

Original Research Article

Study of spectrum of neurological manifestations in patients with hyponatremia: A prospective, observational study in a tertiary care hospital

Dr. Sheela Omprakash Pandey¹, Dr. Pradip Padamsi Shah²

¹Assistant professor, Department of General Medicine, HBT Medical College And Dr. R N Cooper Municipal General Hospital, Bhaktivedanta Swami Marg, Juhu, Vile Parle (West), Mumbai, Maharashtra 400056, India.

²Head of department & Consultant physician, Department of General Medicine, Fortis Hospitals Limited, Mulund Goregaon Link Road, Mulund (West), Mumbai 400 078, India.

***Corresponding author**

Dr. Sheela Omprakash Pandey

Email: doc.sheelapandey@gmail.com

Abstract: Hyponatremia is a commonly observed disorder in hospitalized patients and linked to a poor prognosis and increased length of hospital stay. Prompt recognition and optimal management may reduce in-hospital mortality and improve patients' quality of life. This prospective, observational, descriptive study was conducted to know spectrum of neurological manifestations in patients with hyponatremia and outcome in such patients after treatment in our hospital set up. 80 patients admitted during study period of 2 years, those who were fulfilling inclusion criteria, were enrolled in the study after institutional ethics committee approval. We noticed that, hyponatremia with neurological manifestations was found to be more prevalent among elderly patients than in younger patients (age group of 61-70 years - 38.75% and 71-80 years - 30%). It is more frequent in women (58.75% females & 41.25% males). Drowsiness, headache, confusion were more common symptoms, followed by seizures, disorientation, irritability, irrelevant talk, lethargy. 13 patients had seizures and we found a gradual increase in risk of seizures with falling serum sodium levels rather than a distinct cut off. In our study, commonest cause of hyponatremia was diuretics induced hyponatremia, followed by SIADH, renal loss, fluid overload, gastrointestinal loss, hypothyroidism, drug induced like chemotherapy. Overall mortality was found to be 13.75%, which is less than what was observed in previous literatures. Response to treatment in females was better than males, 88% improved with mortality of 12%, compared to males with mortality of 15%. To conclude, apart from mortality, hyponatremia prolongs the hospital stay significantly and increases the cost of medical care substantially. But a better outcome and minimal complications related to correction of hyponatremia can be obtained if the general guidelines of correction and a standardized regimen are followed and a word of caution should be maintained while prescribing diuretics in the elderly.

Keywords: Hyponatremia, SIADH (Syndrome of Inappropriate Anti Diuretic Hormone secretion), Diuretics

INTRODUCTION:

Hyponatremia is a common finding in hospitalized patients with a prevalence ranging from 15-30%. It is important to recognize hyponatremia as its presence is associated with increased mortality of 9-27% depending on the definition of hyponatremia [1] and 30% of patients are treated in the intensive care unit [2]. It most often has small clinical expression but can significantly increase morbidity and the risk of death, as well as complicate the course of concurrent disease.

Hyponatraemia usually develops when there are underlying conditions that impair the kidney's ability to excrete free water. There are a few clinical

settings where patients most often become symptomatic. Serious complications of hyponatremia most frequently involve the central nervous system. The patient usually presents with headache, nausea, vomiting and confusion, but can present with seizures, respiratory arrest and non-cardiogenic pulmonary edema. A number of conditions and medications are associated with hyponatremia [3-7], and specific factors that increase the risk for this condition have been identified, including surgery or injury, very young or old age [8], renal dysfunction, adrenal insufficiency, hypothyroidism, cirrhosis, congestive heart failure (CHF), and central nervous system (CNS) impairment. It can be associated with low, normal or high tonicity.

Hypotonic hyponatremia is the most common form of hyponatremia. It occurs by two mechanisms (1) usual (or greater than usual) water intake in the setting of impaired renal water excretion leading to dilution of body solutes or less commonly (2) water intake in excess of the normal renal ability to excrete water. This can be classified as hypovolemic, euvolemic and hypervolemic on the basis of ECF volume which can be assessed clinically. (Orthostatic changes in blood pressure and heart rate, edema, jugular venous distension, skin turgor, mucous membranes, ascites).

Treatment of hyponatremia depends on the presence of neurological symptoms and the cause for the hyponatremia [9-10]. Patients who are asymptomatic from the chronic or slowly developing hyponatremia need a slower rate of correction and hypertonic saline is not indicated in them, regardless of the serum sodium [11-15]. Symptomatic hyponatraemia, on the other hand, is a medical emergency and prompt treatment is required in a monitored setting before imaging studies are performed. If symptomatic hyponatraemia is recognized and treated promptly, prior to developing a hypoxic event, the neurological outcome is good [11, 15-16]. However rapid correction of hyponatremia carries the risk for osmotic demyelination (central pontine myelinolysis) [17].

