ISSN: 0975-3583, 0976-2833 VOL15, ISSUE4, 2024

SERUM CHLORIDE IN ACUTE DECOMPENSATED HEART FAILURE: OBSERVATIONAL STUDY

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ABSTRACT

Aim: The aim of the present study was to assess serum chloride level in patient with acute decompensated heart failure.

Methods: The present study included patients of acute decompensated heart failure who were admitted to emergency or ward SGRD HOSPITAL Amritsar. 50 patients of acute decompensated heart failure from April 2021 to March 2022 getting enrolled in emergency /ward of SGRD were selected. Patient fulfilling the below given criteria before their final inclusion, informed consent from the patient taken before participating in their study

Results: Majority of the patients were 61-70 years old (40%) followed by 51-60 years (24%), 71-80 years (14%), 41-50 years (10%), <31 years (6%), 31-40 years (4%), and >80 years (2%). Mean age was 59.68±12.84 years. Out of 50 patients, 33 (66%) were females and 17 (34%) were males. 42% of the patients had BMI >24.9 Kg/m2 followed by 23-24.9 Kg/m2 (38%) and <23 Kg/m2 (20%). 52% patients had hypertension, 50% patients had diabetes mellitus, 6% patients had COPD, and 2% were smokers. 40% patients had diastolic dysfunction grade 2 followed by grade 3 (34%), grade 1 (20%), and 6% patients were normal. In 76% patients, ST was present followed by AF (12%), LBBB (6%), Bifascicular block (4%), and PSVT (2%).

Conclusion: Serum chloride has a key function in heart failure and diuretic resistance regulatory mechanisms. Serum chloride levels in patients were shown to be statistically significant in connection to mean EVEREST scores, mean diuretics levels, duration of hospital stays, and serum salt levels. Those with hypochloremia had a longer average hospital stay than patients with normal or hyperchloremia.

Keywords: serum chloride level, heart failure

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1. INTRODUCTION

Electrolyte imbalances frequently aggravate heart failure (HF). Up-regulation of maladaptive neurohormonal systems may limit solute and free water delivery to the distal nephron as cardiac failure develops into symptomatic HF, increasing free water absorption and potentially lowering serum salt and chloride levels.[1,2] The use of decongestive treatments (such as loop and thiazide diuretics) in both acute and chronic HF may worsen these electrolyte disturbances.[3-5]

Along with acid-base disturbances, heart failure (HF) is linked to a number of serum electrolyte abnormalities, including hyponatraemia, hypokalaemia, and hypochloraemia. These abnormalities have multifactorial causes. Dilutional hyponatraemia and hypochloraemia are brought on by the maladaptive activation of neurohormonal processes, such as an increase in arginine vasopressin, which causes free water absorption and thirst stimulation.[2,3,6] A higher proportion of solutes are lost than free water when loop and thiazide diuretics are used.[7]

The role of chloride in volume hemostasis was appreciated when the concept of volume depletion and chloride responsive metabolic alkalosis became clear. Recent studies have shown that serum chloride levels provide stronger prognostic information for HF than serum sodium levels, and that patients with hypochloraemia have relatively high short and long-term mortality.[8,9] The initial treatment for acute HF is largely based on systemic decongestion with diuretics. Low serum chloride levels can cause decreased diuretic responsiveness owing to the upregulation of sodium and water absorption in the loop of Henle. Reduced intracellular chloride levels increase the number of sodium–potassium–chloride cotransporters (NKCC2) at the apical surface of the thick ascending limb (TAL) of the loop of Henle in the nephron.[10]

Acute decompensated heart failure is a clinical syndrome of new or worsening signs and symptoms of heart failure, often leading to hospitalization or visit to emergency department. the onset and severity of symptoms of acute decompensated heart failure vary and depend importantly on the nature of the underlying cardiac disease and rate at which the syndrome develops the largest population of patients (70%) present with heart failure are admitted due to worsening chronic heart failure, upto 15 -20% of patients present with heart failure first time, and approximately 5% are admitted for advanced or end stage heart failure few patient with acute decompensated heart failure present with low blood pressure(<8%) or shock(<3%).[11]

Despite being widely available in commonly used blood chemistry panels and frequently being linked to contraction alkalosis during excessive decongestion therapy, the effects of hypochloremia in HF are less well understood. Furthermore, an electrolyte-deplete acute decompensated HF (ADHF) phenotype with different prognostic implications may be identified by lower serum chloride levels in comparison to sodium levels. However, there has not been adequate research on the effects of serial changes in serum chloride during hospitalisation on mortality and morbidity in ADHF patients. In the present study, the aim

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was to evaluate the prognostic power of serial change in serum chloride during hospitalization in ADHF patients.
The aim of the present study was to assess serum chloride level in patient with acute decompensated heart failure.

2. MATERIALS AND METHODS

The present study included patients of acute decompensated heart failure who were admitted to emergency or ward SGRD HOSPITAL Amritsar. 50 patients of acute decompensated heart failure from April 2021 to March 2022 getting enrolled in emergency /ward of SGRD Amritsar were selected.
Patients fulfilling the below given criteria before their final inclusion, informed consent was taken from patients for participation in the study.

Inclusion Criteria

All patients older than 18 years with a clinical diagnosing of acute decompensated heart failure due to dilated cardiomyopathy or ischemic cardiomyopathy was included. The clinical criteria to label the patient with acute decompensated heart failure will be based on Framingham heart failure criteria ie:-

Major criteria	**Minor criteria**
Acute pulmonary edema	Ankle edema
Cardiomegaly	Dyspnea on exertion
Hepatojugular reflux	Hepatomegaly
Neck vein distension	Nocturnal cough
Paroxysmal nocturnal dyspnoea or orthopnoea	Pleural effusion
Pulmonary rales Third heart sound (s3 gallop rhythm)	Tachycardia (HR>120)
Weight loss >4.5 kg in 5days in response to treatment	

Diagnosis of acute decompensated heart failure: - 2 Major criteria or 1 Major +2 Minor criteria with supportive evidence of BNP > 400 pg /ml

Exclusion criteria

i) If patient is known case of chronic kidney disease or having acute kidney injury
ii) If patient had sepsis (based on qSOFA score)
iii) If there is any evidence of ACS OR MYOCARDITIS based on history, elevated troponin levels, dynamic ECG changes.
iv) Pregnancy
v) Malignancy

Proper history from the patient was taken and general physical and systemic examination was done and final diagnosis was made after doing all necessary investigations baseline investigations CBC, RFT, arterial blood gas and electrolyte chest X Ray ECG and ECHO was

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done routinely. During hospital stay EVEREST score, NYHA class, NT-proBNP, hemoglobin and IVC size monitoring was done.

NYHA class

I. No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II. Slight limitation of physical activity. Comfortable at rest Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III. Marked limitation of physical activity. Comfortable at rest Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV. Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest, if any physical activity is undertaken discomfort increases.

