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Ursachen von Störungen und Parametern des Volumenstatus bei Patienten mit Hyponatriämie

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Dedicated to my beloved parents and family

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1. Introduction

Hyponatremia (American English) or hyponatraemia (British English) is defined as serum sodium concentration (Na$^+$) <135 mmol/l (Reynolds *et al*. 2006; Spasovski *et al*. 2014). It is the most common electrolyte disorder and correlated with increased morbidity and mortality.

Hyponatremia poses substantial diagnostic and management problems for physicians. The diagnostic challenge comes from several factors, firstly; the heterogeneity of hyponatremia as this disorder has multifactorial etiologies and several causes may be found in the same patient (Sterns *et al*. 1994), secondly; hyponatremia is not a disease *per se* but mainly a result from disturbances in water hemostasis in most instances (Sterns, 2015). Low serum sodium level is commonly a feature or complication of other medical illness although it can be seen as an isolated disorder (Simon *et al*. 2015).

There is always a need to improve the ways of evaluation of volume status in order to improve the diagnosis of hyponatremia. Clinical assessment in American and European guidelines takes inferior level in algorithm because it's a matter of experience and subjective procedure. Particularly, hypovolemic and euvolemic hyponatremia are unfortunately difficult to differentiate based on clinical assessment (Hoorn & Zietse, 2017). Although the last years have seen improvement in the diagnosis of hyponatremia, the evidence base is limited.

Acute severe hyponatremia can lead to severe neurological consequences due to cerebral edema, and that can be lethal if not discovered and adequately treated. Even chronic and mild hyponatremia may negatively affect health status, with its effect, particularly, on the central nervous system and the bone, causing attention deficits, gait instability, falls, osteoporosis, and fractures (Renneboog *et al*. 2006; Gankam *et al*. 2008; Kinsella *et al*. 2010; Verbalis *et al*. 2010), it can significantly prolong the hospital stay and increase medical costs (Callahan *et al*. 2009). Although many studies mentioned that patients with hyponatremia were hospitalized for significantly longer durations compared to normonatremic patients, however, little is known about the factors affecting hospital stay of patients with hyponatremia

especially in patients admitted to endocrinology wards. According to Corona *et al*., hyponatremia was associated with up to around \$3000 higher hospital costs per patient than normonatremic subjects when 8 North American studies were considered (Corona *et al*. 2016).

2. Review of the literature

2.1. Prevalence and incidence

The frequency of hyponatremia varies notably in clinical studies. This can be explained by differences in study population and inclusion criteria of serum sodium concentration. The prevalence of hyponatremia is higher in inhospital patients than outpatients (Simon *et al*. 2015) with a hospital incidence of up to 15-30 % (Callahan *et al*. 2009; DeVita *et al*. 1990; Hawkins, 2003). The incidence is 1-4 % when only patients with serum sodium below 131-130 mmol/l are involved (Hawkins, 2003). The frequency is higher on ICU admissions; it was 34.3 % according to one study (Padhi *et al*. 2014).

2.2. Pathophysiology

Sodium is the major cation of the extracellular space and plays a leading role in maintaining blood volume and blood pressure by attracting and holding water, it is essential in cellular osmotic pressure and in transmitting nerve impulses. As the serum sodium concentration is determined by the amount of extracellular water relative to the amount of sodium, it can be regulated by changing intake or output of water. Osmoreceptive neurons located in the anterior hypothalamus detect changes in cell stretch due to changes in systemic effective osmolality. A decrease in cell stretch stimulates these neurons, which leads to both increased release of vasopressin from the pituitary gland and increased thirst. Vasopressin increases the reabsorption of water from the primitive urine in the distal tubules of the nephron, which leads to production of concentrated urine. To prevent persistent thirst, the threshold for releasing vasopressin is lower than that for triggering thirst (Verbalis, 2003). Under normal circumstances, the kidney has the capacity to excrete as much as 15-20 L of free water per day (Singhi & Jayashre, 2009).

When sodium levels in the blood become seriously low, excess water enters the brain cells and they swell. To avoid this, a volume-regulatory adaptation starts. Excessive extracellular fluid moves into the cerebrospinal fluid within 1-3 hours, which is then shunted into the systemic circulation (Gullans & Verbalis, 1993).

Additionally, stretching of the brain cells stimulates the following two osmoregulatory responses:

- inhibition of both antidiuretic hormone (ADH) secretion from neurons in the hypothalamus and hypothalamic thirst centre. This leads to excess water elimination as dilute urine.
- immediate cellular adjustment with loss of electrolytes, and over the next few days, there is a more gradual loss of organic intracellular osmolytes (Gross *et al.* 2001).

In acute hyponatremia, when serum sodium decreases greater than 0.5 mmol/l/h in patients with severe hyponatremia (<120 mmol/l), permanent neurologic damage or death is the likely outcome. This hyponatremic encephalopathy can be complicated by a sequence of events such as the progression of cerebral edema and increased intracranial pressure to brain herniation, respiratory arrest, hypoxia, fatal brain damage, and death (Soupart & Decaux, 1996). In chronic hyponatremia which is notably common in the elderly and among postmenopausal women, encephalopathy can develop despite the belief that this condition carries a low risk of morbidity (Ayus & Arieff, 1996). Chronic hyponatremia is generally better tolerated than rapid-onset hyponatremia due to the ability of the brain to adapt to hypoosmolality.

Therefore, the chronicity of the condition should be considered during the correction of hyponatremia. Acute hyponatremia can be safely corrected more quickly than chronic hyponatremia. Too rapid correction of serum sodium can precipitate severe neurologic complications (Simon *et al.* 2015).

2.3. Classification and etiology

Hyponatremia can be defined or classified based on serum sodium concentration, rate of development, symptoms severity, serum osmolality, and volume status (see methodology).

Although the differential diagnosis is quite broad, hyponatremia can be divided into the following clinically useful groupings:

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Hypertonic hyponatremia

Patients with hypertonic hyponatremia have normal total body sodium, the presence of osmotically active molecules in the serum causes a water shift from the intracellular compartment to the extracellular compartment leading to a dilutional drop in the measured serum sodium (Simon *et al*. 2015). Osmotically active molecules that create this translocational hyponatremia are like glucose in hyperglycemia, mannitol, maltose (used with intravenous immunoglobulin), and glycine (by absorption of irrigation fluids during urological or gynaecological surgery) (Hillier *et al*. 1999).

On the contrary, high urea concentrations in kidney disease may also increase measured osmolality but not effective osmolality as urea is not an effective osmole because it freely passes across the cellular membrane (Carlotti *et al*. 2001).

In osmotic diuresis, non-reabsorbable solutes obligate the renal excretion of Na^+ and this results in decreased extracellular volume. The continuing intake of hypotonic fluids leads to hypovolemia and hyponatremia and the urinary sodium is frequently greater than 20 mmol/l (Kumar & Berl, 1998).

Normotonic hyponatremia

The plasma water fraction, which is normally 92-94 % of plasma volume decreases with a severe increase in fats and proteins. The measured sodium concentration in the total plasma volume is respectively reduced, although the plasma water sodium concentration and plasma osmolality are constant. This artificial low sodium (so-called pseudohyponatremia) is resolved now by exchange of the old method of flame photometry by direct ion-selective electrode measurement (Simon *et al*. 2015).

Hypotonic hyponatremia

Hypotonic hyponatremia always reflects the inability of the kidneys to handle the excretion of free water to match intake with excess water relative to solute in the extracellular fluid (ECF). This imbalance can be due to solute depletion, solute dilution, or a combination of both (Simon *et al.* 2015). Generally, hyponatremia is of clinical significance only when it reflects a drop in the serum osmolality (i.e. hypotonic hyponatremia).

It can be divided into the following categories, according to volume status: hypovolemic, hypervolemic, and euvolemic.

<u>Hypovolemic hyponatremia</u>

Deficiencies in both total body water (TBW) and total body sodium exist, although proportionally more sodium than water has been lost. Secondary to intravascular depletion there is decreased stretch on baroreceptors in the great veins, aortic arch, and carotid bodies with stimulation of sympathetic tone and release of vasopressin to maintain blood pressure. This along with decreased renal perfusion, results in increased generation of renin and angiotensin which results in an increase in aldosterone and reabsorption of sodium in the distal tubules of the kidney and subsequent decreased delivery of solutes to distal diluting segments, causing an impairment of renal free water excretion. Besides, angiotensin is also a stimulant of thirst. Together, these changes lead to hyponatremia (James, 2011).

Diuretics: diuretic use is one of the most common causes of hypovolemic hyponatremia associated with high urinary sodium excretion. Hyponatremia occurs frequently with thiazide diuretics. Loop diuretics, by inhibiting sodium chloride (NaCl) reabsorption in the thick ascending limb of the loop of Henle, interfere with the generation of a hypertonic medullary interstitium and urinary concentration as well as dilution. Thiazide diuretics act exclusively in the distal tubule, interfering only with urinary dilution.

Gastrointestinal and third-space losses: secondary aldosteronism develops in response to volume depletion and the kidney is forced to respond by conserving NaCl. Urinary sodium is usually less than 10 mmol/l and the urine is hyperosmolar. In some patients with vomiting and metabolic alkalosis, bicarbonaturia obligates execration of sodium as well. In spite of severe volume depletion, the urinary sodium may be greater than 20 mmol/l, the urinary chloride, however, is less than 10 mmol/l (Kumar & Berl, 1998).

Primary adrenal insufficiency: in primary adrenal insufficiency, mineralocorticoid deficiency causes renal sodium excretion (Spasovski *et al*. 2014). The decreased

ECF volume together with a deficit in glucocorticoids stimulates non-osmotic release of ADH, so hypovolemic hyponatremia with urinary sodium higher than 20 mmol/l, especially if associated with a raised serum potassium, urea, and creatinine, suggests mineralocorticoid deficiency (Kumar & Berl, 1998).

Salt-wasting nephropathy: may rarely develop in a range of renal disorders (e.g. interstitial nephropathy, medullary cystic disease, polycystic kidney disease, partial urinary obstruction) with low salt intake (James, 2011). This can inhibit the kidney's ability to re-absorb appropriate amounts of sodium causing hypovolemic hyponatremia (Hamdi *et al*. 2010).

Cerebral salt wasting (CSW): is seen especially after neurologic surgery, it can also seen with other intracranial disorders. Exaggerated renal pressure–natriuresis response caused by increased sympathetic tone and dopamine execration might cause low renin and renal salt wasting, resulting in reduced plasma volume. Plasma renin and aldosterone levels fail to rise appropriately in patients with CSW despite a reduced plasma volume because of a disruption of the sympathetic tone. Impaired free water excretion due to stress-mediated increase in vasopressin also plays a role. In addition, the release of one or more natriuretic factors could also play a role in renal salt wasting (Kojima *et al*. 2005; Palmer, 2003).

Hypervolemic hyponatremia

Hypervolemic hyponatremia is characterized by significant increase in total body water and sodium. The following factors contribute to hyponatremia:

- misbalanced proportion of venous and arterial volume with neurohumoral activation of baroreceptor-mediated vasopressin release, natriuretic peptide release leading to water retention and renal sodium loss.

- secondary aldosteronism with angiotensin II-mediated thirst and pharmaceutical blockade of aldosterone-mediated renal reuptake of sodium in many such conditions.

- decreased glomerular filtration rate (GFR) and direct impairment of renal water excretion.

Urinary sodium excretion is usually <10 mmol/l, and urinary osmolality is high relative to serum osmolality (James, 2011). Examples of this type of hyponatremia are liver cirrhosis, congestive heart failure, nephrotic syndrome, and severe hypoproteinemia (albumin level <1.5-2.0 g/dl) (Simon *et al*. 2015).

In congestive heart failure the fall in cardiac output leads to reduce the effective arterial blood volume, in liver failure, systemic vasodilation and arteriovenous shunting of blood may reduce the effective arterial blood volume and induce the same mechanism as described above for hypervolemic hyponatremia. In nephrotic syndrome, reduction in oncotic pressure and an increase in filtration across the capillary results in tissues edema which in turn decreases circulating blood volume. This combination of increased vasopressin release and diuretic can lead to hyponatremia (Wang, 2000). In kidney disease the ability to dilute urine and excrete free water decreases. The sensitivity to vasopressin decreases, and free water removal is no longer tightly regulated but is more and more determined by the number of osmolites excreted into the urine (i.e. solute intake). Therefore, hyponatremia can easily develop if patients do not adhere to fluid restriction (Gradden *et al*. 2001).

Normovolemic (euvolemic) hyponatremia

In euvolemic (dilutional) hyponatremia, total body sodium and thus ECF volume are normal or near-normal; however, TBW is increased.

The syndrome of inappropriate antidiuretic hormone secretion or SIADH (other names: Schwartz-Bartter syndrome, SIAD): is characterized by excessive secretion of arginine vasopressin (AVP) from the posterior pituitary gland or another origin (Babar, 2013). Patients with SIADH fail to suppress AVP release even when plasma osmolality falls below the normal osmotic threshold triggering AVP release (Smith *et al.* 2004). Hyponatremia in SIADH is thought to be limited by the 'escape phenomenon' in which free urinary water excretion increases and urinary osmolality decreases after a few days to re-establish fluid balance. This effect protects against excessive water retention and severe hyponatremia and may be caused by reduced expression of aquaporin-2 in the collecting ducts (Reynolds *et al*. 2005).

Urinary sodium concentrations are also typically greater than 20 mmol/l on a normal salt diet as sodium excretion will match dietary sodium intake (Simon *et al*. 2015).

Secondary adrenal insufficiency: under normal circumstances, cortisol exerts a negative feedback effect on release of both corticotropin-releasing hormone and vasopressin in the hypothalamus. In adrenal insufficiency, persistently low levels of cortisol fail to suppress vasopressin and lead to hyponatremia. The production of aldosterone is affected in lesser degree in secondary than in primary adrenal insufficiency and renal sodium loss does not contribute too much to the development of hyponatremia (Faustini & Anagni, 2006).

Hypothyroidism: although included in many diagnostic algorithms, hypothyroidism very rarely causes hyponatremia (Kilpatrick, 2006). Only severe cases of hypothyroidism can produce hyponatremia. This may result from a reduction in cardiac output and glomerular filtration rate (Abuzaid & Birch, 2015).

High water and low solute intake: the excess water intake is primarily responsible for hyponatremia. Vasopressin activity is absent, which is reflected by an appropriately low urine osmolality, usually <100 mOsm/kg. Primary polydipsia may occur in combination with psychiatric disorders such as schizophrenia. This problem may even be aggravated by centrally acting drugs used to treat psychiatric disease.

The amount of water that the kidneys can remove on a daily basis depends on solute excretion and hence solute intake. If solute intake is low relative to water intake, the number of available osmolytes can be insufficient to remove the amount of water ingested. This is seen in patients with anorexia nervosa, beer potomania and so-called 'tea and toast' hyponatremia (Thaler, 1998). Same mechanism is postulated to cause acute hyponatremia is associated with ultra-endurance athletes and marathon runners.

Other causes of hyponatremia may include:

Nonsteroidal anti-inflammatory drugs (NSAIDs): NSAIDs use may increase the risk of development of hyponatremia by hindering prostaglandin formation and

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consequently a decrease in renin generation and free water excretion. Prostaglandin decreases NaCl reabsorption in the thick ascending limb of Henle (eventually reducing medullary tonicity) and ADH action in the collecting duct (Baker *et al.* 2005).

Figure 1 - Cartoon on the development of hyponatremia with NSAIDs use
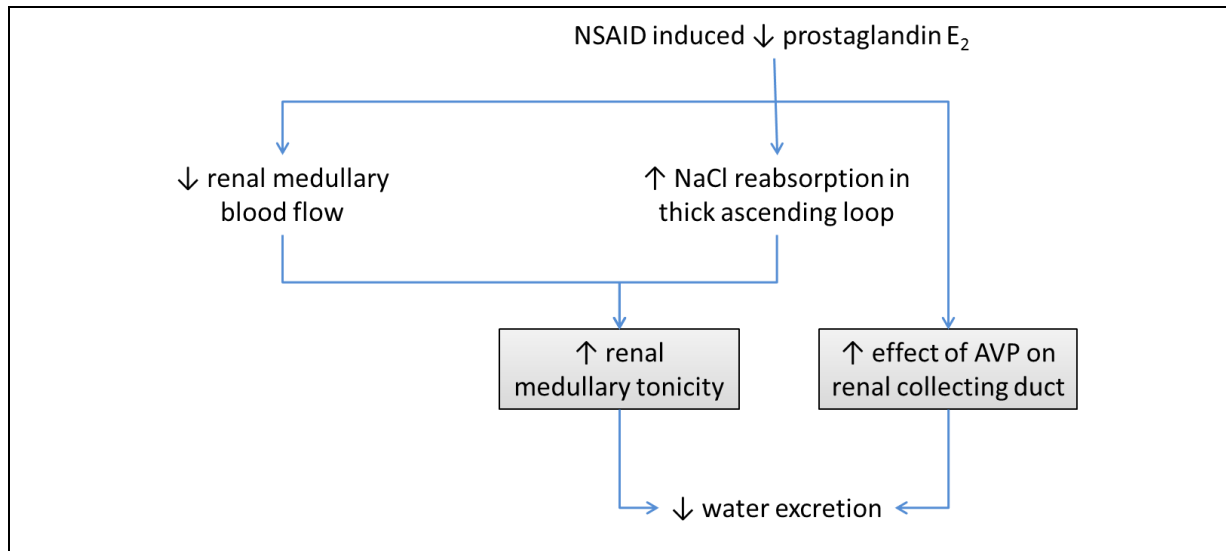
Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit generation of prostaglandin E2 which mediates renin release, reducing medullary tonicity and ADH action in the collecting duct

Nephrogenic syndrome of inappropriate antidiuresis (or NSIAD): is a SIADH-like clinical and laboratory picture but with undetectable plasma AVP levels. It is a rare condition, infrequently seen in males and discovered in infants who present with neurologic symptoms secondary to hyponatremia. This hereditary disorder is secondary to mutations in the V2 vasopressin receptor and results in constitutive activation of the receptor with high cAMP production in the collecting duct cells (Feldman *et al.* 2005).

