THE STUDY OF CLINICAL AND BIOCHEMICAL FACTORS ASSOCIATED WITH HYPOVOLEMIA AMONG HOSPITALISED PATIENTS WITH HYPONATREMIA BASED ON BIOIMPEDENCE ANALYSIS IN HOSPITAL USM KUBANG KERIAN.

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Bismillahirrahmanirrahim.

In the name of ALLAH, the most compassionate and the most merciful. Salutations be upon His messenger Muhammad (peace be upon him), his family and his companions. With the help and success granted by ALLAH, I have finished and completed this dissertation. I would like to express my sincere gratitude and appreciation to the following individuals who have contributed and supported me in many ways in conducting this study:

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LIST OF ABBREVIATIONS

ADH	Antidiuretic Hormone
BIA	Bioelectrical Impedance Analysis
BMI	Body Mass Index
BP	Blood Pressure
CCF	Congestive Cardiac Failure
CI	Confidence Interval
CT	Computed Tomography
DBP	Diastolic Blood Pressure
DKA	Diabetic KetoAcidosis
DM	Diabetes Melitus
DXA	Dual-energy X-ray Absorptiometry
HHS	Hyperosmolar Hyperglycemic State
HPT	Hypertension
HUSM	Hospital Universiti Sains Malaysia
K	Potassium
MRI	Magnetic Resonance Imaging
Na	Natrium/ Sodium
OBB	Outcome Based Budgeting
OR	Odds Ratio

SBP	Systolic Blood Pressure
SD	Standard Deviation
SiADH	Syndrome of Inappropriate Antidiuretic Hormone
TBW	Total Body Water
UA	Uric Acid
USM HREC	Usm Human Research Ethics Committee

ABSTRAK

Latar belakang: Penilaian status air dalam badan adalah penting dalam merawat pesakit yang mempunyai kandungan sodium dalam darah yang rendah. Tiada kajian terdahulu yang menunjukkan hubungan di antara penilaian klinikal dan parameter ujian darah dan air kencing pesakit dengan status air dalam badan pesakit yang mempunyai kandungan sodium dalam darah yang rendah yang dirawat di hospital. Objektif kajian kami adalah untuk melihat hubungan di antara klinikal dan parameter ujian darah dan air kencing dengan pesakit yang mempunyai kekurangan air dan sodium dalam darah yang rendah di kalangan pesakit yang dirawat di hospital.

Kaedah: Kajian hirisan lintang ini dijalankan pada Jun 2020 sehingga Ogos 2020 melibatkan pesakit yang mempunyai kandungan sodium dalam darah yang rendah di Hospital Universiti Sains Malaysia. Sejumlah 87 pesakit yang mempunyai kandungan sodium dalam darah yang rendah telah dipilih. Semua maklumat seperti umur, sejarah penyakit, sejarah ubatan terutamanya diuretik, diagnosis semasa dalam wad, berat, tinggi, indeks jisim badan, penilaian klinikal seperti tekanan darah sistolik dan diastolic, nadi jantung, tahap ketegangan kulit dan parameter ujian darah dan air kencing seperti sodium, urea, asid urik, darah dan air kencing untuk osmolarity dan air kencing untuk melihat kandungan sodium. Pesakit ini kemudian akan dinilai status kandungan air mereka menggunakan mesin Bioelectrical Impedance Analysis (Bodystat Quadscan) dan akan dibahagikan kepada dua kumpulan iaitu kumpulan yang mempunyai kekurangan air dan kumpulan yang tidak mempunyai kekurangan air. Ujian analisis univariable dan multivariable menggunakan analisis regresi logistic dijalankan untuk mengenalpasti faktor penyebab kekurangan air dikalangan pesakit yang mempunyai kandungan sodium yang rendah dalam badan.

