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Research Article

LOW TRIIODOTHYRONINE (T3) SYNDROME IN ACUTE HEART FAILURE AND ASSOCIATION WITH SHORT-TERM OUTCOME

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ABSTRACT

Objectives: The objectives of the study were to find an association between low T3 syndrome and short-term outcome in patients admitted with acute HF.Heart failure (HF) is a clinical syndrome caused by structural and/or functional cardiac abnormality that causes decreased cardiac output and/or elevated intracardiac pressures. The prognosis of cardiac diseases may be negatively impacted by low-T3 states and was independently linked to higher all-cause mortality in hospitalized HF patients.

Methods: 176 patients diagnosed as acute HF fulfilling inclusion criteria were enrolled. Serum fT3, fT4, and thyroid-stimulating hormone were measured. Patients were followed up and length of hospital stay, need for inotropes, mechanical ventilation, and intensive care unit (ICU) facility were compared with thyroid function tests. End points were discharge or death. Data were entered into structured pro forma and analyzed.

Results: There was a statistically significant association between need for ICU/high dependency unit (HDU) facility care and T3 status (χ^2=27.82; p<0.001). There was a statistically significant association between the need for mechanical ventilation with the levels of T3 (χ^2=16.14; p<0.001). There is a statistically significant difference in mean T3 among the patients who expired and patients who were discharged (2.31±0.74 vs. 1.71±0.66; p=0.019).

Conclusion: Low T3 correlated with a higher rate of ICU/HDU admissions (53.5% vs. 14.7%, p<0.001) and an increased need for invasive mechanical ventilation (35.6% vs. 9.3%, p<0.001). Low T3 syndrome is frequently found in patients with acute HF and is associated with a poor short-term outcome in terms of need for intensive care and mechanical ventilation.

Keywords: Low T3 syndrome, Cardiac failure, Mortality, Outcome prediction.

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INTRODUCTION

Heart failure (HF) is a clinical syndrome characterized by symptoms (dyspnea, orthopnea, and lower limb swelling) and signs (elevated jugular venous pressure and pulmonary congestion) often caused by a structural and/or functional cardiac abnormality resulting in reduced cardiac output and/or elevated intracardiac pressures [1]. Incidence of HF is rapidly growing in developed and developing countries. It is also associated with frequent hospitalizations, increased health-care expenditure and it is a major cause of morbidity and mortality worldwide [2,3].

The thyroid hormone is well known for regulating numerous bodily processes [4]. The hypothalamic-pituitary-thyroid axis is a self-regulatory circuit comprised of the thyroid gland, anterior pituitary gland, and hypothalamus. Thyroxine, also known as tetraiodothyronine (T4), and triiodothyronine are the primary hormones produced by the thyroid gland (T3). Low thyroid hormone levels, particularly low serum T3 levels, are frequently observed in patients with nonthyroidal diseases, such as cardiac disorders. In euthyroid patients with HF, changes in peripheral thyroid hormone concentration and metabolism can occur. Low-T3 (triiodothyronine) syndrome is the most common alteration of thyroid function in HF, characterized by a decrease in serum total T3 and free T3, with normal levels of thyroxine and thyrotropin [5]. These changes have primarily been attributed to a decrease in the 5'-monodeiodination of diiodothyronine and reverse triiodothyronine. Free triiodothyronine typically decreases when the total triiodothyronine concentration is significantly reduced. A common interpretation of this low-T3 syndrome is that it is an adaptive, compensatory, and advantageous response that reduces energy consumption in diseased states.

In studies of hospitalized patients with HF, low T3 syndrome was independently associated with higher all-cause mortality, an increased length of hospital stay, higher rates of intensive care unit admission and an increased need for invasive mechanical ventilation. Thyroid function test is easily available in all hospitals. By assessing fT3 status, we can predict the outcome of patients with HF and improve outcome in acute HF patients.

Objectives

The objectives of the study were to find an association between low T3 syndrome and short-term outcome in patients admitted with acute HF.

METHODS

Study design

This was a prospective observational study.