2.4. History and clinical presentation

Patients may present to medical attention with symptoms related to low serum sodium concentrations. However, in many patients hyponatremia is recognized secondarily and they present due to manifestations of primary disease, incl. heart failure or renal failure (Bettari *et al.* 2012). Symptoms of hyponatremia could be subtle or unrecognised such as reduced attention level, increased falls and trauma,

altered posture and gait in mild hyponatremia (serum sodium level >130 mmol/l) (Schrier, 2010; Decaux, 2006). In moderately severe cases, the patients may become confused, have nausea and headache. Severe hyponatremia (serum sodium levels usually <115 mmol/l), can presented with fatal complications and overt neurologic symptoms resulting from intracerebral osmotic fluid shifts and brain edema (hyponatremic encephalopathy) together with seizures, cardiorespiratory distress, deep somnolence or even coma (Glasgow Coma Scale GCS ≤8) (Spasovski *et al.* 2014; Simon *et al.* 2015). Osteoporosis and sustain bone fractures are more frequent in hyponatremic patients (Renneboog, 2006; Hoorn *et al.* 2011; Verbalis *et al.* 2010).

Obtaining a detailed medication history is important because many medications may precipitate hyponatremia. A dietary history with reference to salt, protein, and water intake is useful as well (Simon *et al.* 2015). Examination should include orthostatic vital signs and an accurate assessment of volume status.

2.5. Investigations

There are three key parameters help in establishing the primary underlying etiology of hyponatremia beside history and physical examination:

- serum osmolality: it readily differentiates between true hyponatremia (hyponatremia with a measured osmolality <275mOsm/kg always reflects hypotonic hyponatremia) and pseudohyponatremia, or hypertonic hyponatremia (Spasovski *et al.* 2014; Simon *et al.* 2015)
- urine osmolality: helps to distinguish etiologies associated with impaired free water excretion from polydipsia, in which free water excretion consider being normal. In hyponatremia urine osmolality greater than 100 mOsm/kg indicates impaired ability of the kidneys to dilute the urine. This is commonly secondary to ADH elevation (Simon *et al.* 2015).
- urinary sodium concentration: it is important to collect the serum and urine sample around the same time for appropriate interpretation of the values. European guideline group selected a concentration threshold of 30 mmol/l because several studies indicated good sensitivity and acceptable specificity in

distinguishing hypovolemia from euvolemia or hypervolemia (Musch *et al*. 2001; Fenske *et al.* 2008). A urinary sodium concentration ≤30 mmol/l suggests low effective arterial blood volume, even in patients on diuretics (Schrier, 1988).

Other laboratory tests that will help in the diagnosis:

Uric acid: in SIADH, serum uric acid levels are generally reduced; this is due to reduced tubular uric acid reabsorption.

Serum potassium: if both hypokalemia and metabolic alkalosis are present, consider diuretic therapy or vomiting as the cause of hyponatremia. If hyperkalemia and metabolic acidosis coexist with hyponatremia, consider hyperglycemia, adrenal insufficiency and volume depletion leading to acute kidney injury (Simon *et al.* 2015).

Serum cortisol, thyroid-stimulating hormone (TSH), free thyroxin (FT4) measurement: hyponatremia associated with cortisol deficiency, such as primary or secondary hypoadrenalism, commonly presents subtly and may go undiagnosed. A random cortisol level check, especially in acute illness, can be misleading if the level is normal (when it should be high). Testing for adrenal insufficiency and hypothyroidism should be part of the hyponatremic workup, as the disorders respond promptly to hormone replacement (Simon *et al.* 2015).

Glucose: see methodology

Measurement of vasopressin: based on its little usefulness in the work up of hyponatremia its measurement is not indicated. However, copeptin may be useful if there is more solid data available from clinical studies (Spasovski *et al.* 2014).

2.6. Treatment

In hyponatremia, there is a risk of brain edema before adaptation (<48 h) because the lower extracellular osmolality enhances a shift of water into the cells (Giuliani & Peri, 2014). However, once adaptation is completed, brain cells can again maintain damage with rash elevation of the serum sodium concentration. Breakdown of the myelin can yield what is called the osmotic demyelination syndrome (Hoorn & Zietse,

2017). Acute hyponatremia can be safely corrected more quickly than chronic hyponatremia (Simon *et al*. 2015). If classifying hyponatremia as acute or chronic is not possible, hyponatremia is considered as being chronic; unless there are reasons to suspect it is acute (see methodology).

Hypotonic hyponatremia represents the situation where hyponatremia need to be treated; the followings are general lines in treatment such cases:

- administration of isotonic saline to patients who presented with hypovolemia to replace the reduced intravascular volume.
- fluid and salt restriction to treat patients who are hypervolemic, plus loop diuretics, and correction of the underlying condition. The use of a V2 receptor antagonist may be considered.
- for euvolemic, asymptomatic hyponatremic patients, free water restriction (<1 l/day) is generally the treatment of choice. Correction of underlying condition, and in SIADH patient, who persistently hyponatremic despite water restriction and correction of possible cause, V2 receptor antagonist are indicated.

In the treatment regimen of patients with severe symptomatic hyponatremia (e.g. seizures, severe neurologic deficits), hypertonic (3 %) saline may be included (Simon *et al*. 2015).

2.7. Prognosis

Even when comorbid conditions are taken in consideration, people with a mildly decreased serum sodium concentration have a 30 % higher risk of death and 14 % longer hospitalization to those without hyponatremia (Upadhyay *et al*. 2009; Wald *et al*. 2010). However, the relationship between the severity of hyponatremia and mortality remains a matter of discussion and the underlying disease causing hyponatremia may be more responsible for the mortality than hyponatremia *per se* (Krummel *et al*. 2016).

3. Objectives

General:

There is no data published on the spectrum of etiologies in Mecklenburg-Western Pomerania. In Rostock, it is unclear, what the most likely diagnosis is when a patient is diagnosed with hyponatremia.

Therefore, the aim of our study is to identify the etiologies of hyponatremia and to improve the management of hyponatremia by evaluating the diagnostic value of clinical, hematological, biochemical, and hormonal parameters. Blood and urine sample were taken from patients by admission and discharge, additionally non-invasive test to measure body composition was performed on admission.

More specifically, the following goals are to be aimed at:

- characterization of the distribution of patients with hyponatremia by age, sex, BMI, onset, serum sodium concentration, volume status, and seasons
- identification the factors affecting the length of hospital stay in patients with hyponatremia
- to describe the comorbid conditions and clinical presentation of patients with hyponatremia
- to identify the etiologies of hyponatremia
- to improve the management of hyponatremia by evaluating the diagnostic value of hematological, biochemical, hormonal, and BIS parameters in identifying the volume status and etiology of hyponatremia
- evaluation of the diagnostic value of some clinical, paraclinical parameters, including blood pressure, attention level, serum creatinine, urea, uric acid, serum and urinary sodium, potassium and osmolality and hormonal like aldosterone , renin, N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and their reflection of effectiveness of therapy by discharge.

4. Patients and methods

4.1. Study design

The SHIP-PAGE study (steroid hormones in patients with pituitary, adrenal or gonadal endocrinopathies) allows the analysis of patients with disorders in salt homeostasis or sodium regulation. Its protocol was approved by the Institutional Ethics Committee of the Rostock University Medical Center (# A 2016-0088).

This study is a descriptive prospective study. It was conducted from October 15, 2014 to October 15, 2015 at the Division of Endocrinology and Metabolism of the Rostock University Medical Centre.

Inclusion criteria: we included all patients, who were admitted with hyponatremia with serum sodium ≤130 mmol/l. Inclusion was possible on weekdays as daily clinical assessment of volume status and bioelectrical impedance measurements were carried out by the investigator.

Exclusion criteria: we excluded patients who did not complete the main investigations to identify the cause, who refused to participate in the study or left the hospital before identifying the cause and establishing specific therapy.

Case finding, history taking and clinical assessment

Initial case finding was based on sodium measurement ≤130 mmol/l on admission, sodium measurement is a routine laboratory investigation performed for all patients admitted to medical wards at Rostock University Medical Centre.

Data collection was performed by an interview-guided questionnaire. The sources of information were the patients or attending relatives, they were included after obtaining an informed written consent. History, especially daily water intake, salt consumption, and current medication were the sources of information as well as medical plans and reports written by treating physicians (a list of drugs was included in the questionnaire).

Evaluation of attention level (coin test) was performed in all the patients on admission with the exception of known or suspected dementia, in whom mini mental

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state tests were performed. Clinical evaluation of extracellular status to determine volume status was performed for every patient. Each patient underwent a complete physical examination to evaluate extracellular volume status with special attention to orthostatic changes in blood pressure and pulse rate, jugular venous pressure, skin turgor, hydration of mucous membranes, presence of edema or pulmonary congestion signs. Evaluation of extracellular fluid volume status and the response to therapy, weight and input output charts monitoring was performed for most of days of admission.

Laboratory and bioelectrical impedance measurements

Blood for a complete hemogram, blood glucose, lipid profile, thyroid function test (TSH and free T4), serum albumin, renal function test (creatinine, urea), uric acid, CRP, NT-proBNP, morning serum cortisol, renin, aldosterone, serum and urinary sodium, potassium, and osmolality were determined on admission.

Clinical evaluation, urea, creatinine, uric acid, NT-proBNP, morning renin and aldosterone, serum and urinary sodium, potassium, and osmolality were repeatedly determined on the day of discharge.

Serum and urinary osmolality were measured using cryoscopy method by Osmomat 030 -freezing point osmometer- (Gonotec, Berlin). Chemical analysis was performed by UniCel D×C 800 synchron clinical systems (Beckmann Coulter) while TSH, free T4, cortisol, and NT-proBNP have been measured by electrochemiluminescence immunoassays, including the ECLIA Cobas e411 (Roche, Mannheim). Aldosterone and renin were manually pipetted and have been measured by RIA-tests with the gamma counter LB 2111 multi crystal gamma counter (Berthold, Germany). In addition, body composition was assessed by bioelectrical impedance on a body composition monitor instrument version 3.3.0.1637 (Fresenius, Homburg) for most of patients on admission.

The cause of hyponatremia in every patient was discussed by a panel of three investigators, including me and two consultants in Endocrinology. The likely causes and the main cause of hyponatremia were identified based on history, clinical

assessment and paraclinical investigations, and sometimes the response to therapy. Decisions about the management of hyponatremia were not directly influenced by our study and left primarily to the responsible team of physicians.

Figure 2 - Clinical work-up of patients with hyponatremia
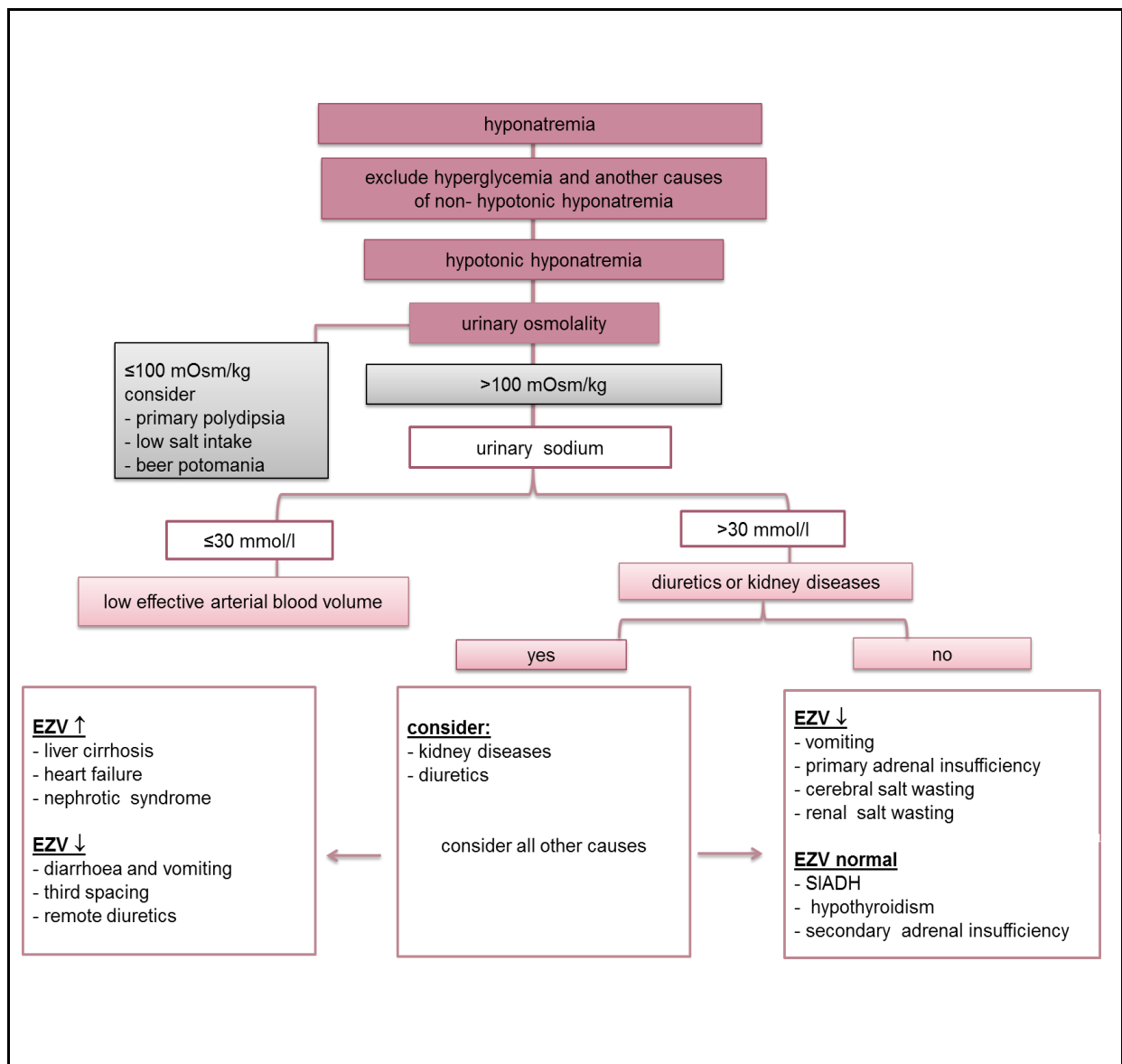
This figure shows diagnostic algorithm for hyponatremia based on European guidelines (modified from Spasovski *et al*. 2014)

4.2. Definitions of the variables and classifications:

Age groups

We divided the patients into the following groups:

- <50 years

- 50-70 years

- >70 years.

Classification of hyponatremia according to serum sodium concentration

We classified the patients into the following categories:

- hyponatremia with a serum sodium concentration 126-130 mmol/l

- hyponatremia with a serum sodium concentration 121-125 mmol/l

- hyponatremia with a serum sodium concentration ≤120 mmol/l.

Classification of hyponatremia according to the onset

Hyponatremia was classified as:

- acute hyponatremia that is documented to exist <48 h.

- chronic hyponatremia that is documented to exist for at least 48 h.

Cases of hyponatremia, who could not be classified, were considered as chronic unless this opposed by clinical clues or information from the case history and drugs or conditions associated with acute hyponatremia (<48 h) (Spasovski *et al*. 2014):

- postoperative phase

- post-resection of the prostate, post-resection of endoscopic uterine surgery

- polydipsia

- exercise

- recent thiazides prescription in combination with medication to interfere with generation or action of renin, angiotensin, and/or aldosterone, desmopressin, recently started terlipressin, 3,4-methylenedioxymethamfetamine (MDMA), cyclophosphamide (i.v.), oxytocin

- colonoscopy preparation.

Classification of hyponatremia according to serum osmolality

Hyponatremia was classified according to effective serum osmolality as follows:

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- hypotonic hyponatremia (plasma osmolality <275 mOsm/kg)

- isotonic hyponatremia (plasma osmolality 275-300 mOsm/kg)

- hypertonic hyponatremia (plasma osmolality >300 mOsm/kg).

Clinical classification of hyponatremia according to volume status

Volume status assessment was based on history, clinical examination, laboratory findings, daily assessment and sometimes treatment response. Hyponatremia is classified according to a clinically assessed volume status, as follows:

Hypovolemic hyponatremia

Diagnosis was made from history of extracellular volume depletion due to:

- non renal sodium loss such as gastrointestinal fluid loss e.g. vomiting, diarrhea or decrease water and salt intake.

