A study on prevalence and significance of low T3 syndrome in chronic heart failure

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CERTIFICATE

This is to certify that the dissertation titled **"A study on prevalence and significance of low T3 syndrome in chronic heart failure"** is the bonafide original work of DR. **JAISURESH.K** in partial fulfillment of the requirements for **M.D. Branch I General Medicine** Examination of the Tamilnadu DR. M.G.R Medical University to be held in March 2007. I forward this to the DR. M.G.R Medical University, Chennai, Tamilnadu, India.

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DECLARATION

I, DR. **JAISURESH.K**, solemnly declare that dissertation titled "**A study on prevalence and significance of low T3 syndrome in chronic heart failure**" is a bonafide work done by me at Madras Medical College & Government General Hospital, Chennai during 2004- 2006 under the guidance and supervision of Prof.Dr.D.Rajasekaran M.D

This dissertation is submitted to Tamilnadu DR. M.G.R Medical University towards part fulfillment of requirements for the award of **M.D. Degree (Branch – I) in General Medicine.**

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TABLE OF CONTENTS

ABBREVIATIONS

ACC/AHA	American college of cardiology/American heart association
CAD	Coronary Artery Disease
CHOD	CHolesterol Oxidase
ECHOES	Echocardiographic Heart Of England Sreening study
EF	Ejection Fraction
HDL	High Density Lipoprotein
HF	Heart Failure
LV	Left Ventricle
LDL	Low Density Lipoprotein
LVEDD	Left Ventricular End Diastolic Diameter
LVESD	Left Ventricular End Systolic Diameter
MONICA	Monitoring of trends in and determinants of mortality from cardiovascular disease
NHANES I	First National Health And Nutritional Examination Survey
PAP	Peroxidase,4-Aminoantipyrine and Phenol.
rT3	reverse Triiodothyronine
T3	Triiodothyronine
T4	Thyroxine
TSH	Thyroid Stimulating Hormone
TRH	Thyrotrophin releasing Hormone
TGL	Triglyceride
VLDL	Very Low Density Lipoprotein

INTRODUCTION

Thyroid hormone has a fundamental role in the 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. 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.

Heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorders that impairs the ability of ventricles to fill with or eject blood[1]. Coronary artery disease accounts for a substantial portion of patients with chronic heart failure.

Survival is markedly shortened in patients with heart failure. The over all 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[2].

The role of various biological and neurohormonal factors in risk stratification of chronic heart failure has been studied in various clinical trials. Noradrenaline,angiotensinII, Atrial natriuretic peptide (ANP) and Brain natriuretic peptide (BNP) are used as important prognostic markers in patients with heart failure[3].Recent studies have explored the use of triiodothyronine levels to predict mortality in heart failure patients.

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[4,5].

AIM OF THE STUDY

- To estimate the prevalence of low-T3 (triiodothyronine) syndrome in chronic heart failure

- To assess the role of Total T3 as an adjunct to clinical and functional parameters when estimating mortality in patients with chronic heart failure.

REVIEW OF LITERATURE

In the past decade, progress in the understanding of heart failure has proceeded at an unprecedented rate. Scientific discovery and development in fields as disparate as epidemiology and molecular biology, has provided profound insights into the mechanism and treatment methods of heart failure.

DEFINITION OF HEART FAILURE

In 1933,Thomas Lewis defined heart failure as "A condition in which the heart fails to discharge its contents adequately".

The Task Force of the European Society of Cardiology[6] in 1995 stated diagnosis of heart failure consists of "Symptoms of heart failure, objective evidence of cardiac dysfunction and response to treatment directed towards heart failure".

The most accepted and practical definition of heart failure appeared in 2001 ACC/AHA guidelines[7] for the evaluation and

management of chronic heart failure in adults, which states “Heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorders that impairs the ability of ventricles to fill with or eject blood”.

Heart failure is a clinical syndrome that is characterized by specific symptoms (dyspnea and fatigue) in the medical history and signs (edema, rales) on the physical examination. There is no single test for heart failure because it is largely a clinical diagnosis that is based on careful history and physical examination. Because not all patients have volume overload at the time of initial or subsequent evaluation the term heart failure is preferred over the older term “congestive heart failure”.

EPIDEMIOLOGY OF HEART FAILURE

The Framingham heart study[8] has been the most important longitudinal source of data on the epidemiology of heart failure. The prevalence of HF 7.4/1000 in males, 7.7/1000 in females. The annual incidence of HF per 1000 population is 2.3 in males and 1.4 in females.

The recent Hillingdon study examined the incidence of heart failure, defined on the basis of clinical and radiographic findings, with echocardiography, in a population in west London. The overall annual incidence was 0.08%, rising from 0.02% at age 45-55 years to 1.2% at age 86 years or over.

ACUTE vs. CHRONIC HEART FAILURE

Acute heart failure is defined as the rapid onset of symptoms and signs secondary to abnormal cardiac function. It may occur with or without previous cardiac disease. The cardiac dysfunction can be related to systolic or diastolic dysfunction, to abnormalities in cardiac rhythm, or to preload and afterload mismatch. It is often life threatening and requires urgent treatment.

Chronic heart failure develops and progresses slowly. LV dysfunction begins with injury or stress to the myocardium and is a progressive process. This progression leads to change in geometry and structure of LV such that the chamber dilates or hypertrophies, a process termed cardiac remodelling.cardiac remodelling contributes substantially to

progressive worsening of heart failure .The course of development of heart failure is classified into 4 stages.

STAGES OF CHRONIC HEART FAILURE[9]

STAGE A. AT HIGH RISK FOR HEART FAILURE – conditions strongly associated with development of heart failure. No identifiable structural or functional abnormalities of pericardium, myocardium or cardiac valves. No history of signs and symptoms of heart failure

STAGE B. STRUCTURAL HEART DISEASE BUT WITH OUT SIGNS AND SYMPTOMS OF HEART FAILURE

STAGE C. CURRENT OR PRIOR SYMPTOMS OF HEART FAILURE ASSOCIATED WITH UNDERLYING STRUCTURAL HEART DISEASE

STAGE D. ADVANCED STRUCTURAL HEART DISEASE AND MARKED SYMPTOMS OF HF AT REST DESPITE MAXIMAL MEDICAL THERAPY. REQUIRE SPECIAL INTERVENTIONS

ETIOLOGY OF CHRONIC HEART FAILURE

Impairment of left ventricle function accounts for majority of symptoms in heart failure. Coronary artery disease, hypertension and dilated cardiomyopathy accounts for substantial proportion of heart failure.valvular heart disease and anemia are common causes of HF in Indian population. Arrhythmias, pericardial diseases, shunts and thyrotoxicosis are other less common causes.

World wide CAD accounts for two thirds to three fourths of the causes of HF. In NHANES I epidemiological follow-up study[10] coronary artery disease was the major cause of HF in 61.1% of patients. The Glasgow group of the MONICA study and the ECHOES Group have found that coronary artery disease is the most powerful risk factor for impaired left ventricular function AND HF.

CORONARY ARTERY DISEASE AND CHRONIC HEART FAILURE

Several factors contributing to LV dysfunction and hence symptoms of chronic heart failure in coronary artery disease. Almost 50% of patients surviving myocardial infarction develop heart failure.

Loss of functioning myocytes and myocardial fibrosis following acute myocardial infarction leads to LV remodeling and chamber dilatation. Significant atherosclerotic disease in coronary arteries other than the infarct-related artery and neurohormonal activation lead to progressive dysfunction of the remaining viable myocardium. In addition recurrent myocardial infarction may produce future deterioration of LV function.

Exertion superimposes ischemia on the ventricle with irreversibly damaged myocardium, which may cause prolonged systolic dysfunction that persists even after the ischemic insult itself has resolved. This phenomenon is termed exercise-induced "stunning,"[11] and has been shown to be associated with progression of LV dysfunction.

Myocardial "hibernation."[12] refers to adaptive response to sustained reduction in myocardial blood flow, in which the level of tissue perfusion is sufficient to maintain cellular viability but insufficient for normal contractile function, further compromising LV function.

The baroreceptor mediated activation of sympathetic nervous system[13] that occurs with ventricular dysfunction leads to vasoconstriction, tachycardia, increased contractility, increased preload and after load. Increased local and systemic levels of norepinephrine induce apoptosis and is directly toxic to the myocytes.

The activity of renin angiotensin aldosterone system is increased in patients with heart failure. Raised angiotensin II and aldosterone levels have a mitogenic effect on cardiac myocytes with resultant LV remodeling.Chronic neurohormonal activation affects myocyte growth, interstitial connective tissue, myocardial energy utilization, and receptor regulation further detoriating LV function.

SYSTOLIC AND DIASTOLIC HEART FAILURE

In chronic ischemic heart disease systolic heart failure is caused by both the chronic loss of contracting myocardium secondary to prior myocardial infarction and the acute loss of myocardial contractility induced by transient ischemia. Diastolic heart failure is due to ventricle's reduced compliance caused by replacement of normal, distensible

myocardium with nondistensible fibrous scar tissue and by acute reduction of diastolic distensiblity during ischemia.

The principle manifestation of systolic heart failure is due to inadequate cardiac output or salt and water retention or both. Diastolic heart failure leads to elevated ventricular filling pressures leading to pulmonary and systemic venous congestion.