Study setting

This study was conducted at the Department of General Medicine, Government Medical College, Kottayam.

Study period

9 months.

Study population

Patients admitted in the Department of General Medicine with acute HF.

Study sample

From a hospital-based study published by Saurav *et al*. and others in The Journal of the Association of physicians in India [7], the prevalence of low T3 syndrome in HF is 38%.

Sample size, $N = \frac{4pq}{d^2}$

p = prevalence (38%)
q = 100-p (62%)
d = accepted error (20% of p = 7.6)
N = 4×38×62
$(7.6)^2$ = 163.

Study tool
Structured Pro forma.

Inclusion criteria
Patients diagnosed with acute HF, admitted to the Department of General Medicine, Government Medical College, Kottayam.

Exclusion criteria
The following criteria were excluded from the study:

- Patients with documented thyroid disease.
- Patients with documented liver disease, malignancy, chronic kidney disease, and chronic Obstructive Airway Disease.
- Patients with present or past history of trauma, brain injury within 3 months.
- Patients who had ischemic stroke, intracranial hemorrhage within 3 months.
- Patients taking medications causing thyroid dysfunction, such as glucocorticoids, amiodarone, lithium, and tyrosine kinase inhibitors.
- Pregnant patients.

Study procedure
After getting clearance from the institutional review board and written informed consent from the patient or immediate relatives, the selected patients diagnosed to have acute HF were taken for study. A history was taken, and previous records were analyzed in detail. A detailed clinical examination was done. The diagnosis of HF was made based on modified Framingham criteria. Investigations including thyroid function test, renal function test, liver function test, and electrocardiogram were done at the time or within 24 h of admission. The serum levels of thyroid hormones (fT3, fT4, and thyroid-stimulating hormone [TSH]) were measured by Chemiluminescence Immunoassay method (Beckman Coulter Access 2 Immunoassay System). A screening transthoracic echocardiographic evaluation was performed during the course of hospital stay.

The reference values for fT3, fT4, and TSH for adults at our hospital are 2.5–3.9 pg/ml, 0.6–1.1 ng/ml, and 0.34–5.2 μIU/ml, respectively.

Patients were followed up in ward/intensive care unit (ICU). Their length of hospital stay, need for inotropes, need for mechanical ventilation, and need for ICU facility were noted. End points of study were either discharge from the hospital or death of the patient.

Data management and statistical analysis
Data were entered into Microsoft excel and analyzed using IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. IBM Corp. Categorical variables were expressed as frequency (percentage) and continuous variables were expressed in mean and standard deviation. Association of T3 status, outcome variable, and T4 status with categorical variables was done using Pearson Chi-square test. Test for the association of T3 status, outcome variable, and T4 status with the number of days in ICU or hospital was assessed using Mann–Whitney U test. Factors affecting the need for mechanical ventilation were assessed using multiple logistic regression analysis. $p<0.05$ was considered the threshold for statistical significance.

RESULTS AND OBSERVATIONS

A total of 176 subjects were included in the final analysis.

Inference
Among 176 patients, 101 were males and 75 were females.

The minimum age was 15 and the maximum age was 90 years.

Maximum number of patients was in the age group of 51–60 years (35 males and 22 females).

The prevalence of low T3 syndrome was comparable across all age groups as seen in Graph 1 and Table 1.

Inference
Among 176 patients, 101 patients (57.39%) had low T3 syndrome. 75 patients had normal T3 values. Of 73 female patients, 58.9% had Low T3 syndrome. Among 103 male patients, 56.3% had low T3 syndrome, as seen in Table 2 and Graphs 2 and 3.

There was no statistical association between gender and T3 status in this population, as seen in Table 3 and Graph 4.

Inference
The mean number of days of hospital stay was 5.09 days with a standard deviation of 1.79.

65 of 176 patients were admitted to either ICU or high dependency unit (HDU). The mean number of ICU/HDU stay among all subjects was 1.00 day. Among patients who were treated in ICU/HDU, the mean number of ICU/HDU stay was 2.70 days. This is seen in Tables 4 and 5, and Graph 5.

