THE ASSOCIATION OF HYPONATREMIA WITH MORBIDITY AND MORTALITY: A RETROSPECTIVE STUDY ON OLDER HOSPITALIZED ADULTS

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ABSTRACT

Background: Hyponatremia is one of the most common electrolyte disorders to affect the older persons and is associated with impaired quality of life and survival. With the acceleration of population ageing especially in developing nations, hyponatremia would likely post a greater strain on the running and costs of the healthcare system. The aim of this study was to investigate hyponatremia associated clinical characteristics of hospitalized geriatric patients and its association with morbidity and mortality.

Methods: In this retrospective cohort study, sodium levels were categorized as normonatremia (135-145mmol/L); mild (130-134mmol/L), moderate (125-129mmol/L), profound (<125mmol/L) hyponatremia; and hypernatremia (>145mmol/L) based on serum sodium levels on admission. The characteristics of patients with these different sodium levels and the influence on length of hospital stay, 30-day readmission and 30-day mortality were then tested.

Results: Hyponatremia was detected in 338 (42.8%) out of the 789 patients evaluated. The mean sodium level of this study population was 135.18 (SD 10.440). Of the 338 patients with hyponatremia, 176 (52.1 %) had mild, 62 (18.3%) had moderate, while by 98 (29.0 %) had profound hyponatremia. Of the overall population of 789, 63 (8.0%) were having hypernatremia. Younger age (OR 0.967; 95% CI 0.947-0.988, P=0.002), thiazide diuretics (OR 2.666; 95% CI 1.1517-4.686; P value 0.001), and diabetes mellitus (OR 1.7976; 95% CI 1.324-2.438; P value <0.001) were independent risk factors for hyponatremia. Hyponatremia had no influence on the mean length of hospital stay (Hyponatremia, Mean 15.59, SD 17.264 VS Non-hyponatremia, Mean 14.60, SD 11.417; Mean difference 0.992 (-1.016-2.999); P Value 0.333). The presence of profound hyponatremia was significantly associated with 30-day readmission (OR 1.921, 95% CI

1.129-3.271; P=0.016) whereas hypernatremia was associated with higher 30-day mortality (OR 1.869, 95% CI 1.057-3.305, P= 0.032).

Conclusions: Hyponatremia is common among hospitalized geriatric patients. Hyponatremia and hypernatremia in the older patients have an impact on the rate of readmission and mortality respectively. Further studies could be conducted to measure any improvements in the readmission and mortality rates when the serum sodium abnormalities are corrected.

Keywords: Hyponatremia, Hypernatremia, Geriatrics, 30-day readmission, 30-day mortality

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Last but not least, I would like to dedicate this thesis to my baby…. “Mummy and Pappy love you lots…. We will always miss you..... See you again in Heaven…”

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CHAPTER 1: INTRODUCTION

1.1 Background

Older persons are considered those aged 65 years and above according to the World Health Organization. Population aging will continue and accelerate especially in developing nations due to declining fertility rate and increase in life expectancy. The number of people aged 65 or older is projected to grow from an estimated 524 million in 2010 to nearly 1.5 billion in 2050 representing 16% of the world population. Chronic and degenerative diseases are now the most common conditions affecting the aging population in the developed world and fast affecting the developing world regardless of income level as infectious diseases which previously contributed to the high mortality among the young are brought under control with improved infrastructure and public health initiatives (Organization, 2010). 80% of older persons have at least one and 68% have at least two or more of chronic conditions. The most common illnesses affecting adults aged 65 years and above in descending order of frequency are hypertension, arthritis, ischemic heart disease, diabetes mellitus, chronic kidney disease, congestive cardiac failure, depression, Alzheimer Disease and Dementia, and chronic obstructive pulmonary disease(Aging, 2018).

The most common reasons for admissions among older persons are congestive cardiac failure, pneumonia, coronary artery disease, chronic obstructive pulmonary disease, stroke, osteoarthritis, electrolyte imbalance, urinary tract infection, hip fracture and rehabilitation (Quality, 2003). When patients are admitted to the acute medical take, they would nearly always receive investigations, namely the blood count, electrolytes, blood gases and radiological studies as indicated to complement the history and physical examination in order to facilitate an accurate diagnosis and subsequent management plan. Hyponatremia, defined as serum sodium level of less than 135mmol/L, is one of the most common blood test abnormalities among inpatients (Spasovski et al., 2014). Despite this, little is currently known about the prevalence, risk factors or clinical significance of hyponatraemia among older adults. Recent evidence has suggested that even mild hyponatraemia may be associated with reduced physical and mental function (Renneboog, Musch, Vandemergel, Manto, & Decaux, 2006) (Myron Miller, 2006).

