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# A CROSS-SECTIONAL STUDY OF HYPONATRAEMIA AMONG ELDERLY PATIENTS WITH HEART FAILURE IN UGANDA

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**ABSTRACT**

**Objectives:**

1. To determine the prevalence of hyponatraemia among patients aged sixty years and above with heart failure attending Mulago National Referral Hospital.

2. To describe the factors associated with hyponatraemia among patients aged 60 years and above with heart failure attending Mulago National Referral Hospital.

**Setting:** The study was conducted in a tertiary hospital located northeast of Kampala, Uganda.

**Participants:** 211 older adults aged sixty years and above with a clinical diagnosis of heart failure using Framingham's criteria were consecutively recruited into the study. The patients who could not follow the study procedures were excluded.

**Results:** The prevalence of hyponatraemia was 24.2% (51/211) found mainly in patients with mild to moderate heart failure New York Heart Association classes 2 and 3. Of this 27/51(52.9%) had mild hyponatraemia, while 24/51(47.1%) had moderate to severe hyponatraemia of 130-125mmol/l.

History of vomiting (OR=2.94, 95% CI 1.29-6.70, p= 0.010) and use of loop diuretics (OR=2.71, 95% CI 1.13-6.52, p= 0.026) were identified as independent factors associated with hyponatraemia among older patients with heart failure.

**Conclusion:**

Our study revealed a relatively high prevalence of hyponatraemia among older patients with mild to moderate heart failure. Patients presenting with a history of vomiting from any cause or use of loop diuretics are more likely to have hyponatraemia. Further research should be carried out to determine at what dose and duration of loop diuretics hyponatraemia develops.

**Strengths and limitations:**

- We believe that our results can be generalized to similar settings in other countries in sub-Saharan Africa.
- Our study was cross-sectional and so causal relationships cannot be established.

- The sample size was small for assessing factors associated with hyponatraemia and weak associations may have been missed.

- Blood pressure measurements were taken only once and so patients may have been misclassified as having hypertension.

**INTRODUCTION**

Heart failure is becoming more common in sub-Saharan Africa because of the epidemiologic transition to non-communicable diseases and increasing numbers of older people. The population of people aged 60 years of age and over is increasing in Uganda(1).Heart failure is a common health problem among older people in Uganda and Africa mainly because of Dilated cardiomyopathy, rheumatic heart disease and hypertension(2).The prevalence of heart failure, (n= 30/141,21.3%) was highest among patients aged 60-69 years in a study done in Uganda by Achadu, 2002 (unpublished). Older people are particularly sensitive to the development of various electrolyte abnormalities, especially hyponatraemia, which is a serum sodium level below 135mmol/L (3, 4).Serum sodium falls by about 1mmol/l with each decade increase in age (5).  Globally, 18-27% of all patients admitted to hospital with heart failure have hyponatraemia (6, 7).Because heart failure involves fluid retention in the body, it may lead to dilution hyponatraemia.  In heart failure, diuretics normally are used to induce negative balance of sodium. The cause of hyponatraemia is the benefit of effective hypovolemia and (for thiazides) alteration of dilution of the urine. When fatal, hyponatraemia is symptomatic and may result from treatment challenges of too fast correction of the low sodium level(4, 8-10).Hyponatraemia is a potent predictor of poor outcome among older in-patients with heart failure (11). There is little understanding of the burden of disease due to heart failure in sub-Saharan African, nor its causes and related complications.  To our knowledge the prevalence and factors associated with hyponatraemia among older adults have not been well studied in Uganda or any other sub-Saharan African countries. The patients present later, with severe symptoms. The difference in the genetic make- up may contribute to the differences in the response to the anti-hypertensive drugs, including diuretics. In Uganda, we commonly use Furosemide as the main loop diuretic therefore we did not analyze the difference among the different loop diuretics.

## MATERIALS AND METHODS

We conducted a cross-sectional study between August 2013 and March 2014 of the prevalence of, and factors associated with, hyponatraemia among patients aged 60 years and above with heart failure. We consecutively recruited 211 patients with predominately acute decompensated heart failure from the cardiac clinics and wards of Mulago National Referral Hospital and Uganda Heart Institute. Both study sites are within the same location in the Northeast of Kampala, the capital city of Uganda. Mulago National Referral Hospital is a public hospital offering services at no cost and has the largest bed capacity in the country with about 1500 beds. The Uganda Heart Institute is an autonomous institution that offers private services to both adult and child patients with heart conditions. It has a bed capacity of about 40 beds. Patients were eligible for inclusion if they were: aged 60 years and above with a clinical diagnosis of heart failure using Framingham criteria(12).

We ascertained the socio-demographic characteristics of the patients with a written questionnaire completed by the principal investigator or research assistant. The patients were specifically asked if their doctor had ever told them that they had diabetes mellitus, stroke, chronic kidney disease or hypertension. The carer was asked of any recent behavior changes in the patient and the history of current or previous medication the patient was taking. A physical examination was done to ascertain the weight, height, presence of pallor, oedema, hepatomegaly, raised jugular venous pressure, rales, gallop rhythm and the level of consciousness (mental alteration) using the Glasgow Coma scale. The blood pressure of the patients was taken using a manual sphygmomanometer in either lying or sitting position depending on the functional status of the patient. Hypertension was defined as systolic blood pressure above 140mmHg and diastolic blood pressure above 90mmHg.

Patients who met the study inclusion criteria were requested to have overnight fasting for at least eight hours. Two milliliters of venous blood were withdrawn the next morning for measurement of sodium, chloride, potassium, sugar, lipids, creatinine and urea. The blood samples were centrifuged then mounted into the Cobas Integra 400 plus machine manufactured by Roche and analyzed the same day in an accredited laboratory. A urine sample was collected at the same time as the blood for measurement of sodium, potassium, chloride; renal function test and analyzed mainly using the same machine as for the blood in the same laboratory. The plasma and urine osmolality were calculated from the values obtained using the following formula; calculated osmolality = 2 Na+ (serum/urine) + Glucose

(blood/urine) + Urea (all in mmol/l).Glomerular filtration rate, GFR (ml/min per 1.73m²) was calculated using Cockcroft-Gault formula: eGFR = (140- Age) x weight (kilogram) x 0.85 (in females) / serum creatinine (mg/dl) x 72. Chronic kidney disease was classified as; stage 1 >90, stage 2 60-89, stage 3 30-59, stage 4 15-29 and stage 5 <15 depending on the GFR.

**Statistical analysis**

We determined the prevalence of hyponatraemia using frequency analysis. We performed multivariate logistic regression analysis to study associations between predefined risk factors and hyponatraemia. All analyses were done using STATA version 12.0. Variables with a p-value less than 0.05 were considered statistically significant.

The study was reviewed and approved by the Institution Research Board (IRB) school of Medicine Makerere University College of Health Sciences. Patients or /carers gave written informed consent to participate in the study. If a patient was found to have hyponatraemia, his/her clinician was informed and the patient was managed appropriately.

**RESULTS**

Among the 211 patients in the study (n=51, 24.2%) had hyponatraemia of serum sodium below 135mmol/l. At a serum level of 130mmol/L and below, the prevalence of hyponatraemia was 11.0% and at a serum sodium level below 125mmol/L (severe hyponatraemia), the prevalence of hyponatraemia was 5.7%. Of these 51 patients with hyponatraemia, more than half had mild hyponatraemia (n= 27, 52.9%).  Nineteen (70.4%) of the patients with hyponatraemia had a normal body mass index.

The socio- demographic and clinical characteristics of the patients are shown in Table 1.The largest group of patients was aged 60-69 years (40.3%). The median (IQR) age of the patients was 70.0 (65- 77) years, with the oldest patient being 102years. Less than half of the study patients were males (n= 81/211, 38.4%). Most patients had been previously hospitalized for heart failure (n= 148, 70.1%) they presented with worsening symptoms and (n=63, 29.9%) of the patients had been newly diagnosed with heart failure with symptoms for less than a month. More than half, (n=134, 63.5%), of the patients were New York Heart Association (NYHA) class 2. The patients mainly with hyponatraemia (n=47/51, 92.2%) were NYHA classes 2 and 3 which are mild - moderate heart failure  as shown in Table 1. Few of the patients, (n= 52/211, 24.6%), had smoked tobacco and (n=90, 42.7%) consumed alcohol either occasionally. Very few patients presented with clinical characteristics suggestive of hyponatraemia such as seizures (n=4, 1.9%), falls (n=16, 7.6%), abnormal behavior (n=9, 4.3%), altered mentation (n=26, 12.3%) and vomiting (n=39, 18.5%) as shown in Table 1.Of the thirty nine patients who presented with vomiting, sixteen (n=16/51, 31.4%) had hypovolaemic hyponatraemia and 68.6% with dilutional hyponatraemia. The majority, (n= 118/211, 55.9%); of the study patients had been known to have hypertension and a small minority known chronic kidney disease (n=7, 3.3%) as shown in Table 1. More than three quarters of the patients were using medicines (n= 165, 78.2%), with the majority using loop diuretics (n=134, 81.2%) and (40/134, 29.9%) of these patients using loop diuretics had hyponatraemia.  Out of the 211 study patients, only (n=2, 1.3%) used psychotropic drugs (Amitriptyline and Carbamazepine). More than three quarters of the patients, (n=192, 91.0%), added salt onto their food and, of these; (n= 43/192, 22.4%) had hyponatraemia.

 Forty three (93.5%); of the patients with hyponatraemia were losing sodium in their urine; all study patients had normal spot urine osmolality. As shown in Table 2, according to the calculated Glomerular Filtration Rate (n=98/157, 62.4%) patients had chronic kidney disease

with (n=16/28, 57.1%) with hyponatraemia and (n=82, 64%) normal sodium. Many (n=11, 39.3%) of the patients with hyponatraemia had stage 3 kidney disease. In total, (n=114, 54.0%) of the study patients had high calculated plasma osmolality, but; only (n=4, 8.7%) of these had hyponatraemia. The minority of patients had high fasting blood sugar; (n=46, 21.8%) and only one had high triglycerides.

The statistically significant factors associated with hyponatraemia were use of loop diuretics (OR=2.51, 95% CI 1.20-5.26, p= 0.01), vomiting (OR=2.72, 95% CI 1.30-5.70, p= 0.01), falls (OR= 3.53, 95% CI 1.25-9.97, p= 0.02), abnormal behavior (OR= 6.98, 95% CI 1.68-29.01, p= 0.01) and altered mentation (OR= 3.21, 95% CI 1.37-7.49, p= 0.01) as shown in Table 2. High blood pressure was associated with a decrease in odds of hyponatraemia (OR=0.47, 95% CI 0.24-0.91, p= 0.03).