Keputusan: Daripada jumlah 87 pesakit yang mempunyai kandungan sodium dalam badan yang rendah, 35 (40.2%) pesakit mempunyai kekurangan kandungan air dalam badan manakala 52 (59.8%) pesakit tidak mempunyai kekurangan kandungan air dalam badan. Kumpulan yang mempunyai kekurangan kandungan air dalam badan terdiri daripada 23 (65.7%) orang dikalangan perempuan dan 12 (34.3%) orang dikalangan lelaki. Purata kandungan sodium dalam badan bagi kumpulan yang mempunyai kekurangan kandungan air dalam badan adalah 126.9 (±4.27) manakala bagi kumpulan yang tidak mempunyai kekurangan kandungan air dalam badan adalah 127 (±4.52). Dikalangan pesakit yang mempunyai kekurangan air dalam badan, 5 (14.3%) mempunyai latar belakang penyakit kanser dan 14 (40%) mempunyai penyakit kencing manis. Purata indeks jisim tubuh bagi kumpulan yang mempunyai kekurangan kandungan air dalam badan adalah 23.6 (±4.24) dan bagi kumpulan yang tidak mempunyai kandungan air dalam badan yang rendah adalah 22.7 (±2.84). Faktor yang telah dikenal pasti berkait rapat dengan kekurangan kandungan air dalam badan di kalangan pesakit yang mempunyai kandungan sodium dalam badan yang rendah ialah tekanan darah sistolik yang rendah dan bacaan urea dalam darah yang tinggi (adj OR 0.92, 95% CI 0.873, 0.969, p=0.002; adj OR 1.27, 95% CI 1.12, 1.43, p <0.001).

Kesimpulan: Tekanan darah sistolik yang rendah dan bacaan urea dalam darah yang tinggi adalah faktor yang penting dan berkait rapat dengan kekurangan air dalam badan dikalangan pesakit yang mempunyai kandungan sodium dalam darah yang rendah. Oleh itu, penilaian terhadap tekanan darah sistolik dan kandungan urea dalam darah dapat membantu dalam merawat pesakit yang mempunyai kandungan sodium dalam darah yang rendah bagi membantu ujian selanjutnya yang perlu dijalankan bagi mencari kemungkinan punca dan seterusnya rawatan yang seharusnya diberi kepada pesakit.

ABSTRACT

Background: Hydration status assessment is important in management of patient with hyponatremia. There is no previous study that shows association between patients's clinical and biochemical assessment with hydration status in hospitalized patients with hyponatremia. Objective of this study was to look at the association between clinical and biochemical parameters in patient and hypovolemic hyponatremia.

Methods: This cross-sectional study was conducted in June 2020 till August 2020 involving patients with hyponatremia, hospitalized in Hospital Universiti Sains Malaysia. A total of 87 patients with hyponatremia were selected. All patients' information such as age, comorbidities, drug history particularly diuretics, diagnosis during admission, weight, height, body mass index, clinical assessment including systolic and diastolic blood pressure , heart rate and sternal skin turgor as well as biochemical parameters such as serum sodium, serum urea, serum uric acid, serum and urine osmolarity, urine sodium were obtained, followed by assessment of hydration status using Biolectrical Impedance Analysis Machine (Bodystat Quadscan). Results of hydration status will be divided into hypovolemic and non-hypovolemic group based on total body water analysis. Univariable and multivariable analysis by logistic regression were conducted to identify association of this clinical and biochemical parameters with hypovolemic hyponatremia.

Results: Among 87 patients with hyponatremia**,** 35 (40.2%) of them had hypovolemia and 52 (59.8%) had non-hypovolemia. Hypovolemic group consists of 23 (65.7%) female and 12 (34.3%) male. The mean (SD) serum Na for hypovolemic group and non-hypovolemic group were 126.9 (±4.27) and 127 (±4.52) respectively. In hypovolemic group, 5 (14.3%) had underlying malignancy and 14 (40%) had

underlying DM. Mean BMI for hypovolemic group was 23.6 (±4.24) and 22.7 (±2.84) for non-hypovolemic hyponatremia group. Significant association of low systolic BP and high serum urea with hypovolemic hyponatremia have been found (adj OR 0.92, 95% CI 0.873, 0.969, p=0.002; adj OR 1.27, 95% CI 1.12, 1.43, p <0.001)

Conclusion: Low systolic BP and high serum urea are significantly associated with hypovolemic hyponatremia among hospitalized patients with hyponatremia. Hence, assessment of systolic BP and measurement of serum urea can helps in predicting hospitalized patient with hypovolemic hyponatremia and to guide for further workout to look for the possible etiology and endorsing subsequent management.

