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ORIGINAL ARTICLE

Estimating Prevalence and Prognostic Impact of Sick Euthyroid Syndrome in Patients with Acute Heart Failure

Sreena Sreedhar,[1] Satarla Narendra,[2] Pulkit Jindal,[3,*] Deepak Sha K,[4] Nithin C[5] and Navpreet Kaur Batth[6]

[1]*Senior Resident, Department of Neurology, Ram Manohar Lohya hospital, Lucknow*
[2]*Senior Resident, Department of Medicine, GMCH-32, Chandigarh*
[3]*Assistant Professor, Department of Medicine, Adesh Medical College, Kurukshetra*
[4]*Medical Officer, Department of Medicine, ESIC, VK Nagar, New Delhi*
[5]*Resident Medical Officer, Smitha Memorial Hospital, Thodupuzha*
[6]*Resident Medical Officer, Hazrat Haleema Hospital, Malerkotla*

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Abstract

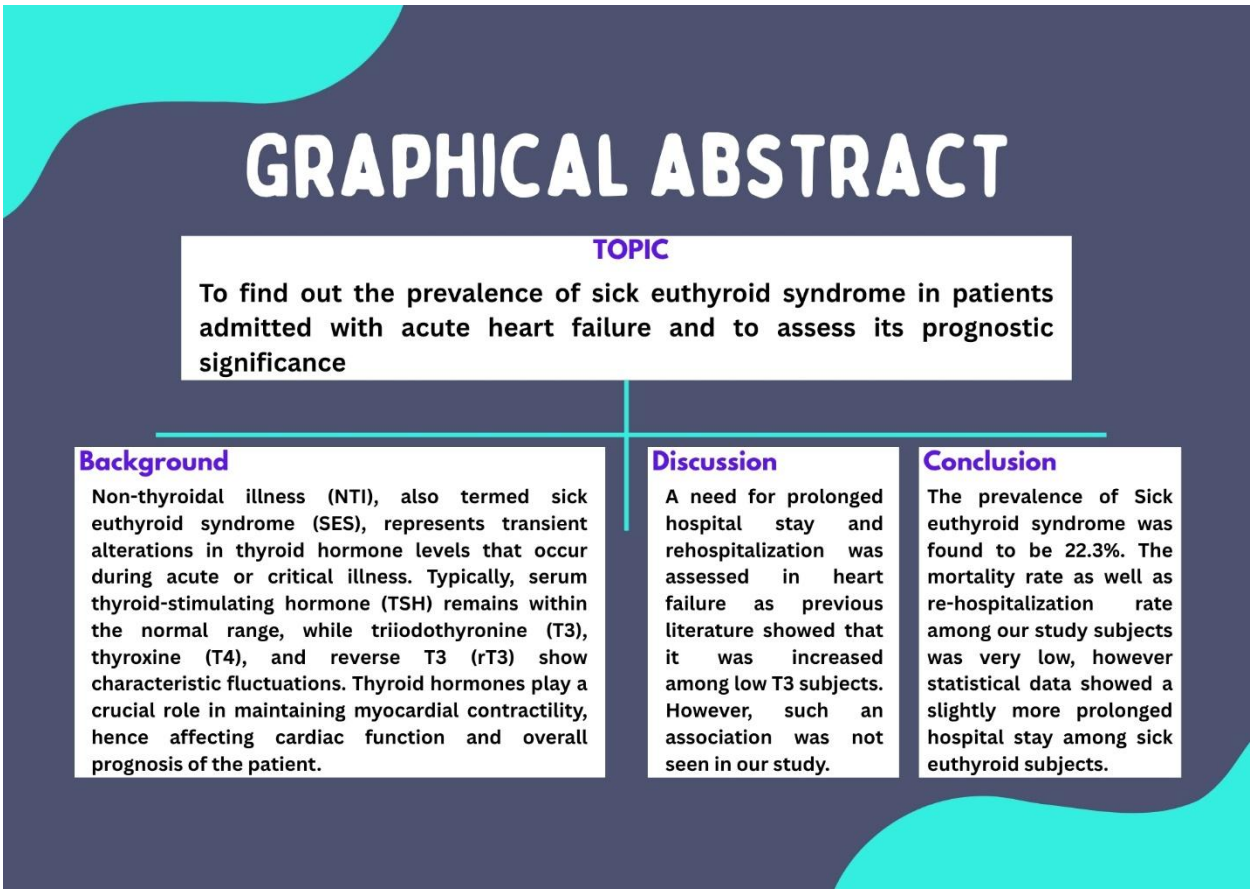
Background: Non-thyroidal illness (NTI), also termed sick euthyroid syndrome (SES), represents transient alterations in thyroid hormone levels that occur during acute or critical illness. Typically, serum thyroid-stimulating hormone (TSH) remains within the normal range, while triiodothyronine (T3), thyroxine (T4), and reverse T3 (rT3) show characteristic fluctuations. Thyroid hormones play a crucial role in maintaining myocardial contractility, hence affecting cardiac function and overall prognosis of the patient. **Aim:** To estimate prevalence of sick euthyroid syndrome in patients admitted with acute heart failure and to assess its prognostic significance. **Discussion:** Morbidity of heart failure was assessed as a need for prolonged hospital stay and re-hospitalization as previous literature review showed that it was increased among low T3 subjects. However, such an association was not seen in our study. **Conclusion:** The prevalence of Sick euthyroid syndrome was found to be 22.3%. The mortality rate as well as re-hospitalization rate among our study subjects was very low, however statistical data showed a slightly more prolonged hospital stay among sick euthyroid subjects. Thyroid function assessment and its treatment whenever indicated is of paramount importance especially among heart failure subjects.

