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Hypochloraemia as a predictor of developing hyponatraemia and poor outcome in acute heart failure patients

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Abstract

Aims—Heart failure (HF) is a major public health issue currently affecting more than 23 million patients world-wide. Hyponatraemia has been shown to be a predictor of poor outcome in patients with acute and chronic HF. Therefore, we aimed at finding a marker for early detection of patients at risk for developing hyponatraemia. To this end, the present study investigated the relationship between initial serum chloride and follow-up sodium levels in acute heart failure (AHF) patients.

Methods and results—The present study was performed as a prospective, single-centre, observational research with a total of 152 hospitalised AHF patients. Compared to patients with initial normochloraemia, patients with initial hypochloraemia had a statistically significantly higher incidence of hyponatraemia after a 3-month follow-up [$P < 0.001$; odds ratio (OR) = 27.08, CI: 4.3–170.7]. A similar finding was obtained upon exclusion of patients with initial hyponatraemia with Fishers test [$P = 0.034$; odds ratio (OR) = 15.5, CI:1.7–140.6]. Binary logistic regression revealed a significantly increased in-hospital mortality in the hypochloraemic/normonatriaemic (OR = 4.08, CI 1.08–15.43, $P = 0.039$), but not in the hypochloraemic/

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Conflicts of interest

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hyponatraemic, normochloraemic/hyponatraemic or normonatriaemic/normochloraemic patients. Ejection fraction (EF) at admission was significantly higher in hypochloraemic/normonatriaemic, compared to normonatriaemic/normochloraemic patients, but similar to EF in both hypochloraemic/hyponatraemic and normochloraemic/hyponatraemic patients. The N-terminal precursor Brain Natriuretic Peptide (Nt-proBNP) levels at admission were significantly lower in hypochloraemic/normonatriaemic compared to hypochloraemic/hyponatraemic and normonatriaemic/normochloraemic patients, respectively.

Conclusion—The data show that initial low serum chloride concentration is predictive of developing hyponatraemia and associated with increased in-hospital mortality in AHF patients.

Keywords

Acute heart failure; Hyponatraemia; Hypochloraemia; Survival

1 Introduction

Due to longer life expectancy, heart failure (HF) has become a growing health issue currently affecting more than 23 million patients worldwide, and, consequently, emerging as the topic of many interesting and intriguing studies [1]. For the last ten years, it has been a well-known and established fact that hyponatraemia in chronic and AHF acute heart failure is a predictor of poor outcome [2–4]. Due to its importance, the level of serum sodium has been incorporated in predictive models for heart failure such as the Heart Failure Survival Score and the Seattle Heart Failure Model [5,6]. Hyponatraemia is not only a nemesis in heart failure, but also a predictor of poor outcome in pneumonia [7], cirrhosis [8,9] and neurological disorders [10]. The prevalence of dilutional (hypervolaemic) hyponatraemia, defined as a sodium value lower than 136 mmol/L, in AHF is 15–20% [3,11]. Numerous studies have shown that during HF exacerbation patients with hyponatraemia have higher in-hospital and post-discharge mortality, longer hospital stay and higher incidence of rehospitalisation due to recurrence of heart failure [2–4,12,13]. Interestingly, this indicator is independent of ejection fraction (EF) [2]. Understandably, researchers have directed their focus on finding an optimal treatment for correcting this independent prognostic indicator of morbidity and mortality in patients with AHF. Although one would presume, that the correction of sodium levels in AHF patients with hyponatraemia would benefit the patient, studies have shown the opposite [14]. Since 1992, several non-peptide vasopressin receptor antagonists (vaptans) have been developed in an attempt to treat hyponatraemia [15,16]. In Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) [11] and Effects of Oral Tolvaptan in Patients Hospitalised for Worsening Heart Failure (EVEREST) [17], studies performed on patients with AHF, vaptans did provide some clinical benefit in terms of the form of shorter hospital stay, but did not lower the incidence of total and cardiovascular mortality. Although it is still unknown whether hyponatraemia is just a marker or the core of the problem of poor outcome in patients with HF, one is certain: early detection of patients at risk for developing hyponatraemia could help to initiate earlier intervention and thereby reduce mortality in hyponatraemic AHF patients. Therefore, the present study investigated whether initial low serum chloride concentration is predictive of developing hyponatraemia in AHF patients.