Discharge criteria

1. Oral medication regimen, stable for at-least 24 hrs (transition from iv to oral diuretics successfully.)
2. No intravenous vasodilators or ionotropic agent for at-least 24hr.
3. Decongestion targets

Morbidity parameters in acute decompensated heart failure

i. Total dose of diuretics
ii. Total dose of inotropes, if any required
iii. Duration of hospital stay

First day of serum chloride level was taken. The serum chloride level was divided into tertiles

<96meq/l (tertile 1)
96-101 meq/l (tertile 2)
>101 meq/l (tertile3)

3. RESULTS

Table 1: Patient details

		Frequency	**Percent**
Age (In Years)	<31	3	6.0
	31-40	2	4.0
	41-50	5	10.0
	51-60	12	24.0
	61-70	20	40.0
	71-80	7	14.0
	>80	1	2.0
Mean±SD	59.68±12.84		
Gender	Female	33	66.0
	Male	17	34.0
BMI	<23	10	20.0
	23-24.9	19	38.0

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	>24.9	21	42.0
Co-morbidities	Diabetes Mellitus	25	50.0
	Hypertension	26	52.0
	COPD	3	6.0
	SMOKER	1	2.0

Majority of the patients were 61-70 years old (40%) followed by 51-60 years (24%), 71-80 years (14%), 41-50 years (10%), <31 years (6%), 31-40 years (4%), and >80 years (2%). Mean age was 59.68±12.84 years. Out of 50 patients, 33 (66%) were females and 17 (34%) were males. 42% of the patients had BMI >24.9 Kg/m2 followed by 23-24.9 Kg/m2 (38%) and <23 Kg/m2 (20%). 52% patients had hypertension, 50% patients had diabetes mellitus, 6% patients had COPD, and 2% were smokers.

Table 2: Distribution of Diastolic Dysfunction, ECG findings

		Frequency	Percent
Diastolic Dysfunction	N	3	6.0
	1	10	20.0
	2	20	40.0
	3	17	34.0
		Frequency	Percent
ECG	AF	6	12.0
	BIFASCICULAR BLOCK	2	4.0
	LBBB	3	6.0
	PSVT	1	2.0
	ST	38	76.0

40% patients had diastolic dysfunction grade 2 followed by grade 3 (34%), grade 1 (20%), and 6% patients were normal. In 76% patients, ST was present followed by AF (12%), LBBB (6%), Bifascicular block (4%), and PSVT (2%).

Table 3: Distribution of serum chloride

		Frequency	Percent
Se. chloride	<96	12	24.0
	96-101	18	36.0
	>101	20	40.0
	Total	50	100.0

24% patients had serum chloride levels < 96 mEq/L, 36% had 96-101 mEq/L, and 40% had >101 mEq/L.

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Table 4: Distribution of serum chloride levels according to NYHA class 3 and 4 and levels according to Everest score <6, 6-12, 13-18

NYHA	Serum chloride			Total
	<96	96-101	>101	
Class 3	1	8	14	23
	4.3%	34.8%	60.9%	100.0%
Class 4	11	10	6	27
	40.7%	37.0%	22.2%	100.0%
EVERST Score	Serum chloride			Total
	<96	96-101	>101	
<6	0	1	4	5
	0.0%	20.0%	80.0%	100.0%
EVERST Score	Serum chloride			Total
	<96	96-101	>101	
6-12	8	16	16	40
	20.0%	40.0%	40.0%	100.0%
EVERST Score	Serum chloride			Total
	<96	96-101	>101	
13-18	4	1	0	5
	80.0%	20.0%	0.0%	100.0%

Out of patients with NYHA class 3, 60.9% had serum chloride levels >101 mEq/L, 34.8% had 96-101 mEq/L, and 4.3% had <96 mEq/L. Out of patients with NYHA class 4, 22.2% had serum chloride levels >101 mEq/L, 37% had 96-101 mEq/L, and 40.7% had <96 mEq/L. Out of patients with EVEREST score <6, 80% had serum chloride levels >101 mEq/L and 20% had 96-101 mEq/L. Out of patients with EVEREST score 6-12, 40% had 96-101 mEq/L, 40% had >101 mEq/L, and 20% had <96 mEq/L serum chloride levels. Out of patients with EVEREST score 13-18, 20% had 96-101 mEq/L, 0% had >101 mEq/L, and 80% had <96 mEq/L serum chloride levels.

Table 5: Mean values of dose of loop diuretics according to serum chloride levels

		Serum Chloride		
		<96	96-101	>101
Diuretic	N	12	18	20
	Mean	391.6667±170.23157	273.6667±97.86966	216.0000±72.28598
	p=0.001 (Sig.)			

Mean dose of loop diuretics value of patients with serum chloride levels <96 mEq/L was 391.6667±170.23157, 96-191 mEq/L was 273.6667±97.86966, and >101 mEq/L was 216.0000±72.28598. The relation was found statistically significant.

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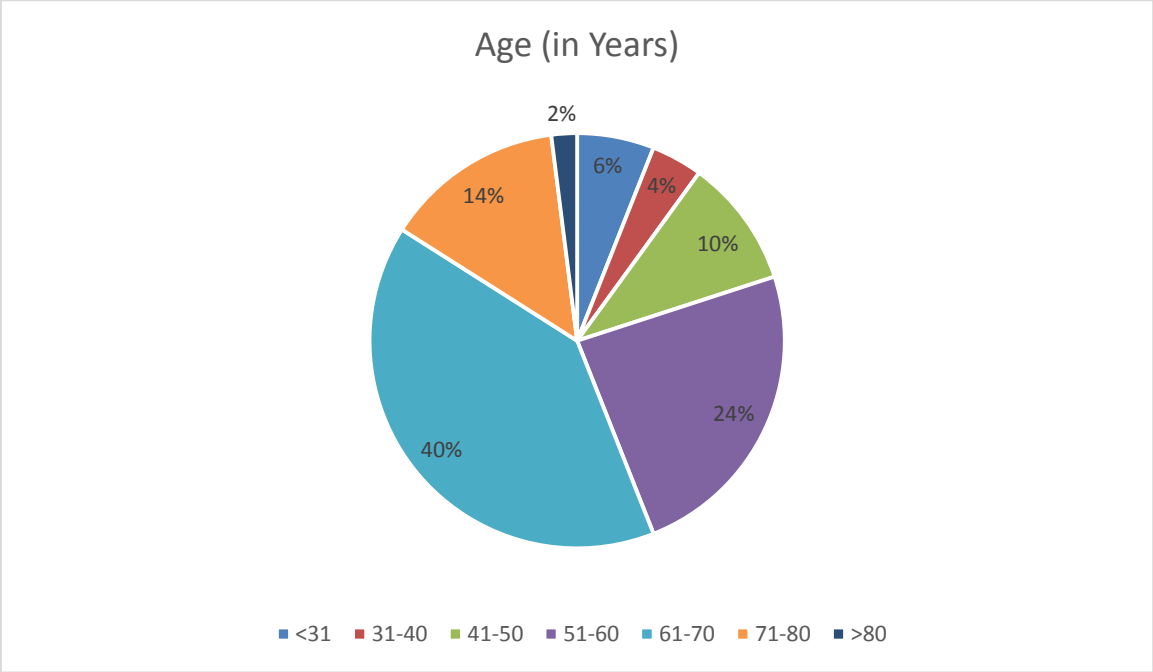
Table 6: Mean values of Hospital stay according to serum chloride levels

		Serum Chloride		
		<96	96-101	>101
Hospital stays	N	12	18	20
	Mean	7.6667±1.55700	5.8889±1.52966	5.5000±1.57280
	p=0.001 (Sig.)			