Keywords: Sick Euthyroid, Reverse T3, non-thyroidal illness, Ejection Fraction

*Corresponding Author: Pulkit Jindal
Email: jindalpulkit768@gmail.com

Abbreviations

SES	:	Sick Euthyroid Syndrome
rT3	:	reverse Triiodothyronine
LVD	:	Left Ventricular Dysfunction
HFpEF	:	Heart Failure with preserved Ejection Fraction
FT3	:	Free Triiodothyronine
TSH	:	Thyroid Stimulating Hormone
NTI	:	Non-Thyroidal Illness
T3	:	Total Triiodothyronine
ICU	:	Intensive Care Unit
FTI	:	Free Thyroxine Index
T4	:	Total Thyroxine or Tetraiodothyronine
FT4	:	Free Tetraiodothyronine
TBG	:	Thyroid Binding Globulin



Introduction

Non-thyroidal illness (NTI), also termed sick euthyroid syndrome (SES), represents transient alterations in thyroid hormone levels that occur during acute or critical illness. It is not a primary thyroid disorder but rather a reflection of temporary dysregulation in the hypothalamic–pituitary–thyroid axis in individuals without prior thyroid disease. Such abnormalities are reported in nearly three-quarters of critically ill patients [1]. Typically, serum thyroid-stimulating hormone (TSH) remains within the normal range, while triiodothyronine (T3), thyroxine (T4), and reverse T3 (rT3) show characteristic fluctuations. A decline in T3 concentration has been identified as an independent predictor of mortality in heart failure. Given the crucial role of thyroid hormones in maintaining myocardial contractility and hemodynamic stability, the presence of SES in acute heart failure merits further research to elucidate its prognostic relevance [2].

Thyroid abnormalities in critical illnesses

Several abnormalities in thyroid function tests have been documented among patients with NTIs. A common finding is a reduction in serum T3 accompanied by an increase in rT3, a pattern often referred to as the “low T3 syndrome.” Alterations in TSH, T4, FT4, and the free thyroxine index (FTI) have also been observed, with the degree of change varying according to the severity and duration of the illness as shown in Figure 1 [3] It has been well established that as the severity of the non-thyroidal illness increases, serum T3 and T4 concentrations tend to decline progressively, returning to normal once the acute condition resolves [4].

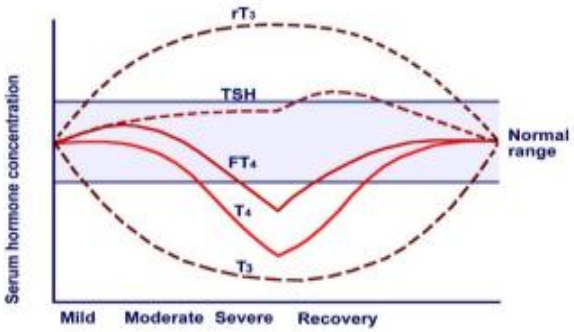


Figure 1. Relationship between serum thyroid hormone concentrations and severity of NTI [5]