- renal sodium loss as usage of diuretics.

Besides, clinical signs of hypovolemia were used and included:

- dry skin and mucous membranes, thirst and decreased urine output, darkness in urine color (Armstrong scale), a weak and sometimes fast pulse, orthostatic hypotension, history of dizziness or lightheadedness and sometimes fainting.

Hypervolemic hyponatremia

Was diagnosed based on history of heart failure, renal failure, hepatic cirrhosis or nephrotic syndrome with some of the following manifestations:

- exertional dyspnea and/or dyspnea at rest and orthopnea

- crackles on auscultation

- jugular vein distension

- ascites

- edema particularly feet and ankles

- manifestation of pulmonary congestion on chest X-ray

- absence of historical and clinical evidence of volume depletion (Lewis, 2011).

Euvolemic hyponatremia

Euvolemic hyponatremia was diagnosed in absence of a reliable history or clinical signs of hypo- or hypervolemia.

Urinary osmolality

Reference range with random urine sample is 50 to 1200 mOsm/kg. Urine osmolality falling below 100 mOsm/kg of water in this setting, the hyponatremia is probably caused by intake of excess water with low solute intake like in polydipsia, anorexia nervosa, beer potomania and what's called tea and toast eating habit (Thaler *et al*. 1998; Musch *et al*. 2003).

Urinary sodium

Hyponatremic cases were classified according to urinary sodium excretion into:
- increased urine sodium concentration (>30 mmol/l)
- decreased urine sodium concentration (≤30 mmol/l) (Spasovski *et al*. 2014, Musch *et al*. 2001).

Serum sodium to urinary sodium to (serum potassium)^2 to urinary potassium (SUSPPUP)

Is an expression of sodium retention in comparison to the amount of renal potassium loss that happens in exchange for sodium.

SUSPPUP   = serum sodium : urinary sodium / (serum potassium)^2 : urinary
                          potassium.

A sample of spontaneous urine was collected (fasting state). Sodium and potassium values were measured in both serum and urine (Willenberg *et al*. 2009).

The trans-tubular potassium gradient (TTKG)

Is an index reflecting the conservation of potassium in the cortical collecting ducts (CCD) of the kidneys. It is useful in diagnosing the causes of hyperkalemia or hypokalemia. The TTKG estimates the ratio of potassium in the lumen of the CCD to that in the peritubular capillaries. The following is the formula for calculating the TTKG: TTKG = urinary K / plasma K ÷ urine osmolality / plasma osmolality.

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(this formula is valid only when U osm >300 mOsm/kg and U Na$^+$ >25 mmol/l (Choi & Ziyadeh 2008).

Coin test

We used this test to evaluate the attention level of patients by giving the patient coins, some of them were old and not used any more or from other countries and we asked the patient to give us 4.84 Euro with shortest possible time with measuring the time with timer.

The following table illustrates the reference values.

Note: patients with dementia, difficulty in vision or hearing were given 112 sec.

Table 1 - Coin test or evaluation of patient's attention level

age (years)	performance time (sec)		
	−2 SD	Mean	+2 SD
18-39	5.1	22.1	39.3
40-49	4.3	29.0	53.7
50-59	5.4	38.5	71.5
60-80	9.5	51.6	112.8

SD; Standard deviation

Overhydration (OH)

Bioelectrical impedance spectroscopy BIS was carried out using the Body Composition Monitor BCM with four conventional electrodes being placed in the patient, who is lying in the supine position: two in the hand and two in the foot. OH or excess fluid represents an expansion of only the extracellular water ECW, whereas intracellular water ICW remains unchanged. The difference between "normal" ECW and measured ECW is the excess fluid, OH. With the following reference range (−1 - +1 L), negative OH means that the patient is under- or dehydrated.

4.2.1. Etiologies

Syndrome of inappropriate antidiuretic hormone secretion or SIADH

Laboratory findings include

- effective plasma osmolality <275 mOsm/kg

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- urine osmolality >100 mOsm/kg of water during hypotonicity
- clinical euvolemia
- urine sodium concentration >30 mmol/l with normal dietary salt and water intake
- absence of adrenal, thyroid, pituitary or renal insufficiency
- no recent use of diuretics agents.

Other findings:

- serum uric acid <0.24 mmol/l (<4 mg/dl)
- serum urea <3.6 mmol/l (<21 mg/dl)
- failure to correct hyponatremia after 0.9 % saline infusion
- fractional sodium excretion >0.5 %
- fractional urea excretion >55 %
- fractional uric acid excretion >12 %
- correction of hyponatremia through water restriction (Spasovski *et al*. 2014; Schwartz *et al*. 2001; Janicic *et al*. 2003).

Hyperglycemia

The following formula is usually recommended to calculate the effect of hyperglycemia on hyponatremia:

- every increase in blood glucose levels by 100 mg/dl (5.55 mmol/l) above the normal glucose levels 100 mg/dl (5.55 mmol/l) can decrease sodium levels by 2.4 mmol/l.
- at glucose levels >400 mg/dl (22.2 mmol/l), every additional increase of glucose by 100 mg/dl (5.55 mmol/l) can decrease sodium levels by 4 mmol/l (Hillier *et al*. 1999).

Renal failure

Acute renal failure is defined as any of the following:
- increase in serum creatinine SCr by ≥0.3 mg/dl (≥26.5 mmol/l) within 48 hours; or
- increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
- urine volume <0.5 ml/kg/h for 6 hours (KDIGO, 2012).

Chronic kidney disease is defined as: either kidney damage or GFR <60 ml /min/1.73 m^2 for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies (KDIGO, 2013).

Heart failure

The diagnosis of heart failure consists of the concurrent presence of either 2 major criteria or 1 major and 2 minor criteria according to Framingham criteria (Ho *et al.* 1993).

Hypothyroidism

The combination of serum TSH levels >20 mU/l with fT4 levels below the reference range was defined as diagnostic of severe primary hypothyroidism (Tzoulis *et al.* 2015). Serum sodium concentration decreased by 0.14 mmol/l for every 10 mU/l rise in TSH (Warner *et al.* 2006).

Glucocorticoid deficiency (secondary adrenal insufficiency)

We were used a basal serum cortisol of 450 nmol/l as the cut-off point below which glucocorticoid deficiency cannot be excluded (Dorin *et al.* 2003; Cooper *et al.* 2003; Tzouliz *et al.* 2015) confirmed by Metyrapone test (Oelker *et al.* 1996).

Diuretics + Renin angiotensin aldosterone system RAAS affecting drugs

RAAS affecting drugs including angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor antagonists (ARA II), drugs suppress renin release such as beta blockers and aldosterone receptor antagonists such as spironolactone – also in combination with thiazide or sulfonylurea diuretics.

Drugs

Drugs other than diuretics that implicated in our study in the genesis of hyponatremia, especially euvolemic type, including: ACE inhibitors or ARA II (when used unaccompanied with diuretics), desmopressin, antidepressant; selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants, antipsychotics;

phenothiazines or haloperidol, antiepileptics drugs; carbamazepines or valoprate, and non-steroidal analgesics.

Diuretics

Diuretic-induced hyponatremia: was defined as hyponatremia in patients receiving diuretics especially: amiloride, triamterene, spironolactone (when used unaccompanied with ACE inhibitors, ARA II or beta blockers).

Gastrointestinal fluid loss

Vomiting or diarrhea.

Decreased water intake

Normal fluid requirements for adults ≥19 years including plain water, milk and other drinks

Men: 2.6 L/day (about 10 cups)

Women: 2.1 L/day (about 8 cups)

(Water Nutrient Reference Values for Australia and New Zealand, 2014).

Psychogenic Polydipsia (PPD)

Was diagnosed based on history of frequency of drinking due to unnatural thirst and passing large volumes of diluted urine, the urine is very dilute before water is restricted (<100 mOsm/kg H2O). It achieves an osmolality of >750 mOsm/kg H2O after restricting water and giving vasopressin, is diagnostic of PPD (Goldman *et al.* 1996).

4.3. Statistical analysis

The statistical analysis was done with the help of SPSS 22. For non-parametric variables results were expressed as the median of individual data points, comparison between patient groups was evaluated by Wilcoxon's test for paired and by Kruskal Wallis for unpaired data sets. For parametric variables results were expressed as the mean of individual data points, comparison between patient groups was evaluated by paired samples T Test for paired and by Anova for unpaired data sets. To find out

the relationships of qualitative variables, Chi square Test was used. The level of significance was considered <0.05. The results were presented in statistical tables and graphs.

5. Results

5.1. Baseline characteristics

During the one year study period, 59 patients were identified as having had a serum sodium concentration of 130 mmol/l or less. Nine patients were not included in the analysis because treatment of hyponatremia had already been started or they did not agree to participate. Finally, 50 patients were included in the final statistical analysis. The age of patients ranged from 35 to 93 years with a mean of 72.8 ± 15.8 years. Most of patients were females (n= 32, 64 %). The mean sodium level was 120.9 ± 7.6 mmol/l. The baseline characteristics of patients admitted with hyponatremia are illustrated in Table 2.

Table 2 - Baseline characteristics of patients admitted with hyponatremia

	mean	SD
age (years)	72.8	± 15.8
systolic BP (mmHg)	147.1	± 28.8
diastolic BP (mmHg)	77.8	± 13.2
serum sodium (mmol/l)	120.9	± 7.6
serum potassium (mmol/l)	4.0	± 0.9
hemoglobin (mmol/l)	7.6	± 1.4
hematocrit (%)	35.0	± 6.5
albumin (g/l)	33.4	± 6.0
	median	range
stay in hospital (days)	7.5	3-21
WBC (Tsd./µl)	10.4	4.6-22.7
CRP (mg/l)	8.8	1-248
BMI (kg/m^2)	25.5	20-40
serum creatinine (µmol/l)	87.2	20.8-834
serum osmolality (mOsm/kg)	260.5	218-404
coin test results (sec)	70.0	20-180

Figure 3 - Distribution of patients with hyponatremia according to sex
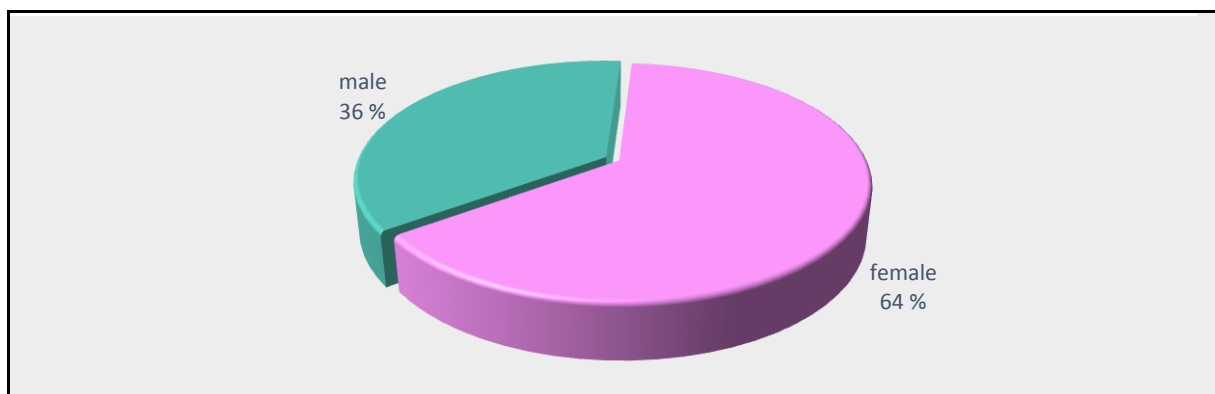
Hyponatremia has a female predominance

The most frequent age group in both genders was >70 years (n= 33, 66 %) with female to male ratio 3.1:1 (Table 3). There is significant relationship between age and sex as most of patients between 50 and 70 years were males and most of patients >70 years were females (P= 0.042).

Table 3 - Distribution of patients with hyponatremia by age and sex

age groups	female	%	male	%	total
<50 years	4	50.0	4	50.0	8
50-70 years	3	33.3	6	66.7	9
>70 years	25	75.8	8	24.2	33
total	32	64.0	18	36.0	50

Hyponatremia is more frequent in older population >70 years, three-fourths of them are females. with P= 0.042

5.2 Factors affecting the length of stay in hospital (LOS)

The stay in hospital ranged from 3 to 21 days with a median 7.5 days. We have found an inverse correlation of LOS with albumin, hemoglobin and a positive correlation with age, white blood cells count, and low attention level. Interestingly, there was no significant relationship between serum sodium concentration and LOS (the baseline characteristics and their relation to LOS are given in Table 4).
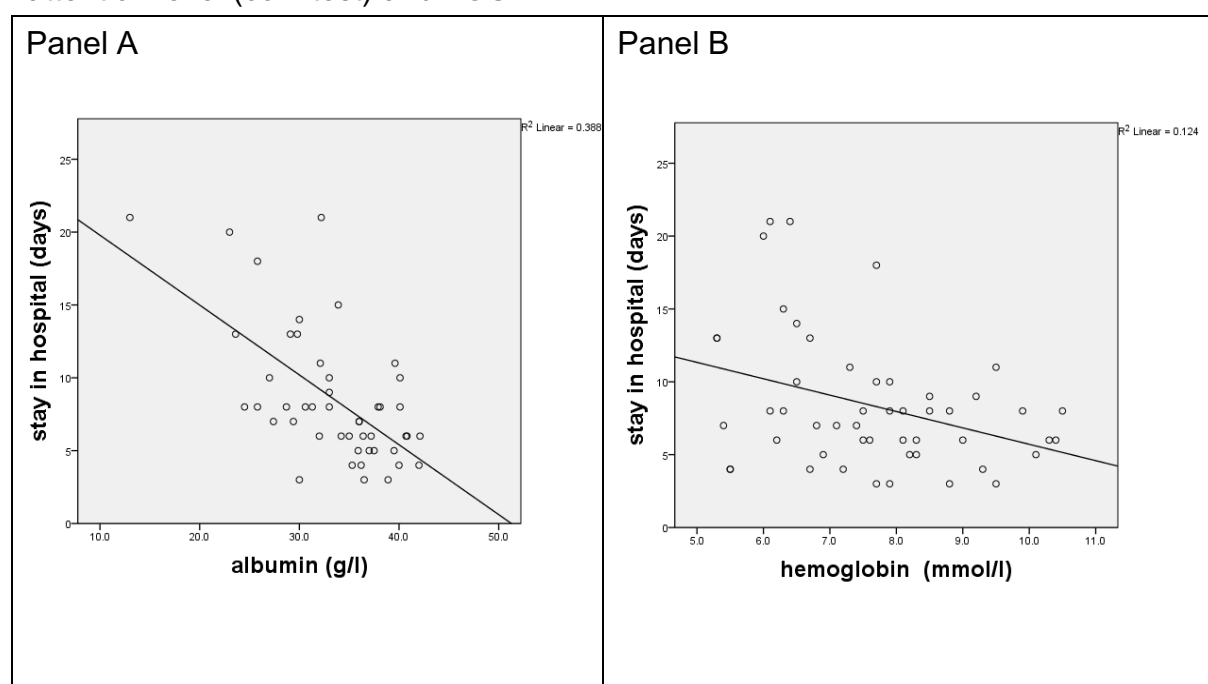
Table 4 - Baseline characteristics of patients admitted with hyponatremia and their relation to LOS (n= 50)

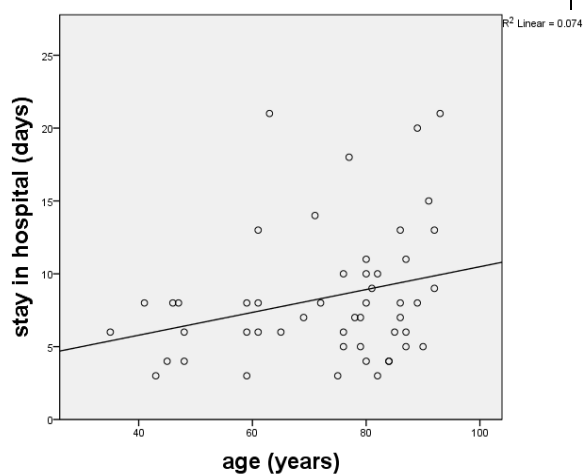|	Mean	sig. relationship	correlation
age (years)	72.8	*P*= 0.046	0.28
systolic BP (mmHg)	147.1	*P*= 0.589	−0.08
diastolic BP (mmHg)	77.8	*P*= 0.807	0.03
s. sodium (mmol/l)	120.9	*P*= 0.212	−0.18
s. potassium (mmol/l)	4.0	*P*= 0.803	−0.04
hemoglobin (mmol/l)	7.6	*P*= 0.035	−0.30
hematocrit (%)	35.0	*P*= 0.061	−0.27
albumin (g/l)	33.4	*P*<0.01	−0.55
	Median		
WBC (Tsd./µl)	10.4	*P*= 0.012	0.35
CRP (mg/l)	8.8	*P*=0.546	0.08
BMI (kg/m^2)	25.5	*P*= 0.101	−0.23
s. creatinine (µmol/l)	87.2	*P*= 0.200	−0.18
s. osmolality (mOsm/kg)	260.5	*P*= 0.599	−0.08
coin test results (sec)	70.0	*P*= 0.016	0.34