Mean hospital stay duration of patients with serum chloride levels <96 mEq/L was 7.6667±1.55700 days, 96-191 mEq/L was 5.8889±1.52966 days, and >101 mEq/L was 5.5000±1.57280 days. The difference in duration of hospital stay was found significant.

Graph 1: Age distribution



Graph 2: Gender distribution

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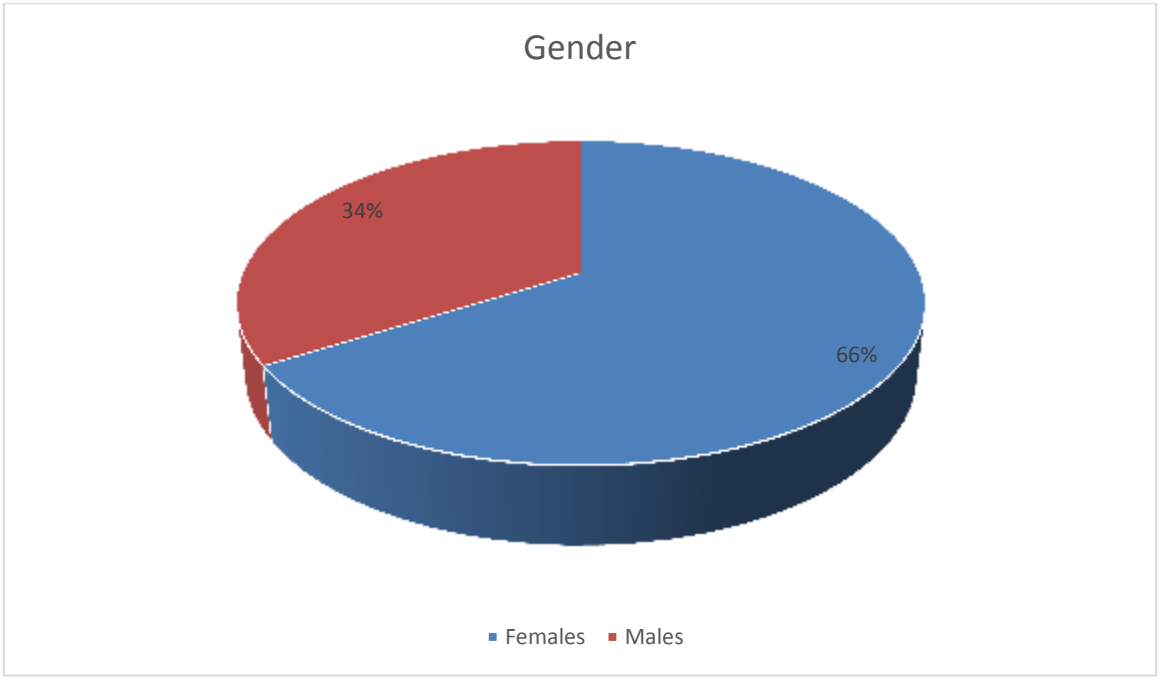
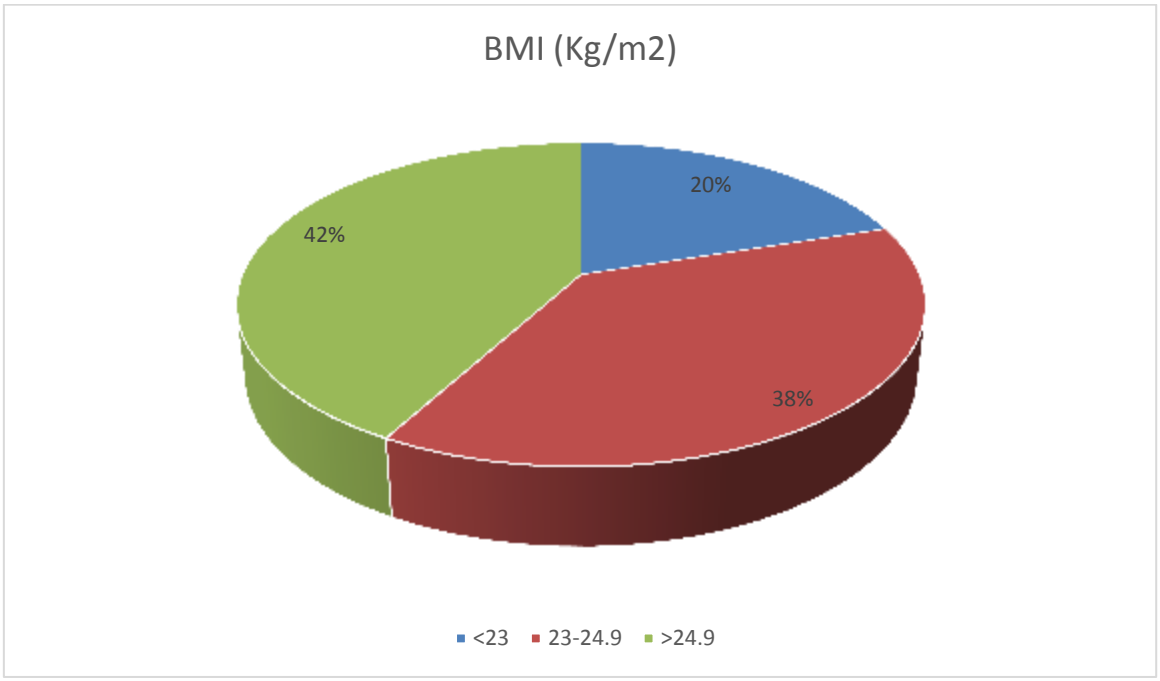