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2 Methods

2.1 Study design and patients

The study was performed as a prospective, single-centre, observational research study including consecutive adult hospitalised AHF patients. The study was approved by the local Ethics Committee of the University Hospital Centre Sisters of Charity, Zagreb, Croatia (UHC SC). Written informed consent was obtained from each patient, and the investigation conformed with the principles outlined in the Declaration of Helsinki [18].

2.2 Data collection

In total, 152 patients were recruited from the Emergency Department of University Hospital Centre Sisters of Charity from November 2013 to February 2015. The patients were defined and categorised according to the European Society of Cardiology (ESC), the American College of Cardiology Foundation and the American Heart Association Guidelines (ACCF/AHA) classification for AHF, the initial values of chloride, the final clinical presentation and the EF. All patients were treated in accordance with the standard ESC guidelines for AHF [19]. Patients with renal replacement therapy, hepatic cirrhosis, malignancy, trauma, surgical diseases, pregnancy, patients younger than 18 years and those who had major systemic diseases were not included. For each patient, the collected data included: demographic profile, past medical history and vital signs and symptoms at admission. Blood samples for routine laboratory assays with blood gas analysis were obtained at admission. Electrocardiography, chest radiography and echocardiography were performed in the first 24 h of hospitalisation. Patients were followed up on the 2nd, 3rd and 7th days of hospitalisation, as well as 3 months post-hospitalisation. Follow-up included collecting data about vital signs, symptoms, daily diuresis, electrocardiography, serum electrolytes, creatinine, urea and blood gas analysis.

2.3 Laboratory assays

Whole blood samples were drawn by venepuncture, and blood analysis (including complete blood count, blood gas analysis, metabolic and electrolyte panel, urea nitrogen, creatinine, lipid profile, C-reactive protein, urinalysis and NT-proBNP) was done at the time of admission. Serum electrolyte, creatinine, urea, total plasma cholesterol, LDL cholesterol, HDL cholesterol and triglycerides were measured using a Beckman Coulter instrument AU 2700, 2007 (Brea, CA, US) and Architect c8000, Abbott 2013 (Chicago, IL, US). Total blood count was automatically counted by Coulter:Counter S plus junior (Coulter Electronics Limited, Luton, England). Nt-proBNP was determined by electrochemiluminescence immunoassay (ECLIA) with Elecsys e411 (Roche Diagnostics GmbH, Mannheim, Germany). The results were shown in pg/mL.

2.4 Statistical analysis

The type of distribution for quantitative data was assessed by the Kolmogorov–Smirnov test and according to the results, appropriate, mainly nonparametric, statistical tests were used. Quantitative data are presented by the median and interquartile ranges. Categorical variables are presented in absolute frequencies and related interests. The difference in quantitative

data between the groups was assessed by the Mann–Whitney U or Kruskal–Wallis tests for assessing data among more than three groups. The difference in categorical data was analysed by the χ^2 test. Spearman's coefficient of rank correlation was calculated for the difference between clinical features of patients. Binary logistic regression was used to assess the prediction of in-hospital and 3-month mortality. The differences were considered significant if the P value was <0.05. The statistical analysis was done with MedCalc statistical software for Windows, version 15.1 (MedCalc Software, Ostend, Belgium).