Non-Parametric test (Spearman test) showed significant correlation between age, hemoglobin, albumin, WBC, low attention level and LOS
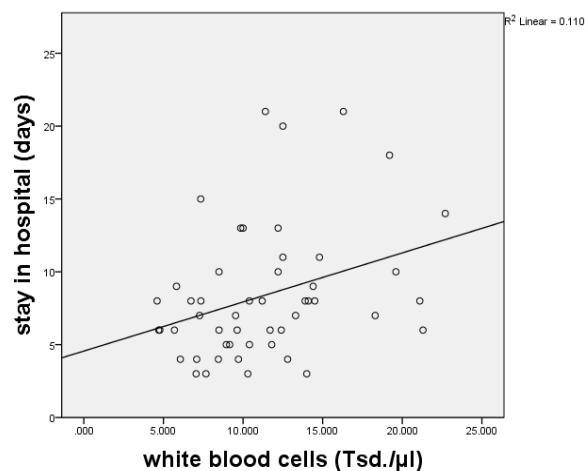There was no significant relationship between serum sodium concentration and LOS

Figure 4 - Correlations between serum albumin, hemoglobin, age, WBC, low attention level (coin test) and LOS
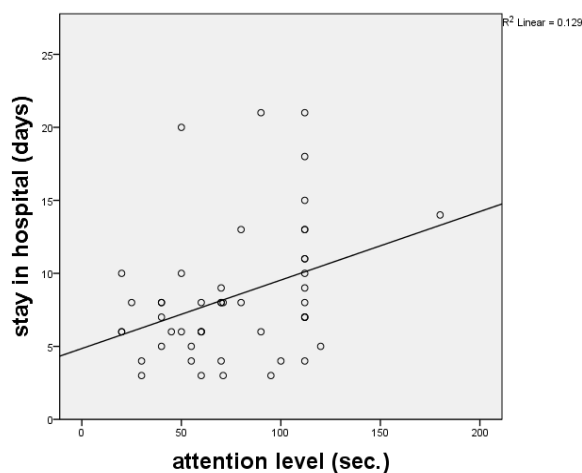
Panel C — stay in hospital (days) vs age (years). R^2 Linear = 0.074

Panel D — stay in hospital (days) vs white blood cells (Tsd./µl). R^2 Linear = 0.110

Panel E — stay in hospital (days) vs attention level (sec.). R^2 Linear = 0.129

There was statically significant negative correlation between LOS and serum albumin, hemoglobin and statically significant positive correlation between LOS and patients age, WBC count, and low attention level

5.3. Patients distribution according to epidemiological, clinical and paraclinical parameters

The most frequent type of hyponatremia is hypovolemic hyponatremia (n= 24, 48 %) followed by euvolemic (n= 17, 34 %) and hypervolemic hyonatremia (n= 9, 18 %).

Figure 5 - Distribution of patients with hyponatremia according to volume status
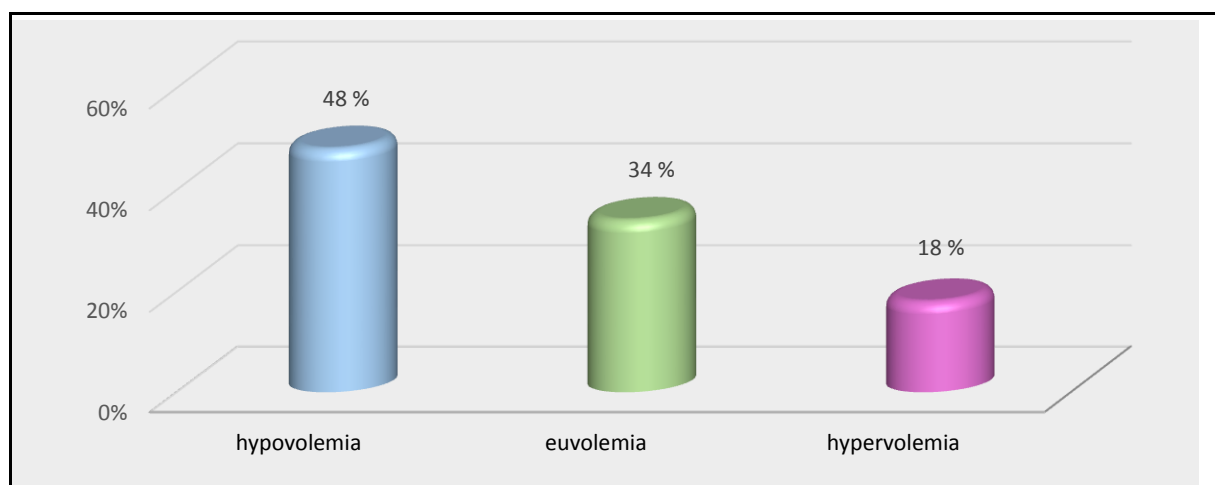
Nearly half of the patients (n= 24, 48 %) were hypovolemic, followed by euvolemic and hypervolemic subjects

The minimum sodium level was 104 mmol/l, most of patient were with sodium ≤120 mmol/l or 126-130 mmol/l (40 %, 40 %), respectively. The level of sodium is also significantly related to volume status in our study as most of patients with hypovolemia and hypervolemia with sodium level (126-130 mmol/l), while most of patients with euvolemia with sodium level ≤120 mmol/l, (P= 0.03) (Table 5).

Table 5 - Distribution of patients with hyponatremia according to sodium levels

sodium level (mmol/l)	hypovolemia	euvolemia	hypervolemia	total	%
≤120	8	9	3	20	40.0
121-125	4	6	0	10	20.0
126-130	12	2	6	20	40.0
total	24	17	9	50	100.0

Half of patients with hypovolemia and two thirds of patients with hypervolemia having sodium level (126-130 mmol/l), while more than half of patients with euvolemia having sodium level ≤120 mmol/l, (P= 0.03)

The median BMI was 25.5 kg/m^2, the minimum BMI was 20 kg/m^2, while maximum BMI was 40 kg/m^2. About half of the patients with hyponatremia with normal BMI (Table 6).

Of the patients, 46 (92 %) presented with chronic hyponatermia while in 4 patients, (8 %) hyponatremia was of acute onset (two patients due to gastroenteritis, one

patient with newly prescribed thiazide diuretics in addition to previous ACE inhibitor and beta blockers treatment and one patient after resection of a pituitary macroadenoma) (Figure 6). In 30 patients (60 %), the diagnosis of hyponatremia was established for the first time while in 20 patients (40 %) hyponatremia had been found at an earlier occasion as pre-existed symptomatic or subtle hyponatremia.

Table 6 - Distribution of patients with hyponatremia according to BMI

BMI (kg/m^2)	frequency	%
18.5-24.9	24	48.0
25-29.9	17	34.0
≥30	9	18.0
total	50	100.0

Nearly half of patients with hyponatremia having a normal body weight

Figure 6 - Distribution of patients according to the onset of hyponatremia
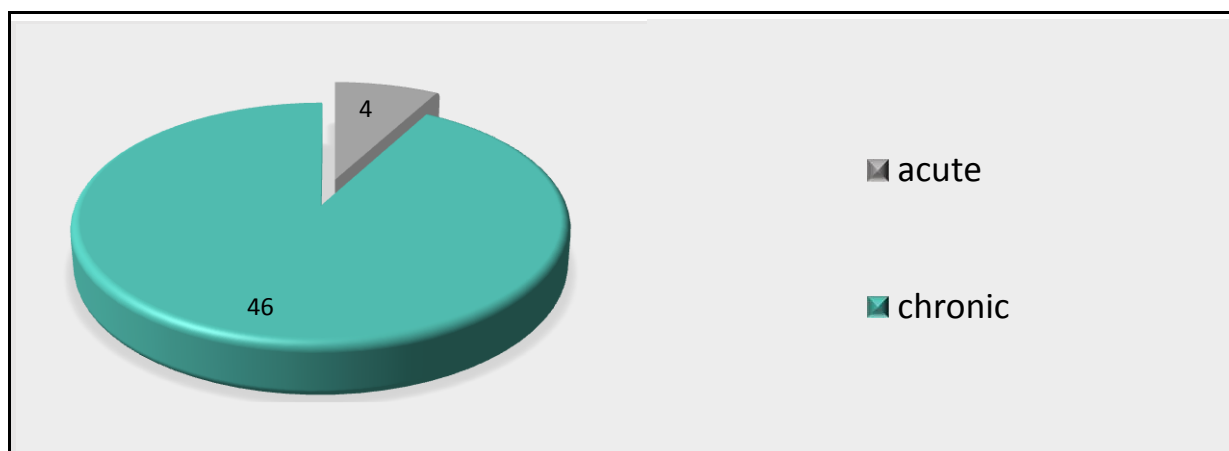
46 (92 %) of patients with hyponatremia have a chronic onset

The Less specific symptoms like fatigue, loss of appetite, nausea, vomiting are frequently founded in patients with hyponatremia, only 3 patients were asymptomatic. Low attention level sometimes was difficult to decide as symptom if we took in consideration that most of patients >70 years and part of them with dementia (already diagnosed or as defined by mini mental test), additionally some symptoms especially nonspecific non neurological symptoms were difficult to be attributed to hyponatremia, they could be part of the cause more than hyponatremia *per se*. There is only significant relationship between nausea and onset of

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hyponatremia as all patients with acute onset have nausea and less than half of patients with chronic onset (47.8 %) have nausea (Figure 7).

Figure 7 - Frequency of symptoms in patients with hyponatremia
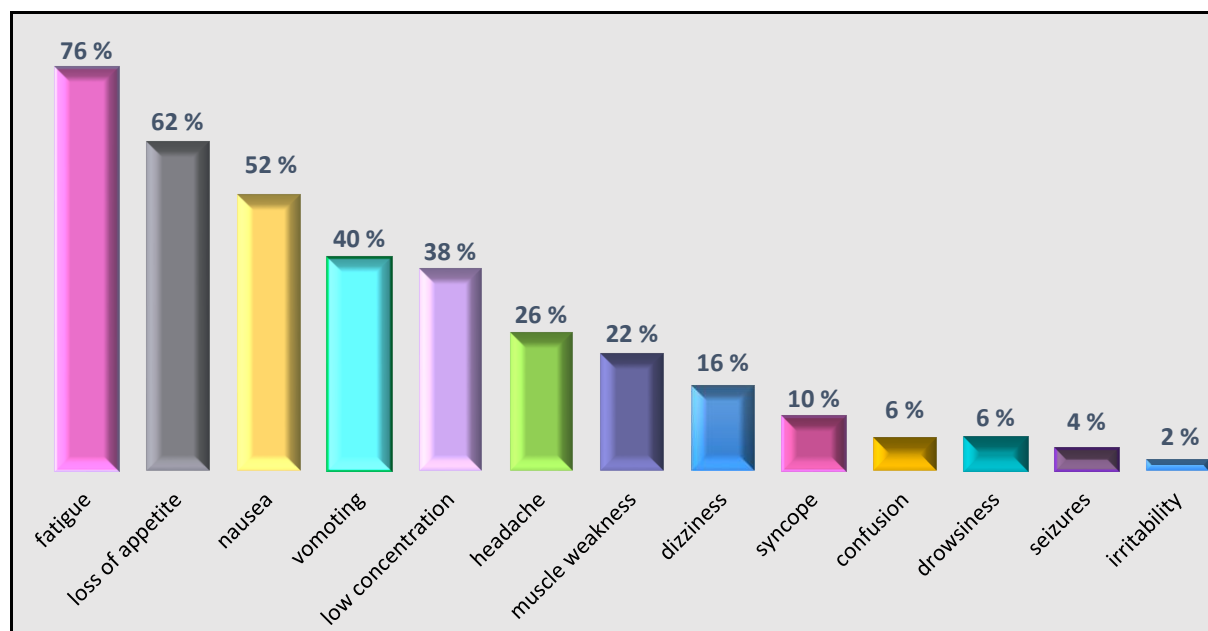
Less specific non neurological symptoms are more frequent in hyponatremic patients

5.4. Risk factors

Hypertension is the most frequent risk factor associated with hyponatremia followed by diabetes mellitus and renal failure.

Table 7 - Frequency of risk factors in patients with hyponatremia

| risk factors	frequency	%
arterial hypertension	38	76.0
diabetes mellitus	20	40.0
renal failure	18	36.0
congestive heart failure	9	18.0
pneumonia	5	10.0

Hypertension is the most frequent comorbidity associated with hyponatremia

5.5. Etiologies of hyponatremia

Diuretics combined with ACE inhibitors, ARA II, and or BB was the most common cause of hyponatermia was found in more than half of the patients.

Other drugs included AVP high dose in two patients, antidepressants; mirtazapin and citalopram in two patients plus ARA II (valsartan) in one of them, ACE inhibitor and beta blockers in two patients, antipsychotics; quetiapin and metformin in one patient and antiepileptic; carbamazepin and ACE inhibitor (lisinopril) in one patient (Figure 8). Out the 29 patients with hyponatremia due to diuretic therapy, 19 (65 %) on diuretic were females.

Figure 8 - Frequency of possible causes in patients with hyponatremia
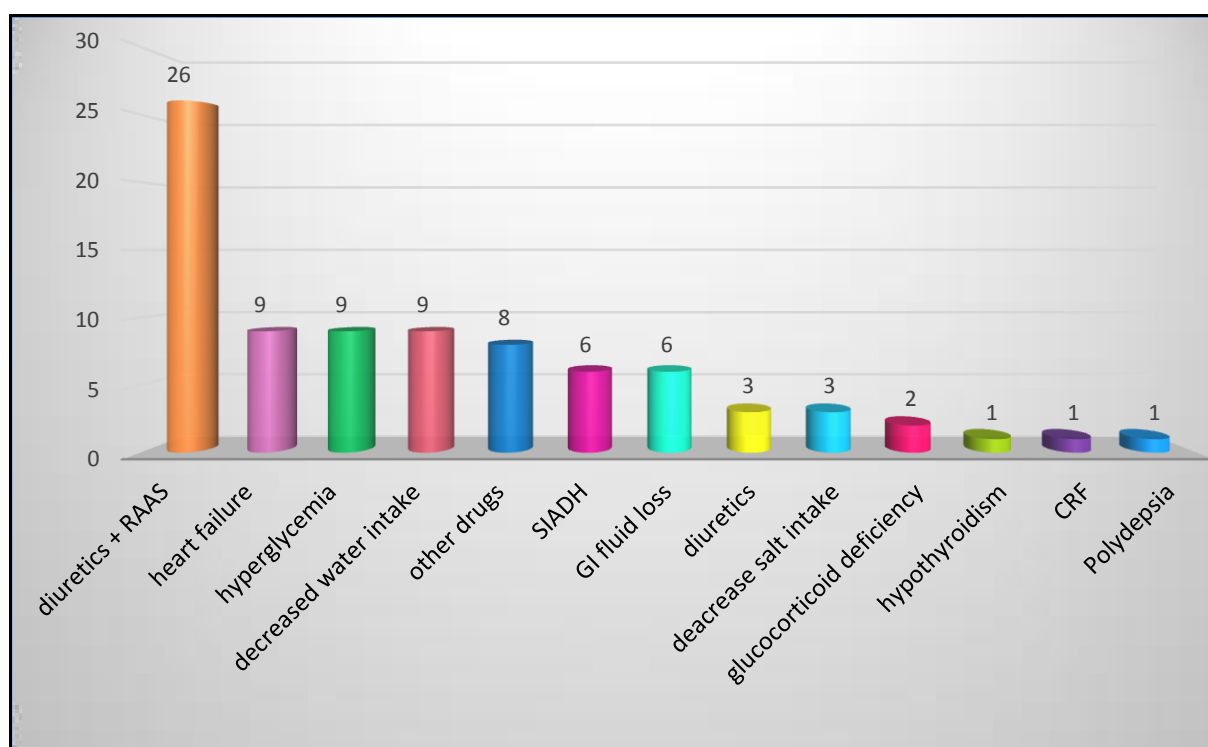
In more than half of the patients the possible cause of hyponatremia is diuretics + RAAS
Abbreviations: RAAS: renin angiotensin aldosterone affecting drugs, GI: gastrointestinal, CRF: chronic renal failure

In most of the patients (58 %), the cause of hyponatremia is likely multifactorial although some conditions may be leading or more dominant than others (Table 8).

Table 8 - Distribution of patients with hyponatremia according to the number of possible causes

cause	frequency	%
one cause	21	42.0
two causes	24	48.0
three causes	5	10.0
total	50	100

Hyponatremia is multifactorial in more than half of patients

Interestingly, most patients had been admitted in summer (n= 19, 38 %), followed by spring (n= 14, 28 %), autumn (n= 10, 20 %), and in winter (n= 7, 14 %). In summer, most of the patients were admitted because of hypovolemia (n= 11, 57.9 %), (n= 8, 42.1 %) were on diuretics and RAAS inhibitors. Most of them were female (n= 14, 73.7 %), 13 of them were older than 70 years (68.4 %).