Thyroid abnormalities in SES

SICK EUTHYROID	LOW T3	NORMAL	LOW	NORMAL
	HIGH T4	NORMAL	NORMAL	HIGH
	LOW T3 LOW T4	NORMAL	LOW	LOW
	LOW T4	NORMAL	NORMAL	LOW

Figure 2. Types of thyroid abnormalities in SES [6]

Low T3 Syndrome

In low T3 syndrome, serum TSH, T4, and free thyroxine (FT4) levels generally remain within the normal range, while T3 levels are decreased as shown in Figure 2. Free T3 concentrations may be normal or reduced, whereas rT3 levels are typically elevated, except in patients with renal impairment.

A progressive daily decline in T3 production has also been observed during acute illness. Among hospitalized patients with severe systemic conditions, more than 70% exhibit reduced total T3 levels. This

pattern is particularly common in individuals with heart failure, affecting nearly half of those who are otherwise euthyroid and has been identified as an independent predictor of adverse outcomes in patients with cardiac failure [7].

Low T3 and Low T4 Syndrome

Studies have shown that serum T3 and T4 levels are reduced in approximately 30% to 50% of patients admitted to medical ICUs. In critically ill or moribund individuals, daily production of T4 may be normal or slightly diminished as shown in Figure 2. Reduced serum T4 is linked to increased mortality in systemic illnesses. Moreover, among patients with low T4, the coexistence of low T3 levels was associated with the worst prognosis [8].

High T4 Syndrome

In certain patient groups, particularly those with hepatic dysfunction or patients on amiodarone or radiocontrast agents, an isolated elevation in total serum T4 has been observed. This increase is primarily attributed to elevated levels of thyroxine-binding globulin (TBG), reduced hepatic metabolism of T4, or a combination of both mechanisms as shown in Figure 2. Despite the rise in total T4, the concentration of free T4 in these patients typically remains within the normal range [9].

Increased Serum Reverse T3

Another notable thyroid function abnormality observed in non-thyroidal illness is an elevation in serum reverse triiodothyronine (rT3) levels, which occurs in the majority of systemic disorders. An exception to this pattern is seen in renal impairment, where rT3 concentrations typically remain within the normal range as shown in Figure 2. Elevated serum rT3 levels, as well as a reduced T3/rT3 ratio have been identified as independent predictors of mortality in patients with congestive heart failure [10].

Acute Cardiac Failure and Heart failure with preserved ejection fraction

Cardiovascular disease is recognized as the foremost cause of death worldwide and encompasses a range of disorders affecting the heart and blood vessels. These include coronary artery disease, cerebrovascular disease, rheumatic heart disease, and various other related conditions. Heart failure represents the final stage of most cardiac disorders, contributing to its significant prevalence. Despite advancements in medical management, heart failure continues to be associated with high mortality rates [11].

Heart failure with preserved ejection fraction (HFpEF) is a condition in which patients exhibit the typical signs and symptoms of heart failure due to elevated left ventricular filling pressures, despite having normal left ventricular systolic function. The exact prevalence of HFpEF remains uncertain; however, recent studies estimate it to range between 40% and 70%. Currently, there is no established effective treatment for HFpEF [12].

Mechanisms of cardiac function affect by thyroid hormone abnormalities

T3 influences cardiovascular function through multiple mechanisms.

1. First, T3 binds to nuclear receptors within cardiac myocytes, thereby regulating gene expression and directly affecting myocardial structure and performance.
2. Second, it modulates cardiac responsiveness to the sympathetic nervous system, enhancing the heart's sensitivity to catecholamines.
3. Third, T3 induces peripheral hemodynamic changes that increase venous return and cardiac filling, while also influencing the force and efficiency of myocardial contraction [13].

Mechanisms contributing to low T3 and T4 levels

1. Compromised nutritional status and alterations in selenium status.
2. Increased generation of free radicals in tissues and cytokines.
3. Circulating inhibitors of the activity of iodothyronine 5′-monodeiodinase in tissues.
4. Increased cortisol in circulation.
5. Decreased uptakes of T4 by tissues.
6. Decrease in TSH or its effect on the thyroid.
7. Circulating inhibitors of binding of T4 to serum proteins.
8. Increased reverse T3
9. Decreased serum binding of T3 and T4
10. Abnormalities in T4-binding globulin (14)

Methodology

It was a prospective cohort study undertaken for 2 years at Little Flower Hospital, Angamaly, Kerala for prevalence estimation of the sick euthyroid syndrome in heart failure patients. 121 patients were admitted in medicine and cardiology departments with acute heart failure.

