PREVALENCE OF EUTHYROID SICK SYNDROME IN NEWLY DETECTED PULMONARY TUBERCULOSIS PATIENTS AND THE CORRELATION OF THE SAME WITH FAILURE AT THE END OF INTENSIVE PHASE

A Dissertation Submitted to

THE TAMILNADU DR. M.G.R MEDICAL UNIVERSITY

CHENNAI

In Partial Fulfillment of the Regulations

for the Award of the Degree of

M.D. (GENERAL MEDICINE) - BRANCH – I

GOVERNMENT KILPAUK MEDICAL COLLEGE & HOSPITAL, KILPAUK, CHENNAI – 600 010. TAMILNADU.

May – 2018

BONAFIDE CERTIFICATE

This is to certify that this dissertation title "**PREVALENCE OF EUTHYROID SICK SYNDROME IN NEWLY DETECTED PULMONARY TUBERCULOSIS PATIENTS AND THE CORRELATION OF THE SAME WITH FAILURE AT THE END OF INTENSIVE PHASE**" submitted by **Dr. R. SHARMILA DEVI** to the faculty of General Medicine, The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of MD degree branch I General Medicine, is a bonafide research work carried out by her under our direct supervision and guidance.

Dr. T.S. SANTHI M.D.,
Professor of Medicine
Chief, II Medical Unit
Govt. Kilpauk Medical
College, Chennai - 10

Dr. K.V. RAJALAKSHMI M.D.,
Professor and Head
Department of Medicine
Govt. Kilpauk Medical
College, Chennai – 10.

Dr. P. VASANTHAMANI., MD, DGO,
DEAN
GOVERNMENT KILPAUK MEDICAL
COLLEGE & HOSPITAL, CHENNAI -10.

DECLARATION

I, **Dr. R. SHARMILA DEVI,** solemnly declare that the dissertation titled **"PREVALENCE OF EUTHYROID SICK SYNDROME IN NEWLY DETECTED PULMONARY TUBERCULOSIS PATIENTS AND THE CORRELATION OF THE SAME WITH FAILURE AT THE END OF INTENSIVE PHASE"** has been prepared by me under the guidance of **Prof. Dr. T.S. SANTHI, M.D.,** Department of General Medicine. This is submitted to **"The Tamil Nadu Dr. M.G.R. Medical University, Chennai"** in partial fulfillment of the requirement for the award of **MD Degree Branch I (General Medicine).**

Place: Chennai **Dr. R. SHARMILA DEVI**

Date:

ACKNOWLEDGEMENT

At the outset, I wish to thank our beloved Dean, **Dr. P. VASANTHAMANI MD, DGO,** for permitting me to use the facilities of Government Kilpauk Medical College and Hospital to conduct this study.

I wish to express my due respect and gratitude to **Dr. K.V. RAJALAKSHMI MD**, Professor & HOD, Department of Medicine, Govt. Kilpauk Medical College, Chennai for his generous support and encouragement for this study.

My beloved unit chief and guide **Dr. T.S. SANTHI., MD,** Professor of Medicine was instrumental in guiding me through the entire period of my study and helping me complete my work. I owe my sincere thanks to him.

I offer my heartfelt thanks to my Assistant professor **Dr. P. BOOPATHY RAJAN MD, DTCD.,** for his constant encouragement, timely help and critical suggestions throughout the study and also for making my stay in the unit both informative and pleasurable.

I sincerely thank my beloved my Assistant professors **Dr. G. GURUNAMASIVAYAM DPM., MD.,** Dept. of Medicine and **Dr. M. VASANTHA KUMAR, DTCD., MD., Dept. of Medicine.**

I extent my love and gratitude to my family and friends especially **Dr. Chitra M.S.** who were with me in times of need. My patients, who formed the most integral part of the work were kind and cooperative. They have lent themselves for this study without any grudge. I thank them all and also pray for their good health.

Last but not the least I thank God, the almighty for allowing me to finish this work.

INSTITUTIONAL ETHICS COMMITTEE
GOVT. KILPAUK MEDICAL COLLEGE,
CHENNAI-10
Protocol ID. No.07/2017 Meeting held on 03.03.2017

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "**Prevalence of Euthyroid Sick Syndrome in Newly Detected Pulmonary Tuberculosis Patients and the Correlation of the Same with Failure at the End of Initiation Phase** " submitted by Dr.R.Sharmiladevi, M.D. General Medicine, PG Student, GKMC, Chennai-10

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

DEAN 23/3/17
Govt. Kilpauk Medical College,
Chennai-10.

28/3/17

My Comp<E Colon< ME 1 Sec> Ethical Committee

URKUND

Urkund Analysis Result

Analysed Document: SHARMI11.10.2017 (Autosaved)1.docx (D31282816)
Submitted: 10/13/2017 11:07:00 AM
Submitted By: drsharmi2k@gmail.com
Significance: 11 %

Sources included in the report:

THESIS COMBINED.docx (D22977108)
thesis krishnakumar.docx (D31265985)
http://jpma.org.pk/full_article_text.php?article_id=189
http://jpma.org.pk/PdfDownload/189.pdf

Instances where selected sources appear:

6

CONTENTS

ABBREVATIONS

TB	-	Tuberculosis
ESS	-	Euthyroid Sick Syndrome
TFT	-	Thyroid Function Test
NTI	-	Non Thyroidal Illness
T3	-	Triiodothyronine
T4	-	Thyroxine
TSH	-	Thyroid Stimulating Hormone
TRH	-	Thyrotropin Releasing Hormone
TBG	-	Thyroid Binding Globulin
AFB	-	Acid Fast Bacillus
CMI	-	Cell Mediated Immunity
MDR-TB	-	Multi Drug Resistant tuberculosis
DST	-	Drug Susceptibility Testing

INTRODUCTION

Tuberculosis is one of the ancient disease which is caused by Mycobacterium tuberculosis affecting humans. It commonly affects the lungs and also affect organs like bones, intestines, meninges, lymphnodes, skin and other tissues of the body. India is the highest Tuberculosis (**TB**) burden country accounting for one fifth of Global incidence[1]. In 2015 it was estimated that there were 104 lakh of new cases of tuberculosis globally among which 28 lakh of cases were reported in India.

Multi-Drug Resistant TB constitutes about 2-3% of new TB cases and about 12-17% of Re-treatment cases. Estimated 1.3 lakh incident Multi drug resistant TB patients emerge annually in India which includes 79000 MDR-TB patients estimates among notified pulmonary cases[2]. Drug resistance may be either primary or acquired. Primary Drug resistance occurs in a patient who has never been exposed to anti-TB drugs. Acquired type is due to the consequence of inappropriate or irregular therapy. The diagnosis of MDR-TB is mainly of Bacteriological diagnosis[53]. Compared to drug susceptible TB, the treatment of MDR-TB is less effective, more toxic and much more expensive.

In total TB cases 85% constitutes pulmonary TB. The primary route of transmission of infection is airborne. In India Primary infection of TB occurs mainly in Childhood. The treatment for TB began when Selman Abraham Waksman in 1944 discovered Streptomycin for which he got Nobel Prize for Medicine in 1952. The RNTCP is based on WHO's Global strategy for TB

control. The DOTS strategy is today recognized as the cornerstone of efficient TB manangement. TB affects predominantly economically productive age group leading to huge socio-economic impact. The deaths due to TB constitutes about 280000 each year.

Euthyroid Sick Syndrome is a state of abnormal thyroid function test in the setting of non thyroidal illness (NTI) in the absence of pre existing thyroid gland dysfunction and presence of normal Hypothalamo- Pitutary axis[26]. It is all about abnormal thyroid blood tests without low thyroid symptoms. ESS is more prevalent in critically ill patients and is closely associated with morbidity and mortality. ESS is of three types. They were

Type 1: Low T3

Type 2: Combined low T3 and T4

Type 3: Low TSH

The abnormal concentration of the circulating thyroid hormone level may be occur in a variety of non thyroidal illness, without associated pituitary or thyroid disorder .There is also alteration in thyroid hormone levels in patients with non-thyroid illnesses such as TB have also been reported. It could be due to various factors acting on enzyme known as Monodeiodinase, a enzyme which is essential for the conversion of T4 to T3 and also acting on transport system of thyroid hormones. The action of cytokines and other

inflammatory mediators on hyporthalamus, pituitary and thyroid gland has been investigated, but their action remains unclear.

Euthyroid Sick Syndrome is more common in pulmonary tuberculosis & its prevalence has been described in upto 92% of subjects. About 60% of subjects were reported to have low Triiodothyronine (T3) level. The pathogenesis of ESS in TB cases is due to decreased T4 to T3 conversion, decreased TSH production and action of drugs such as Ethionamide and prothionamide.

So far Prevalence of ESS in Pulmonary tuberculosis is under studied. Since Pulmonary Tuberculosis carries high morbidity in the developing world. We designed this study to identify the prevalence of ESS in PTB patients.

AIM OF THE STUDY

1. To prospectively evaluate the Euthyroid Sick syndrome in patients presenting with newly diagnosed sputum positive pulmonary tuberculosis.

2. To correlate the presence of Euthyroid Sick syndrome and Bacilli burden in sputum positive pulmonary tuberculosis patients.