5.6. Volume Status and etiology

All of patients with gastrointestinal loss and inadequate salt and water intake as the main etiology are hypovolemic, all of patients with other drugs are euvolemic and all of CHF are hypervolemic. Most of patients with SIADH are euvolemic and with hyperglycemia are hypovolemic. Patients who are using diuretics or diuretics + RAAS affecting drugs either hypovolemic or euvolemic. Less common causes include; one case due to glucocorticoid deficiency which was hypovolemic, one case due to polydipsia which was euvolemic, and one case due to chronic renal failure was hypervolemic. There is significant relationship between volume status and etiology ($P<0.01$).

Table 9 - Distribution of patients by volume status and main etiology

etiology	hypovolemia		euvolemia		hypervolemia		total	
	n	%	n	%	n	%	n	%
diuretics + RAAS drugs	7	29.2	5	29.4	0	0.0	12	24.0
CHF	0	0.0	0	0.0	8	88.9	8	16.0
hyperglycemia	8	33.3	1	5.9	0	0.0	9	18.0
decrease water intake	2	8.3	0	0.0	0	0.0	2	4.0
other drugs	0	0.0	4	23.5	0	0.0	4	8.0
SIADH	1	4.2	5	29.4	0	0.0	6	12.0
gastrointestinal loss	4	16.7	0	0.0	0	0.0	4	8.0
diuretics	1	4.2	1	5.9	0	0.0	2	4.0
less common causes	1	4.2	1	5.9	1	11.1	3	6.0
total	24	100	17	100	9	100	50	100

*Abbreviations: RAAS: renin angiotensin aldosterone affecting drugs, CHF: congestive heart failure, SIADH: syndrome of inappropriate antidiuretic hormone
**There is significant relationship between volume status and etiology ($P<0.01$)

Figure 9 - Frequency of main causes according to volume status
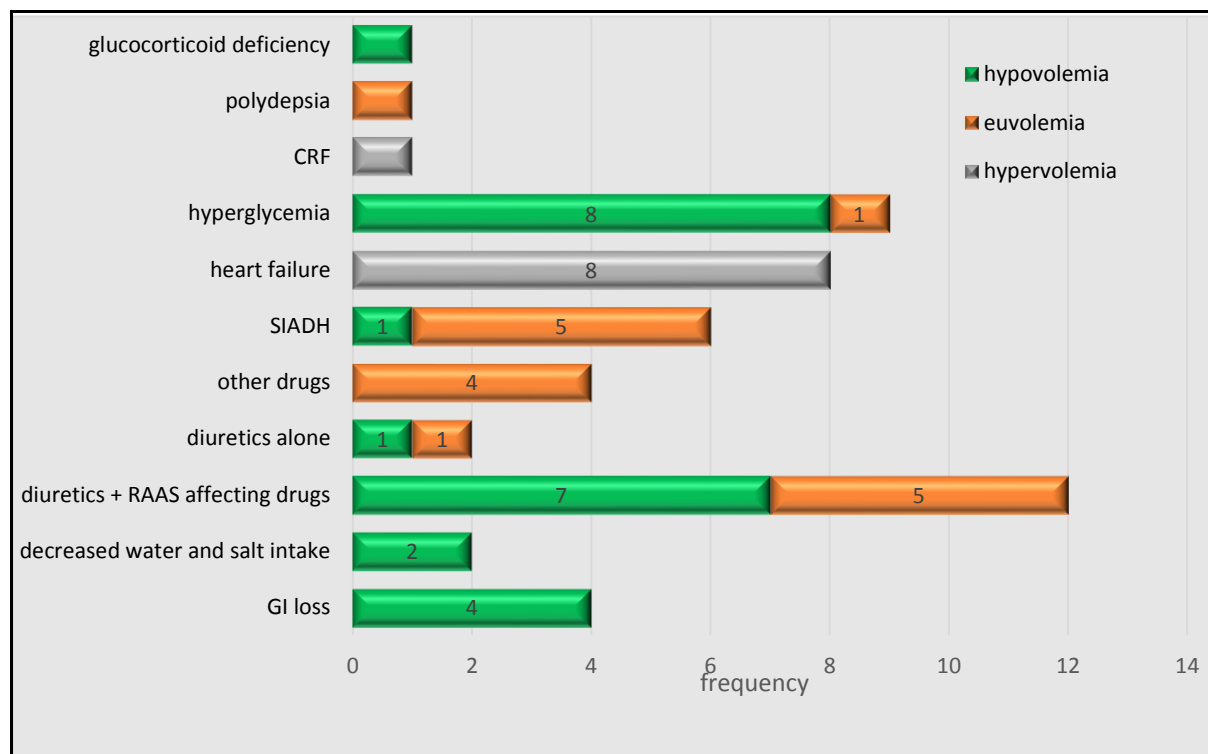
There is significant relationship between volume status and etiology $P= 0.00$ as all of patients with CHF, GI loss, other drugs are hypervolemic, hypovolemic and euvolemic, respectively. Most of patients with SIADH, hyperglycemia are euvolemic, hypovolemic, respectively

5.7. Hematological, urinary and BIS parameters distribution by volume status

In our study we studied the relationship between several hematological, urinary indices in addition to BIS indices and volume status. We found that creatinine, urea, and uric acid were significantly higher in hypervolemic hyponatremia followed by hypovolemic hyponatremia and they were lowest in euvolemic hyponatremia. Serum osmolality was the lowest in euvolemia reflecting the lowest sodium concentration in blood in this group with a mean of 116.8 mmol/l in comparison with other groups. Sodium in urine is the lowest in hypervolemic hyponatremia (as most of cases due to HF) which also reflected by elevation of SUSPPUP. Serum renin and aldosterone are clearly elevated in hypervolemic and hypovolemic hyponatremia. Serum albumin concentration and hematocrit were clearly reduced in hypervolemic hyponatremia, while NT-proBNP is significantly higher in hypervolamic hyponatremia in comparison to the other etiologic groups reflecting the dilutional status and volume overload. BIS was corresponding significantly with clinical diagnosis in our study (Table 10, 11).

Table 10 - Means of hematological, urinary and BIS parameters by volume status

	hypovolemia	euvolemia	hypervolemia	P-value
serum sodium (mmol/l)	120.2 ±7.6	116.8 ±7.1	124.1 ±6.5	0.060
urinary osmolality (mOsm/kg)	327.7 ±126.7	370.9 ±120.7	314.1 ±154.8	0.285
uric acid (µmol/l)	348.6 ±141.9	246.0 ±116.2	530.3 ±166.5	0.001
albumin(g/l)	32.7 ±4.7	34.6 ±7.4	30.1 ±4.7	0.250
serum potassium (mmol/l)	3.8 ±0.9	4.0 ±0.7	3.7 ±0.5	0.534
hematocrit (%)	33.7 ±5.6	33.7 ±4.2	30.3 ±4.8	0.205
overhydration (L)	−0.6 ± 1.2	−0.26 ± 1.2	3.2 ± 1.2	0.002

*Only cases with hypotonic hyponatremia were included
**Uric acid and BIS were corresponding significantly with clinical diagnosis in our study
Statistical significance was determined by parametric testing, using Anova test. *P*<0.05 was considered statistically significant

Table 11 - Medians of hematological and urinary parameters by volume status

	hypovolemia	euvolemia	hypervolemia	P-value
urea (mmol/l)	5.5 (2.3-13.1)	3.7 (0.94-12.4)	14.8 (4.7-23.0)	0.002
urinary sodium (mmol/l)	52.5 (24-253)	51.5 (9-156)	17.5 (8-140)	0.013
creatinine (µmol/l)	90.2 (49.0-169.0)	63.4 (20.8-140.0)	133.0 (55.4-834.0)	0.013
serum osmolality (mOsm/kg)	258.0 (218-269)	249.5 (222-275)	273.0 (249-283)	0.004
NT-proBNP (pg/ml)	529.0 (45-7391)	492.0 (42-3623)	19282.0 (1638-111323)	0.000
aldosterone (pmol/l)	271.0 (30-3452)	171.5 (38-1203)	191.5 (93-11638)	0.638
renin (pmol/l/hr)	34.1 (1.0-725.0)	12.7 (3.9-200.0)	42.5 (2.3-819.0)	0.550
SUSPPUP	4.6 (1.8-11.5)	4.3 (0.5-18.6)	15.5 (0.55-23.6)	0.011

*Urea, urinary sodium, creatinine, serum osmolality, NT-proBNP, and SUSPPUP were corresponding significantly with clinical diagnosis in our study
**Range is illustrated between brackets
***Abbreviations: SUSPPUP=Serum sodium to urinary sodium to (serum potassium) ^{2} to urinary potassium
****Statistical significance was determined by non-parametric testing, using the Kruskal–Wallis test. $P<0.05$ was considered statistically significant

5.8. Hematological, urinary parameters distribution by etiologies

In our study, we compared different hematological and urinary parameters between the etiologies of hyponatremia. Serum sodium, plasma osmolality, uric acid, urea and creatinine are the lowest in patients with SIADH. Hematocrit, urinary and plasma osmolality are the highest in hyperglycemia. Urinary sodium is the lowest in CHF (in all cases below 30 mmol/l) with elevation of SUSPPUP. Serum creatinine is the highest in hyperglycemia followed by CHF. Urinary and serum potassium are the lowest in GI loss and SUSPPUP is the highest in CHF as compared to other causes.

Figure 10 – Medians/ means of hematological, urinary and BIS parameters distribution by volume status
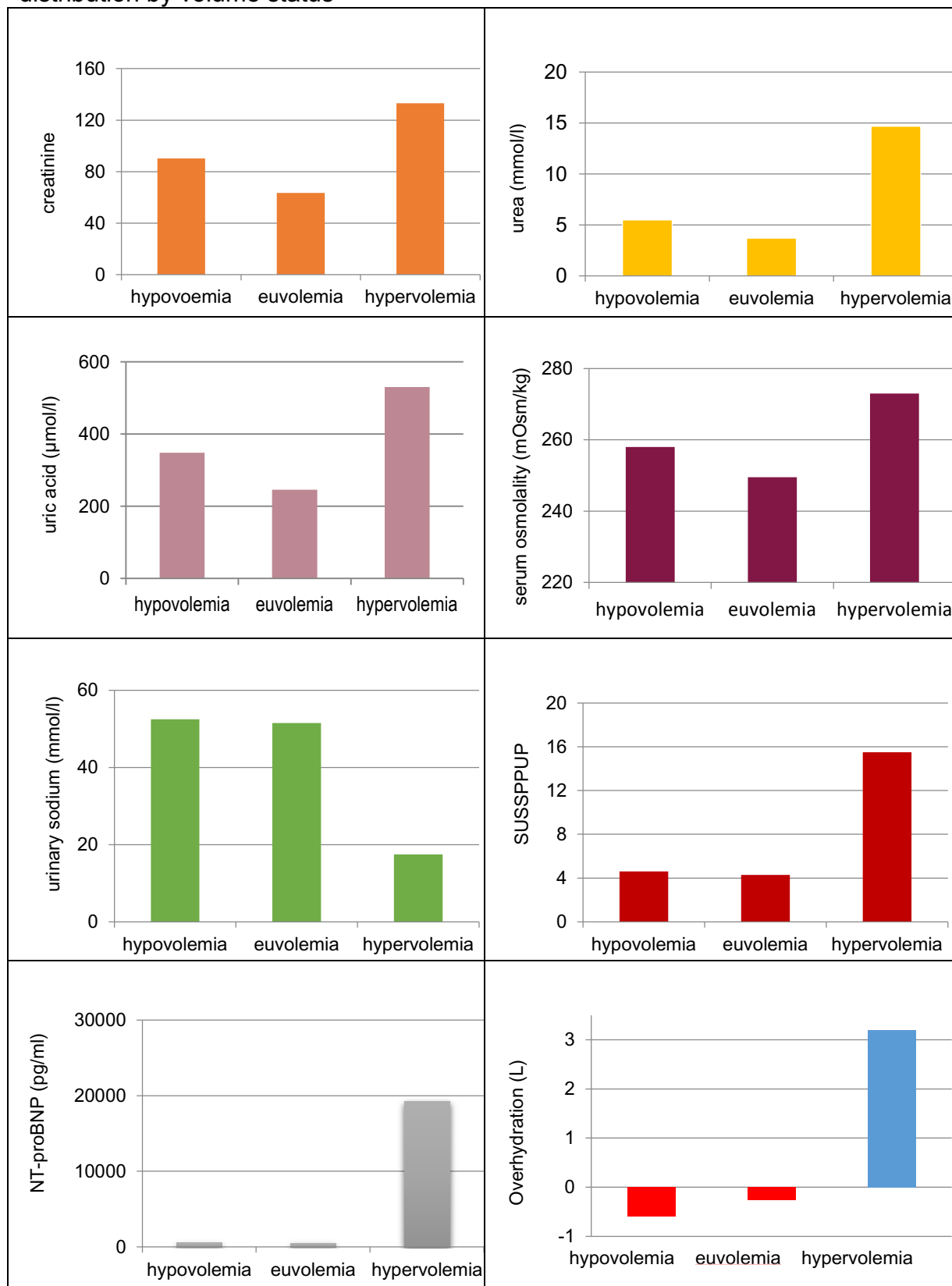
Serum urea, creatinine, uric acid, serum osmolality, urinary sodium, SUSPPUP, NT-proBNP and overhydration were significantly related to volume status

Table 12 - The relationship between means of paraclinical parameters and etiologies of hyponatremia

	GI loss	decrease water intake	diuretics	diuretics + RAAS drugs	other drugs	SIADH	heart failure	hyperg-lycemia	less common causes	P-value
serum sodium (mmol/l)	121.2 ± 4.6	119.0 ± 12.7	122.0 ± 7.1	118.6 ± 7.5	118.7 ± 7.4	113.5 ± 9.1	123.7 ± 6.9	127.0 ± 3.4	124.3 ± 2.3	0.038
urinary osmolality (mOsm/kg)	300.7 ± 185	113 ± 0.0	412 ± 55.1	364.9 ± 94.6	337.2 ± 79.2	404.5 ± 165.3	334.9 ± 154.8	550.3 ± 119.3	245.3 ± 90.3	0.005
uric acid (µmol/l)	371.5 ± 200.8	429.0 ± 243.3	448.0 ± 96.2	331.5 ± 99.2	221.5 ± 50.8	170.8 ± 75.9	561.0 ± 166.2	404.0 ± 165.2	282.3 ± 100.4	0.002
albumin (g/l)	33.5 ± 6.1	28.9 ± 0.28	19.4 ± 9.0	36.2 ± 4.0	37.0 ± 2.4	32.3 ± 5.5	30.1 ± 4.7	35.1 ± 5.5	36.9 ± 5.5	0.003
serum potassium (mmol/l)	2.87 ± 7.0	4.6 ± 0.2	4.0 ± 0.1	4.0 ± 0.9	4.1 ± 1.2	4.0 ± 0.3	3.7 ± 0.5	4.7 ± 1.0	3.7 ± 0.5	0.026
hematocrit (%)	35.2 ± 5.4	25.5 ± 0.7	29.0 ±1.4	34.7 ± 5.4	36.2 ± 1.3	32.8 ± 4.2	30.9 ± 4.8	44.0 ± 4.6	32.0 ± 5.3	0.000

Serum sodium and uric acid are the lowest in patients with SIADH, urine osmolality is the highest in hyperglycemia, serum potassium is the lowest in GI loss
Abbreviations: GI loss: gastrointestinal loss, RAAS: renin angiotensin aldosterone affecting drugs

Table 13 - The relationship between medians of paraclinical parameters and etiologies of hyponatremia

	GI loss	decrease water intake	diuretics	Diuretics + RAAS drugs	other drugs	SIADH	heart failure	hypergl-ycemia	less common causes	P-value
urinary sodium (mmol/l)	57.0 (24-82)	40.0 (25-55)	60.0 (43-77)	50.0 (32-253)	52.5 (47-117)	62.0 (22-156)	16.0 (8-28)	38.0 (5-95)	29.0 (9-140)	0.057
urea (mmol/l)	4.6 (2.6-7.1)	9.5 (5.9-13.1)	5.3 (5.2-5.5)	4.6 (2.3-12.4)	4.2 (2.5-5.7)	2.0 (0.9-3.7)	12.4 (4.7-22.2)	9.7 (2.4-19.2)	9.1 (3.2-23.0)	0.019
serum creatinine (µmol/l)	84.4 (49-169)	96.5 (94.5-98.5)	87.7 (64.4-111)	90.2 (60.5-140)	63.9 (52.2-86.2)	49.6 (20.8-61.9)	132.5 (55.4-185)	171.0 (62.8-250)	96.0 (44.8-834)	0.012
NT-proBNP (pg/ml)	340.0 (111-900)	1219.5 (603-1836)	611.0 (128-1094)	885.0 (45-7391)	464.5 (79-1135)	355.5 (236-3623)	8605.5 (163-12500)	192.0 (15-1104)	76.7 (42-111323)	0.008
plasma osmolality (mOsm/kg)	260.5 (244-270)	261.5 (227-296)	264.0 (253-275)	255.5 (218-269)	252.0 (228-261)	239.5 (222-280)	272.5 (249-280)	302.5 (285-404)	260.0 (256-283)	0.000
urinary potassium (mmol/l)	10.0 (9-26)	28.8 (9-49)	22.4 (21-24)	33.3 (8-76)	26.9 (24-46)	23.9 (12-58)	20.0 (15-60)	22.5 (9-32)	10.2 (4-11)	0.28
SUSPPUP	5.0 (2.6-9.8)	3.4 (2-4.9)	3.2 (1.9-4.4)	3.3 (0.8-18.6)	5.0 (1.1-7.8)	5.0 (0.5-9.5)	15.9 (9.5-23.6)	2.6 (1.9-15)	4.2 (0.5-4.3)	0.032
TTKG	4.3 (4.2-6.6)	4.0 (4.0-4.0)	3.6 (2.9-4.4)	6.0 (1.6-18.9)	6.3 (3.3-7.9)	3.9 (1.4-5.9)	4.9 (2.3-13.8)	2.5 (2.1-3.7)	3.7 (0.9-4.4)	0.126
renin (pmol/l/hr)	20.0 1.0-70.4	40.3 7.9-72.7	390.5 22.0-581.0	16.9 1.7-725.0	8.1 3.9-19.5	12.9 3.9-38.3	48.8 9.0-819	50.7 8.3-348.0	30.0 2.3-196.0	0.338
aldosterone (pmol/l)	251 90-285	87 30-144	1177.5 654-1701	271 85-3452	159 116-198	175.5 38-1203	218 93-11638	288.5 102-802	184 165-461	0.464

plasma osmolality, serum creatinine and urea are the highest in hyperglycemia and CHF and are the lowest in SIADH, SUSPPUP is the highest and urinary sodium is the lowest in CHF as compared to other causes. GI loss: gastrointestinal loss, RAAS: renin angiotensin aldosterone affecting drugs, SUSPPUP: Serum sodium to urinary sodium to (serum potassium)[2] to urinary potassium

5.8. Important clinical and paraclinical findings before and after therapy

The mean/median of BP, creatinine, urea, uric acid, SUSPPUP, aldosterone, and renin were higher in patients with hyponatremia before than after therapy, while the mean /median of serum osmolality, serum sodium, attention level were lower, with significant P value <0.05.