3 Results

From November 2013 to February 2015, a total of 152 patients were hospitalised for AHF, 52% of which were female. The median age was 77 years (70–82). 14% of the studied patients had hyponatraemia at admission. Worsening of chronic HF was present in the majority (69%) of the patients. The most frequently recorded comorbidities were hypertension (89.5%), metabolic syndrome (55.9%) and type 2 diabetes mellitus (51.7%). The patients' baseline characteristics are presented in Table 1. After a 3-month follow-up, 7 patients from 152 in our study were alive, but not reachable.

After a 3-month follow-up, out of the 11 patients with hypochloraemia at admission, 5 patients (45.5%) developed hyponatraemia, whereas out of 67 patients without hypochloraemia at admission, only 2 patients (3%) developed hyponatraemia (Table 2). X^2 test showed that hypochloraemia at admission and hyponatraemia after 3 months are statistically significantly associated ($P < 0.001$), with an odds ratio (OR) of 27.08 (95 CI: 4.3–170.7) (Table 2). To further investigate the relationship between sodium and chloride in normonatraemic patients, we excluded the initially hyponatraemic patients (19 patients, 13%) and calculated by Fisher exact test the chance to develop hyponatraemia, for the initially normochloraemic/normonatraemic as well as hypochloraemic/normonatraemic patients. While after a 3-month follow-up 2 patients (3.1%) out of 64 normochloraemic/normonatraemic patients developed hyponatraemia, out of 6 hypochloraemic/normonatraemic patients 2 patients (33.3%) developed hyponatraemia ($P = 0.034$, OR = 15.5; CI 1.7–140.6;) (Table 3).

Binary logistic regression of in-hospital outcome demonstrated that in contrast to hypochloraemic/hyponatraemic as well as normochloraemic/hyponatraemic patients, the patients hypochloraemic/normonatraemic at admission exhibited statistically significantly higher in-hospital mortality (OR 4.08, CI 1.08–15.43, $P = 0.039$) (Table 4).

Investigation of EF in various groups showed that EF was statistically significantly different only between hypochloraemic/normonatraemic and normochloraemic/normonatraemic patients (test and control groups) (Fig. 1). Next, we examined the differences in Nt-proBNP plasma concentrations. As shown in Fig. 2 the Nt-proBNP levels were significantly higher in hypochloraemic/hyponatraemic (median 17,527 pg/mL; IQR = 6081–39,045 pg/mL) compared to both hypochloraemic/normonatraemic (median = 5101 pg/mL; IQR = 1151–9965 pg/mL) and normonatraemic/normochloraemic patients (median = 9410,50 pg/mL; IQR = 3501–17,238 pg/mL). Moreover, the Nt-proBNP levels were significantly lower in hypochloraemic/normonatraemic (median = 5101 pg/mL; IQR = 1151–9965 pg/mL)

compared to normonatraemic/normochloraemic patients (median = 9410,50 pg/mL; IQR = 3501–17,238 pg/mL).

4 Discussion

During the 1990s, chloride was called the “queen of electrolytes “due to its role in the then relatively new approach to acid–base pathophysiology, the Stewart approach [20,21]. Although chloride was the first electrolyte in our bodies that could be quantified, its importance had always been overshadowed by other serum electrolytes like sodium, potassium and calcium. This was emphasised in an article written by Yunos et al. In 2010, when those authors searched PubMed for the term ‘hyperchloraemia’, it generated only 181 citations, while ‘hypernatraemia’ and ‘hypercalcaemia’ generated 2481 and 15,518 citations, respectively [22].

Searching the relevant literature related to AHF with hyponatraemia, we could not find results that included concentrations of chloride and their statistical interpretation. Nevertheless, we did find an article by Tani, Morimatsu, Takatsu and Morita [23], who investigated the incidence and prognostic value of hypochloraemia in critically ill patients. They found that patients hospitalised in ICU with hypochloraemia had statistically significantly greater in-hospital mortality and a longer hospital stay. While hyponatraemia was associated with hypochloraemic patients, remarkably, not all patients with hypochloraemia had hyponatraemia, as found in dilatational hypochloraemia [24]. Using the Stewart approach, the authors revealed that in all patients with alkalosis, the alkalosis was caused by hypochloraemia. This study showed that hyponatraemia is not always accompanied by hypochloraemia and that chloride, although undeniably involved in acid–base and sodium disorders, has its own physiology that has not been completely elucidated yet.

