**Title**

Hypochloraemia following admission to hospital with heart failure is common and associated with an increased risk of readmission or death: a report from OPERA-HF

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**Abstract (250 words)**

**Objective:** Hypochloraemia is common in patients hospitalised with heart failure (HF) and associated with a high risk of adverse outcomes during admission and following discharge. We assessed the significance of changes in serum chloride concentrations in relation to serum sodium and bicarbonate concentrations during admission in a cohort of 1,002 consecutive patients admitted with HF and enrolled into an observational study based at a single tertiary centre in the UK.

**Methods:** Hypochloraemia (<96 mmol/L), hyponatraemia (<135 mmol/L), and metabolic alkalosis (bicarbonate >32 mmol/L) were defined by local laboratory reference ranges. Outcomes assessed were all-cause mortality, all-cause mortality or all-cause re-admission, and all-cause mortality or heart failure re-admission. Cox regression and Kaplan Meier curves were used to investigate associations with outcome.

**Results:** During a median follow up of 856 days (interquartile range 272 - 1416), discharge hypochloraemia, regardless of serum sodium or bicarbonate levels, was associated with greater all-cause mortality (hazard ratio (HR) = 1.44 (95% confidence interval (CI) = 1.15 – 1.79); P=0.001), all-cause mortality or all-cause re-admission (HR = 1.26 (1.04 – 1.53); P=0.02), and all-cause mortality or heart failure re-admission (HR = 1.41 (1.14 – 1.74); P=0.002) after multivariable adjustment. Patients with concurrent hypo- chloraemia and natraemia had lower haemoglobin and haematocrit, suggesting congestion; those with hypochloraemia and normal sodium levels had more metabolic alkalosis, suggesting decongestion.

**Conclusion:** Hypochloraemia is common at discharge after a hospitalisation for HF and is associated with worse outcome subsequently. It is an easily measured clinical variables that is associated with morbidity or mortality of any cause.

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## Introduction

Low serum chloride concentrations are associated with higher plasma concentrations of natriuretic peptide, prescription of higher doses of loop diuretics and a high rate of cardiovascular hospitalisation and mortality in patients with either acute,[1-4] or chronic heart failure (HF).[5, 6] Evidence from both laboratory and clinical studies suggests that hypochloraemia may be associated with diuretic resistance,[2, 6, 7] renin-angiotensin-aldosterone activation,[6, 9] and sudden death in patients with HF.[5, 9] If hypochloraemia is somehow a driver of worse outcome in patients with HF it might also be a therapeutic target.

In a post hoc analysis of patients enrolled in the PROTECT trial, those with hypochloraemia that resolved by the time of discharge had a similar post-discharge prognosis as patients with normal chloride levels throughout admission; whereas incident hypochloraemia was associated with a greater risk of adverse outcome.[2] Conversely, post-hoc analysis of the ROSE-AHF trial found that changes in serum chloride were not associated with outcome.[3] However, patients enrolled in clinical trials are highly selected not only by the protocol's inclusion and exclusion criteria but also by investigator choice and by the nature of the patients who agree to participate.[8, 9]

Accordingly, we investigated the prognostic significance of serum chloride measured at admission and discharge in relation to serum sodium and bicarbonate concentrations a substantial cohort of consecutive admissions due to HF at a single tertiary centre in the UK.

## Methods

*Patient population*

OPERA-HF (An Observational registry to assess and PrEdict the in-patient course, risk of Re-Admission and mortality for patients hospitalized for or with Heart Failure) is a prospective observational study of consecutive patients admitted to hospital with heart failure at a single tertiary centre in the UK.

Patients were invited to participate if they were aged >18 years, lived in the region served by the local National Health Service trust, were hospitalised for HF, were treated with loop diuretics, and met at least one of the following criteria to confirm a diagnosis of HF: left ventricular ejection fraction (LVEF) $\leq$40%, left atrial diameter >4 cm, or N-terminal pro-B-type natriuretic peptide (NTproBNP) >400 ng/L for those in sinus rhythm (SR) or >1200 ng/L for those in atrial fibrillation (AF). Those unwilling or unable to give valid consent were excluded. Patients were enrolled between October 2012 and January 2017. Ethical approval was awarded by the South Yorkshire Research Ethics Committee (REC ref.: 12/YH/0344). The study was conducted in accordance with the Declaration of Helsinki.