ECHOCARDIOGRAPHY IN CHRONIC HEART FAILURE

The ACC/AHA guidelines recommend that, two-dimensional echocardiography should be performed during initial evaluation of patients presenting with HF to assess LV ejection fraction, LV size, wall thickness and valve function. It improves diagnostic accuracy and guides treatment of heart failure[14]. Recent studies support the use of echocardiography as a screening tool for heart failure in high risk patients[15].

LV systolic function can be assessed by M-mode, 2-D and Doppler techniques.M-mode gives excellent resolution and measurement of LV dimensions and wall thickness.

2-D technique is used to measure LV volumes and ejection fraction. The LV is divided into 16 segments and an assessment of regional wall motion is made. A segments systolic motion[16] is classified as

- Normal
- Hypokinetic (reduced movement)
- Akinetic (absent movement)
- Dyskinetic (movement in wrong direction)
- Aneurysmal (out pouching of all layers of the wall)

The echocardiographic evidence of regional wall motion abnormalities has been used in clinical diagnosis of coronary artery disease[17]. Presence of frank scars, aneurysm and any truly normally functioning segments point to the diagnosis of ischemic LV dilatation and dysfunction.

Doppler echo is useful in estimating the severity of mitral regurgitation and to measure pulmonary artery pressure using the gradient of tricuspid regurgitation.

Coronary artery disease is the most common condition in which systolic and diastolic dysfunction coexists. Functional capacity appears related not only to systolic function, but also to diastolic function[18]. M-mode techniques have been used to record the rate of relaxation of ventricular cavity. Doppler echo[19] currently is the primary technique used for evaluating ventricular diastolic function. With normal pressures the early diastolic mitral velocity (E) exceeds the following atrial systole or late mitral (A) velocity (E/A ratio greater than 1). Decreased LV relaxation due to diastolic dysfunction decrease in E velocity and increase in A velocity. The E/A ratio is less than 1 and the isovolumic relaxation time (IVRT) is prolonged.

Ejection Fraction (EF) measured by echocardiography is the most important measure of LV systolic function. Though MUGA scan can measure Ejection Fraction more accurately, the ability of echocardiography to measure valvular and wall motion abnormalities makes it a class I (definite evidence that it is useful and beneficial) investigation in initial evaluation of HF.

Studies involving chronic heart failure use reduced ejection fraction as definite evidence of LV dysfunction. EF of less than 45% is used as a cut off in most of these studies.

RISK STRATIFICATION IN CHRONIC HEART FAILURE[6]

Risk stratification is prudent to determine the mortality and morbidity profile of patients with HF. It helps to identify patients who is at low risk and therefore can be managed medically. Invasive procedures should be reserved for patients at high risk of mortality.

The following parameters are strongly associated with increased mortality in chronic heart failure and are recommended in risk stratification.

- Advanced age
- Low serum sodium
- VO_2 max (mL/kg per min <10–14)
- Low LV ejection fraction[20]
- Resuscitated sudden death

- NYHA functional Class III–IV
- Persistent low BP
- High serum BNP[30,21]
- Increased left ventricular volumes
- High serum creatinine
- High serum bilirubin

Studies show that Low body-mass index, Broad QRS[22], T-wave alternans[23], Low heart rate variability, Low 6 min walking ability, High left ventricular filling pressure, Restrictive mitral filling pattern[24], Impaired right ventricular function, High serum uric acid [25],high plasma Interleukin –6[26], high plasma Oxidised LDL[27] Low cardiac index, High resting heart rate and High serum norepinephrine[28] portend bad prognosis in these patients. Recently Homocysteine[29]Levels are found to be associated with Increased risk of HF.

The inherent limitations associated with these factors necessitate the use of more than one factor in prognostication of chronic HF. Predictability and cost efficacy concerns have inculcated

further studies in this area. Recently the prognostic role of T3 in this population is being explored by various studies.

THYROID HORMONE & HEART

Thyroid hormone increases cardiac contractility directly and indirectly by increasing peripheral oxygen consumption and substrate requirements.

Triiodothyronine decreases systemic vascular resistance by dilating the resistance arterioles of the peripheral circulation. The vasodilation is due to a direct effect of triiodothyronine on vascular smooth-muscle cells that promotes relaxation. Thyroid hormone increases blood volume. Thyroid hormone also stimulates erythropoietin secretion. The combined effect of these two actions is an increase in blood volume and preload, which further increases cardiac output[31].

Predictable changes in myocardial contractility and hemodynamics occur across the entire spectrum of thyroid disease. Hyperthyroidism is characterized by increased cardiac contractility, cardiac

output and high output failure. Hyperthyroidism induced sustained sinus tachycardia or atrial fibrillation further reduces ventricular contractility[32]. Experimental studies have shown that there is increased expression of beta 1 adrenergic receptors and enhanced cathecholamine sensitivity in hyperthyroidism. Hypothyroidism is associated with diastolic hypertension and decreased contractility of myocardium. Hypothyroidism can lead to severe, progressive systolic dysfunction and increased chamber diameter/wall thickness ratio despite a reduction in cardiac mass[33.] There is often pericardial effusion but rarely produces any symptoms.

Subclinical hypothyroidism is diagnosed when serum TSH is high and both T4 and T 3 are normal. Studies indicate that Subclinical hypothyroidism is associated with impaired vasodilatation , which can be corrected with thyroxine therapy[34]. Subclinical hyperthyroidism is diagnosed when serum TSH is low and both T4 and T 3 are normal. There is increased prevalence of atrial fibrillation and increased cardiovascular mortality[35] in subclinical hyperthyroidism. In contrast Low T3 syndrome is diagnosed when TSH is normal and T3 levels are low.

MECHANISM OF ACTION

Triiodothyronine is the active form that enters the myocyte. In the myocyte, triiodothyronine enters the nucleus and binds to nuclear receptors that then bind to thyroid hormone response elements in target genes and regulates transcription of these genes including those for Ca^{2+}-ATPase[36] and phospholamban[37] in the sarcoplasmic reticulum, myosin, β-adrenergic receptors, adenylyl cyclase, guanine-nucleotide–binding proteins, Na^{+}/Ca^{2+} exchanger, Na^{+}/K^{+}–ATPase, and voltage-gated potassium channels[u]. In the absence of triiodothyronine, the receptors repress genes that are positively regulated by thyroid hormone. Studies have shown that thyroid hormone can regulate the genetic expression of its own nuclear receptors within the cardiac myocytes.

Thyroxine (T4), which is derived solely from the thyroid gland, normally constitutes the greatest volume of serum thyroid hormone. Triiodothyronine (T3), which is three to five times more potent than T4, is produced both by the thyroid gland and by peripheral conversion of T4 to T3. Conversion involves peripheral monodeiodination of thyroxine in tissues such as heart, liver, kidney, and gut mucosa by the

type I deiodinase. T_3 induces expression of type I deiodinase[38]. The type II deiodinase provides intracellular triiodothyronine in specific sites such as central nervous system and pituitary[39].In addition, T4 is converted to reverse T3 (rT3), a metabolically inactive thyroid hormone, by 5-deiodinase.

LOW T3 SYNDROME

The terms sick euthyroid syndrome, nonthyroidal illness syndrome, euthyroid sick syndrome (ESS) and low T3 syndrome are used interchangeably.

The term low T3 syndrome or sick euthyroid syndrome is defined as “The transient changes in serum thyroid hormone levels as well as the alterations in thyroid hormone metabolism induced by systemic illnesses in patients without concurrent hypothalamic, pituitary or thyroid diseases, and does not imply thyroid hormone status”.

The syndrome has been described in various illnesses like

- Chronic kidney disease[40]
- Tuberculosis, respiratory failure[41]

- Heart failure
- Acute myocardial infarction[42]
- Cardiopulmonary bypass
- Starvation
- Sepsis
- Burns
- Trauma
- Surgery
- Malignancy
- Bone marrow transplantation[43]

The frequency of varies from 20 to 50%. Frequency depends on the severity of illness than on the type of illness. The highest incidence occurs in the most severely ill group.

The syndrome affects both sexes equally and affects people at all ages. Because of the increased incidence of chronic illness at advanced ages the syndrome is more common in elderly age groups.

There is no specific imaging study to diagnose low T3 syndrome. Thyroid sonogram, thyroid uptake scan and thyroid biopsy have

no role in the diagnose of this syndrome. There is no typical histological finding in thyroid biopsies.

THYROID PROFILE IN LOW T3 SYNDROME

Thyroid hormone estimation is the only test to diagnose low T3 syndrome. The most common[44] hormone pattern in sick euthyroid syndrome is a decrease in total T3 and free unbound T3 levels with normal levels of T4 and TSH. Reverse T3 levels are increased.

As the severity of the sick euthyroid syndrome increases, both serum T3 and T4 levels drop[45] and gradually normalize as the patient recovers. TSH is affected in variable degrees, but, in the overwhelming majority of patients, TSH is in normal range. In severe, critical illness, some patients have reduced T4 levels.

PATHOPHYSIOLOGY OF LOW T3 SYNDROME.

The following mechanisms are implicated in the pathogenesis of low T3 syndrome.