Inference
The mean age of patients with Low T3 syndrome was 59.12, with a standard deviation of 11.908. The mean age among patients with normal T3 was 58.05 with a standard deviation of 13.828 (Table 6).

There was no association between age with the T3 status in this population.

Inference
About 53.5% of patients with low T3 syndrome required ICU/HDU admission, whereas only 14.7% of patients with normal T3 were treated in ICU/HDU.

Table 1: Age-wise distribution of T3 status

Age group (years)	Male		Female		Total	
	Normal T3, n (%)	Low T3, n (%)	Normal T3, n (%)	Low T3, n (%)	Normal T3, n (%)	Low T3, n (%)
≤30	2 (4.4)	0	3 (10)	1 (2.3)	5 (6.7)	1 (1.0)
31–40	0	5 (8.6)	-	-	0	5 (5.0)
41–50	8 (17.8)	9 (15.5)	5 (16.7)	10 (23.3)	13 (17.3)	19 (18.8)
51–60	17 (37.8)	18 (31.0)	10 (33.3)	12 (27.9)	27 (36.0)	30 (29.7)
61–70	10 (22.2)	19 (32.8)	7 (23.3)	14 (32.6)	7 (22.2)	33 (32.7)
71–80	7 (15.6)	6 (10.3)	4 (13.3)	4 (9.3)	11 (14.7)	10 (9.9)
>80	1 (2.2)	1 (1.7)	1 (3.3)	2 (4.7)	2 (2.7)	3 (3.0)
Total	45 (100.0)	58 (100.0)	30 (100.0)	43 (100.0)	75 (100.0)	101 (100.0)

T3: Thyroid gland

Table 2: Gender status in the study population

T 3 levels	Gender		Total
	Male, n (%)	Female, n (%)	
Low T3	58 (56.3)	43 (58.9)	101
Normal T3	45 (43.7)	30 (41.1)	75
Total	103	73	176

T3: Thyroid gland

Table 3: Association between the T3 status and gender

Sex of patients	T3 status		χ^2	p
	Low T3, n (%)	Normal, T3 n (%)		
Male	58 (57.4)	45 (60.0)	0.12	0.76
Female	43 (42.6)	30 (40.0)		

Pearson's Chi-square test. T3: Thyroid gland

Table 4: Description of the study population

Variable	n (%)
Gender	
Male	103 (58.5)
Female	73 (41.5)
Inotropes given	
No	158 (89.8)
Yes	18 (10.2)
Admitted to ICU/HDU	
No	111 (63.1)
Yes	65 (36.9)
Mechanical ventilation	
No	133 (75.6)
Yes	43 (24.4)
Outcome	
Discharged	167 (94.9)
Expired	9 (5.1)

ICU: Intensive care unit, HDU: High dependency unit

Table 5: Mean of different variables

Variable	Mean±SD
Age	58.66±12.73
T3	2.28±0.75
T4	0.90±0.38
TSH	2.51±1.66
Number of days in ICU/HDU	1.00±1.50
Number of days of hospital stay	5.09±1.79

ICU: Intensive care unit, HDC: High dependency unit, SD: Standard deviation, T4: Tetraiodothyronine, T3: Thyroid gland

Table 6: Comparison of mean age according to thyroid gland status

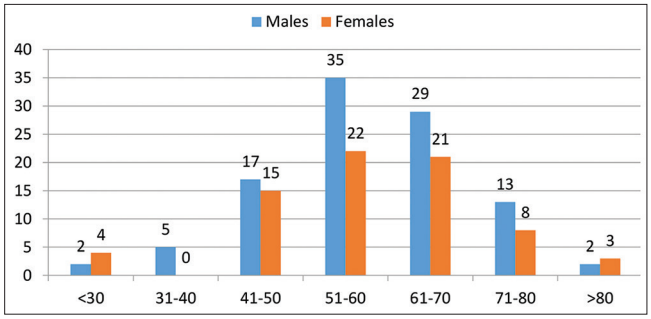
T3 status	n	Mean±SD	SEM	p
Low T3	101	59.12±11.908	1.185	0.58
Normal T3	75	58.05±13.828	1.597	