Patients were enrolled on, or shortly after, admission. However, some patients were eventually diagnosed as having a primary diagnosis other than heart failure, and we thus only included those patients who had heart failure coded in the first position on the electronic record. Patients with missing values for serum chloride on admission **or** discharge were also excluded from the analysis.

Data on demographics, symptoms, bed-side observations, echo- and electro-cardiograms, haematology and biochemistry profiles, and N-terminal pro-B-type natriuretic peptide (NTproBNP) were collected on admission and blood results and bed-side observations on the

day of, or just before, discharge. The data underlying this article will be shared on reasonable request to the corresponding author.

Left ventricular ejection fraction (LVEF) was classified as normal (LVEF ≥50%), mildly reduced (LVEF 40-49%), or reduced (LVEF <40%). Outcome data were collected from the electronic hospital record. Outcomes assessed were all-cause mortality, all-cause mortality or first re-admission for any reason, and all-cause mortality or first re-admission for HF. For patients who died *after* being re-admitted, re-admission but not death was included in the composite outcomes.

Glomerular filtration rate was estimated using the Modification of Diet in Renal Disease (MDRD) formula.

*Statistical analysis*

Hypochloraemia (<96 mmol/L), hyponatraemia (<135 mmol/L), hypokalaemia (<3.5 mmol/L), hyperchloraemia (>109 mmol/L), hypernatraemia (>144 mmol/L), hyperkalaemia (>5.4 mmol/L) and metabolic alkalosis (bicarbonate >32 mmol/L) were defined by the reference ranges of the local laboratory. Worsening renal function (WRF) was defined as an increase in serum creatinine of >26.5 μmol/L between admission and discharge.[13] NTproBNP was measured at least once during admission for most patients (N = 854).

Patients were split into groups depending upon admission and discharge serum chloride concentrations, and by the presence or absence of hypochloraemia and/or hyponatraemia at the time of discharge (group 1 – normal sodium and chloride; group 2 – hyponatraemia and normal chloride; group 3 – normal sodium and hypochloraemia; group 4 – hyponatraemia and hypochloraemia). Very few patients had either hyperchloraemia or hypernatraemia on admission or discharge (hyperchloraemia N = 30 on admission and N = 10 on discharge;

hypernatraemia N = 5 on admission and N = 7 on discharge) and so were included in the "normal" groups.

Categorical data are presented as percentages, continuous data are presented as mean ± standard deviation for normally distributed data, and as median and interquartile range (IQR) for non-normally distributed data. Chi-squared tests were used to compare categorical variables and independent samples t-test was used to compare continuous variables across the groups. Mann-Witney U and Kruskal-Wallis tests were used to compare non-normally distributed continuous variables across the groups.

The relationship between admission chloride, discharge chloride and change in chloride (Δ chloride) and other variables was assessed by Pearson correlation coefficients. The relationship between incident hypochloraemia and other variables was investigated by uni- and multi-variable binary logistic regression amongst a subset of patients who had 1) normal chloride on admission; and 2) were hospitalised for 8-12 days (median length of stay 10 days +/- 2 days) to avoid confounding by prolonged admissions.

Associations between variables and outcome were assessed using Kaplan-Meier curves and two different Cox proportional hazard regression models which included all variables that were associated with outcome on univariable analysis $P<0.1$ (an arbitrary cut-off): 1) demographic variables plus admission variables; and 2) demographic variables plus discharge variables.

## Results

Of 1277 patients enrolled, 244 patients did not have a discharge diagnosis of HF, 31 had missing information of serum chloride, and 39 patients died during admission leaving 963 patients with complete data on discharge (table 1).

The prevalence of hypochloraemia was 15% on admission and 36% on discharge. The incidence of hypochloraemia during admission was 28% which account for 65% of all cases of hypochloraemia on discharge. One in five patients with hypochloraemia on admission had a normal chloride by discharge. Approximately half of patients had reduced LVEF.

### *Patients with hypochloraemia*

Compared to patients with normal chloride on discharge, those with hypochloraemia had a higher rate of worsening renal function, longer in-patient stays (P<0.001 for both), and were less likely to be prescribed an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), or beta-blocker on discharge (P=0.01 for both) (table 1). Patients with hypochloraemia were more likely to be taking a thiazide diuretic on discharge regardless of serum sodium concentrations, although the overall number of patients prescribed a thiazide diuretic was small (N=75) (tables 1 and 2).