3. To find out the failure of sputum conversion at the end of Intensive Phase

REVIEW OF LITERATURE

DEFINITION

Euthyroid Sick Syndrome is a state of abnormal thyroid function test in the setting of non thyroidal illness (NTI) in the absence of pre existing thyroid gland dysfunction and presence of normal Hypothalamo- Pitutary axis.

HISTORY OF MYCOBACTERIUM TUBERCULOSIS

Mycobacterium tuberculosis is discovered by Robert Koch in 1882. In fact, for his efforts in etiology of tuberculosis he received the 1905 Nobel Prize in Medicine. In the 5th century BCE the great Hippocrates claimed[52] that tuberculosis as phthisis. It is the most widespread of all the diseases in his time. The Bacille Calmette Guerin vaccine was first used in humans in 1921, and became widely used and has a variable effectiveness against pulmonary tuberculosis. The modern era of tuberculosis treatment and control was heralded by the discovery of Streptomycin in 1944 and Isoniazid in 1952.

AETIOLOGICAL AGENT

Mycobacteria belong to the family mycobacteriaceae and belonging to M.tuberculosis complex which comprises eight subgroups. Mycobacterium tuberculosis[50] is the most common and important agent of human disease. M.tuberculosis is a rod shaped, non spore forming, thin aerobic bacterium measuring about 0.5 to 3 micrometer. Mycolic acid present in its cell wall makes acid fast.

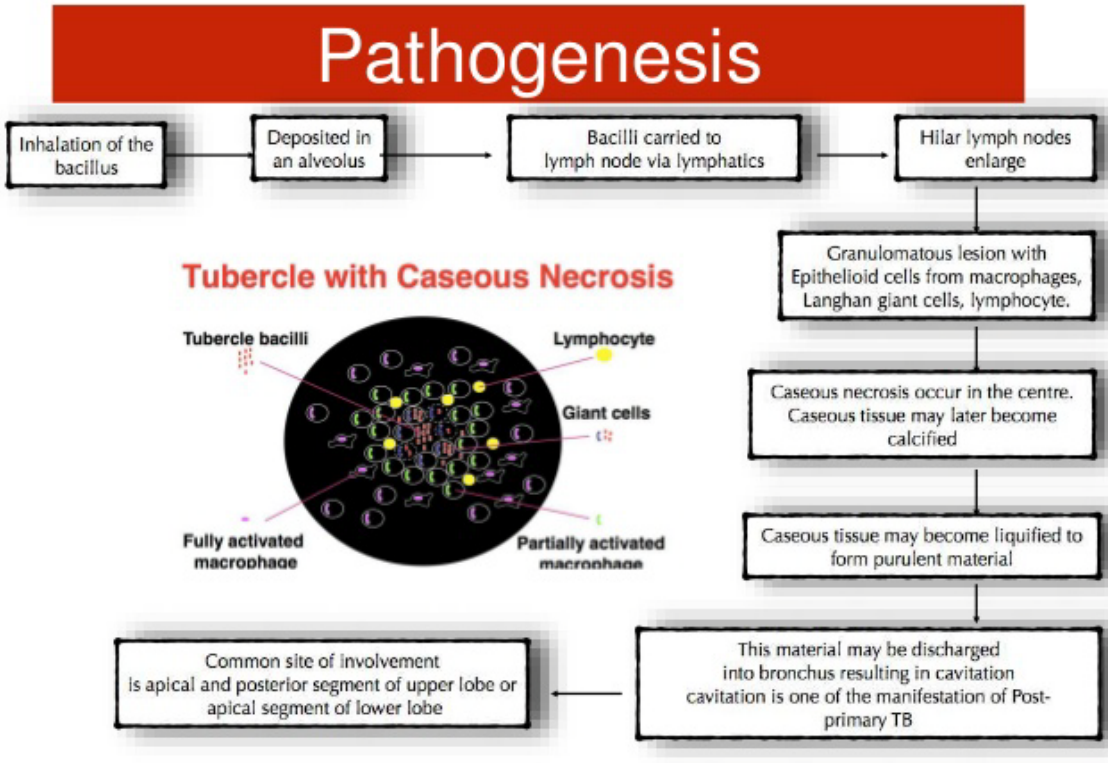
In the mycobacterial cell wall, lipids (e.g mycolic acid) are linked to underlying arabinogalactan and peptidoglycan. This structure results in very low permeability of the cell wall, thus reducing the effectiveness of most antibiotics.

PATHOGENESIS

Tuberculosis spreads from person to person by aerosol route called droplet nuclei and primarily affects the lung, travel to the alveoli and multiply in alveoli. A small number of tubercle bacilli enter the bloodstream and spread throughout the body. The tubercule bacilli may reach any part of the body such as brain, larynx, lymphnode, lung, spine, bone and kidney.

Within 2 to 8 weeks special immune cells called macrophages ingest and surround the tubercle bacillus. The cells form a barrier shell called a granuloma, that keeps the bacilli contained and under control (LTBI). If the immune system cannot keep the tubercle bacilli under control, the bacilli begin to multiply rapidly (TB disease).

The current paradigm of the pathogenesis of TB considers TB to be a one act play in which the caseating granuloma modulated by cell mediated immunity (CMI)is the characteristic lesion of all TB.



RISK FACTORS

1. Close contact with someone who have active TB[4].
2. Immunocompromised status (Elderly, cancer)
3. Drug abuse and alcoholism
4. Tobacco smoking
5. Immunodeficiency disorders affecting cell mediated immunity-e.g HIV
6. People lacking adequate health care
7. Pre existing medical conditions (Diabetes mellitus, chronic renal failure)
8. Organ transplantation
9. Immunosuppressive therapy

10. Immigrants from countries with higher incidence of TB.

11. Institutionalization (long term care facilities)

12. Living in substandard conditions

13. Occupation (Health care workers)

CLINICAL MANIFESTATIONS

CONSTITUTIONAL SYMPTOMS

1. Anorexia

2. Low grade fever

3. Night sweats

4. Fatigue

5. Weight loss

PULMONARY SYMPTOMS

1. Dyspnea

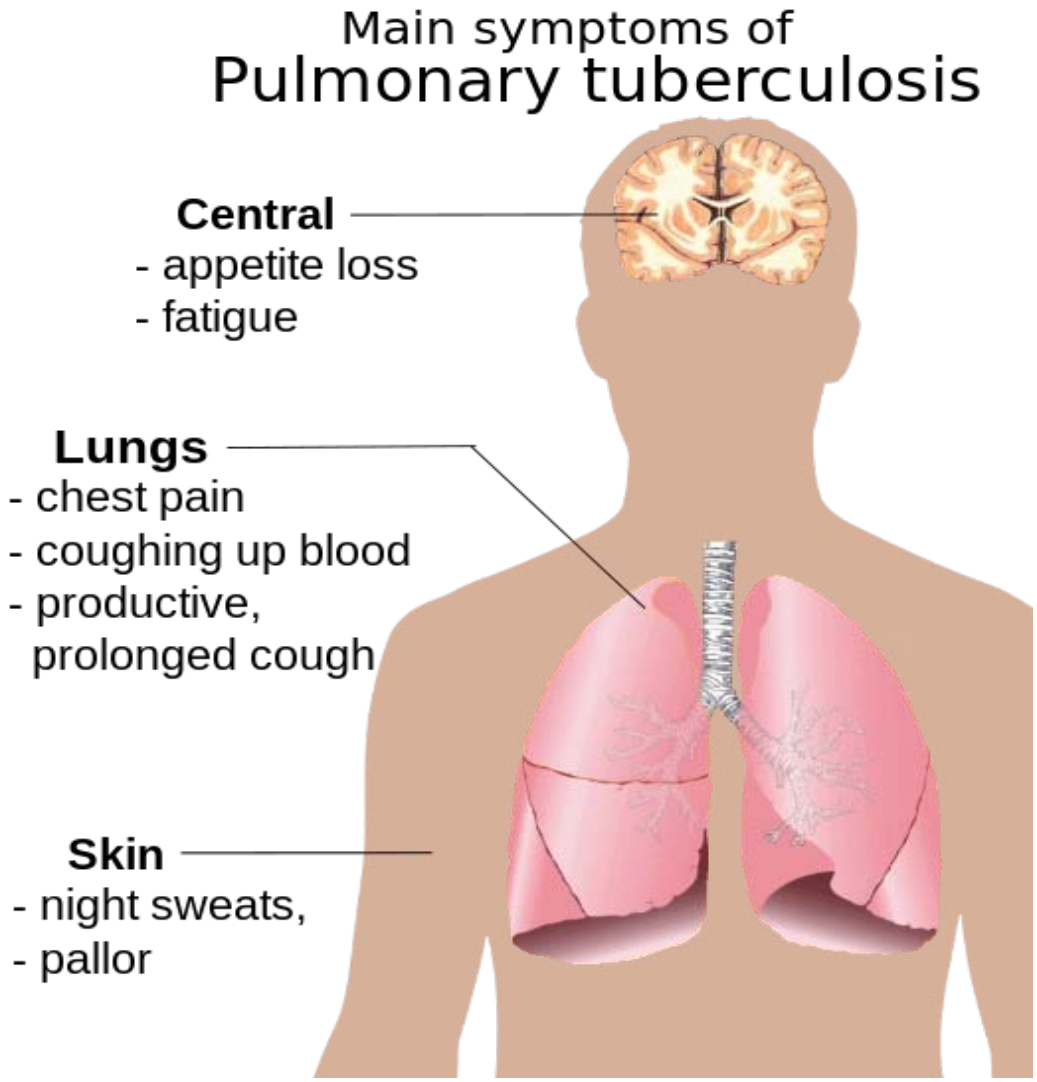
2. Non resolving bronchopneumonia

3. Chest tightness

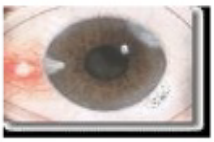
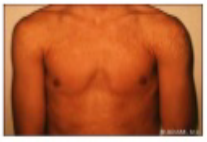
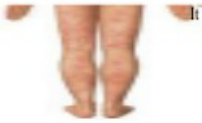
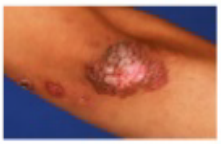
4. Non productive cough