In the present study we examined whether chloride is relevant as a predictor for patients developing hyponatraemia in HF. The data showed that patients who were initially hypochloraemic had a 27-fold increased chance of developing hyponatraemia after 3 months. As one can argue that patients with low serum chloride develop hyponatraemia more frequently than patients without hypochloraemia, we selected only patients who had hypochloraemia with normal sodium levels at admission and compared that group with a group of patients who had normal levels of sodium and chloride. It turned out that after a 3-month follow-up, the patients in the hypochloraemic group with initially normal sodium levels also developed hyponatraemia more frequently than normochloraemic/normonatraemic group. The results show that chloride could be a predictor for increased incidence of hyponatraemia in AHF, opening a whole range of possibilities for physicians to react timely and favourably. In the article by Yoo et al., the outcome of patients after hospitalisation with improved hyponatraemia did not differ from the outcome in those with persistent hyponatraemia [25]. Lee et al. reported similar results showing no difference in mortality or rehospitalisation between patients with improved hyponatraemia during hospitalisation and those without [14]. According to these results, although hyponatraemia is a predictor of greater in-hospital and post-discharge mortality and rehospitalisation, short-term improvement of already evolved hyponatraemia seems to be ineffective in term of

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improving outcome. However, it is tempting to assume that the efficacy of therapeutic intervention might be improved if applied before the development of hyponatraemia.

In our study, in-hospital mortality was higher in the group with hypochloraemia and normal sodium, however we found no impact of hypochloraemia on 3-month mortality. We could argue that patients with hypochloraemia are obviously a high-risk group with higher short-term mortality and a long-term predisposition of developing hyponatraemia. Interestingly, compared to the control group of patients with both normal sodium and chloride levels, our test group, namely hypocloraemic patients with normonatraemia had lower initial Nt-proBNP plasma levels and higher EF, but a higher in-hospital mortality. Based on this observation it is tempting to speculate that the treatment with vaptans could be used in those patients to prevent hyponatraemia and thereby associated poor outcome.

To our knowledge, this is the first study that investigated the relationship between chloride- and sodium levels in HF. We propose a novel use of chloride as a predictor for the development of hyponatraemia and of poor outcome in patients with AHF.

4.1 Study strengths and limitations

The study strengths lie in a structured and uniformed protocol with well-defined data collection and statistical analysis. The subject has never been discussed and investigated so far. However, the overall sample size was modest in the term of studies with acute heart failure patients. The main problem lies in the inability of most patients to maintain a proper follow-up, due to the overall poor general condition of patients with HF.

5 Conclusion

Chloride, a long forgotten electrolyte, emerges as a possible predictor for the development of hyponatraemia in patients with AHF. The optimal window of opportunity to treat patients with HF would be before the onset of hyponatraemia. The present study shows that chloride could be a useful predictor for developing hyponatraemia and could therefore be used to start appropriate therapy early enough to prevent development of hyponatraemia and thereby associated complications and poor outcome. The main advantage of that chloride-status based diagnostics is its wide availability, practicability and low cost. Considering our modest sample size, further larger studies should be done to confirm our findings.

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Abbreviations

HF	heart failure
AHF	acute heart failure

NYHA	New York Heart Association
EF	ejection fraction
ESC	European Society of Cardiology
ACCF/AHA	American College of Cardiology Foundation/American Heart Association
NT-proBNP	N-terminal pro-Brain Natriuretic Peptide.