Review of literature shows, various studies were conducted in past related to hyponatremia. Misra SC, Mansharamani GG, studied 100 elderly patients in a hospital with hyponatremia & found that 67% of those patients were asymptomatic / had nonspecific symptoms & remainder had symptoms of altered sensorium without any focal neurological deficit, cause of it was iatrogenic in 30%, while 17% had underlying infection [18]. M Chakrapani, D Shenoy, A Pillai carried out a study to determine seasonal variation in incidence of hyponatremia, which showed statistically significant correlation between rainfall pattern & hyponatremia [19]. Danish researchers studied the prognostic value of serum sodium levels in 671 middle aged & older community dwellers without known heart disease, stroke, cancer or other life threatening illnesses and found that mild hyponatremia was associated with a higher all cause mortality [20]. In a retrospective study of 168 patients with severe hyponatremia (< 115 mmol/L) at a tertiary teaching hospital, by Nzereu *et al.*; it was found that the mortality (20.2 %) with severe hyponatremia is high [21]. A study by Kang *et al.*; followed 116 patients with mean sodium level of 114.9 +/- 5.2 mmol/L at the time of diagnosis. It showed euvolemic status in 37.9%, hypervolemic 31.9% and hypovolemic 15.5%. 20.7% of euvolemic patients were

diagnosed with Syndrome of Inappropriate Anti Diuretic Hormone secretion (SIADH) [22]. Another study on the etiological profile of hyponatremics among 70 Indian patients showed [23] that most patients had multiple precipitating factors, decreased intake being the most common (82.9%) followed by increased losses in 65.7% patients (gastrointestinal 50.5%, followed by renal 25.7% and cutaneous loss due to excessive sweating in manual laborers in 8.6% patients).

The objectives our study were to know common presenting neurological signs and symptoms of hyponatremia, to study lab findings and there correlation with clinical findings, to find out possible common causes of hyponatremia with CNS manifestations on basis of history, signs & symptoms and investigations and to study outcome in such patients after starting correction treatment. To our knowledge, this study was the first attempt to assess the hyponatremic patients with neurological manifestations. Previous studies had enrolled all symptomatic and asymptomatic patients in their study. We studied only those patients, who had neurological symptoms. Previous most of the studies were based on retrospective data.

EXPERIMENTAL SECTION/MATERIAL AND METHODS:

This study was carried out at Fortis hospitals limited, Mumbai, a tertiary care hospital, after obtaining institutional ethics committee permission. The study was prospective, observational and not interventional. During the study period of two years, 80 patients, aged 18 years and above, admitted in wards & intensive care unit, which had a serum sodium level less than 135 mmol/L and who were fulfilling inclusion criteria, were enrolled in the study.

Inclusion Criteria:

- Age >18 years
- Both Genders Eligible
- Patients whose serum sodium level <135mEq/lit.
- With CNS related signs & symptoms (Headache, nausea, vomiting and confusion, seizures, drowsiness, disorientation)

Exclusion Criteria:

- Patient not willing to give consent.
- Patients with Diabetes ketoacidosis (Hyperglycemia).
- Hyperlipidemia.
- Hyperproteinemia

- Post TURP patients
- Patients who receive IVIG or mannitol.
- Symptomatic patients due to other reasons e.g. hepatic causes, hypoxia, hypoglycemia, active central nervous system infection, stroke or drug induced.

From all eligible patients, the data was collected by obtaining the clinical history & noting findings of physical examination. Before that, proper consent from the patient/patient's relatives for their enrollment in the study was taken. All patients underwent complete physical examination and an assessment of the volemic status. The laboratory work up included a complete blood count, a panel of biochemical laboratory tests, urinary sodium and serum and urinary osmolality. Thyroid-stimulating hormone levels were obtained in all patients and cortisol levels in most of them. All patients underwent a chest X-ray. Other radiological tests were performed as considered necessary by the attending physician.

All patients were treated according to standardized regimen used in our hospital to treat symptomatic hyponatremia. They were treated, based on severity of their illness and neurological manifestations, with either intravenous hypertonic (3%) or normal saline or oral salt supplementation, fluid restriction. Finally patients were evaluated for outcome of given treatment in hospital. Following methods of statistical analysis was used in the study. The excel & SPSS software packages were used for data entry & analysis.