1. Impaired Peripheral deiodination of T4 to T3 secondary to decreased activity of type I deiodinase enzyme, which deiodinates T4 to T3. Normally 20% of T3 production comes from thyroidal secretion and 80% from peripheral deiodination of T4. Though production of T3 by thyroid gland is normal, peripheral production of T3 is decreased. Production of rT3 is unchanged, while its clearance is diminished leading to raised rT3 levels.

2. Increased levels of Cytokines interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-alpha and interferon-beta decrease the activity of type I deiodinase and the binding capacity of T3 nuclear receptors.

3. Presence of binding inhibitor in the serum and in body tissues that might inhibit uptake of thyroid hormones by cells or prevent binding to nuclear T3 receptors, thus inhibiting the action of the hormone.This inhibitor is associated ith the nonesterified fatty acid (NEFA) fraction in the serum.

4. Serum factors, such as bilirubin, NEFA, furanoic acid, hippuric acid, and indoxyl sulphate, present in various non thyroidal illness, have been shown to inhibit transport of thyroid hormones.

5. Diminished T4 has been proposed to be due to low T4 binding globulin caused by protease cleavage at inflammatory sites in acute inflammatory conditions. Another hypothesis for the cause of disproportionately low serum T4 concentrations in patients with low T3 syndrome is the presence of abnormal serum binding due to desialation of T4 binding globulin.

6. Decreased nocturnal TSH surge ,blunting of TSH response to exogenous TRH and Decreased TRH gene expression[46].

MORTALITY/MORBIDITY IN LOW T3 SYNDROME

Mortality and morbidity depend on the severity and, possibly the duration of the underlying non-thyroid illness. The magnitude of the thyroid function test result abnormalities depend on the severity, rather than the type of illness.

LOW T3 SYNDROME AND CHRONIC HEART FAILURE

The cardiovascular system is one of the most important systems on which the thyroid hormones act. Animal studies show that Cardiac myocyte gene expression and cardiac contractility are reduced in low T3 syndrome and improve significantly with T3 treatment[24.] The LV content of the SERCA2 mRNA is decreased significantly in the low-T_3 syndrome[47]. It is not known whether low-T_3 syndrome is the cause or the effect of chronic heart failure[48].However majority considered Low T3 syndrome as an adaptive factor in minimizing the catabolic phenomena of heart failure.

Studies indicate that there is a poor relation between measures of cardiac performance and the symptoms of heart failure. Patients with very low ejection fraction may be asymptomatic, where as patients with preserved ejection fraction may develop severe symptoms. This discordance has necessitated research into the role of non-cardiac factors in determining clinical outcomes of heart failure. The existence of these non-cardiac factors may explain why similar pharmacological measures may not produce the same degree of response

in all patients. Thyroid hormone due to its fundamental role in cardiovascular homeostasis has been a major area of research in this context. Low T3 syndrome occurs early in chronic heart failure than in other chronic illnesses[49].

The landmark study by Iervasi et al concluded that low T3 concentrations are a strong, independent predictive marker of poor prognosis in heart disease. Studies indicate the prevalence of low T3 syndrome in heart failure between 18 % and 20 %. Recently pingitore et al[50] have shown that alterations in thyroid profile occur in asymptomatic and mildly symptomatic patients with LV dysfunction.

Opasich C et al[51] in a large representative population of moderate to severe heart failure found that sick euthyroid patients have higher NYHA class, weight loss and low insulin levels. Serum norepinephrine levels and atrial natriuretic peptide levels were significantly higher in these patients.

Decreased FT3 levels and FT3/FT4 ratios correlate with reduced ejection fraction and increased chamber

dimension[52]..Shimoyama et al, demonstrated lower FT3 values in heart failure patients with ventricular tachycardia [53]. A low free T3 index/reverse T3 ratio was associated with higher right atrial, pulmonary artery and pulmonary capillary wedge pressures and lower ejection fraction, cardiac index, serum sodium, albumin and total lymphocyte count[54.] It is not known whether sick euthyroid syndrome contributes to the development of heart failure or is only an attendant syndrome.

LOW T3 SYNDROME THERAPEUTIC ASPECTS

Limited numbers of studies have determined the effects of thyroid hormone supplementation in low T3 syndrome. In 23 patients with advanced heart failure Hamilton et al found a single intravenous dose of 58 µg of triiodothyronine resulted in an increase in cardiac output and a decrease in systemic vascular resistance two hours after administration, without any evidence of myocardial ischemia, rhythm disturbances, or other untoward effects. High dose of triiodothyronine decreased systemic vascular resistance and increased cardiac output within hours after coronary artery bypass grafting[55].

Moruzzi et al[56], in a placebo controlled study of 20 patients with chronic heart failure found that treatment with 0.1 mg of thyroxine daily for 12 weeks improved exercise performance, increased the cardiac index, and decreased systemic vascular resistance.

Psirropoulos, D et al have found exercise training, through a wide variety of mechanisms, can normalise free triiodothyronine levels reverses sick euthyroid syndrome in heart failure[57].

3,5 doiodothyropropionic acid (DITPA) is a thyroid hormone analog with relative selectivity for a form of the thyroid hormone receptor in the liver. DITPA improves systolic as well as diastolic function[58] and is presently under trials.

Whether thyroid hormones should be used in all patients with low T3 syndrome remains controversial due to lack of large scale controlled trials. Safety and hemodynamic benefits of longer infusions, combined infusion with inotropic agents, oral triiodothyronine replacement therapy, and new triiodothyronine analogs have to be studied in future.

MATERIALS AND METHODS

STUDY DESIGN

Prospective study

SETTING

All patients were prospectively enrolled from the Cardiology and Internal medicine department of Government General Hospital, chennai.3.

SAMPLE

145 patients with clinical evidence of heart failure were enrolled in this study. 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.

INCLUSION CRITERIA

1. Duration of heart failure for a minimum period of one month
2. Left ventricle ejection fraction less than 45%
3. Left ventricle end diastolic diameter more than 56 mm

EXCLUSION CRITERIA

1. History or clinical or laboratory evidence of hypothyroidism
2. History or clinical or laboratory evidence of hyperthyroidism
3. Subclinical hypothyroidism and Subclinical hyperthyroidism
4. Amiodarone therapy
5. History of revascularisation procedures
6. Clinical evidence of Sepsis
7. Evidence of renal failure
8. Any other severe systemic illness

PROCEDURE

A questionnaire prepared noted the duration, symptoms and treatment of heart failure. Questions were asked in relation to chest pain, dyspnoea, syncope, cough, smoking and medications. 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.

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 and 2 hour post prandial), 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 all patients. All patients had an ejection fraction of less than 45 percent and left ventricular end diastolic diameter greater than 56 mm.

Thyroid hormone measurements TSH, total T3, total T4, free T3, free T4 were made in all patients in the same fasting morning sample. All the above data were obtained between two to five days of enrollment in the study.

INSTRUMENTS

1. ELECTROCARDIOGRAM:

All patients had 12 lead ECG, which was reviewed for evidence of atrial enlargement, ventricular

hypertrophy, evidence of antecedent myocardial infarction and conduction blocks

2.CHEST X RAY:

Chest x ray posteroanterior view was done in all patients to note pulmonary congestion, pleural effusion and to estimate cardio thoracic ratio.

3. ECHOCARDIOGRAPHY:

M-mode echocardiography was used to assess left ventricle dimensions. Left ventricle internal dimension in end systole (LVESD) and end diastole (LVEDD) are measured at the level of mitral valve leaflet tips in parasternal long axis view. Measurements are taken from the endocardium of the left surface of the interventricular septum to the endocardium of the left ventricle posterior wall. In adults the normal range of LVEDD is 3.5 to 5.6 centimeter. The normal range of LVESD is 2 to 4 centimeter[59].

2-D echo imaging in apical 4 chamber, parasternal long axis and parasternal short axis views were used to assess ventricular and valvular movement. Ejection fraction was

estimated using Simpson's method[60]. In this method multiple short axis views are taken along the LV long axis. Endocardial border is traced accurately and left ventricle cavity is divided into 20 slices of known thickness and diameter (D). Left ventricle end diastole and Left ventricle end systole volumes are estimated.

Area of each slice=22/7 $(D/2)^2$

Volume of each slice = area X thickness.

LV volume= volume of each slice X number of slices (20)

$$EF = \frac{\text{(Left ventricle end diastole volume - Left ventricle end systole volume) X 100}}{\text{Left ventricle end diastole volume}}$$

LABORATORY METHODS

Fasting plasma glucose was measured using glucose oxidase and pyruvate oxidase methods from overnight fasting sample and results were read by autoanalyser.2 hr postprandial glucose was measured 2 hrs after routine morning breakfast.

From patients height and weight body mass index (BMI) was calculated using the formula weight in kilograms

divided by square of height in meters. Serum cholesterol (enzymatic oxidase-peroxidase method),

Serum HDL (polyethylene glycol-CHOD-PAP method) Triglycerides (enzymatic calorimetric method) were measured using Erba XL 300 autoanalyser. Serum LDL was calculated using Friedewald's formula[61].

LDL-C = Total cholesterol-TGL/5 If TC less than 400 mg/dl.

TSH, Total T3, Free T3, Total T4 and Free T4 were measured by chemiluminescent immuno assay (CLIA) method. The normal values of our laboratory were

TSH: 0.35 to 4 mIu/L, Total T3: 80 to 200 ng/dl,

Free T3: 2.3-4.2 pg/ml, Total T4: 4.5-12 microgram/dl, and

Free T4 7.5 to 18 pg/ml.