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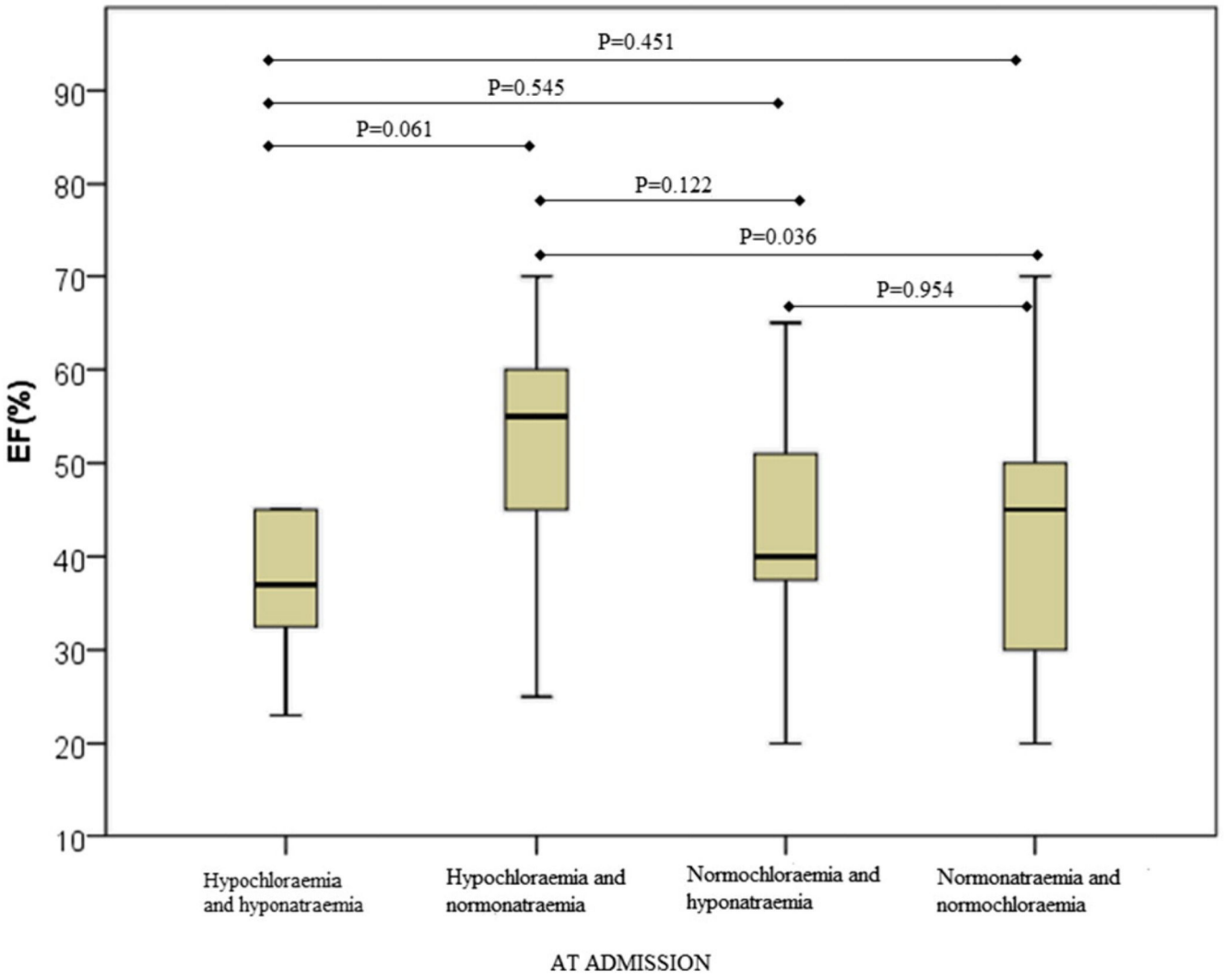

Fig. 1.

EF in AHF patients with different sodium/chloride status at admission. EF was measured by echocardiography and data analysed by post-hoc Mann–Whitney U test and shown with Box and Whiskers plots.