RESULTS AND DISCUSSION:

80 patients with sodium level $<135\text{mMol/L}$, with neurological manifestations were studied. Among these, 41.25% patients were males and 58.75% were females (Table 1). Incidence was more in elderly patients, age group of 61-70 years (38.75%) and 71-80 years (30%). Reason of developing hyponatremia in these patients could be attributed to age related physiological changes in function of kidneys and associated multiple co-morbid conditions (Fig.1 and Fig.2). In this study, associated co-morbid conditions, in decreasing order of frequency, were hypertension, diabetes, infection/sepsis, congestive cardiac failure, cerebrovascular attacks, chronic kidney diseases, malignancy and cirrhosis (Fig.3).

Patients had various neurological signs and symptoms on presentation. In our study we noticed, drowsiness, headache, confusion being more common, followed by seizures, disorientation, irritability,

irrelevant talk, lethargy. These symptoms were attributed to hyponatremia (Fig.4). 13 patients had seizures. It has been suggested that neurologic symptoms are rare with serum sodium levels above 120mMol/L , and that convulsions or coma generally do not occur until serum sodium values decline to $95\text{--}110\text{mMol/L}$. Among 13 patients with seizures, 5 had seizures with serum sodium $>110\text{mMol/L}$, and 8 out of 13 with serum sodium of <110 (Table 2). So we found a gradual increase in risk with falling serum sodium levels rather than a distinct cutoff. In our study, 66.25 % patients were suffering from the severe hyponatremia i.e. serum sodium <120 and 33.75 % with moderate (serum sodium $120\text{--}129$) (Fig.5). Their volume status was as follows, 50% were hypovolemic, and euvolemic being 25% and hypervolemic status were 25%. After all clinical evaluation and biochemical investigations, more common type of hyponatremia evident in our study was hypotonic hypovolemic (47%), followed by hypotonic euvolemic (24%), hypotonic hypervolemic (23%) and others (Fig.6).

In this study commonest cause of hyponatremia was diuretics induced hyponatremia, followed by SIADH, renal loss, fluid overload, GI loss, hypothyroidism, drug induced like chemotherapy. Diuretics are used as a drug for treatment of hypertension, as per JNC VII (The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) recommendations [24], which recommended the use of thiazide-type diuretics for the treatment of uncomplicated hypertension, thiazides have been prescribed more frequently [25-26]. The endocrine causes of hyponatremia are not infrequently missed and as they can be easily treated with hormone replacement, they should be looked for; these include hypothyroidism, primary adrenal insufficiency and hypopituitarism. Our study had 6 patients with hypothyroidism.

In a study, done by Shapiro *et al.*; [27], 86 elderly patients with severe hyponatremia (Sodium <125) were involved, they found that it was more frequent in women (60 out of 86 patients), similar observation was noted in our study also (Females 58.75%). In their study, the leading cause of hyponatraemia was the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (39 patients) followed by heart failure (23), diuretics induced (21) and others like, respiratory diseases, malignancy, gastrointestinal loss, low intake, renal failure, CVA etc. Etiology was multifactorial in 51% of patients. Whereas in our study, commonest cause of hyponatremia was

diuretics induced hyponatremia, followed by SIADH, and others as shown in Fig.7.

All patients were treated according to standardized regimen used in our hospital to treat symptomatic hyponatremia. They were treated, based on severity of their illness and neurological manifestations, with either intravenous hypertonic (3%) or normal saline or oral salt supplementation, fluid restriction. In our study, we did not find any complications related to rapid correction of hyponatremia. Among the patients studied, it was noticed that females (58.75%) were more affected than males (41.25%), still respond to treatment in females was better than males, 88% improved with mortality of 12%, compared to males with mortality of 15% (Fig. 8). Overall mortality in our study was found to be 13.75% (Shapiro *et al.*; 19%), which is less than what was

observed in previous literature. The patients who had died, among them the cause of death was secondary to severe sepsis or other conditions like cerebrovascular disease, advanced malignancy, progressive renal failure, acute coronary events. Whereas no case of clinically evident central myelinosis was documented, following the treatment of hyponatremia. So a better outcome and minimal complications related to correction of hyponatremia can be obtained if the general guidelines of correction and a standardized regimen are followed. Average stay in hospital for patients with serum sodium less than 120mMol/L was 6 days for correction, and in patients with more than 120mMol/L, it was 4 days, which shows that it increases the hospital stay (Table 3). A limitation of this study was the small number of patients. Moreover, the study was hospital based rather than population based, therefore further prospective population based studies are required.

