# Hyponatraemia as a predictor of mortality in medical admissions in Ghana - A case control study

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# Abstract

Background Hyponatraemia is the most common electrolyte abnormality in hospital admissions. It occurs in a quarter of medical admissions in Ghana and its associated with high mortality. Mortality has been suggested to be due to the underlying medical condition and not necessarily the hyponatraemia. We set out to compare the outcomes of patients with documented hyponatraemia as compared to those with normonatraemia in terms of mortality and length of hospital stay.

Methods We conducted a case control study of patients with hyponatraemia as compared to those with normonatraemia on the medical ward at the Komfo Anokye Teaching hospital between May 2018 to December 2018. The medical diagnoses, demographics and laboratory data of the patients were recorded. Participants' age and gender were matched. Student t test was used to test for differences in continuous variables when parametric and Wilcoxon Signed Rank test for non-parametric variables. Multiple logistic regression was used to identify predictors of mortality. A p value of <0.05 was considered statistically significant.

Results Within the study period there were 846 patients recruited. This included 406 patients with hyponatraemia and 440 patients as controls. Serum albumin and protein were significantly lower in the hyponatraemia patients as compared to those with normal sodium concentration. The mortality rate in patients with hyponatraemia was significantly higher than those with normonatraemia 129 (31.8%) vs 98 (22.3%) [OR 1.62 (CI 1.19-2.22) p=0.002]. In-hospital stay was longer in patients with hyponatraemia than normonatraemia 7 (4-10) vs 6 (3-10) but not statistically significant (p=0.09). Multiple logistic regression showed that low serum sodium concentration (p<0.001) and low serum albumin concentration (p=0.009) were the predictors of in-hospital mortality.

Conclusion Hyponatraemia is associated with significantly higher mortality than normonatraemia and predicts worse prognosis in patients on medical admission. Low serum albumin is also a predictor of mortality in medical admission.


# Background

Hyponatraemia is the most common electrolyte abnormality in hospitalized patients[1]. It is defined as serum sodium concentration of less than 135 mmol/L[2]. Hyponatraemia occurs in 27.6% of hospitalized medical patients in Ghana [3] and associated with high mortality[4]. Hyponatraemia indicates a disruption in the body's water balance due to abnormal handling of water by the kidneys from anti-diuretic hormone (ADH) secretion (appropriately or inappropriately) or an excessive water intake[2, 5]. There are multiple causes of hyponatraemia among medical admissions. These include the use of some medications, malignancies, infections, chronic heart failure, chronic liver disease and chronic kidney disease[3]. Hyponatraemia is most commonly seen in patients admitted in the intensive care unit [6]. Non-osmotic states such as pain, anxiety and nausea are also reported as causes of hyponatremia in acute

cases[7]. Infections have been shown to be the most common cause of hyponatraemia among medical admissions in Ghana [3].

Hyponatraemia is associated with poor prognosis and mortality in chronic hospitalized medical cases even when mild to moderate[4, 8]. Mortality rates associated with hyponatraemia range from 0.9–29.6% in hospital medical admissions with the highest among patients admitted in the intensive care unit [6, 9]. The in-hospital mortality in medical patients was found to be 31.8% in a recent hospital based study in Ghana [3]. It is however not certain whether hyponatraemia is direct cause of mortality, a poor prognostic indicator for chronic medical conditions such as malignancies, chronic kidney disease, chronic liver disease, brain tumour and intracerebral hemorrhage [4] or just an 'innocent bystander' as the underlying condition causes mortality[10].

It has been suggested that most patients die with hyponatraemia rather than from hyponatraemia [11] with the underlying medical condition as the most likely cause of death. This is because mortality varies with the underlying condition. It has been shown that drug induced hyponatraemia is associated with less mortality [11] while almost half of patients with malignancy die with hyponatraemia[3].

In Ghana, there has been a single centre study to describe the demographics, causes and outcomes of patients with hyponatraemia[3] but there has not been any study to compare the mortality of patients with hyponatraemia and those with normal sodium concentration in hospitalized patients to ascertain if there is a difference in mortality and length of hospital stay. With our knowledge of the mortality in patients with hyponatraemia, we set out to compare the outcomes of patients with documented hyponatraemia to those with normonatraemia in terms of in-hospital mortality and length of hospital stay and to determine the predictors of in-hospital mortality among medical admissions in tertiary institution in Ghana.