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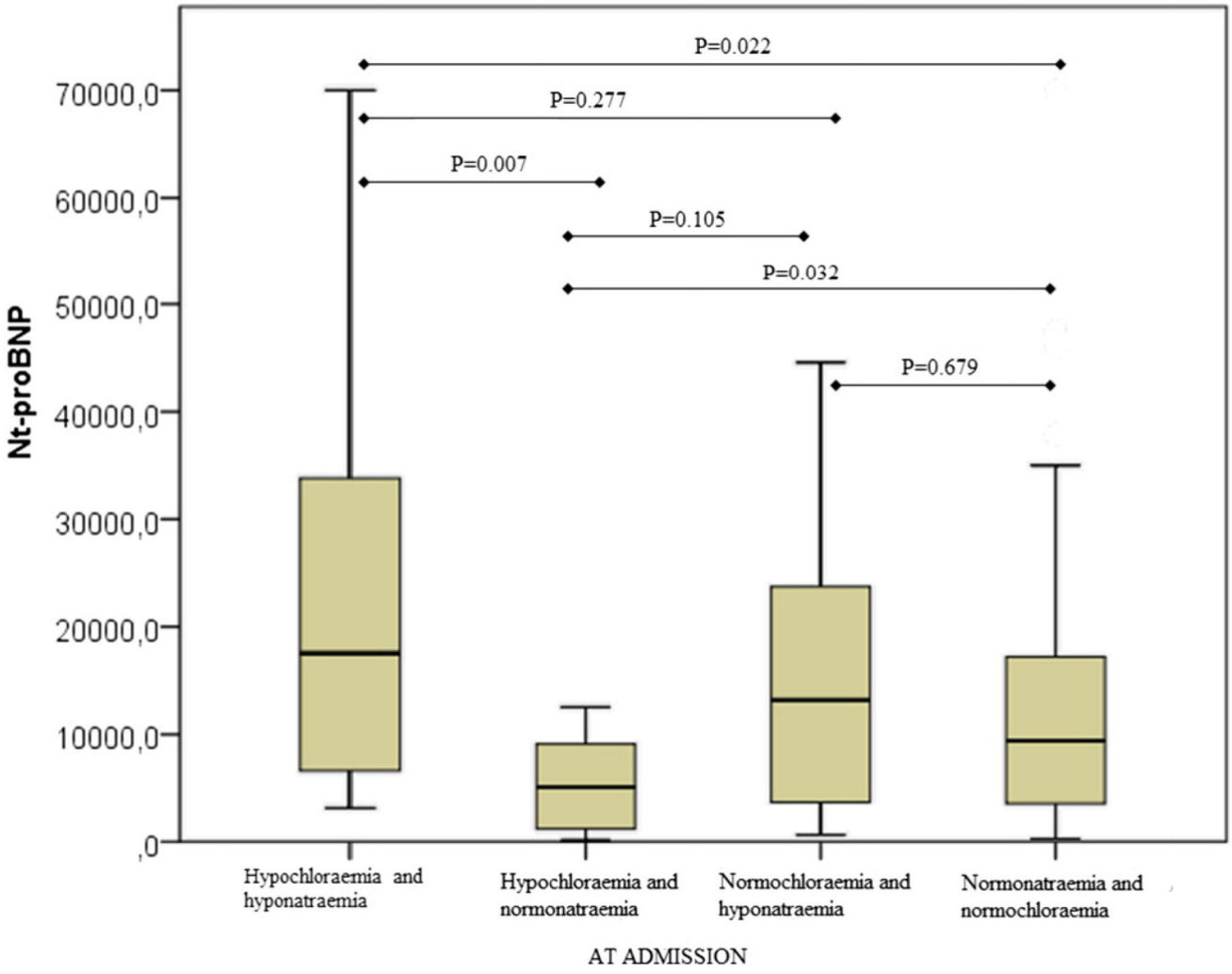

Fig. 2.