In multivariate analysis, only vomiting (OR= 2.94, 95% CI 1.29-6.70, p= 0.010) and taking loop diuretics (OR =2.71, 95% CI 1.13-6.52, p= 0.026) were found to be statistically significantly associated with hyponatraemia (see Table 3). There was also a suggestion (p=0.077) that high blood pressure was inversely associated with hyponatraemia (OR= 0.51, 95% CI 0.25-1.07).

**DISCUSSION**

During the previous decades, heart failure was an uncommon condition among older people in sub-Saharan Africa because of low life expectancy and low prevalence of non-communicable diseases. Now life expectancy has improved with more people living longer than 60 years of age. We were, therefore, able to collect a big sample size of 211 older patients with heart failure in one hospital in a short period of seven months.

The results of our study in Uganda show relatively a high prevalence of hyponatraemia (24.2%) among patients aged 60 years and above with mainly mild to moderate heart failure NYHA classes 2 and 3. This finding is different from previous studies done in developed countries where hospitalized elderly patients had a much lower prevalence of hyponatraemia ranging from 7 to 12% (8, 13). Hyponatraemia is a marker of heart failure severity, this was a similar finding from our study (14). To our knowledge there have been no other studies of hyponatraemia among patients with heart failure in sub-Saharan Africa.

Low or no salt in-take predisposes to hyponatraemia but not in severe heart failure. In our study nearly all patients (91.0%) added salt onto their food. In other studies it was found that older people tend to take food with very little salt or none, thus predisposing them to hyponatraemia (10). Patients with hyponatraemia in our study were more likely to present with altered mentation, abnormal behavior and falls as found in other studies by Adrogue et al and Cumming et al (15-17).

The study found that many of the patients presented with generalized body weakness (87.2%), headache (23.2%), altered mentation (12.3%) and vomiting (18.5%). The clinical presentation was similar in all the classes of hyponatraemia (mild, moderate and severe) in our study. However, in studies done elsewhere patients with mild hyponatraemia tended to be asymptomatic (18), while those with moderate hyponatraemia tended to have anorexia, nausea and headache (18) and those with severe hyponatraemia had confusion, coma, seizures or death (18, 19). These clinical presentations are in keeping with the central nervous system effects of hyponatraemia. In general, older chronically ill patients with hyponatraemia develop more symptoms than younger otherwise healthy patients. The symptoms are also more severe with faster onset of hyponatraemia and they generally occur when the effective plasma osmolality falls to less than 240mOsm/kg. The symptoms can be subtle and consist mainly of changes in mental state, including altered personality, lethargy and confusion. As

the serum sodium falls to less than 115mEq/l, stupor, neuromuscular hyperexcitability, hyperreflexia, seizures and coma occur(20).

Our results in Uganda suggest that an elderly patient with hyponatraemia can present with any of a range of symptoms regardless of the serum sodium level and so management should be individualized. This differs somewhat from studies in developed countries where hyponatraemia manifestations are mostly neurological and are related to the severity of the hyponatraemia (18, 19).

The majority of the patients in our study were known to have hypertension (55.9%) which is a similar finding to that in a study conducted by Achadu in Uganda in 2002 (unpublished). Most patients (78.2%) in our study were on medication for heart failure, hypertension and other comorbidities with the majority using loop diuretics (62.5%) and either ACE inhibitors or Angiotensin 11 receptor blockers (52.9%) which increase sodium loss in urine.

The osmolality, blood pressure and cardiac output determine the release of vasopressin from the pituitary gland. Vasopressin is a hormone that causes retention of sodium and water. In heart failure, there is inappropriate and continued release of vasopressin due to reduced cardiac output despite a normal or reduced osmolality leading to hyponatraemia. Hyponatraemia in heart failure can also be due to maladaptive neurohormonal, renal changes and diuretic treatment (14). This was a similar finding from our study whereby hyponatraemia was more in patients with GFR stage 3 (39.3%) and those using diuretics.

We found the factors independently associated with hyponatraemia among elderly patients with heart failure in Uganda were diuretics and vomiting. Use of loop diuretics; was the factor most strongly associated with hyponatraemia in our study. This is different from studies in developed countries which have found that thiazides are the diuretic most strongly associated with hyponatraemia though loop diuretics are most used (14, 21, 22). In Uganda; loop diuretics are more commonly used than thiazide diuretics for symptom relief in patients with heart failure both as in-patients and outpatients. This is because there are no available parenteral thiazide diuretics but parenteral loop diuretics are available and more affordable. Loop diuretics act at the ascending loop of Henle of the kidney tubule by inhibiting the sodium-potassium-chloride channel leading to salt wasting while thiazide diuretics inhibit the sodium-chloride co-transporter at the distal convoluted tubule by blocking sodium re-absorption by the tubular cells. Vomiting was a factor found to be associated with

hyponatraemia in our study. This may have been due to other undiagnosed co-morbidities like infections or side effects of the drugs the patients were using.

**Study limitations**

A number of potential limitations need to be acknowledged. First, our study was cross-sectional and so causal relationships cannot be established. Secondly, the sample size was small for assessing factors associated with hyponatraemia and weak associations may have been missed. Finally, blood pressure measurements were taken only once and so patients may have been misclassified as having hypertension because of factors like "white coat" fear or recent caffeine consumption.

**Study strength**

We recruited a consecutive series of patients' at large teaching hospital in Uganda. We believe that our results can be generalized to similar settings in other countries in sub-Saharan Africa.

**Conclusion**

Hyponatraemia is a common electrolyte abnormality among older patients in Uganda with mild to moderate heart failure and is strongly associated with use of loop diuretics. Both parenteral and oral loop diuretics are widely used in Uganda for symptom relief in acute decompensated heart failure. They are cheap and available both in urban and rural areas of the country.

All older patients with heart failure and other co-morbidities should have their serum sodium level monitored during their hospital visits or hospitalization.

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**TABLES AND FIGURES**

**Table 1. Socio-demographic and clinical characteristics of the study patients by serum sodium level**

| Characteristic | Overall (n=211, %) | Serum sodium level | | p-values* |
| --- | --- | --- | --- | --- |
| | | Hyponatraemia (n, %) | Normal (135-150mmol/l) n (%) | |
| Age group | | | | 0.828 |
| 60-69 | 85 (40.3) | 20 (23.5) | 65 (74.5) | |
| 70-79 | 84 (39.8) | 22 (26.2) | 62 (73.8) | |
| ≥ 80 | 42 (19.9) | 9 (21.4) | 33 (78.6) | |
| Sex | | | | 0.602 |
| Female | 130 (61.6) | 33 (25.4) | 97 (74.6) | |
| Smoking | | | | 0.364 |
| Yes | 52 (24.6) | 15 (28.8) | 37 (71.2) | |
| Salt in-take | | | | 0.056 |
| Yes | 192 (91.0) | 43 (22.4) | 149 (77.6) | |
| BMI, n=151 | | | | 0.283 |
| Underweight | 18 (11.9) | 4 (22.2) | 14 (77.8) | |
| Normal | 87 (57.6) | 19 (21.8) | 68 (78.2) | |
| Overweight | 34 (22.5) | 3 (8.8) | 31 (91.2) | |
| Obesity | 12 (8.0) | 1 (8.3) | 11 (91.7) | |
| NYHA | | | | 0.005 |
| Class 1 | 1 (0.5) | 1 (100.0) | 0 (0.0) | |
| Class 2 | 134 (63.5) | 23 (17.2) | 111 (82.8) | |
| Class 3 | 70 (33.2) | 24 (34.3) | 46 (65.7) | |
| Class 4 | 6 (2.8) | 3 (50.0) | 3 (50.0) | |
| Diabetes mellitus | | | | 0.120 |
| Yes | 20 (9.5) | 2 (10.0) | 18 (90.0) | |
| Hypertension n=207 | | | | 0.024 |
| Yes | 145 (70.1) | 28 (19.3) | 117 (80.7) | |
| Stroke | | | | 0.955 |
| Yes | 8 (3.8) | 2(25.0) | 6 (75.0) | |
| Chronic kidney disease | | | | 0.782 |
| Yes | 7 (3.3) | 2 (28.6) | 5 (71.4) | |
| Seizures | | | | 0.223 |
| Yes | 4 (1.9) | 2 (50.0) | 2 (50.0) | |
| Falls | | | | 0.012 |
| Yes | 16 (7.6) | 8 (50.0) | 8 (50.0) | |
| Vomiting | | | | 0.006 |
| Yes | 39 (18.5) | 16 (41.0) | 23 (59.0) | |
| Body weakness | | | | 0.224 |
| Yes | 184 (87.2) | 47 (25.5) | 137 (74.5) | |
| Medication history n=210 | | | | |
| ACEi/ARB | | | | 0.510 |
| Yes | 111 (52.9) | 29 (26.1) | 82 (78.9) | |
| Psychotropics | | | | 0.421 |
| Yes | 2 (1.0) | 0 (00.0) | 2 (100.0) | |
| Thiazides diuretics | | | | 0.730 |
| Yes | 22 (10.5) | 6 (27.3) | 16 (72.7) | |
| Loop diuretics | | | | 0.013 |
| Yes | 134 (63.8) | 40 (29.9) | 94 (70.1) | |
| Potassium sparing diuretic | | | | 0.069 |
| Yes | 36 (17.1) | 13 (36.1) | 23 (63.9) | |

*Chi- square p-value, BMI= Body mass index, ACEi= Angiotensin converting enzyme inhibitor, ARB= Angiotensin 11 receptor blocker, NYHA= New York Heart Association