Independent t-test. SEM: Standard error of mean, SD: standard deviation, T3: Thyroid gland

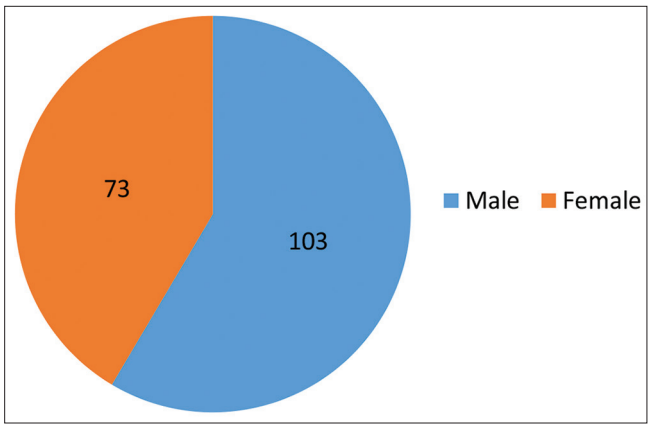
Of 65 patients who required ICU/HDU care, 54 patients (83.07%) patients had Low T3. There was a statistically significant association between ICU/HDU admission and T3 status, with a p<0.001 (Table 7).

Inference

There was no statistically significant association between T3 status and duration of stay in ICU (Table 8).



Graph 1: Age-wise distribution of study population



Graph 2: Gender distribution among study population

Inference

Among patients with low T3 syndrome, 35.6% required mechanical ventilation. Among patients with normal T3, only 9.3% required mechanical ventilation. Of 43 patients who required mechanical ventilation, 36 patients (83.7%) were from low T3 group. There was a statistically significant association between the need for mechanical ventilation with the levels of T3, with a p<0.001 (Table 9).

Of 43 patients who required mechanical ventilation, 31 patients were treated with non-invasive ventilation, and 12 patients needed invasive ventilation (Table 10 and Graph 10).

About 13.9% of patients with low T3 syndrome required inotrope support. About 5.3% of patients with normal T3 group required inotrope support. There was no statistically significant association between inotrope requirement and T3 status.

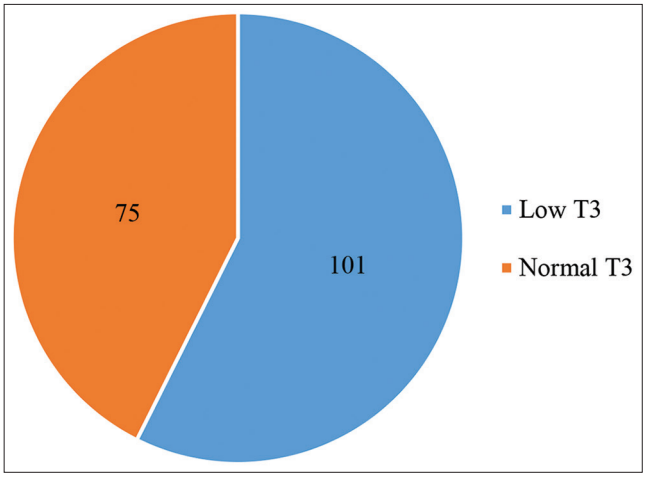
Inference

There is a statistically significant difference in mean T3 among the outcome groups. The T3 value was lower in patients who expired, the p-value being 0.019.

