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A Study On Low T3 Syndrome In Chronic Heart Failure- Prevalence And Prognostic Significance

Dr.S. Ashok Kumar
Professor, Department Of Medicine, Madha Medical College And Research Institute, Kovur, Chennai

***Corresponding Author:**
Dr.S. Ashok Kumar
Professor, Department Of Medicine, Madha Medical College And Research Institute, Kovur, Chennai

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Abstract

Background: In heart failure, the main alteration of the thyroid function is referred to as low-T3 (triiodothyronine) syndrome or euthyroid sick syndrome, characterized by the reduction in serum total T3 and free T3 with normal levels of thyroxine and thyrotropin. This low-T3 syndrome has commonly been interpreted as an adaptive compensatory and beneficial response that decreases energy consumption in diseased states but this view is now being challenged.

Aim Of The Study: To assess the role of T3 as an adjunct to clinical and functional parameters when estimating morbidity and mortality in patients with chronic heart failure.

Methods: This study was conducted in the department of medicine, Madha medical college and research institute, kovur, Chennai throughout 2020-2021. 100 patients with clinical evidence of heart failure were enrolled in this study after applying inclusion and exclusion criteria. All patients had documented evidence of prior myocardial infarction and were on heart failure treatment for at least one month. Informed consent was obtained from all patients. All previous clinical records of the patients were analyzed in detail. Based on the degree of effort needed to elicit symptoms patients were assigned to NYHA (New York Heart Association) class I to IV.

Results: compared to patients who are alive, left ventricular end-diastolic diameter was higher in those who died. The mean ejection fraction in dead and alive groups was 28.36 and 34.88 respectively. Persons who died had a significantly lower ejection fraction than those alive. When the mean ejection fraction was compared between patients with low total T3(T3<80 ng/dl) and normal T3, patients with low T3 had a mean ejection fraction of 29.2, and those with normal T3 levels had a mean ejection fraction of 34.78. This indicates mean ejection fraction is lower in patients with low total T3 levels. The distribution shows a trend towards lower T3 values among the deceased population compared to the patients on follow-up. The mean Total T3 values were 75.09 ng/dl (dead) and 130.23 ng/dl (alive). The association between low T3 and mortality was statistically significant. (P=0.001) In the alive group, 9.8% had low total T3 levels (< 80 ng/dl) as against 80% in those who died. The mean total T3 and free T3 levels were significantly less in dead patients. The results show a significant correlation of total T3 with ejection fraction, indicating patients who have low ejection fraction have low total T3 levels. Total T3 levels did not correlate with sex. There is a significant correlation between advancing age and lower total T3 levels.

Conclusion: Advancing age correlates with reduced total T3 levels. Total T3, ejection fraction, and age are the most important predictors of mortality in this patient population. Total T3 levels can be used as an adjunct to other parameters for risk stratification and survival estimation in chronic heart failure.

Keywords: Coronary Artery Disease, Ejection Fraction, Heart Failure, Thyroid Stimulating Hormone

Introduction

Thyroid hormone has a fundamental role in cardiovascular homeostasis, both in physiological and pathological conditions. Changes in peripheral thyroid hormone concentration and metabolism can occur in euthyroid patients suffering from heart failure.[1] In heart failure, the main alteration of the thyroid function is referred to as low-T3 (triiodothyronine) syndrome or euthyroid sick syndrome, characterized by the reduction in serum total T3 and free T3 with normal levels of thyroxine and thyrotropin. [2]This low-T3 syndrome has commonly been interpreted as an adaptive compensatory and beneficial response that decreases energy consumption in diseased states but this view is now being challenged. [3]Heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of ventricles to fill with or eject blood. Coronary artery disease accounts for a substantial portion of patients with chronic heart failure. [4] Survival is markedly shortened in patients with heart failure. The overall 5-year mortality for all patients with heart failure is approximately 50 percent and the 1-year mortality in patients with end-stage heart failure may be as high as 75 percent. [5]The role of various biological and neurohormonal factors in the risk stratification of chronic heart failure has been studied in various clinical trials. Noradrenaline**,** angiotensin II, Atrial natriuretic peptide (ANP), and Brain natriuretic peptide (BNP) are used as important prognostic markers in patients with heart failure.[6]Recent studies have explored the use of triiodothyronine levels to predict mortality in heart failure patients.[7]Studies suggest that low T3 (triiodothyronine) levels correlate with increased mortality in chronic heart failure patients and benefits can be gained from thyroid hormone supplementation.[8]