5. Mucopurulent sputum with hemoptysis

6. Chest Pain


Main symptoms of
Pulmonary tuberculosis
Central
- appetite loss
- fatigue
Lungs
- chest pain
- coughing up blood
- productive,
prolonged cough
Skin
- night sweats,
- pallor

EXTERNAL MARKERS OF TB

LUPUS VULGARIS 	REDDISH – BROWN JELLY LIKE NODULES (**APPLE - JELLY NODULES**) SEEN TYPICALLY OVER NOSE. ALSO SEEN OVER HEAD , NECK ,LIMBS , TRUNK , GLUTEAL AREA & PENIS.
SCROFULODERMA (Tuberculosis cutis colliquativa) 	FIRM , PAINLESS , SKIN NODULES THAT ULCERATE . OCCURS AS DIRECT EXTENSION OF TB INFECTION OF LYMPH NODES, BONES & JOINTS .
PHLYCTENULOSIS 	2 TYPES - CORNEAL & CONJUCTIVAL CONJUCTIVAL PHLYCTEN - 1-2 mm YELLOWISH , NODULE WITH SURROUNDING HYPEREMIA SEEN NEAR THE INFERIOR LIMBUS CORNEAL PHLYCTEN - MAY EXTEND INTO CORNEA AS GREY – WHITE SUPERFICIAL ULCER
TINEA VERSICOLOR 	OVAL SCALY MACULES/ PAPULES & PATCHES CONCENTRATED ON CHEST, SHOULDERS & BACK (SHAWL LIKE DISTRIBUTION). CAUSED BY NORMAL INHABITANT OF SKIN, **MALASSEZIA FURFUR**.
SCROFULA 	PAINLESS CERVICAL TUBERCULOUS LYMPHADENOPATHY. POSTERIOR & SUPRACLAVICULAR NODES INVOLVED COMMONLY.
ERYTHEMA NODUSUM 	It is a t IS TYPE III HYPERSENSITIVITY REACTION TENDER, SMOOTH, SHINY, RED NODULES OF 1 – 10 cm ; SEEN ON SHIN COMMONLY ALSO OCCUR UNDER SKIN (THIGHS, ARM, TRUNK, FACE & NECK)
TUBERCULOUS VERRUCOSA CUTIS 	WARTY,SOLITARY PLAQUE WITH CENTARL INVOLUTION & ATROPIC SCAR SEEN ON HANDS IN ADULTS & IN LOWER EXTREMITIES IN CHILDREN OCCUR DUE TO DIRECT INOCULATION OF TB OVER SKIN
LICHEN SCROFULOSORUM	GROUPED, PERIFOLLICULAR, LICHENOID PAPULES OF 1 –2 mm . SEEN OVER TRUNK.
PAPULONECROTIC TUBERCULID	NECROTIZING SKIN PAPULE S, OCCUR IN CLUSTERS. APPEAR ON EXTERIOR ASPECTS OF EXTRIMITIES (KNEE ,ELBOW ,BUTTOCK ,LOWER TRUNK) IN A SYMMETRICAL DISTRIBUTION .

REFERENCESS : COMPREHENSIVE TEXTBOOK OF TB , HARRISON (17 th EDITION)
Dr. Bhuvaneshwari , 2nd year PG bhuv_doc@yahoo.co.in

DIAGNOSIS

Bacteriologic examination of clinical specimen like sputum, urine, or cerebrospinal fluid are of critical diagnostic importance. The specimens should be examined and cultured in a laboratory that specializes in testing for M. tuberculosis. The bacteriologic examination has five parts:

Step1 : Specimen collection, processing, and review

Step 2 : AFB smear classification and results

Step3 : Direct detection of M.tuberculosis in clinical specimen using nucleic acid amplification (NAA)

Step4 : Specimen culturing and identification

Step5 : Drug-susceptibility testing

Step 2: AFB MICROSCOPY

Examination of smears is a rapid, convenient and inexpensive test. All types of specimens can be evaluated like sputum, tissue, body fluids, etc. Positive AFB smear results provide a first indication of mycobacterial infection and potential TB disease. It must be accompanied by additional testing including culture for confirmatory diagnosis. AFB microscopy[1] has low sensitivity which has 40% - 60% in cultured confirmed cases of pulmonary tuberculosis.

The traditional method is light microscopy of specimens stained with Ziehl-Neelson(ZN) basic fuchsin dyes. It requires heat during staining and higher magnification. In this method more fields are examined (e.g 300 fields

at 1000X). It takes more time to read the slide.It requires use of oil immersion. This method stains all Non- Tubercle Mycobacterium well.

Smear Results- 1000X (magnification)

No AFB	0 AFB/Smear
Report exact count; Order repeat specimen	1-2/300fields
1+	1-9/100fields
2+	1-9/10fields
3+	1-9/field
4+	>9/field

AFB Microscopy Staining Techniques includes two basic techniques. First one is Fluorescence:

Auramine staining–Also known as Fluorochrome staining.Second one is Brightfield: Carbol fuchsin staining.

- Primary stain is Fluorescent, - CDC recommends fluorochrome staining for detecting AFB in primary patient .

- Next common stain is–Auramine-O, Auramine Rhodamine, -It reads at lower magnification, less fields examined (e.g, 30 fields at 200X).It Faster screening of smears than with ZN.It is 10% more sensitive than ZN.It does not require use of oil immersion. It is expensive, because it requires mercury vapor light sources and a dark room.Nowadays less expansive LED-light emiotting diode fluorescence microscopes are available[1].

Step3: NAAT (NUCLEIC ACID AMPLICATION TECHNOLOGY)

This is the most important test to confirm tuberculosis in persons with AFB positive specimens. **REAL TIME NAAT** is called as Xpert MTB/RIF assay. It is a new PCR –based TB diagnostic test. It is used to diagnose tuberculosis & rifampicin resitance in less than 2hours.It is a fully automated test. This test has high specificity & sensitivity to diagnose tuberculosis. TheWHO recommends that it is the initial diagnostic test in adults and children presumed to have MDR-TB or HIV associated TB. It has 98% sensitivity among AFB positive cases and 70% among AFB negative specimens.

Step4: MYCOBACTERIAL CULTURE

This is one of the definitive diagnostic method to isolate and identify M.tuberculosis. For culture we are using Lowenstein-jenson or Middlebrook 7H10 medium and incubated at 37degree C.

M.tuberculosis grow slowly 4-8 weeks. The disadvantage of this test is taking longer time and expensive and complex procedure. So new methods like MGIT-Mycobacterial growth indicator tube, which is a liquid culture using modified Middlebrook 7H9 broth. It has an oxygen sensitive fluorescent sensor at the bottom. It takes 2-3week for bacteriological confirmation of TB by this method. MGIT can also be used as a rapid method for the detection of drug resistant strains of MTB[32] directly from acid-fast smear positive samples as well as from indirect drug susceptibility studies**.**

Step5: DRUG SUSCEPTIBILITY TESTING (DST)

This test may be conducted directly or indirectly on solid or liquid medium. By direct susceptibility testing on liquid medium, the results are reported with an average time of 3 weeks. By indirect testing[6] on solid medium, results may be unavailable for >8 weeks**.** MODS -Microscopic Observation Drug Suscepitibility assay is a low cost alternate to the detection of drug resistance.

LINE PROBE ASSAY (LPA)

Line probe assay is a DNA strip test which is a rapid and manual NAAT. It uses PCR and reverse hybridization methods. It can diagnose MDR-TB directly from smear positive sputum samples, providing results in just 5 hours. In 2008 –WHO issued a recommendation for the use of molecular LPA for the rapid diagnosis of MDR-TB in high TB burden, low income settings. It is highly accurate in detecting MDR-TB and cost effective when compared with TB culture and DST.

Diagnosis of Latent M.Tuberculosis infection

SpecificTest:

IGRAs (Interferon – Gamma Release Assay): There are two in vitro assays[7] that measure T cell release of IFN –gamma in response to stimulation with highly TB specific antigens which are ESAT- 6

(Early secretory antigen target-6) and CFP-10 (Culture filtrate protein).

1. T- Spot TB test-Directly count the number of IFN gamma secreting T cells. (ELISPOT)

2. Quantiferon TB Gold In-Tube test-Measure the concentration of IFN gamma secretion. (ELISA)

NON SPECIFIC TEST

TUBERCULIN TEST (MANTOUX)

Robert Koch discovered ‘old tuberculin’ were capable of eliciting a skin reaction when injected subcutaneously into patients with TB in 1891.Seibert and Munday purified this product by ammonium sulfate precipitation to produce PPD (tuberculin purified protein derivative) in 1932.Seibert and Glenn developed PPD-S in 1941as the International standard. In later WHO and UNICEF sponsored PPD (RT23) made it available for general use. It is most widely used in screening for LTBI (latent TB infection), but it lacks specificity and sensitivity.