Keywords:

Hypovolemic hyponatremia, bioimpedance analysis, blood pressure, urea, hospitalized

CHAPTER 1: INTRODUCTION

Hyponatremia is one of the most common electrolyte imbalance encountered among hospitalized patient with a reported prevalence of up to 30% in hospitalised patients and severe hyponatremia is seen in 1% of patients with various health problems[1,2]. Measurement of serum Na is a common baseline blood investigation taken among hospitalized patient to assess electrolytes, acid-base and water balance, as well as renal function. Normal serum Na level ranges between 135-145mmol/L. Hyponatremia is defined as serum Na of less than 135mmol/L.

Hyponatremia is associated with increased morbidity and mortality. The risk of death during hospitalization is increased by more than 50% in patients admitted with hyponatremia compared with normonatremia[3,4,5,8]. Even mild hyponatremia that previously was regarded as a relatively benign condition has been implicated in increased morbidity, longer length of hospital stay, cognitive impairment, and falls[7]. Meta- analysis performed by Corona et al[6] reported a prolonged hospital length of stay with higher risk of readmission in hospitalized patients with hyponatremia and this may represent one of an important determinant of the hospitalization costs.

Clinical manifestation of hyponatremia varies from asymptomatic to symptomatic with devastating manifestation. Mild hyponatraemia is generally asymptomatic, but where the decrease in serum sodium is marked ($\leqslant$125 mmol/l) or acute (occurring over <48 h), serious neurological complications can ensue as a result of cerebral oedema. Early symptoms of headache, muscular weakness, nausea, lethargy, ataxia and confusion can progress to seizures, irreversible neurological damage, coma and death, if unrecognized and untreated. In chronic hyponatraemia, cerebral wasting of intracellular potassium followed by organic osmolytes reduces cerebral swelling,

delaying the onset of symptoms. Hyponatremia in the elderly may manifest with frequent falls and gait disturbances.

Serum Na accounts for approximately 95% of osmotically active substances in the extracellular compartment provided that the patient is not in renal failure or does not have severe hyperglycaemia. Hyponatremia results from the inability of the kidney to excrete a water load or excess water intake. Water intake depends upon thirst mechanism, which is stimulated by increase in osmolarity. Thirst is sensed by osmoreceptors located in the hypothalamus and leads to the release of ADH from the posterior pituitary. ADH acts on the V2 receptors located at the basolateral aspect of the collecting duct cells and leads to increased aquaporin expression on the luminal aspect of the collecting duct cells which increases water absorption and abolishes thirst[9]. Hyponatremia occurs if there is persistent ADH stimulation which can be seen in situations whereby ADH secretion is normal but persistently secreted in patients with volume depletion, either true volume depletion or in edematous patients with heart failure or cirrhosis, in whom tissue perfusion is reduced because of a low cardiac output or arterial vasodilation, respectively. In another situation, ADH is abnormally secreted in SiADH, which is commonly seen in patients with CNS disturbances, malignancies, pulmonary diseases and drug induced.

Hyponatremia reflects an excess of TBW relative to total body sodium content. Because total body sodium content is reflected by extracellular fluid volume status, hyponatremia must be considered along with status of the extracellular fluid volume: hypovolemia, euvolemia, and hypervolemia. Hypovolemic hyponatremia occurs due to low plasma volume due to renal or extrarenal loss, while hypervolemic hyponatremia occurs in patients with heart failure, liver cirrhosis, nephrotic

syndrome and chronic kidney disease. Euvolemic hyponatremia is commonly caused by SiADH.

Volume status assessment plays an important roles in managing patients with hyponatremia as this will lead physician to the possible etiologies and different approach of management.