Patients with hypochloraemia and normal serum sodium (group 3) on discharge had higher haemoglobin (P=0.04), haematocrit (P=0.001), mean cell volume (P=0.01), and serum bicarbonate (P<0.001) than those with hypochloraemia and hyponatraemia on discharge (group 4) (table 2). The haemoglobin, haematocrit, and MCV of those with hyponatraemia was similar regardless of chloride levels (group 2 and group 4) (table 2).

*Correlations with serum chloride*

Chloride on admission and discharge, and change in chloride correlated with serum sodium and bicarbonate (figure 1 A and B). NTproBNP was not correlated with either admission or discharge chloride.

On admission, 75% of patients with hypochloraemia were also hyponatraemic and 20% had metabolic alkalosis. On discharge, 66% of patients with hypochloraemia were hyponatraemic and 46% had metabolic alkalosis (figure 2).

During admission, both serum sodium and potassium regressed towards the mean, but chloride tended to decrease and bicarbonate tended to increase from admission to discharge (supplementary figure 1).

*Risk factors for incident hypochloraemia*

Among the 207 patients with normal chloride at admission and who were in hospital for between 8 and 12 days, 67 (32%) developed hypochloraemia by the time of discharge. The presence of diabetes, higher systolic blood pressure, lower serum sodium and chloride on admission, and worsening renal function during admission were associated with incident hypochloraemia ($P \leq 0.10$) (supplementary table 4). Admission chloride $\leq$100 mmol/L (hazard ratio (HR) = 2.79 (95% confidence interval (CI) 1.41 – 5.54); P=0.003) and worsening renal function (HR = 2.94 (95% CI = 1.31 – 6.60); P=0.03) were independently associated with incident hypochloraemia after multivariable adjustment.

*Outcome*

In the year following discharge, 249 patients died. Compared to those who survived, patients who died in the first year were older, more likely to be men, were more likely to have IHD, had a lower sodium on admission but not on discharge, had a lower chloride on admission and discharge, and were less likely to be taking a loop diuretic, ACEI or ARB, beta-blocker or MRA on discharge.

During a median follow up of 856 days (IQR 272 - 1416) 583 patients died, and a further 334 patients were hospitalised for any cause, of whom 224 were hospitalised for HF.

Lower chloride as a continuous variable on either admission (HR = 1.05 (95% CI = 1.02 – 1.08; $X^2$ = 8; P=0.004)) or discharge (HR = 1.04 (95% CI = 1.02 – 1.06); $X^2$ = 13; P<0.001) was associated with increased risk of all-cause mortality after multivariable adjustment. By contrast, serum chloride as a continuous variable was not a predictor of the combined end-points which included re-admission. Hypochloraemia at discharge as a categorical variable was, however, associated with an increased risk of the combined end-points of all-cause mortality or all-cause re-admission (HR = 1.26 (1.04 – 1.53); P=0.02), and all-cause mortality or heart failure re-admission (HR = 1.41 (1.16 – 1.78); P=0.001) (supplementary tables 1-3).

Patients with incident hypochloraemia at discharge had a greater risk of death compared to patients with normal chloride levels throughout admission (HR = 1.41 (1.16 – 1.70); P<0.001). By contrast, those with hypochloraemia on admission whose chloride returned to normal during admission were at no greater risk (HR = 1.09 (0.66 – 1.81); P=0.73) (figure 3) (supplementary table 5). Compared to those with normal sodium and chloride on discharge, those with hyponatraemia only were at no greater risk of mortality. In contrast, those with hypochloraemia, regardless of serum sodium, had an approximately 50% greater risk of death (figure 4).

Serum sodium and bicarbonate as continuous variables, and hyponatraemia (versus normal sodium levels) and metabolic alkalosis (versus normal bicarbonate levels) were not associated with outcome after multivariable adjustment. However, amongst those with normal chloride (groups 1 and 2) or hypochloraemia (groups 3 and 4), the proportion of patients who died during the first year was numerically greater amongst those with concurrent hyponatraemia or metabolic alkalosis. The greatest proportion of deaths during the first year occurred in patients with hypochloraemia, hyponatraemia **and** metabolic alkalosis (figure 5).