Graph 3: Distribution of BMI



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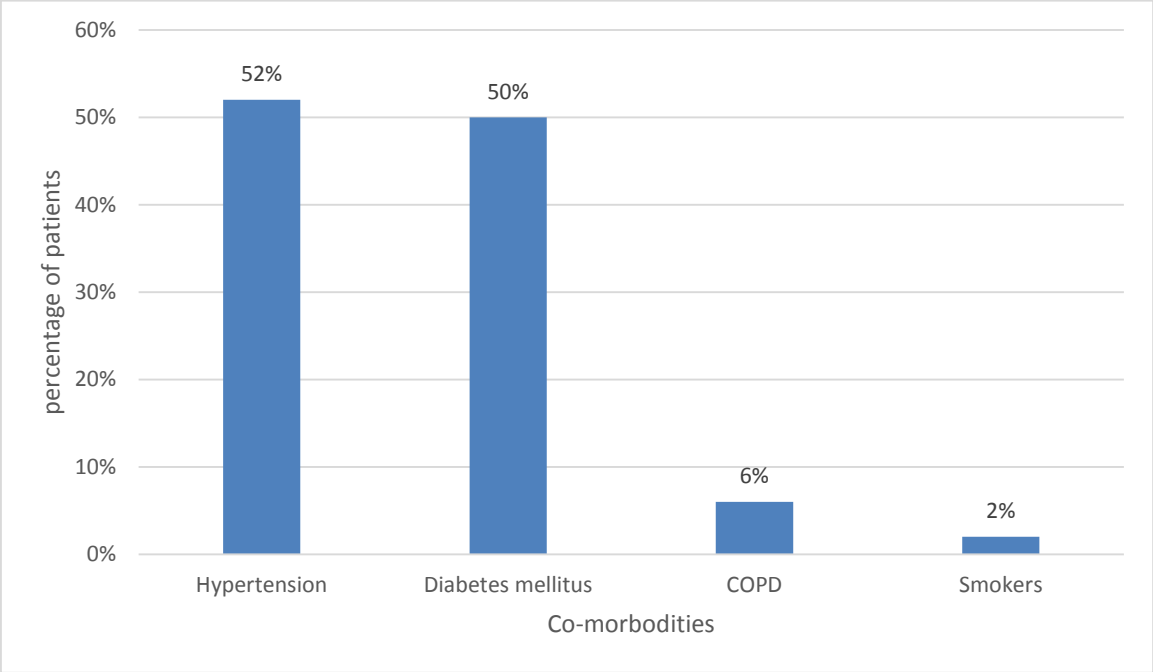
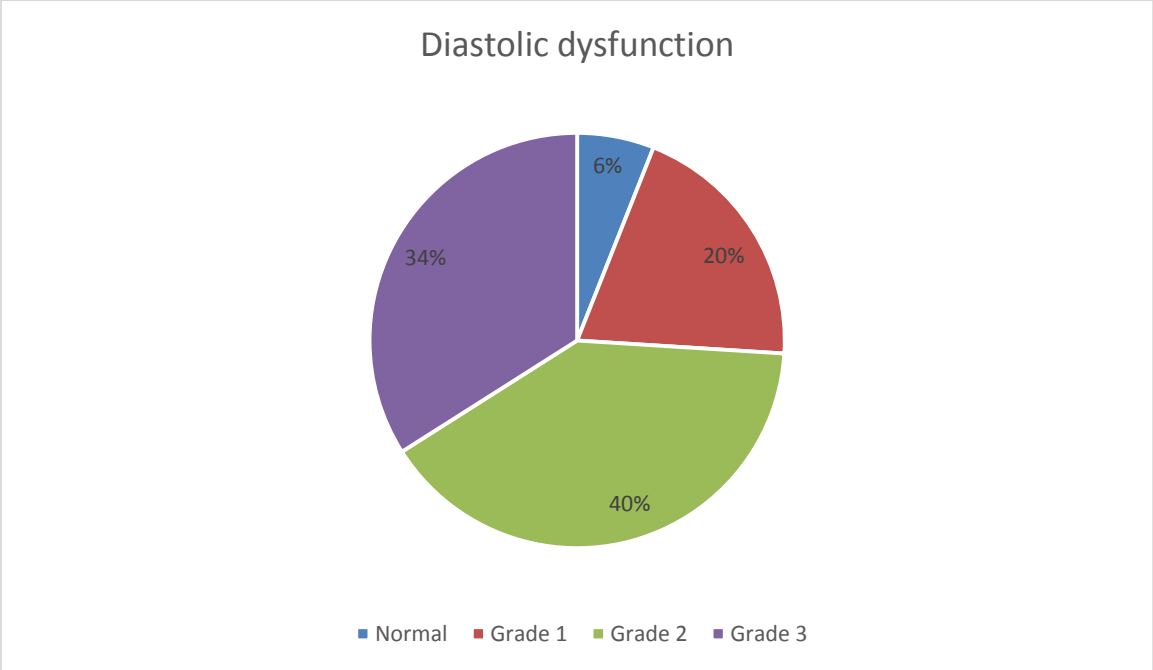
Graph 4: Distribution of Comorbidities