Therefore, hyponatremia could provide a prognostic yardstick for geriatric admissions and its proper management may improve the outcome of the geriatric patients.

1.2 Literature Review

The literature review was conducted by searching previous published articles via the PubMed-NCBI and Google Scholar search engines with key words such as "geriatric", "hyponatremia", "hypernatremia", "physiology of sodium balance", "mortality associated with hyponatremia, hypernatremia", "length of hospital stay", "readmission rates", "causes of hyponatremia", "thiazides".

Clinicians often face difficulties in diagnosing and managing hyponatremia despite it being the most common disorder of electrolyte and body fluid balance (Spasovski et al., 2014). Older persons are more prone to developing hyponatremia due to age-related physiological changes, polypharmacy and existing premorbid conditions.

Physiologically, older subjects are prone to hyponatremia due to the age-related reduction in total body water, reduction in glomerular filtration rate and reduction in intrarenal production of prostaglandin which is essential in water reabsorption in the renal tubules. All these would contribute to a state of hypovolemia with essentially lower levels of serum sodium. In addition, there has been postulation that the older age group is more sensitive to osmotic diuresis giving rise to preponderance towards syndrome of inappropriate anti-diuretic hormone secretion (SIADH) for which the patients would have euvolemic hyponatremia. Hypovolemic hypovolaemia often do not happen by itself but develops only when there is increased water intake and additional precipitating or predisposing factors. Older patients often consume medications which by themselves could alter the sodium-water homeostasis such as thiazide diuretics, antipsychotics namely selective serotonin reuptake inhibitors (SSRIs), and non-steroidal anti-inflammatory drugs (NSAIDs). In addition, older persons are also more prone to diseases which by themselves could cause hyponatremia such as diabetes mellitus, chronic kidney disease, congestive cardiac failure, and chronic liver disease. The diet intake and nutrition of the older age group may also predispose them to hyponatremia as they are often on salt restricted diet for their underlying diseases such as hypertension, heart or kidney diseases. A malnourished older person might also have hypoalbuminemia, contributing to a fluid retention and dilutional hyponatremia. (Filippatos, Makri, Elisaf, & Liamis, 2017)

Older patients do not usually present to the hospital with the diagnosis of hyponatremia alone but with an unrelated illness. It is most often an incidental diagnosis during the review of the blood analysis. Hence, hyponatremia is not an isolated disease but an additional factor to an underlying disorder.

Symptoms attributable to hyponatraemia are caused chiefly by excessive entry of water into brain cells and include malaise, headache, nausea and confusion. Since brain cells can adapt to changes in plasma tonicity over time, more severe symptoms such as seizures, coma or even death occur mainly in rapid-onset hyponatraemia (Soiza & Talbot, 2011).

Hyponatremia has many negative implications to older persons. It may be an important contributor to the major geriatric syndromes such as cognitive impairment (Myron Miller, 2006), bone demineralization (Verbalis et al., 2010), immobility and falls (Renneboog, Musch, Vandemergel, Manto, & Decaux, 2006), and hip fractures (Gankam Kengne, Andres, Sattar, Melot, & Decaux, 2008).

In several previous studies, hyponatremia leads to a higher mortality rate either as a direct consequence of the electrolyte imbalance or complicating the underlying illness (Soiza & Talbot, 2011), (Brouns et al., 2014), (Mohan, Gu, Parikh, & Radhakrishnan, 2013).

Wilson et al constructed a simple 5 point scoring system, namely the NaURSE score to prognosticate the mortality of geriatric patients aged 90 years and above. However, in his publication, hypernatremia was the variable included instead of hyponatremia based on the fact that in the oldest old (aged 90 years and above), hypernatremia has been identified as a significant predictor of in patient mortality (Wilson et al., 2014). As for hyponatremia, a prognostication scoring system is not currently available.

In view of the numerous negative impact hyponatremia has on the older persons, , a research studies which would aid a better understanding of the aetiology and characteristics of hyponatraemia , as well as its prognostic implications are urgently required.

1.3 Research Questions

1. What are the factors associated with hyponatraemia among older patients admitted to a geriatric ward?
2. Is hyponatremia associated with increased mortality and morbidity among patients on a geriatric ward in a teaching hospital?

1.4 Objectives of Study

(1) To identify factors associated with hyponatraemia among patients on a geriatric ward.