**Table 2. Unadjusted odds ratios for associations between socio-demographic, clinical characteristics and hyponatraemia.**

| Characteristic | | Serum sodium level Hyponatraemia N (%) | Normal N (%) | Crude OR (95%CI) | p-values* |
|---|---|---|---|---|---|
| Age | | | | | 0.83 |
| | 60-69 | 20 (39.2) | 65 (40.6) | 1 | |
| | 70-79 | 22 (43.1) | 62 (38.8) | 1.15(0.57-2.32) | |
| | ≥80 | 9 (17.7) | 33 (20.6) | 0.89 (0.36-2.16) | |
| Sex | | | | | 0.60 |
| | Male | 18 (35.3) | 63 (39.4) | 1 | |
| | Female | 33 (64.7) | 97 (60.6) | 0.84 (0.44-1.62) | |
| GFR n= 157 | | | | | |
| | Stage 1 | 5 (17.9) | 18 (13.9) | 1 | |
| | Stage 2 | 7 (25.0) | 29 (22.5) | 0.87 (0.24-3.16) | 0.69 |
| | Stage 3 | 11 (39.3) | 63 (48.8) | 0.63 (0.19-2.05) | |
| | Stage 4 | 2 (7.1) | 13 (10.1) | 0.55 (0.09-3.31) | |
| | Stage 5 | 3 (10.7) | 6 (4.7) | 1.80 (0.33-9.89) | |
| Falls | | | | | 0.02 |
| | No | 43 (84.3) | 152 (95.0) | 1 | |
| | Yes | 8 (15.7) | 8 (5.0) | 3.53 (1.25-9.97) | |
| Altered mentation | | | | | 0.01 |
| | No | 39 (76.5) | 146 (91.3) | 1 | |
| | Yes | 12 (23.5) | 14 (8.7) | 3.21 (1.37-7.49) | |
| Abnormal behavior | | | | | 0.01 |
| | No | 45 (88.2) | 157 (98.1) | 1 | |
| | Yes | 6 (11.8) | 3 (1.9) | 6.98 (1.68-29.01) | |
| Salt in-take | | | | | 0.07 |
| | No | 8 (15.7) | 11 (6.9) | 1 | |
| | Yes | 43 (84.3) | 149 (93.1) | 0.40 (0.15-1.05) | |
| Vomiting | | | | | 0.01 |
| | No | 35 (68.6) | 137 (85.6) | 1 | |
| | Yes | 16 (31.4) | 23 (14.4) | 2.72 (1.30-5.70) | |
| Diabetes Mellitus | | | | | 0.09 |
| | No | 49(96.1) | 142 (88.7) | 1 | |
| | Yes | 2 (3.9) | 18 (11.3) | 3.10(0.69-13.87) | |
| Stroke | | | | | 0.95 |
| | No | 49 (96.1) | 154 (96.2) | 1 | |
| | Yes | 2 (3.9) | 6(3.8) | 0.95 (0.19-4.88) | |
| CKD | | | | | 0.79 |
| | No | 49 (96.1) | 155 (96.9) | 1 | |
| | Yes | 2 (3.9) | 5 (3.1) | 0.79 (0.15-4.20) | |
| Loop diuretics | | | | | 0.01 |
| | No | 11 (21.6) | 65 (40.9) | 1 | |
| | Yes | 40 (78.4) | 94 (59.1) | 2.51 (1.20-5.26) | |
| Potassium sparing | | | | | 0.08 |
| | No | 38 (74.5) | 136 (85.5) | 1 | |
| | Yes | 13 (25.5) | 23 (14.5) | 2.02 (0.94-4.36) | |
| BP n=207 | | | | | 0.03 |
| | Normal | 21 (42.9) | 41 (25.9) | 1 | |
| | High | 28 (57.1) | 117 (74.1) | 0.47 (0.24-0.91) | |

GFR= Glomerular filtration rate, BP= Blood pressure CKD= Chronic kidney disease

**Table 3. Age and sex- adjusted odds ratios for characteristics associated with hyponatraemia.**

| Characteristic | Adjusted OR (95%CI) | p-values* |
|---|---|---|
| Vomiting | 2.94 (1.29-6.70) | 0.010 |
| Falls | 2.45(0.72-8.38) | 0.153 |
| Altered mentation | 1.91(0.65-5.60) | 0.336 |
| Abnormal behavior | 3.44(0.59-20.18) | 0.171 |
| Loop diuretics | 2.71 (1.13-6.52) | 0.026 |
| Potassium sparing | 1.46 (0.61-3.49) | 0.390 |
| High blood pressure | 0.51 ( 0.25-1.07) | 0.077 |

*P- value for adjusted odds, adjusted for age and sex

STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No | Recommendation |
|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found |
| **Introduction** | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses |
| **Methods** | | |
| Study design | 4 | Present key elements of study design early in the paper |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up |
| | | *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls |
| | | *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed |
| | | *Case-control study*—For matched studies, give matching criteria and the number of controls per case |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group |
| Bias | 9 | Describe any efforts to address potential sources of bias |
| Study size | 10 | Explain how the study size was arrived at |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding |
| | | (*b*) Describe any methods used to examine subgroups and interactions |
| | | (*c*) Explain how missing data were addressed |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed |
| | | *Case-control study*—If applicable, explain how matching of cases and controls was addressed |
| | | *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy |
| | | (*e*) Describe any sensitivity analyses |

**Results**

| | | |
|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed |
| | | (b) Give reasons for non-participation at each stage |
| | | (c) Consider use of a flow diagram |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders |
| | | (b) Indicate number of participants with missing data for each variable of interest |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included |
| | | (*b*) Report category boundaries when continuous variables were categorized |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses |

**Discussion**

| | | |
|---|---|---|
| Key results | 18 | Summarise key results with reference to study objectives |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results |

**Other information**

| | | |
|---|---|---|
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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# A CROSS-SECTIONAL STUDY OF HYPONATRAEMIA AMONG ELDERLY PATIENTS WITH HEART FAILURE IN UGANDA

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# A CROSS-SECTIONAL STUDY OF HYPONATRAEMIA AMONG ELDERLY PATIENTS WITH HEART FAILURE IN UGANDA

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## ABSTRACT

### Background

Hyponatraemia is a common electrolyte disturbance among older patients. We determined the prevalence of, and factors associated with, hyponatraemia among older patients with predominantly acute decompensated heart failure attending a tertiary hospital in Kampala, Uganda.

### Objectives:

**Main study aim:** 1. To determine the prevalence of hyponatraemia among patients aged sixty years and above with heart failure attending Mulago National Referral Hospital.

2. To describe the factors associated with hyponatraemia among patients aged 60 years and above with heart failure attending Mulago National Referral Hospital.

**Setting:** The study was conducted in one tertiary hospital located northeast of Kampala, Uganda.

**Participants:** 400 older adults aged sixty years and above were recruited into the study. 188 were excluded because they did not fulfill the inclusion criteria and one declined to participate. 211 older adults aged sixty years and above with a clinical diagnosis of heart failure using Framingham's criteria we consecutively recruited into the study. The patients who could not follow the study procedures were excluded.

**Results:** The prevalence of hyponatraemia was 24.2% (51/211) found mainly in patients with mild to moderate heart failure New York Heart Association classes 2 and 3. Of this 27/51 (52.9%) had mild hyponatraemia, while 24/51 (47.1%) had moderate to severe hyponatraemia of 130-125mmol/l.

History of vomiting (OR=2.94, 95% CI 1.29-6.70, p= 0.010) and use of loop diuretics (OR=2.71, 95% CI 1.13-6.52, p= 0.026) were identified as independent factors associated with hyponatraemia among older patients with heart failure.

### Conclusion:

Our study revealed a relatively high prevalence of hyponatraemia among older patients with mild to moderate heart failure. Patients presenting with a history of vomiting from any cause

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or use of loop diuretics are more likely to have hyponatraemia.   Further research should be carried out to determine at what dose and duration of loop diuretics hyponatraemia develops.

**Strengths and limitations:**

- We believe that our results can be generalized to similar settings in other countries in sub-Saharan Africa.
- Our study was cross-sectional and so causal relationships cannot be established.
- The sample size was small for assessing factors associated with hyponatraemia and weak associations may have been missed.
- Blood pressure measurements were taken only once and so patients may have been misclassified as having hypertension.

**Keywords:** Vomiting; Loop diuretics; Heart failure; Epidemiology; Hyponatraemia

**INTRODUCTION**

Heart failure is becoming more common in sub-Saharan Africa because of the epidemiologic transition to non-communicable diseases and increasing numbers of older people. The population of people aged 60 years of age and over is increasing in Uganda (1). Heart failure is a common health problem among older people in Uganda and Africa, mainly because of Dilated cardiomyopathy, rheumatic heart disease and hypertension (2).

Older people are particularly sensitive to the development of various electrolyte abnormalities, especially hyponatraemia, which is a serum sodium level below 135mmol/L (3, 4). Serum sodium falls by about 1mmol/l with each decade increase in age (5). Globally, 18-27% of all patients admitted to hospital with heart failure have hyponatraemia (6, 7). Because heart failure involves fluid retention in the body, it may lead to dilution hyponatraemia. In heart failure, diuretics normally are used to induce negative balance of sodium. The cause of hyponatraemia is the benefit of effective hypovolemia and (for thiazides) alteration of dilution of the urine. When fatal, hyponatraemia is symptomatic, and may result from treatment challenges of too fast correction of the low sodium level (4, 8-10). Hyponatraemia is a potent predictor of poor outcome among older in-patients with heart failure (11). There is little understanding of the burden of disease due to heart failure in sub-Saharan African, nor its causes and related complications. To our knowledge the prevalence and factors associated with hyponatraemia among older adults have not been well studied in Uganda or any other sub-Saharan African countries. The patients present later, with severe symptoms. The difference in the genetic make- up may contribute to the differences in the response to the anti-hypertensive drugs, including diuretics.

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**MATERIALS AND METHODS**

We conducted a cross-sectional study between August 2013 and March 2014 to determine the prevalence of, and factors associated with, hyponatraemia among patients aged 60 years and above with heart failure.  Patients were eligible for inclusion if they were: aged 60 years and above with a clinical diagnosis of either new on-set (acute) or worsening (chronic) heart failure using Framingham criteria  (12).  We consecutively recruited 211 patients with predominately acute decompensated heart failure from the cardiac clinics and wards of Mulago National Referral Hospital and Uganda Heart Institute.   Patients were considered to have decompensated heart failure if they had; two major or one major and two minor criteria present concurrently  (12).  The major features we considered in our study were; rales, neck vein distension, hepatojugular reflux, third heart sound and paroxysmal nocturnal dyspnoea while the minor features were; bilateral ankle oedema, nocturnal cough, hepatomegaly, dyspnoea on exertion and tachycardia.   Both study sites are within the same location in the Northeast of Kampala, the capital city of Uganda. Mulago National Referral Hospital is a public hospital offering services at no cost and has the largest bed capacity in the country with about 1500 beds.  The Uganda Heart Institute is an autonomous institution that offers private services to both adult and pediatric patients with heart conditions.   It has a bed capacity of about 40 beds.

