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Study of Clinicoetiological profile of hyponatremia patients admitted in Medical wards

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Abstract
Hyponatraemia is the most common electrolyte disorder in hospitalized patients. Its epidemiology depends on the serum sodium used to define hyponatraemia, which varies from study to study. It can be an early or even first sign of important underlying disease. It can be complicated by two types of neurological disorders cerebral oedema and osmotic demyelination syndrome. It is associated with increased morbidity and mortality rates in hospitalized patients, although it remains unclear whether these associations are mainly due to the underlying disease, direct effects of hyponatraemia, or a combination of both. Aims and Objectives - to study clinical profile of hyponatremia in hospitalized subjects. To study the aetiology of hyponatremia in hospitalized subjects. To assess morbidity and mortality due to hyponatremia. Materials and Methods - 100 patients with hyponatremia were studied. Most common symptoms were Lethargy and tremors, followed by headache, nausea, altered sensorium, convulsion and coma, in order. Hypervolemic hyponatremia is most common followed by euvolemic hyponatremia and hypovolemic hyponatremia. Euvolemic subjects had propensity to develop more severe and symptomatic hyponatremia. Dilutional hyponatremia is the most prevalent underlying pathophysiology of hyponatremia followed by diuretic use, SIADH, GI loss, Hypothyroidism, extra renal/GI loss and Cerebral salt wasting in order. Congestive cardiac failure was the most common cause of hypervolemic hyponatremia, followed by cirrhosis of liver and renal failure. Acute gastroenteritis was most common cause of hypovolemic hyponatremia. SIADH was the most common cause of euvolemic hyponatremia, followed by thiazide diuretics and hypothyroidism, in order.

Introduction

Hyponatremia is the most common electrolyte disturbance with a reported prevalence of up to 30% in hospitalised patients. Severe hyponatremia is seen in 1% of patients [1-3].

Hyponatremia is defined as a serum sodium concentration of less than 135 mEq/L [4,5].

Mild hyponatremia with plasma sodium 130 - 135 mEq/L is found in as many as 15-30% of hospitalized patients or in the institutionalized elderly [6].

Symptomatology depends more on the rate of development of the electrolyte abnormality than on its severity [1]. The clinical presentation has a wide spectrum, varying from asymptomatic patients to ones having seizures and coma [7]. Symptoms range from nausea and malaise, with mild reduction in the serum sodium, to lethargy,

decreased level of consciousness, headache, seizures and coma. Hyponatremia can be classified on the basis of serum osmolality, volume status and urinary sodium into hypertonic, isotonic and hypotonic types.

Hypotonic hyponatremia is further classified into hypervolemic, euvolemic and hypovolemic as follows: [8]

1) Hypovolemic hyponatremia: Decreased total body sodium and decreased total body water. The sodium deficit exceeding water deficit.
2) Euvolemic hyponatremia: Normal body sodium with increase in total body water.
3) Hypervolemic hyponatremia: Increase in total body sodium with greater increase in total body water.

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is an important cause of hyponatremia but different aetiologies can dominate in different clinical settings. The incidence is much more in the elderly mainly owing to impaired ability to maintain water and electrolyte homeostasis in response to dietary and environmental changes [10].

Clinically hyponatremia is often unrecognized when it is mild or when it develops slowly. But severe hyponatremia (plasma sodium < 120 mEq/L), particularly of rapid onset, is associated with substantial morbidity and can be life threatening [11]. Also moderate to severe hyponatremia bears a substantial associated morbidity and mortality [12].

The treatment of hyponatremia depends on the duration of hyponatremia and volume status of the patients. There is serious neurologic sequel if hyponatremia is inappropriately treated. Hyponatremia is associated with varying morbidity. Morbidity varies widely in severity; serious complications can arise from the disturbances itself as well as from the underlying causative conditions.

