High serum osmolarity at admission determines a worse outcome in patients with heart failure: Is a new target emerging?

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A B S T R A C T

Aims: The osmolarity of human serum is restricted to a tightly regulated range, and any deviation has clinical implications. Our aim in this study was to establish whether differences in serum osmolarity in heart failure (HF) patients are related with a worse outcome.

Methods: We evaluated the prognostic value of serum osmolarity in patients with HF from the Spanish National Registry on Heart Failure (RICA), a multicenter, prospective registry that enrolls patients admitted for decompensated HF and follows them for 1 year. Patients were divided into quartiles according to osmolarity levels. Primary endpoint was the combination of all-cause mortality and hospital readmissions for HF.

Results: A total of 2568 patients (47.46% men) were included. Patients with higher osmolarity were older, presented more comorbidities (especially diabetes mellitus and chronic kidney disease), and consequently had higher levels of glucose, urea, creatinine and potassium. During the 1-year follow-up, mortality among the quartiles was 18% (Q1), 18% (Q2), 23% (Q3) and 28% (Q4), p < 0.001. After adjusting for baseline characteristics, high serum osmolarity was significantly associated with all-cause mortality (RR 1.02, 95% CI 1.01–1.03, p < 0.001). We also found a significant increase in the combined endpoint of mortality and readmission among quartiles with higher osmolarity (p < 0.001). Diabetes, eGFR, Barthel index, systolic blood pressure, body mass index, hemoglobin, NYHA class and beta-blocking agents were also independently associated with the primary endpoint.

Conclusions: In patients admitted for decompensated HF, high serum osmolarity predicts a worse outcome, and is associated with a higher comorbidity burden, supporting its use as a candidate prognostic target in HF.

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1. Introduction

Hyponatremia has been identified in several studies as a risk factor for increased morbidity and mortality in patients with congestive heart failure (CHF) [1]. It can be broadly classified into two types, dilutional or depletional, depending on the underlying pathophysiology. Dilutional hyponatremia, caused by excess water retention, is the most common form. Hyponatremia can be further categorized as either hypervolemic or euvolemic, depending on the patient’s volume status, which can be measured by serum osmolarity [2].

Serum osmolarity is normally maintained within a narrow range of 275–295 mOsm/L. Stability is achieved by the rapid raising or lowering of total body water to compensate for changes in sodium intake and obligatory insensible and urinary water loss. These adjustments in body water content are made by overlapping hypothalamic osmostats that regulate thirst and secretion of the antidiuretic hormone arginine vasopressin (AVP) [2].

However, serum osmolarity is not only determined by serum sodium. Glucose and urea, which are often abnormal in CHF patients with other comorbidities, such as diabetes mellitus or chronic
kidney disease, are also involved. Moreover, a number of disorders are associated with systemic elevations in extracellular fluid osmolarity, including diabetes or inflammatory bowel disease [3], and recent studies have shown how higher osmolarity may contribute to acute and chronic inflammation [4].

In CHF, hypervolemic hyponatremia develops as a compensatory response to decreasing cardiac output and effective circulating volumes [5] that activate the release of AVP [6]. In patients with HF, the administration of vaptans, a class of competitive AVP-receptor antagonists, have been shown to increase overall plasma sodium levels, but they fail to improve long-term mortality or readmission rates. This effect could be related with a worse outcome in patients with higher serum osmolalities [7].

The aim of the present study was to identify differences in serum osmolarity among hospitalized CHF patients and to evaluate if high osmolarity is related with a worse outcome, irrespective of serum sodium levels.

2. Methods

Patients were recruited through the National Registry of Heart Failure (RICA), supported by the Heart Failure Working Group of the Spanish Society of Internal Medicine (SEMI-IC). The RICA Registry is an ongoing multicenter, prospective cohort study. Previous reports from RICA have recently been published [8]. This registry included consecutive unique patients with CHF, defined according to the criteria of the European Society of Cardiology [9], admitted to internal medicine wards of public and private hospitals in Spain between March 2008 and March 2013. They were enrolled at discharge after

Table 1
Baseline characteristics of patients according to serum osmolarity quartiles.

