Prevalence and documented causes of hyponatraemia among geriatric patients attending a primary care clinic

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ABSTRACT

Introduction: Hyponatraemia is the commonest electrolyte abnormality and has major clinical implications. However, few studies of hyponatraemia in the primary care setting has been published to date. OBJECTIVES: To determine the prevalence, potential causes and management of hyponatraemia and to identify factors associated with severity of hyponatraemia among older persons in a primary care setting.

Methods: Electronic records were searched to identify all cases aged ≥60 years with a serum sodium <135mmol/l, attending outpatient clinic in 2014. Patients' medical records with the available blood test results of glucose, potassium, urea and creatinine were reviewed.

Results: Of the 21,544 elderly, 5873 patients (27.3%) had electrolyte profile tests. 403 (6.9%) had hyponatraemia in at least one blood test. Medical records were available for 253, mean age 72.9±7.3 years, 178 (70.4%) had mild hyponatraemia, 75 (29.6%) had moderate to severe hyponatraemia. Potential causes were documented in 101 (40%). Patients with moderate to severe hyponatraemia were five times more likely to have a cause of hyponatraemia documented (p<0.01). Medications were the commonest documented cause of hyponatraemia (31.7%). Hydrochlorothiazide use was attributed in 25 (78.1%) of 32 with medication-associated hyponatraemia. Repeat renal profile (89%) was the commonest management of hypotonic hyponatraemia.

Conclusion: Whilst hyponatraemia was common in the clinic setting, many cases were not acknowledged and had no clear management strategies. In view of mild hyponatraemia has deleterious consequences, future studies should determine whether appropriate management of mild hyponatraemia will lead to clinical improvement.

KEY WORDS:
Hyponatraemia, aged, electrolytes, sodium

INTRODUCTION

Hyponatraemia affects 7.7% of community dwelling individuals aged 55 years and above.[1] Mild hyponatraemia is usually considered asymptomatic. Older adults with hyponatraemia are more likely to experience falls, osteoporosis and myocardial infarction compared to normonatraemic individuals.[2,3] Mild hyponatraemia can be a precursor to severe symptomatic hyponatraemia or could be an early manifestation of sinister disease such as malignancy which may present as syndrome of inappropriate antidiuretic hormone production (SIADH).[4,5] Recent evidence suggest that even mild hyponatraemia is associated with cognitive impairment, and, correction of hyponatraemia conversely improves cognition.[6] Acute, severe untreated hyponatraemia, on the other hand, can lead to serious neurological outcomes or death.[7]

Symptoms of hyponatraemia are non-specific. Nausea and malaise may be the earliest findings seen when the plasma sodium concentration falls below 130 to 125mmol/L and with worsening hyponatraemia, overt central nervous system (CNS) symptoms predominate and range from confusion to coma to seizures.[8] Due to its non-specific presentation, hyponatraemia is often missed, misdiagnosed or undertreated.[9] Making an accurate diagnosis of the underlying causes of hyponatraemia is the key to successful treatment because the type of hyponatraemia dictates the approach to therapy.[10] Management of hyponatraemia is challenging for both primary care physicians because there are a myriad of treatment-related reviews and publications with no clear guide as to evidence-based treatment for hyponatremia.[11]

The aetiology of hyponatraemia was recorded in only 42% of cases in a study conducted at a UK teaching hospital.[12] Physicians often tolerate chronic mild hyponatraemia as if it was benign, with evidence suggesting that they tend to investigate only when the level was severely low. Doctors in the UK study were four to six times more likely to initiate investigation if the serum sodium was less than 125mmol/L.[12] Established causes of hyponatraemia include medications, chronic kidney disease, congestive heart failure, SIADH and Addison's disease.

Ageing is associated with reduced total body water, thirst sensation, renal responsiveness to anti-diuretic hormone, and glomerular filtration rate. As a result, older persons have decreased capacity to cope with drug-related stresses in

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sodium and water balance.[13] Therefore, older patients are prone to medication-related hyponatraemia thus easily preventable and reversible.[12]

There has been a dearth of literature on hyponatraemia in primary care settings, particularly in low and middle-income countries.[6] Therefore, this study aimed to identify the prevalence of hyponatraemia among elderly attending a primary care facility in a middle-income country in South East Asia, and the characteristics of patients with hyponatraemia, as well as current management strategies employed for hyponatraemia in this setting.