Graph 5: Distribution of Diastolic Dysfunction



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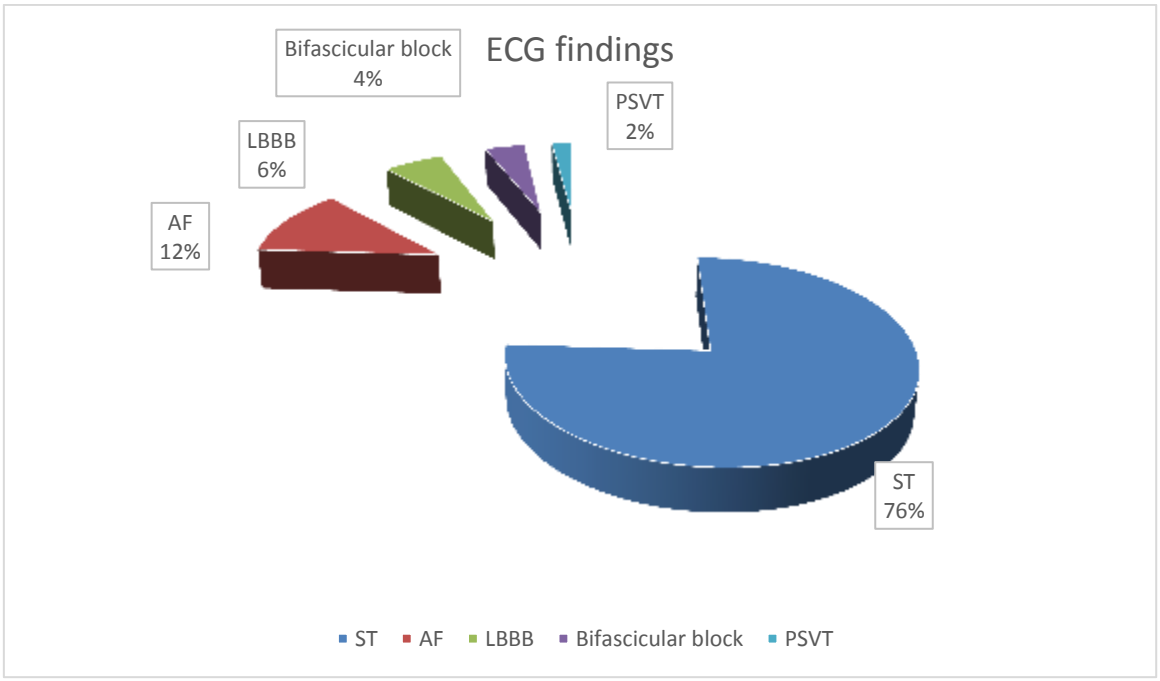
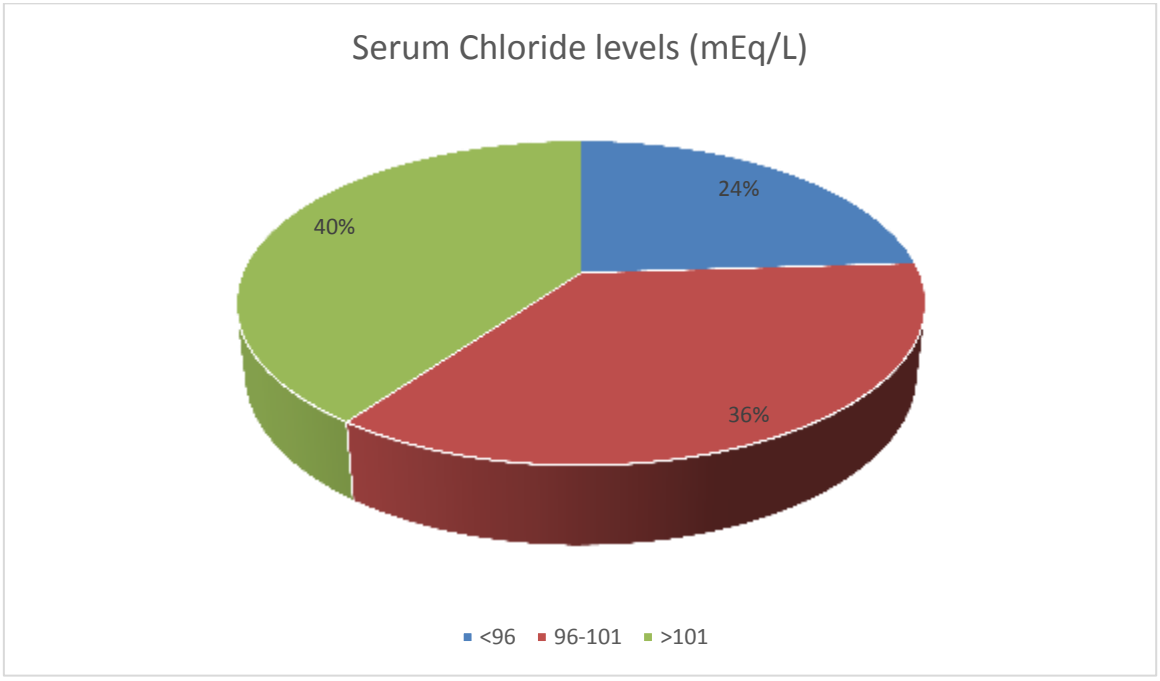
Graph 6: ECG findings



Graph 7: Distribution of serum chloride



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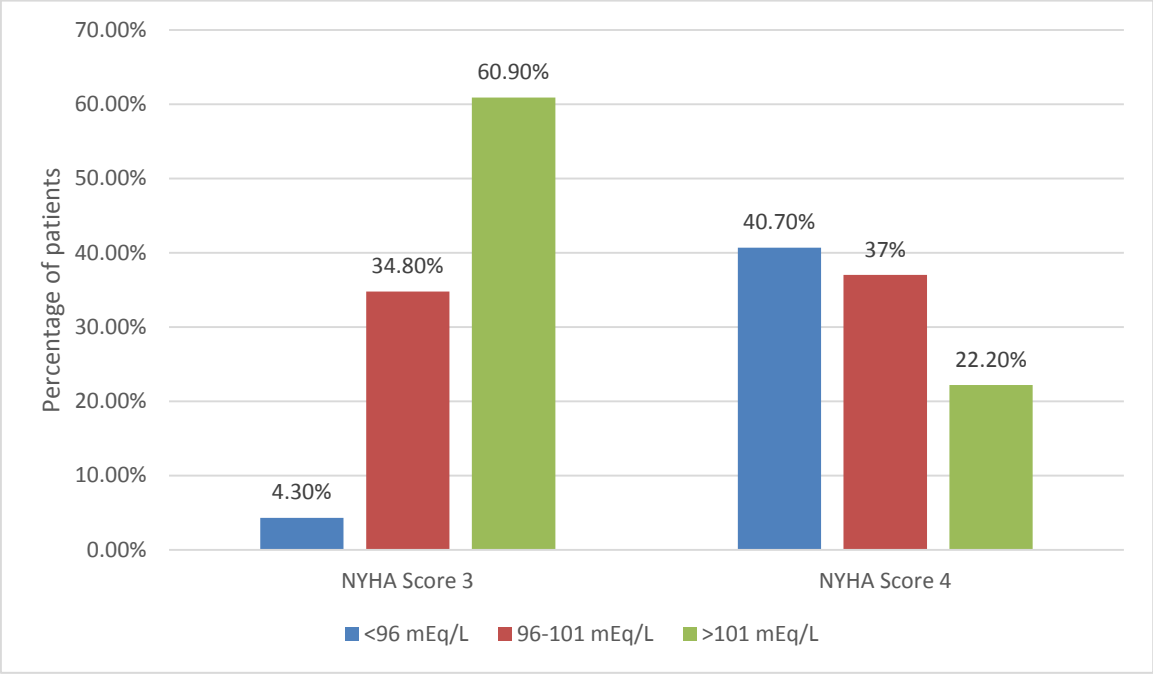
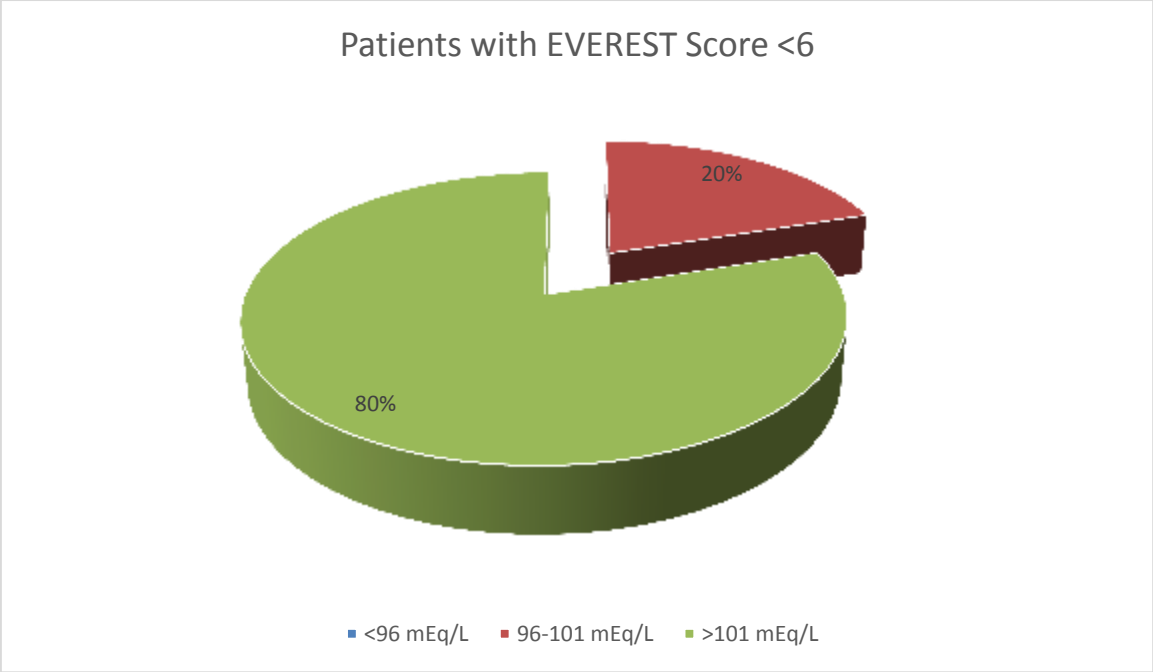
Graph 8: Distribution of serum chloride levels according to NYHA class 3 and 4