Table 14 - Comparison between important clinical and paraclinical findings before and after therapy of the patients with hyponatremia

normally distributed values	baseline		after intervention		P value
	mean	SD	mean	SD	
uric acid (µmol/l)	350.1	± 162.3	303.7	± 143	0.021
serum sodium(mmol/l)	120.9	± 7.6	134.5	± 4.2	0.000
s. potassium (mmol/l)	4.04	± 0.9	3.98	± 0.7	0.647
u. osmolality (mOsm/kg)	387.6	± 161.7	367.7	± 146	0.456
a. systole (mmHg)	147.1	± 28.8	131.4	± 14.7	0.000
a. diastole (mmHg)	77.8	± 13.2	73.8	± 8.7	0.034
coin test (sec)	76.2	± 35.1	71.2	± 34.7	0.012
non-normally distributed values	median	range	median	range	P value
s. creatinine (µmol/l)	87.2	20.8-834.0	82.3	43.9-845.0	0.020
urea (mmol/l)	5.2	0.9-23	4.2	1.0-23.1	0.001
s. osmolality (mOsm/kg)	260.5	218-404	285	267-324	0.000
u. sodium (mmol/l)	47	5-253	77.5	10-204	0.000
u. potassium (mmol/l)	23.1	4.0-76.0	24.4	5.6-74.0	0.145
SUSPPUP	4.4	0.54-23.6	2.7	0.5-13.7	0.041
TTKG	4.1	0.9-18.9	4.7	2.1-14.0	0.128
NT-proBNP (pg/ml)	603	15-111323	514	2-11230	0.828
aldosterone (pmol/l)	234.5	30-1638	103	4-2223	0.000
renin (pmol/l/hr)	20	1-819	13.2	1-505	0.007

The following parameters: BP, creatinine, urea, uric acid, urinary sodium, SUSPPUP, aldosterone, renin, serum osmolality, serum sodium, attention level are changed significantly after therapy, *P*< 0.05
Abbreviations: s.: serum, u.: urinary, a: arterial, SUSPPUP: serum sodium to urinary sodium to (serum potassium) [2] to urinary potassium, TTK: trans-tubular potassium gradient

Discussion

Hyponatremia is one of the most common electrolyte and water balance disorders the physician faces in hospital. Although in last years, development in approaches of the diagnosis and treatment of hyponatremia was seen, it still poses diagnostic and therapeutic challenges. However, little is known about the etiology of hyponatremia among patients in Mecklenburg-Western Pommeranian hospitals and the best parameters help to establish a diagnosis.

Many studies showed female predominance in patients with hyponatremia while in others, there is male predominance. The mean age of patients in our study was 72.8 ± 15.8 years (range 35-93 years) with a female predominance (n=32, 64 %). The higher incidence of hyponatremia in elderly patients in our study could be attributed to several factors such as decreased glomerular filtration rate, presence of comorbidities, and polypharmacy leading to impairment in water and electrolyte hemostasis and the response to dietary and environmental factors (Fregan *et al*. 2005; Beck *et al*. 2000; Chua *et al*. 2007). It is nearly similar to a study involving two Swiss academic centres and included patients with profound hyponatremia (sodium <125 mmol/l), the median age of the participants was 71 years (interquartile range (IQR) 60-80), (65 %) were female (Nigro *et al*. 2015). In another study, there was also a female predominance (55 %) (Rao *et al*. 2010). The mean age of patients in our study was higher than what reported in an Indian study involving ICU patients (60.4 ± 17.2 years) but with similarly female predominance (56.5 %) (Padhi *et al*. 2014). However, in another two studies there was a male predominance (51.2 %, 62.7 %) (Coenraad *et al*. 2007; Chatterjee *et al*. 2012), respectively. This variation can be explained by the inclusion criteria in our study (serum sodium ≤130 mmol/l), study population and specificity of each department.

In our study, the mean sodium level on admission was 120.9 ± 7.6 mmol/l, which was nearly similar to Nigro *et al*. (2015) with a mean serum sodium concentration of 120 mmol/l and lower than Coenraad *et al*. (2007) who observed 128 mmol/l in his cohort.

Many studies showed a prolongation of hospital stay in patients with hyponatremia in comparison with normonatremic patients and included patients admitted to internal medicine or neurosurgical departments or concerned specific diseases such as pneumonia, heart failure or cancer (Garcia *et al*. 1994; Gill *et al*. 2006; Zilberberg *et al*. 2008; Ali *et al*. 2016; Marco *et al*. 2013; Zanocchi *et al*. 2002; Scherlock *et al*. 2009; Hennrikus *et al*. 2015; Brouns *et al*. 2014; Conway *et al*. 2014; Callahan *et al*. 2009). However, one study was not able to prove this difference in the LOS between patients with or without hyponatremia (Lim & Yap, 2001). It focussed on geriatric patients, paying attention to the fact that the people are elderly, fragile and hospitalized principally for acute medical conditions.

The median stay of patients with hyponatremia was 7.5 days in our study which was similar to patients with moderate-to-severe hyponatremia as compared to other studies (Callahan *et al*. 2009; Zilberberg *et al*. BMC Pulm Med 2008; Zilberberg *et al*. Curr Med Res Opin 2008). However, in one study the LOS was much higher and compromised 16 ± 12 days (Gill *et al.* 2006). There was no clear reason for prolonged LOS in the last study even if we take into consideration that the hospital-based studies involved severe hyponatremic patients with a serum sodium concentration <125 mmol/l. It should be emphasized that the mean LOS of randomly chosen normonatremic patients was also long in this analysis (13 ± 11 days).

According to our knowledge, there are few if no studies which illustrate the factors, affecting LOS in patients with hyponatremia and if the level of serum sodium *per se* mediates the effect on LOS or whether there are other factors such as demographic factors, other laboratory parameters or comorbidities to play a role.

In our study (Table 4), there was no significant relation between serum sodium concentrations and LOS, which was similarly found by a recent study and a meta-analysis (Callahn *et al*. 2009; Corona *et al*. 2016). The stay in hospital in our study was strongly negatively correlated with serum albumin and also to a lesser extent with hemoglobin and positively correlated with patient's age, WBC, and low attention level.

One important such factor which was associated with LOS in our hyponatremic patients was the concentration of serum albumin which showed a medium but strongly significant correlation with LOS. Serum albumin concentrations serve as a marker of a patient's nutritional state, acute and chronic inflammatory responses. Besides malnutrition-inflammation complex syndrome there are other factors playing a role in development of hypoalbuminemia such as hemodilution, liver dysfunction, increased transcapillary escape rate, protein-losing enteropathy and renal loss (Arques & Ambrosi, 2011; Haller, 2005). Interestingly, hypoalbuminemia was found to be a predictor of neurological manifestations of hyponatremia and the only independent risk factor for death (Shapiro *et al.* 2010). Also, hypoalbuminemia was an independent risk factor for LOS and or mortality in patients with COPD, heart failure, end stage renal disease ESRD as well as elderly patients (Zanocchi *et al.* 2002; Wang *et al.* 2014; Martín-Sánchez *et al.* 2016). Additionally, it is not uncommon to find in patients with nutritional deficiency due to chronic diseases electrolytes, including sodium and vitamins depletion beside hypoalbuminemia.

Albumin is an important transporter for non-water-soluble protein-bound drugs and toxins in addition to various substances, fatty acids, metals, ions, and hormones. Presence of drugs with high binding characteristics to plasma proteins allows for higher drug levels and more rapid hepatic metabolism. Hypoalbuminemia is linked with adverse outcome in patients with end stage renal diseases and hepatic insufficiency could be attributed to the increase in the free albumin-bound toxins (Meijers *et al.* 2008). Additionally, albumin plays an important role as circulating antioxidant, about 80 % of the thiol groups in blood are derived from albumin molecule. The reduction of blood thiol content aggravates oxidative stress (Anraku *et al.* 2011). Hypoalbuminemia favours also volume overload and diuretic resistance.

In our study, anemia was one of the factors associated with LOS in patients with hyponatremia which was mentioned as one of the parameters that increased hospital stay by internal medicine patients in general or patients with specific diseases such as heart failure or cancer (Nathavitharana *et al.* 2012; Lin *et al.* 2013; Martín-Sánchez *et al.* 2016; Shayne *et al.* 2013). Infection reflected by increased WBC also affects LOS which was similarly found in cancer patients (Shayne *et al.* 2013).

In our study (Figure 5), nearly half of the patients 24 (48 %) were hypovolemic, followed by euvolemic 17 (34 %) and hypervolemic subjects 9 (18 %). This is nearly similar to what was found by other studies (Coenraad *et al*. 2003; Hochman *et al*. 1989), but different from a study in patients in department of internal medicine as hypervolemic hyponatremia (n= 41, 49.4 %) associated with liver cirrhosis and hearth failure was most frequent (Rudnay *et al*. 2013) and similarly by (Gross *et al*. 1988). However, the largest group of hyponatremic patients were euvolemic in two other studies carried in internal medicine ward in tertiary care hospital and in critically ill patients on intensive care unit ICU (Chatterjee *et al*. 2012; Padhi *et al*. 2014).

The tendency to hyponatremia could be explained also near to old age, to the use of thiazide diuretics by patients with thin body composition. In our study about half of the patients (48 %) with BMI 18.5-24.9 kg/m^2. Several studies mentioned the risk factors of thiazide induced hyponatremia TIH like reduced body mass (Sharabi *et al*. 2002; Clayton *et al*. 2006; Chow *et al*. 2003; Rodenburg *et al*. 2013). The reason is not completely clear; the level of sodium in the plasma is determined by the total body water. Thus, its concentration changes significantly in subject with smaller body mass and consequently less total body water. Besides, decreased body mass or muscle wasting might also signify underlying disease (Abramow & Cogan, 1984).

46 (92 %) patients were presented with chronic hyponatermia, while in 4 patients (8 %) hyponatremia was of acute onset (two patients due to gastroenteritis, one patient with newly prescribed thiazide diuretics in addition to previous ACE inhibitors and BB therapy and one patient presented after pituitary macroadenoma resection).

In 30 (60 %) of patients the diagnosis of hyponatremia was established for the first time while in 20 (40 %) they were already diagnosed before with pre-existing symptomatic or subtle hyponatremia.

(Figure 7) illustrates frequency of symptoms in patients with hyponatremia from the most frequent to less frequent. Less specific symptoms like fatigue, loss of appetite, nausea, vomiting are more frequent with the following frequencies, fatigue (n= 38, 76 %), loss of appetite (n= 31, 62 %), nausea (n= 26, 52 %), vomiting (n= 20, 40 %). This findings are comparable to Nigro *et al*. 2015 study, clinical symptoms were

generalized weakness (n= 205, 69 %), fatigue (n= 175, 59 %), nausea (n= 130, 44 %), acute vomiting (n= 91, 30 %). More severe symptoms such as acute epileptic seizures were identified in 2 (4 %) participants which was similarly found by Nigro *et al*. (2015). A low attention level was sometimes difficult to be interpreted as a symptom if we took in consideration that most of patients were over 70 years of age. In addition, some symptoms, incl. loss of appetite, nausea and vomiting, were difficult to be attributed to hyponatremia because they could well have been part of the disease complex causing hyponatremia rather than a consequence of it *per se*. There is only significant relationship between nausea and onset of hyponatremia as all patients with acute onset have nausea and less than half of patients with chronic onset (47.8 %) have nausea. Following Chatterjee *et al*. 2012, a large fraction of cases (48.2 %) are asymptomatic. In our study was not the same, only 6 % were asymptomatic. This could be explained by the inclusion criteria in our study with sodium concentration ≤130 mmol/l while by Chatterjee *et al*. <135 mmol/l.

In our study arterial hypertension was the most common comorbidity associated with hyponatremia (76 %) followed by DM (40 %), renal failure (36 %), congestive heart failure (18 %), and pneumonia (10 %) (Table 7). By (Kayar, 2016), comorbidities of the patients with hyponatremia were hypertension (73.8 %) followed by diabetes mellitus (52.2 %), (49.4 %) had chronic kidney disease and (34 %) had congestive heart failure. Similarly, the common co-morbid conditions were hypertension then diabetes mellitus by (Rao *et al*. 2010; Mohan *et al*. 2013). Due to Nigro *et al*. 2015, the most common comorbidities were hypertension (n= 199, 67 %), pulmonary disease (n= 82, 28 %), chronic renal failure (n= 64, 21 %) and congestive heart failure (n= 44, 15 %).

The use of diuretics in combination with inhibitors of the renin-angiotensin system was one of the most common clinical scenarios promoting development of hyponatremia in our study (Figure 8). The concept of promoting natriuresis together with blockade of aldosterone secretion or action was implemented in more than a half of the patients (52 %), and are in concordance with the observation of others who associated diuretics with hyponatremia in half the portion of patients (Al Barqawie *et al*. 2007), two-third (Kennedy *et al*. 1978) and even three-fourth of cases

(Cumming *et al*. 2014). The importance of thiazide-induced hyponatremia (TIH) is reemerging because thiazide diuretic prescription seems to be increasing after appearance of evidence-based statements on thiazides as a possible first-line treatment in essential hypertension (Mancia *et al*. 2007). In an Indian study, the most common causes of hyponatremia included the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and use of diuretics in elderly hospitalized patients (Rao *et al.* 2010). This was differing from other studies in which SIADH was the most common suspected cause (by Liamis *et al*. 2007; Padhi *et al*. 2014; Shapiro *et al*. 2010). Of note, gastrointestinal fluid loss may also be a main cause of hyponatremia in a selected patient cohort (Coenraad *et al*. 2003; Chatterjee *et al*. 2012). These differences can be explained by the heterogeneity of patient populations and inclusion criteria. In addition, study results obtained in entire hospital populations including intensive care units and neurosurgery departments may not be fully comparable to our analysis and those of others.

Out the 29 patients with hyponatremia due to diuretic therapy (Figure 8), from them 19 (65 %) were females. This was nearly similar to Al Barqawi. 2007 stud*y,* in which (60 %) of hyponatremic patients caused by diuretic therapy were female.

Another two studies have shown that (70 %, 71 %), respectively of their hyponatremic patients were female (Sharabi *et al*. 2002; Ashraf *et al*. 1981). Similar results found by (Fishman *et al*. 1971; Abramow *et al*. 1986), the reason is questionable but women possibly drink more than men and may develop dilutional hyponatremia (Kone *et al*. 1986), they treated more often with diuretics (Klungel *et al*. 1997) and hence more prone to dilutional hyponatremia and they are more symptomatic than men (Ayus *et al*. 1992).

There is significant relationship between volume status and etiology P= 0.00. In (Table 9) patients in whom either diuretics alone or in combination with other RAAS affecting drugs (total14) 8 were hypovolemic and 6 were euovolemic. This was also prescribed by (Guyatt *et al*. 2008; Hamburger *et al*. 1981) as diuretics may cause normal or mildly increased extracellular fluid volume state. Diuretics alone or in combination with other RAAS drugs followed by SIADH are the most common causes of euvolemic hyponateremia in our study. Similarly, the most common

causes of euvolemic hyponatremia by Runday *et al*. are SIADH and thiazide diuretics therapy.