MATERIALS AND METHODS

Study Design and Participants

This was a retrospective review of electronic medical records (EMR) involving consecutive patients attending clinics at a primary care department of a large teaching hospital in Kuala Lumpur, Malaysia from 1 January to 31 December 2014. Inclusion criteria for medical records examination were age 60 years and above, with at least one laboratory test indicating a serum sodium lower than 135mmol/L,[14] and concomitant availability of serum glucose, potassium, creatinine and urea results on the date of the abnormal laboratory test in order to calculate the estimated glomerular filtration rates and the estimated serum osmolality. The United Nations defines older persons as individuals aged 60 years and above. This definition has been adopted by policy makers in Malaysia to categorise its older population and the new retirement age of 60 years has been effective since 2012.[15] This study was approved by the Medical Ethics Committee, University Malaya Medical Centre (MECID No: 20147-411). As this was a retrospective case record analysis, informed consent was not needed, and this was waived by the medical ethics committee.

Case identification

The electronic medical records (EMR) of the University of Malaya Medical Centre (UMMC) (iPesakit) were first interrogated to identify all older individuals attending primary care clinic during the study period to identify the denominator. Subsequently, the hospital clinical diagnostic laboratories provided the biochemistry results of all blood samples received from the primary care clinic from individuals aged 60 years and above. The personal details of individuals with a serum sodium below 135mmol/L was then obtained from laboratory records of all individuals within this list.

Data collection

The EMR of all individuals aged 60 years and over, attending the primary care clinic, who had recorded a serum sodium of below 135mmol/l on at least one occasion in 2014 were then reviewed for retrospective data collection. Information on age, gender, ethnicity, medical history, medications, diagnoses and likely causes documented (documented causes) during the first consultation after the blood tests, investigations and management initiated were obtained from iPesakit. In addition, serum sodium, urea, creatinine and glucose results were obtained from the electronic results of the first or only abnormal sodium sample recorded in EMR.

Hyponatraemia

Hyponatraemia was defined as a serum sodium of less than 135mmol/l. This was then subdivided into mild (130-134mmol/L), moderate (126-129mmol/L) and severe (less than 126mmol/L) according to established international ranges.[16] Serum osmolality was estimated using the formula: Serum osmolality = 2Na+2K+urea+glucose (in mmol/L).[17] While the Glomerular Filtration Rate (eGFR) was estimated using the CKD-epi equation.[18] Chronic kidney disease (CKD) was considered present if the eGFR was less than 60ml/min/1.73m^2.

The manifestation of hyponatraemia was then further classified into hypertonic, hypotonic and isotonic hyponatraemia according to the calculated serum osmolality.[17] If serum osmolality was more than 295mmol/L with high serum glucose level, hyperglycaemia was recorded as the potential cause of hypertonic hyponatraemia. Individuals with hyperlipidaemia or hyperproteinaemia with estimated serum osmolality of 275 to 295mmol/L were classified as pseudohyponatraemia. Serum osmolality of less than 275mmol/L, was considered hypotonic hyponatraemia. The presence of possible medication-induced hyponatraemia was defined by the presence of hyponatraemia in a patient with a prescription of any medication that is known to be associated with hyponatraemia as stated in the patients' EMR. Acute conditions such as acute vomiting or diarrhoea, Addisonian's crisis and third space loss due to urosepsis or intestinal obstruction were also considered as the potential causes of hyponatraemia.

Data analysis and sample size estimation

Data analysis was conducted with SPSS version 23.0 (Chicago, IL, US). Categorical data were presented as frequencies with percentages in parentheses and analysed using the Chi-squared test. Continuous data were plotted as histograms to ensure normal distributions. Parametric data were presented as means with standard deviations and analysed using the independent t-test or analysis of variance. Hyponatraemia severity was dichotomised into mild and moderate-severe to facilitate logistic regression analyses. Logistic regression analyses were employed to adjust for potential confounders of severity of hyponatraemia. Epi info version 7 was used to calculate the sample size. Based on previously reported prevalence.[1] An estimated 20,000 patients attend the Primary Care Department, UMMC. A sample size of 187 would therefore be adequate to determine a similar prevalence with a confidence level of 99% and significance level set at $p<0.05$.