DEFINITIONS:

1.Newyork Heart Association classification of heart failure[62]

Class I No limitation: ordinary physical exercise does not cause undue fatigue, dyspnoea, or palpitations

Class II Slight limitation of physical activity: comfortable at rest but ordinary activity results in fatigue,

palpitation or dyspnoea

Class III Marked limitation of physical activity: comfortable at rest but less than ordinary activity results in symptoms.

Class IV Unable to carry out any physical activity without discomfort: symptoms of heart failure are present even at rest with increased discomfort with any physical activity

2.DYSLIPIDEMIA[63]

Any one of

- Serum total cholesterol >/= 240 mg/dl
- Serum HDL </= 40 mg/dl
- Serum triglycerides >/= 200 mg/dl
- Serum LDL >/= 160 mg/dl (ATP III guidelines)

3.DIABETES MELLITUS[64]

1. Plasma glucose of 126mg/dl or greater after overnight fasting
2. Post prandial Plasma glucose of 200 mg/dl or greater
3. Symptoms of DM with random glucose 200 mg/dl or greater

4.SYSTEMIC HYPERTENSION

Based on JNC 7[65] classification systolic BP of

140 mm Hg and above and diastolic BP of 90 mm Hg and above was defined as systemic hypertension.

5.OBESITY

Obesity is defined as body mass index more than 30 $kg/m^{2.}$

FOLLOW UP

Based on exclusion criteria 44 patients were excluded during initial evaluation. Follow up of 101 patients began when thyroid hormone levels were measured. Data were obtained during the scheduled monthly visits. 24 patients were lost during follow up period.

25 patients died during the follow up period of 24 months. Of the 25 patients, 15 patients died due to progressive heart failure, arrythmia, cardiac arrest or myocardial infarction.3 patients had sudden death outside hospital. The cause of death in the other 7 patients could not be ascertained as some did not seek medical attention or hospital records during the time of death could not be obtained. 51 patients survived the 24-month period.25 patients were lost during the follow up period. At the end of the

follow up period characteristics of the all-cause mortality of the died group and the survived group were compared and analysed.

STATISTICAL ANALYSIS

Statistical analysis was carried out for the 76 subjects (51 alive, 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 analysed.Results were expressed as Mean and Standard Deviation(SD). The significance of difference in means between two groups was calculated using student t test and the significance of difference in proportions using 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. Pearsons correlation was used to analyse 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	18.24
T3>/=80	52	

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 18.24%.

Comparison of continuous variables age, BMI, NYHA class, EF, LVEDD and thyroid profile values was done with student t test. The mean age of patients in died group was 65.96 and 58.23 in the survived group.

Table 2

Comparison of Age, BMI and NYHA class

variable	Group	Number	Mean	SD	P value Student t test
Age	Died	25	65.96	4.18	0.001 Significant
	Alive	51	58.23	6.07	
BMI	Died	25	26.87	2.86	0.43 NS
	Alive	51	27.44	3.04	
NYHA Class	Died	25	3.32	0.8	0.02 Significant
	Alive	51	2.8	0.98	

NS- Not Significant

P value less than 0.05 is considered statistically significant. Values are rounded up to two decimals. SD denotes standard deviation.

There is significant difference in age and NYHA class between the two groups. The mean age was higher in the died group and these patients were in worse NYHA class.

Table 3

Analysis of Echocardiography 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	

Compared to patients who are alive, left ventricular end diastolic diameter was higher in those who died. The mean ejection fraction in died and alive groups were 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.

Table 4

Analysis of TSH, Total T3, Free T3 levels

	Group	N	MEAN	SD	Student t test
TSH	Died	25	2.81	0.83	P=0.51 NS
	Alive	51	2.68	0.86	
Total T3	Died	25	75.09	25.64	P=0.001 Significant
	Alive	51	130.23	33.39	
FreeT3	Died	25	2.04	0.85	P=0.001 Significant
	Alive	51	3.35	0.67	

In 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 died patients.

Table 5

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 NS
	Alive	51	7.97	1.83	
Free T4	Died	25	13.76	2.67	P=0.26 NS
	Alive	51	14.47	2.53	

NS- Not Significant

Mean total T4 was less in those who died. 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 analysed using chi-square test.

Table 6

Sex characteristics

Variable		Alive		Died		Test value
		N	%	N	%	Chi-square Test
Sex	Male	32	62.7	22	88	$\chi 2=4.57$ P=0.03 Significant
	Female	19	37.3	3	12	

22 (28.94%) of the 76 analysed were females. Males accounted for 88% of those who died. There exists a statistically significant difference in mortality between male and female sex.

Table 7

Analysis of BMI, Diabetes, Hypertension

Variable		Alive		Dead		Test value
		N	%	N	%	Chi-square test
BMI	<25	16	31.4	6	24	$\chi 2=0.44$ P=0.51 NS
	>/=25	35	68.6	19	76	
DM	NO	32	62.7	15	60	$\chi 2=0.05$ P=0.81 NS
	YES	19	32.3	10	40	
SHT	NO	26	51	15	60	$\chi 2=0.55$ P=0.45 NS
	YES	25	49	10	40	

NS- Not Significant

Presence of diabetes, systemic hypertension or BMI>/= 25 were not significantly different in those who died, compared to those who survived.

Table 8

Analysis of Dyslipidemia, Obesity,B-blocker use, smoking

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

NS- Not Significant

Dyslipidemia, Obesity, B-blocker use, 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 died 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 9

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

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

Table 10

Association of total T3 with EF, Age, Sex

Variable		EF	Age	Sex
	Pearson Correlation. r (2 tailed)	0.405	-0.346	0.054
Total T3	Significance	<0.001 Significant	0.002 Significant	0.641 NS
	N	76	76	76

NS- Not Significant

Correlation is significant at 0.01 level (2-tailed).

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 significant correlation between advancing age and lower total T3 levels.

Using a cutoff 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 24 months in low total T3 group was found to be less than the group with total T3 80 ng/dl and above.

Table 11

Analysis of follow up period

	Survival	N	Mean	Std. Deviation	Student t-test
Months	Alive	51	24.00	.000	P=0.001 Significant
	Died	25	12.80	5.315	

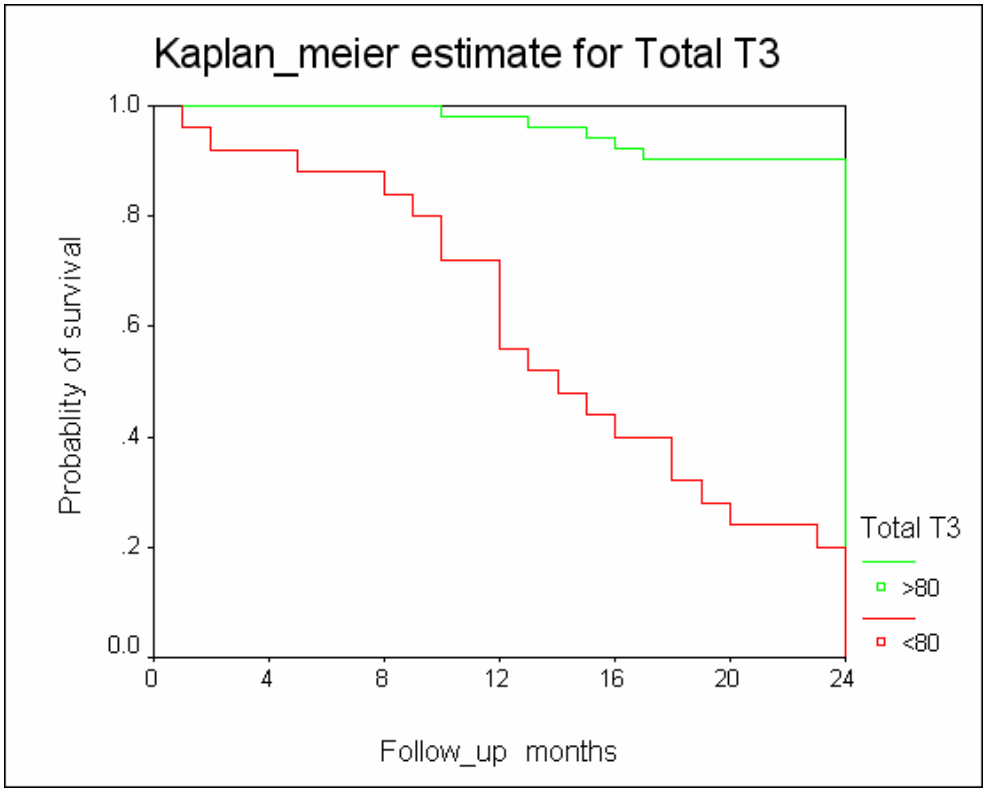
There was statistical significance in the follow up period. The median survival was 14 months (95% confidence interval (CI): 9-19 mths).