## Discussion

Previous reports on serum chloride concentration in patients with acute HF have included either highly selected trial populations,[2, 3] or only had short-term follow up.[2-4] We report, for the first time, the prognostic significance of hypochloraemia in a relatively unselected cohort of patients admitted to hospital for the treatment of HF with long-term follow up, including all-cause re-admissions. Similar to other reports, we found that hypochloraemia was common,[1-4] most often developing during the course of an admission,[2] was often associated with a metabolic alkalosis and, in multi-variable models that included serum sodium, was a strong and independent predictor of both re-admission and death.

### *Chloride and Sodium*

Our data supports the theory that patients with hypochloraemia may exist in two distinct phenotypes.[5] About two-thirds of in-patients with hypochloraemia have concurrent hyponatraemia and also have lower haemoglobin, haematocrit, mean cell volume (MCV) and bicarbonate, suggesting haemodilution and congestion. About one third have a normal serum sodium and a higher haemoglobin, haematocrit, MCV and bicarbonate, suggesting more effective decongestion due to administration of high doses of diuretics,[11] leading to a "contraction" metabolic alkalosis.[11,12] Patients with residual congestion at the time of discharge are known to have a worse outcome than those who are clinically euvolaemic.[13] However, hypochloraemia in the presence or absence of hyponatraemia had a similarly poor prognosis.

*Chloride and Bicarbonate*

Our analysis suggests that in-patient diuresis leading to hypochloraemia (+/- hyponatraemia) with a metabolic alkalosis is also associated with an increased risk of adverse outcomes. Diuretic use is associated with a rise in serum bicarbonate as plasma volume contracts.[12] In addition renal bicarbonate re-absorption is increased by neurohormonal activation,[14] by low serum potassium,[15] and by high urinary sodium.[16] Increased re-absorption of bicarbonate increases excretion of chloride ions.[17] Consistent with this, we found an inverse correlation between serum chloride and bicarbonate; most patients with a metabolic alkalosis also have hypochloraemia. There are many possible mechanisms by which hypochloraemia combined with a metabolic alkalosis might drive a worse prognosis in patients with HF,[7] including diuretic resistance and increased renin-angiotensin-aldosterone system activation.[2, 6] Treatments that reduce the risk of electrolyte abnormalities developing during diuresis may be useful. However, hypochloraemia is also associated with adverse outcomes in patients with non-cardiac diseases, many of whom do not take loop diuretics, including chronic kidney disease,[18] sepsis,[19] stroke,[20] and after non-cardiac surgery.[21] Hypochloraemia may thus be a marker of poor physiological status rather than just severe HF and administration of high doses of loop diuretics.

*Chloride and Outcome*

Over the last 30 years, the cumulative impact of improvements in treatment of many diseases has substantially delayed the average age of the onset of HF, whilst advances in treatment for HF have extended life thereafter, at least for those with HF with a reduced ejection fraction. Consequently, patients with HF are now, on average, much older, have a greater burden of co-morbidities,[22] and a greater risk of hospitalisation and death due to non-cardiovascular

causes.[23, 24] Failure to control congestion, leading to hospital admission, is a major driver of an adverse outcome in HF. Whilst severity of left ventricular systolic dysfunction did not seem to be related to outcome following an admission for heart failure, chloride certainly was. Similarly, NTproBNP was a strong predictor of mortality, but less so for re-admission.

Our data suggest that hypochloraemia is may be a stronger prognostic marker than age, LVEF or NTproBNP for predicting mortality or all-cause hospitalisation. Patients with hypochloraemia on discharge should perhaps be prioritised for more intensive management to reduce the risk of re-admission and, where appropriate, death.

We found that patients with hypochloraemia at presentation in whom serum chloride returned to normal before discharge had a similar prognosis to those with normal values throughout admission, as previously reported by others.[2] We found a lower rate of "recovered hypochloraemia" compared to patients enrolled in the PROTECT study (19% vs. 45%).[2] This may be because the time between chloride measurements and, therefore the time on focussed diuretic treatment, was shorter in our study (median length of stay 11 days for those with hypochloraemia on admission vs. 14 days in the PROTECT analysis – for patients in who hypochloraemia is due to haemodilution longer diuresis may increase the rate of recovery. Alternatively, patient selection may have influenced the different findings. Our data suggest that "recovered hypochloraemia" over the course of an admission is relatively rare with conventional existing therapy in largely unselected patients admitted with heart failure.