RESULTS

Patients' characteristics

A total of 21,544 patients aged 60 years and above attended the primary care clinic in 2014. Serum biochemistry tests were performed in 5873 patients (27.3%). Hyponatraemia was present in at least one such blood test in 403 (6.9%) individuals (Figure 1).

Of those with hyponatraemia, records were retrievable for 253 individuals. The remaining individuals' records were either irretrievable or incomplete. The mean age of the total study sample was 72.9±7.3 years (ranging from 60 to 93 years

old). There were 130 (51.4%) men and 123 (48.6%) women with hyponatraemia. Almost all patients (99.6%) had underlying comorbidities (Table I).

Characteristics of hyponatraemia
A total of 178 (70.3%) patients had mild hyponatraemia. Sixty-seven (26.5%) had moderate hyponatraemia and only eight patients (3.2%) had severe hyponatraemia. There was a significant difference in age between hyponatraemia severity groups, suggesting that older patients tended to have more severe hyponatraemia.

Of all 253 individuals with hyponatraemia and adequate clinical records, 244 (96.4%) had a pre-existing diagnosis of hypertension, 176 (69.6%) had dyslipidaemia, 149 (58.9) had diabetes and 72 (28.5%) had chronic kidney disease.

The presence of medical conditions with established associations with hyponatraemia were cancer (3.6%, n=9), heart failure (3.2%, n=8), chronic liver disease (2.4%, n=6) and Addison's disease (0.8%, n=2). Patients with underlying dyspepsia were significantly more likely to have moderate to severe hyponatraemia (p=0.018). One hundred and fifty-two (60.1%) medical records had no documental probable cause of hyponatraemia.

Documented probable causes of hyponatraemia
Probable cause of hyponatraemia was recorded by the attending primary care doctor in 101 (39.9%) of our 253 patients with hyponatraemia and adequate clinical records. Patients were five times more likely to have a documented definite or probable cause of hyponatraemia if they had moderate to severe hyponatraemia (66.7%) compared to those with mild hyponatraemia (28.7%) (p<0.01).

Twenty-two (21.8%) individuals had documented diagnosis of hypertonic hyponatraemia due to hyperglycaemia (Table II). Of the 79 individuals with hypotonic hyponatraemia, 32 (41%) were attributed to medications. Total body sodium depletion due to chronic poor oral intake was mentioned in 15 (19%), while the presence of chronic kidney disease was identified as the most plausible cause in 10 (13%). Other probable causes of hyponatraemia in our patients with hyponatraemia and documented underlying causes are listed in Table II. Individuals documented to have hypotonic hyponatraemia were significantly more likely to report moderate to severe hyponatraemia (odds ratio [OR]=4.5: 95% confidence interval [95%CI] 1.56 to 11.85). There was no significant difference in severity of hyponatraemia with medication-induced vs. non-medication induced hyponatraemia (OR=2.17: 95%CI 0.94 to 4.91).

Medications
The culprit long term medications associated with hyponatraemia that had previously been prescribed for at least four weeks was extracted from the patients' case records. This cut-off point of four weeks was based on the recommendation of repeat renal profile within the first four weeks after initiation of hydrochlorothiazide or selective serotonin reuptake inhibitors (SSRI) to detect medications-associated hyponatraemia.[19,20] Of the 32 individuals diagnosed with probable medication-induced hyponatraemia, hydrochlorothiazide was implicated either as a single agent or in combination with one to three other drugs in 25 (78%) individuals (Table III). Of the twenty individuals with moderate to severe medication-induced hyponatraemia, 17 (85%) were taking hydrochlorothiazide in isolation or in combination. As a single agent, hydrochlorothiazide was implicated in all six (100%) of all hyponatraemia attributed to a single culprit. Losartan, Perindopril and Furosemide were implicated as solitary culprits in only one case (6%) each, and all three cases had mild hyponatraemia. Two (17%) of those with mild hyponatraemia were on two or more culprits, compared to 14 (70%) of those with moderate to severe hyponatraemia (OR=11.67: 95%CI 2.20 to 60.18).