<table>
<thead>
<tr>
<th></th>
<th>Q1 (240.10–299.80 mOsm/kg)</th>
<th>Q2 (299.80–306.39 mOsm/kg)</th>
<th>Q3 (306.39–311.23 mOsm/kg)</th>
<th>Q4 (313.23–362.50 mOsm/kg)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>642</td>
<td>641</td>
<td>643</td>
<td>642</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>79.4 (72.9–84.5)</td>
<td>79.7 (73.6–84.5)</td>
<td>81.2 (75.5–85.3)</td>
<td>81.2 (75.6–85.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male (%)</td>
<td>302 (47%)</td>
<td>269 (46%)</td>
<td>321 (50%)</td>
<td>301 (47%)</td>
<td>0.527</td>
</tr>
<tr>
<td>Hypertension</td>
<td>524 (82%)</td>
<td>532 (83%)</td>
<td>564 (88%)</td>
<td>574 (89%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>251 (39%)</td>
<td>248 (39%)</td>
<td>323 (50%)</td>
<td>384 (60%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoke</td>
<td>249 (39%)</td>
<td>232 (36%)</td>
<td>257 (40%)</td>
<td>243 (38%)</td>
<td>0.558</td>
</tr>
<tr>
<td>Alcohol</td>
<td>154 (24%)</td>
<td>139 (22%)</td>
<td>138 (21%)</td>
<td>121 (19%)</td>
<td>0.169</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>301 (47%)</td>
<td>298 (46%)</td>
<td>322 (50%)</td>
<td>316 (51%)</td>
<td>0.298</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>361 (56%)</td>
<td>359 (56%)</td>
<td>362 (56%)</td>
<td>332 (52%)</td>
<td>0.273</td>
</tr>
<tr>
<td>Liver disease</td>
<td>69 (11%)</td>
<td>24 (3.7%)</td>
<td>33 (5.1%)</td>
<td>43 (6.7%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**CKD**
- No: 0 (0)
- eGFR > 60 ml/min: 374 (58%) 339 (53%) 246 (38%) 110 (17%) <0.001
- eGFR 30–59 ml/min: 235 (37%) 334 (52%) 344 (54%) <0.001
- eGFR < 30 ml/min: 53 (8%) 61 (9%) 188 (29%) <0.001