(2) To determine the influence of hyponatraemia among patients on length of hospital stay, 30- day readmission, and mortality among geriatric inpatients

CHAPTER 2: METHODOLOGY

2.1 Study design

This was a retrospective cohort study involving consecutive older patients admitted to the Geriatric Ward of the University of Malaya Medical Centre, Kuala Lumpur from 2014 till 2015. The geriatric age group in this study was defined as 65 years and above coinciding with age criteria of patients admitted to the Geriatric Ward. Hyponatremia was defined as a serum sodium level of less than 135mmol/L.

2.2 Data Collection

The data for this study was obtained from the Frailty among In-patients on a Geriatric Ward (FIG) database. The FIG study was funded by a University of Malaya Research Programme grant (RP-010-2012). The study had obtained ethical approval from the University of Malaya Medical Centre ethics committee (UMMC Ethics Approval no: 925.5) (Appendix A). Detailed demographic information, medical history and medications were collected using a comprehensive geriatric assessment (CGA) checklist (Appendix B). Information on the CGA was then entered into a database by a data entry personnel, who also helped ensured completion of the CGA by attending doctors. Information for the length of stay and 30- day readmission was collected from the hospital's electronic medical records based on the dates of admission, discharge and readmission if any. The blood results on admission were obtained from the hospital laboratory records. Incomplete data were further reconciled by referring to hospital case notes. Information on inpatient mortality including the date of demise was obtained from the hospital records. Information on mortality occurring beyond the hospital admission was obtained from the National Death Registry with the assistance of the Clinical Research Centre (CRC) of Kuala Lumpur General Hospital. Based on the actual date of death, the frequency of mortality within 30 days of the index admission was determined.

2.3 Definitions

2.3.1 Cases

Older patients identified within the dataset with a serum sodium below 135 mmol/L.

2.3.2 Controls

Older patients identified within the dataset with a serum sodium of 135 mmol/L or above

2.3.3 Classification of Hyponatraemia and Definition of Normonatremia and Hypernatremia

Hyponatremia was further subdivided into mild (130-134mmol/L), moderate (125-129mmol/L) and profound (less than 125mmol/L) in accordance to European Guidelines (Spasovski et al., 2014).

Normonatremia was defined as serum sodium of 135-145mmol/L.

Hypernatremia was defined as serum sodium of above 145mmol/L.

2.4 Outcomes

2.4.1 Morbidity

Measured by the length of hospital stay and the frequency of re-admission within 30 days following the index admission.

2.4.2 Mortality

Measured by the frequency of mortality within 30 days of the index admission.

2.5 Data analysis

Data analysis was conducted with SPSS version 21.0. Serum sodium was categorized into hyponatremia and non-hyponatremia (includes normal levels and hypernatremia). Continuous variables were tested with the independent t test whereas categorical variables were tested with the Chi Square test. Univariate analysis was used to describe the data followed by multivariate analysis to identify the independent risk factors for hyponatremia. Variables were selected for multiple regression model if between categories yielded a p-value of 0.20 or below. Logistic regression was also used to determine the influence of natraemic state on to the length of stay, 30- day readmission and 30- day mortality. Hyponatremia was further categorised based on its severity and non-hyponatremia was categorised to hypernatremia and normonatremia. The influence of each natraemic subcategory on 30- day readmission and 30- day mortality were determined using logistic regression with dummy variables as compared to with normonatremia as the reference variable. The hazard ratios (HR) and 95% confidence intervals (CI) for mortality was determined for the different categories of natraemic status using Cox's proportional hazards regression with the normonatraemic category considered the reference category, using forced entry for natraemic status and backward stepwise method for potential confounders identified from variables with a p-value of <0.20 in Table 1. Cox's proportional hazards was used to test the influence of hypernatremia, hyponatremia and normonatremia on mortality. In this study, statistical significance was defined as P value <0.05.

CHAPTER 3: RESULTS

From the FIG database, a total of 793 patients were listed. However, 4 were excluded from this study due to missing or incomplete data. As a result, the total number of patients included in this study was 789.

Of those included (n=789), 338 (42.8%) fulfilled criteria for hyponatremia. The mean age of all patients included in this study was 80.31 (SD 7.294). Patients with hyponatremia had a mean age of 79.20 (SD 7.53) which was slightly lower compared to those with no hyponatremia with a mean age of 81.14 (SD 7.00); (P value <0.001). Patients with hyponatremia were more likely to have diabetes mellitus (182 (53.8%) vs 167 (37/0%); P value <0.001) and were more likely to be on thiazide diuretics (41 (12.1%) vs 21(4.7%); P value 0.010). There was no significant difference between the two groups for the other pre-morbidities and medications (Table 1), (Table 2).