Acetazolamide is a carbonic anhydrase inhibitor which has been little used as a diuretic since the emergence of mercurial and loop diuretics in the 1960s. It increases natriuresis and diuresis when combined with loop diuretics in patients with acute heart failure.[28, 29] Acetazolamide increases urinary bicarbonate excretion, by inhibiting carbonic anhydrase in the renal tubule and proximal convoluted tubule (PCT), which increases chloride re-

absorption and may correct hypochloraemia.[7, 30] Acetazolamide may also prevent uptake of chloride from the blood into the cells of the PCT.[7] However, it may be better to use acetazolamide to prevent rather than correct hypochloraemia.[7, 30] The ADVOR trial, the largest trial of acetazolamide in patients hospitalised with HF to date, will assess the diuretic effect of acetazolamide. It might be, however, that acetazolamide is better used to maintain normal chloride concentrations, regardless of diuretic effect. Alternative strategies for the treatment of hypochloraemia include oral chloride supplementation: a proof-of-concept study in patients with chronic HF (N=10) found that large doses of lysine chloride (14 tablets or 7 grams of powder in a diluent of choice, three times per day) caused a small but significant rise in serum chloride concentrations (2.2 mmol/L; P=0.01) in stable out-patients without hypochloraemia.[6] Further work is ongoing (NCT03446651).

*Study limitations*

Although our cohort was enrolled prospectively, the limitations of post-hoc analyses apply to our study and confounding factors cannot be excluded. For example, although we had data on some medications given during admission such as the use of intravenous diuretics, nitrates and inotropic agents, we did not have data on dose or duration of loop diuretics. Similarly, we did not have sufficient data on symptoms or signs of congestion either on admission or discharge to include this in the final analysis. We also did not have more detailed echocardiographic assessment beyond classification of the severity of left ventricular systolic dysfunction in the majority of patients. The reason for hospital admissions were not adjudicated and were taken from the hospital electronic record. Additionally, we cannot exclude the possibility of missing outcome data on hospitalisations in patients who may have moved out of the region during follow up. We do not anticipate such a problem with

mortality outcomes as such data is linked on all electronic records throughout the NHS in the UK. As an observational study we are unable to comment on a causative link between low serum chloride levels and an adverse prognosis. Finally, not all patients who were invited to participate consented to do so. Thus, some selection bias cannot be excluded.

## Conclusion

Hypochloraemia, often linked with a metabolic alkalosis and hyponatraemia, commonly develops during the course of an admission for HF and may reflect intensification of diuretic therapy. Hypochloraemia predicts an adverse outcome, independent of serum sodium concentrations, age, renal function, LVEF and NT-proBNP. Normalisation of serum chloride, which might be increased by giving acetazolamide, is associated with a better prognosis. A randomized trial of acetazolamide is underway.

**Tables**

Table 1 – Patients with hypochloraemia on discharge

| Variable | Missing | All patients N = 963 | Normal chloride on discharge N = 619 | Hypochloraemia on discharge N = 344 | P |
|---|---|---|---|---|---|
| Chloride on admission – mmol/L | 0 | 101 (97 – 104) | 103 (100 – 105) | 98 (94 – 101) | <0.001 |
| Chloride on discharge – mmol/L | 0 | 97 (94 – 101) | 99 (98 – 102) | 92 (89 – 94) | - |
| ΔChloride – mmol/L | 0 | -3 (-7 – 0) | -2 (-5 – 0) | -6 (-10 - -2) | <0.001 |
| Hypochloraemia on admission – N (%) | 0 | 148 (15) | 28 (5) | 120 (35) | <0.001 |
| Hypochloraemia on discharge – N (%) | 0 | 344 (35) | - | - | - |
| **Demographics** | | | | | |
| Age – years | 0 | 75 (±13) | 74 (±13) | 75 (±12) | 0.39 |
| Sex – male | 0 | 581 (60) | 390 (63) | 191 (56) | 0.02 |
| Heart rate on admission – bpm | 6 | 86 (±24) | 87 (±25) | 83 (±22) | 0.05 |
| Systolic BP on admission – mmHg | 9 | 133 (±25) | 134 (±26) | 131 (±25) | 0.14 |
| Ischaemic heart disease – N (%) | 0 | 347 (36) | 217 (35) | 130 (38) | 0.40 |
| Diabetes mellitus – N (%) | | 349 (36) | 215 (35) | 134 (39) | 0.21 |
| Hypertension – N (%) | | 551 (57) | 360 (58) | 191 (56) | 0.46 |
| Chronic kidney disease – N (%) | | 226 (24) | 145 (23) | 81 (24) | 1.00 |
| Cancer – N (%) | | 121 (13) | 81 (13) | 40 (12) | 0.54 |
| Concurrent infection on admission – N (%) | | 184 (19) | 113 (18) | 71 (21) | 0.39 |
| Atrial fibrillation – N (%) | 136 | 436 (45) | 268 (43) | 168 (49) | 0.08 |
| Normal LVEF – N (%) | 43 | 253 (26) | 155 (25) | 98 (29) | 0.11 |
| Mildly reduced LVEF – N (%) | | 157 (16) | 101 (16) | 56 (16) | |
| Reduced LVEF – N (%) | | 517 (54) | 246 (56) | 171 (50) | |
| *LVEF <30% – N (% of whole group)* | | 353 (37) | 233(38) | 120 (35) | |
| **Blood results** | | | | | |
| NTproBNP – ng/L | 148 | 4742 (2018 – 10497) | 4347 (1960 – 10082) | 4937 (2108 – 11575) | 0.24 |