# Methods

We conducted a case control study of patients with hyponatraemia and compared to those with normonatraemia on the medical ward at the Komfo Anokye Teaching Hospital (KATH) between May 2018 to December 2018 as a follow up to an earlier study of patients with only hyponatraemia conducted from October 2017 to April 2018[3]. We identified medical patients on admission with normonatraemia and recorded their medical diagnoses, demographics and laboratory data. Participants with normonatraemia where age and gender matched as much as possible with those with hyponatraemia.

Data was collected from medical records of patients on admissions into the renal registry data at the KATH. KATH is a 1200 bed hospital in the Ashanti region. KATH receives referrals from about half of Ghana's estimated population of about 30 million people[12] and serves the northern half of the country. The hospital has twelve (12) clinical directorates including the Internal Medicine directorate which has a bed capacity of 203. Ethical approval was granted before the commencement of the study by the Committee on Human Research, Publications and Ethics (CHRPE), School of Medical Sciences, Kwame Nkrumah University of Science and Technology (KNUST).

### Study participants

Participants were recruited into two arms if they had a recorded serum sodium and were 18 years and above. Hyponatraemia was defined as serum sodium concentration of less than 135mmol/L[2]. Those presenting with serum sodium concentration above 135mmol/L but less than 146mmol/L were recruited into the normonatraemia arm as controls. Demographic data including age and gender were recorded and matched as much as possible. Laboratory investigations including serum albumin, serum protein, serum creatinine and serum urea concentrations were also documented. The medical diagnoses in patients' folder were also recorded and the most likely cause of hyponatraemia as per the clinical and laboratory parameters were then established by the nephrologist or as stated in the patients' medical records. The medical diagnoses of those with normonatraemia was also recorded and classified broadly as those for hyponatraemia to aid analysis. Outcome variables documented were the length of hospital stay and in-hospital mortality. Length of hospital stay refers to the duration of stay from admission to discharge of the patient from the medical ward and in-hospital mortality was defined as death from any cause occurring during hospital admission.

### Statistical analysis

Data was collected onto a data capturing sheet and entered into Microsoft Excel software by two independent data entry clerks. Data was then exported to Stata 13® statistical software for analysis. Means and standard deviation were used to describe parametric variables and medians and interquartile range for non-parametric variables. Figures and tables were used to describe data where appropriate. Chi square was used to test for significant differences in categorical variables for hyponatraemia and normonatraemia arms and odds ratios determined. Student t test was used to test for differences in continuous variables when normally distributed involving two means and Wilcoxon signed rank test for continuous variables when not normally distributed for the two arms. Multiple logistic regression was then used to identify predictors of mortality and a p value of $<0.05$ was considered statistically significant.

## Results

The study involved 846 hospitalized patients on the medical ward of the Komfo Anokye Teaching Hospital. They included 406 patients with hyponatraemia as cases and 440 patients with normonatraemia as controls. The mean age of all participants was 52.1 ± 18.8 years and there were 460 (54.4%) males. There was no statistical difference in demographics data with respect to age and gender between the patients with hyponatraemia and those with normonatraemia as shown in Table 1.

Table 1 Showing a comparison of patients with hyponatraemia as compared to normonatraemia n=846

| able | All cases N= 846 | Hyponatremia N=406 | Controls N= 440 | P value |
|---|---|---|---|---|
| e gender n (%) | 460 (54.4) | 217 (53.5) | 243 (55.2 ) | 0.604 |
| (years) µ (SD) | 52.1 ±18.8 | 51.5 ±19.0 | 52.7 ± 18.6 | 0.340 |
| ım Sodium (mmol/L) µ (SD) | 133.8±7.6 | 128 ±7.8 | 138.0 ± 5.0 | < 0.001 |
| ım albumin (g/L) µ (SD | 33.9 ±19.8 | 31.6 ±16.5 | 36.1 ± 22.4 | <0.001 |
| ım protein (g/L) M (IQR) | 66.5 (58-75.6) | 64 (55.2-75.6) | 71 (63.3-78.8) | <0.001 |
| ım urea mmol/L M (IQR) | 5.8 ( 3.44-12.0) | 6.9 (3.9-15.8) | 5.2 (3.3-9.6) | <0.001 |
| ım creatinine (µmol/L) M (IQR) | 90 (61.1-170) | 95 (61-232.5) | 88 (62-144) | 0.091 |
| tality n (%) | 227 (26.9%) | 129 (31.8) | 98 (22.3) | 0.002 |
| ation of hospital stay (days) M (IQR) | 6 (3-10) | 7(4-10) | 6 (3-10) | 0.090 |

n,number; µ, mean; SD, Standard deviation; M, median; IQR, interquartile range; mmol, millimol; L, litre;g, grams; µmol/L, micromole per litre