Inclusion Criteria:

- Age > 18 years
- No history or clinical evidence of structural heart disease
- No history of intake of medications altering thyroid function.

Exclusion Criteria:

- Age < 18 years
- are not willing to participate
- Non-cardiac acute illness including sepsis along with acute cardiac dysfunction.

Thyroid Function tests

Venous blood samples were obtained at the time of study entry and thyroid function test was done using Cobas e 411 instruments for thyroid profile analysis in the hospital laboratory. The values mentioned in Table 1 were considered for normal thyroid values as well as for the sick euthyroid syndrome diagnosis.

Table 1. Reference Range of Thyroid Function Test [15]

TSH	0.27 - 4.2 µIU/ml
T3	80-200 ng/dL
T4	4.5-12 µg/dL

Severity of heart failure was assessed as a token of ejection fraction which was noted by performing a 2D-echocardiography at our heart care center at admission.

Other methods for acute heart failure quantification like NT-ProBNP and pulmonary edema on chest xray were not taken in this study as the parameters for heart failure assessment.

Ejection fraction was classified in different categories as follows (16):

- Preserved Ejection Fraction >50%
- Mild LVD: 41-49%
- Moderate LVD: 31-40%
- Severe LVD: <30%

Thyroid samples were repeated only if the samples were found defective via lab parameters otherwise it was no resampling done. No thyroid replacement therapy or drugs for myocardial remodeling prevention were initiated unless patient was already on such drugs which were commenced promptly as it was an observational study and not an interventional study [17,18].

Patients were followed up for 6 months from the date of discharge for life events like re-hospitalization mortality [19].

Data collected were coded and entered in Microsoft Excel sheet which was checked and analyzed using SPSS statistical software version 22.

Quantitative variables were summarized using mean and standard deviation. Categorical variables were represented using frequency and percentage. Pearson Chi-square test and Fisher's exact test were used for comparing categorical variables between groups. A P value of <0.05 was considered statistically significant.

Results

The age of the participants ranged from 41 to 88 years. Maximum number of study subjects were in the age group of 71-80 years. Age distribution of the patients is shown in Table 2 and Figure 3.

Mean age of the study population was 68.3 years. Standard deviation was 10.85. Median age was 70 years.

Table 2. Age distribution

Age Group	No. of patients	%age
40-50 years	7	5.8
51-60 years	24	19.8
61-70 years	30	24.8
71-80 years	45	37.2
81-90 years	15	12.4

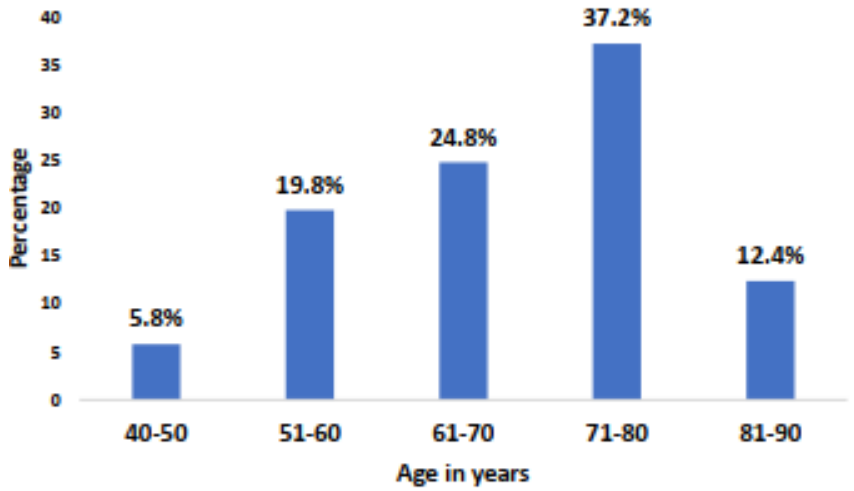


Figure 3. Graphical representation of age distribution of the study participants

Table 3. Distribution of participants as per their ejection fraction

EJECTION FRACTION	NO. OF SUBJECTS (%AGE)
Preserved EF (>50%)	23(19%)
Mild LVD (41%-49%)	19(15.7%)
Moderate LVD (31%-40%)	39(32.2%)
Severe LVD (<30%)	40(33.1%)

40 had severe LVD, 39 had moderate LVD, 23 had preserved ejection fraction and 19 had mild LVD which was diagnosed on Echocardiography as shown in Table 3.