WHO definitions: The following definitions are given to avoid diversity in diagnosis of various cases of Tuberculosis.

NEW CASE:

A patient who has never had treatment for TB or who has taken anti-tuberculosis drugs for less than one month.

RELAPSE:

A patient previously treated for TB who has been declared cured or treatment completed, and is diagnosed with bacteriologically positive (smear or culture) tuberculosis.

TREATMENT AFTER FAILURE:

A patient who is started a re-treatment regimen after having failed previous treatment.

TREATMENTAFTER DEFAULT:

A patient who returns to treatment, positive bacteriologically, following interruption of treatment for two months or more.

MDR-TB (MULTI DRUG RESISTANTB TB):

A patient who has active tuberculosis with bacilli resistant atleast to both rifampicin and isoniazid.

X DR-TB- (EXTREMELY DRUG RESISTANT TB):

It is due to multi drug resistant (MDR)strains that are resistant to all fluoroquinolones and to atleast one of three second line injectable agents (Amikacin, Kanamycin, Capreomycin).

CHRONIC CASE:

A patient with TB who is sputum positive at the end of a standard re-treatment regimen with essential antituberculosis drugs.

TREATMENT

AIMS OF TREATMENT:

1. To cure the disease without relapse and improve quality of life and productivity.
2. By treating tuberculosis we can prevent morbidity and death.
3. To prevent transmission by rendering patients non-infectious.
4. To prevent the development and transmission of drug resistance.

Drug treatment consists of two phases:

1.INTENSIVE PHASE:

It is designed to kill bacteria which is growing actively (i.e) bactericidal phase. It Shortens the duration of infectiousness and patient become non-infectious. It should be given for two months. In this phase minimum three drugs should be added. In addition possibility of drug resistance ethambutol or streptomycin can also be added.

2. CONTINUATION PHASE:

It is designed to eliminate residual bacteria and to prevent relapse. This phase consists usually of two drugs which are Isoniazid and Rifampin. It should be continued for 4 months.

ANTI TUBERCULOSIS DRUGS

Chemotherapy for TB[8] started only after the discovery of Streptomycin in 1944.Streptomycin is a first line agent formerly used. It is more toxic and high resistance than with other aminoglycosides. So nowadays it is rarely used in drug resistant tuberculosis.

Standardized treatment regimens are one of the pillars of DOTS strategy. Most of the DOTS regimen followed by the government, have schedules in which drugs are given for three times a week and patient is usually treated for 6-9 months.

There are four major drugs which are considered as **first line drugs**

1. ISONIAZID (H) (bacteriostatic)
2. RIFAMPIN (R) (bacteriocidal)
3. PYRAZINAMIDE (Z) (bacteriostatic and partly bacteriocidal)
4. ETHAMBUTOL (E) (bacteriostatic)
5. STREPTOMYCIN (bacteriocidal)

The details of each drug are:

ISONIAZID

It is the most powerful antituberculous drug. It is the hydrazide of Isonicotinic acid. In early 1950s it is the most active drug for the treatment for patients whose Mycobacteria are susceptible to it. It inhibits most tuberculous bacilli in a concentration of 0.2microgramper milliliter or less.

Mechanism of action:

- It acts by inhibition of enzymes essential for the synthesis of mycolic acid.
- Resistance to INH occurs due to deletion of a gene katG which codes for catalase and peroxidase enzymes.
- About 90% of dose of isoniazid is excreted in the urine within as metabolites.
- INH reaches its peak level in blood 1 to 2 hours after the dose.
- It is metabolized primarily by acetylation and dehydrazination.
- It is distributed diffusely readily into cerebrospinal, pleural, ascitic fluid, tissues, organs, saliva, sputum, feces, placental barrier and in breast milk.
- 50%to 70% drugs excreted in the urine in 24hrs.

DOSAGE:

Adults: PO/IM 5mg/kg/day as a single dose (max, 300mg/day) or 15mg/kg 2 to 3times/wk (max,900mg).

Infants and children:PO/IM 10 to 20mg/kg/day in single daily dose (max, 300mg/day) or 20-40mg/kg 2 or 3 times/week (max, 400mg).

Adverse effects:

Common- Asymptomatic elevation of serum hepatic enzymes.

Uncommon- Hepatitis, cutaneous hypersensitivity, peripheral neuropathy.

Rare- Fever, giddiness, convulsions, optic neuritis, hemolytic anemia, aplastic anemia, lupoid reactions, arthralgia, gynaecomastia.

RIFAMPICIN

It is a semisynthetic derivative of Rifamycin. It sterilizes bacteria better than INH. It is effective against both intracellular and extracellular bacteria.

Mechanism of action:

- It inhibits DNA dependent RNA polymerase of the bacteria.
- It inhibits RNA synthesis in bacteria but human RNA polymerase is not affected.
- Rifampicin is eliminated in bile and an enterohepatic circulation ensures.

- It is distributed all over the body and reaches high concentration in many organs and body fluids including the CSF.

Dosage:

Adult-PO/IV 10mg/kg/day (max,600mg/day) or 1omg/kg 2 or 3 times/wk (max,600mg).

Children-PO/IV 10 to 20mg / kg / day (max,600mg / day) or 10 to 20mg/kg

2 to 3 times / wk (max, 600mg).

Adverse effects:

Common- Pruritis

Uncommon- Hepatitis, cutaneous hypersensitivity, thrombocytopenia, febrile reactions, flu syndrome.

Rare- Breathing difficulty, shock, hemolytic anemia, acute kidney failure, thrombotic thrombocytopenic purpura.

PYRAZINAMIDE

It is more effective against slow multiplying intracellular bacilli. It increases the sterilizing effect of Rifampicin. Pyrazinamide is an analog of nicotinamide.

Mechanism of Action:

- It exhibits bactericidal activity at acidic pH only.
- The target of pyrazinamide appears to be the mycobacterial fatty acid synthase I gene involved in mycolic acid biosynthesis.
- This drug is excreted through kidney. It is well absorbed orally and is widely distributed.
- Half life is 8 to11hrs.

Dosage:

50 to 70mg/kg/day for twice /thrice weekly treatment regimens.

Adverse effects:

Common- Anorexia, nausea, flushing, photosensitization

Uncommon- Hepatitis, vomiting, arthralgia, cutaneous reactions.

Rare- Sideroblastic anemia, and gout.

ETHAMBUTOL

This drug used as a part of combination therapy drug resistance.

Mechanism of Action:

- It is a synthetic water soluble heat stable compound. Drug is absorbed within 24hrs.

- Most of the absorbed ethambutol is excreted unchanged in the urine.
- The drug is excreted by tubular secretion in addition to glomerular filtration.

Dosage: 15 to 25mg /kg as a single dose.

Adverse effects:

Uncommon- Retrobulbar neuritis, cutaneous reactions, arthralgia

Rare-peripheral neuropathy.

It does not produce hepatotoxicity.

STREPTOMYCIN

The last first line drug is streptomycin which is less active against slow multipliers. It causes renal failure rather than hepatic failure. It is given by injection. It penetrates into cells poorly and ineffective for intracellular tubercle bacilli. Protein bound is only 34%. It crosses BBB & achieves therapeutic concentration. If meninges are inflammed.

Mechanism of action:

- It binds to 12S ribosomal sub unit.
- It reversibly inhibits bacterial protein synthesis and causes the death of microbial cells.

- Half life elimination in newborn is 4-10hrs and for adults 2- 4.7hrs. It is prolonged with renal impairment.
- 90% of the drug excreted through urine as unchanged drug. 1% excreted through feces, saliva, sweat, tears.

DOSAGE

Adults:15 to 20mg/kg daily (max dose 1000mg)

Children:20 to 40mg/kg (max dose 1000mg)

ADVERSE EFFECTS

Hypotension, neurotoxicity, drowsiness, drug fever, skin rash, nausea, vomiting, eosinophilia, arthralgia, tremor, ototoxicity, nephrotoxicity.

WHO Recommended Doses of the First-line – anti tuberculosis drugs

Drugs	Daily doses (mg/kg)	Route	Thrice weekly dosage (mg/kg/dose)
Isoniazid (H)	5(4-6)	Oral	10(8-12)
Rifambin (R)	10(8-12)	Oral	10(8-12)
Ethambutol (E)	15(15-20)	Oral	30(25-35)
Pyrazinamide(Z)	25(25-30)	Oral	35(30-40)
Streptomycin (S)	15(12-18)	Oral	15(12-18)

TB resistant to first line of drugs[9], we have to consider about six classes of **second line drugs.**

1. Fluoroquinolones-Levofloxacin, moxifloxacin, gatifloxacin
2. Injectable Aminoglycosides-Amikacin, Kanamycin, streptomycin
3. Injectable polypeptide- capreomycin
4. Thioamides-Ethionamide(oral), prothionamide (oral)
5. Cycloserine(oral) and terizidone (oral)
6. PAS (para amino salicylicacid) (oral).