Methods: This study was conducted in the department of medicine, Madha medical college and research institute, kovur, Chennai throughout 2020-2021100 patients with clinical evidence of heart failure were enrolled in this study after applying inclusion and exclusion criteria. All patients had documented evidence of prior myocardial infarction and were on heart failure treatment for at least one month. Informed consent was obtained from all patients. All previous clinical records of the patients were analyzed in detail. Based on the degree of effort needed to elicit symptoms patients were assigned to NYHA (New York Heart Association) class I to IV.inclusion criteria: Duration of heart failure for a minimum period of one month, Left ventricle ejection fraction less than 40%.exclusion criteria: History or clinical or laboratory evidence of hypothyroidism.History or clinical or laboratory evidence of hyperthyroidism, Subclinical hypothyroidism, and Subclinical hyperthyroidism, Amiodarone therapy, History of revascularization procedures, Clinical evidence of Sepsis. A questionnaire prepared noted the duration, symptoms, and treatment of heart failure. Questions were asked about chest pain, dyspnoea, syncope, cough, smoking, and medications. A detailed physical examination was conducted to assess patients' volume status (rales, edema, jugular venous distension), weight, height, body mass index, and orthostatic blood pressure changes. Complete blood count, blood glucose, fasting serum lipid profile, blood urea, serum creatinine, and serum electrolytes were measured in all patients. Two-dimensional echocardiography was done in the cardiology department of Government General Hospital for all patients. Thyroid hormone measurements TSH, total T3, total T4, free T3, free T4 were done in all patients.

Statistical analysis: Statistical analysis was carried out for the 76 subjects (51alive,25 died). Age, sex, BMI, diabetes, hypertension, dyslipidemia, obesity, smoking, left ventricle end-diastolic diameter, NYHA class, Ejection fraction, TSH, Total T3, Free T3, Total T4, and Free T4 were analyzed. Results were expressed as Mean and Standard Deviation(SD). The significance of the difference in means between two groups was calculated using the Student t-test and the significance of the difference in proportions using the chi-square statistic. Statistical significance was taken when $p<0.05$. All variables with significant associations were entered in Cox Proportional Hazard Model for multivariate analysis with 95% confidence intervals. Pearson's correlation was used to analyze the correlation between variables that were found to be significant in multivariate analysis. All statistical analyses were performed using SPSS (statistical package for social sciences) software for windows.

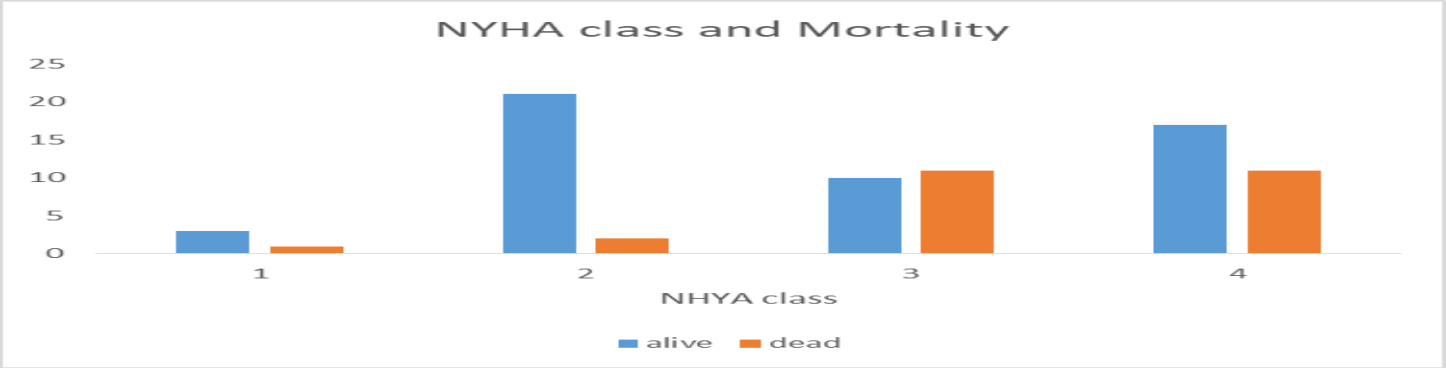
Results

Table: 1 Prevalence of low T3 levels

Total T3	N= 76	Percent with low T3
T3< 80	24	31.57
T3>/=80	52	

TABLE :1 Total T3 values of all the 76 patients were computed.24 of the 76 patients had Total T3 less than the lower limit of 80 ng/dl. The prevalence of low T3 Is found to be 31.57%. Comparison of continuous variables age, BMI, NYHA class, EF, LVEDD, and thyroid profile values was done with a student t-test. The mean age of patients in the dead group was 65.96 and 58.23 in the survived group.

