 4th 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) | | |
| **Baseline characteristics** | | | | | |
| 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 |
| **Primary end point** | | | | | |
| Cardiovascular mortality | 63 (51%) | 36 (29%) | 28 (23%) | 47 (38%) | < 0.001 |
| **Laboratory findings** | | | | | |
| 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 |
| **Medication** | | | | | |
| 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; HLD — 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 |
| **Statistically significant variables** | | | | | | |
| 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 | | | |
| **Variables which correlated with osmolality** | | | | | | |
| 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 1st quartile having the worse prognosis, followed by the 4th and the 2nd quartiles, while the 3rd 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.

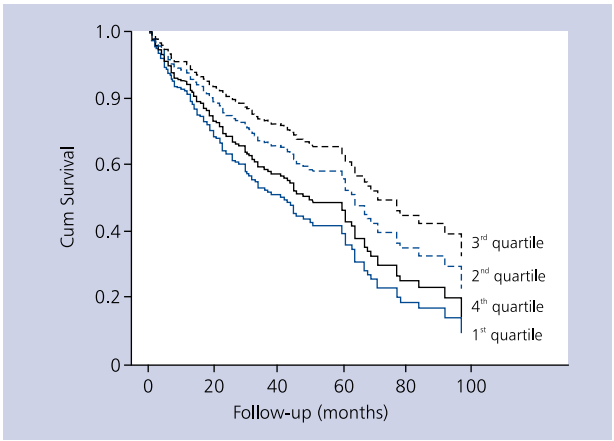


Figure 1. Kaplan-Meier curves for cardiovascular mortality

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*

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

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## 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. Kompletne dane z obserwacji zebrano od 496 chorych. Osmolalność osocza obliczano wg wzoru: $(2 \times Na)+(BUN/2,8)+(glukoza/18)$. 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 ± 22 miesiące. Średni wiek badanych wynosił 56,5 ± 17,3 roku, a średnia frakcja wyrzutowa — 26 ± 8%. Średnie poziomy osmolalności osocza miały następujące wartości w poszczególnych kwartylach: 1. kwartyl % = 280 ± 6, 2. kwartyl% = 288 ± 1, 3. kwartyl % = 293 ± 2 (95% przedział ufności 292,72–293,3), 4. kwartyl % = 301 ± 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 hipoosmolalnością 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. kwartylu, 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

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