Management of hyponatraemia
Monitoring of serum sodium level via repetition of renal profile (RP) was performed in 70 out of 79 patients (89%) with identified hypotonic hyponatraemia. All patients (100%) with documented medications-associated hyponatraemia, Addison's disease, syndrome of inappropriate antidiuretic hormone (SIADH), congestive heart failure (CHF) and liver cirrhosis had their RP repeated. Thirteen out of 15 patients (87%) with hyponatraemia due to chronic poor oral intake, five out of six patients (83%) with vomiting and/or diarrhoea, eight out of ten patients (80%) with CKD had RP repeated. All 32 patients (100%) with medications-associated hyponatraemia had subsequent omission or dosage reduction of potential culprit medication.

A total of 31 out of the 79 patients with hypotonic hyponatraemia (39%) were either referred to medical specialist clinic or admitted to a hospital ward for further management. Among five patients (16%) with medications-associated hyponatraemia who received additional care, four were admitted for severe hyponatraemia due to medications and one with mild hyponatraemia was referred to the geriatric clinic. Five patients (33%) with hyponatraemia due to poor oral intake were referred to the geriatric clinic for further management. Three patients (50%) with vomiting and / or diarrhoea were admitted to the medical ward. All four patients (100%) with hyponatraemia due to intestinal obstruction or urosepsis were admitted. Four patients (80%) with Addison's disease and all two patients (100%) with SIADH associated hyponatraemia, had been referred to the endocrinology clinic. Seven patients (70%) with CKD were referred to the nephrology clinic. One patient (50%) with liver cirrhosis had been referred to the gastroenterology clinic.

Three out of five patients (60%) with hyponatraemia secondary to Addison's disease, four patients (13%) with medications-associated hyponatraemia, and one out of two patients (50%) with SIADH had follow up with further investigations. Three out of 15 patients (20%) with chronic poor oral intake and two patients (6%) with medication-associated hyponatraemia were prescribed oral sodium chloride. One patient (10%) with CKD, (the only ESRF patient among all CKD patients), one patient (50%) with liver cirrhosis and all three patients (100%) with CHF were advised to restrict fluid intake. There was no documentation on advice on lowering dietary salt for patients with CHF and liver cirrhosis. Two out of 15 patients (13%) with poor oral

Table I: Socio-demographic characteristics of patients (n= 253)

Characteristics	Total patients n (%)	Severity of hyponatraemia	
		Mild (n=178)	Moderate to severe (n=75)
Age (years)			
Mean±SD	72.88±7.32		
60 – 69	88 (34.8)	66 (37.1)	22 (29.3)
70 – 79	120 (7.4)	87 (48.9)	33 (44.0)
80 – 89	41 (16.2)	24 (13.5)	17 (22.7)
>90	4 (1.6)	1 (0.6)	3 (4.0)
Gender			
Male	130 (51.4)	94 (52.8)	36 (48)
Female	123 (48.6)	84 (47.2)	39 (52)
Ethnicity			
Malay	42 (16.6)	28 (15.7)	14 (18.7)
Chinese	122 (48.2)	89 (50.0)	33 (44.0)
Indian	87 (34.4)	61 (34.3)	26 (34.7)
Others	2 (0.8)	0 (0)	2 (2.7)
Comorbidity			
Yes	252 (99.6)	178 (100)	74 (98.7)
No	1 (0.4)	0 (0)	2 (2.7)
Medical History*			
Hypertension	244 (96.4)	171 (96.1)	73 (97.3)
Dyslipidaemia	176 (69.6)	126 (70.8)	50 (66.7)
DM	149 (58.9)	107 (60.1)	42 (56.0)
IHD	42 (16.6)	25 (14.0)	17 (22.7)
CKD	41 (16.2)	27 (15.2)	14 (18.7)
Stroke	30 (11.9)	19 (10.7)	11 (14.7)
Dyspepsia	11 (4.3)	4 (2.2)	7 (9.3)
Asthma	9 (3.6)	5 (2.8)	4 (5.3)
Malignancy	9 (3.6)	6 (3.4)	3 (4.0)
CHF	8 (3.2)	5 (2.8)	3 (4.0)
Hypothyroidism	7 (2.8)	6 (3.4)	1 (1.3)
Epilepsy	7 (2.8)	4 (2.2)	3 (4.0)
Liver cirrhosis	6 (2.4)	4 (2.2)	2 (2.7)
Schizophrenia	3 (1.2)	2 (1.1)	1 (1.3)
Depression	3 (1.2)	3 (1.7)	0 (0)
Addison's disease	2 (0.8)	0 (0)	2 (1.1)