Table 12

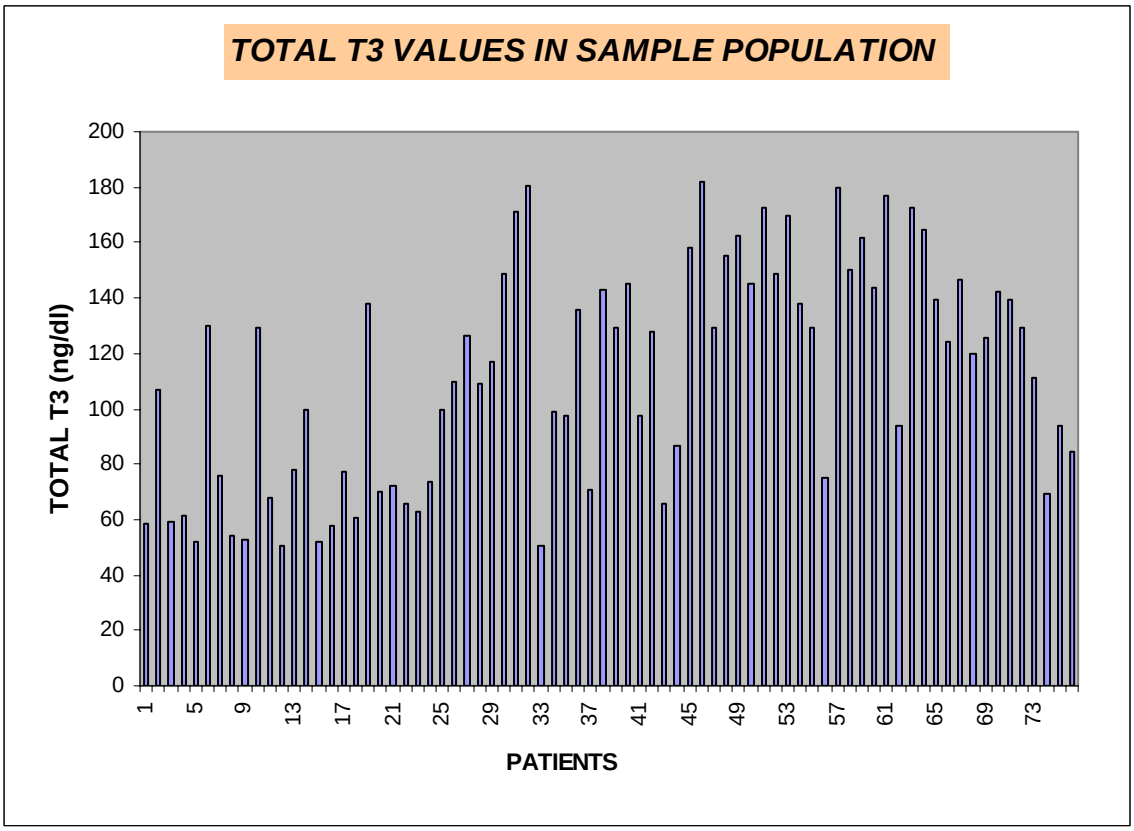
Analysis of median survival in months

Group	Median survival	95% CI
Alive	24	22-24
Dead	14	9-19

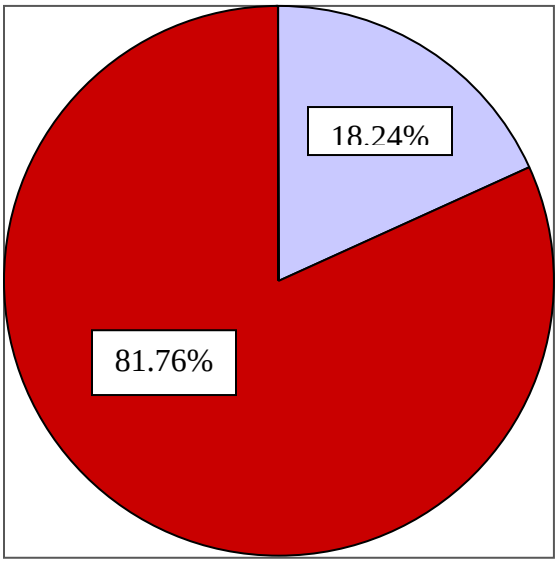
Kaplan-Meier 24-month survival curves for all cause mortality in two sub groups identified according to total T3 cutoff value of 80 ng/dl.