Table 1: Sex distribution

Sex	Numbers (n/80)	Percentage
Male	33	41.25%
Female	47	58.75%

Table 2: Frequency of seizures according to sodium level

Sodium level	No. of patients having seizures
<110	8
>110	5

Table 3: Mean stay of hyponatremic patients in our study

	Mean sodium (on admission)	Mean sodium (after correction)	Mean Stay	Death
<120	112.28	135.85	6	6
>120	122.75	136.79	4	5

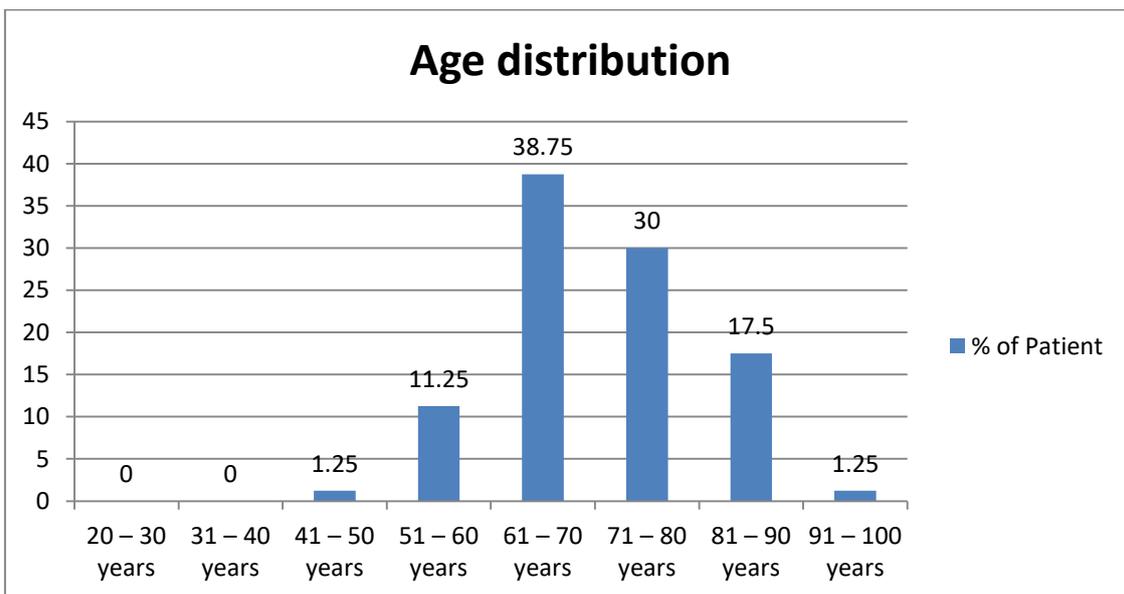


Fig 1: Age distribution

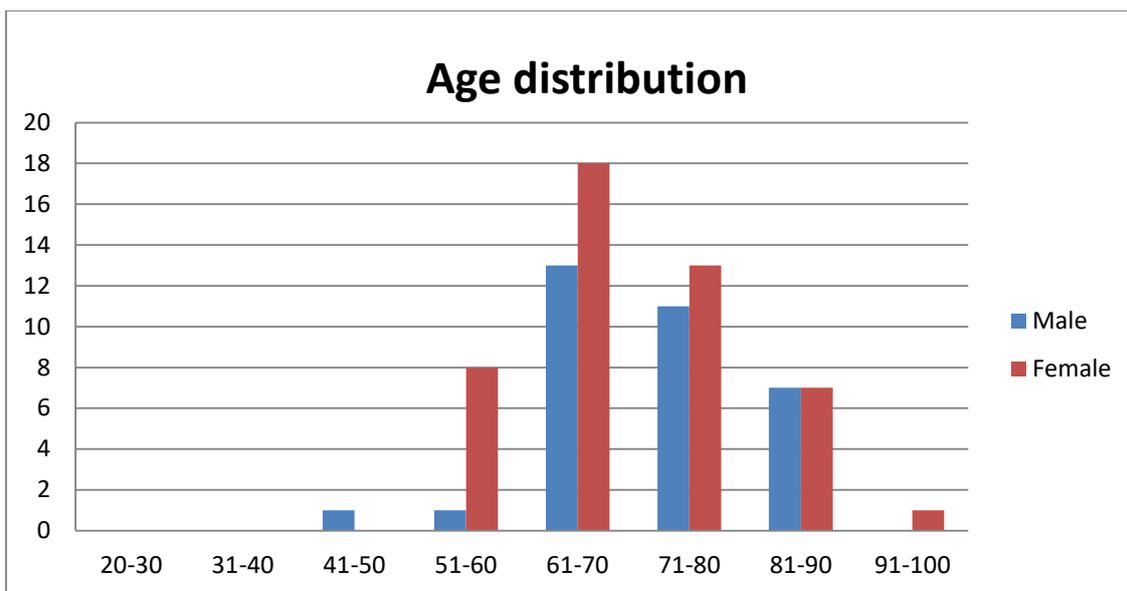


Fig 2: Age distribution of hyponatremia among males and females

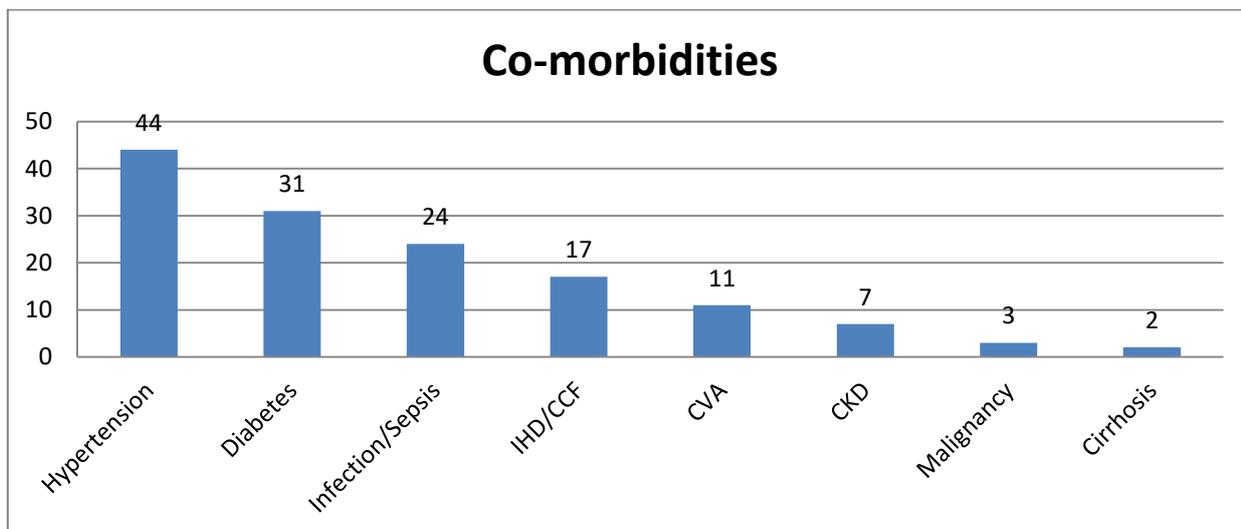


Fig 3: Co-morbidities associated with hyponatremia

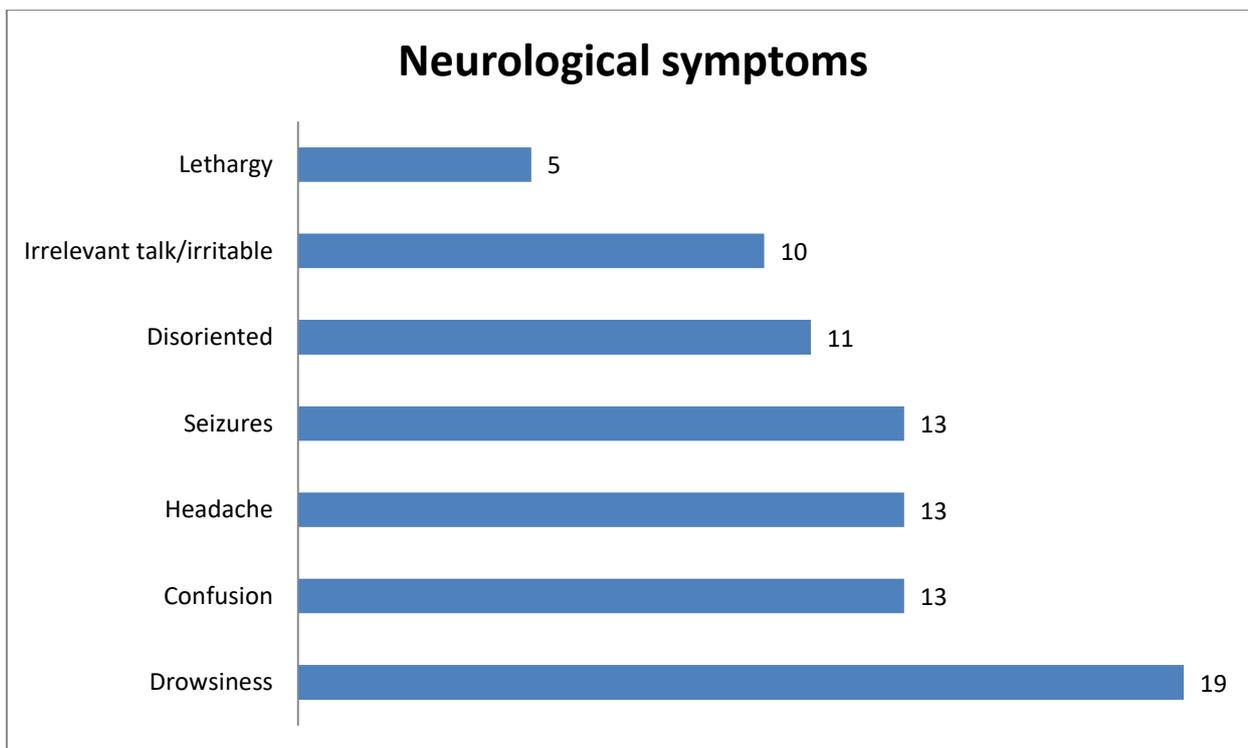


Fig 4: Neurological symptoms in hyponatremic patients

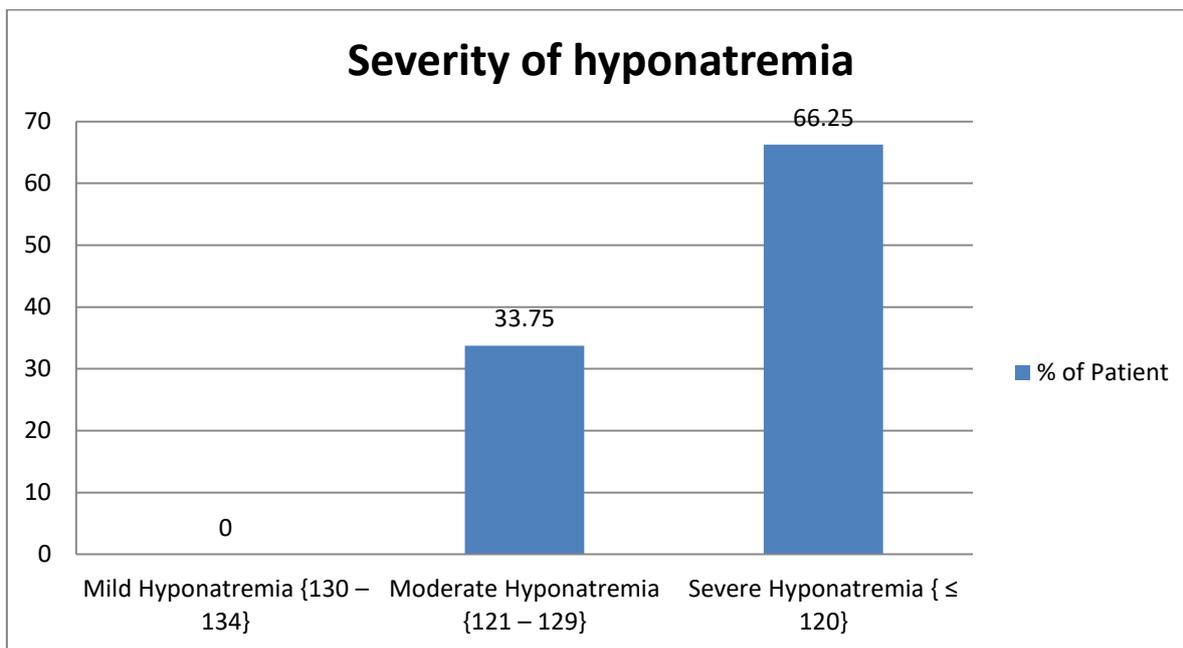