*each patient may have more than one comorbidity
DM=diabetes mellitus IHD=ischaemic heart disease
CKD=chronic kidney disease CHF=congestive heart failure

Table II: Documented causes of hyponatraemia among patients (n=101)

Documented Causes	Total n(%) (n=101)	Severity of hyponatraemia	
		Mild (n=178)	Moderate to severe (n=75)
Hypertonic hyponatraemia due to Hyperglycaemia	22 (21.8)	17 (33.3)	5 (10)
Hypotonic hyponatraemia	79 (78.2)	34 (66.6)	45 (90)
Medications	32 (40)	12 (35)	20 (44)
Poor oral intake	15 (19)	6 (18)	9 (20)
CKD	10 (13)	6 (18)	4 (9)
Vomiting &/ Diarrhoea	6 (8)	5 (15)	1 (2)
Addison's disease	5 (6)	1 (3)	4 (9)
Third space loss due to Urosepsis / Int. Obs.	4 (5)	1 (3)	3 (7)
Heart failure	3 (4)	1 (3)	2 (4)
Liver cirrhosis	2 (3)	1 (3)	1 (2)
SIADH	2 (3)	1 (3)	1 (2)

CKD=chronic kidney disease; Int. Obs.= intestinal obstruction
SIADH=syndrome of inappropriate antidiuretic hormone

Table III: Medication-associated hyponatraemia

Medications, n (%)	Total n = 32	Severity of hyponatraemia	
		Mild (n=12)	Moderate to severe (n=20)
One potential culprit:	16 (50)	10 (83)	6 (30)
HCTZ	13 (81)	7 (70)	6 (100)
Losartan	1 (6)	1 (10)	0 (0)
Perindopril	1 (6)	1 (10)	0 (0)
Frusemide	1 (6)	1 (10)	0 (0)
Two potential culprits:	14 (44)	2 (17)	12 (60)
HCTZ + Losartan	3 (21)	1 (50)	2 (17)
HCTZ + Perindopril	7 (50)	0 (0)	7 (58)
Perindopril + Omeprazole	1 (6)	0 (0)	1 (8)
Perindopril + Sodium valproate	1 (6)	0 (0)	1 (8)
Lisinopril + Indapamide	1 (6)	0 (0)	1 (8)
Lisinopril + Frusemide	1 (6)	1 (50)	0 (0)
Three potential culprits:	1 (3)	0 (0)	1 (5)
HCTZ + Frusemide + Perindopril	1 (100)	0 (0)	1 (100)
Four potential culprits	1 (3)	0 (0)	1 (5)
HCTZ + Perindopril + Omeprazole + Sertraline	1 (100)	0 (0)	1 (100)