WHO Recommended Doses of second- line anti tuberculosis drugs

Drugs	Daily doses (mg/kg)	Route	Maximum daily dose
Kanamycin (K)	15	IM	Up to 1 g
Amikacin (A)	15	IM	Up to 1 g
Ethionamide (Eto)	10-15	Oral	Up to 1 g
Cycloserine (Cs)	10	Oral	Up to 1 g
Para amino salicylic acid (PAS)	250	Oral	Up to 1 g
Ofloxacin (Ofx)	15-20	Oral	800-1000 mg
Levofloxacin	7.5-10	Oral	750-1000 mg
Moxifloxacin	7.5-10	Oral	400 mg

OTHER DRUGS: (Group 5 drugs referred by" WHO")

In resistant tuberculosis for first and second line drugs, following drugs[10] can be used

.Amoxicillin/clavulinic acid

.Clarithromycin

.Linezolid

.Carbopenams-imipenem/cilastatin and meropenam

.Clarithromycin

.Clofazimine

.Thioacetozone

Novel Drugs

There are two **Novel drugs** have been approved recently for MDR-TB cases by FDA (the U.S.Food and Drug Administration) and EMA(European Medicine Agency) which are

BEDAQUILINE(DIARYLQUINOLINE):

FDA granted accelerated approval to this drug in late 1920. The dosage is 400mg daily for 2weeks followed by 200mg thrice weekly for 22weeks[1]. The total duration is 24weeks. It has high efficacy and faster sputum conversion. This drug is added to the WHO-recommened standard MDR_TB regimen,

being currently provided in six sites across the country which are Delhi, Mumbai, Chennai, Guwahati, and Ahmedabad. RNTCP will expand the access to bedaquiline across India by the end of 2017. SIDE EFFECTS:

QT interval prolongation and hepatotoxicity.

DELAMANID(NITROIMIDAZOLE): In early 2014, European Medical Agency granted accelerated approval to this new drug. It crossed phase 2B clinical trial and added to the WHO recommended standard MDR_TB regimen. It shows increased culture conversion at 2months.

SIDE EFFECT: QT interval prolongation.

RECOMMENDED DOSAGE FOR INITIAL TREATMENT OF TUBERCULOSIS IN ADULTS

Drugs	Daily Dose	Thrice-Weekly Dose
Isoniazid	5mg/kg, max 300mg	10mg/kg, max 900mg
Rifampin	10mg/kg, max 600 mg	10 mg/kg, max 600mg
Pyrazinamide	25 mg/kg, max 2g	35 mg/kg, max 3g
Ethambutol	15mg/kg	30 mg/kg

DRUG REGIMENS AND CATEGORIES

CATEGORY 1

- New sputum smear positive patients
- New sputum smear negative
- New extra-pulmonary tuberculosis

TREATMENT REGIMEN:

- Two months intensive phase-H3 R3 Z3 E3
- Four months continuation phase-H3 R3

CATEGORY II

- Relapse after treatment
- Treatment failure
- Treatment after default
- Sputum smear negative or extra pulmonary disease and who can have recurrence

TREATMENT REGIMEN:

- Three months intensive phase-2 months H3 R3 Z3 E3 S3 and one month H3 R3 Z3
- Five months continuation phase-H3 R3 E3

RECOMMENDATIONS ON

TREATMENT OF DRUG-SUSCEPTIBLE TB

1. For drug-susceptible pulmonary TB, 4-month fluoroquinolone containing regimens should not be used and the 6-month rifampicin-based regimen 2HRZE/4HR remains the recommended regimen.

2. The use of fixed-dose combination (FDC) tablets is recommended over separate drug formulations in treatment of patients with drug-susceptible TB.

3. In all patients with drug-susceptible pulmonary TB, the use of thrice-weekly dosing is not recommended in both the intensive and continuation phases of therapy, and daily dosing remains the recommended dosing frequency

4. Initiation of antiretroviral treatment in TB patients living with HIV.ART should be started in all TB patients living with HIV regardless of their CD4 cell count.

5. TB treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment. HIV-positive patients with profound immunosuppression (e.g. CD4 counts less than 50 cells/mm3) should receive ART within the first 2 weeks of initiating TB treatment.

6. In patients with drug-susceptible pulmonary TB who are living with HIV[33] and receiving antiretroviral therapy during TB treatment, a 6-month standard treatment regimen is recommended over an extended treatment for 8 months or more.

7. In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks should be used.

8. In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used.

9. In patients who require TB retreatment, the category II regimen should no longer be prescribed and drug-susceptibility testing should be conducted to inform the choice of treatment regimen.

Newer recommendations:

New patients with pulmonary tuberculosis:

- Treatment should be given daily throughout the course.
- However during intensive phase daily treatment and continuation phase three times weekly is an alternate option for patients who can be directly supervised and properly supported.

Absence of HIV infection:

- A fully supervised three times weekly regimen can be offered throughout the course but drug resistance will be higher than patients treated daily for the full course.

- Those who remain culture positive at 2 months should be tested immediately for drug resistant TB, and change of regimen should be considered.

THYROID

The first recorded mention of the thyroid is in terms of goitre in Chinese texts circa 2700 BCE, of which there is general agreement. Hippocrates and Plato in the fourth century BCE provided some of the first descriptions of the gland itself, proposing its function[25] as a salivary gland.

In 1500 polymath Leonardo da Vinci provides the first illustration[21] of the thyroid. In 1543 Anatomist

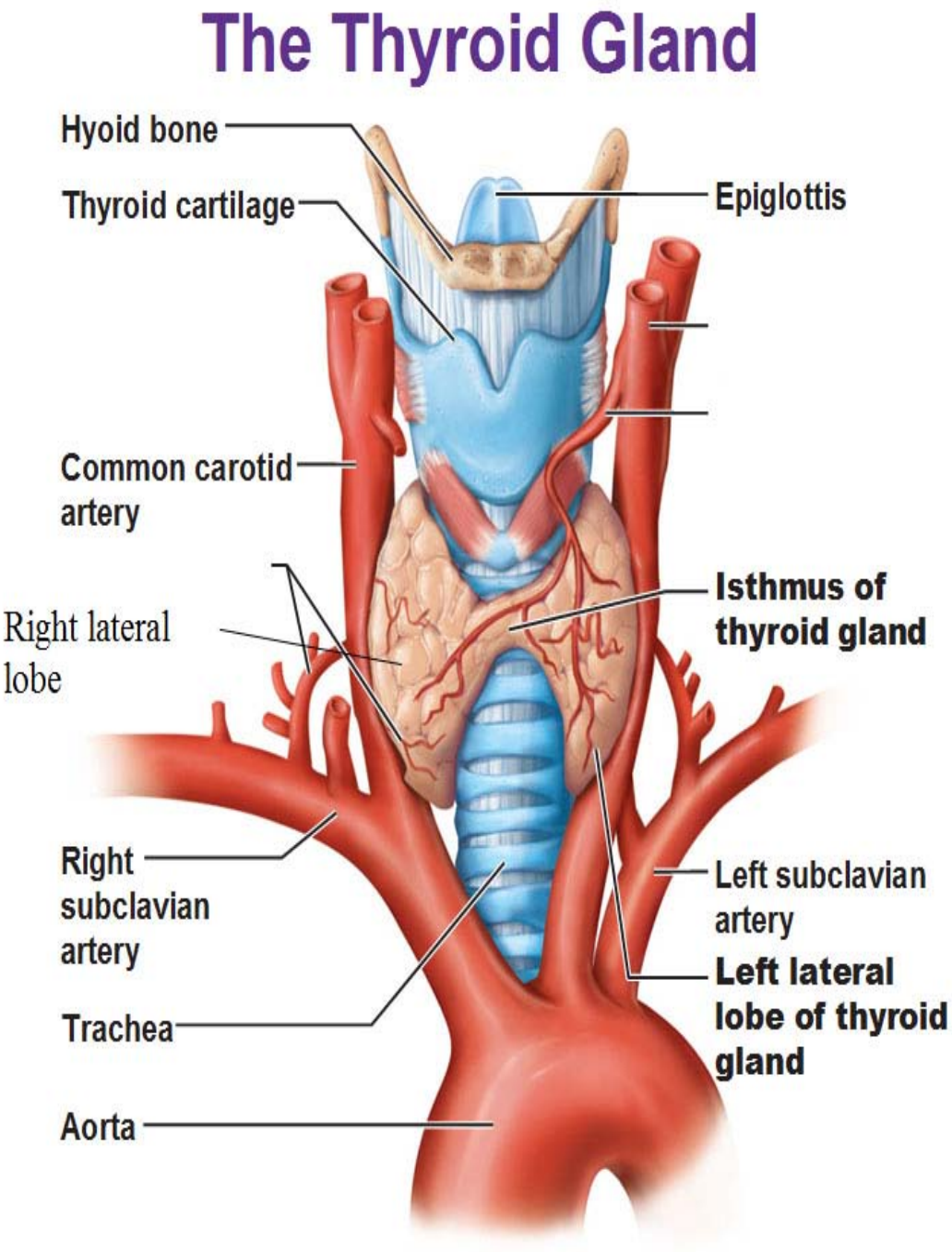
Andreas Vesalius gave the first anatomic description and illustration of the gland. In 1656 the thyroid received its name, by the anatomist Thomas Wharton.