Table 4. Distribution of SES in Study population

SICK EUTHYROID SYNDROME	NO. OF SUBJECTS (%AGE)
Present	27(22.3%)
Absent	94(77.7%)

Out of 121 subjects, 27 subjects (22.3%) had sick euthyroid syndrome and rest of 94 patients didn't fit into the diagnosis of sick euthyroid syndrome as shown in Table and Figure 4.

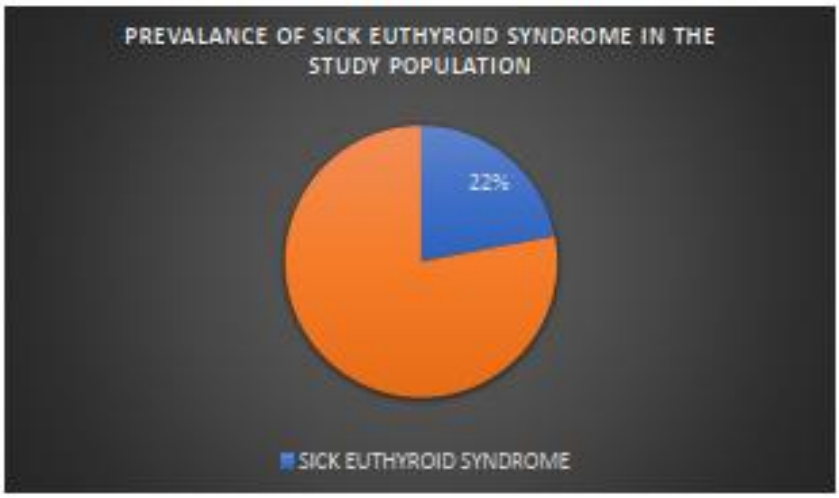


Figure 4. Pie chart showing prevalence of SES in Study population

Table 5. Distribution of SES components in Study population

SICK EUTHYROID SYNDROME	NO. OF SUBJECTS (%AGE)
LOW T3	20(16.5%)
HIGH T4	3(2.5%)
LOW T3 LOW T4	2(1.7%)
LOW T4	2(1.7%)

Among the 27 subjects with sick euthyroid syndrome, 20 subjects had low T3 syndrome: 3 had high T4 levels, 2 had low T3 low T4 levels and 2 had low T4 levels as shown in table 5.

Table 6. Duration of In-patient care required in the Study population

DURATION OF IN-PATIENT CARE	NO. OF SUBJECTS (%age)
≤5 days	65(53.7%)
>5 days	56(46.3%)

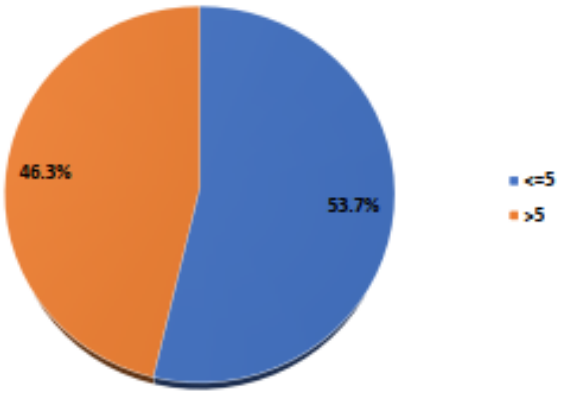


Figure 5. Pie chart showing duration of In-patient care

The mean days of hospitalization were 5.71 days. Standard deviation was 3.49. 53.7% of study subjects required only less than 5 days of hospitalization whereas 46.3% required more than 5 days of hospitalization as shown in Table 6 and Figure 5.