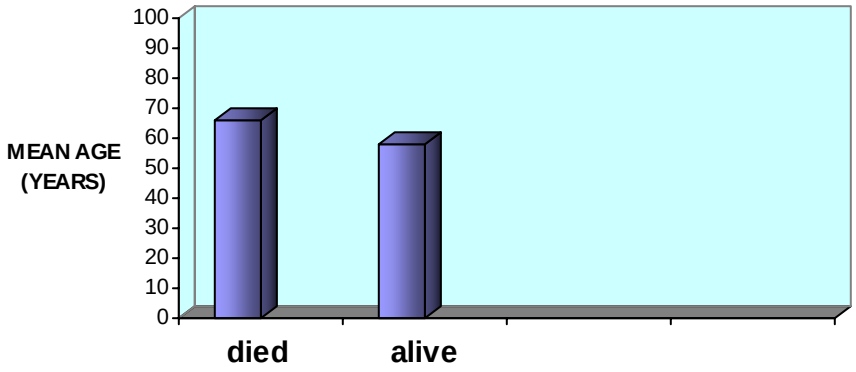
CHARTS



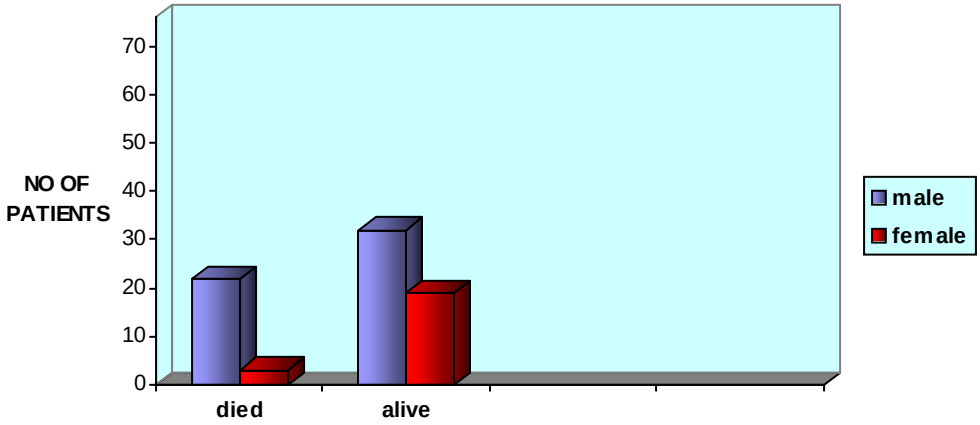
PREVALENCE OF LOW T3 SYNDROME-18.24%



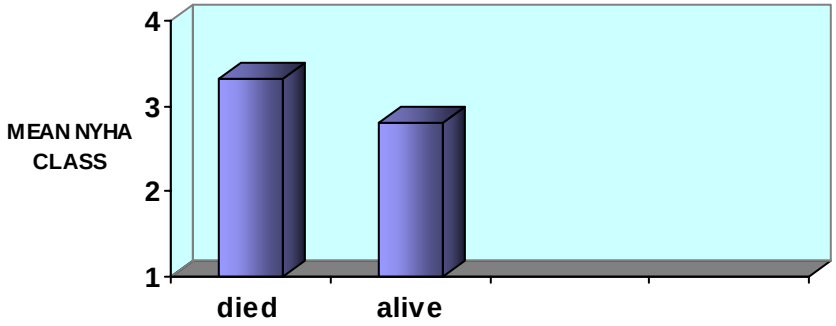
AGE DISTRIBUTION OF THE SAMPLE POPULATION



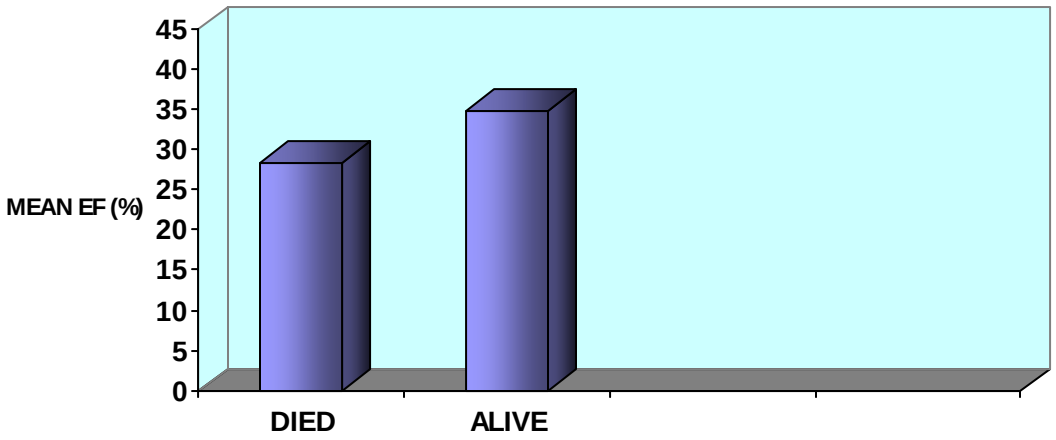
SEX DISTRIBUTION OF THE SAMPLE POPULATION



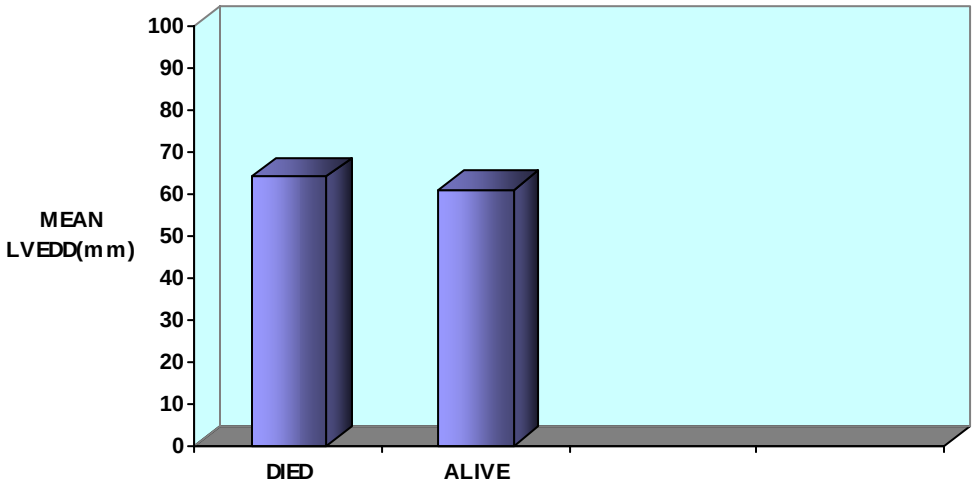
MEAN NYHA CLASS OF THE SAMPLE POPULATION



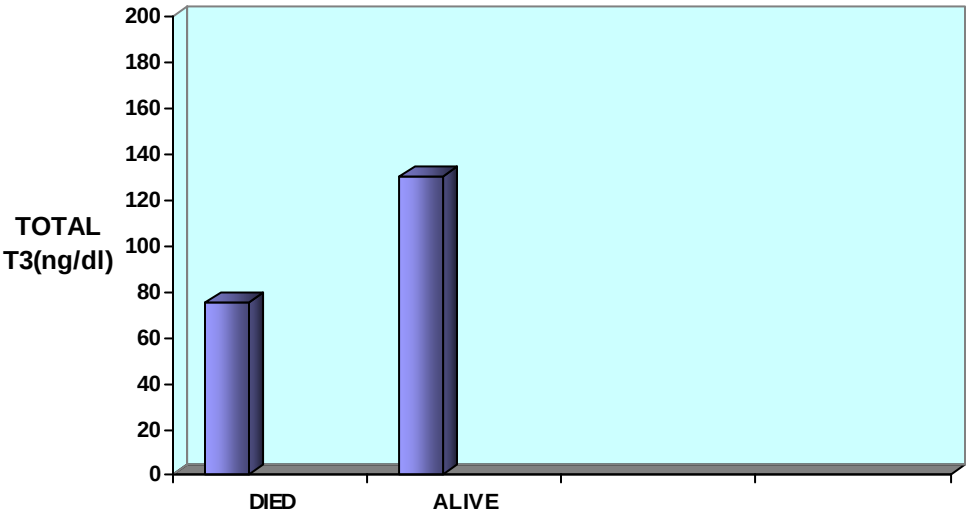
MEAN EJECTION FRACTION (EF)OF SAMPLE POPULATION

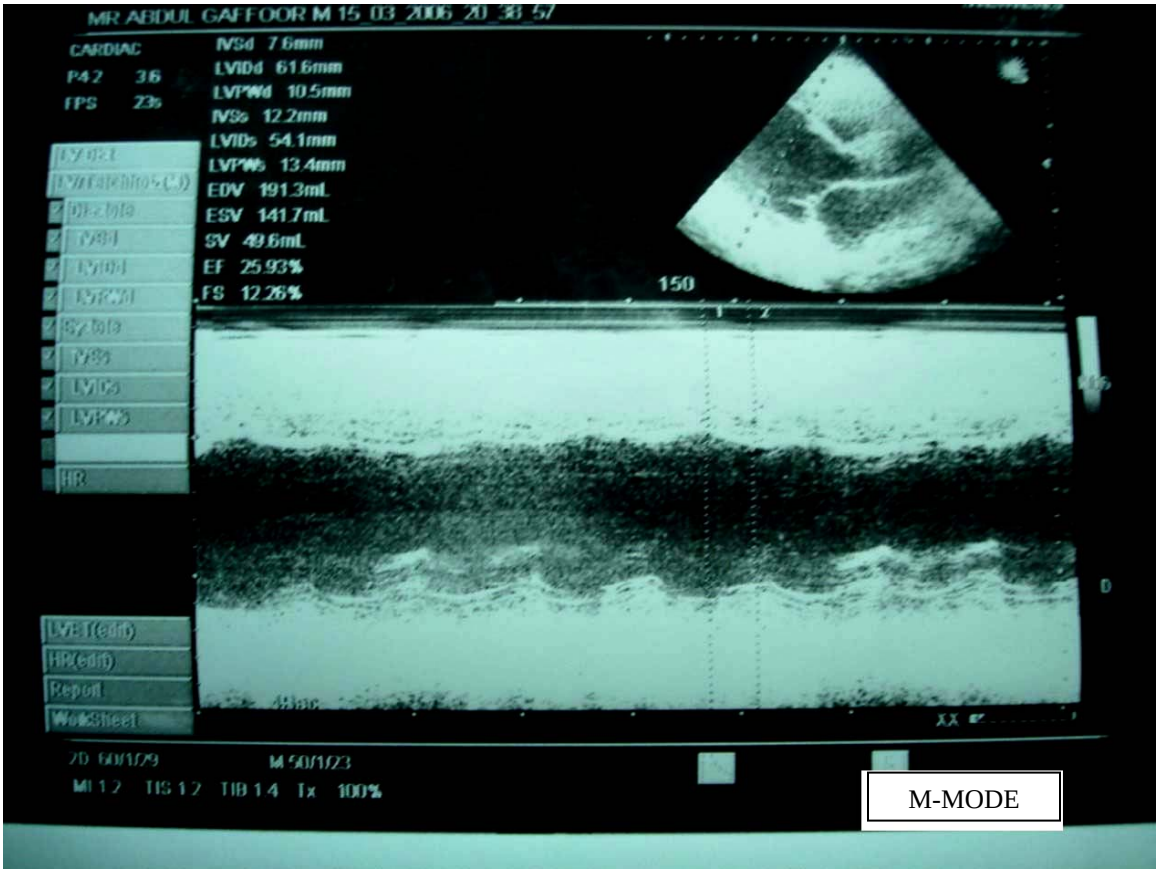


MEAN LEFT VENTRICULAR END DIASTOLIC DIAMETER OF THE SAMPLE POPULATION



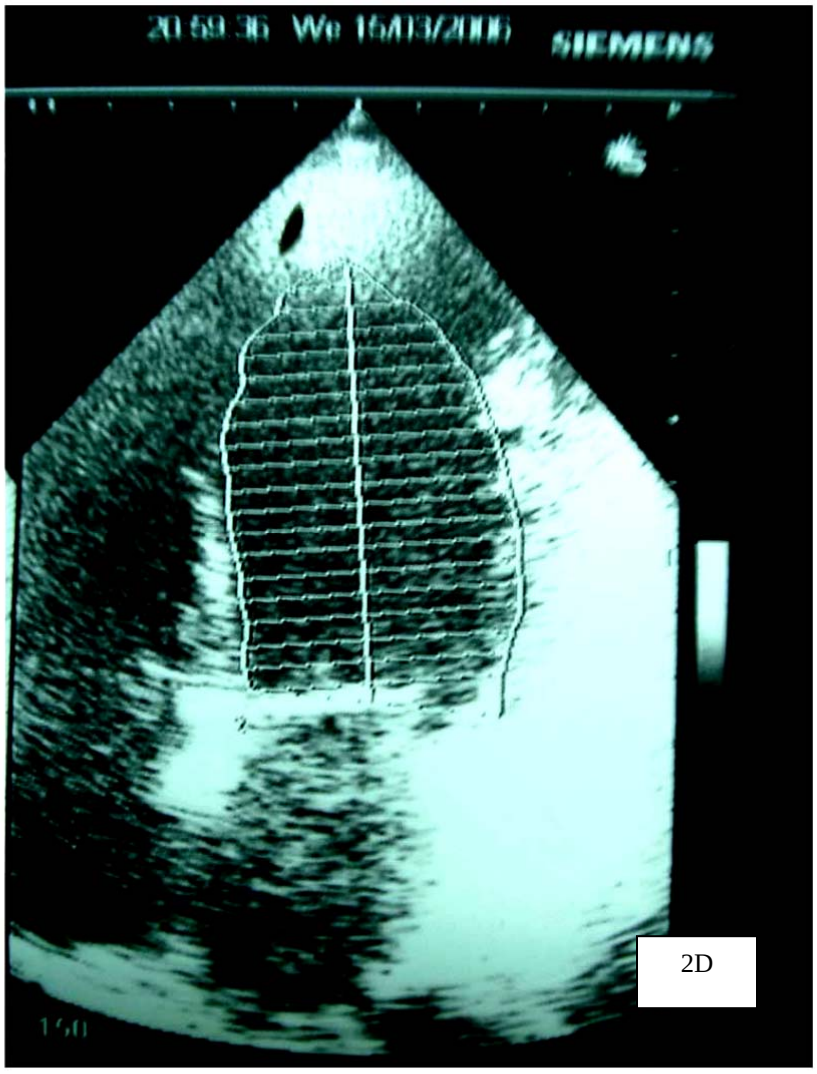
MEAN TOTAL T3 VALUES OF THE SAMPLE POPULATION