There is lack of standardized method of assessing volume status in clinical setting. Hydration status is often assessed based on haematological and urinary markers supported by physical signs and symptoms. Physical examination such as skin turgor, pulse volume, capillary refill time, blood pressure and heart rate has been generally used to estimate body fluid status. However there are no studies that look at the association of these clinical examination with hydration status.

Physical sign and symptoms usually have poor sensitivity and specificity[10,11] and may differ in different age groups but they may be a useful tool to suspect water and electrolyte disturbances and prompt clinical investigations for confirmation. The greatest limitation associated with assessment of signs and symptoms is the fact that most signs are subjective and there are usually no 'normal' ranges associated with them. They may also be associated with other diseases or normal physiological states. Skin turgor is usually assessed by pulling the skin and observing how long it takes to return to the baseline state; with values longer than 2 seconds associated with dehydration[12]. Chassagne et al have found that turgor of the thigh, forearm, clavicle and sternum may indicate dehydration in the elderly. Gross et al[13] found that forearm, but not the sternum may indicate dehydration, while Vivanti et al found no relationship with turgor of the sternum. Hypotension and tachycardia has been traditionally used

as an indicator of dehydration but there is no consistent associations as well as lack of support from those established in the literature.

Plasma osmolality is the concentration of solutes in the blood is arguably the most valuable hematologic parameter to assess hydration status and is considered by some, a gold standard technique to detect dehydration in the clinical setting. The value of greater than 300mOsm/kg is considered to be a threshold value for clinical dehydration[14]. The value of this technique as a dehydration marker is still debatable. Armstrong et al[15] argues that plasma osmolality changes with many stimuli and its correlation with dehydration and rehydration in not linear. This is supported by Popowski et al[16] who demonstrated that the rapid water turnover resulting from heat and exercise dehydration op to 5% and rehydration that aimed to recover the lost body weight was not followed by equally prompt changes in plasma osmolality. They concluded that the lag behind the rapid water turnover is most likely the result of perturbed fluid compartments and that the acute changes in water balance cannot be measured by plasma osmolality. Despite its controversy, plasma osmolality is still the widely accepted method in clinical setting. Measurement of urea and uric acid often used in assessment of renal function in clinical practice, may also be utilised to assess plasma concentration. As an osmotically active molecule, urea is absorbed during water reabsorption, resulting in increased level of urea in patient with dehydration. Urine osmolality is the best tool for measuring the concentration of the solutes and is the best indicator of kidney concentrating ability, but it is less reliable in measuring hydration status as the concentration of solutes is determined by many variables independent of water balance including diet and cultures, reported in a study done by Manz et al[17]. In another study by Armstrong et al[18], showed that urine osmolality reflects dehydration more accurately than blood indices, with sensitivity of 91%,

almost equal to that of plasma osmolality (90%). Urine Na has been generally used when the underlying cause is inconclusive between SIADH and hypovolemia, and when only basic laboratory results are available at the time of initial evaluation to guide on initial fluid management[20]. The urine sodium value of 50 mEq/L conferred the best accuracy in separating SIADH from hypovolemic hyponatremia.

Biochemical parameters such as serum urea, uric acid, serum and urine osmolarity as well as urine sodium have been proposed as an indicator for hydration status. However, there are no studies that shows the association of these biochemical parameters with hydration status in clinical setting.

Several methods for assessing body composition exist such as anthropometry, BIA, DXA, MRI and CT. CT and MRI have shown excellent accuracy in assessing muscle and fat areas in cadaveric studies[21]. However, because these methods are expensive, time-consuming and/or require radiation, and may have limited availability, they are impractical in clinical settings and for large research studies. DXA has been widely used for osteoporosis screening and diagnosis. It is readily available, relatively inexpensive, and requires minimal radiation exposure. DXA is also used to measure body composition, and studies have shown strong correlations between body composition parameters obtained by DXA and those obtained by CT or MRI in adults and adolescents of normal weight[22]. However, obesity and anorexia nervosa can cause changes in body composition that may impact the assessment of fat mass and lean soft tissue mass by DXA.