The mean sodium concentration was 128.0 ± 7.8 mmol/L in the hyponatraemia group as compared to 138.0 ± 5.0 mmol/L among the normonatraemia group ($p < 0.001$). Serum albumin was also significantly lower in patients with hyponatraemia as compared to those with normonatraemia 31.6 ± 16.5 vs 36.1 ± 22.4 p value < 0.001. Median serum protein was also significantly lower in the hyponatremia patients as compared to those with normal sodium concentration. 64 (55.2–75.6) vs 71 (63.3–78.8), $p < 0.001$. All as shown in Table 1.

The most common medical conditions associated with hyponatraemia were infections 105 (25.9%), chronic liver disease 69 (17.0%), diabetes mellitus 68(16.8%) and chronic kidney disease in 66(16.3%) patients as shown in Fig. 1.

The most common medical conditions in the normonatraemia group were intracranial pathologies 131(29.8%), chronic heart failure 76 (17.3%), and infections in 72 (16.4%) all as shown in Fig. 2.

The proportions of some medical conditions varied in the hyponatraemia and normonatraemia groups. Infections, chronic kidney disease and diabetes mellitus were significantly of higher proportions in patients with hyponatraemia as compared to patients with normonatraemia. Malignancies and alcoholism did not vary significantly within the two groups. There were lower proportions of patients with heart failure and cranial pathologies in hyponatraemia groups as compared to those with normonatraemia. All as shown in Table 2.

**Table 2** Showing the medical conditions associated with hyponatraemia as compared to normonatraemia n= 846

| Medical condition | All patients n=846 | Hyponatraemia n=406 | Normonatraemia n=440 | P value |
|---|---|---|---|---|
| Infections | 177 (20.9) | 105 (25.9) | 72 (16.4) | 0.001 |
| Malignancies | 22 (2.6) | 11 (2.7) | 11 (2.5) | 0.848 |
| Heart failure | 109 (12.9) | 33 (8.1) | 76 (17.3) | <0.001 |
| Cranial pathologies | 154 (18.2) | 23 (5.7) | 131 (29.8) | <0.001 |
| Kidney disease | 96 (11.4) | 66 (16.3) | 30 (6.8) | <0.001 |
| Diabetes mellitus | 98 (11.6) | 68 (16.8) | 30 (6.8) | <0.001 |
| Liver diseases | 116 (13.7) | 69 (17.0) | 47 (10.7) | 0.008 |
| Alcoholism | 27 (3.2) | 16 (3.9) | 14 (3.18) | 0.551 |

Infections were significantly higher in hyponatraemia patients as compared to normonatraemia patients 105 (25.9%) vs 72 (16.4), P = 0.001. As well as patients with chronic kidney disease 66 (16.3%) vs 30 (6.8%), p < 0.001 and in patients with hyperglycaemia 68 (16.8) versus 30 (6.8) p < 0.001 and those with liver disease. Malignancies and alcoholism did not vary significantly with hyponatraemia. There were proportionally lower patients with heart failure and cranial pathologies in the hyponatraemia group as compared to those with normonatraemia. All as shown in Table 2.

The highest proportion of mortality in the normonatraemia patients occurred in patients with hyperglycemia 10(33.3%), followed by liver disease 13(27.6%) and pain presentations 3 (25%) but mortalities did not vary significantly with diagnoses (P = 0.741) as shown in Fig. 2.

In-hospital mortality was significantly higher in patients with hyponatraemia as compared to patients with normonatraemia 129(31.8%) versus 98(22.3%) p = 0.002 as shown in Table 1. Hyponatraemia was associated with increased odds of in-patient mortality [OR = 1.62, (95% CI 1.18–2.22) and p = 0.002)] as compared to normonatraemia as shown in Table 4. Hypoalbuminemia was associated with increased odds of in-hospital mortality with OR of 2.08 (1.46–2.99, 95% CI, p < 0.001). Hyperglycaemia was significantly protective of in-hospital mortality [OR = 0.50 (95% CI 0.26–0.87, p = 0.012) as shown in Table 3.