| | | | | | |
|---|---|---|---|---|---|
| Sodium on admission – mmol/L | 0 | 137 (134 – 139) | 138 (135 – 139) | 135 (132 – 136) | <0.001 |
| Sodium on discharge – mmol/L | 0 | 136 (133 – 138) | 137 (135 – 139) | 133 (130 – 136) | <0.001 |
| Urea on admission | 0 | 8.6 (6.2 – 12.5) | 8.5 (6.1 – 11.9) | 8.7 (6.4 – 13.3) | 0.04 |
| Urea on discharge | 3 | 9.7 (6.9 – 14.2) | 9.1 (6.4 – 12.9) | 11.2 (7.6 – 17.5) | <0.001 |
| Creatinine on admission - µmol/L | 0 | 104 (80 – 138) | 104 (83 – 137) | 102 (77 – 139) | 0.84 |
| Creatinine on discharge - µmol/L | 3 | 106 (84 – 142) | 104 (84 – 141) | 110 (84 – 151) | 0.13 |
| eGFR on admission – ml/min/1.73m$^2$ | 0 | 58 (41 – 76) | 58 (42 – 76) | 59 (38 – 78) | 0.54 |
| eGFR on discharge – ml/min/1.73m$^2$ | 3 | 54 (40 – 74) | 56 (40 – 74) | 53 (38 – 74) | 0.36 |
| Worsening renal function – N (%) | 3 | 167 (17) | 85 (14) | 82 (24) | <0.001 |
| **Medications on admission** | | | | | |
| Loop diuretic – N (%) | 0 | 498 (52) | 296 (48) | 202 (59) | 0.001 |
| ACEI or ARB – N (%) | | 490 (51) | 312 (50) | 178 (52) | 0.74 |
| Beta-blocker – N (%) | | 487 (51) | 303 (49) | 184 (54) | 0.18 |
| MRA – N (%) | | 158 (16) | 100 (16) | 58 (17) | 0.79 |
| Thiazide diuretic – N (%) | | 104 (11) | 38 (8) | 37 (17) | 0.001 |
| **Medications on discharge** | | | | | |
| Loop diuretic – N (%) | 0 | 907 (94) | 577 (93) | 330 (96) | 0.09 |
| ACEI or ARB – N (%) | | 695 (72) | 465 (75) | 230 (67) | 0.01 |
| Beta-blocker – N (%) | | 747 (78) | 496 (80) | 251 (73) | 0.01 |
| MRA – N (%) | | 475 (49) | 291 (47) | 184 (54) | 0.06 |
| Thiazide diuretic – N (%) | | 75 (8) | 29 (5) | 75 (22) | <0.001 |
| **Outcome** | | | | | |
| Length of stay – days | 0 | 10 (6 – 16) | 9 (5 – 15) | 12 (8 – 19) | <0.001 |
| 1 year all-cause mortality – N (%) | 0 | 250 (26) | 136 (22) | 114 (33) | <0.001 |

Abbreviations used: N – number; LVEF – left ventricular ejection fraction; LVSD – left ventricular systolic dysfunction; NTproBNP – N-terminal pro-B-type natriuretic peptide; ACEI – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker.