In most of the patients (58 %), the cause of hyponatremia was multifactorial (1.68 causes per patient) although there may be conditions with a more dominant direct effect than others. As shown in a cohort of elderly patients with fragility fractures, the cause of hyponatremia was assumed to be of multi-factorial in etiology in 73 % of cases (Cumming *et al*. 2014). Likewise, other studies discussed the hyponatremia to be of multifactorial origin in 51 % of patients (1.7 etiological factors per patient) by (Shapiro *et al*. 2010), and 54 % (Al Barqawie *et al*. 2007).

The relationship between hyponatremia and season was clear in our study whereas (n=19, 38 %) of patients had been admitted in summer, most of them due to hypovolemia 11/19 (57.9 %), were female 14 (73.7 %) and old age >70 years 13 (68.4 %). 8 (42.1 %) were using diuretics. An Indian study by Kalaiselvan *et al*. 2015 on critically ill patients admitted to ICU due heat related illness especially in summer, the most common metabolic abnormality found was hypontremia (75 % of patients). Another Indian study by Chatterjee *et al*. 2012, illustrated increased incidence of hyponatremia in the monsoon season.

The assessment of volume status takes in most guidelines a central role (Verbalis *et al*. 2013; Hoorn *et al*. 2013; Nagler *et al*. 2014). In the last European guidelines and based on the low sensitivity and specificity of clinical assessments of volume status, they used it far down in diagnostic algorithm to make the misclassification less likely (Spasovski *et al*. 2014). However, presence of renal disease and or using of diuretics still also affect urine sodium concentration in addition to the possibility of more than one cause affecting every classification. Therefore, there is increasingly need to improve the classification based on volume status by finding of objective beside subjective measures which in many cases are matter of experience. Various indices have been used to assess hydration status adjacent to physical examination, including change in body weight, hematological indices, urinary indices, BIA and cardiovascular indices.

In our study we tried to study the relationship between several hematological, urinary indices in addition to BIA indices and volume status as illustrated in table (10, 11). We found that creatinine, urea, uric acid and plasma osmolality were higher in hypervolemic hyponatremia followed by hypovolemic hyponatremia and they were lowest in euvolemic hyponatremia, which was similar to Coenraad *et al*. 2003 study. A similar pattern of elevated serum urea, creatinine and uric acid concentrations in hyponatremic patients with hypervolemia and normal or slightly decreased concentrations in patients with SIADH has been shown by Decaux *et al*. 1994.

In addition, there was statically significant relationship between serum creatinine, urea, uric acid, plasma osmolality, urinary sodium and volume status which also described by Coenraad *et al*. 2003 study. Elevated concentrations of serum urea, creatinine and uric acid confirmed effective circulating volume depletion in hypervolemia and hypovolemia. Near normal values for concentrations of serum urea, creatinine, uric acid confirmed the normovolemic status of patients with euvolemia. Serum potassium, urine osmolality were statistically not significantly related to volume status, which is also similar to Coenraad study.

However, serum albumin concentration was clearly reduced in hypervolemic patients in comparison to the other etiologic groups, which was mentioned by Coenraad study. Similarly, hematocrit was reduced in hypervolemic patients reflecting the dilutional status. Although there was clear elevation in serum renin and aldosterone in hypervolemic and hypovolemic hyponatremia reflecting effective circulating volume depletion and inhibition of renin-aldosterone as a respond to water retention in euvolemia such relationship was not statistically significant. This could be explained by the need of reliable baseline measurements such as posture and using of tourniquet when parameters like hemoglobin, hematocrit, renin, and aldosterone are taken for accurate assessment of volume status (Stowasser *et al*. 2012; Shirreffs *et al*. 2003; Kavouras 2002). Additionally, we must take in consideration the using of diuretics and RAAS affecting drugs.

NT-proBNP is significantly higher in hypervolemic hyponatremia. It is worth mentioning that another concluded that, NT-proBNP levels of the patients with

hypovolemia were significantly lower than the patients with euvolemia study (Bunnag *et al*. 2012), which was not found in our study.

Plasma osmolality and sodium concentration have also been used to assess hydration status. During dehydration, especially during hypertonic hypovolemic dehydration from poor fluid intake, both plasma sodium and osmolality are significantly elevated. But these parameters also depend on salt intake or loss and degree of AVP stimulation.

Urinary parameters especially USG, urine osmolality and colour are widely used not only because they provide correct and rapid information on hydration status, but also because they are comparatively easy to measure, however in our study and coenraad *et al.* study urine osmolality was not significantly different between the patients.

There were several studies performed to evaluate bioimpedance spectroscopy role in evaluation of hydration status in hemodialysis patients (Garagarzaa *et al*. 2013; Machek *et al*. 2010) and patients undergo peritoneal dialysis (Siaphi *et al*. 2011). However, there are still studies found clinical judgment guided by a single clinical examination were better as multifrequency bioimpedance analysis (Vasko *et al*. 2013). In other hand, a few studies were studied the role of bioimpedance spectroscopy in the estimation of body fluid status in hyponatremia (Kim *et al*. 2014; Comming *et al*. 2014; Kose *et al*. 2015). In these studies, BIS was corresponding significantly with clinical diagnosis, which was also founded in our study.

In our study, we compared different hematological and urinary parameters between the causes of hyponatremia. Serum sodium, serum osmolality, uric acid, urea and creatinine are the lowest in patients with SIADH followed by other drugs. Hematocrit, creatinine, urinary and plasma osmolality are the highest in hyperglycemia as a result of osmotic diuresis and subsequently volume depletion. NT-proBNP is the highest in HF patients. Sodium in urine is the lowest in HF (less than 30 mmol /l in all cases) and SUSPPUP ratio is the highest reflecting activation of renin-angiotensin-aldosterone system with secondary renal sodium retention despite body volume overload. Serum and urinary potassium are the lowest in GI loss.

In our study, there is significant increase in serum sodium and consequently serum osmolality and significant reduction in creatinine, urea, uric acid, SUSPPUP, aldosterone and renin concentrations after therapy of hyponatremia reflecting improvement in effective circulating volume (Table 14). Clinical parameters as blood pressure and attention level significantly improved after correction of hyponatremia.

Other parameters such as urinary osmolality, NT-proBNP, and TTKG were not significantly changed after therapy. This is comparable to a study by (Coenraad *et al.* 2007) in which plasma AVP and ANP concentrations did not change during treatment of hyponatremia despite a significant increase in serum osmolality.

However, there are some limitations of this study. Firstly, the study population was recruited from a single department. Secondly, the included population was relatively small; therefore, the external validity of our results might be limited.

Conclusion

We infer from our study:

- Hyponatremia was more common in older people with a mean age of 72.8 ± 15.8 years. Most of the patients with hyponatremia were of female gender (n= 32, 64 %).

- The median stay in hospital of patients with hyponatremia was 7.5 days. Interestingly, in our study, there was no significant relation between serum sodium concentrations and LOS. In our study, the stay in hospital was strongly negatively correlated with serum albumin and also to lesser extent with hemoglobin and positively correlated with patient's age, WBC, and low attention level.

- 46 (92 %) patients were presented with chronic hyponatremia. Less specific symptoms like fatigue, loss of appetite, nausea, vomiting were more frequent.

- In our study arterial hypertension was the most common comorbidity associated with hyponatremia (76 %) followed by DM (40 %), renal failure (36 %), and congestive heart failure (18 %).

- The use of diuretics in combination with inhibitors of the renin-angiotensin-aldosterone system was one of the most common clinical scenarios promoting development of hyponatremia in our study found in more than half of the patients (n= 26, 52 %).

- In more than half of patients (58 %), the cause of hyponatremia was multifactorial (1.68 causes per patient).

- The relationship between hyponatremia and season was clear in our study since 38 % of patients had been admitted in summer, most of them due to hypovolemia 11/19 (57.9 %), were female 14 (73.7 %).

- There was statically significant relationship between serum creatinine, urea, uric acid and volume status. Elevatetion of these parameters confirm effective arterial volume depletion in hypervolemia and hypovolemia. Near normal values or even lower concentrations confirm normovolemic state. Serum osmolality was the lowest in euvolemia reflecting the lowest sodium concentration in blood in this group with a mean of 116.8 mmol/l in comparison with other groups. Sodium in

urine is the lowest in hypervolemic hyponatremia (as most of cases due to HF). Therefore there is elevation of SUSPPUP reflecting activation of renin-angiotensin-aldosterone system with secondary renal sodium retention despite body volume overload. In addition, NT-pro BNP was significantlyy elevated in hypervolemia.

- Although there was clear elevation in serum renin and aldosterone in hypervolemic and hypovolemic hyponatremia, such elevation was not statistically significant.

- BIS was corresponding significantly with clinical diagnosis and can be used as useful diagnostic procedure to reach a diagnosis.

- In our study, there was a significant increase in serum sodium, serum osmolality and significant reduction in creatinine, uric acid, urea, aldosterone, renin, and SUSPPUP concentrations after therapy of hyponatremia reflecting improvement in effective circulating volume. Clinical parameters like blood pressure and low attention level were significantly improved after correction of hyponatremia.

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List of abbreviations

ACE   angiotensin converting enzyme

ADH   antidiuretic hormone

ARA   angiotensin receptor antagonists

AVP   arginine vasopressin

BCM   body composition monitor

BIA   bioelectrical impedance analysis

BIS   bioelectrical impedance spectroscopy

BMI   body mass index

BP   blood pressure

cAMP   cyclic adenosine monophosphate

CCD   cortical collecting ducts

CRF   chronic renal failure

CRP   C-reactive protein

COPD   chronic obstructive pulmonary disease

CSW   cerebral salt wasting

DM   diabetes mellitus

DWI   daily water intake

ECF   extracellular fluid

ECW   extracellular water

ESRD   end stage renal disease

GFR   glomerular filtration rate

GI   gastrointestinal

FT4   free thyroxin

HF   heart failure

ICU   intensive care unit

ICW   intracellular water

IQR   interquartile range

i.v.   Intravenous

LOS   length of stay in hospital

n   number

Na^+ Sodium

NaCl   sodium chloride

NT-proBNP   N-terminal prohormone of brain natriuretic peptide

MDMA	3,4-methylenedioxymethamfetamine
NSAID	nonsteroidal anti-inflammatory drug
OH	overhydration
osm	osmolality
prim.	primary
PPD	psychogenic polydipsia
RAAS	renin angiotensin aldosterone system
s	serum
SCr	serum creatinine
SD	standard deviation
sec.	secondary
SIADH	inappropriate antidiuretic hormone secretion
sig.	significant
SPSS	statistical Package for the Social Sciences
SSRIs	selective serotonin reuptake inhibitors
SUSPPUP	serum sodium to urinary sodium to (serum potassium)^2 to urinary potassium
TBW	total body water
TIH	thiazide induced hyponatremia
TSH	thyroid-stimulating hormone
TTKG	trans-tubular potassium gradient
u	urinary
WBC	white blood cell count

List of units

g/dl	gram per deciliter
h	hour
kg/m^2	kilogram per square metre
L	liter
nmol/l	nanomole per liter
mmol/l	millimole per liter
mmol/l/h	millimole per liter per hour
mOsm/kg	milliosmoles per kilogram of water
mg/dl	milligrams per deciliter
ml/kg/h	milliliter per kilogram per hour
mU/l	milliunits per liter
mmHg	millimeter of mercury
µmol/l	millimoles per liter
pg/ml	picogram per milliliter
pmol/l	picomole per liter
pmol/l/hr	picomole per liter per hour
sec.	second
Tsd./µl	thousands per microliter

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10. Declaration of original work

I hereby declare that the work presented here is, to the best of my knowledge and belief original and the results of my own investigations, except as acknowledged, and has not been submitted, either in part or whole, for a degree at this or any other University. Formulations and ideas taken from other sources are cited as such. This work has not been published yet.

Rostock, den   ....   Hadeel Ghaleb

Theses of Dissertation

- In Mecklenburg-Western Pommerania hyponatremia was more common in older people with mean age of 72.8 ± 15.8 years especially females (64 %). The mean sodium level was 120.9 ± 7.6 mmol/l. The most frequent type of hyponatremia is hypovolemic hyponatremia (48 %).

- The length of stay in hospital of patients with hyponatremia was not related to serum sodium concentrations. There are other important factors play a role like hypoalbuminemia, anemia, increased age, infection or inflammation, and low attention level.

- In more than half of patients (58 %), the cause of hyponatremia was multifactorial (1.68 causes per patient). The use of diuretics in combination with inhibitors of the renin-angiotensin system was one of the most common clinical scenarios promoting development of hyponatremia in our study found in more than half of the patients (52 %).

- The relationship between hyponatremia and season was clear in our study since 38 % of patients had been admitted in summer, most of them due to hypovolemia (57.9 %), were female (73.7 %).

- Serum urea, creatinine, uric acid, serum osmolality, urinary sodium, SUSPPUP, NT-proBNP are the best parameters helping in evaluation of volume status. Elevated concentrations of serum urea, creatinine, uric acid confirmed effective circulating volume depletion in hypervolemia and hypovolemia. Near normal values of of these parameters confirmed the normovolemic status. Serum osmolality was the lowest in euvolemia reflecting the lowest sodium concentration in blood in this group. Sodium in urine is the lowest in hypervolemic hyponatremia (as most of cases due to HF). Therefore there is elevation of SUSPPUP reflecting activation of renin-angiotensin-aldosterone system with secondary renal sodium

retention despite body volume overload. In addition, NT-pro BNP was significantly higher in hypervolamic hyponatremia reflecting the dilutional state.

- Although there was clear elevation in serum renin and aldosterone in hypervolemic and hypovolemic hyponatremia, such elevation was not statistically significant.

- Bioelectrical impedance spectroscopy measurements were corresponding significantly with clinically evaluated volume status and can be used as useful diagnostic procedure to reach a diagnosis.

- In our study, there was a significant increase in serum sodium, serum osmolality and significant reduction in creatinine, uric acid, urea, aldosterone, renin, and SUSPPUP (serum sodium to urinary sodium to (serum potassium)² to urinary potassium) concentrations after therapy of hyponatremia reflecting improvement in effective circulating volume. Clinical parameters like blood pressure and low attention level were significantly improved after correction of hyponatremia

I am grateful to the God for the good health and wellbeing that were necessary to complete this work.

This thesis would not have been possible without the guidance and the help of several individuals who in one way or another contributed and extended their valuable assistance and available support in the preparation and completion of this study. I would like to owe my deepest gratitude to:

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Last but not the least, I would like to thank my family: my parents and my brothers for supporting me spiritually throughout writing this thesis and in my life in general.

My husband Hani for the love, friendship, affection and patience. None of this would have been possible without you.

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- Education and study

Post-Graduate

2016-Now   Master Degree study in Internal Medicine (Facharzt),

                Physicians' Association Westphalia-Lippe, Germany.

2005-2009   Master Degree in Internal Medicine, Faculty of Medicine and Health

                Sciences, Aden University, Yemen.

Under-Graduate

1997-2003   Bachelor Degree in Human Medicine, MD(MB,chB) Faculty of

                Medicine and Health Sciences, Aden University, Yemen (Including

                one year of Internship).

Primary and Secondary School

1993-1996   Secondary education, Saba Secondary School, Aden.

1984-1993   Primary education, Alkahdi School, Aden.

- Professional Experience

2016-Now   Postgraduate student, Department of Internal Medicine,
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2013-2014   One year course for German language at University of Rostock.

2009-2012   Internist, Faculty of Medicine and Health Sciences
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2005-2009   Instructor, Internal Medicine Resident Doctor and Postgraduate
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2003-2005   Physician, Alburiqa polyclinic, Saber private hospital,
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- Articles and Publications

- **Ghaleb H**, Knauerhase A, Fischer DC, Bastian M, Novikova E, Willenberg HS. Volume status, hypoalbuminemia, white blood cell counts and anemia affect length of hospital stay in hyponatremic patients. 60th German Congress of Endocrinology Würzburg, 2017.

Hadeel Ghaleb

14.1 Data collection sheet

Causes of disturbances and parameters of the volume status in patients with hyponatremia

No. Of questionnaire …………

File No. ………………………..

- Patient name: ……………………………………………
- Date of births: I__I__I I__I__I I__I__I
- Sex: □ Male   □Female
- Height: I__I__I__I cm   Weight: I__I__I__I, I__I kg
- Date of admission: I__I__I I__I__I I__I__I
- Date of discharge: I__I__I I__I__I I__I__I
- Type of hyponatremia: □ Acute (< 48 h)   □ Chronic
- Hyponatremia diagnosis: □ First time   □ Not first time
- Volume status:

    □ Hypovolemia   □ Euvolemia   □ Hypervolemia

Diagnosis: …………………………………………………………….

…………………………………………………………………………….