Table 3 Showing the predictors associated with in-hospital mortality

| Variable | Odds ratio | 95% Confidence interval | P value |
|---|---|---|---|
| Male gender | 1.14 | 0.84 - 1.58 | 0.375 |
| Age greater than 50yrs | 1.05 | 0.77 – 1.45 | 0.720 |
| Hyponatraemia | 1.62 | 1.18 - 2.22 | 0.002 |
| Infection | 1.01 | 0.68 - 1.49 | 0.932 |
| Malignancies | 1.92 | 0.71- 4.93 | 0.132 |
| Heart failure | 1.11 | 0.69 - 1.77 | 0.644 |
| Cranial pathologies | 0.87 | 0.57 – 1.32 | 0.498 |
| Kidney disease | 1.50 | 0.92 – 2.40 | 0.078 |
| Hyperglycaemia | 0.50 | 0.26 - 0.87 | 0.012 |
| Liver disease | 1.39 | 0.89 – 2.16 | 0.123 |
| Alcoholism | 0.67 | 0.22 – 1.72 | 0.389 |
| Hypoalbuminaemia | 2.08 | 1.46 - 2.99 | <0.001 |

Hypoalbuminaemia, serum albumin of less than 35g/L; yrs, years; hyperglycaemia, serum random blood glucose above11.1mmol/L on admission

In-hospital stay was longer in patients with hyponatraemia than normonatraemia 7 (4–10) vs 6 (3–10) but not statistically significant p = 0.09 as shown in Table 1

Multiple logistic regression shows that serum sodium concentration [OR = 0.94 (95% CI 0.92–0.97) (p < 0.001)] and serum albumin concentration [OR = 0.97 (95% CI 0.94–0.99) (0.007)] where significantly protective of mortality. Serum protein, urea, creatinine and length of hospital stay were not significant predictors of in-hospital mortality as shown in Table 4.

Table 4 Showing the multiple logistic regression independent variable for mortality

| Variable | Z | Standard error | Odds ratio | 95% confidence interval | P value |
|---|---|---|---|---|---|
| Serum sodium | - 4.14 | 0.013 | 0.93 | 0.92-0.97 | <0.001 |
| Serum albumin | - 2.62 | 0.013 | 0.96 | 0.94 -0.99 | 0.009 |
| Total protein | 0.19 | 0.009 | 1.00 | 0.98-1.02 | 0.846 |
| Serum Urea | 1.39 | 0.009 | 1.01 | 0.99-1.03 | 0.164 |
| Serum creatinine | - 0.42 | 0.002 | 0.99 | 0.99-1.00 | 0.675 |
| Length of hospital stay | - 1.21 | 0.139 | 0.98 | 0.96-1.01 | 0.227 |

# Discussion

This is the first study according to our knowledge that compares patients with hyponatraemia with those with normonatraemia in Ghana. We found out that patients with hyponatraemia had significantly higher in-hospital mortality as compared to those with normonatraemia. Our study showed that the odds of mortality in a patient with hyponatraemia was 62% higher as compared to those with normonatraemia. Low serum sodium and low serum albumin was predictive of mortality. Our study adds to the growing evidence of the significant role of hyponatraemia in predicting in-hospital mortality among medical admission and the need to monitor and appropriately manage such patients[4, 8, 9].

We found patients with hyponatraemia to have significantly higher proportions of chronic kidney disease, diabetes mellitus and chronic liver disease than those with normonatraemia. This has also been shown in other studies as associations and notable causes of hyponatraemia[3, 13, 14]. Hyponatraemia has been shown in other studies to be associated with chronic medical conditions such as chronic liver disease[15], chronic heart failure [16] and chronic kidney disease[17] as a poor prognostic indicator of these conditions. Mortality in chronic medical conditions has been shown to be predicted by the serum sodium concentration [8, 9, 17] as also found in our study.

With strong associations of hyponatraemia and mortality in most studies, it is still not proven whether hyponatraemia is the direct cause of mortality or just an ‘innocent bystander’ as the underlying medical condition causes the mortality[10]. It has been shown by Chawla et al that mortality rate increased with moderate hyponatraemia but this trend reversed with hyponatraemia of less than 120mmol/L[11]. The authors inferred that patients with moderate hyponatraemia were admitted because of the underlying

condition but those with severe hyponatraemia may have been admitted because of their sodium concentration alone not necessarily because they were ill. Their finding contrasted with a single centre study in Ghana where most patients were admitted primarily because of their underlying medical conditions but the in-hospital mortality increased with severity of hyponatraemia [3].