We informed all eligible patients about the study and the procedures involved and then, if they agreed to participate, we asked them to sign a consent form.  We then ascertained the socio-demographic characteristics of the patients with a written questionnaire completed by the principal investigator or research assistant.  The patients were specifically asked if their doctor had ever told them that they had diabetes mellitus, stroke, chronic kidney disease or hypertension.  The care taker was asked of any recent behavior changes in the patient and the history of current or previous medication the patient was taking.   A physical examination was done to ascertain the weight, height, presence of  pallor, oedema, hepatomegaly, raised jugular venous pressure, rales, gallop rhythm and the  level of consciousness  (mental alteration) using the Glasgow Coma scale.  The blood pressure of the patients was taken using a manual sphygmomanometer in either lying or sitting position depending on the

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functional status of the patient.  Hypertension was defined as systolic blood pressure above 140mmHg and diastolic blood pressure above 90mmHg.

Patients who met the study inclusion criteria were requested to have overnight fasting for at least eight hours.  Two milliliters of venous blood were withdrawn the next morning for measurement of sodium, chloride, potassium, sugar, lipids, creatinine and urea.  The blood samples were centrifuged then mounted into the Cobas Integra 400 plus machine manufactured by Roche and analyzed the same day in an accredited laboratory.   A urine sample was collected at the same time as the blood for measurement of sodium, potassium, chloride; renal function test and analyzed mainly using the same machine as for the blood in the same laboratory.  The plasma and urine osmolality were calculated from the values obtained using the following formula; calculated osmolality = 2 Na+ (serum/urine) + Glucose (blood/urine) + Urea (all in mmol/l).Glomerular filtration rate, GFR (ml/min per 1.73m²) was calculated using Cockcroft-Gault formula: eGFR = (140- Age) x weight (kilogram) x 0.85 (in females) / serum creatinine (mg/dl) x 72.  Chronic kidney disease was classified as; stage 1 >90, stage 2 60-89, stage 3 30-59, stage 4 15-29 and stage 5 <15 depending on the GFR. Most of our patients had been previously hospitalized, and had echocardiograms done but our study mainly focused on clinical diagnosis of heart failure using Framingham's criteria for inclusion.  Given the fact that echocardiography is not readily available in most hospitals of the country, we used the clinical criteria to ease applicability of the findings.  For proportions, the sample size was calculated using the following formula  n= N / 1+N (e)² proposed by Yamane (13).

**Statistical analysis**

We determined the prevalence of hyponatraemia using frequency analysis.  We performed multivariate logistic regression analysis to study associations between predefined risk factors and hyponatraemia.  All analyses were done using STATA version 12.0.  Variables with a p-value less than 0.05 were considered statistically significant.

The study was reviewed and approved by the Institution Research Board (IRB) school of Medicine Makerere University College of Health Sciences.  Patients or /care takers gave written informed consent to participate in the study.  If a patient was found to have hyponatraemia, his/her clinician was informed and the patient was managed appropriately.

**RESULTS**

The socio- demographic and clinical characteristics of the patients are shown in Table 1. The largest group of patients was aged 60-69 years (40.3%). The median (IQR) age of the patients was 70.0 (65- 77) years, with the oldest patient being 102 years. Less than half of the study patients were males (n= 81/211, 38.4%). Most patients had been previously hospitalized for heart failure (n= 148, 70.1%) and presented with worsening symptoms while (n=63, 29.9%) of the patients had been newly diagnosed with heart failure with symptoms for less than a month. More than half, (n=134, 63.5%), of the patients were New York Heart Association (NYHA) class 2.

The patients mainly with hyponatraemia (n=47/51, 92.2%) were NYHA classes 2 and 3 which are mild - moderate heart failure as shown in Table 1. Few of the patients, (n= 52/211, 24.6%), had smoked tobacco and (n=90, 42.7%) consumed alcohol either occasionally. Very few patients presented with clinical characteristics suggestive of hyponatraemia such as seizures (n=4, 1.9%), falls (n=16, 7.6%), abnormal behavior (n=9, 4.3%), altered mentation (n=26, 12.3%) and vomiting (n=39, 18.5%) as shown in Table 1. Of the thirty nine patients who presented with vomiting, sixteen (n=16/51, 31.4%) had hypovolaemic hyponatraemia and 68.6% with dilutional hyponatraemia. The majority, (n= 118/211, 55.9%); of the study patients had been known to have hypertension and a small minority known chronic kidney disease (n=7, 3.3%) as shown in Table 1. More than three quarters of the patients were using medicines (n= 165, 78.2%), with the majority using loop diuretics (n=134, 81.2%) and (40/134, 29.9%) of these patients using loop diuretics had hyponatraemia. We however, did not analyze the difference among the different loop diuretics. Out of the 211 study patients, only (n=22, 10.5%) used thiazide diuretics and of these (6/22, 27.3%) had hyponatraemia and, (n=2, 1.3%) used psychotropic drugs (Amitriptyline and Carbamazepine). More than three quarters of the patients, (n=192, 91.0%), added salt onto their food and, of these; (n= 43/192, 22.4%) had hyponatraemia.

Among the 211 patients in the study (n=51, 24.2%) had hyponatraemia of serum sodium below 135mmol/l. At a serum level of 130mmol/L and below, the prevalence of hyponatraemia was 11.0% and at a serum sodium level below 125mmol/L (severe

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hyponatraemia), the prevalence of hyponatraemia was 5.7%.  Of these 51 patients with hyponatraemia, more than half had mild hyponatraemia (n= 27, 52.9%).   Nineteen (70.4%) of the patients with hyponatraemia had a normal body mass index which was different from other studies where low body mass index is associated with hyponatraemia (14).

 Forty three (93.5%); of the patients with hyponatraemia were losing sodium in their urine; all study patients had normal spot urine osmolality.  As shown in Table 2, according to the calculated Glomerular Filtration Rate (n=98/157, 62.4%) patients had chronic kidney disease with (n=16/28, 57.1%) hyponatraemia and (n=82/129, 64%) normal sodium. Many (n=11, 39.3%) of the patients with hyponatraemia had stage 3 kidney disease.  In total, (n=114, 54.0%) of the study patients had high calculated plasma osmolality, but; only (n=4, 8.7%) of these had hyponatraemia.  The minority of patients had high fasting blood sugar; (n=46, 21.8%) and only one had high triglycerides.

The statistically  significant factors associated with hyponatraemia were use of loop diuretics (OR=2.51, 95% CI 1.20-5.26, p= 0.01), vomiting (OR=2.72, 95% CI 1.30-5.70, p= 0.01), falls (OR= 3.53, 95% CI 1.25-9.97, p= 0.02), abnormal behavior (OR= 6.98, 95% CI 1.68-29.01, p= 0.01) and altered mentation (OR= 3.21, 95% CI 1.37-7.49, p= 0.01) as shown in Table 2.  High blood pressure was associated with a decrease in odds of hyponatraemia (OR=0.47, 95% CI 0.24-0.91, p= 0.03).

In multivariate analysis, only vomiting (OR= 2.94, 95% CI 1.29-6.70, p= 0.010) and taking loop diuretics (OR =2.71, 95% CI 1.13-6.52, p= 0.026) were found to be statistically significantly associated with hyponatraemia (see Table 3).  There was also a suggestion (p=0.077) that high blood pressure was inversely associated with hyponatraemia (OR= 0.51, 95% CI 0.25-1.07).

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## DISCUSSION

During the previous decades, heart failure was an uncommon condition among older people in sub-Saharan Africa because of low life expectancy and low prevalence of non-communicable diseases.   Now life expectancy has improved with more people living longer than 60 years of age.  We were, therefore, able to collect a big sample size of 211 older patients with heart failure in one hospital in a short period of seven months.

The results of our study in Uganda show relatively a high prevalence of hyponatraemia (24.2%) among patients aged 60 years and above with mainly mild to moderate heart failure NYHA classes 2 and 3.  This finding is different from previous studies done in developed countries where hospitalized elderly patients had a much lower prevalence of hyponatraemia ranging from 7 to 12% (8, 15).  Hyponatraemia is a poor prognostic marker for heart failure associated with longer hospital stays and in-hospital and early post discharge mortality (16-18).   To our knowledge there have been no other studies of hyponatraemia among patients with heart failure in sub-Saharan Africa.

Low or no salt in-take predisposes to hyponatraemia but not in severe heart failure. In our study nearly all patients (91.0%) added salt onto their food.  In other studies it was found that older  people tend to take food with very little salt or none, thus predisposing them to hyponatraemia (10).  Patients with hyponatraemia in our study were more likely to present with altered mentation, abnormal behavior and falls as found in other studies  by Adrogue et al and Cumming et al  (19-21).

The study found that many of the patients presented with generalized body weakness (87.2%), headache (23.2%), altered mentation (12.3%) and vomiting (18.5%).  The clinical presentation was similar in all the classes of hyponatraemia (mild, moderate and severe) in our study.   However, in studies done elsewhere patients with mild hyponatraemia tended to be  asymptomatic (22), while those with moderate hyponatraemia tended to have  anorexia, nausea and headache (22) and those with severe hyponatraemia  had confusion, coma, seizures or death (22, 23).   These clinical presentations are in keeping with the central nervous system effects of hyponatraemia.  In general, older chronically ill patients with hyponatraemia develop more symptoms than younger otherwise healthy patients.   The symptoms are also more severe with faster onset of hyponatraemia and they generally occur

when the effective plasma osmolality falls to less than 240mOsm/kg.   The symptoms can be subtle and consist mainly of changes in mental state, including altered personality, lethargy and confusion.   As the serum sodium falls to less than 115mEq/l, stupor, neuromuscular hyperexcitability, hyperreflexia, seizures and coma occur (24).

The majority of the patients in our study were known to have hypertension (55.9%) which is a similar finding to that in a study conducted by Achadu in Uganda in 2002 (unpublished data).   Most patients (78.2%) in our study were on medication for heart failure, hypertension and other comorbidities with the majority using loop diuretics (62.5%) and either ACE inhibitors or Angiotensin 11 receptor blockers (52.9%) which increase sodium loss in urine.