Graph :1 Nyha Class And Mortality



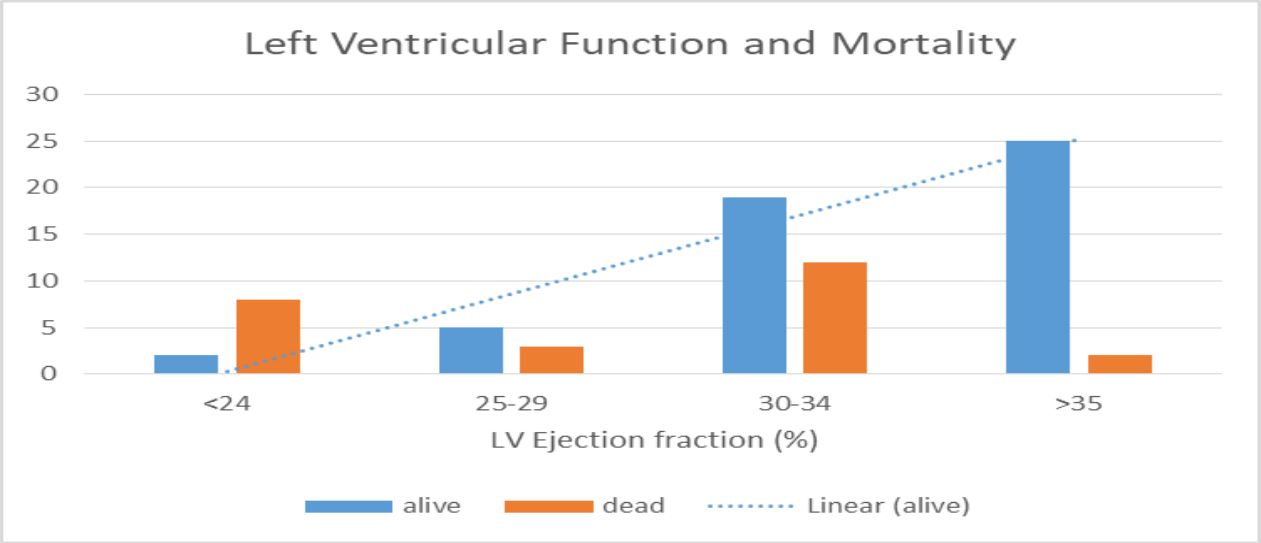
GRAPH :1 There is a significant difference in age and NYHA class between the two groups. The mean age was higher in the dead group and these patients were in worse NYHA class.

Table 2:Analysis of Echocardiographic parameters

Variable	Group	N	Mean	SD	P-value Student t-test
Ejection Fraction	Died	25	28.36	6.75	0.001 Significant
	Alive	51	34.88	5.45	
LVEDD	Died	25	64.04	5.26	0.001 Significant
	Alive	51	60.84	3.49	

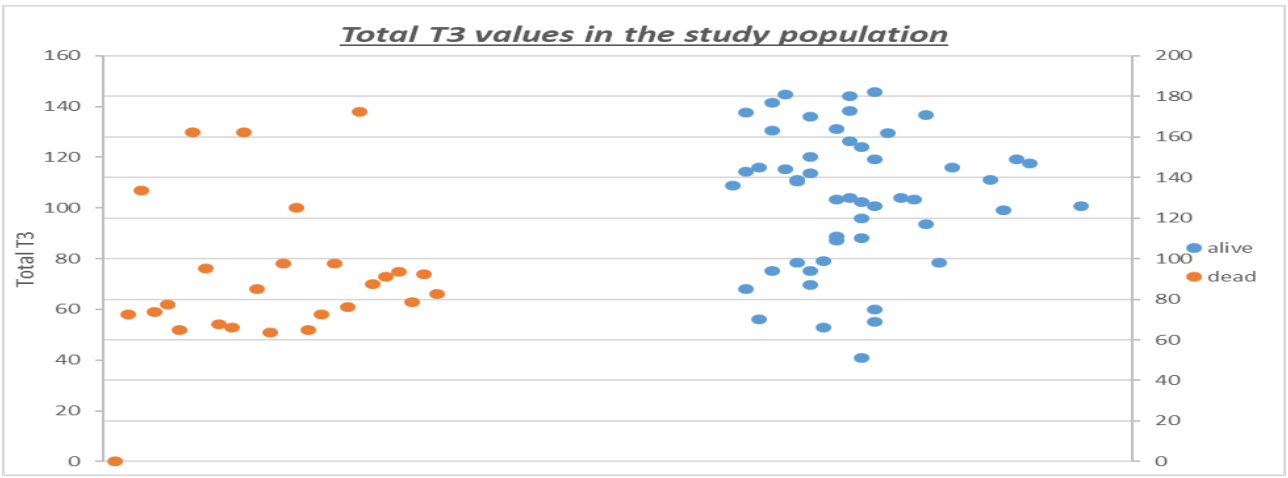
TABLE:2 Compared to patients who are alive, left ventricular end-diastolic diameter was higher in those who died. The mean ejection fraction in dead and alive groups was 28.36 and 34.88 respectively.