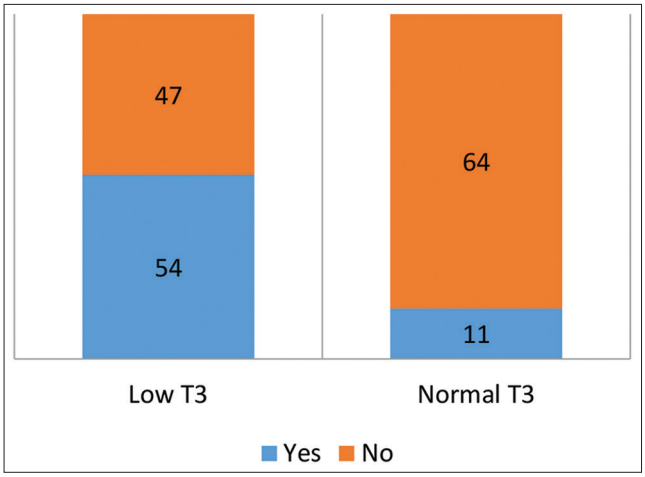
The average length of hospital stay in this study group was 5.09 days with a standard deviation of 1.79 days, which is 5.29±1.85 days in the low T3 group and 4.8±1.65 days in the normal T3 group (Table 11). The median length of hospital stay was 5 and 4 in the low T3 group and the normal T3 group, respectively. No statistical association was found between T3 status and length of hospital stay.

DISCUSSION

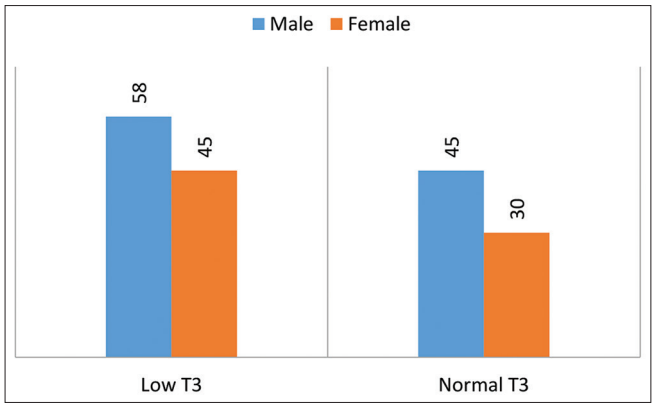
In this study, 176 patients with acute HF who met the inclusion criteria, admitted to the General Medicine department of Government Medical College Kottayam were enrolled. A diagnosis of HF was made by Framingham criteria. The thyroid profile was sent at admission.



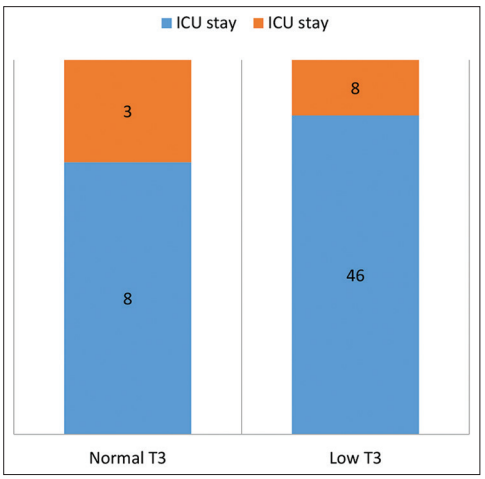
Graph 3: Prevalence of low T3 syndrome in study population