The question still remains as to whether hyponatraemia can directly cause death. Hyponatraemia can directly cause death in acute hyponatraemia as a result of cerebral oedema or rapid correction of chronic hyponatraemia leading to osmotic demyelination [5, 18] but osmotic demyelination syndrome is rarely reported as a cause of death in patients with hyponatraemia [3]. Osmotic demyelination syndrome has been shown to occur more commonly in alcoholics, malnourished and hypokalaemia patients with chronic hyponatraemia[19] when rapidly corrected. Such patients are managed with a lot of caution to avoid osmotic demyelination syndrome with very careful correction of chronic hyponatraemia.

Hyponatraemia may cause organ dysfunction which may also lead to mortality. Hyponatraemia can cause falls, osteoporosis and fractures [20] but there has not been any proof of effect on other organs such as the heart, liver and kidneys. Hyponatraemia has been shown to be an independent predictor of mortality in various studies [4, 8, 9, 21] as also shown in this study.

We also found low serum albumin as an independent predictor of mortality also shown in many acute and chronic medical conditions such as chronic kidney disease, strokes and hospitalized patients in general [22-25]. In this study, those with hyponatraemia had significantly lower serum albumin as compared to those with normonatraemia (31.6 ±16.5 versus 36.1 ± 22.4 $p<0.001$).

Serum albumin is a major component of plasma protein and it is required to maintain oncotic pressure and also serve as a means of assessing nutritional status in both acute and chronically ill patients[26]. The levels of serum albumin may decrease as a result of many factors. These include poor nutritional status, chronic inflammation as a result of the underlying chronic disease causing the hyponatraemia such as infection or malignancy due to interleukin-1 and tumor necrosis factor which decrease hepatic albumin production. Albumin could also be lost via the kidneys in glomerular diseases or during burns as well as in high metabolic and catabolic states [22].

Low albumin has been associated with increased morbidity and mortality in hospitalized patients, but the role of hypoalbuminemia directly on mortality is still debated [22-25].

We have also shown that hyponatraemia is an independent predictor or mortality but not necessarily a direct cause of mortality. Looking out for hyponatraemia may help prognosticate chronic medical conditions and to avoid rapid correction to prevent osmotic demyelination syndrome especially in those with hypokalaemia, alcoholics and chronic malnutrition who present with chronic hyponatraemia[19]. Routine serum sodium measurements may help decrease mortality in patients with chronic medical conditions and appropriately managed them.

Our study had a number of limitations. It was a retrospective study and we reported only those with documented parameters in their clinical notes. The diagnoses were those made by the attending physicians and those with no clear diagnosis for the hyponatraemia were sent to the nephrologist to come up with diagnosis based on the available data which may be prone to bias. The authors therefore recommend a prospective randomized control trial to establish the risk of mortality with hyponatraemia and match other confounders such as diagnoses, serum albumin and serum protein and to exclude patients with other co-morbidities such as hypoalbuminemia which confounds as a predictor of mortality.

# Conclusion

The in-hospital mortality of patients with hyponatraemia is significantly higher than those with normonatraemia. Hyponatraemia predicts worse prognosis in patients on medical admission irrespective of their underlying diagnosis. Low serum albumin is also a predictor of increased in-hospital mortality.

# Abbreviations

ADH – Anti-diuretic hormone

KATH – Komfo Anokye Teaching Hospital

CHRPE - Committee on Human Research, Publications and Ethics

KNUST - Kwame Nkrumah University of Science and Technology

SD – standard deviation

IQR – interquartile range

OR – Odds ratio

CI – Confidence Interval

# Declarations

### Ethics approval and consent to participate

Ethical approval was obtained by the Institutional Review Board from the Committee on Human Research, Publications and Ethics (CHRPE), Kwame Nkrumah University of Science and Technology and Komfo Anokye Teaching Hospital (KATH) before the commencement of the study. Informed consent was waivered by the institution Review Board as it was a retrospective study and did not involve direct interaction with participants but clinical notes of patients admitted to the medical ward of the KATH.