Table 2 – Patients with hypochloraemia and / or hyponatraemia on discharge

| **Variable** | **Patients who survived to discharge N = 963** | | | | **P** |
|---|---|---|---|---|---|
| | **Normal Sodium Normal Chloride** | **Hyponatraemia Normal Chloride** | **Normal Sodium Hypochloraemia** | **Hyponatraemia Hypochloraemia** | |

| | **N = 478** | **N = 141** | **N = 116** | **N = 227** | |
|---|---|---|---|---|---|
| Sodium on discharge – mmol/L | 138 (136 – 139) | 133 (132 – 134) | 137 (136 – 138) | 132 (129 – 133) | - |
| Chloride on discharge – mmol/L | 100 (98 – 103) | 98 (97 – 99) | 93 (91 – 95) | 92 (88 – 94) | - |
| **Demographics** | | | | | |
| Age – years | 75 (±13) | 74 (±14) | 74 (±12) | 76 (±12) | 0.27 |
| Sex (male) – N (%) | 174 (37) | 55 (39) | 57 (49) | 96 (42) | 0.07 |
| Heart rate on admission – bpm | 86 (±25) | 88 (±24) | 85 (±23) | 83 (±22) | 0.18 |
| Systolic BP on admission – mmHg | 135 (±26) | 129 (±25) | 131 (±23) | 131 (±26) | 0.03 |
| Ischaemic Heart Disease – N (%) | 161 (34) | 56 (40) | 42 936) | 88 (39) | 0.47 |
| Diabetes Mellitus – N (%) | 168 (35) | 46 (33) | 45 (39) | 89 (39) | 0.55 |
| Hypertension – N (%) | 284 (60) | 76 (54) | 60 (52) | 131 (58) | 0.37 |
| Chronic Kidney Disease – N (%) | 115 (24) | 30 (21) | 26 (22) | 55 (24) | 0.89 |
| Cancer – N (%) | 59 (12) | 22 (16) | 8 (7) | 32 (14) | 0.17 |
| Concurrent infection on admission – N (%) | 86 (18) | 27 (19) | 25 (22) | 46 (20) | 0.81 |
| Atrial fibrillation – N (%) | 219 (46) | 49 (35) | 68 (59) | 100 (44) | 0.01 |
| Normal LVEF – N (%) | 128 (28) | 27 (20) | 39 (35) | 59 (28) | 0.16 |
| Mildly reduced LVEF - N (%) | 81 (17) | 20 (15) | 21 (19) | 35 (16) | |
| Reduced LVEF – N (%) | 256 (54) | 90 (64) | 51 (44) | 120 (53) | |
| *LVEF <30% – N (% of whole group)* | 117 (25) | 46 (33) | 21 (19) | 62 (29) | |
| **Discharge blood results** | | | | | |
| NTproBNP – ng/L | 4236 (1941 – 9688) | 5600 (2359 – 11931) | 4266 (1932 – 10220) | 5097 (2169 – 11412) | 0.41 |
| Haemoglobin – g/L | 122 (109 – 137) | 120 (104 – 139) | 128 (115 – 148) | 122 (108 – 136) | 0.04 |
| MCV – fL | 88 (85 – 92) | 87 (84 – 90) | 91 (86 – 96) | 86 (82 – 92) | 0.01 |
| Haematocrit - fraction | 0.38 (0.34 – 0.41) | 0.36 (0.32 – 0.41) | 0.39 (0.35 – 0.45) | 0.37 (0.33 – 0.41) | 0.001 |
| Potassium – mmol/L | 4.2 (3.8 – 4.5) | 4.5 (4.1 – 4.8) | 4.1 (3.7 – 4.4) | 4.2 (3.8 – 4.5) | 0.002 |
| *Hypokalaemia – N (%)* | 24 (5) | 4 (3) | 11 (10) | 21 (9) | 0.03 |
| Bicarbonate – mmol/L | 29 (26 – 32) | 27 (25 – 29) | 35 (32 – 39) | 30 (28 – 34) | <0.001 |
| *Metabolic alkalosis – N (%)* | 86 (18) | 1 (1) | 86 (74) | 73 (32) | <0.001 |
| Urea – mmol/L | 9.0 (6.4 – 12.9) | 9.6 (6.5 – 13.1) | 11.1 (7.9 – 16.7) | 11.4 (7.5 – 18.2) | 0.001 |
| Creatinine – µmol/L | 103 (85 – 139) | 108 (81 – 144) | 107 (82 – 149) | 110 (87 – 154) | 0.40 |
| eGFR – ml/min/1.73m$^2$ | 56 (41 – 74) | 56 (39 – 74) | 54 940 – 77) | 52 (36 – 73) | 0.83 |