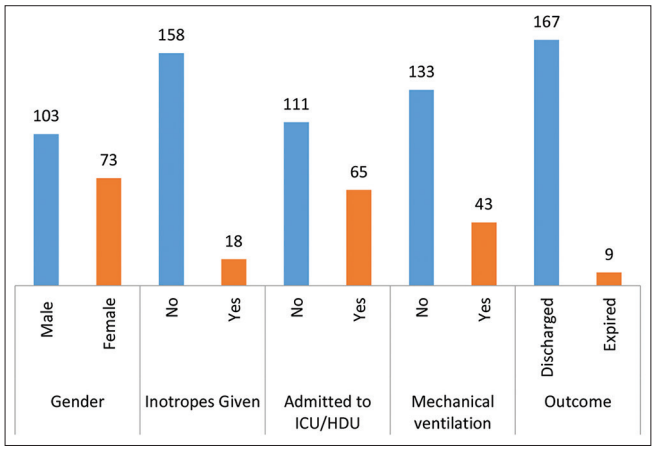
Graph 6: Admission to ICU/HDU



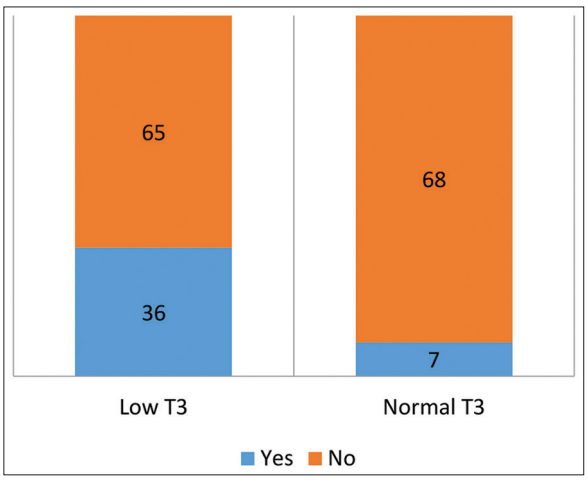
Graph 4: Association between the T3 status and gender



Graph 7: Distribution of patient according to ICU stay



Graph 5: Distribution of the total participants



Graph 8: Requirement of mechanical ventilation

The mean age of patients in this study was 58.66±12.73 years. The minimum and maximum ages were 15 and 90 years. In the study by Iervasi *et al*.,[6] the mean age of patients with HF was 66±12 years [67]. This is comparable to our study.

In this study, 58.5% were males and 41.5% were females. In the study conducted by Iervasi *et al*. [6] 56% were males, which is similar to our study.

The mean T3, T4, and TSH in our study were 2.28±0.75 pg/ml, 0.90±0.38 ng/ml, and 2.51±1.66 μIU/ml, respectively.

101 patients among 176 (57.39%) had Low T3 syndrome. Among 73 female patients, 58.9% had low T3 syndrome. Among 103 male patients, 56.3% had low T3 syndrome. In India, Saurav *et al*. [7] studied sick euthyroid syndrome in HF and found a prevalence of 38%. Sharadha *et al*. [10] found a prevalence of 31.57% low T3 syndrome in patients with chronic HF. Studies by Opasich *et al*. [5] and Kozdag *et al*. [8] observed a prevalence of 18% and 21%,

Table 7: Association between the thyroid gland status and other variables

Outcome variables	Status	T3 status		χ^2	p
		Low T3, n (%)	Normal, T3 n (%)		
Whether inotropes required?	No	87 (86.1)	71 (94.7)	3.41	0.08
	Yes	14 (13.9)	4 (5.3)		
Whether admitted to ICU/HDU?	No	47 (46.5)	64 (85.3)	27.82	<0.001*
	Yes	54 (53.5)	11 (14.7)		
Whether mechanical ventilation required?	No	65 (64.4)	68 (90.7)	16.14	<0.001*
	Yes	36 (35.6)	7 (9.3)		
Outcome	Discharged	94 (93.1)	73 (97.2)	1.61	0.30
	Expired	7 (6.9)	2 (2.7)		
Hospital stay (days)	<5	33 (50.8)	32 (49.2)	1.85	0.21
	≥5	68 (61.3)	43 (38.7)		

*p<0.05, Pearson's Chi-square test. ICU: Intensive care unit, HDU: High dependency unit, T3: Thyroid gland

Table 8: Association between T3 status and intensive care unit stay

T 3 levels	ICU stay (days)		χ^2	p
	≤3	>3		
Normal T3	8 (72.7)	3 (27.3)	1.00	0.38
Low T3	46 (85.2)	8 (14.8)		

Fisher's exact test. ICU: Intensive care unit, T3: Thyroid gland

Table 9: Comparison between types of mechanical ventilation and thyroid gland status