Graph 9: Distribution of serum chloride levels according to Everest score <6



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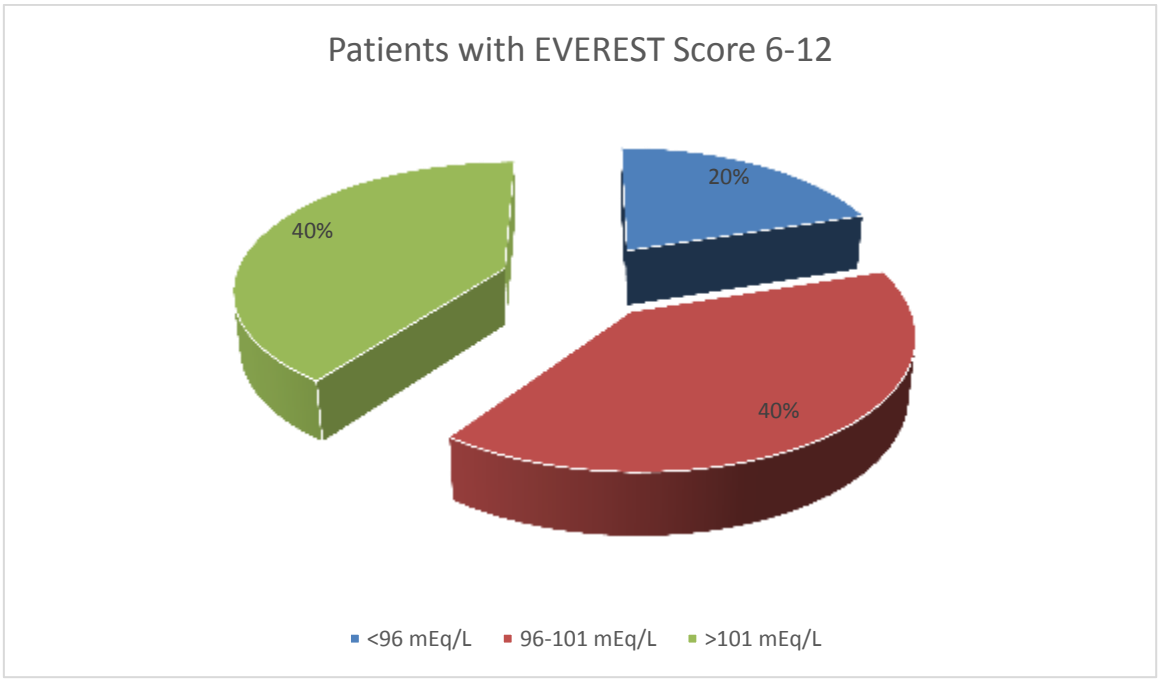
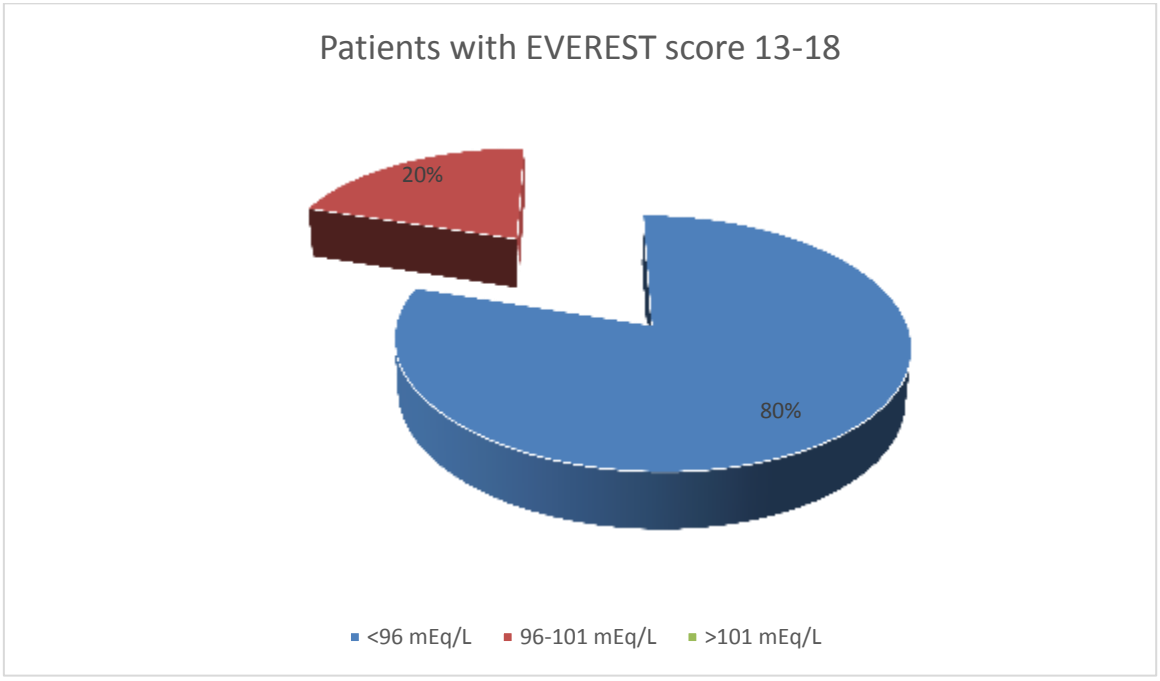
Graph 10: Distribution of serum chloride levels according to Everest score 6-12