Etiologie:

□ Diuretics	□ RAAS	□ GI fluid loss
□ Decreased water intake	□ CHF	□ Liver cirrhosis
□ Renal failure	□ Nephrotic syndrome	□ SIADH
□ Decreased salt intake	□ Drugs	□ Glucocorticoid deficiency
□ Hypothyroidism	□ Psychogenic polydepsia	□ Hyperglycemia
□ Others		

Risk factors:

☐   Art. Hypertension   ☐   Diabetes mellitus   ☐   Pneumonia

☐   Congestive heart failure   ☐   Renal failure   ☐   Others

Clinical picture and complications:

☐   Nausea   ☐   Vomiting   ☐   Loss of appetite

☐   Lethargy and fatigue   ☐   Muscle weakness   ☐   Headache

☐   Low concentration   ☐   Cofusion   ☐   Irretability

☐   Drowsiness   ☐   Coma   ☐   Seizures

☐   Syncope   ☐   Falls or trauma   ☐   Ataxia

☐   Cardiac arrest   ☐   Respiratory arrest   ☐   Other symptoms

Investigations on admission:

Blood pressure (mmHg) …………   LDL (mmol/l) …………
Coin test (sec) …………   HDL (mmol/l) …………
BIA (L) …………   Serum sodium (mmol/l) …………
Hemoglobin (mmol/l)…………   Serum potassium (mmol/l) …………
Hematocrit (%)…………   Serum osmolality (mOsm/kg) …………
WBC (Tsd./µl) …………   Urinary sodium (mmol/l) …………
CRP (mg/l) …………   Urinary potassium (mmol/l) …………
Glucose (mmol/l) …………   Urinary osmolality (mOsm/kg) …………
Urea (mmol/l) …………   S.Cortisol (nmol/l) …………
Uric acid (µmol/l) …………   TSH (mU/l) …………
Serum creatinine (µmol/l) …………   FT4 (pmol/l) …………
Serum albumin (g/l) …………   Aldosterone (pmol/l) …………
Triglyceride (mmol/l) …………   Renin (pmol/l/hr) …………
Total cholestrol(mmol/l) …………   NT-proBNP (pg/ml) …………

Investigations at discharge:

Blood pressure (mmHg) …………   NT-proBNP (pg/ml) …………
Coin test (sec) …………   Serum sodium (mmol/l) …………
Urea (mmol/l) …………   Serum potassium (mmol/l) …………
Uric acid (µmol/l) …………   Serum osmolality (mOsm/kg) …………
Serum creatinine (µmol/l) ………… Urinary sodium (mmol/l) …………
Aldosteron (pmol/l) …………   Urinary potassium (mmol/l) …………
Renin (pmol/l/hr) …………   Urinary osmolality (mOsm/kg) …………

Drugs implicated in development of hyponatremia

- □ Amiloride or triamterene
- □ Spironolactone
- □ Loop diuretics
- □ Thiazides
- □ ACE inhibitors or ARBs
- □ Beta blockers
- □ Moxonidine or clonidine
- □ NSAID
- □ Benzodiazpines
- □ Antidepressants: SSRI or tricyclic anti-depressants
- □ Antipsychotics: Phenothiazines or haloperidol
- □ Antiepileptic drugs: Carbamazepine or valproate
- □ Anticancer drugs
- □ Pain killers: Acetaminophen or opiates
- □ Antidiuretic hormone analogues: Oxytocin
- □ Hypoglycemic agents: Metformin or tolbutamide or chlorpropamide
- □ Antibiotics: Ciprofloxacin, co-trimoxazole
- □ Antiarrhythmic drugs: Amiodarone or propafenone
- □ Theophylline
- □ Proton pump inhibitors
- □ Bromocriptin

□ Clofibrate

□ Others

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Betr.: Rostocker Hyponatriämiestudie im Rahmen des Konzeptes:
»Wo Zucker ist, ist auch Salz«

Eine Studie zur Ermittlung Ursachen von Störungen und Parametern des Volumenstatus bei Patienten mit Hyponatriämie.

Sehr geehrte Patientin, sehr geehrter Patient,

in unserer Sektion für Endokrinologie und Stoffwechselerkrankungen untersuchen wir bei unseren Patienten den Zucker- und Salzstoffwechsel. Hier scheint es enge Verbindungen zwischen beiden Stoffwechselwegen zu geben. Bisher sind diese Wechselwirkungen aber nicht gut genug erforscht und beschrieben. Deshalb führen wir zu diesem Thema eine Studie durch. In dieser Studie werden wissenschaftlich die Ursachen, Symptome, hormonellen Veränderungen und die Wirksamkeit der Behandlung von Patienten mit Hyponatriämie untersucht. Unter einer »Hyponatriämie« versteht man einen zu niedrigen Natriumspiegel im Blut bzw. einen »Salzmangel«.

Wenn Sie eine Hyponatriämie haben, werben wir um Ihre Teilnahme an dieser Studie.

Wir würden uns freuen, wenn wir Ihre Aufmerksamkeit geweckt haben.

Mit besten Grüßen,

Ihre

Fr. cand. med. Hadeel Ghaleb
Studienärztin

Prof. Dr. med. Holger S. Willenberg
Sektionsleiter

Sehr geehrte Patientin, sehr geehrter Patient,

Ihre Ärztin/Ihr Arzt hat Ihnen angeboten, an dieser Studie teilzunehmen. Bevor Sie eine Entscheidung treffen, lesen Sie bitte dieses Informationsblatt sorgfältig durch. Bitte stellen Sie alle Fragen zur Registerstudie, die für Sie wichtig sind. Diese Einverständniserklärung beinhaltet möglicherweise Begriffe, die Sie nicht kennen. Bitte fragen Sie Ihre Ärztin/Ihren Arzt oder das Studienpersonal, wenn Sie Wörter oder Begriffe nicht verstehen. Durch die Unterzeichnung dieser Einverständniserklärung stimmen Sie zu, den Prüfärzten (die Ärztinnen und Ärzte, die sich um die Registerstudie kümmern) Ihre medizinischen Informationen zur Verfügung zu stellen. Sie können Ihr Einverständis jederzeit auch ohne Angabe von Gründen zurückziehen/widerrufen. Dadurch entstehen Ihnen keine Nachteile.

Leitender Prüfarzt: **Prof. Dr. med. Holger S. Willenberg**

Studienärztin: **Frau cand. med. Hadeel Ghaleb**

24-Stunden-Telefonnummer: **0381 / 494-7525**

1. HINTERGRUND UND ZWECK DER REGISTERSTUDIE

Die »Hyponatriämie« ist eine sogn. »Elektrolytstörung« bzw. »Blutsalzstörung«, bei der die Salzmenge (Natriumkonzentration) im Blut niedriger als normal ist. Die Hyponatriämie ist die häufigste Elektrolytstörung und tritt oft bei Krankenhaus-Patienten auf. Sie wird mit vielen Krankheiten und Medikamenten in Zusammenhang gebracht, unter anderem Erkrankungen der hormonellen Regulation (z.B. SIADH-Syndrom, Nebennierenunterfunktion, Schilddrüsenunterfunktion), der Lungen, Nieren, Herzschwäche, Leberzirrhose und bösartigen Erkrankungen. Es stehen verschiedene Möglichkeiten zur Behandlung der Hyponatriämie zur Verfügung.

Der Zweck dieser Untersuchung ist es, die verschiedenen Ursachen und Behandlungen (auch ohne medikamentöse Behandlung) der Hyponatriämie zu vergleichen. Ihnen wurde angeboten, an dieser Studie teilzunehmen, weil Ihre medizinischen Informationen dabei helfen können, mehr über die Hyponatriämie und ihre Behandlung im Krankenhaus zu erfahren.

2. BESCHREIBUNG DER REGISTERSTUDIE

Diese Studie sammelt Informationen über Patienten, deren Natriummangel als Folge verschiedener Erkrankungen im Krankenhaus behandelt wird, und vergleicht die Wirksamkeit verschiedener Therapiemöglichkeiten in Bezug auf die Ursachen. Die Registerstudie erfasst außerdem Informationen über den Krankenhausaufenthalt (z.B. seine Dauer) und darüber, wie die Hyponatriämie während des Krankenhausaufenthalts diagnostiziert und behandelt wird. Ziel ist es, ungefähr 100 Patienten mit Hyponatriämie in diese Registerstudie aufzunehmen.

3. TEILNAHME AN DIE STUDIE

Ihre Prüfärztin/Ihr Prüfarzt hat geprüft, ob Sie für die Teilnahme an dieser Registerstudie in Frage kommen. Sollten Sie sich für eine Teilnahme entscheiden, werden Sie gebeten, diese Einverständniserklärung sorgfältig zu lesen und nach Klärung aller Ihrer Fragen zu unterzeichnen. Mit Ihrer Unterschrift geben Sie Ihre Einwilligung zur Teilnahme an dieser Registerstudie. Ist diese Einwilligung erfolgt, wird Ihr Prüfarzt Daten aus Ihrer Patientenakte erfassen, einschließlich »demographische« Daten (z.B. Alter, Geschlecht, Gewicht, u.ä.), die Vorgeschichte Ihrer Krankheit, Ihre aktuellen Beschwerden, Ihre Flüssigkeitsaufnahme und – ausscheidung, Ihre Laborergebnisse, die Befunde der durchgeführten Untersuchungen, Symptome in Verbindung mit der Hyponatriämie, Medikamente, die Sie einnehmen und Informationen zu Ihrer Entlassung. Sie werden ausschließlich durch Ihre Ärztinnen und Ärzte des medizinischen Zentrums behandelt, es finden keine zusätzlichen Untersuchungen oder Behandlungen statt und Sie müssen keine weiteren Angaben machen. Informationen werden bis zu Ihrer Entlassung aus dem Krankenhaus erfasst.

4. BEHANDLUNGSMÖGLICHKEITEN

Über die für Sie am besten geeignete Hyponatriämie-Behandlung entscheidet Ihre Ärztin/Ihr Arzt und nicht die Registerstudie. Sie können sich auch entscheiden, nicht an der Registerstudie teilzunehmen. Wenn Sie sich gegen eine Teilnahme entscheiden, erhalten Sie die gleiche medizinische Versorgung, Ihre Daten werden jedoch nicht erfasst.

5. DAS RECHT, FRAGEN ZU STELLEN UND/ODER DIE REGISTERSTUDIE ZU BEENDEN

Durch die Unterzeichnung dieser Einverständniserklärung verzichten Sie <u>nicht</u> auf Ihre gesetzlichen Rechte. Ihre Teilnahme an dieser Registerstudie ist absolut freiwillig. Sie haben das Recht, die Registerstudie jederzeit zu beenden. Sie müssen weder Nachteile/Sanktionen befürchten noch auf irgendwelche Vorteile verzichten. Wenn Sie sich entscheiden, nicht teilzunehmen oder Ihre Teilnahme an dieser Registerstudie abzubrechen, werden sich die Prüfärztin/der Prüfarzt und ihre/seine Kollegen weiterhin um Ihre medizinische Versorgung kümmern.

Sie haben das Recht, jederzeit Fragen zur Registerstudie zu stellen. Während Ihrer Teilnahme an dieser Registerstudie beantworten Ihre Prüfärztin/Ihr Prüfarzt oder ihre/seine Kollegen alle Ihre Fragen zur Registerstudie. Bei Fragen zu Ihren Rechten als Registerstudienpatient wenden Sie sich bitte an Ihre Studien- und Prüfärzte bzw. die Stations- und Oberärzte. Alle Informationen, die während dieser Registerstudie verfügbar werden und die Ihre Ärztin/Ihr Arzt als wichtig in Bezug auf Ihre Bereitschaft für eine weitere Teilnahme erachtet, werden Ihnen mitgeteilt.

Sie haben außerdem das Recht, Ihre persönlichen Daten, die während der Registerstudie erfasst werden, einzusehen. Sie können jederzeit Ihr Recht auf Einsichtnahme und Berichtigung ausüben. Zur Ausübung Ihres Rechts (auf Einsichtnahme und Berichtigung Ihrer medizinischen Daten oder andere Anfragen) wenden Sie sich an die Ärztin/den Arzt, die/der Sie während der Registerstudie betreut.

6. NUTZEN

Die Registerstudie gibt weder eine bestimmte Behandlung noch ein bestimmtes Medikament für die Behandlung Ihrer Hyponatriämie vor. Daher gewinnen Sie keinen gesonderten Nutzen durch ein bestimmtes Medikament. Jedoch kann Ihre Teilnahme an dieser Registerstudie dabei helfen, mehr über die Hyponatriämie zu erfahren und so anderen Patienten zukünftig nutzen, auch wenn Sie persönlich keine Vorteile davon haben. Des Weiteren entstehen Ihnen keine Kosten für die Teilnahme an dieser Registerstudie.

7. RISIKEN UND UNANNEHMLICHKEITEN

Diese Registerstudie erfasst Informationen darüber, wie die Hyponatriämie standardmäßig an den jeweiligen teilnehmenden medizinischen Zentren behandelt wird. Patienten erhalten keine Prüfpräparate (d.h. keine Medikamente, die sich noch

in Erprobung befinden) oder zusätzliche Untersuchungen im Rahmen dieser Registerstudie; daher sind keine körperlichen Risiken oder zusätzliche Belastungen mit der Teilnahme an der Registerstudie verbunden.

8. KÖRPERLICHE SCHÄDEN

Sie nehmen freiwillig an dieser Registerstudie teil. Sie erhalten während der Registerstudie keine Prüfmedikamente und es werden keine zusätzlichen Untersuchungen durchgeführt. Die Registerstudie sammelt Informationen über die Behandlung, die Sie für Ihre Hyponatriämie erhalten. Mit Ihrer Teilnahme an dieser Registerstudie ist deshalb kein Risiko eines körperlichen Schadens zu erwarten.

9. VERWENDUNG DER REGISTERSTUDIENERGEBNISSE UND VERTRAULICHKEIT

Das Forschungspersonal sowie Aufsichtsbehörden erhalten direkten Zugriff auf Ihre Originalpatientenakte zur Überprüfung der Daten. Diese Personen müssen ggf. auch Informationen aus Ihrer Patientenakte kopieren. Alle Informationen, die Sie identifizieren könnten, werden gelöscht. Der Schutz Ihrer persönlichen Daten wird im Rahmen der anwendbaren Gesetze und Bestimmungen gewahrt. Durch die Unterzeichnung dieser Einverständniserklärung erlauben Sie dem Sektionspersonal, diese Registerstudie durchführen und den Aufsichtsbehörden den Zugriff auf Ihre Daten.

Die Erfassung und Übermittlung der medizinischen Daten aus dieser Registerstudie an Aufsichtsbehörden erfolgt unter Einhaltung der Datenschutzrichtlinien. Wenn Ergebnisse dieser Registerstudie in medizinischen Fachzeitschriften veröffentlicht werden, wird Ihre Identität nicht offengelegt.

Ihr medizinisches Zentrum folgt etablierten Verfahren zur Wahrung des Datenschutzes. Ihre Daten erhalten lediglich einen Nummerncode. Niemand wird Sie anhand dieses Nummerncodes identifizieren können. Es werden keine Informationen, die Ihre Identität offenlegen könnten, veröffentlicht oder bei wissenschaftlichen Konferenzen vorgestellt.

Wenn Sie Bedenken hinsichtlich Vertraulichkeit, Übermittlung oder Sicherheit der von Ihnen oder über Sie bereitgestellten Daten haben, besprechen Sie dies bitte mit Ihrer Ärztin/Ihrem Arzt, die/der Sie während der Registerstudie betreut.

10. BEENDIGUNG DER TEILNAHME

Unter bestimmten Umständen kann Ihre Teilnahme an dieser Registerstudie ohne Ihre Zustimmung beendet werden, z.B. wenn nicht alle Einschlusskriterien (Anforderungen) für diese Registerstudie erfüllt sind. Außerdem kann die Universitätsmedizin entscheiden, die Registerstudie jederzeit zu beenden. Wenn Ihre Teilnahme an dieser Registerstudie beendet wird, erfahren Sie die Gründe hierfür. Die medizinische Versorgung Ihrer Hyponatriämie wird selbstverständlich ohne Unterbrechung weitergeführt.

11. PATIENTENEINWILLIGUNG

Die Registerstudie wurde mir ausreichend erläutert und ich hatte die Gelegenheit, Fragen zu stellen. Alle Fragen, die ich zu diesem Zeitpunkt hatte, wurden zu meiner Zufriedenheit beantwortet. Ich verstehe, dass ich ohne meine Einwilligung nicht an dieser Registerstudie teilnehmen kann. Ich habe das Recht, weiterhin Fragen zu stellen und Antworten zu erhalten. Ich kann jederzeit meine Teilnahme beenden. Dies wird meine weitere medizinische Versorgung an der Universiätsmedizin Rostock in keinster Weise beeinträchtigen.

Ich habe diese Einverständniserklärung und die Beschreibung der Registerstudie gelesen und verstanden. Ich unterzeichne freiwillig diese Erklärung als Nachweis meiner Entscheidung, an dieser Registerstudie teilzunehmen. Ich werde eine Kopie dieser unterzeichneten Einverständniserklärung erhalten.

Name, Vorname (Patient)	Ort, Datum	Unterschrift

Name, Vorname (Arzt)	Ort, Datum	Unterschrift

From the Division of Endocrinology and Metabolism

Rostock University Medical Center

Director: Prof. Dr. med. Holger Sven Willenberg

Causes of disturbances and parameters of the volume status in patients with hyponatremia

Inaugural Dissertation

to

Obtain the academic degree

Doctor of Medicine

Faculty of Medicine

University of Rostock

Submitted by

Hadeel Ghaleb

from Aden/Yemen

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