**Charlson index (points)**
- 2 (1–4): 3 (1–5) 1 (2–5) <0.001
- 1 (0–3): 1 (0–3) 1 (0–3) 0.214

**BMI (Kg/m2)**
- 22.4 (18.3–27.6): 28.3 (25.0–32.5) 28.5 (24.5–32.0) 0.304

**SBP (mm Hg)**
- 131 (119–151): 136 (120–154) 137 (120–156) 0.001

**DBP (mm Hg)**
- 71 (64–83): 75 (65–89) 72 (62–82) <0.001

**Hemoglobin (g/dl)**
- 12.2 (10.8–13.5): 12.0 (10.7–13.4) 11.5 (10.2–13.0) <0.001

**Creatinine (mg/dl)**
- 1.00 (0.80–1.30): 1.07 (0.89–1.32) 1.21 (0.95–1.60) 1.55 (1.22–2.60) <0.001

**Urea (mg/dl)**
- 45 (34–60): 52 (41–67) 52 (40–69) 92 (88–128) 0.001

**Sodium (mEq/l)**
- 135 (122–137): 139 (138–141) 141 (139–143) 142 (140–145) <0.001

**Glucose (mg/dl)**
- 4.3 (3.9–4.6): 4.3 (4.0–4.7) 4.4 (4.0–4.9) <0.001

**Uric acid (mg/dl)**
- 7.4 (5.7–9.0): 7.3 (5.9–9.2) 7.6 (6.6–9.3) 8.6 (7.0–10.1) <0.001

**BNP (pg/ml)**
- 622 (324–1,535): 685 (351–1,167) 821 (494–1,802) 0.304

**LVEF (%)**
- 54 (40–62): 55 (40–62) 55 (40–62) <0.001

**LVEF > 45**
- 438 (68%): 424 (66%) 443 (69%) 445 (69%) 0.625

**Atrial diameter (mm)**
- 48 (43–53): 48 (42–52) 47 (42–52) 0.179

**Estimated PASP (mm Hg)**
- 47 (35–55): 45 (35–55) 47 (40–58) 0.046

**Osmolarity (mOsm/kg)**
- 294 (290–298): 303 (302–305) 309 (308–311) 319 (316–323) <0.001

**NYHA**
- I: 60 (9.5%): 81 (13%) 62 (9.8%) 42 (6.7%) 0.004
- II: 346 (53%): 342 (54%) 339 (54%) 301 (48%) 0.062
- III: 206 (33%): 197 (31%) 213 (34%) 251 (40%) 0.005
- IV: 19 (3.0%): 14 (2.2%) 17 (2.7%) 33 (5.3%) 0.012

**Etiology of HF**
- Ischemic: 175 (27%): 153 (24%) 171 (27%) 181 (28%) 0.368
- Hypertensive: 121 (19%): 134 (21%) 85 (13%) 123 (19%) 0.002
- Valvular: 219 (34%): 225 (35%) 290 (45%) 246 (38%) <0.001
- Other: 127 (20%): 125 (20%) 94 (15%) 92 (14%) 0.007

**Medications at discharge**
- ACE inhibitors: 338 (53%): 342 (53%) 317 (49%) 271 (42%) <0.001
- ARBs: 194 (30%): 197 (31%) 223 (35%) 225 (35%) 0.128
- Beta-blocking agents: 421 (66%): 414 (65%) 437 (68%) 418 (65%) 0.592
- Loop diuretics: 599 (93%): 595 (93%) 607 (94%) 601 (94%) 0.706
- Thiazides: 97 (15%): 88 (14%) 74 (12%) 126 (20%) <0.001
- Aldosterone antagonists: 292 (45%): 247 (39%) 229 (36%) 211 (33%) <0.001

Qualitative data are shown as number (percentage) and quantitative data as median (interquartile range). ACE: angiotensin converting enzyme; ARBs: angiotensin II receptor blockers; BMI: body mass index; BNP: brain natriuretic peptide; CKD: chronic kidney disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; PASP: pulmonary arterial systolic pressure; and SBP: systolic blood pressure.
acute decompensated heart failure (ADHF), and followed up for 1 year, with visits at 3 and 12 months after inclusion. The Ethics Committee of the University Hospital “Reina Sofia”, Córdoba, Spain, approved the overall protocol. All patients signed an informed consent before being included in the cohort.

2.1. Data collection and follow-up

Upon admission, we obtained a comprehensive medical history and undertook a detailed physical examination. We tested comorbidity with the Charlson comorbidity index (CCI) [10], baseline functional status with the Barthel index (BI) [11], and cognitive status with the Pfeiffer questionnaire [12]. We recorded laboratory data (creatinine, urea, uric acid, glucose, sodium, potassium, BNP, and hemoglobin), complications during admission, and prescriptions at discharge. We excluded patients whose laboratory data were not complete, patients without echocardiographic examination, and patients who died during hospitalization. Patients with primary pulmonary hypertension, anticipated inability to undergo follow-up (impossible to program ambulatory follow-up or expected survival less than 3 months), and those who refused to participate in the study and did not sign the informed consent were also excluded.

Serum osmolarity was calculated using the following formula: OSM = 2(Na + K) + Glucose/18 + Urea/5.6. Patients were divided into four groups, on the basis of the distribution quartiles of osmolarity levels.

2.2. Endpoints

Primary endpoint was combined all-cause mortality and/or readmission due to CHF decompensation after 1 year of follow-up. The secondary endpoint was all-cause mortality. Additional prespecified outcomes included the number of days hospitalized during the first admission, and the presence of complications during this admission, such as worsening renal function (defined by elevated basal creatinine levels ≥ 2 mg/dl), hyperpotassemia (defined by elevated serum potassium ≥ 5.3 mEq/ml), pleural effusion, acute confusional state, need for blood transfusion or hemofiltration, or need for either isotropic or hypotensive drugs.