BIA is one of a reliable method for the estimation of body fluid volume. The body is composed mostly of water with ions, through which an electric current can flow. The water in the body is localized in two compartments: extra-cellular water

(approximately 45%) and intracellular water (approximately 55%). On the other hand, the body also contains non-conducting materials (body fat) that provide resistance to the flow of electric current. Adipose tissue is significantly less conductive than muscle or bone. The principal of BIA[24,25] is that electric current passes through the body at a different rate depending on body composition. Hence, there is a direct relationship between the concentrations of ions and the electrical conductivity and an indirect relationship exists between the ion concentration and the resistance of the solution. Study conducted by Kim et al[23] suggests that BIA could replace physical examination for estimating body fluid status in hyponatremia and in addition might correspond better with clinical diagnosis than physical examination in the estimation of body fluid status in hyponatremia. The main advantage of this method is that it provides a rapid feedback, simple, non-invasive and can be carried out bedside. Its greatest limitation is the fact that the values have been generated from statistical models and that the method is largely dependent on many variables. Cox- Rejiven et al[26] found BIA to lack sensitivity in an overweight population. The change in electrode position has been underlined by Sinning & Morgan[27]. Roos et al[28] and O' Brien et al[29] also highlighted the change in electrolyte composition as a significant cause of variations in BIA measurements. Changes in skin and ambient temperatures are also responsible for variations in BIA measurements[30]. However, it gives a reliable measurements of body composition with minimal intra- and inter-observer variability; the results are available immediately and reproducible with <1% error on repeated measurements.

Other tool used in clinical practice for hydration status assessment is ultrasonography, measuring inferior vena cava diameter and collapsibility index. Study conducted by Prekker et al in 2013 concluded that the maximal inferior vena cava diameter is a more robust than the inferior vena cava collapsibility index (percent decrease in inferior vena

cava diameter with inspiration) in estimating central venous pressure that reflects the amount of blood returning to the heart. However, this method is operator dependent, require special training. A study conducted by Bowra et al in 2015 demonstrate a poor interrater agreement between the IVC US measurements obtained by expert and learner users in the assessment of fluid status and these ranges are greater than clinically acceptable.

CHAPTER 2: OBJECTIVES OF STUDY

GENERAL OBJECTIVE:

To study the association of clinical and biochemical parameters with hypovolemia among hospitalised patients with hyponatremia based on bioimpedance analysis.

SPECIFIC OBJECTIVES:

i. To determine association between selected clinical parameters and hypovolemic hyponatremia.

   - Blood pressure systolic and diastolic
   - Heart rate
   - Sternal skin turgor

ii. To determine correlation between selected biochemical parameters and hypovolemic hyponatremia.

   - Serum urea
   - Serum uric acid
   - Serum osmolarity
   - Urine osmolarity
   - Urine Na

CHAPTER 3: MANUSCRIPT

JOURNAL: Malaysian Journal of Medical Sciences

TITLE: The Study Of Clinical And Biochemical Factors Associated With Hypovolemia Among Hospitalised Patients With Hyponatremia Based On Bioimpedance Analysis In Hospital USM Kubang Kerian.

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INTRODUCTION

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BIA is one of a reliable method for the estimation of body fluid volume. The body is composed mostly of water with ions, through which an electric current can flow. The water in the body is localized in two compartments: extra-cellular water (approximately 45%) and intracellular water (approximately 55%). On the other hand, the body also contains non-conducting materials (body fat) that provide resistance to the flow of electric current. Adipose tissue is significantly less conductive than muscle or bone. The principal of BIA[24,25] is that electric current passes through the body at a different rate depending on body composition. Hence, there is a direct relationship between the concentrations of ions and the electrical conductivity and an indirect relationship exists between the ion concentration and the resistance of the solution. Study conducted by Kim et al[23] suggests that BIA could replace physical examination for estimating body fluid status in hyponatremia and in addition might correspond better with clinical diagnosis than physical examination in the estimation of body fluid status in hyponatremia. The main advantage of this method is that it provides a rapid feedback, simple, non-invasive and can be carried out bedside. Its greatest limitation is the fact that the values have been generated from statistical models and that the method is largely dependent on many variables.