Table 1: Patients' Characteristics

Characteristic	Hyponatremic (n=338)	Non-Hyponatremic (n=451)	P value
Age (years); Mean (SD)	79.20 (7.53)	81.14 (7.00)	<0.001*
Gender, n (%)			
Male	116(34.3)	183(40.6)	0.073
Female	222(65.7)	268(59.4)	
Ethnicity, n (%)			
Chinese	181(53.6)	261(57.9)	0.054
Malay	83(24.6)	106(23.5)	
Indian	70(20.7)	69(15.3)	
Others	4(1.2)	15(3.3)	
Existing co-morbidities, n (%)			
Ischemic Heart Disease	67(19.8)	106(23.5)	0.216
Congestive Cardiac Failure	15(4.4)	22(4.9)	0.772
Atrial Fibrillation	28 (8.3)	41 (9.1)	0.691
Stroke	95 (28.1)	154 (34.1)	0.071
Hypertension	245 (72.5)	327 (72.5)	0.995
Diabetes Mellitus	182 (53.8)	167 (37.0)	<0.001*
Parkinson	12 (3.6)	28 (6.2)	0.092
Epilepsy	3 (0.9)	5 (1.1)	0.759
Osteoarthritis	15 (4.4)	23 (5.1)	0.667
Asthma	12 (3.6)	24 (5.3)	0.238
Tuberculosis	3 (0.9)	3 (0.7)	0.722
Gastrointestinal bleed	9 (2.7)	5 (1.1)	0.102
Liver disease	4 (1.2)	1(0.2)	0.092
Chronic Kidney Disease	38 (11.2)	47 (10.4)	0.713

*statistically significant to p<0.001

Table 2: Medication on Admission and Risk of Hyponatraemia

Medications, n (%)	Hyponatremic (n=338)	Non-Hyponatremic (n=451)	P value
Thiazides	41 (12.1)	21(4.7)	0.010*
Frusemide	37 (10.9)	48 (10.6)	0.918
Angiotensin Converting Enzyme Inhibitor	61 (18)	68 (15.1)	0.574
Angiotensin Receptor Blocker	33 (9.8)	40 (8.9)	0.861
Beta Blocker	65 (19.2)	98 (21.5)	0.551
Calcium-Channel Blocker	98 (29.0)	135 (29.9)	0.827
Alpha Blocker	19 (5.6)	28 (6.2)	0.651
Anti-psychotic	5 (1.5)	21 (4.7)	0.038*
Selective serotonin reuptake inhibitor	5 (1.5)	9 (2.0)	0.780
Tricyclic Antidepressant	3 (0.9)	4 (0.9)	0.920
Proton Pump Inhibitor	51 (15.1)	81 (18.0)	0.444
Steroids	9 (2.7)	13 (2.9)	0.897
Statin	127 (37.0)	172 (38.1)	0.787
Anti-epileptic	17 (5.0)	40 (8.9)	0.091

*statistically significant to $p<0.05$

As for independent risk factors for hyponatremia, younger age (OR 0.967; 95% CI 0.947-0.988, P=0.002), thiazide diuretics (OR 2.666; 95% CI 1.1517-4.686; P value 0.001), and diabetes mellitus (OR 1.7976; 95% CI 1.324-2.438; P value <0.001) were independent risk factors for hyponatremia (Table 3).

Table 3: Independent Risk Factors for Hyponatremia

Factors	**Odds Ratio (95% CI)**	**P Value**
Age	0.967 (0.947-0.988)	0.002*
Gender	1.293 (0.948-1.763)	0.104
Thiazides	2.666 (1.1517-4.686)	0.001*
Anti-epileptics	0.604 (0.325-1.121)	0.110
Liver Disease	5.535 (0.604-50.737)	0.130
Parkinson	0.601 (0.291-1.239)	0.168
Stroke	0.770 (0.558-1.064)	0.114
Diabetes Mellitus	1.796 (1.324-2.438)	<0.001*

*statistically significant, p<0.05, after adjustment for gender, anti-epileptics, liver disease, Parkinson's disease and stroke.

Table 4 summarizes the overall sodium profiles of the population. The mean sodium level of this study population was 135.18 (SD 10.440). Of the 338 patients with hyponatremia, 176 (52.1 %) had mild (130-134mmol/L), 62 (18.3%) had moderate (125-129mmol/L), while by 98 (29.0 %) had profound (<125mmo/L) hyponatremia. Of the overall population of 789, 63 (8.0%) were having hypernatremia.