The thyroid gland plays an important role in the maintenance of body metabolism. It secretes mainly of thyroxine (T4) and triiodothyronine (T3) due to the influence of thyroid stimulating hormones[48]. The thyroid hormones have a wide range of effects on metabolic, cardiovascular and development system of the body.

ANATOMY

The thyroid gland weighs 10 to 20grams in normal adults. It increases with age and body weight. It decreases with iodine intake. The thyroid is one of the most vascular organs in the body. The normal thyroid gland is immediately caudal to larynx and encircles the anterolateral portion of the trachea. The thyroid is bordered by the trachea and esophagus medially and the carotid

sheath laterally. It consists of two lobes connected by a narrow isthmus. Each lobe is pyramidal in shape, with its apex directed upward and its base directed downward.

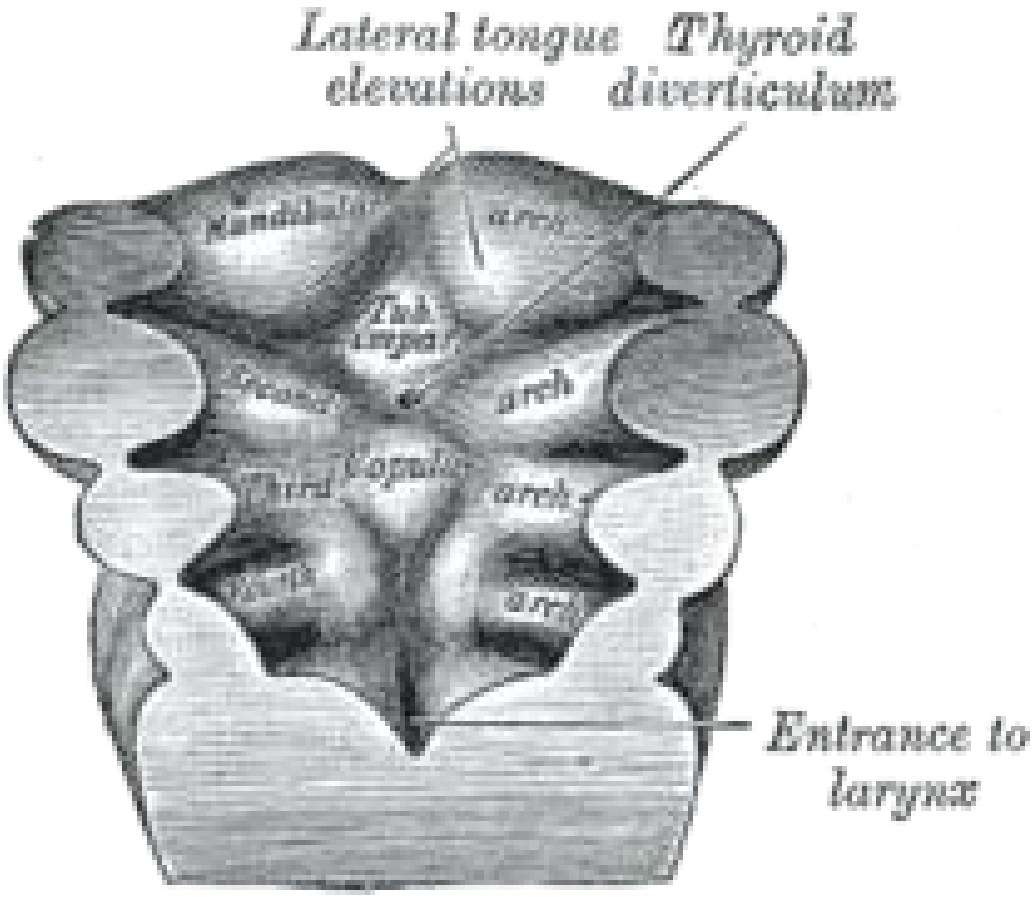


Gross anatomy of the thyroid gland, anterior view

Thyroid hormone (TH) includes thyroxine (T4) and triiodothyronine (T3), which increase[47] the rate of cellular metabolism. Consequently, oxygen use and heat production rise. Secretion of thyroid hormone, prompted by TSH, requires reuptake of the stored colloid by the follicle cells and splitting of the hormones from the colloid for release. Rising levels of thyroid hormone feedback to inhibit the pituitary and hypothalamus. Most T4 is converted to T3 (the more active form) in the target tissues.

The thyroid may be affected by several diseases.

DEVELOPMENT



at 3–4 weeks gestational age, the thyroid gland appears as an epithelial proliferatio **Floor of pharynx of embryo between 18 and 21 days**

In the development of the embryon in the floor of the pharynx at the base of the tongue between the tuberculum impair and the copula linguae. The copula soon becomes covered over by the hypopharyngeal eminence[12] at a point later indicated by the foramen cecum. The thyroid then descends in front of the pharyngeal gut as a bilobed diverticulum through the thyroglossal duct. Over

the next few weeks, it migrates to the base of the neck, passing in front of the hyoid bone. During migration, the thyroid remains connected to the tongue by a narrow canal, the thyroglossal duct[13]. At the end of the fifth week the thyroglossal duct degenerates and the detached thyroid continues on to its final position over the following two weeks.

The fetal hypothalamus and pituitary start to secrete thyrotropin-releasing hormone (TRH) and thyroid stimulating hormone (TSH). TSH[27] is first measurable at 11 weeks. By 18–20 weeks, the production of thyroxine (T_4) reaches a clinically significant and self-sufficient level. Fetal triiodothyronine (T_3) remains low, less than 15 ng/dL until 30 weeks, and increases to 50 ng/dL at full-term. The fetus needs to be self-sufficient in thyroid hormones in order to guard against neuro developmental disorders that would arise from maternal hypothyroidism. The presence of sufficient iodine is essential for healthy neurodevelopment.

The neuroendocrine parafollicular cells, also known as C cells, responsible for the production of calcitonin, are derived from neural crest cells, which migrate to the pharyngeal arches. This part of the thyroid then first forms as the ultimopharyngeal body, which begins in the ventral fourth pharyngeal pouch and joins the primordial thyroid gland during its descent to its final location.

Aberrations in prenatal development can result in various forms of thyroid dysgenesis which can cause congenital hypothyroidism, and if untreated this can lead to cretinism.

Function

The primary function[14] of the thyroid is the production of the iodine-containing thyroid hormones, triiodothyronine (T_3) and thyroxine (T_4) and the peptide hormone calcitonin. T_3 is so named because it contains three atoms of iodine per molecule and T_4 contains four atoms of iodine per molecule. The thyroid hormones have a wide range of effects on the human body.

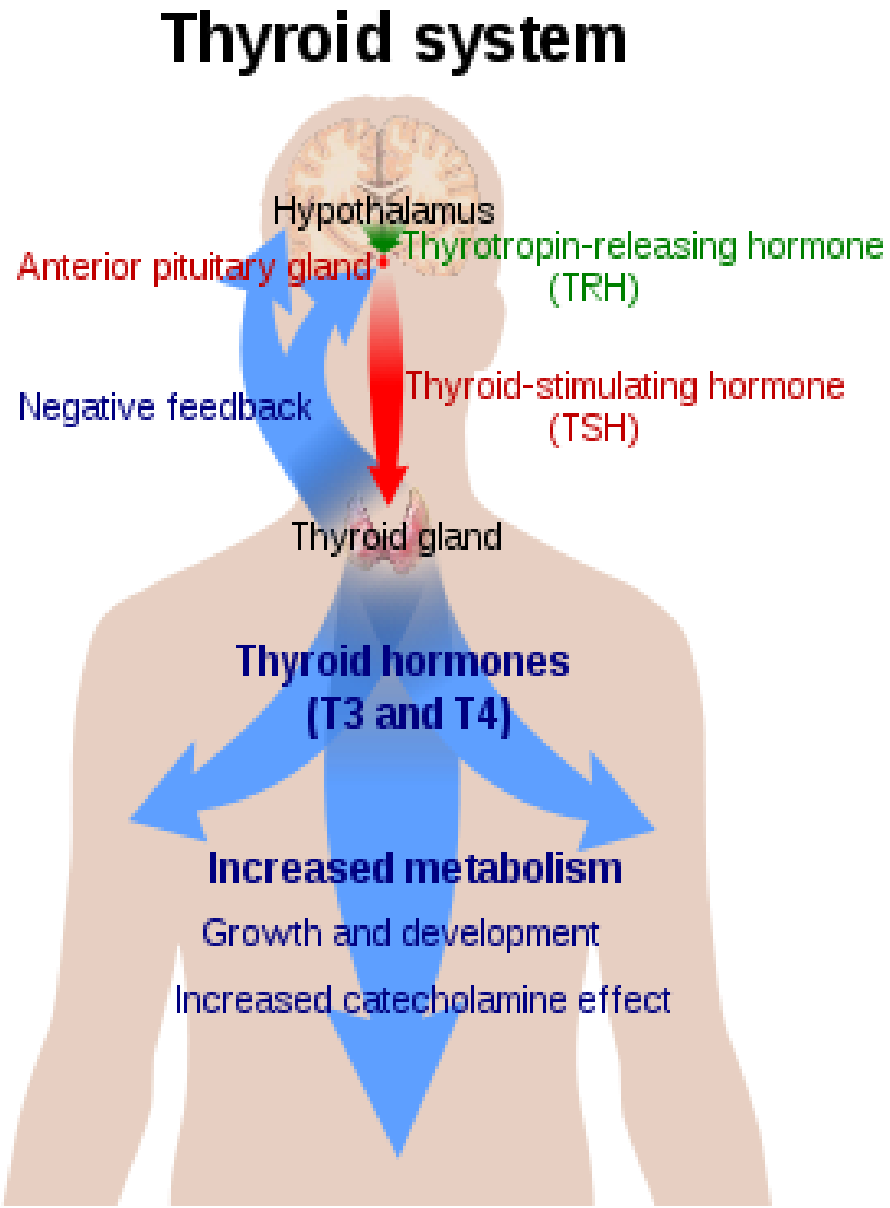
NORMAL VALUES:

Free T3-2.30 -4.20pg/ml

Free T4-0.89-1.76ng/ml

TSH-0.550-4.780uIU/ml.