The osmolality, blood pressure and cardiac output determine the release of vasopressin from the pituitary gland.   Vasopressin is a hormone that causes retention of sodium and water.  In heart failure, there is inappropriate and continued release of vasopressin due to reduced cardiac output despite a normal or reduced osmolality leading to hyponatraemia. Hyponatraemia in heart failure  can also be due to maladaptive neurohormonal,  renal changes and diuretic treatment (17).   This was a similar finding from our study whereby hyponatraemia was more in patients with GFR stage 3 (39.3%) and those using diuretics.

We found the factors independently associated with hyponatraemia among elderly patients with heart failure in Uganda were diuretics and vomiting.   Use of loop diuretics; was the factor most strongly associated with hyponatraemia in our study.  This is different from studies in developed countries which have found that thiazides are the diuretic most strongly associated with hyponatraemia though loop diuretics are most used (14, 17, 25).   In Uganda; loop diuretics are more commonly used than thiazide diuretics for symptom relief in patients with heart failure both as in-patients and outpatients.  This is because there loop diuretics are readily available and more affordable.   Loop diuretics act at the ascending loop of Henle of the kidney tubule by inhibiting the sodium-potassium-chloride channel leading to salt wasting while thiazide diuretics inhibit the sodium-chloride co-transporter at the distal convoluted tubule by blocking sodium re-absorption by the tubular cells.  Vomiting was a factor found to be associated with hyponatraemia in our study.  This may have been due to other undiagnosed co-morbidities like infections or side effects of the drugs the patients were using.

**Study limitations**

 A number of potential limitations need to be acknowledged.  Majority of the patients had been previously hospitalized with echocardiograms done however, we were unable to perform repeat echocardiograms for this study because of limited availability and very high cost at the study hospital (26).  We used the Framingham's criteria for the clinical diagnosis of heart failure.  Hence we were unable to identify patterns of heart failure.  We were also unable to assess fluid intake because the patients used different containers to correctly quantify the amount of fluids consumed.  Other limitations include the fact that, our study was cross-sectional and so causal relationships cannot be established and the sample size was small for assessing factors associated with hyponatraemia and so weak associations may have been missed.   Finally, blood pressure measurements were taken only once and so patients may have been misclassified as having hypertension because of factors like "white coat" fear or recent caffeine consumption.

**Study strength**

We recruited a consecutive series of patients' at large teaching hospital in Uganda.  We believe that our results can be generalized to similar settings in other countries in sub-Saharan Africa.

**Conclusion**

Hyponatraemia is a common electrolyte abnormality among older patients in Uganda with mild to moderate heart failure and is strongly associated with use of loop diuretics.   Both parenteral and oral loop diuretics are widely used in Uganda for symptom relief in acute decompensated heart failure.   They are cheap and available both in urban and rural areas of the country.

All older patients with heart failure and other co-morbidities should have their serum sodium level monitored during their hospital visits or hospitalization to avert the adverse outcomes associated with hyponatraemia.   Older patients with heart failure should have health education about fluid restriction.    There is a need to carry out a similar study with only

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community-dwelling older adults to determine the prevalence and factors associated with hyponatraemia.

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**TABLES AND FIGURES**

**Table 1. Socio-demographic and clinical characteristics of the study patients by serum sodium level**

| Characteristic | Overall (n=211, %) | Serum sodium level | | p-values* |
| | | Hyponatraemia (n, %) | Normal (135-150mmol/l) n (%) | |
|---|---|---|---|---|
| Age group | | | | 0.828 |
| 60-69 | 85 (40.3) | 20 (23.5) | 65 (74.5) | |
| 70-79 | 84 (39.8) | 22 (26.2) | 62 (73.8) | |
| ≥ 80 | 42 (19.9) | 9 (21.4) | 33 (78.6) | |
| Sex | | | | 0.602 |
| Female | 130 (61.6) | 33 (25.4) | 97 (74.6) | |
| Smoking | | | | 0.364 |
| Yes | 52 (24.6) | 15 (28.8) | 37 (71.2) | |
| Salt in-take | | | | 0.056 |
| Yes | 192 (91.0) | 43 (22.4) | 149 (77.6) | |
| BMI, n=151 | | | | 0.283 |
| Underweight | 18 (11.9) | 4 (22.2) | 14 (77.8) | |
| Normal | 87 (57.6) | 19 (21.8) | 68 (78.2) | |
| Overweight | 34 (22.5) | 3 (8.8) | 31 (91.2) | |
| Obesity | 12 (8.0) | 1 (8.3) | 11 (91.7) | |
| NYHA | | | | 0.005 |
| Class 1 | 1 (0.5) | 1 (100.0) | 0 (0.0) | |
| Class 2 | 134 (63.5) | 23 (17.2) | 111 (82.8) | |
| Class 3 | 70 (33.2) | 24 (34.3) | 46 (65.7) | |
| Class 4 | 6 (2.8) | 3 (50.0) | 3 (50.0) | |
| Diabetes mellitus | | | | 0.120 |
| Yes | 20 (9.5) | 2 (10.0) | 18 (90.0) | |
| Hypertension n=207 | | | | 0.024 |
| Yes | 145 (70.1) | 28 (19.3) | 117 (80.7) | |
| Stroke | | | | 0.955 |
| Yes | 8 (3.8) | 2 (25.0) | 6 (75.0) | |
| Chronic kidney disease | | | | 0.782 |
| Yes | 7 (3.3) | 2 (28.6) | 5 (71.4) | |
| Seizures | | | | 0.223 |
| Yes | 4 (1.9) | 2 (50.0) | 2 (50.0) | |
| Falls | | | | 0.012 |
| Yes | 16 (7.6) | 8 (50.0) | 8 (50.0) | |
| Vomiting | | | | 0.006 |
| Yes | 39 (18.5) | 16 (41.0) | 23 (59.0) | |
| Body weakness | | | | 0.224 |
| Yes | 184 (87.2) | 47 (25.5) | 137 (74.5) | |
| Medication history n=210 | | | | |
| ACEi/ARB | | | | 0.510 |
| Yes | 111 (52.9) | 29 (26.1) | 82 (78.9) | |
| Psychotropics | | | | 0.421 |
| Yes | 2 (1.0) | 0 (00.0) | 2 (100.0) | |
| Thiazides diuretics | | | | 0.730 |
| Yes | 22 (10.5) | 6 (27.3) | 16 (72.7) | |
| Loop diuretics | | | | 0.013 |
| Yes | 134 (63.8) | 40 (29.9) | 94 (70.1) | |
| Potassium sparing diuretic | | | | 0.069 |
| Yes | 36 (17.1) | 13 (36.1) | 23 (63.9) | |

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*Chi- square p-value, BMI= Body mass index, ACEi= Angiotensin converting enzyme inhibitor, ARB= Angiotensin 11 receptor blocker, NYHA= New York Heart Association

**Table 2.Unadjusted odds ratios for associations between socio-demographic, clinical characteristics and hyponatraemia.**

| Characteristic | | Serum sodium level | | Crude OR (95%CI) | p-values* |
| | | Hyponatraemia N (%) | Normal N (%) | | |
|---|---|---|---|---|---|
| Age | | | | | 0.83 |
| | 60-69 | 20 (39.2) | 65 (40.6) | 1 | |
| | 70-79 | 22 (43.1) | 62 (38.8) | 1.15(0.57-2.32) | |
| | ≥80 | 9 (17.7) | 33 (20.6) | 0.89 (0.36-2.16) | |
| Sex | | | | | 0.60 |
| | Male | 18 (35.3) | 63 (39.4) | 1 | |
| | Female | 33 (64.7) | 97 (60.6) | 0.84 (0.44-1.62) | |
| GFR n= 157 | | | | | |
| | Stage 1 | 5 (17.9) | 18 (13.9) | 1 | |
| | Stage 2 | 7 (25.0) | 29 (22.5) | 0.87 (0.24-3.16) | 0.69 |
| | Stage 3 | 11 (39.3) | 63 (48.8) | 0.63 (0.19-2.05) | |
| | Stage 4 | 2 (7.1) | 13 (10.1) | 0.55 (0.09-3.31) | |
| | Stage 5 | 3 (10.7) | 6 (4.7) | 1.80 (0.33-9.89) | |
| Falls | | | | | 0.02 |
| | No | 43 (84.3) | 152 (95.0) | 1 | |
| | Yes | 8 (15.7) | 8 (5.0) | 3.53 (1.25-9.97) | |
| Altered mentation | | | | | 0.01 |
| | No | 39 (76.5) | 146 (91.3) | 1 | |
| | Yes | 12 (23.5) | 14 (8.7) | 3.21 (1.37-7.49) | |
| Abnormal behavior | | | | | 0.01 |
| | No | 45 (88.2) | 157 (98.1) | 1 | |
| | Yes | 6 (11.8) | 3 (1.9) | 6.98 (1.68-29.01) | |
| Salt in-take | | | | | 0.07 |
| | No | 8 (15.7) | 11 (6.9) | 1 | |
| | Yes | 43 (84.3) | 149 (93.1) | 0.40 (0.15-1.05) | |
| Vomiting | | | | | 0.01 |
| | No | 35 (68.6) | 137 (85.6) | 1 | |
| | Yes | 16 (31.4) | 23 (14.4) | 2.72 (1.30-5.70) | |
| Diabetes Mellitus | | | | | 0.09 |
| | No | 49(96.1) | 142 (88.7) | 1 | |
| | Yes | 2 (3.9) | 18 (11.3) | 3.10(0.69-13.87) | |
| Stroke | | | | | 0.95 |
| | No | 49 (96.1) | 154 (96.2) | 1 | |
| | Yes | 2 (3.9) | 6(3.8) | 0.95 (0.19-4.88) | |
| CKD | | | | | 0.79 |
| | No | 49 (96.1) | 155 (96.9) | 1 | |
| | Yes | 2 (3.9) | 5 (3.1) | 0.79 (0.15-4.20) | |
| Loop diuretics | | | | | 0.01 |
| | No | 11 (21.6) | 65 (40.9) | 1 | |
| | Yes | 40 (78.4) | 94 (59.1) | 2.51 (1.20-5.26) | |
| Potassium sparing | | | | | 0.08 |
| | No | 38 (74.5) | 136 (85.5) | 1 | |
| | Yes | 13 (25.5) | 23 (14.5) | 2.02 (0.94-4.36) | |
| BP n=207 | | | | | 0.03 |
| | Normal | 21 (42.9) | 41 (25.9) | 1 | |
| | High | 28 (57.1) | 117 (74.1) | 0.47 (0.24-0.91) | |