<u>Table 4: Distribution of Sodium Levels</u>

Variables	n (%)
Any Hyponatremia, N (%)	338 (42.8)
Mean Sodium Level (SD)	135.18 (10.440)
Hyponatremia	n (%)
Mild (130-134)	176(22.3)
Moderate (125-129)	62 (7.9)
Profound (<125)	98 (12.4)
Normal level (135-145)	390 (49.4)
Hypernatremia (>145)	63 (8.0)

As seen in Table 5, presence of hyponatremia had no influence on the mean length of hospital stay.

<u>Table 5: Influence of any hyponatraemia on length of hospital stay</u>

	Hyponatremia (n=338)	**Non Hyponatremia (n=451)**	**Mean Difference (95% CI)**	**P value**
Length of Stay (Mean) , SD	15.59 (17.264)	14.60 (11.417)	*0.992 (-1.016-2.999)	0.333

*Values indicate mean difference

Tables 6 shows that hyponatremia was not significantly associated with a 30-day readmission (OR 1.450, 95% CI 0.988-2.127, P=0.057). Whereas hypernatremia was associated with higher 30-day mortality (OR 1.869, 95% CI 1.057-3.305, P= 0.032).

Table 6: Influence of Hyponatremia and Hypernatremia on 30-day readmission and 30-day mortality

Categories of Sodium Levels (mmol/L)	30-days Readmission (OR; 95% CI)	P Value	30-day Mortality (OR; 95% CI)	P Value
Normal (135-145)	1 (Reference)	-	1 (Reference)	-
Hyponatremia (<135)	1.450 (0.988-2.127)	0.057	0.933 (0.655-1.330)	0.702
Hypernatremia (>145)	1.059 (0.510-2.197)	0.879	1.869 (1.057-3.305)	0.032*

*statistically significant to p<0.05

As displayed in Table 7, the presence of profound hyponatremia was significantly associated with 30-day readmission (OR 1.921, 95% CI 1.129-3.271; P=0.016) compared to those with normal sodium.

Table 7: Influence of severity of hyponatraemia on 30-day readmission and 30-day mortality

Range Of Serum Sodium (mmol/L)	30-days Readmission (OR; 95% CI)	P Value	30-days Mortality (OR; 95% CI)	P Value
135-145	1 (Reference)	-	1 (Reference)	-
<125	1.921 (1.129-3.271)	0.016*	0.838 (0.481-1.459)	0.531
125-129	1.079 (0.519-2.242)	0.839	0.836 (0.426-1.639)	0.602
130-134	1.343 (0.843-2.140)	0.214	1.024 (0.669-1.568)	0.912
>145	1.059 (0.510-2.197)	0.879	1.869 (1.057-3.05)	0.032*

*statistically significant to $p<0.05$

Table 8 shows that hypernatremia and increasing age are associated with increased risk of mortality.

Table 8: Hazard Ratio Mortality and Natraemic Status

Variable	Hazard Ratio (95% Confidence Interval)	P Value
Natraemic State		0.003
Normonatraemia	Reference	
Mild hyponatraemia	0.917 (0.680-1.237)	0.570
Moderate hyponatraemia	1.209 (0.861-1.696)	0.273
Severe hyponatraemia	1.064 (0.841-1.347)	0.603
Hypernatraemia	1.805 (1.327-2.454)	<0.001
Age*	1.039 (1.025-1.053)	<0.001
Female Gender	0.800 (0.666-0.962)	0.018
Diabetes	0.824 (0.681-0.996)	0.045
Ethnicity		0.094
Malay	Reference	
Chinese	0.927 (0.745-1.153)	0.495
Indian	0.918 (0.535-0.965)	0.028
Others	0.606 (0.295-1.242)	0.151

*per year increase

The cumulative mortality according to natraemic status adjusted for age, gender, ethnicity and diabetes is demonstrated in Figure 1. Cox regression analysis identified a significant increase in mortality with hypernataremia compared to those with normonatraemia, while no significant increase in risk of mortality was observed for all three hyponatraemia severity categories compared to those with normonatraemia.