The thyroid hormones T_3 and T_4 have a number of metabolic, cardiovascular and developmental effects on the body. The production is stimulated by release of thyroid stimulating hormone (TSH), which in turn depends on release[36,39] of thyrotropin releasing hormone (TRH). Every downstream hormone has negative feedback and decreases the level of the hormone that stimulates its release



BLOOD, LYMPH AND NERVE SUPPLY

The thyroid is supplied with arterial blood from the superior thyroid artery is a branch of the external carotid artery, and the inferior thyroid artery is a branch of the thyrocervical trunk, and sometimes by an anatomical variant the thyroid ima artery, which has a variable origin. The superior thyroid artery splits into anterior and posterior branches[12] supplying the thyroid, and the inferior thyroid artery splits into superior and inferior branches. The superior and inferior thyroid arteries join together behind the outer part of the thyroid lobes. The venous blood is drained via superior and middle thyroid veins,

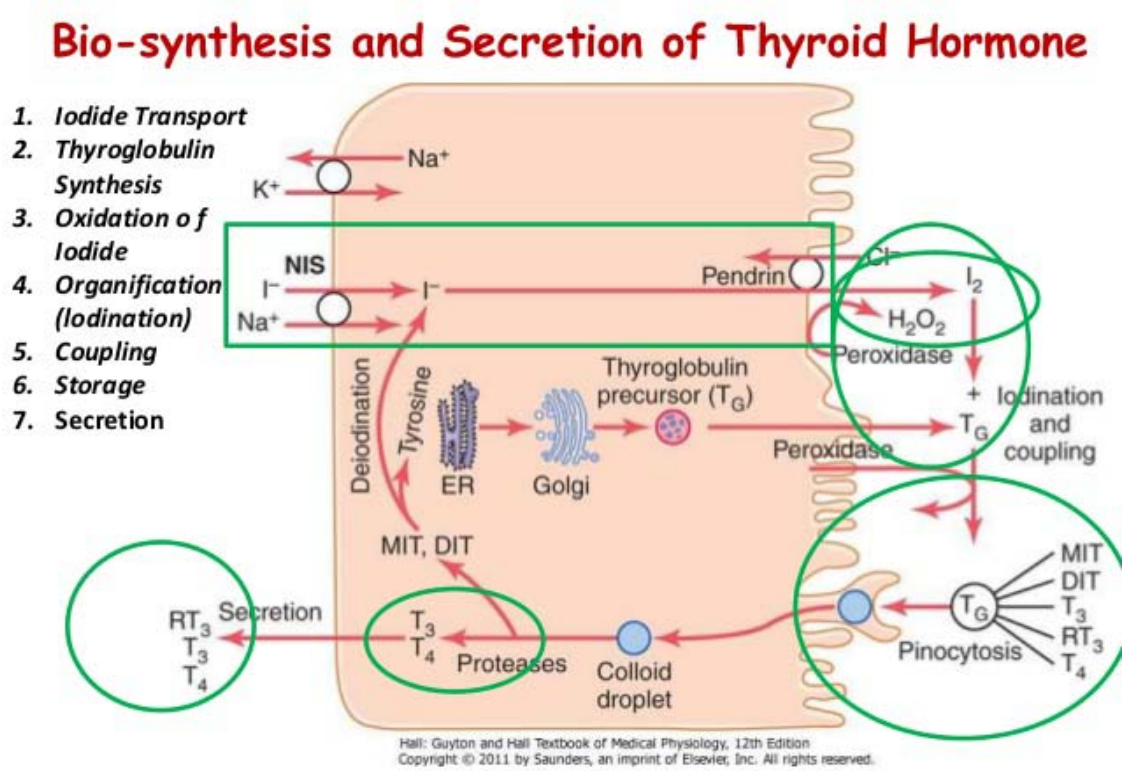
which drain to the internal jugular vein, and via the inferior thyroid veins. The inferior thyroid veins originate in a network of veins and drain into the left and right brachiocephalic veins. Both arteries and veins form a plexus between the two layers of the capsule of the thyroid gland.

Lymphatic drainage frequently passes the prelaryngeal lymph nodes (located just above the isthmus), and the pretracheal and paratracheal lymph nodes. The gland receives sympathetic nerve supply from the superior, middle and inferior cervical ganglion of the sympathetic trunk. The gland receives parasympathetic nerve supply from the superior laryngeal nerve and the recurrent laryngeal nerve.

Tests include a battery of blood tests including the measurement[35] of the thyroid hormones T3 and T4, as well as the measurement of TSH. T3 and T4 can be measured directly. However, as the two thyroid hormones travel bound

to other molecules, and it is the "free" component that is biologically active, free T3 and free T4 levels can be measured.

THYROID HORMONE PHYSIOLOGY



Follicular cells synthesize thyroglobulin in their golgi apparatus. This is a glycoprotein consisting of 70 linked tyrosine molecules[48], 10% of which are *iodinated*, and is stored in the colloid.

The thyroglobulin is then split to form the two amino acid derivative hormones produced in the thyroid gland which are triiodothyronine (T3) and thyroxine (T4). Thyroxine contains 4 iodine atoms, triiodothyronine contains 3. Creation of these two hormones is the only role of iodine in the body.

The majority (90%) of hormone produced by the follicular cells is T4. T4 can only be made in the thyroid gland. It can then be converted by other tissues into T3.

Iodine Uptake

Iodine circulates within the blood as iodide (I^-). It is actively transported into the follicular cells by an $Na+/I^-$ symport in the basal membrane[14]. This pump concentrates iodine in the colloid at a level up to 250x greater than the plasma level. This process is known as *iodide trapping.* The pump is activated by thyroid stimulating hormone (TSH) a hormone from the pituitary gland. Any excess iodide is excreted via the kidneys.

Secretion of Thyroid Hormones

Colloid uptake into the follicular cells takes place by endocytosis. The intracellular vesicles containing the colloid then fuse with lysosomes, where enzymes split the thyroglobulin into T3 and T4. The hormones diffuse across the basal plasma membrane into the interstitium (they are lipid soluble hormones).

Transport

Thyroid hormones are lipid soluble, thus need a transporting protein in order to travel in the blood.

Half-life in the blood is 1 day for T3, 6 days for T4. 99% of thyroid hormones in circulation are bound.

The primary transport protein for thyroid hormones is thyroid binding globulin (TBG). Synthesized in the liver, this protein binds 70-80% of the circulating thyroid hormones.

The remainder are carried by thyroxine-binding prealbumin or albumin.

Degradation

Only free T3 and free T4 can enter cells to exert their actions. T4 is deiodinated to T3 in many cells of the body, particularly the liver and kidneys.

The thyroid secretes 90% T4, with 50% of this being deiodinated to T3. The remainder is converted to reverse T3 (rT3). This is an inactive form of T3, and so creation of it is a regulatory mechanism. More rT3 is created when the body needs to reduce the action of T3 and T4. The hormones[14] are further deiodinated to diiodothyronine and monoiodothyronine in the liver and kidneys. Iodine is recycled or excreted in the urine.

Regulation

The hypothalamus[42] releases thyrotropin releasing hormone (TRH) which stimulates the adenohypophysis (anterior pituitary gland) to release thyroid stimulating hormone (TSH). This water soluble hormone travels in the blood to activate the thyroid gland by 5 actions:

1. Increased endocytosis and proteolysis of thyroglobulin from colloid
2. Increased activity of the Na^+/I^- symport

3. Increased iodination of tyrosine

4. Increased size and secretory activity of thyroid follicular cells

5. Increased number of follicular cells

INFLUENCE OF EXTERNAL FACTORS

Euthyroid sick syndrome: concurrent disease such as starvation, sepsis, trauma[38,15] or stress can cause a depression in basal thyroid levels as a normal response, to minimise the catabolic effects of thyroid hormones. This occurs in many species and may lead to false diagnoses of hypothyroidism or a missed diagnosis of hyperthyroidism.

Changes in Thyroid Hormone Levels during Illness

Severity of Illness	Free T3	Free T4	Reverse T3	TSH	ProbableCause
Mild	↓	N	↑	N	↓ D2, D1
Moderate	↓↓	N, ↑↓	↑↑	N, ↓	↓↓ D2, D1, ?↑ D3
Severe	↓↓↓	↓	↑	↓↓	↓↓ D2, D1, ↑D3
Recovery	↓	↓	↑	↑	?

D1 through D3, iodothyronine deiodinases; N, no change; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone.