Graph 11: Distribution of serum chloride levels according to Everest score 13-18



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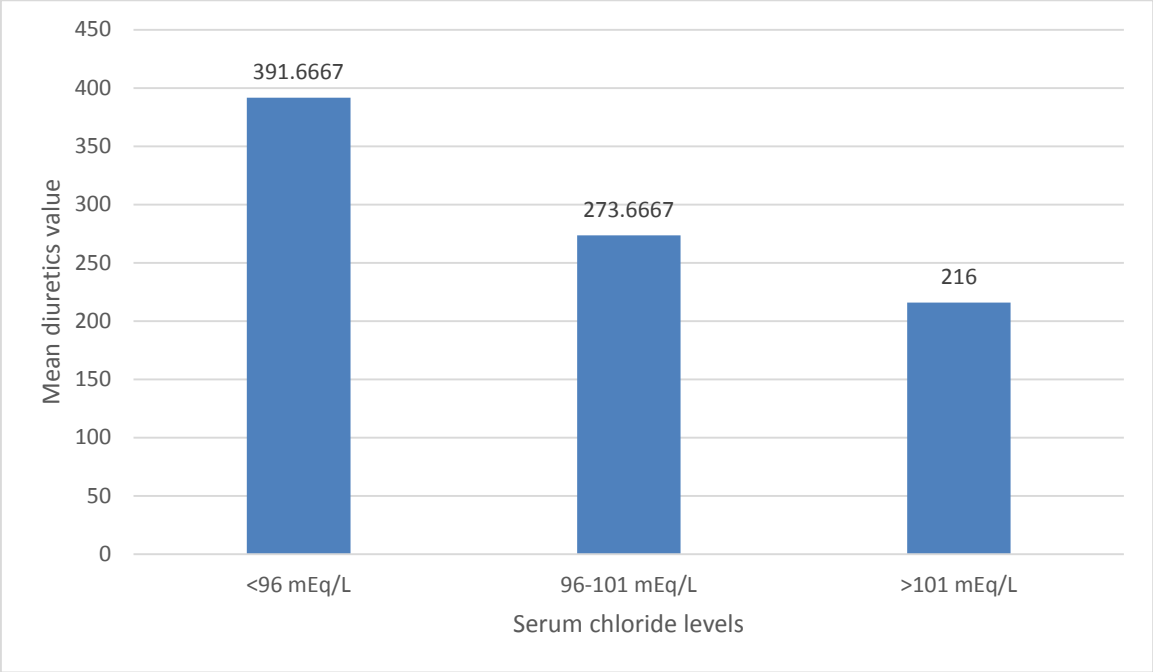
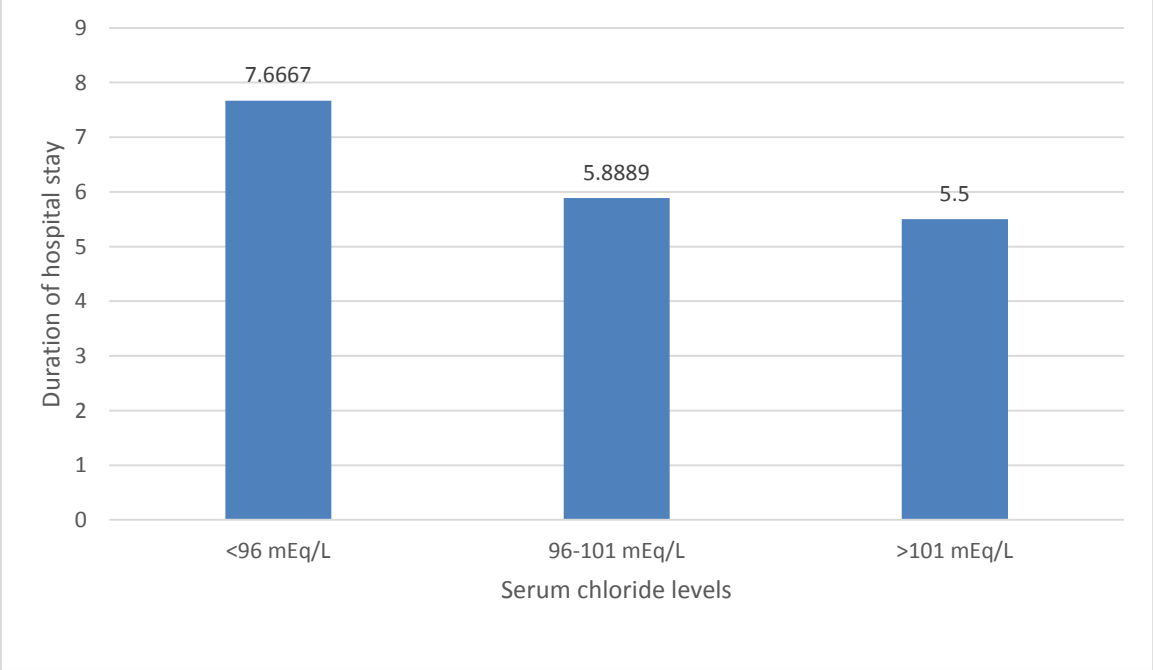
Graph 12: Mean values of diuretics according to serum chloride levels



Graph 13: Mean values of Hospital stay according to serum chloride levels



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4. DISCUSSION

In addition to acid-base disturbances, heart failure (HF) is linked with various serum electrolyte abnormalities, including hyponatraemia, hypokalaemia, and hypochloraemia, the reasons of which are multifactorial. Maladaptive activation of neurohormonal mechanisms, such as an increase in arginine vasopressin, causes dilutional hyponatraemia and hypochloraemia by increasing free water absorption and thirst activation.[2,6,12] Loop and thiazide diuretics cause disproportionately more solute loss than free water loss.[7,12] Recent research has demonstrated that blood chloride levels give better predictive information for HF than serum sodium levels, and that hypochloraemia is associated with relatively high short and long-term mortality.[8,9] The mechanism of action of diuretics, which are the major therapy option for ADHF, is mediated via the chloride ion. Chloride binds directly to the catalytic sites of serine-threonine kinases (with-no-lysine [K] [WNK]), whose activation controls sodium chloride homeostasis through affecting RAAS and transporters that are targets of loop and thiazide diuretics, influencing downstream sodium transport pathways.[14,15]

The majority of patients in the current study (40%) were 61-70 years old, followed by 51-60 years (24%), 71-80 years (14%), 41-50 years (10%), 31 years (6%), 31-40 years (4%), and >80 years (2%). The average age was 59.6812.84 years. In comparable research conducted by Goyal A. et al[16], the study participants' mean standard deviation and median (interquartile range) ages were 63.0513.76 and 63 (55-73) years, respectively. The majority of the patients were females, with 33 (66%) females and 17 (34% men) in the current research. Similarly, in research conducted by ZDEM R S et al[17], 43.3% of the participants were men and 56.7% were girls.