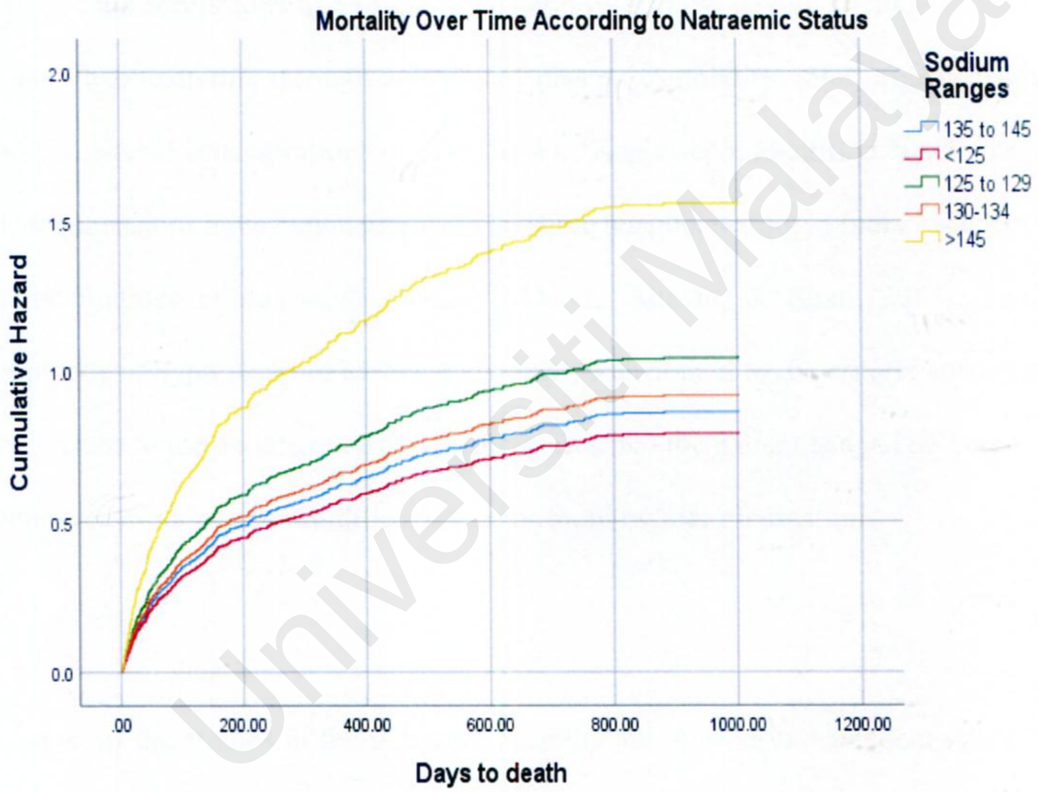

Figure 1: Survival Analysis of Different Ranges of Serum Sodium Levels

Cumulative mortality curve adjusted for age, gender, ethnicity and diabetes according to natraemic status. Individuals with hypernatraemia (yellow), had significantly higher risk of mortality compared to those with normal sodium levels (blue) on admission. There was no significant difference in mortality with mild (orange), moderate (green) or profound (red) hyponatraemia compared to normonatraemia.

CHAPTER 4: DISCUSSION

Hyponatremia was surprisingly common among our admissions to the geriatric ward. The frequencies of hyponatremia in older populations with previous studies in the literature indicating differing rates depending on the differences in definitions and study populations . Hawkins et all reported a prevalence of 23.6% for individuals aged 60 years and above with sodium levels of less than 135mmol/L for patients in Singapore (Hawkins, 2003). Miller et al identified a rate of 18% of patients in a nursing home setting (M. Miller, Morley, & Rubenstein, 1995). Similarly, Kayar et al reported a prevalence of 18% for the admissions to a teaching hospital in Turkey; having excluded patients with pseudo-hyponatremia through analysis of plasma osmolality, total protein, triglyceride and cholesterol concentrations (Kayar, 2016). . Kaeley et al identified that 45.6% of their older admissions have hyponatremia in an acute hospital setting in India, which is similar to the findings of this study (Kaeley, Akram, Ahmad, & Bhatt, 2017). The higher frequency of hyponatremia in this study may be attributed to the criteria and methods of admissions to the geriatric ward, which requires that the patient is aged 65 years or over, with three or more comorbidities or four or more regular medications.

Most of the studies in the literature attribute aging as an independent risk factor for hyponatremia. The study in Singapore showed that patients >81 years were at increased risk of hyponatremia compared to individuals aged <30 years (Na <136mmol/L, OR 1.89 95% CI 1.78-2.01; P value <0.05) (Hawkins, 2003). The German study showed that the prevalence of hyponatremia peaked in the oldest age groups (>85 years) (Gosch, Joosten-Gstrein, Heppner, & Lechleitner, 2012). The patients with hyponatremia in this study were slightly younger than those with no hyponatremia. Hyponatremia was compared against those without hyponatremia in this study which actually included a number of individuals with hypernatraemia which may have confounded the age preponderance in our study. However subsequent multinomial logistic regression comparing the different categories of sodium levels and age groups still showed no statistical significance influence of age in risk of hyponatremia. As we had not included anyone aged below 65 years in our study, we are unable to conclude that age is not a risk factor for hyponatremia. However, there did not appear to be any increase in likelihood of hyponatremia with increasing age among inpatients in our geriatric ward. This is likely to be influenced by patient selection, but also reflects on the regional differences in characteristics of geriatric patients and highlights the need for local studies since evidence generated from existing published studies may lack relevance in our region.