Graph:2 Left Ventricular Function And Mortality



GRAPH:2 Persons who died had a significantly lower ejection fraction than those alive. When the mean ejection fraction was compared between patients with low total T3(T3<80 ng/dl) and normal T3, patients with low T3 had a mean ejection fraction of 29.2, and those with normal T3 levels had a mean ejection fraction of 34.78. This indicates mean ejection fraction is lower in patients with low total T3 levels. The trend line shows a linear correlation between declining Left ventricular systolic function and mortality.

Graph :3 T3 Values In The Study Population



GRAPH :3 This scatter diagram shows the distribution of the Total T3 values (ng/dl) of our study population. The distribution shows a trend towards lower T3 values among the deceased population compared to the patients on follow-up. The mean Total T3 values were 75.09 ng/dl (dead) and 130.23 ng/dl (alive). The association between low T3 and mortality was statistically significant. (P=0.001).In the alive group, 9.8% had low total T3 levels (< 80 ng/dl) as against 80% in those who died. The mean total T3 and free T3 levels were significantly less in dead patients.

Table 3:Analysis of Total T4, Free T4 levels

	Group	N	MEAN	SD	Student t test
Total T4	**Died**	**25**	**7.21**	**1.52**	**P=0.07 Not Significant**
	Alive	**51**	**7.97**	**1.83**	
Free T4	**Died**	**25**	**13.76**	**2.67**	**P=0.26 Not Significant**
	Alive	**51**	**14.47**	**2.53**	

Mean total T4 was less in those who died but there was no statistical significance between the two groups in total T4 and Free T4 levels. Dichotomized, variables sex, hypertension, obesity, diabetes, dyslipidemia, smoking were analyzed using the chi-square test.

Table:4 Analysis of Dyslipidemia, Obesity, B-blocker use, smoking

Variable			Alive	Dead		Test value
		N	%	N	%	Chi-square test
Dyslipidemia	NO	27	53	16	64	$\chi 2=0.84$
	YES	24	47	9	36	P=0.36 NS
Obesity	NO	33	64.7	20	80	$\chi 2=1.86$
	YES	18	35.3	5	20	P=0.17 NS
B-b B-Blocker Use	NO	20	39.2	11	44	$\chi 2=0.16$
	YES	31	60	14	56	P=0.69 NS
Smoking	NO	25	49	12	48	$\chi 2=0.01$
	YES	26	51	13	52	P=0.091NS

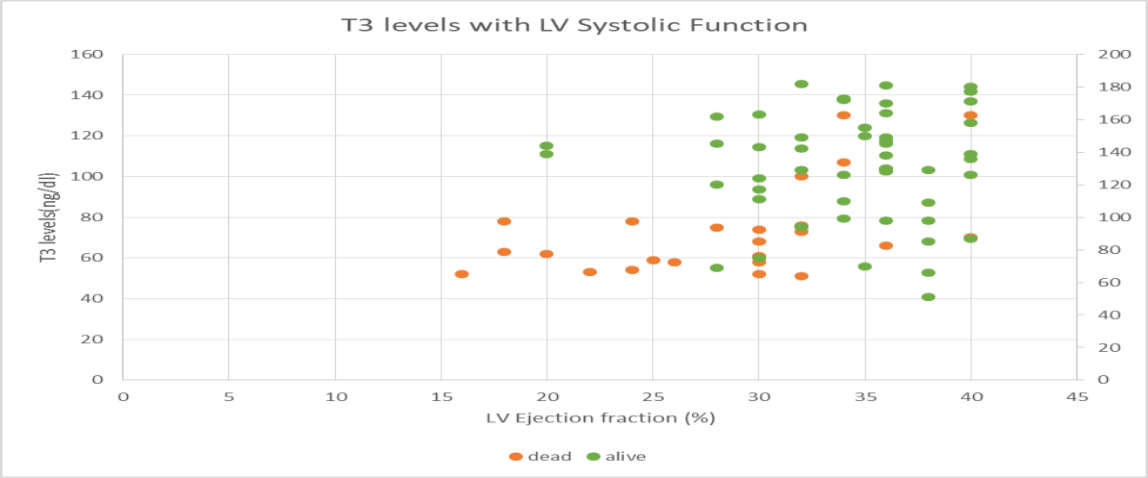
TABLE:4 Dyslipidemia, Obesity, Beta blocker use, and smoking did not influence mortality significantly. From the above analysis Age, sex, NYHA class, ejection fraction, LVEDD, Total T3and Free T3 were significantly altered in dead patients. To assess the influence of these parameters on mortality multivariate analysis was done. Because total T3 and free T3 are highly correlated we did not include free T3 in the same proportional hazard model.