In the current study, 52% of patients had hypertension, 50% had diabetes, 6% had COPD, and only 2% were smokers. In research conducted by Goyal A. et al16, hypertension was present in 66.47% of the participants, diabetes was prevalent in 61.68%, 1.8% were smokers, and 7.78% had COPD. Diabetes was diagnosed in 73.9% of patients with serum chloride levels of 96 mEq/L, compared to 68.1% and 42.3% in patients with 96-100 and >101 mEq/L, respectively (p 0.002). In the current study, the mean SBP was 120.8±24.89488 mmHg and the mean DBP was 78.0±13.09307 mmHg. Grodin J.L et al (2015)[8] found that the average SBP was 131.3±24.2 mmHg and the average DBP was 76.7±14.2 mmHg. In their study, SBP was 124.1±22.9, 132.1±24.0, and 137.4±23.8 mmHg in individuals with serum chloride levels of 100, 100.1-104.7, and >104.7 mEq/L, respectively. DBP was 73.6±13.6, 76.8±13.9, and 79.6±14.4 mmHg in individuals with serum chloride levels of 100, 100.1-104.7, and >104.7 mEq/L, respectively. The difference was likewise statistically significant in all three tertiles. The average heart rate in their research was 82.0, whereas ours was 120.9.

In the current investigation, mean serum chloride levels were 99.1920±6.37562 mEq/L and serum sodium levels were 136.0±6.59623 mEq/L. Grodin J.L et al (2015)[8] found that mean blood chloride levels were 101.8±6.0 mmol/L and serum sodium levels were 139.0 mmol/L. In research conducted by Goyal A et al[16], the mean serum chloride level was 97.96±7.27 meq/L. In the current study, 24% of 50 patients with decompensated heart failure exhibited hypochloremia and 40% had hyperchloremia. The difference between patients from all three

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tertiles was determined to be statistically significant. In research conducted by Fu Z et al[18], the prevalence of hypochloremia in heart failure patients was 26.1% (521/1996). In research conducted by ZDEMR S et al[17], individuals with chloride levels less than 98.5 mmol/L had an increased risk of hospitalization when blood chloride levels of the 120 patients included in their study were evaluated (p=0.041). However, there was no statistically significant connection between serum chloride levels and ICU or clinical ward admission (p=0.818). Because of the low death rate (2.5%) in their investigation, they were unable to undertake a statistical analysis of the connection between blood chloride levels and mortality. The mean blood sodium levels of individuals with serum chloride levels of 96 mEq/L were 127.3333±4.61880 mEq/L, 96-191 mEq/L were 136.3889±3.77513 mEq/L, and >101 mEq/L were 140.8500±3.84263 mEq/L in the current research. This distinction was determined to be statistically significant. According to Fu Z et al[18], the Pearson correlation between serum chloride and sodium was 0.747 (p 0.001), indicating that these measures may contain comparable information.

In the current study, the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan) score was also computed. The EVEREST score (range, 0-18) was created on participants in the EVEREST study and is based on the assessment of basic clinical markers such as dyspnea, orthopnea, jugular venous distension, rales, edoema, and fatigue69, which were gathered prospectively by the research team. In patients hospitalized with ADHF, an EVEREST score of 2 has been advocated as a decongestion aim upon discharge.[19,20] For categorical variables, results were given as counts and percentages, and for continuous variables as mean standard deviation (SD).

Serum chloride levels in patients were shown to be statistically significant in connection to mean EVEREST scores, mean IVC size, mean diuretics levels, duration of hospital stay, and serum salt levels. According to the findings of the Fu Z et al[18] study, low serum chloride upon admission was linked with low BMI, low BNP, severe symptoms, high hematocrit, decreasing renal function, and high co-morbidity. Ter Maaten JM et al[21] discovered that low baseline chloride levels were linked to excessive bicarbonate levels, poor diuretic response, and severe heart failure (all p 0.01). Because these characteristics appear after continuous diuretic medication, the source of hypochloremia is thought to be depletion from pre-hospital decongestive therapy. According to them, the management of chronic heart failure has been greatly improved as a result of the broad application of heart failure guidelines in primary care clinics in recent years. Oral diuretics are now often used for out-of-hospital decongestion. When oral diuretics fail, hospitalization is required. As a result, the majority of hospitalized heart failure patients, particularly those with a history of congestive heart failure, are in the second phase of decongestive treatment, which involves the clearance of residual tissue congestion. At this stage, the signs of congestion are largely high CA125, peripheral pitting edoema, and pulmonary rales, rather than high BNP, low haemoglobin, hematocrit, and other intravascular congestion markers.[22]

In a related study by Grodin J.L. et al8, higher chloride levels were negatively associated with markers of neurohormonal activation (blood urea nitrogen and N-terminal pro-B-type natriuretic peptide) and indicators of end-organ function (haemoglobin and bilirubin), but

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positively associated with increasing LV ejection fraction, beta-blocker and renin-angiotensin system-blocker use, and renal dysfunction. They were also connected to hospital duration of stay and net weight change during admission. Our data imply that, while sodium levels are essential, serum chloride levels provide more strong predictive information. Although low sodium has been found to be a powerful predictor of short- and long-term morbidity and death in patients with both systolic and diastolic HF.[23-25] There was no discussion of the influence of chloride on sodium level interpretation in these analyses. As our findings indicate, earlier studies may have overlooked serum chloride levels. Prior evidence regarding chloride's predictive relevance is limited, and there are no established criteria of hypochloremia in HF.

The mean hospital stay length for patients with serum chloride levels of 96 mEq/L was 7.6667±1.55700 days, 96-191 mEq/L was 5.8889±1.52966 days, and >101 mEq/L was 5.5000±1.57280 days in the current research. The difference in hospital stay time was considerable. The duration of hospital stay changed considerably amongst the three tertiles in research conducted by Goyal A. et al[47]. Patients with serum chloride levels of 96 mEq/L, 96-101 mEq/L, and >101 mEq/L had median hospital stays of 8, 7, and 6 days, respectively.

5. CONCLUSION

Serum chloride has a key function in heart failure and diuretic resistance regulatory mechanisms. Serum chloride levels in patients were shown to be statistically significant in connection to mean EVEREST scores, mean diuretics levels, duration of hospital stays, and serum salt levels. Those with hypochloremia had a longer average hospital stay than patients with normal or hyperchloremia. Serum chloride levels were shown to be strongly related to serum sodium levels but not to serum potassium levels. Our findings highlight the importance of better understanding chloride homeostasis and preserving it as a potential therapeutic consideration, particularly in the setting of ADHF, where loop diuretics primarily inhibit the sodium-potassium-chloride cotransporter, resulting in inevitable and excessive chloride wasting.

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