Table 7: Readmission required in the Study population

READMISSION STATUS	NO. OF SUBJECTS (%AGE)
Readmission	19(15.7%)
No readmission	102(84.3%)

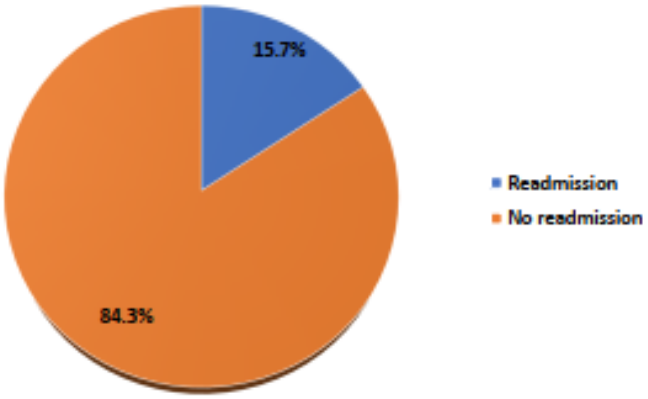


Figure 6. Pie chart showing Readmission percentage in Study Population

15.7% (19 out of 121) required re-hospitalization within 6 months of index inpatient care as shown in Table 7 and Figure 6.

Table 8. Hospital mortality in the Study population

HOSPITAL MORTALITY	NO. OF SUBJECTS (%AGE)
Yes	1(0.8%)
No	120(99.2%

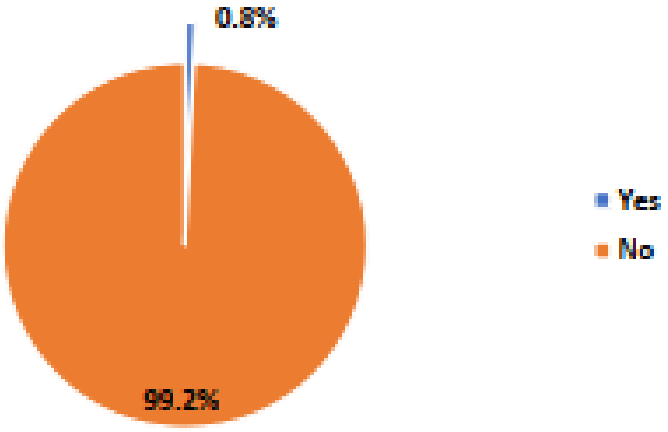


Figure 7. Pie chart showing mortality percentage in Study Population

Mortality within six months of index inpatient care was only 0.8%. Only 1 patient died out of 121 as shown in table 8 and figure 7.

Table 9. Association of SES with age

Age	Sick euthyroid syndrome		P-Value
	No. & %age	No. & %age	
40-50 years	0	7(7.4%)	0.354
51-60 years	8(29.6%)	16(17%)	
61-70 years	5(18.5%)	25(26.6%)	
71-80 years	11(40.7%)	34(36.2%)	
81-90 years	3(11.1%)	12(12.8%)	
Total	27 (22.3%)	94(77.7%)	

Out of 27 subjects with sick euthyroid syndrome, 11(40.7%) were in the age group of 71-80 years; 8 (29.6%) belonged to age group of 51-60 years; 5 (18.5%) belonged to age group of 61-70years and 3(11.1%) belonged to the age group of 81-90 years. Whereas in the non-sick euthyroid category, 34 (36.2%) were in the age group of 71-80 years; 25 (26.6%) were in the age group of 61-70 years; 16 (17%) were in the age group of 51-60 years; 12 (12.8%) were in the age group of 81-90 years and 7 (7.4%) belonged to 40-50 years as shown in table 9. Correlation between incidence of sick euthyroid syndrome in acute heart failure and age at admission was inconclusive in our study because P-value could not establish a statistical association.

Table 10. Association of SES with ejection fraction

Ejection Fraction	Sick euthyroid syndrome		P-Value
	Present No. & %age	Absent No. & %age	
Preserved EF	7(25.9%)	16(17%)	0.724
Mild LVD	4(14.8%)	15(16%)	
Moderate LVD	7(25.9%)	32(34%)	
Severe LVD	9(33.3%)	31(33%)	

Out of 27 subjects with sick euthyroid syndrome, 9(33.3%) had severe LVD; 7(25.9%) had heart failure with preserved ejection fraction; 7(25.9%) had moderate LVD; 4(14.8%) had mild LVD. Whereas in non-sick euthyroid subjects 31 (33%) had severe LVD; 32 (34%) had moderate LVD; 15 (16%) had mild LVD and 16 (17%) had preserved EF as shown in Table 10.