Aims

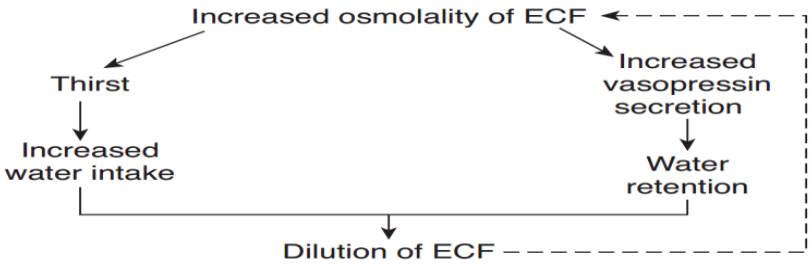
To study clinicoetiological profile of hyponatremia in patients admitted in Medical wards.

Objectives

- To study clinical profile of hyponatremia in hospitalized subjects.
- To study the aetiology of hyponatremia in hospitalized subjects.
- To assess morbidity and mortality due to hyponatremia.

Review of Literature

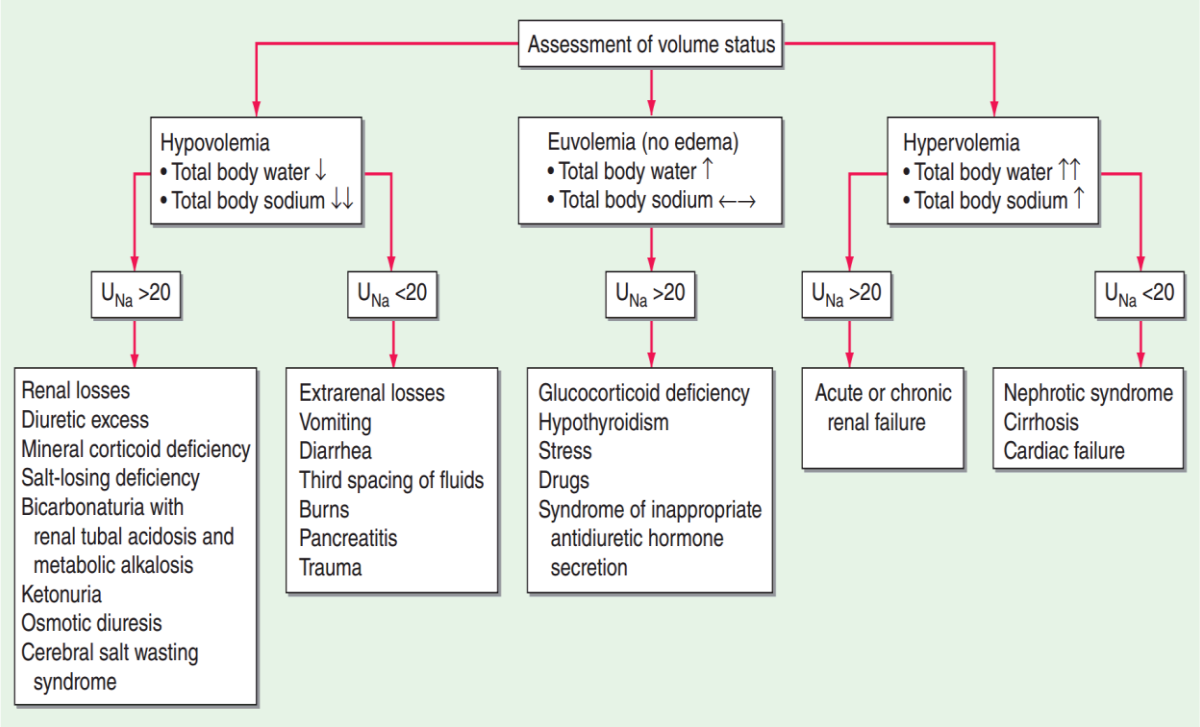
Sodium (Na+) is the most important contributor to the osmolality of the extracellular fluid (ECF), and hence is a major determinant of the ECF volume. Maintenance of serum sodium involves complex balance between the kidneys and water and SIADH. The urinary Na+ excretion has to precisely balance the daily Na+ intake to avoid changes in ECF volume. The intravascular volume of the ECF is critically dependent on changes in body Na+ content and represents an important determinant of systemic blood pressure. . In humans, a relation between salt intake and blood pressure is well documented from epidemiological studies [14-16]. The effect of Na+ on blood pressure is certainly complex and may include factors other than the Na+ handling by the kidney. More than 99% of the filtered load of Na+ is reabsorbed along the nephron and in the collecting tubule. The major fraction (90%) of the filtered Na+ is reabsorbed along the proximal tubule and in the thick ascending limb (TAL). The remaining 8–10% of the filtered Na+ is reabsorbed in the distal convoluted tubule (DCT), the connecting tubule (CNT), and the collecting duct; the Na+ absorption in the distal nephron and the collecting duct is tightly regulated by aldosterone and vasopressin.