Treatment decisions, timing of discharge and medications at discharge were at the discretion of the attending physicians, who were aware of the ongoing registry.

2.3. Statistical analysis

Continuous variables were reported as median/interquartile range, as the data were not normally distributed, while categorical variables were presented as percentages of non-normality. Admission serum osmolarity was analyzed as a continuous variable, and also categorized into four discrete groups, according to the quartile distribution. Serum osmolarity was assessed as a continuous measure in all statistical tests. Patient characteristics, evidence-based treatments and clinical outcomes were compared using the discrete osmolarity groups. Univariate comparisons were made using Kruskal-Wallis tests for continuous variables, and Chi-square tests for categorical values.

Cox proportional hazard models were used to examine the association between osmolarity levels and time to all-cause mortality, readmissions for heart failure, and the combination of both. The model covariates were selected a priori (based on previous prognostic reports in patients with heart failure and clinical experience), either because of their prognostic relevance or their potential to confound the osmolarity-risk relationship. These included age, sex, history of hypertension, diabetes, or atrial fibrillation, estimated glomerular filtration rate (eGFR), Barthel index (BI), body mass index (BMI), hemoglobin, sodium, NYHA class, treatment with beta-blockers or anticoagulants, and osmolarity. Further stepwise variable selection was performed and a final model was generated.

Cumulative event curves were estimated by the Kaplan-Meier method and compared by log-rank testing. Analyses were performed using the SPSS program version 20.0 (SPSS, Inc., Chicago, Illinois).

3. Results

3.1. Baseline characteristics

A total of 2568 patients (47.46% men) were included. Table 1 shows baseline data according to serum osmolarity quartiles. The groups with higher osmolarity were older (p < 0.001), and had poor functional status (BI 90 points, p < 0.001), more comorbidity (CCI 3 points, p < 0.001), hypertension (p < 0.001), and diabetes mellitus (p < 0.001), and chronic kidney disease (CKD) defined by an estimated glomerular filtration rate (eGFR) < 60 ml/min (p < 0.001). We found significantly lower systolic blood pressure (SBP) in the groups with lower osmolarity, and significantly lower diastolic blood pressure (DBP) in groups 1 and 4 (the lowest and the highest osmolarity quartiles) (p < 0.001).

A significant positive association was found between osmolarity groups and glucose, urea, sodium and potassium levels (p < 0.001), as expected, and also with uric acid (p < 0.001) and creatinine (p < 0.001) levels, while the association with hemoglobin levels was negative (p < 0.001).

There were no differences between serum osmolarity groups with regard to left ventricular ejection fraction (LVEF). Pulmonary arterial systolic pressure was higher in the Q1 and Q4 groups (p < 0.046).

Finally, before admission, patients with higher osmolarity were receiving significantly more thiazides (p < 0.001), and significantly fewer aldosterone antagonists (p < 0.001) and ACE inhibitors (p < 0.001).

3.2. Complications during admission

More patients in the higher osmolarity groups (Q3 and Q4) had worsening kidney function (27% in group 4, p < 0.001) and hyperpotassemia (p < 0.001). However, the length of stay was longer in group 1 (8 days, p < 0.001). No differences between the groups were found in the rest of the variables (Table 2).

3.3. Endpoints

Median follow-up duration was 362.5 days. Rates of death among the osmolarity quartiles were 118 (18%), 114 (18%), 144 (22%) and 181 (28%), respectively, p < 0.001. We found a significant increase in the combined endpoint of mortality and readmission among the quartiles with higher osmolarity (p < 0.001). Figs. 1 and 2. Tables 3 and 4 show final regression models for osmolarity. For mortality, osmolarity showed a RR of 1.02 (95% CI 1.01–1.03, p < 0.001). Diabetes, eGFR, Barthel index, systolic blood pressure, body mass index, hemoglobin, NYHA class and beta-blocking agents were also independently associated with primary and secondary endpoints.