Nt-proBNP levels in AHF patients with different sodium/chloride status at admission. Nt-proBNP concentrations were measured by ECLIA and data analysed by post-hoc Mann–Whitney U test and shown with Box and Whiskers plots.

Table 1

Baseline characteristics, biochemical laboratory parameters, comorbidities, classification and outcome of AHF patients (n = 152).

Baseline characteristics		
Age (years)		77 (70–82)
Sex	Male	73 (48%)
	Female	79 (52%)
NYHA 2		11 (7.2%)
NYHA 3		83 (54.6%)
NYHA 4		58 (38.2%)
Classification of acute heart failure by time of onset		
Worsening of chronic heart failure		105 (69.1%)
De novo		47 (30.9%)
Classification of acute heart failure by Ejection Fraction *		
HFrEF		83 (57.6%)
HFpEF		61 (42.4%)
EF (%)		45 (35–55)
Outcome of hospitalisation		
Improvement		130 (85.5%)
Death	ICU	12 (7.9%)
	Ward	10 (6.6%)
Vital signs and symptoms on admission		
Systolic blood pressure (mmHg)		140 (120–160)
Diastolic blood pressure (mmHg)		80 (80-100)
Heart rate		100 (80–120)
Respiratory rate		28 (21–32)
Dyspnoea		143 (94.1%)
Peripheral oedema		82 (54.7%)
Syncope		8 (5.3%)
Biochemical laboratory parameters at admission		
Sodium (mmol/L)		140 (138–143)
Potassium (mmol/L)		4.4 (3.9–4.7)
Chloride (mmol/L)		104 (100–106)
Creatinine (μmol/L)		106 (87–138)
Blood urea nitrogen (mmol/L)		8 [6–13]
Nt-proBNP (pg/mL) **		9494 (3629–17,325)

AHF — Acute Heart Failure.
HFpEF — Heart Failure with preserved Ejection Fraction.
HFrEF — Heart Failure with reduced Ejection Fraction.
NYHA — New York Heart Association Functional Classification.
Nt-proBNP (pg/mL) - N-terminal pro-Brain Natriuretic Peptide.

*Based on measurements in 144 patients.

**Based on measurements in 147 patients.

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Table 2

Association between patients with initial hypochloraemia and 3-month hyponatraemia.

	Without hyponatraemia after 3 months	Hyponatraemia after 3 months	P	OR	95% CI
Without hypochloraemia at admission	65 (97.0%)	2 (3.0%)	< 0.001	27.1	4.3–170.7
Hypochloraemia at admission	6 (54.5%)	5 (45.5%)			

Association was calculated with X^2 test. OR = odds ratio; CI = confidence interval.

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Table 3

Association between initial hypochloraemia and 3-month hyponatraemia in initially normonatriaemic patients.[a]*

	Without hyponatraemia after 3 months *	Hyponatraemia after 3 months*	P	OR	95% CI
Without hypochloraemia with normonatraemia	62 (96.9%)	2 (3.1%)	0.034	15.5	1.7–140.6
Hypochloraemia with normonatraemia at admission	4 (66.6%)	2 (33.3%)			

Association was calculated with Fisher exact test. OR = odds ratio; CI = confidence interval.

[a]Without patients with initial hyponatraemia.

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Table 4
Association of in-hospital mortality with sodium/chloride status at admission.

	Death/Total (N)	OR	95% CI	P
Normonatraemia and normochloraemia (ref.)	13/119			0.130
Hypochloraemia and hyponatraemia	3/13	2.45	0.60–10.05	0.215
Hypochloraemia and normonatraemia	4/12	4.08	1.08–15.43	0.039
Normochloraemia and hyponatraemia	2/8	2.72	0.50–14.89	0.249

Association of in-hospital mortality was calculated with binary logistic regression. N = total number of patients in category; OR = odds ratio; CI = confidence interval.