Vasopressin is often called the antidiuretic hormone (ADH). It increases the permeability of the collecting ducts of the kidney, so that water enters the hypertonic interstitium of the renal pyramids. The urine becomes concentrated, and its volume decreases. The overall effect is therefore retention of water in excess of solute; consequently, the effective osmotic pressure of the body fluids is decreased. In the absence of vasopressin, the urine is hypotonic to plasma, urine volume is increased, and there is a net water loss, vasopressin is often called the antidiuretic hormone (ADH). It increases the permeability of the collecting ducts of the kidney, so that water enters the hypertonic interstitium of the renal pyramids. The urine becomes concentrated, and its volume decreases. The overall effect is therefore retention of water in excess of solute; consequently, the effective osmotic pressure of the body fluids is decreased. In the absence of vasopressin, the urine is hypotonic to plasma, urine volume is increased, and there is a net water loss

Vasopressin Secretion Increased	Vasopressin Secretion Decreased
Increased effective osmotic pressure of plasma	Decreased effective osmotic pressure of plasma
Decreased ECF volume	Increased ECF volume
Pain, emotion, "stress," exercise	Alcohol
Nausea and vomiting	
Standing	
Clofibrate, carbamazepine	
Angiotensin II	

Classification	Criteria	Comment
Mild vs severe	Serum sodium concentration	Degree of hyponatraemia does not always correlate with symptoms
Acute vs chronic	Time in which hyponatraemia developed	Time of development is often unknown
Symptomatic vs asymptomatic	Presence or absence of (severe) symptoms	Overlap between symptoms occurring in acute or chronic hyponatraemia
Hypotonic, isotonic, hypertonic	The accompanying serum osmolality	Useful for diagnostic purposes
Hypovolaemic, euvolaemic, hypovolaemic	The assessment of volume status	Assessment of volume status is often unreliable



Materials and Methods

- The study was conducted in Department of General Medicine, Govt. Medical College, Sir T. General hospital, Bhavnagar after taking permission from IRB(HEC).
- Study Design: Cross Sectional
- Duration: 1 year (August '15 - August '16)

Inclusion Criteria

- Age ≥ 12 yrs
- Serum sodium levels < 135 mEq/L

Exclusion Criteria

- Subjects not consenting for study

Data Collection

Based on the inclusion and exclusion criteria subjects were selected and following details were elicited.

- Demographic profile - Name, age, sex, occupation, address, contact no.
- Chief complaints and history of presenting illness
- Past medical history - diabetes mellitus, hypertension, liver disorder, kidney disease (CKD, AKI, nephrotic syndrome, interstitial nephritis etc.), previous neurological disease (stroke, SOL, multiple sclerosis intracranial haemorrhage, AIDP, meningitis), pulmonary diseases (tuberculosis, bronchial asthma, COPD, ILD), tumour and malignancy (bronchogenic carcinoma, meningioma), details of chemotherapeutic drugs in case of malignancy.
- Drug history – Detailed history of drug usage with respect to particular drug, its dosages, its route of administration, duration for which the drug was consumed.
- Other significant medical or surgical history.
- Examination of the Patients
  - ✓ Vital signs
  - ✓ General Physical Examination
  - ✓ Signs of dehydration or hypervolemia
  - ✓ Systemic examination – CVS, RS, PA, CNS