Table 2

| Clinical complications during admission, by serum osmolarity quartiles. |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Q1 (243.10–299.80 mOsm/Kg) | Q2 (299.80–306.39 mOsm/Kg) | Q3 (306.39–313.23 mOsm/Kg) | Q4 (313.23–362.50 mOsm/Kg) |
| Length of stay (days)       | 8 (5–13)                   | 7 (5–12)                   | 7 (5–10)                    | 7 (5–12)                   |
| Worsening renal function    | 3 (4.8%)                   | 32 (5.0%)                  | 69 (11%)                   | 173 (27%)                  |
| Hypopotassemia              | 22 (3.4%)                  | 15 (2.3%)                  | 24 (3.7%)                  | 44 (6.9%)                  |
| Need for vasoactive drugs   | 19 (3.0%)                  | 20 (3.1%)                  | 16 (2.5%)                  | 24 (3.7%)                  |
| Need for hypothermic drugs  | 43 (6.7%)                  | 50 (7.8%)                  | 52 (8.1%)                  | 44 (6.9%)                  |
| Need for ultrafiltration    | 3 (0.47%)                  | 0 (0.00%)                  | 1 (0.16%)                  | 3 (0.47%)                  |
| Acute confusional state     | 39 (6.1%)                  | 26 (4.1%)                  | 30 (4.7%)                  | 39 (6.1%)                  |
| Thromboembolic disease      | 5 (0.78%)                  | 2 (0.31%)                  | 5 (0.78%)                  | 4 (0.62%)                  |
| Pleural effusion            | • 325 (51%)                | 355 (56%)                  | 347 (54%)                  | 347 (54%)                  |
| • Unilateral                | 129 (20%)                  | 120 (19%)                  | 128 (20%)                  | 118 (18%)                  |
| • Bilateral                 | 325 (51%)                  | 355 (56%)                  | 347 (54%)                  | 347 (54%)                  |
4. Discussion

Our results show that in patients admitted for decompensated heart failure, high serum osmolarity is associated with 1-year mortality and HF readmissions, so this parameter could be a marker of patients’ comorbidity burden.

Although osmolarity emerged as an independent predictor of mortality, we found differences in the profile of our cohort of HF patients, depending on their osmolarity quartile. The analysis showed that the group with higher osmolarity was older, and had more comorbidities (especially diabetes mellitus and chronic kidney disease), and, consequently, higher levels of glucose, urea, creatinine, and potassium: all these findings could influence the higher rates of mortality and readmissions in this group. Nevertheless, our findings raise some questions.

Other studies published to date have identified low osmolarity as a strong risk factor for increased morbidity and mortality in patients with HF [13], but our findings did not confirm this hypothesis. Several rational hypotheses can be put forward to explain how high serum osmolarity negatively influences the prognosis of HF patients. Firstly, in healthy people, AVP secretion is sensitive to changes not only in the effective solute concentration of the extracellular fluid, mediated by receptors located in the hypothalamus, but also in intravascular volume, cardiac filling pressure, arterial pressure, and other parameters [14]. In patients with advanced heart failure and hyponatremia, AVP levels are elevated even during acute water overload [6,15], due to non-osmotic release, depending on the activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system. However, when serum osmolarity is higher, additional AVP seems to be secreted as consequence of osmotic stimuli. AVP itself has cardiovascular effects that can worsen heart failure, including hemodynamic and neurohormonal effects.

Secondly, higher serum osmolarity levels could influence redistribution of the venous reservoir. The change in oncotic pressure, as a consequence of higher serum osmolarity in the arterial system and in nonsplanchnic venous vessels, leads to mobilization of fluid from the venous capacitance vessels to the effective circulatory volume, determining an increase in preload, causing congestion even if body weight remains stable [16]. This increase in effective circulatory volume in the lungs could be reflected in an increase in pulmonary artery pressure, with no changes in body weight [17,18]. This would subsequently act as a trigger for increased pulmonary edema. Other authors have demonstrated this relationship between osmolarity and increased extravascular lung water index [19].