Fig 5: Severity of hyponatremia

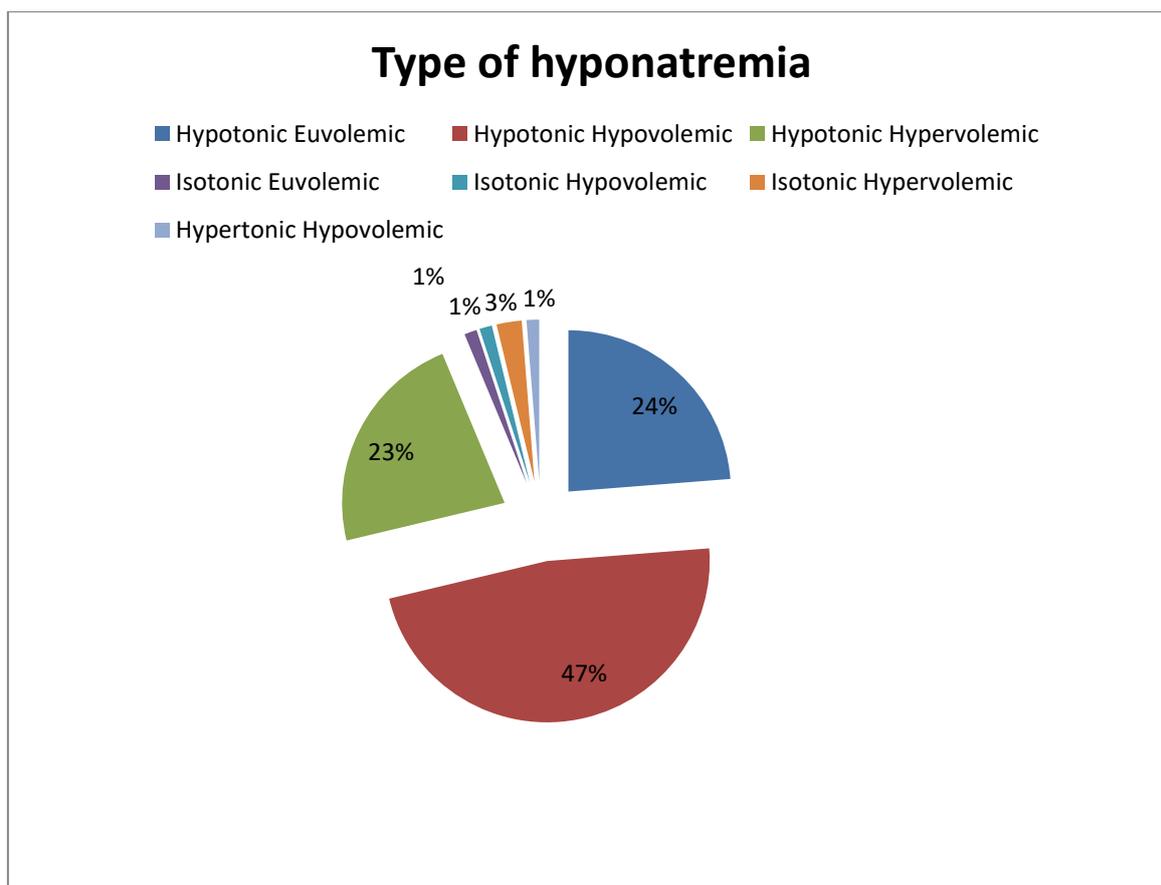


Fig 6: Type of hyponatremia in our study

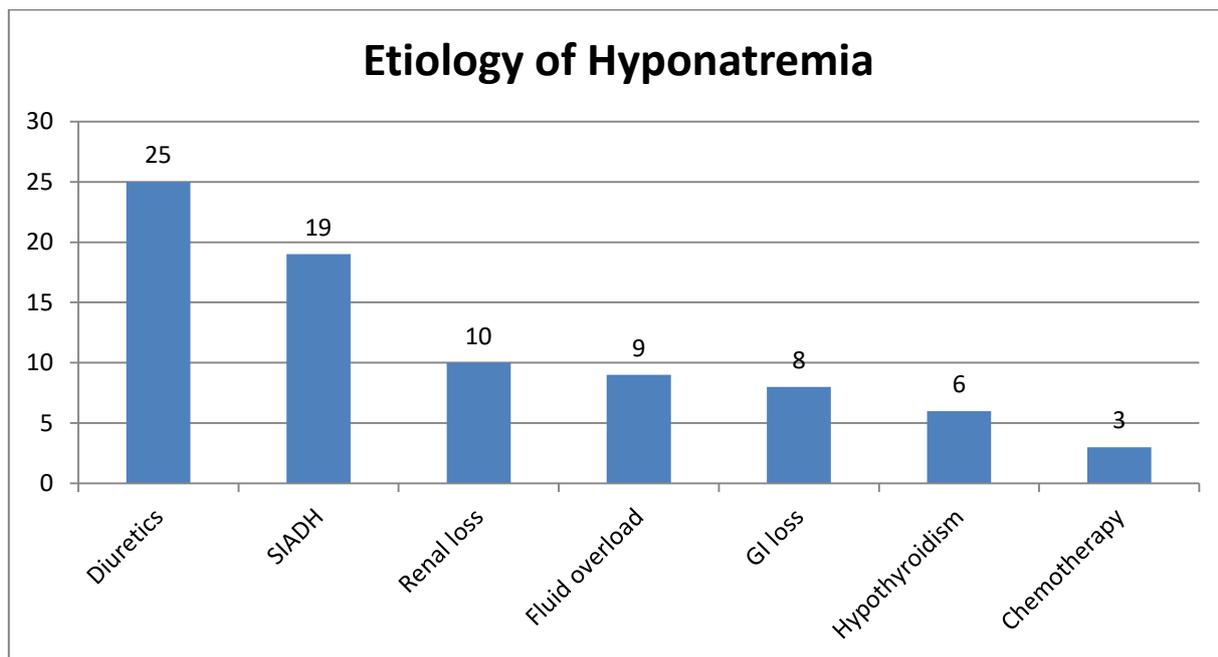


Fig 7: Etiology of hyponatremia

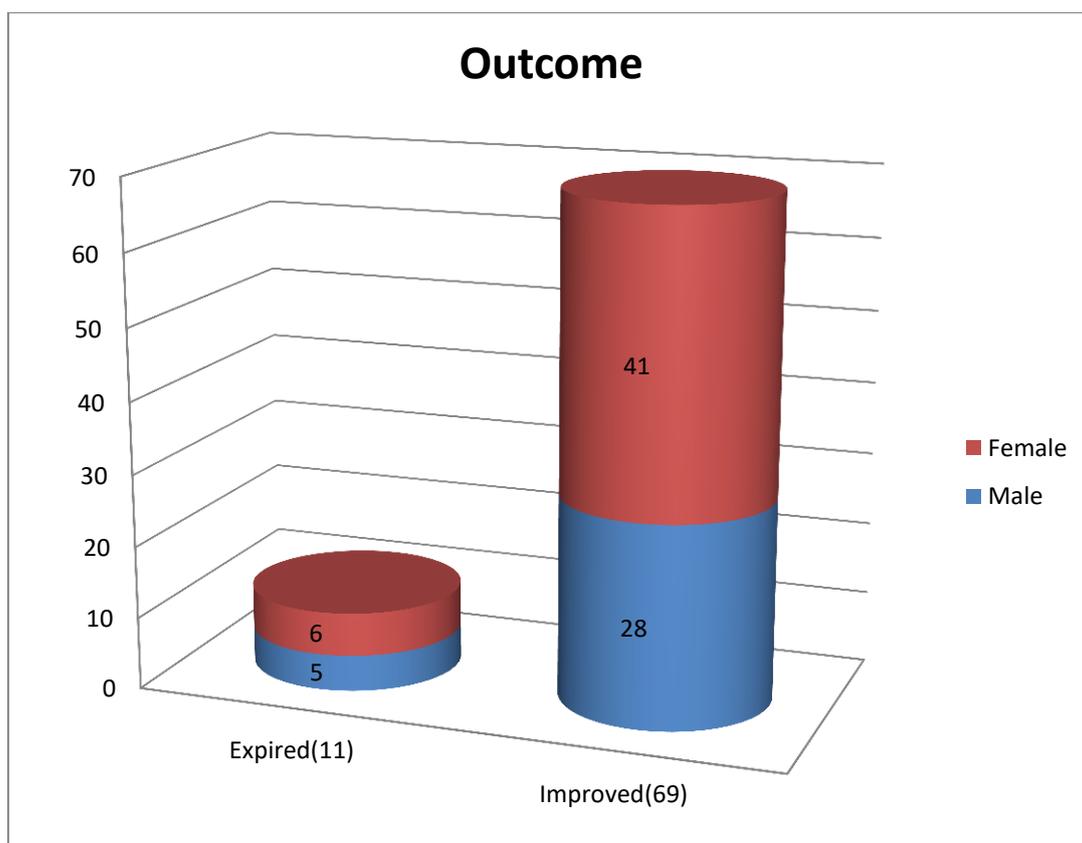


Fig 8: Outcome in the studied group

CONCLUSION:

Hyponatremia with neurological manifestations was found to be more prevalent among elderly patients than in younger patients. It is more frequent in women. Diuretics induced and SIADH were the most frequent causes of hyponatremia in our study. A word of caution should be maintained while prescribing diuretics in the elderly. Drowsiness was common presenting neurological symptoms in most of the patients. We also noticed a gradual increase in risk of seizures with declining sodium levels. Overall mortality in our study was 13.75%. Mortality could have been related to the range of severity of the underlying clinical conditions. Moreover, apart from mortality, it prolongs the hospital stay significantly and increases the cost of medical care substantially.

DECLARATIONS

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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