Gender did not significantly influence the likelihood of hyponatremia as demonstrated in other Asian studies from Singapore (Hawkins, 2003) and Turkey (Kayar, 2016). However, several studies conducted in predominantly Caucasian populations showed that female gender was a significant risk factor for hyponatremia. Clayton et al found that 60% of their patients with hyponatremia were women in his prospective study (Clayton, Le Jeune, & Hall, 2006). Shapiro et al reported a higher prevalence of hyponatremia among older women (8.1% women vs 4.0% men, P value <0.001) (Shapiro, Sonnenblick, Galperin, Melkonyan, & Munter, 2010). One of the reasons for the female preponderance of hyponatremia is the increased usage of psychotropic medications and diuretics (Madhusoodanan et al., 2002), (Sonnenblick, Friedlander, & Rosin, 1993). In addition, older women have a total body water predisposing them to dehydration and disruption in the homeostasis between fluids and serum sodium levels (RULOP Jr, 1985). The absence of any significant difference between the genders in this study and the studies conducted in other Asian populations may be attributed to limited differences in body composition and weight between genders.

This study showed that the use of thiazide diuretics was an independent risk factor for hyponatremia. Hydrochlorothiazide was the most commonly prescribed thiazide in our patient population. A study by Clayton et al reported that 13.7% of thiazide treated outpatients had hyponatremia and among them, those aged 70 years and above were associated with a fourfold increase in risk of hyponatremia (Clayton, Rodgers, Blakey, Avery, & Hall, 2006). The study by Gosch et al on the other hand, showed no significant association between hyponatremia and thiazide (Gosch et al., 2012). However from the same study, patients with hyponatremia tend to be on more oral medications (mean 8.4 SD 3.8) compared to the control group (6.9 SD 3.6; P value 0.002) and more likely to be on more medications that may induce hyponatremia such as diuretics, neuroleptics, anti-depressive and antiepileptic drugs) (mean 3. SD 1.8 vs 2.85 SD 1.3; P value 0.034). For the treatment of hypertension according to the National Institute of Clinical Excellence (NICE) guidelines; those aged 55 years and above or of Afro-Caribbean descent, who could not tolerate calcium-channel blocker; thiazide-like diuretics such as chlortalidone or indapamide would be the medication of choice in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide. This could be due to the fact that the thiazide-like diuretics significantly further reduce the systolic (Mean difference -5.59, 95% CI -5.69, -5.49; P Value <0.001) and diastolic blood pressure (Mean difference -1.98, 95% CI -3.29, -0.66; P Value 0.003) better than the conventional thiazide-type diuretics without having any significant difference in the side effects profile such as hyponatremia and hypokalemia (Liang, Ma, Cao, Yan, & Yang, 2017). As a summary, if thiazide diuretics were to be prescribed as the anti-hypertensive of choice for older patients, the thiazide-type diuretics namely chlorthalidone or indapamide should be the preferred choice and the prescriber should be aware of the co-existing hyponatremia inducing medications that the patients are on in order to reduce the risk of hyponatremia. As a result, clinicians should therefore consider reviewing the prescription of hydrochlorothiazide in older patients in our setting, though subsequent studies to determine whether avoidance of prescription of hydrochlorothiazide may result in fewer admissions with hyponatremia or lower likelihood of developing hyponatremia with associated improvements outcomes, should ideally be conducted to back this recommendation.

Diabetes mellitus was an independent risk factor for hyponatremia. The presence of hyperglycaemia could give rise to "pseudo hyponatremia". This is due to the fact that glucose itself is an osmotic active substance and marked hyperglycaemia could increase the plasma osmolality leading to movement of water out of cells and subsequent reduction of serum sodium levels. In such instances, the serum sodium concentration should be corrected for the degree of hyperglycaemia by adding to measured serum sodium 1.6mmol/L for 5.5mmol/L increment of serum glucose above normal up to 22.2mmol/L and by adding to measured serum sodium 2.4mmol/L when serum glucose concentrations are higher than 22.2mmol/L (Filippatos et al., 2017). Interestingly, Liamis et al found that diabetes mellitus itself causes hyponatremia regardless of serum glucose levels (Liamis et al., 2013). This could be explained by the altered vasopressin regulation in diabetes mellitus, the increased insulin induced potentiation of vasopressin-induced aquaporin AP2 water channel expression and the absorption of water from the GI tract due to slower gastric emptying in gastroparesis (Bustamante et al., 2005), (Bankir, Bardoux, & Ahloulay, 2001).