Finally, higher osmolarity could also affect renal function in different ways. On the one hand, the increase of vasopressin secretion may have a role in exacerbating chronic kidney disease [20]. In addition, hyperosmolarity can activate a variety of pathways, including the central sympathetic nervous system and the aldose reductase pathway, leading to local oxidative stress resulting in tubular injury and increased fibrosis [21].

Beyond these hypotheses, an increase in extracellular osmolarity damages cells by promoting water excretion, triggering shrinkage and intracellular dehydration that contribute to the onset and development of both local and systemic disorders [3,22].

Importantly, our findings could explain some controversial results that emerged from the treatment of heart failure with vaptans. In the EVEREST clinical trial, the administration of tolvaptan to patients with HF resulted in greater weight loss, but improved neither dyspnea nor survival [7]. Conivaptan was studied in a single-dose experience in patients with chronic stable HF, and showed reduced cardiac filling pressures [23]. However, pulmonary arterial systolic pressure did not change significantly, and the absence of changes in pulmonary capillary wedge pressure related to an increase in urine output has not been

![Fig. 1. Kaplan–Meier function for all-cause mortality and readmissions for HF, according to osmolarity quartiles.](image)

![Fig. 2. Kaplan–Meier function for all-cause mortality, according to osmolarity quartiles.](image)

Table 3
Final Cox multivariate regression model for mortality.

<table>
<thead>
<tr>
<th>Variables</th>
<th>RR</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>1.42</td>
<td>1.19–1.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR</td>
<td>0.99</td>
<td>0.99–1.00</td>
<td>0.001</td>
</tr>
<tr>
<td>Barthel Index</td>
<td>0.98</td>
<td>0.98–0.98</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP</td>
<td>0.99</td>
<td>0.99–1.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>0.95</td>
<td>0.91–0.96</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.95</td>
<td>0.91–0.99</td>
<td>0.017</td>
</tr>
<tr>
<td>Sodium</td>
<td>0.95</td>
<td>0.93–0.98</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA</td>
<td>0.95</td>
<td>0.93–0.98</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA I</td>
<td>1</td>
<td>(Ref.)</td>
<td></td>
</tr>
<tr>
<td>NYHA II</td>
<td>1.2</td>
<td>0.83–1.73</td>
<td>0.344</td>
</tr>
<tr>
<td>NYHA III</td>
<td>1.49</td>
<td>1.02–2.16</td>
<td>0.038</td>
</tr>
<tr>
<td>NYHA IV</td>
<td>1.86</td>
<td>1.12–3.10</td>
<td>0.017</td>
</tr>
<tr>
<td>Beta-blocking agents</td>
<td>0.64</td>
<td>0.54–0.76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Osmolarity</td>
<td>1.02</td>
<td>1.01–1.03</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BM1: body mass index; eGFR: estimated glomerular filtration rate; NYHA: New York Heart Association; and SBP: systolic blood pressure.
totally clarified [23]. These findings may be explained by the redistribution of fluids caused by increased serum osmolarity.

Limitations of this study include the use of opportunistic rather than random sampling of osmolarity groups, so hidden biases or inability to account for all factors related to osmolarity might have limited our multivariate approach. In addition, we enrolled hospitalized patients, so the results should be applied with caution to other populations. Only admission osmolarity was considered, so differential effects of persistent vs modified osmolarity could not be determined. Additionally, urine osmolarity was not measured, so its relationship with serum osmolarity vs modification osmolarity was considered, so differential effects of persistent results should be applied with caution to other populations. Only admission sampling of osmolarity groups, so hidden biases or inability to account for all factors related to osmolarity might have limited our multivariate approach.

In conclusion, high serum osmolarity in patients admitted for decompensated HF is an easily determined parameter that predicts a worse outcome and is associated with a higher comorbidity burden, making it a candidate for a new marker in HF. Further studies are necessary to clarify our findings.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Acknowledgements

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Appendix 1. Membership of RICA registry


References