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GFR= Glomerular filtration rate, BP= Blood pressure CKD= Chronic kidney disease

**Table 3. Age and sex- adjusted odds ratios for characteristics associated with hyponatraemia.**

| Characteristic | Adjusted OR (95%CI) | p-values* |
|---|---|---|
| Vomiting | 2.94 (1.29-6.70) | 0.010 |
| Falls | 2.45(0.72-8.38) | 0.153 |
| Altered mentation | 1.91(0.65-5.60) | 0.336 |
| Abnormal behavior | 3.44(0.59-20.18) | 0.171 |
| Loop diuretics | 2.71 (1.13-6.52) | 0.026 |
| Potassium sparing | 1.46 (0.61-3.49) | 0.390 |
| High blood pressure | 0.51 ( 0.25-1.07) | 0.077 |

*P- value for adjusted odds, adjusted for age and sex

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STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No | Recommendation |
|---|---|---|
| **Title and abstract** <br> **( Done- see title and abstract pages 1, 2, 3 )** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found |
| **Introduction (see introduction page 4)** | | |
| Background/rationale ( see page 2) | 2 | Explain the scientific background and rationale for the investigation being reported |
| Objectives (see page 2) | 3 | State specific objectives, including any prespecified hypotheses |
| **Methods ( see pages 5, 6)** | | |
| Study design ( see page 5) | 4 | Present key elements of study design early in the paper |
| Setting ( see page 5) | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <br> *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <br> *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants ( see page 5) |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed <br> *Case-control study*—For matched studies, give matching criteria and the number of controls per case |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (see pages 5 and 6) |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). (Page 5 and 6) Describe comparability of assessment methods if there is more than one group (N/A) |
| Bias | 9 | Describe any efforts to address potential sources of bias (page 6) |
| Study size | 10 | Explain how the study size was arrived at  (page 6) |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. (page 6) If applicable, describe which groupings were chosen and why |
| Statistical methods ( see page 6) | 12 | (*a*) Describe all statistical methods, including those used to control for confounding |
| | | (*b*) Describe any methods used to examine subgroups and interactions |
| | | (*c*) Explain how missing data were addressed |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed <br> *Case-control study*—If applicable, explain how matching of cases and controls was addressed <br> *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy |
| | | (*e*) Describe any sensitivity analyses |

Continued on next page

**Results**

| | | |
|---|---|---|
| Participants (see page 7) | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed |
| | | (b) Give reasons for non-participation at each stage |
| | | (c) Consider use of a flow diagram |
| Descriptive data (see page 7) | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders |
| | | (b) Indicate number of participants with missing data for each variable of interest |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures (page 7 and 8) |
| Main results ( see page 7, 8) | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included |
| | | (*b*) Report category boundaries when continuous variables were categorized |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses |

**Discussion (see discussion section)**

| | | |
|---|---|---|
| Key results ( see page 9) | 18 | Summarise key results with reference to study objectives |
| Limitations ( see page 11) | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias |
| Interpretation (see page 11) | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results |

**Other information ( included)**

| | | |
|---|---|---|
| Funding (see page 12) | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

# BMJ Open

## A CROSS-SECTIONAL STUDY OF HYPONATRAEMIA AMONG ELDERLY PATIENTS WITH HEART FAILURE IN UGANDA

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# A CROSS-SECTIONAL STUDY OF HYPONATRAEMIA AMONG ELDERLY PATIENTS WITH HEART FAILURE IN UGANDA

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**ABSTRACT**

**Background**

Hyponatraemia is a common electrolyte disturbance among older patients. We determined the prevalence of, and factors associated with, hyponatraemia among older patients with predominantly acute decompensated heart failure attending a tertiary hospital in Kampala, Uganda.

**Objectives:**

**Main study aim:**

1. To determine the prevalence of hyponatraemia among patients aged 60 years and above with heart failure attending Mulago National Referral Hospital.

2. To describe the factors associated with hyponatraemia among patients aged 60 years and above with heart failure attending Mulago National Referral Hospital.

**Setting:** The study was conducted in one tertiary hospital located in the northeast of Kampala, Uganda.

**Participants:** 400 adults aged 60 years and above were identified for the study. 188 were excluded because they did not fulfill the inclusion criteria and one declined to participate, leaving a final study group of 211 older adults aged 60 years and above with a clinical diagnosis of heart failure using Framingham's criteria.

**Results:** The prevalence of hyponatraemia was 24.2% (51/211). Hyponatraemia was mainly found in patients with mild to moderate heart failure, New York Heart Association classes 2 and 3. Of the 51 patients with hyponatraemia 27 (52.9%) had mild hyponatraemia, while 24 (47.1%) had moderate to severe hyponatraemia of 130-125mmol/l.

History of vomiting (OR=2.94, 95% CI 1.29-6.70, p= 0.010) and use of loop diuretics (OR=2.71, 95% CI 1.13-6.52, p= 0.026) were identified as independent factors associated with hyponatraemia among older patients with heart failure.

**Conclusion:**

Our study revealed a relatively high prevalence of hyponatraemia among older patients with mild to moderate heart failure.  Patients presenting with a history of vomiting from any cause or use of loop diuretics were more likely to have hyponatraemia.

**Strengths and limitations:**

- The results of this study can be generalized to similar settings in other countries in sub-Saharan Africa.
- The study was cross-sectional and so causal relationships cannot be established.
- The sample size was small for assessing factors associated with hyponatraemia and weak associations may have been missed.
- Blood pressure measurements were taken only once and so patients may have been misclassified as having hypertension.

**Keywords:** Epidemiology; Heart failure; Hyponatraemia; Loop diuretics; Vomiting

**INTRODUCTION**

Heart failure is becoming more common in sub-Saharan Africa because of the epidemiologic transition to non-communicable diseases and the increasing numbers of older people. The population of people aged 60 years of age and over is increasing in Uganda (1, 2). Heart failure is a common observed health problem among older people in Uganda and elsewhere in sub-Saharan Africa and is believed to be, mainly caused by dilated cardiomyopathy, rheumatic heart disease and hypertension (3).

Older people are particularly sensitive to the development of various electrolyte abnormalities, especially hyponatraemia, which is a serum sodium level below 135mmol/L (4, 5). Serum sodium falls by about 1mmol/l with each decade increase in age (6). Globally, 18-27% of all patients admitted to hospital with heart failure have hyponatraemia (7, 8). Because heart failure involves fluid retention in the body, it may lead to dilution hyponatraemia. In heart failure, diuretics normally are used to induce negative balance of sodium. Hyponatraemia is a potent predictor of poor outcome among older in-patients with heart failure (9). There is limited data on the burden of hyponatraemia and its complications in patients with heart failure in sub-Saharan Africa. To our knowledge the prevalence and factors associated with hyponatraemia among older adults with heart failure have not been studied in Uganda or any other sub-Saharan African countries.

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**MATERIALS AND METHODS**

We conducted a cross-sectional study between August 2013 and March 2014 to determine the prevalence of, and factors associated with, hyponatraemia among patients aged 60 years and above with heart failure.  Patients were eligible for inclusion if they were: aged 60 years and above with a clinical diagnosis of either new on-set (acute) or worsening (chronic) heart failure according to Framingham criteria (10).  Patients who could not follow the study procedures were excluded.  We consecutively recruited 211 patients with predominately acute decompensated heart failure from the cardiac clinics and wards of Mulago National Referral Hospital and Uganda Heart Institute.   Patients were considered to have decompensated heart failure if they had either; two major or one major and two minor criteria present concurrently  (10).  The major criteria we considered in our study were; rales, neck vein distension, hepatojugular reflux, third heart sound and paroxysmal nocturnal dyspnoea while the minor criteria were; bilateral ankle oedema, nocturnal cough, hepatomegaly, dyspnoea on exertion and tachycardia.  Both study sites are within the same location in the northeast of Kampala, the capital city of Uganda. Mulago National Referral Hospital is a public hospital offering services at no cost and has the largest bed capacity in the country with about 1500 beds.  The Uganda Heart Institute is an autonomous institution that offers private services to both adult and pediatric patients with heart conditions.  It has a bed capacity of about 40 beds.

We informed all eligible patients about the study and the procedures involved and then, if they agreed to participate, we asked them to sign a consent form.  We then ascertained the socio-demographic and clinical characteristics of the patients with a written questionnaire completed by the principal investigator or research assistant.  The patients were specifically asked if their doctor had ever told them that they had diabetes mellitus, stroke, chronic kidney disease or hypertension.  The care taker was asked of any recent behavior changes in the patient and a history was taken of current or previous medication use by the patient.   A physical examination was done to ascertain weight, height, presence of  pallor, oedema, hepatomegaly, raised jugular venous pressure, rales, gallop rhythm and the  level of consciousness  (mental alteration) using the Glasgow Coma scale.  Blood pressures of patients were taken using a manual sphygmomanometer in either lying or sitting position depending on the functional status of the patient.  Hypertension was defined as systolic blood pressure above 140mmHg and /or diastolic blood pressure above 90mmHg.

Patients who met the study inclusion criteria were fasted overnight for at least eight hours and two milliliters of venous blood was withdrawn the next morning for measurement of sodium, chloride, potassium, sugar, lipids, creatinine and urea. The blood samples were centrifuged then mounted into the Cobas Integra 400 plus machine manufactured by Roche and analyzed the same day in an accredited laboratory. A morning urine sample was collected for measurement of sodium, protein, sugar, and presence of casts and red blood cells. Plasma and urine osmolality were calculated from the values obtained using the following formula; Calculated osmolality = 2 Na+ (serum/urine) + Glucose (blood/urine) + Urea (all in mmol/l). Glomerular filtration rate, GFR (ml/min per 1.73m²), was calculated using Cockcroft-Gault formula: eGFR = (140- Age) x weight (kilogram) x 0.85 (in females) / serum creatinine (mg/dl) x 72. Chronic kidney disease was classified as; stage 1 GFR >90, stage 2 GFR 60-89, stage 3 GFR 30-59, stage 4 GFR 15-29 and stage 5 GFR <15. Most of the patients in this study had been previously hospitalized, and had had echocardiograms done but our study mainly focused on clinical diagnosis of heart failure using Framingham criteria. Given the fact that echocardiography is not readily available in most hospitals in Uganda, we used clinical criteria to increase applicability of the findings to a wide range of settings.