### Consent for publication

All authors read the final manuscript and consented to publication.

### Availability of data and materials

Not applicable

### Competing interests

The authors declare that they have no competing interests

### Funding

None (The research project was self-funded by the authors).

### Authors' contributions

EKT, EA and AYT initiated the study and wrote up the first version of the manuscript. EA, YAB managed the data collection and cleaning of the data for analysis. EKT also cleaned the data and performed the data analysis. EKT, AYT then revised the first version of the manuscript. All authors were involved in critically revising the manuscript, read and approved the manuscript before submission. All authors had full access to all the data in the study and take responsibility for the integrity and the accuracy of the study.

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# Figures

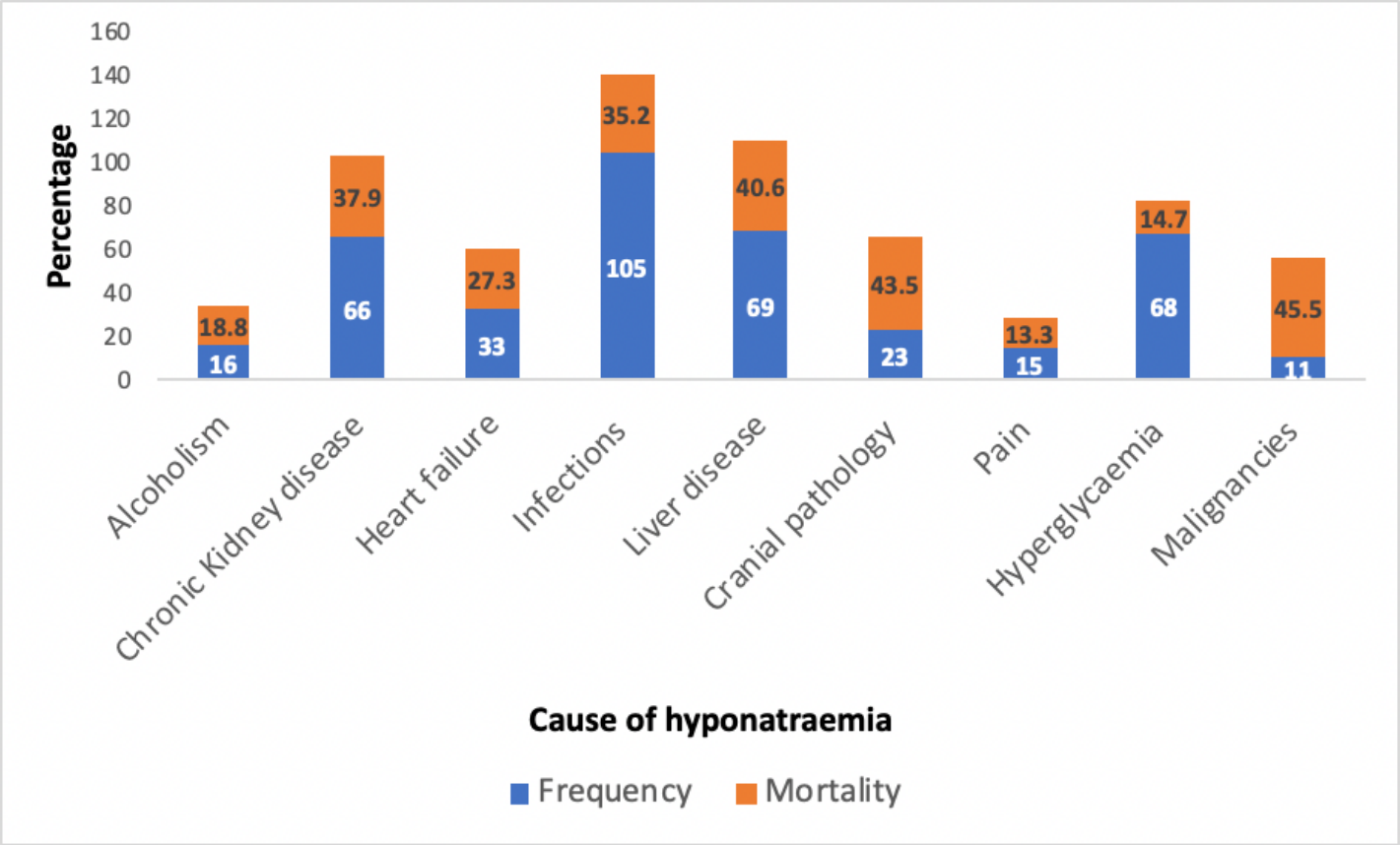


**Figure 1**

Causes of hyponatraemia and associated in-hospital mortality in medical admissions at KATH.