Investigations

- ✓ Complete blood counts (Hb, TLC, platelet count)

- ✓ Urine routine evaluation-protein, sugar specific gravity
- ✓ Random blood glucose level
- ✓ Blood urea and serum creatinine level
- ✓ Baseline serum electrolytes evaluation – Na^+, K^+, Cl^-, HCO_3^-.
- ✓ Serum osmolality
- ✓ Urinary sodium and potassium level and Osmolality
- ✓ ECG
- ✓ Chest X ray
- ✓ Liver Function Test (If clinically indicated)
- ✓ 2D Echocardiography (If clinically indicated)
- ✓ Arterial blood gas (If clinically indicated)
- ✓ Serum aldosterone level (If clinically indicated)
- ✓ Serum cortisol level (If clinically indicated)
- ✓ Thyroid function test (If clinically indicated)
- ✓ USG (If clinically indicated)
- ✓ CSF (If clinically indicated)
- ✓ CT Brain (If clinically indicated)
- ✓ MRI BRAIN (If clinically indicated)

Based on the above clinical data and investigations the diagnosis of the patients was established and the patients were subclassified accordingly.

Statistical Analysis

The collected data was subjected to standard statistical analysis, classified and represented accordingly. Frequencies (number of cases) and percentages were used when appropriate. For comparing qualitative data, Chi square test was performed. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2016 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc. Chicago, IL, USA) version 17.

Discussion

This is a prospective observational study conducted at Tertiary Care Hospital and included 100 patients admitted in medical wards during June 2016 to May 2017. A detailed analysis was undertaken with respect to common clinical features, laboratory parameters and morbidity and mortality associated with hyponatraemia. The observations and comparative analysis with other similar studies is discussed.

Demographic Profile

Out of the 100 subjects, there was male preponderance with 68% males and 32% females with sex ratio of 2.1:1.

Table No.1 Demographic Profile

	Male	Female
Present study	68%	32%
Chatterjee N et al.	62%	38%

In a study by **Chatterjee N et al,** where 201 cases of hyponatremia were studied a similar male preponderance was observed with 62% cases being males. [100]

Age

Majority of subjects belonged to age group of 41-60yr of age with mean age of 53.4. the age of subjects ranged from 14yr to 80yr.

Table No.2 Age

	Mean Age ± SD
Present Study	53.4± 15.2
Agarwal SM et al.	48.1 ± 16.1
Padhi R et al.	60.4+17.2

In a prospective cross-sectional study on Clinical Profile of Hyponatremia of 100 patients at **Yenepoya Medical College, Mangalore (Panikar G I et al.)** during the study period September' 2012 to October'2012 they found the most common age group affected was 51 - 60 yrs. and 61 - 70 yrs. which is similar to our study [101].

Agarwal SM et al, in their study, found that the mean age of patients was 48.1 ± 16.1 yr. (15- 82 yr.)[102].

Padhi R et al found that the mean age was 60.4+17.2 [103].

Age and Gender

Majority of, both males and females, belonged to age group of 41 to 60yr and there was male preponderance in all age groups.

Symptomatology

Lethargy (29%) was most common symptom followed by headache (28%), tremors (25%), nausea/vomiting (18%), altered sensorium (9%), convulsion (6%) and coma (4%). 18% were asymptomatic.