**Statistical analysis**

We used multivariate logistic regression analysis to study associations between predefined risk factors and hyponatraemia. All analyses were done using STATA version 12.0. Variables with a p-value less than 0.05 were considered statistically significant. For proportions, the sample size was calculated using the following formula  n= N / 1+N (e)² proposed by Yamane (11).

The study was reviewed and approved by the Institution Research Board (IRB) School of Medicine Makerere University College of Health Sciences. Patients or care takers gave written informed consent to participate in the study. If a patient was found to have hyponatraemia, his/her clinician was informed and the patient was managed appropriately.

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**RESULTS**

The socio- demographic and clinical characteristics of the 211 patients in the study are shown in Table 1.  The largest group of patients was aged 60-69 years (40.3%).  The median (IQR) age of the patients was 70.0 (65- 77) years, with the oldest patient being 102 years old.  Less than half the study patients were males (n= 81, 38.4%).  Most patients had been previously hospitalized for heart failure (n= 148, 70.1%) and presented with worsening symptoms while 63 (29.9%) of the patients were newly diagnosed with heart failure with symptoms for less than a month.  More than half, (n=134, 63.5%), the patients were New York Heart Association (NYHA) class 2.  Few of the patients, (n= 52/211, 24.6%), had smoked tobacco and 90 (42.7%) consumed alcohol at least occasionally.  Forty six study patients had high fasting blood sugar (21.8%) and only one had high triglycerides.

Most of the 51 patients  with hyponatraemia (n=47, 92.2%) were NYHA classes 2 and 3, which is mild - moderate heart failure,  as shown in Table 1. Very few of the 211 patients in the study presented with clinical characteristics suggestive of hyponatraemia such as seizures (n=4, 1.9%), falls (n=16, 7.6%), abnormal behavior (n=9, 4.3%), altered mentation (n=26, 12.3%) and vomiting (n=39, 18.5%). Sixteen of the 51 patients with hyponatraemia presented with vomiting and likely had hypovolaemic hyponatraemia while the remaining 35 patients had dilutional hyponatraemia.

 The majority, (n= 118, 55.9%); of the 211 study patients were known to have hypertension and seven were known to have chronic kidney disease (3.3%) as shown in Table 1.  More than three quarters of the patients were using at least one medicine (n= 165, 78.2%), with the majority using loop diuretics (n=134, 81.2%).  Forty of the 134 patients (29.9%) using loop diuretics had hyponatraemia.  We did not analyze differences among the different loop diuretics.  Out of the 211 study patients, only 22 (10.5%) used thiazide diuretics and, of these six (27.3%) had hyponatraemia.  Only two study patients used psychotropic drugs (amitriptyline and carbamazepine).  More than three quarters of the study patients, (n=192, 91.0%), added salt to their food and, 43 of these; (22.4%) had hyponatraemia.  Most (19, 70.4%) of the patients with hyponatraemia had a normal body mass index which was different from other studies where low body mass index has been associated with hyponatraemia (12).

Among the 211 patients in the study (n=51, 24.2%) had hyponatraemia with serum sodium below 135mmol/l.  At a serum level of 130mmol/L and below, the prevalence of hyponatraemia was 11.0% and at a serum sodium level below 125mmol/L (severe hyponatraemia), the prevalence of hyponatraemia was 5.7%.  Of the 51 patients with hyponatraemia, more than half had mild hyponatraemia, serum sodium between 135 – 130mmol/L (n= 27, 52.9%).

 Forty three (93.5%); of the patients with hyponatraemia were losing sodium in their urine but; all study patients had normal spot urine osmolality.  As shown in Table 2, according to the calculated Glomerular Filtration Rate, 62.4% of patients (n=98/157) had chronic kidney disease and (n=16/51 31.4%) had hyponatraemia.  Many (n=74, 47.1%) of the 157 patients had stage 3 kidney disease.  In total, 114, (54.0%) of the study patients had high calculated plasma osmolality; only 4 of these had hyponatraemia.

The statistically  significant factors associated with hyponatraemia were use of loop diuretics (OR=2.51, 95% CI 1.20-5.26, p= 0.01), vomiting (OR=2.72, 95% CI 1.30-5.70, p= 0.01), falls (OR= 3.53, 95% CI 1.25-9.97, p= 0.02), abnormal behavior (OR= 6.98, 95% CI 1.68-29.01, p= 0.01) and altered mentation (OR= 3.21, 95% CI 1.37-7.49, p= 0.01) as shown in Table 2.  High blood pressure was associated with a decrease in odds of hyponatraemia (OR=0.47, 95% CI 0.24-0.91, p= 0.03).

In multivariate analysis, only vomiting (OR= 2.94, 95% CI 1.29-6.70, p= 0.010) and taking loop diuretics (OR =2.71, 95% CI 1.13-6.52, p= 0.026) were found to be statistically significantly associated with hyponatraemia (see Table 3).  There was also a suggestion (p=0.077) that high blood pressure was inversely associated with hyponatraemia (OR= 0.51, 95% CI 0.25-1.07).

**DISCUSSION**

In the past, heart failure was an uncommon condition among older people in sub-Saharan Africa because of low life expectancy and low prevalence of non-communicable diseases. Life expectancy has now improved with more people living past 60 years of age. We were, therefore, able to collect a large sample size of 211 older patients with heart failure in one large hospital in Uganda in the short period of seven months.

The results of our study show a relatively a high prevalence of hyponatraemia (24.2%) in Uganda among patients aged 60 years and above with mainly mild to moderate heart failure NYHA classes 2 and 3. This finding is different from previous studies done in developed countries where hospitalized older patients had a much lower prevalence of hyponatraemia ranging from 7 to 12% (13, 14). Hyponatraemia is a marker of poor prognosis for heart failure and is associated with longer hospital stays and high in-hospital and early post discharge mortality (15-17). To our knowledge there have been no other studies of hyponatraemia among patients with heart failure in sub-Saharan Africa.

Low salt in-take predisposes to hyponatraemia. In our study nearly all patients (91.0%) added salt to their food. In other studies it been found that some older people add very little salt to their food, predisposing them to hyponatraemia (18). Patients with hyponatraemia in our study were more likely to present with altered mentation, abnormal behavior and falls, as found in studies by Adrogue et al and Cumming et al (19-21).

Our study found that many patients presented with generalized body weakness (87.2%), headache (23.2%), altered mentation (12.3%) and vomiting (18.5%). The clinical presentation was similar across all the classes of hyponatraemia (mild, moderate and severe). However, in studies done elsewhere, patients with mild hyponatraemia tended to be asymptomatic (22), while those with moderate hyponatraemia tended to have anorexia, nausea and headache (22) and those with severe hyponatraemia had confusion, coma, seizures or death (22, 23). These clinical presentations are in keeping with the central nervous system effects of hyponatraemia. In general, older chronically ill patients with hyponatraemia develop more symptoms than younger otherwise healthy patients. Symptoms also tend to be more severe when the onset of hyponatraemia is rapid and when the effective plasma osmolality falls to less than 240mOsm/kg. Symptoms of hyponatraemia can be subtle and consist mainly of changes in mental state, including altered personality, lethargy and

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confusion.   As the serum sodium falls to less than 115mEq/l, stupor, neuromuscular hyperexcitability, hyperreflexia, seizures and coma occur (24).

The majority of the patients in our study were known to have hypertension (55.9%) which is a similar finding to that in a study conducted by Achadu in Uganda in 2002 (unpublished data).  Most patients (78.2%) in our study were on medication for heart failure, hypertension and other comorbidities; with the majority using loop diuretics (62.5%) and either ACE inhibitors or Angiotensin 11 receptor blockers (52.9%), which increase sodium loss in urine.

Plasma osmolality, blood pressure and cardiac output determine the release of vasopressin from the pituitary gland.   Vasopressin is a hormone that causes retention of sodium and water.  In heart failure, there is inappropriate and continued release of vasopressin due to reduced cardiac output despite a normal or reduced osmolality and this leads to hyponatraemia.  Hyponatraemia in heart failure  can also be due to maladaptive neurohormonal and, renal changes and diuretic treatment (16).  In our study hyponatraemia was more frequent in patients with renal failure and among those using diuretics.

We found that use of diuretics and vomiting was independently associated with hyponatraemia among older patients with heart failure in Uganda.   Use of loop diuretics; was the factor most strongly associated with hyponatraemia in our study.  This is different from studies in developed countries which have found that thiazides are the diuretic most strongly associated with hyponatraemia (12, 16, 25).  In Uganda, loop diuretics are more commonly used than thiazide diuretics for symptom relief in patients with heart failure both as in-patients and outpatients.  This is because loop diuretics are more readily available and more affordable.   Loop diuretics act at the ascending loop of Henle of the kidney tubule by inhibiting the sodium-potassium-chloride channel leading to salt wasting, while thiazide diuretics inhibit the sodium-chloride co-transporter at the distal convoluted tubule by blocking sodium re-absorption by the tubular cells.  Vomiting was a factor found to be associated with hyponatraemia in our study.  This may have been due to other undiagnosed co-morbidities like infections or side effects of the drugs the patients were using.

**Study limitations**

A number of potential limitations need to be acknowledged.  We used Framingham's criteria for the clinical diagnosis of heart failure without, echocardiography, and so we were unable to identify patterns of heart failure.  The majority of  study patients had been previously hospitalized and had had echocardiograms, however, we were unable to perform repeat echocardiograms for this study because of limited availability and very high cost at the study hospital (26).  We were also unable to assess fluid intake because the patients used different sized containers to drink fluids.  Other limitations include the fact that; our study was cross-sectional and so causal relationships cannot be established and the fact that sample size was small for assessing factors associated with hyponatraemia and so weak associations may have been missed.   Finally, blood pressure measurements were taken only once and so patients may have been misclassified as having hypertension because of factors like "white coat" fear or recent caffeine consumption.

**Study strength**

We recruited a consecutive series of patients at a large teaching hospital in Uganda.  We believe that our results can be generalized to similar settings in other countries in sub-Saharan Africa.

**Conclusion**

Hyponatraemia is a common electrolyte abnormality among older patients in Uganda with mild to moderate heart failure and is strongly associated with use of loop diuretics.   Both parenteral and oral loop diuretics are widely used in Uganda for symptom relief in acute decompensated heart failure.   They are cheap and available both in urban and rural areas of the country.

All older patients with heart failure and other co-morbidities should have their serum sodium level monitored to avert the adverse outcomes associated with hyponatraemia.   Older patients with heart failure should have health education about fluid restriction.  There is a need to carry out a similar study among community-dwelling older adults to determine the prevalence and factors associated with hyponatraemia.