METHODOLOGY

This cross sectional study was conducted from June 2020 till August 2020. Patients who were admitted with hyponatremia irrespective of the diagnosis upon admission were screened based on the inclusion and exclusion criteria. The inclusion criteria were age more than 18 years old with serum Na of less than 135mmol/L. Those patients with CKD stage 4 and 5, taking any rate limiting agent medications such as beta blocker, calcium channel blocker; and had missing limb were excluded.

Study populations were hospitalized patient with hyponatremia, admitted in any wards in HUSM for any medical or surgical problem.

Information of patients selected to enter this study was collected during encounter. The patient's age, gender, comorbidities, drug history particularly diuretics, diagnosis upon admission were recorded. Patient's weight and height were measured for BMI calculation. Blood pressure, heart rate and sternal skin turgor were taken and assessed by me as the only researcher in this study. Subsequently, volume status for each of these patients were measured using bioelectrical impedance activity machine (Bodystat Quadscan). During this procedure, patient's age, height and weight were entered into the machine's system after electrodes attached to patient's limb on the same side. Patient's body composition was analysed by BIA machine and based on this analysis, patient will be divided into 2 groups: hypovolemic and non-hypovolemic group. Finally, patient's blood and urine tests results including serum Na, urea, uric acid, serum and urine osmolarity and urine Na were taken and sent to laboratory. Once blood and urine results available, the results will be recorded in data collection sheet.
Sample size was calculated using two independent proportion v4.0 calculator based on each objectives of the study and the largest number obtained based on power of study 90% and

anticipated dropout rate of 10% was taken as the required sample size for this study which in total includes 94 patients.

All the data collected were entered into a SPSS database. The statistical analysis was performed with IBM Statistic Program for Social Sciences (SPSS version 26) software. Demographic and physical characteristic (age, gender, weight, height, BMI) and mean serum Na were tabulated for descriptive statistics. The numerical data were described in mean and standard deviation (SD). The numerical data comparing groups analysed using independent t-test. A p-value of less than 0.25 ($p<0.25$) was considered to be statistically significant. Result reported with its 95% CI. Simple and multiple logistic regression analysis were used to determine factors associated with hypovolemic and non-hypovolemic volume status among patients with hyponatremia.

Ethical clearance was sought from USM Human Research Ethics Committee (USM HREC). This study was approved by the Research Ethics Committee (Human) School of Medical Sciences (PPSP) University Sains Malaysia (USM/JEPeM/20070352). The study complied with acceptable international standards including the Declaration of Helsinki. Besides that, before obtaining the data and medical record review, permission from the hospital director and Secretariat Outcome Based Budgeting (OBB) were obtained.

RESULTS

Among 87 patients with hyponatremia, 35 (40.2%) of them were hypovolemic and 52 (59.8%) were non hypovolemic based on BIA. The demographic characteristic of participant involved in this study were summarized in Table 1. The mean age for hypovolemic hyponatremia group was 58.4 (±15.4); almost comparable with mean age of non-hypovolemic group which was 56.9 (±18.0). The male patients participate in this study were 41 (47.1%) and female patients were 46 (52.9%). For clinical characteristics, 14.3% of patients in hypovolemic hyponatremia group and 17.3% of patients in non-hypovolemic hyponatremia group has underlying malignancy. Patients with underlying DM were 40% in hypovolemic group and 40.4% in non-hypovolemic group. Mean BMI for hypovolemic hyponatremia was 23.6 (±4.24) and for non-hypovolemic hyponatremia group was 22.7 (±2.84). Mean serum Na for both group was almost comparable with mean level of 126.9 (±4.27) for hypovolemic hyponatremia group and 127.1(±4.52) for non-hypovolemic group.