T 3 levels	NIV	Invasive ventilation
Low T3	26	10
Normal T3	5	2
Total	31	12

NIV: Non-invasive ventilation, T3: Thyroid gland

Table 10: Comparison of mean thyroid gland across the outcome groups

Outcome	n	Mean±SD	p
Discharged	167	2.31±0.74	0.019*
Expired	9	1.71±0.66	

*p=0.05. Independent *t*-test. SD: Standard deviation

Table 11: Length of hospital stay

T 3 levels	Mean±SD (days)	Median days
Low T3	5.29±1.85	5
Normal T3	4.8±1.65	4

SD: Standard deviation, T3: Thyroid gland

Table 12: Prevalence of low T3 syndrome among various studies

Study	Population	Country	Prevalence of low T3 syndrome (%)
Saurav *et al*., 2014 [7]	HF	India	38
Sharadha *et al*., 2018 [10]	Chronic HF	India	31.57
Opasich *et al.,* 1998 [5]	Chronic HF	Italy	18
Iervasi *et al*., 2007 [6]	Patients with heart disease	Italy	30
Present study	Acute HF	India	57.38

HF: Heart failure, T3: Thyroid gland

Table 13: Comparison of length of hospital stay

Study	Length of hospital stay	
	Low T3	Normal T3
Rothberger *et al*. [71]	11	7
Present study	5	4

T3: Thyroid gland

Table 14: Comparison of need for intensive care unit admission

Study	Requirement of ICU	
	Low T3 (%)	Normal T3 (%)
Rothberger *et al.*	31.8	16.9
Present study	53.5	14.7

ICU: Intensive care unit, T3: Thyroid gland

Table 15: Comparison of need for mechanical ventilation

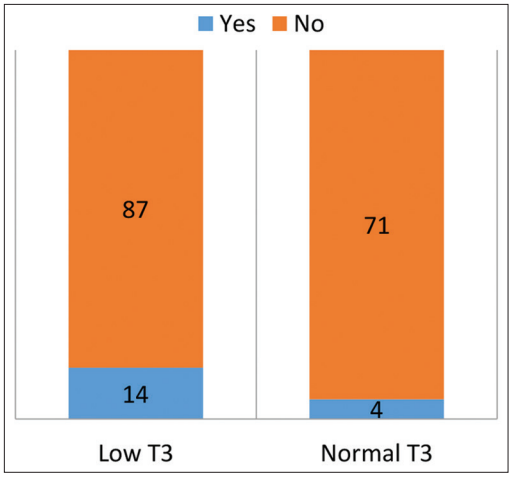
Study	Need for mechanical ventilation	
	Low T3 (%)	Normal T3 (%)
Rothberger *et al*. [71]	9.0	1.4
Zhao *et al*. [82]	18.5	1.7
Present study	35.6	9.3

T3: Thyroid gland

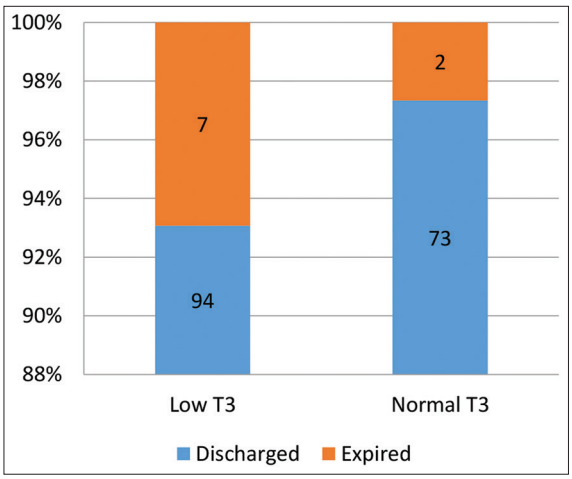
respectively. The landmark study by Iervasi *et al*. [6] involving 573 patients with heart disease found a prevalence of 30%. In a study by Zargar *et al*. [9] the prevalence of sick euthyroid syndrome in chronic non-thyroidal illness was 20.60%. This could be because our study population consisted of patients with acute HF, while the other quoted studies consisted of patients with chronic HF or both acute and chronic HF.