Table 5: Cox proportional Hazard Model for Heart failure mortality

Variable	Significance	Odds ratio	95% CI	
			Lower	Upper
Age	.001	45.453	5.420	381.145
Sex	.045	.260	.070	.968
LVEDD	.636	.784	.286	2.148
EF	.041	2.455	1.025	6.967
Total T3	.001	19.05	4.65	111.1
NYHA	.118	1.564	.892	2.741

TABLE:5 Age, sex, EF (ejection fraction), and total T3 were significant. Association between these variables was evaluated by the Pearson product-moment correlation test.

Graph:4 T3 Levels With Lv Systolic Function



GRAPH:4 The results show a significant correlation of total T3 with ejection fraction, indicating patients who have low ejection fraction have low total T3 levels. Total T3 levels did not correlate with sex. There is a significant correlation between advancing age and lower total T3 levels. Using a cut-off total T3 level of 80 ng/dl (the lower limit of normal) two subgroups were identified and Kaplan-Meier survival analysis was compiled. Survival at 6 months in the low total T3 group was found to be less than the group with a total T3 80 ng/dl and above.

Discussion

In this study of the Indian population involving 76 patients, we evaluated the prevalence of low T3 syndrome in chronic heart failure. We found the prevalence of low T3 syndrome to be 31.57%. This is similar to one study but higher than those described in other studies. Patients with Low total T3 values (T3<80ng/dl) had a lower mean ejection fraction (29.2) than those with total T3 values of 80 ng/dl and above (34.78).[9] This observation is consistent with the earlier study by Francis GS et al, who found that patients with low T3 syndrome have lower ejection fractions. We find advancing age, male sex, higher NYHA class, high left ventricular end-diastolic diameter, lower ejection fraction, low total T3, and free T3 levels are associated with increased mortality.

The mean total T3 levels and free T3 levels were lower in patients who died.[10] Similar results were reported by Hamilton MA et al in their study on risk stratification in chronic heart failure, who found age, male sex, NYHA class, left ventricular end-diastolic diameter, ejection fraction, total T3, and free T3 levels and obesity as significant univariate mortality predictors. However, In our study, there was no significant association between obesity and mortality.[11] In a multivariate model with total T3, we find that age, male sex, ejection fraction, and total T3 are the significant predictors of increased mortality. [12]We also found a significant correlation of low total T3 levels with advancing age. However, Hansen et al reported no correlation between age and low T3 levels in a study. From our analysis, we find that age, ejection fraction, and total T3 levels are associated with increased mortality. Also, there is a significant correlation of total T3 levels with age and ejection fraction. Hence, total T3 is an important predictor of mortality, but not the only predictor. [13] Similarly, Harvey L. et al in a study on 199 chronic heart failure patients observed that Low T3 syndrome was not an independent negative prognostic factor but has a definite role when used with other parameters. In conclusion, Total T3 levels are an important parameter in survival estimation of patients with chronic heart failure and should be used along with other conventional parameters like age and ejection fraction[14,15].

Conclusion

Thyroid function tests are significantly altered in patients with chronic heart failure. The prevalence of low T3 syndrome in chronic heart failure is 31.57%. Patients with low total T3 levels have lower ejection fraction and advanced NYHA class. Advancing age correlates with reduced total T3 levels. Total T3, ejection fraction, and age are the most important predictors of mortality in this patient population. Total T3 levels can be used as an adjunct to other parameters for risk stratification and survival estimation in chronic heart failure. Our study has the following limitations. We have studied patients with chronic heart failure following myocardial infarction. We have not included patients with chronic heart failure due to other causes. We could not estimate reverse T3 levels due to economic and practical reasons. In our study, we measured the thyroid profile at the baseline and assessed its relationship to subsequent clinical events. However, if thyroid hormone levels are measured frequently, their association with outcomes can be identified accurately. Correlation with important and established biomarkers like NT- proBNP, CRP, etc was not done due to economic reasons

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