Table No.3 Symptomatology

	Lethargy	Headache	tremors	Nausea/ vomiting	Altered sensorium	Convulsion	Coma
Present study	29%	28%	25%	18%	9%	6%	4%
Agarwal SM et al.	30%	40%	7%	30%	17.1%	2.9%	3%

Agarwal SM et al found that confusion (41.4%), headache (40.0%), malaise (38.6%), lethargy and nausea (30.0% each) were the most common features seen in the patients, followed by altered sensorium (17.1%), flap (7.1%, all alcoholics) and seizures (2.9%); 20.0 per cent patients did not have any symptom or sign [102].

Rao MY et al found that lethargy, drowsiness with slow response and irrelevant talk were the common presenting symptoms [104]

A similar observation was made in a study at **Yenepoya Medical College Hospital (Panikar G I et al.)** where majority of the cases were asymptomatic followed by clouding of consciousness, seizures and coma. [101]

Symptomatology related to gender

Most common symptom in males was lethargy whereas in females it was headache.

Symptomatology related to age

Most common symptom, in age group of 20 to 40yr was nausea/vomiting, in age group of 41 to 60yr was lethargy and in age group of 61 to 80 was lethargy and tremor. There was a clear trend indicating higher incidence of neurological symptoms in higher age group and increasing severity of symptoms with age.

Volume status

Hypervolemic hyponatraemia (43%) was observed in most patients followed by euvolemic hyponatraemia (32%) and hypovolemic hyponatraemia (25%).

Table No.4 Volume status

	Hypervolemic	Hypovolemic	Euvolemic
Present Study	43%	25%	32%
Chatterjee N et al.	26%	22.4%	50.74%
Rao MY et al.	23%	16%	61%

The studies cited above strictly included patients admitted in critical care units. However, the current study included all patients admitted in general medical wards. Thus providing better representation of general population.

Chatterjee N et al found that the largest group of hyponatremic patients were isovolemic [102 (50.74%)], followed by hypervolemic [54 (26.86%)] and hypovolemic [45 (22.4%)] [100]

Rao MY et al found that the commonest type of hyponatremia noted in their study was Isovolemic (61%), hypovolemic (16%), hypervolemic (23%). [104]

Padhi R et al found that the largest group of hyponatremic patients were euvolemic; 148

(58.96%) followed by hypervolemic; 66 (26.29%) and hypovolemic; 37 (14.74%). [103]

Bennani et al. in a study on hyponatremia in ICU, found that euvolumic hyponatremia was the most common (50.6%) type of hyponatremia.[105]

Degree of hyponatremia

Most patients had mild to moderate hyponatraemia with 39% subjects having sodium levels between 126 – 135 mEq/L. 30% had severe hyponatraemia.

	Miid (125-135)	Moderate (121-125)	Severe (<120)
Present Study	39%	31%	30%
Panikar et al.	61%	26%	13%

A similar observation was made in a **study at Yenepoya Medical College Hospital (Panikar G I et al.)** where 61% patient were found to have serum sodium between 125-135, 26% had serum sodium between 121-125 & 13 % had serum sodium <120. [101]

Chatterjee N et al also found that mild hyponatremia was the commonest in their study with the mean sodium level of 126.34 mEq/L. [100]

Dasta J et al found that at admission, 35%, 55%, and 10% of patients had mild, moderate and severe hyponatremia, respectively. [106]

Degree of hyponatraemia related to gender

Male subjects had predominantly moderate to severe hyponatraemia whereas females had predominantly mild to moderate hyponatraemia.

Degree of hyponatraemia related to age

Subjects with higher age had more severe hyponatraemia with 45% of subjects in 61 – 80yr age group having severe hyponatraemia. There was a degree of moderation in serum sodium levels in age groups of 21 – 40 yr. and 41 – 60yr.

Severity related to volume status

Euvolemic subjects had more severe hyponatraemia with 46% of euvolemic subjects having sodium levels </=120. An array of moderate values sprung across hypervolemic and hypovolemic subjects.

Symptomatology relative to degree of hyponatraemia

There was higher incidence of severe neurological symptoms as the severity of hyponatraemia increased with 90% of subjects having sodium levels </=120. Also there was higher chance of patient being symptomatic as the severity of hyponatraemia increased.