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## TABLES AND FIGURES

**Table 1 Socio-demographic and clinical characteristics of the study patients by serum sodium level**

| Characteristic | Overall (n=211, %) | Serum sodium level | | p-values* |
| --- | --- | --- | --- | --- |
| | | Hyponatraemia (n, %) | Normal (135-150mmol/l) n (%) | |
| Age group | | | | 0.828 |
| 60-69 | 85 (40.3) | 20 (23.5) | 65 (74.5) | |
| 70-79 | 84 (39.8) | 22 (26.2) | 62 (73.8) | |
| ≥ 80 | 42 (19.9) | 9 (21.4) | 33 (78.6) | |
| Sex | | | | 0.602 |
| Female | 130 (61.6) | 33 (25.4) | 97 (74.6) | |
| Smoking | | | | 0.364 |
| Yes | 52 (24.6) | 15 (28.8) | 37 (71.2) | |
| Salt in-take | | | | 0.056 |
| Yes | 192 (91.0) | 43 (22.4) | 149 (77.6) | |
| BMI, n=151 | | | | 0.283 |
| Underweight | 18 (11.9) | 4 (22.2) | 14 (77.8) | |
| Normal | 87 (57.6) | 19 (21.8) | 68 (78.2) | |
| Overweight | 34 (22.5) | 3 (8.8) | 31 (91.2) | |
| Obesity | 12 (8.0) | 1 (8.3) | 11 (91.7) | |
| NYHA | | | | 0.005 |
| Class 1 | 1 (0.5) | 1 (100.0) | 0 (0.0) | |
| Class 2 | 134 (63.5) | 23 (17.2) | 111 (82.8) | |
| Class 3 | 70 (33.2) | 24 (34.3) | 46 (65.7) | |
| Class 4 | 6 (2.8) | 3 (50.0) | 3 (50.0) | |
| Diabetes mellitus | | | | 0.120 |
| Yes | 20 (9.5) | 2 (10.0) | 18 (90.0) | |
| Hypertension n=207 | | | | 0.024 |
| Yes | 145 (70.1) | 28 (19.3) | 117 (80.7) | |
| Stroke | | | | 0.955 |
| Yes | 8 (3.8) | 2 (25.0) | 6 (75.0) | |
| Chronic kidney disease | | | | 0.782 |
| Yes | 7 (3.3) | 2 (28.6) | 5 (71.4) | |
| Seizures | | | | 0.223 |
| Yes | 4 (1.9) | 2 (50.0) | 2 (50.0) | |
| Falls | | | | 0.012 |
| Yes | 16 (7.6) | 8 (50.0) | 8 (50.0) | |
| Vomiting | | | | 0.006 |
| Yes | 39 (18.5) | 16 (41.0) | 23 (59.0) | |
| Body weakness | | | | 0.224 |
| Yes | 184 (87.2) | 47 (25.5) | 137 (74.5) | |
| Medication history n=210 | | | | |
| ACEi/ARB | | | | 0.510 |
| Yes | 111 (52.9) | 29 (26.1) | 82 (78.9) | |
| Psychotropics | | | | 0.421 |
| Yes | 2 (1.0) | 0 (00.0) | 2 (100.0) | |
| Thiazides diuretics | | | | 0.730 |
| Yes | 22 (10.5) | 6 (27.3) | 16 (72.7) | |
| Loop diuretics | | | | 0.013 |
| Yes | 134 (63.8) | 40 (29.9) | 94 (70.1) | |
| Potassium sparing diuretic | | | | 0.069 |
| Yes | 36 (17.1) | 13 (36.1) | 23 (63.9) | |

*Chi- square p-value, BMI= Body mass index, ACEi= Angiotensin converting enzyme inhibitor, ARB= Angiotensin 11 receptor blocker, NYHA= New York Heart Association

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**Table 2 Unadjusted odds ratios for associations between socio-demographic, clinical characteristics and hyponatraemia.**

| | Hyponatraemia | Normal | Crude OR (95%CI) | p-values* |
|---|---|---|---|---|
| Characteristic | N (%) | N (%) | | |
| **Age** | | | | 0.83 |
| 60-69 | 20 (39.2) | 65 (40.6) | 1 | |
| 70-79 | 22 (43.1) | 62 (38.8) | 1.15(0.57-2.32) | |
| ≥80 | 9 (17.7) | 33 (20.6) | 0.89 (0.36-2.16) | |
| **Sex** | | | | 0.60 |
| Male | 18 (35.3) | 63 (39.4) | 1 | |
| Female | 33 (64.7) | 97 (60.6) | 0.84 (0.44-1.62) | |
| **GFR n= 157** | | | | |
| Stage 1 | 5 (17.9) | 18 (13.9) | 1 | |
| Stage 2 | 7 (25.0) | 29 (22.5) | 0.87 (0.24-3.16) | 0.69 |
| Stage 3 | 11 (39.3) | 63 (48.8) | 0.63 (0.19-2.05) | |
| Stage 4 | 2 (7.1) | 13 (10.1) | 0.55 (0.09-3.31) | |
| Stage 5 | 3 (10.7) | 6 (4.7) | 1.80 (0.33-9.89) | |
| **Falls** | | | | 0.02 |
| No | 43 (84.3) | 152 (95.0) | 1 | |
| Yes | 8 (15.7) | 8 (5.0) | 3.53 (1.25-9.97) | |
| **Altered mentation** | | | | 0.01 |
| No | 39 (76.5) | 146 (91.3) | 1 | |
| Yes | 12 (23.5) | 14 (8.7) | 3.21 (1.37-7.49) | |
| **Abnormal behavior** | | | | 0.01 |
| No | 45 (88.2) | 157 (98.1) | 1 | |
| Yes | 6 (11.8) | 3 (1.9) | 6.98 (1.68-29.01) | |
| **Salt in-take** | | | | 0.07 |
| No | 8 (15.7) | 11 (6.9) | 1 | |
| Yes | 43 (84.3) | 149 (93.1) | 0.40 (0.15-1.05) | |
| **Vomiting** | | | | 0.01 |
| No | 35 (68.6) | 137 (85.6) | 1 | |
| Yes | 16 (31.4) | 23 (14.4) | 2.72 (1.30-5.70) | |
| **Diabetes Mellitus** | | | | 0.09 |
| No | 49(96.1) | 142 (88.7) | 1 | |
| Yes | 2 (3.9) | 18 (11.3) | 3.10(0.69-13.87) | |
| **Stroke** | | | | 0.95 |
| No | 49 (96.1) | 154 (96.2) | 1 | |
| Yes | 2 (3.9) | 6(3.8) | 0.95 (0.19-4.88) | |
| **CKD** | | | | 0.79 |
| No | 49 (96.1) | 155 (96.9) | 1 | |
| Yes | 2 (3.9) | 5 (3.1) | 0.79 (0.15-4.20) | |
| **Loop diuretics** | | | | 0.01 |
| No | 11 (21.6) | 65 (40.9) | 1 | |
| Yes | 40 (78.4) | 94 (59.1) | 2.51 (1.20-5.26) | |
| **Potassium sparing** | | | | 0.08 |
| No | 38 (74.5) | 136 (85.5) | 1 | |
| Yes | 13 (25.5) | 23 (14.5) | 2.02 (0.94-4.36) | |
| **BP n=207** | | | | 0.03 |
| Normal | 21 (42.9) | 41 (25.9) | 1 | |
| High | 28 (57.1) | 117 (74.1) | 0.47 (0.24-0.91) | |

GFR= Glomerular filtration rate, BP= Blood pressure CKD= Chronic kidney disease

**Table 3 Age and sex- adjusted odds ratios for characteristics associated with hyponatraemia.**

| Characteristic | Adjusted OR (95%CI) | p-values* |
|---|---|---|
| Vomiting | 2.94 (1.29-6.70) | 0.010 |
| Falls | 2.45(0.72-8.38) | 0.153 |
| Altered mentation | 1.91(0.65-5.60) | 0.336 |
| Abnormal behavior | 3.44(0.59-20.18) | 0.171 |
| Loop diuretics | 2.71 (1.13-6.52) | 0.026 |
| Potassium sparing | 1.46 (0.61-3.49) | 0.390 |
| High blood pressure | 0.51 ( 0.25-1.07) | 0.077 |

*P- value for adjusted odds, adjusted for age and sex

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STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No | Recommendation |
|---|---|---|
| **Title and abstract**<br>**( Done- see title and abstract pages 1, 2, 3 )** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found |
| **Introduction (see introduction page 4)** | | |
| Background/rationale<br>( see page 2) | 2 | Explain the scientific background and rationale for the investigation being reported |
| Objectives (see page 2) | 3 | State specific objectives, including any prespecified hypotheses |
| **Methods ( see pages 5, 6)** | | |
| Study design ( see page 5) | 4 | Present key elements of study design early in the paper |
| Setting ( see page 5) | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants ( see page 5) |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (see pages 5 and 6) |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). (Page 5 and 6) Describe comparability of assessment methods if there is more than one group (N/A) |
| Bias | 9 | Describe any efforts to address potential sources of bias (page 6) |
| Study size | 10 | Explain how the study size was arrived at  (page 6) |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. (page 6) If applicable, describe which groupings were chosen and why |
| Statistical methods<br>( see page 6) | 12 | (*a*) Describe all statistical methods, including those used to control for confounding |
| | | (*b*) Describe any methods used to examine subgroups and interactions |
| | | (*c*) Explain how missing data were addressed |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy |
| | | (*e*) Describe any sensitivity analyses |

**Results**

| | | |
|---|---|---|
| Participants (see page 7) | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed |
| | | (b) Give reasons for non-participation at each stage |
| | | (c) Consider use of a flow diagram |
| Descriptive data (see page 7) | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders |
| | | (b) Indicate number of participants with missing data for each variable of interest |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures (page 7 and 8) |
| Main results ( see page 7, 8) | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included |
| | | (*b*) Report category boundaries when continuous variables were categorized |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses |

**Discussion (see discussion section)**

| | | |
|---|---|---|
| Key results ( see page 9) | 18 | Summarise key results with reference to study objectives |
| Limitations ( see page 11) | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias |
| Interpretation (see page 11) | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results |

**Other information ( included)**

| | | |
|---|---|---|
| Funding (see page 12) | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.