HCTZ=hydrochlorothiazide

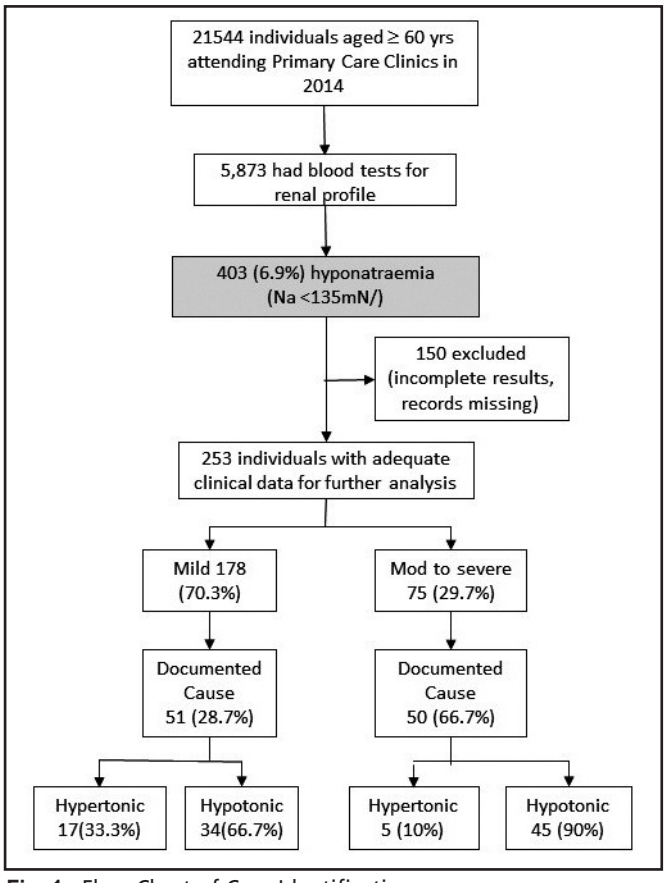

Fig. 1: Flow Chart of Case Identification.

intake were advised to increase salt intake and 33% with hyponatraemia secondary to vomiting and/or diarrhoea were prescribed oral rehydration salts. (Figure 2)

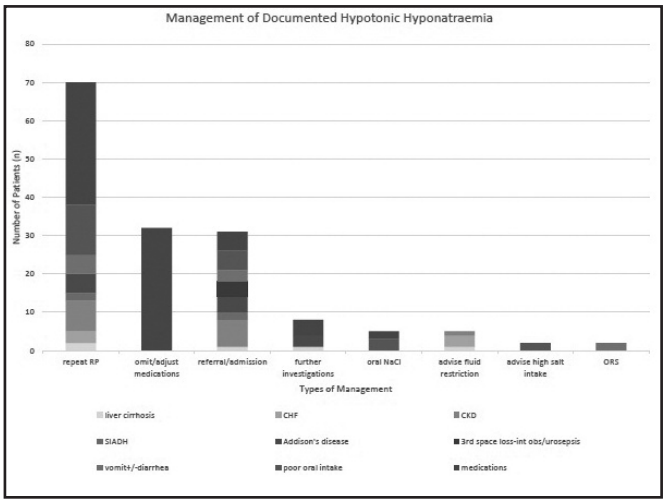

Fig. 2: Histrogram of the management of patients with documented hypotonic hyponatraemia by the primary care doctors (n=79).

DISCUSSION

The one-year period prevalence of hyponatraemia among older patients who had serum biochemistry tests done while attending our primary care clinic was 6.9%. The prevalence of hyponatraemia in outpatient/clinic setting in this study is therefore similar to that reported in a Dutch study which reported a prevalence of 7.7% of among acute medical admissions aged above 54 years.[1] The higher cut-off sodium level of less than 136mmol/L in the inclusion criteria may have contributed to the slightly higher prevalence in the Netherlands, or there may be differences in case-mix.

It was striking that 40% of all cases in whom records were retrievable and adequately complete had a cause of hyponatraemia documented. The teaching hospital involved was a reputed hospital which treated 988,123 patients in

2013, when the total population of Malaysian in 2013 was 29.7 million. Accurate record keeping is therefore a major challenge in this extremely busy environment. The rate of causes documentation of 40%, was however similar to that of a study at a UK teaching hospital, which found that the aetiology of hyponatraemia was recorded in only 42% of hospitalised hyponatraemic patients.[12] Patients were more likely to have a cause of hyponatraemia documented if they had moderate to severe hyponatraemia. This indicated that primary care doctors may have perceived that mild hyponatraemia is benign, and felt it was reasonable to ignore the findings. Perhaps this had occurred due to other competing priorities, in terms of patients actually visiting for a different complaint, or short consultation times allowed in outpatient clinics in response to high patient loads. The ability of primary care doctors to accurately assess elderly may be limited, as suggested by the practice of assigning 'poor oral intake' as a cause of hyponatraemia, and prescribing salt replacement therapy. If sodium homeostasis was intact, hyponatraemia would not occur as the direct result of inadequate intake. Therefore, evaluation for causes of impaired sodium homeostasis should be considered, and poor oral intake should not be considered a cause.[21]