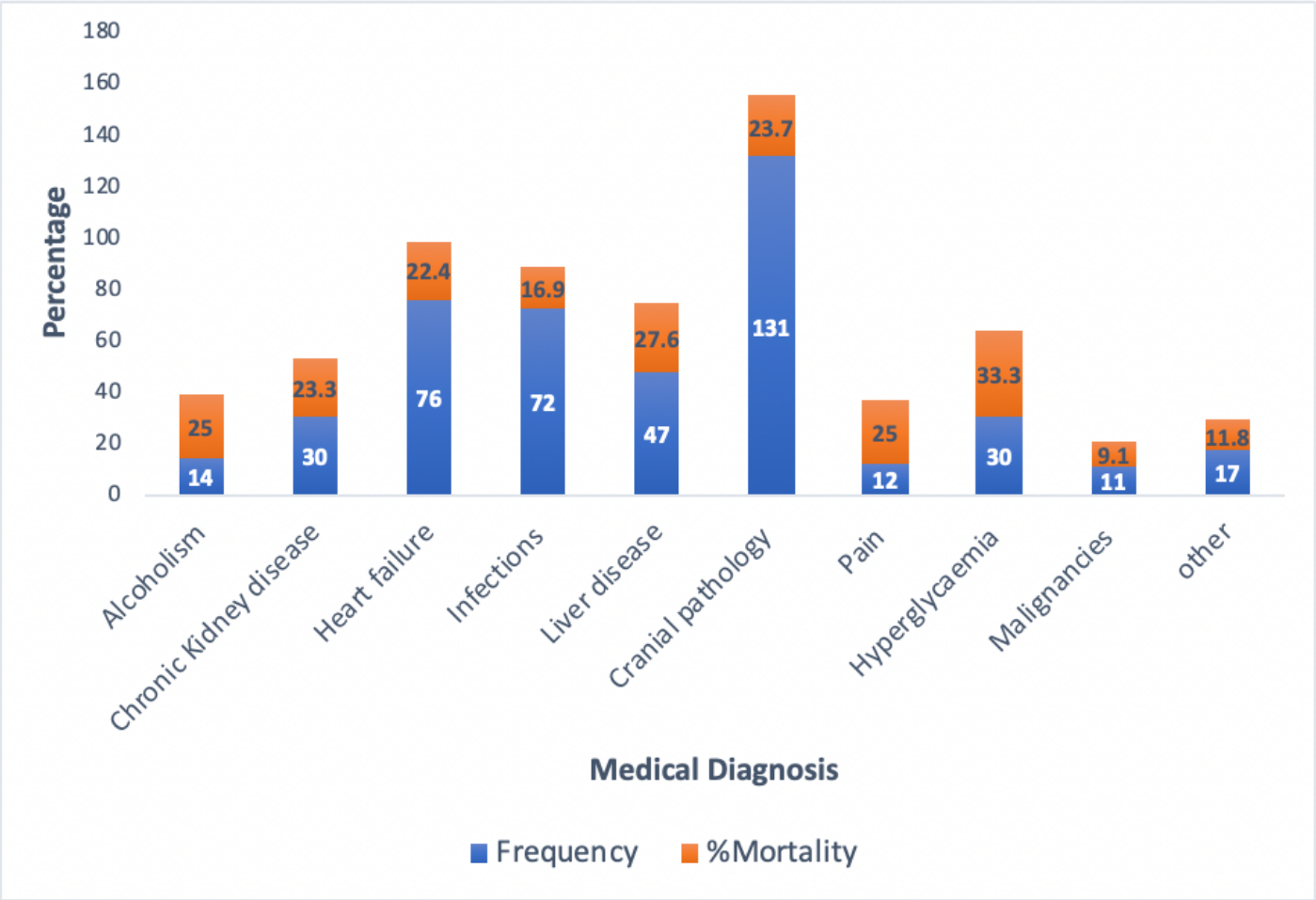


**Figure 2**

The medical diagnosis in patients with normonatraemia with in-hospital mortality in KATH