M-MODE

M MODE ECHO MEASUREMENT OF LV DIMENSION



2D ECHO SIMPSON'S METHOD FOR EJECTION FRACTION

DISCUSSION

In this study of 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 18.24%. This is with in the range as described in other studies. Studies by Opasich et al[51] and Kozdag et al[52] observed a prevalence of 18% and 21% respectively. The landmark study by Iervasi et al[66] involving 573 patients with heart disease found a prevalence of 30%. In India Zargar et al[67] studied sick euthyroid syndrome in chronic non-thyroidal illness and found a prevalence of 20.60%

STUDY	POPULATION	COUNTRY	PREVALENCE OF LOW T3 SYNDROME
Opasich et al	Chronic Heart Failure	Italy	18%
Iervasi et al	Patients with heart disease	Italy	30%
Zargar et al	Chronic non thyroid illness	India	20.60%
This study	Chronic Heart Failure	India	18.24%

Patients with Low total T3 values (T3<80ng/dl) had lower mean ejection fraction (29.2) than those with total T3 values of 80 ng/dl and above (34.78). This observation is consistent with the earlier study by Kozdag et al, who found that patients with Low T3 syndrome have lower ejection fraction.

In univariate analysis, We find advancing age, male sex, higher NYHA ciass, 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. Similar results were reported by Pingitore et al in their study on risk stratification in chronic heart failure, who found age, male sex, NYHA ciass, 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.

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. In comparison, the study by Alessandro et al reported male sex, ejection fraction and total T3 as the multivariate predictors of increased mortality. We find advancing age is also a significant multivariate predictor of increased mortality, in contrast to the study by Pingitore et al[68].

We found a significant correlation of low total T3 levels with ejection fraction, indicating that patients who have low ejection fraction have low total T3 levels. Similarly Kozdag G et al found a significant correlation between low T3 values and reduced ejection fraction. This is in contrast to the study by Pingitore et al who did not find any correlation between low total T3 and ejection fraction.

We also found a significant correlation of low total T3 levels with advancing age. However, Pingitore et al reported no correlation between age and low T3 levels in a study.

From our multi variate analysis, we find that age, ejection fraction and total T3 levels are associated with increased

mortality. Also, there is 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. Similarly, Opasich 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.

There is considerable diversity of opinions as to Whether T3 levels alone can be used to estimate mortality or not. Studies by Pingitore et al and Iervasi et al found T3 levels are independent predictors of mortality in patients with chronic heart failure. But Opasich et al and in this study we find that Total T3 is significant but not the only parameter that estimates mortality.

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.

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 practical reasons. In our study we measured thyroid profile at the base line and assessed its relationship to subsequent clinical events. However if thyroid hormone levels are measured frequently, its association with outcomes can be identified accurately.

CONCLUSIONS

- Thyroid function tests are significantly altered in patients with chronic heart failure
- The prevalence of low T3 syndrome in chronic heart failure is 18.24%
- Patients with low total T3 levels have lower ejection fraction
- 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.

SCOPE FOR FUTURE STUDIES

- Large-scale studies are needed to evaluation of the role of thyroid hormone supplementation in chronic heart failure. If beneficial results could be demonstrated this could be a cost effective measure to reduce the high mortality associated with this condition.
- Frequent estimating thyroid hormone levels at various stages of heart failure can help in better understanding of the role of thyroid hormone in cardiovascular homeostasis.

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PROFORMA

Study on prevalence and significance of low T3 syndrome in chronic heart failure

NAME:

AGE:

SEX:

OCCUPATION:

HEIGHT (METERS):

WEIGHT (Kg):

BODY MASS INDEX (Kg/m^2):

HISTORY OF PRESENTING ILLNESS:

1.DYSPNOEA	YES/NO
2.ORTHOPNEA	YES/NO
3.PND	YES/NO
4. FATIGUE	YES/NO
4.ANGINA	YES/NO
5.SYNCOPE	YES/NO
6.CYANOSIS	YES/NO
7.PALPITATIONS	YES/NO
8.COUGH	YES/NO
9.EXPECTORATION	YES/NO
10.PEDAL EDEMA	YES/NO

PAST HISTORY:

1.DIABETES	YES/NO (HOW MANY YEARS)
2.HYPERTENSION	YES/NO (HOW MANY YEARS)
3.MYOCARDIAL INFARCTION	DATE THROMBOLYSIS/PCI DURATION OF HOSPITALIZATION
4.ARRYTHMIAS	YES/NO
5.AMIODARONE	YES/NO (HOW MANY YEARS)
6.BETA-BLOCKER	YES/NO (HOW MANY YEARS)
7.ACE INHIBITOR	YES/NO (HOW MANY YEARS)
8.SMOKING	YES/NO (HOW MANY YEARS)
9.THYROID ILLNESS	YES/NO (HOW MANY YEARS)
10.ALCOHOL	YES/NO (HOW MANY YEARS)

11.ANY OTHER DRUGS/REMEDIES

GENERAL EXAMINATION:

- CONSCIOUSNESS
- PALLOR
- TEMPERATURE
- CYANOSIS
- PEDAL EDEMA
- ICTERUS
- THYROID SWELLING

PULSE RATE: BLOOD PRESSURE:(STANDING&SUPINE)

JVP: TEMPERATURE :

SYSTEMIC EXAMINATION:

CARDIOVASCULAR SYSTEM:

MURMURS: YES/NO
LVH: YES/NO
RVH: YES/NO
S3: LV/RV YES/NO
NYHA CLASS (I-IV):

RESPIRATORY SYSTEM:

CREPITATIONS: YES/NO
PLEURAL EFFUSION: YES/NO

ABDOMEN

ASCITES: YES/NO
HEPATOMEGALY: YES/NO

CENTRAL NERVOUS SYSTEM:

INVESTIGATIONS:

1. COMPLETE BLOOD COUNT
   - HEMOGLOBIN
   - TOTAL COUNT
   - DIFFERENTIAL COUNT
   - ESR
   - PLATELET COUNT

2. BLOOD UREA

3.BLOOD GLUCOSE FASTING 2hr POST PRANDIAL

4.SERUM CREATININE

5.SERUM ELECTROLYTES

6. FASTING SERUM
CHOLESTEROL
TRIGLYCERIDES
LDL
VLDL

7.SERUM PROTEIN TOTAL
ALBUMIN
GLOBULIN

8.URINE ANALYSIS

9. CHEST X RAY CTR PLEURAL EFFUSION

10.ELECTROCARDIOGRAM
RATE
RHYTHM
P WAVE
P-R INTERVAL
QRS AXIS
QRS MORPHOLOGY
T WAVE
OTHERS

11.ECHOCARDIOGRAPHY
LEFT VENTRICLE END DIASTOLIC DIAMETER(LVEDD)
LEFT VENTRICLE END SYSTOLIC DIAMETER (LVESD)
EJECTION FRACTION (EF %)
LEFT ATRIAL ENLARGEMENT
MITRAL REGURGITATION
WALL MOTION ABNORMALITY
PULMONARY ARTERY PRESSURE
PERICARDIAL EFFUSION

12. THYROID PROFILE
TSH
TOTAL T3
FREE T3
TOTAL T4
FREE T4

FOLLOW UP:

VISIT NUMBER:
COMPLAINTS:
DATE OF DEATH:
CAUSE OF DEATH:

MASTER CHART

	DIED	AGE	S	BMI	DM	HT	SM	TC	TG	HDL	LDL	B-B	EDD	EF	TSH	T T3	FT3	TT4	F T4	NYHA	Follow up
1	karruppan	66	1	23.2	0	0	1	260	211	36	217	1	58	30	3.2	58	1.7	6.2	11	4	11
2	chinnaiah	68	1	27.9	0	1	1	145	150	44	115	0	66	34	2.2	107	3.4	7.9	15	3	15
3	kuppan	72	1	26.4	1	1	1	246	264	50	189	1	65	25	3.8	59	1.6	6.5	13	4	18
4	govindan	76	1	29	0	0	1	180	176	42	141	1	58	20	2.9	62	1.6	9.6	17	4	14
5	selvan	62	1	30.4	1	1	0	221	268	40	214	0	59	16	3.5	52	1.6	6.1	12	2	6
6	duraisamy	68	1	23.3	1	0	1	165	154	46	123	1	60	40	2.5	130	3.9	5.9	9.8	3	23
7	chellappan	66	1	26.2	0	0	0	190	190	42	152	0	66	32	1.9	76	2.2	7.3	14	4	12
8	kaliyaperumal	63	1	29.3	0	0	1	136	154	55	105	1	69	24	3.3	54	1.7	5.8	12	3	9
9	rajamanikkam	68	1	30.8	1	1	1	179	169	48	145	1	75	22	3.6	53	1.4	7.6	16	4	7
10	kabilan	64	1	27.5	1	1	1	298	210	24	256	0	58	34	3.3	130	3.9	9.5	17	3	16
11	thomas	66	1	26	0	1	0	195	162	45	163	1	65	30	2	68	1.6	6.2	11	4	11
12	ismail	63	1	25.4	0	0	1	187	153	42	156	1	67	32	3.5	51	1.1	5.9	13	2	13
13	alla baksh	64	1	22	1	1	0	194	146	47	165	0	64	24	1.5	78	2.2	8.6	18	3	12
14	karmegam	62	1	28.4	0	0	1	176	196	50	137	1	60	32	3	100	2.7	5.3	12	4	9
15	stalin	62	1	31	1	0	1	178	198	42	138	1	61	30	3.8	52	1.4	7.9	15	3	17
16	ravi	59	1	27.1	0	1	0	234	290	20	176	0	64	26	3.7	58	1.6	7.6	15	4	18
17	issac	70	1	26.3	1	0	1	178	155	48	147	0	76	18	2.6	78	2.2	7.9	15	3	4
18	chandran	63	1	22.6	0	0	0	169	189	43	131	1	58	30	3	61	1.5	6.9	15	3	9
19	mayilsamy	69	1	26.7	0	1	1	290	198	28	250	1	57	34	3.1	138	3.9	6.9	15	1	15
20	ranganathan	67	1	23.5	0	0	0	149	150	49	119	0	62	40	1.1	70	1.5	8.4	16	3	16
21	selvam	69	1	26	1	0	0	187	166	44	154	1	63	32	0.9	73	1.9	5.3	11	4	9
22	rajaram	57	1	27	0	0	0	197	154	50	166	0	64	28	2.8	75	2.1	7.2	14	3	14
23	kanaga	66	2	32	0	1	0	190	310	35	128	1	66	18	3.8	63	1.1	11	18	4	2
24	dhanam	69	2	26	0	0	0	190	156	55	159	0	74	30	2.5	74	1.9	5.8	11	4	20
25	mariyammal	70	2	23.8	1	0	0	186	180	48	150	0	65	36	2.6	66	1.7	9.1	17	3	15

	ALIVE	AGE	S	BMI	DM	HT	SM	TC	TG	HDL	LDL	B-B	EDD	EF	TSH	TT3	FT3	TT4	F T4	NYHA	followup
1	muthulaksmi	59	2	31	0	1	0	265	220	35	210	0	57	34	3.6	110	3.3	6.5	11.9	4	24
2	muniammal	60	2	33	0	1	0	186	154	58	155	1	59	40	3.5	126	3.6	5.4	9.5	2	24
3	kanagammal	57	2	26	1	0	0	241	266	40	188	1	60	38	3.3	109	3.2	7.6	15.2	3	24
4	rajathi	64	2	26	0	1	0	310	298	26	250	1	56	30	2.4	117	3.5	9.6	16.2	4	24
5	sundari	71	2	28	0	0	0	234	290	20	176	1	59	32	1.9	149	4	6.1	13.4	4	24
6	papathi	64	2	28	0	1	0	198	189	54	160	1	66	40	3.3	171	3.7	12	17.6	2	24
7	lakshmi	53	2	31	0	0	0	296	180	40	260	0	67	36	3.6	181	3.9	7.3	14.3	1	24
8	seethalakshmi	59	2	23	1	1	0	192	198	48	152	1	58	38	3.6	51	1.6	5.4	9.6	4	24
9	rajammal	56	2	31	0	0	0	260	165	45	227	1	60	34	0.9	99	3.1	12	17.6	2	24
10	shanthamani	65	2	31	1	0	0	250	150	40	220	1	68	36	2.6	98	2.8	11	16.9	4	24
11	sorna	49	2	26	0	1	0	230	190	35	192	0	56	40	3.1	136	3.1	6.2	13.9	2	24
12	jothi	51	2	25	0	1	0	190	150	41	160	1	58	35	2.4	70	2	6.6	12.5	2	24
13	kannagi	50	2	23	0	0	0	154	146	48	125	1	59	30	3.2	143	3.4	6.6	14.7	4	24
14	gethalakshmi	63	2	32	1	1	0	190	256	45	139	0	58	32	0.8	129	3.7	12	15.5	2	24
15	rose	66	2	29	1	0	0	187	146	42	158	1	60	36	1.3	145	3.8	7.9	15.7	3	24
16	anushammal	54	2	31	0	0	0	290	198	30	250	1	61	38	0.8	98	3.3	7.6	14.9	2	24
17	kuppammal	59	2	27	1	1	0	181	175	42	144	0	58	36	3.2	128	3.7	5.8	7.8	3	24
18	natarajan	56	1	32	0	0	1	210	220	45	166	0	57	44	2.2	66	1.8	11	17.2	1	24
19	kaman	55	1	31	1	1	1	243	197	40	104	1	60	40	3.8	87	2.7	10	15.2	4	24
20	rajan	58	1	25	0	1	1	174	187	50	137	0	66	42	2.9	158	3.9	8.4	14.6	2	24
21	subramani	60	1	24	1	0	1	260	168	36	226	1	63	32	3.5	182	4	5.3	7.6	3	24
22	chellan	62	1	23	0	1	0	190	169	30	156	0	61	36	2.4	130	2.9	9.1	14.7	2	24
23	kasi	59	1	25	1	0	1	186	198	43	146	1	61	35	1.9	155	3.7	11	17.5	4	24
24	kannan	52	1	31	0	1	0	210	159	44	178	0	57	30	3.4	163	4.2	5.8	12.6	2	24
25	balasubramani	51	1	24	0	0	1	190	167	45	157	0	59	28	3.6	145	3.4	9.5	12.9	4	24

1-yes
2-no
S = sex,1=male, 2= female

	ALIVE	AGE	S	BMI	DM	HT	SM	TC	TG	HDL	LDL	B-B	EDD	EF	TSH	T T3	F T3	TT4	F T4	NYHA	follow up
26	ajithdas	50	1	31	1	1	0	245	240	35	197	1	60	34	2.2	172	3.8	8.7	16.9	2	24
27	arumugam	60	1	25	1	0	1	300	198	25	260	1	66	42	2	149	3.7	6.8	12.2	4	24
28	pandurangan	55	1	25	0	0	1	176	164	54	143	1	60	36	3.1	170	4	7.4	15.9	2	24
28	sheikh	54	1	24	0	1	1	230	178	40	194	0	58	36	2.3	138	4.1	6.9	14.6	1	24
30	rangasamy	58	1	27	0	1	1	224	159	45	192	1	61	42	3.3	130	3.9	9.5	17	2	24
31	sundaram	60	1	26	1	0	1	187	104	40	166	1	61	30	2.8	75	1.9	8.7	16.6	3	24
32	etti	58	1	26	0	1	0	197	137	50	170	0	60	44	3.6	180	3.4	5.9	8.4	2	24
33	rajan	55	1	30	0	1	1	166	178	36	131	1	57	35	3.9	150	3.8	6.1	14.7	3	24
34	raghavan	61	1	31	0	0	1	290	298	24	231	1	59	28	2.9	162	3.5	6.6	15.5	4	24
35	sundaram	53	1	31	1	1	1	220	146	30	191	0	58	20	2.4	144	3.7	7.3	14.9	2	24
36	gopal	52	1	23	0	1	0	190	158	30	159	1	66	40	1.9	177	3.9	5.8	12.2	4	24
37	vembu	55	1	24	0	0	1	279	145	35	250	1	65	32	2.5	94	2.8	7.6	16.1	2	24
38	mookandi	58	1	25	0	1	0	145	132	48	119	0	69	34	3.6	173	3.8	11	17.2	3	24
39	muniazhagan	57	1	28	1	0	1	240	154	46	209	1	64	36	2.2	164	4	6.2	11.2	2	24
40	avinasi	69	1	26	0	1	1	190	177	42	155	0	59	20	2.6	139	3.6	5.8	13.3	4	24
41	thangaraj	70	1	31	0	0	1	176	167	30	143	0	63	30	0.9	124	3.7	8.7	15.9	2	24
42	duraisamy	72	1	28	1	1	0	156	123	50	131	1	68	40	2	147	3.8	8.1	15.4	3	24
43	umapathy	59	1	25	0	0	1	310	220	35	266	0	60	28	3.5	120	2.4	7.9	14.9	3	24
44	govindan	76	1	30	0	1	1	190	198	52	159	1	59	34	1.5	126	3.1	7.7	13.8	2	24
45	natarajan	55	1	24	1	0	1	230	180	40	194	0	60	32	1.9	142	3.8	7.9	15.2	2	24
46	partheeban	54	1	27	1	0	1	197	178	42	161	1	57	44	3.8	139	3.9	6.9	15.2	4	24
47	manickam	57	1	26	0	0	1	188	167	44	155	1	66	38	3.7	129	2.8	8.6	16.6	2	24
48	veeraraghavan	57	1	31	1	1	1	254	165	45	221	0	65	30	2.6	111	3.6	8.5	17.4	4	24
49	shanthanam	60	1	28	0	0	0	154	109	53	132	1	61	28	1.9	69	1.9	8.2	15.9	4	24
50	kannan	52	1	31	1	0	1	229	190	30	191	0	60	32	2.8	94	3	9.1	14.8	4	24
51	veerapan	50	1	26	0	0	1	163	178	46	127	1	57	42	3.5	85	2.5	11	16.5	3	24

1-yes
2-no
S = sex, 1=male, 2= female