In contrast to pre-existing assumptions that the commonest cause of hyponatraemia is SIADH, medication was the commonest documented cause of hyponatraemia in our setting.[22] This finding was consistent with that of a previous study which suggested that hyponatremia in older ambulatory patients is commonly drug associated.[23] Nearly all participants with adequate medical records in this study had a history of hypertension requiring treatment. Hydrochlorothiazide, a thiazide diuretic use was the leading cause of medication-associated hyponatraemia in our study. Cumming et al., had also found that thiazide diuretics were the medications most commonly associated with hyponatraemia.[24] Despite available evidence linking thiazides with hyponatraemia in older patients, thiazide diuretics remain one of the recommended first-line treatments in international guidelines for the management of hypertension in older persons.[25]

The diagnosis of the underlying cause of hyponatraemia in older people is, therefore, notoriously challenging and often multi-factorial.[22] The study by Mohan S et al., found that CHF, coronary artery disease, chronic obstructive pulmonary disease, diabetes, hypertension, stroke, cancer, cirrhosis, psychiatric disorders, and SIADH secretion are the most commonly reported comorbid conditions among hyponatraemic patients in the outpatient setting.[26] Equally many of our patients had multiple comorbidities, especially diabetes. This may explain the unusually high proportion of individuals with hypertonic hyponatraemia in our study. The presence of hyperglycaemia as a result of uncontrolled diabetes may lead to one of two states: normotonic, requiring adjustment of regular medications, or hypertonic, a potentially life-threatening state requiring urgent medical attention. The relationship between diabetes and hyponatraemia is complex, with increased anti-diuretic hormone among patients with diabetes possibly playing a contributory role.[27]

The findings of our study were limited by the comparatively low proportion of older persons attending primary care clinics in our setting received routine blood tests. The reluctance to perform routine biochemistry tests in our older population may reflect budget constraints where medical care is offered entirely free to senior citizens, fully funded by taxation, with no established national insurance schemes.[28] Nevertheless, the period prevalence of hyponatraemia should fall between 1.9% (if all patients who did not have blood tests were normonatraemic) to around 6.9% if it is assumed that the prevalence of hyponatraemia is similar in those who did not have blood tests. The paucity of documentation may reflect limited knowledge and research on the implications of hyponatraemia, and shortage of evidence-based guidelines for appropriate management strategies. Additionally, we were only able to classify hyponatraemia according to osmolality rather than hydration status since urinary sodium was nearly never requested. In addition, the clinical assessment of volaemic status is unreliable in older people.[24] As previous findings have suggested that the cognitive issues associated with mild hyponatraemic is reversible, the awareness of clinical implications and potential reversibility of mild hyponatraemia may need to be addressed among primary care practitioners. Future studies should seek to identify strategies to improve the identification and management of hyponatraemia in a primary care setting and to determine whether detection and reversal of mild hyponatraemia will improve clinical outcomes.

CONCLUSION

Hyponatraemia was found in 6.9% of elderly who had laboratory blood test investigations at a primary care setting in Malaysia. Only one in three of those with mild hyponatraemia had a probable cause documented and received subsequent management suggesting a lack of awareness that even mild hyponatraemia in older adults has deleterious effects. One in three patients with documented causes had medication-related hyponatraemia, with hydrochlorothiazide being most commonly implicated medications. This study should lead to a future study evaluating the benefits of continuing medical education on hyponatraemia and guidelines for the management of hyponatraemia on improving the management of hyponatraemia in primary care.

CONFLICT OF INTEREST STATEMENT

No conflict of interest is declared.

CONTRIBUTORS

MPT, PKM and RLS conceived the study. CLT, MM and MPT were involved in study design. CLT conducted the data collection and data analysis. All authors contributed in interpretation of results and in making an important intellectual contribution to the manuscript. MPT is the guarantor.

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DATA SHARING STATEMENT

Dataset available on request from the corresponding author.

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