Correlation between severity of heart failure and incidence of sick euthyroid syndrome in acute heart failure was inconclusive in our study because P-value could not establish a statistical association.

Table 11. Association of SES with duration of inpatient care

Duration of inpatient care	Sick euthyroid syndrome		P-Value
	Present No. & %age	Absent No. & %age	
≤5 DAYS	13(48.1%)	52(55.3%)	0.510
>5 DAYS	14(51.9%)	42(44.7%)	

Out of 27 subjects with sick euthyroid syndrome, 14(51.9%) needed a longer hospital stay of more than 5 days whereas 13(48.1%) required hospital stay less than 5 days. In the non sick euthyroid category 52 (55.3%) required hospital stay less than 5 days whereas 42 (44.7%) required hospital stay more than 5 days as shown in Table 11. Correlation between duration of in-patient care and incidence of acute heart failure was inconclusive in our study because P-value could not establish a statistical association.

Table 12. Association of SES with readmission

Status of readmission	Sick euthyroid syndrome		P-Value
	Present No. & %age	Absent No. & %age	
Readmission	2(7.4%)	17(18.1%)	0.238
No readmission	25(92.6%)	77(81.9%)	

Out of 27 patients with sick euthyroid syndrome, only 2 out of 27 (7.4%) subjects got re admitted within six months of index admission. Among the sick euthyroid

subjects 17 out of 94 (18.1%) got readmitted within six months of index admission as shown in table 12.

Correlation between incidence of sick euthyroid syndrome in acute heart failure and the risk of re-admission within 6 months of index admission was inconclusive in our study because P-value could not establish a statistical association.

Table 13. Association of SES with in-hospital mortality

In hospital Mortality	Sick euthyroid syndrome		P-Value
	Present No. & %age	Absent No. & %age	
Yes	0(0)	1(1.3%)	1.000
No	46(100%)	74(98.7%)	

Mortality was zero percentage among subjects with sick euthyroid syndrome. Only single mortality was documented among study subjects during the six months of follow-up as shown in table 13. Correlation between incidence of sick euthyroid syndrome and in-hospital mortality was inconclusive in our study because P-value could not establish a statistical association.

Discussion

Morbidity of heart failure was assessed as a token of need for prolonged hospital stay and the need for re hospitalization within six months of index admission. Previous literature review showed need for prolonged hospital stay and readmission was increased among low T3 subjects. However, such an association was inconclusive in our study, probably limited by low sample size.

Conclusion

The prevalence of Sick euthyroid syndrome was found to be 22.3% More than half the subjects (62%) admitted with acute heart failure had some form of thyroid abnormality. 33.6% were euthyroid. The duration of in-patient care required among the sick euthyroid and non-sick euthyroid category was found to be almost equal, however statistical data showed a slightly more prolonged hospital stay among sick euthyroid subjects. The mortality rate as well as re-hospitalization rate among our study subjects was very low. Thyroid function assessment and its treatment whenever indicated is of paramount importance especially among heart failure subjects.

Strengths and limitations

It is one of the few studies to be done on this topic in India especially in Kerala. Data collection using structured questionnaires was done by the clinician at the time of admission which improves the validity of the data as well as its study findings. Thyroid function tests were done using standardized instruments and standard procedures were followed while collecting samples. The mortality and morbidity within six months of enrolment is alone included in the study as the study was time bound. As our study is an observational one, no definite conclusion can be made regarding the

influence of thyroid hormone abnormalities on the outcome of acute heart failure. As the thyroid function is only one among the many factors both modifiable and non-modifiable influencing the outcome of acute heart failure, the mortality morbidity assessment may not be solemnly dependent on thyroid function. Being a single institutional study, the data might not be representative of the entire picture of the study settings and thus limiting its generalizability.

Future Scope

The prevalence of SES in heart failure varies widely across studies depending on the severity of cardiac illness and underlying comorbidities. This hormonal disturbance is believed to be an adaptive metabolic response to stress, yet persistent or severe changes have been associated with poor clinical outcomes. Although our study was not much conclusive about its role, but several studies have demonstrated that the presence of SES in heart failure correlates with higher in-hospital mortality, prolonged hospital stay, and increased risk of rehospitalization. Thus, recognizing SES in acute heart failure holds prognostic significance and may serve as an indicator of disease severity and adverse outcomes.

Statements and Declarations

Conflicts of interest

The authors declare that they do not have conflict of interest.

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