In a study by **Olsson et.al,** they studied the co-relation of the severity of hyponatremia with the symptoms at presentation. They found a clinical trend which showed that sever neurological symptoms were more common in patients with lower serum sodium values. However, there was no statistically significant co-relation between the severity of neurological symptoms and the degree of hyponatremia due to the small sample size. [107]

A prospective cross-sectional **study at Yenepoya Medical College Hospital (Panikar G I et al.)** to study 100 patients of hyponatremia also shows that most of the patients were asymptomatic with mild hyponatremia, and as the severity of hyponatremia increased the severity of neurological symptoms also increased. [101]

Aetiology of Hyponatraemia

Hyponatraemia secondary to diuretic use (22%) was common cause of hyponatraemia, followed by Congestive Cardiac Failure (16%), Cirrhosis of Liver (13%), Acute Gastroenteritis (13%), Renal Failure (12%), Pneumonia (6%), Hypothyroidism (4%), Subarachnoid Haemorrhage (3%), Meningitis (3%), Pulmonary Tuberculosis (2%), Carcinoma Lung (2%), Ischaemic CV Stroke (1%), Steven Johnson Syndrome (1%), Polydipsia (1%) and Drowning (1%), in order.

Aetiopathogenesis of Hyponatraemia

Based on etiopathogenesis, dilutional hyponatraemia (33%) was most commonly implicated, followed by Drug induced hyponatraemia (22%), SIADH (15%), Gastrointestinal loss (13%), renal failure (12%),

Hypothyroidism (4%), extra renal/GI loss (2%) and cerebral salt wasting (1%).

A prospective cross-sectional **study at Yenepoya Medical College Hospital (Panikar G I et al.)** showed respiratory system disorders were the most common found in 46 % of study population and CNS disorders were the 2nd most common cause found in 23%. [101]

Chatterjee N et al found that the most common underlying predisposing factor for hyponatremia in their case series was gastrointestinal (GI) fluid loss followed by cerebrovascular accident (CVA) and pulmonary sepsis. [100]

Aetiology of Hypervolemic hyponatremia

Hypervolemic hyponatraemia was most commonly caused by Congestive cardiac failure (37%), followed by Cirrhosis of liver (30%), renal failure (28%) Polydipsia (2.5%) and drowning (2.5%).

Padhi R et al found hypervolemic hyponatremia associated with renal failure in 15 (5.97%), heart failure in 13 (5.17%) and liver cirrhosis in 9 (3.58%). [103]

Chatterjee N et al found that hypervolemic hyponatremia associated with renal failure was in 16 (7.96%) patients, CCF in 15 (7.46%) patients, chronic liver disease in 12 (5.97%) patients and nephrotic syndrome in 10 (4.97%) patients. [100]

Aetiology of Hypovolemic hyponatraemia

Hypovolemic hyponatraemia was most commonly caused by acute gastroenteritis (52%) followed by osmotic diuretics (36%), Steven Johnson syndrome (4%), dehydration secondary to pneumonia (4%) and Cerebral salt wasting (4%).

The descriptive **observational hospital-based study, conducted at Hamad General Hospital** from June 2007 to July 2008; which involved adult patients with moderate and severe hyponatraemia, showed that hyponatraemia due to extra-renal loss was the most frequent cause of hyponatraemia, which was found in 18 (33.9%) patients.

Aetiology of Euvolemic Hyponatraemia

Euvolemic Hyponatraemia was most commonly caused by SIADH (47%) followed by Loop diuretics (41%) and hypothyroidism (12%).