Results for clinical factors which includes systolic BP, diastolic BP, heart rate and skin turgor associated with hypovolemic hyponatremia by BIA using univariable regression analysis were summarized in Table 2. From this univariable regression analysis, systolic BP, diastolic BP and skin turgor were significant with p value of <0.25. SBP yielded OR of 0.078 (95% CI 0.009-0.670, p 0.02), DBP yielded OR of 0.8 (95% CI 0.7-0.9, p 0.001), skin turgor yielded OR of 15.1 (95% CI 1.79-127.2, p 0.012). Multiple logistic regression showed that only systolic BP was a significant predictors of hypovolemic hyponatremia with OR of 0.92 (95% CI 0.87-0.96, p=0.002) tabulated in Table 3.

Results for non-clinical factors associated with hypovolemic hyponatremia using univariable regression analysis were summarized in Table 2. From 5 biochemical parameters analysed

using univariable regression analysis, only serum urea, UA and serum osmolarity were significant with serum urea yielded OR of 1.25 (95% CI 1.11-1.4, p 0.0), serum UA yielded OR of 1.005 (95% CI 1.002-1.008, p 0.0) and serum osmolarity yielded OR of 1.05 (95% CI 1.01-1.08, p 0.0). Multivariate logistic regression showed that only serum urea were a significant predictors of hypovolemic hyponatremia with OR of 1.27 (95% CI 1.12-1.43, p<0.001), tabulated in Table 3

DISCUSSION

In this study, the proportion of hospitalized patients with hypovolemic hyponatremia was 40.2%. This is comparable with a cross sectional study done in India, 42% which was carried out over 12 months period involving a larger group of patients with total number of 440 patients aged more than 60 years old who were admitted to the Post-graduate Department of Medicine (Subash Chandra Dash et al., 2019)[31]. Other studies observed the proportion of hyponatremia in general rather than specific group of hypovolemic hyponatremia.

Mean age of patients in hypovolemic group was 58.4 (±15.4) which was similar to non-hypovolemic group which was 56.9 (±18). Most of the previous studies were conducted among elderly patients, aged more than 60 years old. There was a cross sectional study by Siregar et al[32] in 2011 showed the risk of hyponatremia among inpatient elderly patient aged > 60 years was 2.43 times higher compared to younger patients. This is mainly attributed by the physiological changes as well as comorbidities which commonly present among this group of patients.

In our study, 41 (47.1%) were male and 46 (52.9%) were female which showed not much difference in proportion of gender. Mean BMI was 23.6 (±4.24) in hypovolemic group and 22.7 (±2.84) in non-hypovolemic group.

Hyponatremia was more common in subjects with comorbidities mainly DM, stroke and malignancy compared to those without comorbidities, reported in population based cross sectional study done by Mohan et al[33] published in 2013. Mohan et al reported the proportion of cancer among hyponatremia was 3.38%, lower compared to our study in which 16% had underlying malignancy, however almost comparable with another study by Gill et al[8] in 2006 which reported 14% proportion of patient with underlying malignancy among medical inpatients with hyponatremia. The difference is probably due to different types and severity of malignancy and treatment received as well as patient's age during presentation.

In terms of background DM, 40% of our patients had underlying DM, higher compared to Mohan et al[33] conducted in Columbia which was 3.34% but almost comparable with 35.5% reported by Chandra Dash et al[31] in 2018. Different proportion of hyponatremic patients with underlying DM is likely related to the prevalence of DM among the population and glucose controlled among patient which can lead to various acute and chronic complications requiring hospital admission including DKA, HHS and micro/macrovascular complications such as nephropathy/nephrotic syndrome and CCF.

Mean serum Na level in our study was comparable among hypovolemic and non-hypovolemic hyponatremia group which were 126.9(±4.27) and 127.1(±4.52) respectively.

Measurement of hydration status in our study was made based on BIA, which is considered as one of the most reliable methods of hydration status assessment (Baron et al, 2014)[30]. Most of similar studies used clinical assessment in assessing volume status.