Although the length of stay was not significantly affected by hyponatremia in this cohort of patients, the impact of hyponatremia on the healthcare system should be substantial. Calahan et al in the retrospective cohort study of hospitalized patients aged 18 years and above with hyponatremia on admission found that patients with mild to moderate and moderate to severe hyponatremia had significantly longer and more costly hospital stays compared to those with normonatremia. Based on an annual admission of approximately 55,000 patients, the estimated potential burden of hyponatremia on the hospital was reported to be more than 3,400 bed days and $ 2.15 million of additional costs (Callahan, Do, Caplan, & Yoon-Flannery, 2009). Hyponatremia may represent a greater burden on the healthcare system in the near future as the population ages (M. Miller et al., 1995), (Hawkins, 2003).

This study showed that patients with profound hyponatremia were at an increased risk of readmission within 30 days compared to those with no hyponatremia or hypernatraemia. . This finding is consistent with the retrospective observational study of 36,048 patients that had been discharged from 445 hospitals by Deitelzweig et al which reported that primary diagnosis of hyponatremia was associated with an increased risk of hospital readmission within 30 days (OR 4.76, 95% CI 4.31- 5.26; P value <0.001) (Deitelzweig et al., 2013).

This study did not show any significance between hyponatremia and 30-day mortality. On the contrary, published studies do report an increased risk of mortality among patients with hyponatremia. Holland et al reported 30-day mortality of 3.6% in normonatremic patients compared to 7.3, 10.0, 10.4 and 9.6% in patients with serum sodium levels of 130–134.9, 125–129.9, 120–124.9 and <120 mmol/L respectively. The probability of death increased when serum sodium decreased from 139 to 132 mmol/L with no clear increase in mortality observed for lower concentrations (Holland-Bill et al., 2015). Waikar et al reported that risk of mortality was increased even at mild levels of hyponatremia and the risk was attenuated when the hyponatremia was corrected (Waikar, Mount, & Curhan, 2009). The mortality is most probably not caused by hyponatremia alone as hyponatremia is by itself an indication of the severity of an underlying chronic disease such as congestive cardiac failure and chronic liver disease.

Interestingly, this study showed that elderly inpatients with hypernatremia has an increased risk of 30-day mortality compared to normonatremia patients. Hypernatremia has been associated with an increased mortality in the frail elderly (Arinzon, Feldman, Peisakh, Zuta, & Berner, 2005). This might be due to the fact that hypernatremia could be a measure of the degree of dehydration which would also indicate the fluid status and hemodynamic stability of the elderly patients. The correction of the dehydration and maintenance of stable hemodynamic could provide an improved outcome. Further studies could be conducted on this cohort of patients looking further into the patient characteristics and possible risks for hypernatremia.

One of the limitations of this study was that it did not take into account the fluid status and serum osmolality of the patients, hence eliminating the possibility of determining whether the hyponatremic patients were euvolemic, hypovolemic or hypervolemic which could be essential in determining the exact cause of the hyponatremia. The other limitation would be that this is a single centre study and the findings might not be representative of the general population.

The strength of this study was that it involved a large dataset. In addition, it was a unique study involving multi ethnic population in a developing country.

Further studies are recommended to determine whether avoidance of prescription of hydrochlorothiazide may result in fewer admissions with hyponatremia or lower likelihood of developing hyponatremia with associated improvements outcomes. In addition, further studies are also required to look into the characteristics, risk factors, morbidity and mortality of patients with hypernatremia.

CHAPTER 5: CONCLUSION

Hyponatremia and hypernatremia in the older patients have an impact on the rate of readmission and mortality respectively. Further studies could be conducted to measure any improvements in the readmission and mortality rates when the serum sodium abnormalities are corrected as the identification and correction of the sodium abnormalities could provide an improved outcome and reduce healthcare burden. A prognostic tool for hyponatremia, similar to the NaURSE scoring system for hypernatremia could be established in the near future to correctly identify older persons with hyponatremia at risk, so that prompt and adequate treatment could be administered to provide a better outcome.

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