| | | | | | |
|---|---|---|---|---|---|
| Worsening renal function – N (%) | 63 (13) | 22 (16) | 26 (22) | 56 (25) | 0.001 |
| Albumin – g/dL | 33 (30 – 36) | 32 (28 – 36) | 32 (28 – 35) | 32 (29 – 35) | 0.32 |
| **Medications on discharge** | | | | | |
| Loop diuretic – N (%) | 450 (94) | 126 (89) | 115 (99) | 215 (94) | 0.01 |
| ACEI or ARB – N (%) | 357 (75) | 107 (76) | 75 (65) | 155 (68) | 0.04 |
| Beta-blocker – N (%) | 376 (79) | 119 (84) | 86 (74) | 165 (72) | 0.04 |
| MRA – N (%) | 220 (46) | 71 (50) | 54 (47) | 130 (57) | 0.05 |
| Thiazide diuretic – N (%) | 21 (4) | 8 (6) | 28 (24) | 47 (21) | <0.001 |
| **Outcome** | | | | | |
| Length of stay | 8 (5 – 14) | 11 (7 – 18) | 10 (7 – 19) | 13 (8 – 20) | <0.001 |
| 1 year all-cause mortality | 97 (20) | 39 (28) | 37 (32) | 76 (34) | <0.001 |

**Legend**

Abbreviations used – LVSF – left ventricular systolic function; LVSD – left ventricular systolic dysfunction; NTproBNP – N-terminal pro-B-type natriuretic peptide; MCV – mean cell volume; eGFR – estimated glomerular filtration rate; ACEI – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; MRA – mineralocorticoid receptor antagonist; N – number.

## Figure Legends

### Figure 1

Title: Correlation matrices for variables associated with chloride or change in chloride.

Caption: Matrix A – correlations with admission (top line) and discharge (bottom line) variables. Matrix B – correlations with change in chloride between admission and discharge. Grey boxes represent a non significant association (P>0.05). Abbreviations used: NTproBNP – N-terminal pro-B-type natriuretic peptide.

### Figure 2

Title: Venn diagrams of patients with hypochloraemia, hyponatraemia, and metabolic alkalosis on admission and discharge.

Caption: Hypochloraemia was defined as <96 mmol/L, hyponatraemia was defined as <135 mmol/L, and metabolic alkalosis was defined as $HCO_3^-$ >32 mmol/L. Abbreviations used: N – number.

### Figure 3

Title: Survival by chloride status on discharge

Caption: Kaplan Meier curves for all-cause mortality depending upon change in chloride levels from admission to discharge. Univariable hazard ratios for the different groups also included. Abbreviations used: CI – confidence interval. † - median value on discharge.

### Figure 4

Title: Survival by presence or absence of hyponatraemia and / or hypochloraemia on discharge

Caption: Kaplan Meier curves for all-cause mortality depending upon the presence of hypochloraemia and/or hyponatraemia. Univariable hazard ratios for the different groups also included. Abbreviations used: CI – confidence interval. † - median value on discharge.

**Figure 5**

Title: 1 year survival by the presence or absence of hypochloraemia, hyponatraemia or metabolic alkalosis.

Caption: 1 year mortality rate by the presence or absence of metabolic alkalosis within each group. N patients in group 2 with metabolic alkalosis = 1. Numbers and percentages below each group name on the bar chart represent the number in each group as a proportion of the total number of patients alive on discharge (N=963). Group 1 – normal sodium and chloride levels; group 2 – hyponatraemia and normal chloride levels; group 3 – normal sodium levels and hypochloraemia; group 4 – hyponatraemia and hypochloraemia.

**Supplementary Figure 1**

Title: Bland-Altman plots of sodium, potassium, chloride and bicarbonate measured on admission and discharge

Caption: Vertical lines represent cut-offs for different electrolyte abnormalities (hyponatraemia <135 mmol/L; hypokalaemia <3.5 mmol/L; hyperkalaemia >5.4 mmol/L; hypochloraemia <96 mmol/L; metabolic alkalosis >32 mmol/L). Horizontal red dotted line indicates mean change in electrolyte level.

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