Based on our study, systolic BP shown to be independently significant in association with hypovolemic hyponatremia. Drop in systolic BP has been showed in study conducted by Vivanti et al[34] in 2007 among inpatient teaching hospital's Geriatric and Rehabilitation Unit to be clinically significant. Heart rate was not a significant clinical parameter in our study, might be contributed by the autonomic neuropathy which is common in DM and cancer patients. Due

to this pathology, heart rate response may not be manifested in mild degree of hypovolemia. Skin turgor is also not a part of significant parameter for clinical hydration status assessment as it is not a reliable method, a subjective assessment with poor discriminative sign especially in elderly patients.

There were no similar studies conducted previously looking at the correlation of biochemical parameters with volume status in hospitalized patient with hyponatremia. Based on our studies, serum urea was significantly correlated with hypovolemic hyponatremia. Mean serum urea in hypovolemic hyponatremia group was 10.3 (±6.12). Naschitz et al[35] in 2019 conducted a longitudinal survey among residents of long term geriatric and palliative care concluded that serum urea was one of a potential markers of dehydration, however this was done among patients with serum Na level within normal range. Physiologically, increase in serum urea is an adaptive effect, results from urea reabsorption in the renal tubule to potentiate effect of vasopressin and thus allow for greater retention of water in case of hypovolemia.

Other biochemical parameters such as serum UA, serum and urine osmolarity as well as urine Na are widely used as a marker for dehydration but showed no significant correlation with hypovolemic hyponatremia in our study. Observational study conducted by Vivanti et al[34] also concluded that serum osmolarity and UA were not a sensitive dehydration indicators, however it involved only those patients with mild dehydration status. Serum osmolarity is the main homeostatic parameters against which humans regulate intracellular hydration and is the gold standard for determining dehydration as mentioned in a multidisciplinary consensus of dehydration published by Lacey et al[36] in June 2019. The insignificant correlation with hypovolemic hyponatremia in our study probably related to lesser severity of hypovolemia among our patients. Urine osmolarity and urine Na have inter-individual and intra individual diurnal variation which limit their use as instantaneous markers of dehydration (Lacey et al

2019) and thus might contribute to insignificant correlation with hypovolemic hyponatremia other than the error of sample itself in which some of them were not a fresh sample when sent to laboratory.

The possible confounding factors in our studies includes patient's factors such as blood sugar and lipid profile that may contribute to pseudohyponatremia, medications intake that commonly implicated with hyponatremia such as diuretics, steroids and antipsychotics. Underlying endocrinopathy and renal disease may affect other electrolytes as well and may affect blood and urine osmolarity results. Furthermore, BIA interpretation may not be so accurate in overweight and obese patients.

CONCLUSION, LIMITATIONS OF THE STUDY AND RECOMMENDATIONS.

In conclusion, systolic BP of less than 90mmHg and raised serum urea are significantly correlated with hypovolemic hyponatremia among hospitalized patients. These clinical and biochemical factors can be used as an important factors in predicting patients with hypovolemic hyponatremia among hospitalized patients. These may avoid unnecessary use of more specific equipment for body fluid measurement, hence delay the commencement of important immediate management, especially in emergency situation. Other clinical and biochemical parameters may help to support the assessment of volume status.

Our study was limited by the proportion study instead of prevalence, which was conducted in a single tertiary centre that may not represent the whole population in Malaysia. This study involved a small sample size which was 87 patients. Second limitation was that, there was no grading of severity of hypovolemia assessed by BIA to further classify patients into mild, moderate and severe hypovolemia. Lastly, BIA is not the best method of volume status assessment but it is more practical and can be done bedside. The best volume assessment tools

are contrasted CT scan followed by DXA scan. However, the assessment using these tools cannot be done bedside, require patient's transportation to radiology room, costly and exposing patient to contrast.

For future studies, we recommend a multicentre prospective study with added clinical and biochemical parameters, involves a larger sample size which will give a greater picture of proportion and factors than can significantly predict hypovolemic hyponatremia. We also recommend a more specific and accurate assessment of degree of hypovolemia in which patient should be classify into mild, moderate and severe hypovolemia to give a better correlation with clinical and biochemical parameters. Finally, a better tools for volume status assessment using contrasted CT or DXA scan is recommended for more accurate volume status assessment.

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