The mean age of patients with Low T3 syndrome was 59.12±11.908 years, whereas the mean age among patients with normal T3 was 58.05±13.828 years. There was no association between age and T3 status in this population as seen in Table 12.

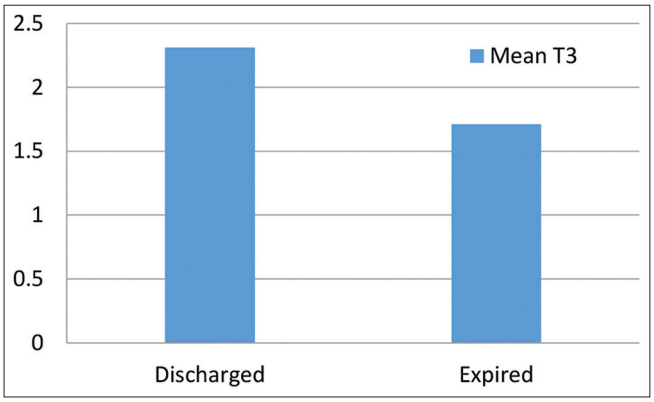
The mean number of days of hospital stay was 5.09±1.79. In a study conducted by Rothberger *et al*., low T3 correlated with an increased length of stay in the hospital (median 11 vs. 7 days, p<0.001) [11]. In our study, the median duration of hospital stay was 5 versus 4 days in low T3 group and normal T3 group. There was no statistical association between low T3 status with length of hospital stay. The mean duration of hospital stay in patient group with low T3 and normal T3 are 5.3 days and 4.8 days, respectivel (Table 13).



Graph 9: Requirement of inotropes



Graph 10: Outcome among study group



Graph 11: Mean T3 across outcome groups

About 36.9% patients were admitted to either ICU or HDU. The mean number of days of ICU/HDU stay was 2.70 days. In our study, low T3 correlated with a higher rate of ICU/HDU admissions (53.5% vs. 14.7% in low T3 group and normal T3 group, respectively, with a p<0.001). The rates of intensive care unit admission in study by Rothberger *et al.* [11] were 31.8% versus 16.9% in low T3 group and normal T3 group, respectively, with a p=0.047 [11]. This is similar to our study (Table 14).

In our study, low T3 correlated with a trend toward an increased need for mechanical ventilation (35.6% vs. 9.3% in low T3 group and normal T3 group, respectively, with a p<0.001). The rates among low T3 and normal T3 groups in the Rothberger *et al.*[11] study were 9.0% and 1.4%, p=0.056, respectively [11]. This is consistent with the results in the present study (Table 15).

About 13.9% of patients with low T3 syndrome required inotrope support, whereas 5.3% of patients with the normal T3 group required inotrope support. There was no statistically significant association between inotrope requirement and T3 status in our study.

The mean T3 levels were lower in patients who died. Similar results were reported by Pingitore *et al.* [13] in their study on risk stratification in chronic HF, who found age, male sex, NYHA class, T3 levels and obesity as significant univariate mortality predictors. In a study by Sato *et al.*, [14] low FT3 was a predictor of cardiac death (hazard ratio 1.926, 95% CI 1.268–2.927; p=0.002) and all-cause death (hazard ratio 2.304, 95% CI 1.736–3.058; p<0.001). In our study, of seven patients who expired, four were females, and three were males. No statistical association could be found out between gender and mortality prediction.

CONCLUSION

1. 57.39% of patients admitted with acute HF had low T3 syndrome.
2. 36.9% of patients were admitted to either ICU or HDU. Low T3 correlated with a higher rate of ICU/HDU admissions (53.5% vs. 14.7%, p<0.001).
3. Low T3 also correlated with a trend toward an increased need for invasive mechanical ventilation (35.6% vs. 9.3%, p<0.001).
4. The mean T3 levels were lower in patients who died.
5. No statistically significant association was noted between T3 status and length of hospital or ICU stay, and need for inotropic support.

Low T3 syndrome is frequently found in patients with Acute HF and is associated with a poor short-term outcome in terms of need for intensive care and mechanical ventilation.

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