Padhi R et al found that in their study, SIADH was the most common cause of hyponatremia. [103]

A study by **Bergman's et al**. also found that SIADH was the most frequent cause of hyponatremia. [108]

Coussement et al. also found SIADH as a common and potentially lethal complication in critically ill patients who had hyponatremia. [109]

Rao MY et al in their study found that SIADH was the most common cause of hyponatremia in their study. [104]

Laczi reported that SIADH was the most common cause of euvolemic hyponatremia in their study in Hungary. [110]

A prospective cross-sectional study on Clinical Profile of Hyponatremia of 100 patients at **Yenepoya Medical College (Panikar G I Et al.)** found that out of the 100 cases, predominant cause for hyponatremia was SIADH. [101]

Aetiology of SIADH

Among subjects with SIADH, pneumonia (34%) was the most common cause followed by meningitis (20%), subarachnoid haemorrhage (20%), pulmonary tuberculosis (13%) and carcinoma lung (13%).

Padhi R et al, in their study, found that SIADH, 91 (36.25%), was the most common cause of hyponatremia. In the SIADH pneumonia, 39 (15.53%) was the most common etiological factor followed by drug and SAH. [103]

Pneumonia was known to be associated with hyponatremia at the time of admission and it was associated with more severe illness, increased risk of mortality and prolonged hospital stays as reported **by Nair et al**. [111]

A prospective cross-sectional study on Clinical Profile of Hyponatremia of 100 patients at **Yenepoya Medical College Hospital (Paniker G**

I et al.) was found that out of the 100 cases, predominant cause for hyponatremia was SIADH. [101]

Chatterjee N et al in their study found that the two most common causes of SIADH were lower respiratory tract infection and stroke. [100]

Comorbidity

Diabetes mellitus (26%) was most common comorbidity followed by ischaemic heart disease (18%), hypertension (13%), Intracerebral haemorrhage (11%) and HIV infection (7%).

	Present study	Rao MY et al.
Hypertension	13%	62%
Ischaemic Heart Disease	18%	18%
Diabetes mellitus	26%	51%

Rao MY et al found that the common co-morbid conditions were Hypertension (62%), Diabetes mellitus (51%), Renal failure (22%) and Ischemic heart disease (18%).[104]

Mortality

Mortality during study was 4%, all having sodium levels <120 mEq/L.

	Mortality
Present study	4%
Panikar G I et al.[101]	3.2%

Summary

The study conducted on 100 subjects of hyponatremia admitted in medical wards is summarised as under, with its salient features.

- Most commonly affected age group in the study population was 41 to 60 years of age, with male preponderance across all age groups.
- Neurological symptom are more common, with most common being Lethargy and tremors.
- As the age advances the ratio of symptomatic patients increases, with elderly population most susceptible to develop severe symptomatic hyponatremia.
- Incidence of acute hyponatremia is more than chronic hyponatremia.
- Hypervolemic hyponatremia is most common followed by euvolemic hyponatremia.
- Most of the patients had mild to moderate hyponatremia and one third patients having severe hyponatremia.
- Males are more susceptible to develop higher degree of hyponatremia as compared to females.
- Elderly subjects are more susceptible to develop more severe hyponatremia.
- Euvolemic subjects had propensity to develop more severe and symptomatic hyponatremia as compared to hypervolemic and hypovolemic hyponatremia.
- As the severity of hyponatremia increases, there are more chances of a subject being symptomatic and of having more severe neurological manifestations.
- Diabetes mellitus was the most common comorbidity associated followed by ischaemic heart disease and hypertension.
- Hyponatremia secondary to diuretic use was the most common cause, followed by congestive cardiac failure and cirrhosis of liver.
- Dilutional hyponatremia is the most prevalent underlying pathophysiology followed by SIADH and diuretic use.
- Congestive cardiac failure was the most common cause of hypervolemic hyponatremia, followed by cirrhosis of liver and renal failure
- Acute gastroentereitis was most common cause of hypovolemic hyponatremia.
- SIADH was the most common cause of euvolemic hyponatremia.
- Pneumonia was the most common cause of SIADH, followed by meningitis and subarachnoid haemorrhage.

- Mortality during the study was 4% and all the expired subjects had severe hyponatremia.

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