Various patterns of thyroid hormone and TSH concentrations have been reported in euthyroid sick syndrome, reflecting the type and severity of illness[30]. Chopra et al[54]. have divided these patterns into following four major types:

1. Low T3 Syndrome

2. Low T3 and T4 syndrome

3. High T4 syndrome

4. Other abnormalities

1. LOW T3 SYNDROME

This is the most common abnormality[37], observed in about 70% of the hospitalized patients. Serum concentration of total triiodothyronine (T3) falls rapidly and progressively within 30 min to 24 hours of the onset of the causative illness[28,24]. The degree of fall reflects the severity of disease process. Levels vary from undetectable to normal, and the mean value is approximately 40% of the normal level. Whenever measured, the concentration of serum free T3 (fT3) is low normal[43] or slightly decreased. The daily production of T3 is decreased, while its clearance remains unchanged. The decreased conversion of thyroxine (T4) to T3 results from the inhibition of enzyme 1,5'-monodeiodinase (5'-MDI) activity, which catalyzes the deiodination of T4 to T3.10 Serum total T4 and free T4 (fT4) are normal in patients with low T3 syndrome.

Generally serum TSH concentration[16] and its response to thyrotropin releasing hormone (TRH) are normal. However TSH level may increase slightly, but returning to normal with recovery. The serum concentration of reverse T3 (rT3) is increased[31] except in renal failure and traumatic brain injury. Daily production rate of rT3 is normal. The increase in the serum rT3 level is mainly due to its reduced metabolic clearance.

2. Low T3 and T4 syndrome

The low T3 and T4 syndrome is observed in severely ill[22], moribund patients admitted to medical intensive care units. About 30-50% of patients have subnormal levels of T3 and T4. The T4 concentration falls over a period of 24-48 hours. However the fT4 values are frequently within normal limits. This disparity between low T4 values and normal fT4 levels is partly due to decreased T4 binding. Kinetic studies have shown reduced hepatic uptake and clearance of T4. The fall in circulating thyroid hormone concentration[43] coupled with reduced clearance implies substantially low thyroidal production rates.

Serum TSH concentration is frequently low, as measured with sensitive TSH assays and TRH responses are blunted. This blunted response is probably due to decrease in the enzyme activity responsible for TRH degradation, leading to impairment of TRH metabolism. TSH level rises with recovery, and may be transiently elevated until T3 and T4 levels are restored to normal. The

rT3 synthesis diminishes due to the decreased availability of its precursor T4, but because of slow degradation rT3 concentrations are frequently increased[48].

Several factors may contribute to low T3 and T4 levels.

These include: (1) reduced binding proteins[44], e.g., thyroxine binding globulin (TBG), albumin and prealbumin especially in chronic liver disease and in renal dialysis, (2) abnormal TBG due to altered sialylation[18], (3) circulating competitive binding inhibitors of T4 to serum protein, including drugs (furosemide in high doses), non-esterified fatty acids (NEFA) and metabolic products. (4) decreased serum TSH, especially in patients treated with dopamine.

3. High T4 syndrome

This is an unusual variant of euthyroid sick syndrome, seen in approximately 1% of sick patients. High serum T4 level is seen in some systemic illnesses-notably acute intermittent porphyria, liver diseases such as chronic active hepatitis and primary biliary cirrhosis, acute psychiatric illness, and patients on certain drugs such as amiodarone, and radiocontrast agents like ipodate and iopanoic acid used for oral cholecystography. The serum concentration of fT4 remains normal. The high serum T4 level is usually the result of increased serum TBG. Serum T3 may be normal or increased, but fT3 concentration is typically decreased[35]. The serum concentration of rT3 is also increased in such patients, a finding related to both a high TBG concentration

and a decreased metabolism of rT3. The serum TSH[19] is usually very low or undetectable, and TRH response is blunted to absent.

4. Other abnormalities

Studies have shown that there is decreased nocturnal TSH surge, unrelated to ambient circulating T4 and T3 levels, but probably related to hypothalamic dysregulation[23]. In addition, evidence suggests that TSH has reduced biological activity in euthyroid sick patients due to some structural abnormality.

Euthyroid sick syndrome is also associated with low serum total protein. Low albumin[20] and high sympathetic response like high cortisol and nor-epinephrine levels are also commonly seen in acutely ill patients.

CONDITIONS ASSOCIATED WITH EUTHYROID SICK SYNDROME

1. Medical

Acute myocardial infarction[40].

Acute renal failure.

Pulmonary tuberculosis[34].

Alcoholic liver disease.

Hepatic cirrhosis.

Lymphomas, leukemia and during their chemotherapy.

Aplastic anemia.

Stroke.

Malignancy.

Obstructive chronic bronchopneumopathy with acute respiratory failure.

Diabetic ketoacidosis.

Acute cerebral vasculopathies.

Collagenopathies.

Hodgkin disease.

Chronic heart failure .

2. Surgical

Acute and chronic spinal cord injury.

Major trauma.

Severe burn.

After elective cholecystectomy.

During and after cardiopulmonary bypass.

3. Infections

Viral hepatitis type A.

Advanced stages of HIV.

Sepsis.

4. Miscellaneous

Patients receiving antituberculosis treatment.

Premature and sick infants.

Bone marrow transplantation.

Haemodialysis.

Progressive systemic sclerosis.

Extensive dermatitis.

Malignant Mediterranean spotted fever**.**

Acute psychiatric illness

5. Drugs

a) Inhibitors of T4 to T3 conversion

Amiodarone

Glucocorticoids

Propranolol in high doses

Propylthiouracil

Radiographic contrast agents

b) Augmentation of clearance of T4 (enzyme induction)

Phenobarbital

Phenytoin

Rifampicin

Carbamazepine

c) Inhibitors of TSH secretion

Dopamine

L-Dopa

Somatostatin

d) Inhibitors of thyroid hormone synthesis or release

Iodine

Lithium

e) Inhibitors of binding of T4/T3 to serum proteins

Nonsteroidal anti-inflammatory agents.

Salicylates.

Heparin.

Furosemide

f) Increasing concentration of T4 binding proteins22

Estrogen

Clofibrate

Opiates

Perphenazine

g) Stimulators of TSH secretion

Haloperidol

Clomiphene Dopaminergic antagonist

MATERIALS AND METHODS

PATIENT SELECTION

The patients are selected from RNTCP Centre at Government Kilpauk Medical college Hospital and Otteri TB Hospital Chennai during the period from March 2017 to October 2017.

INCLUSION CRITERIA

New sputum smear positive pulmonary tuberculosis patients.

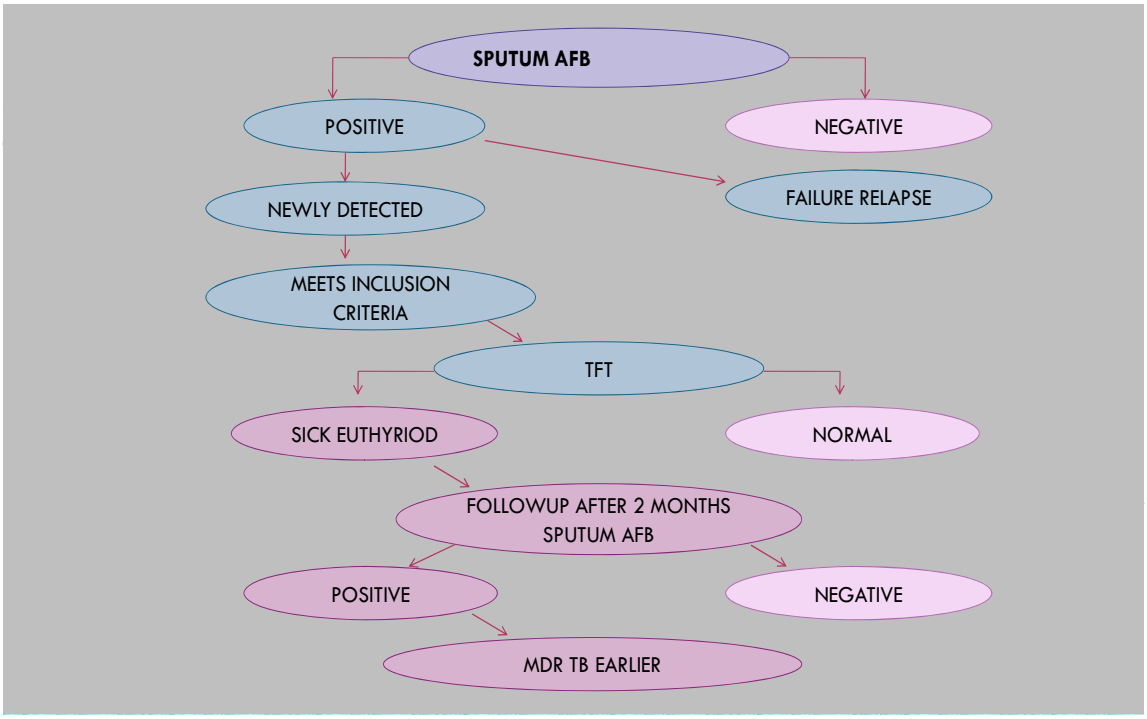
EXCLUSION CRITERIA

- Tuberculosis associated with systemic illness (DM, HIV, CAD, CKD, and CLD)
- Tuberculosis with known thyroid disease.
- Tuberculosis with drugs that interfere with thyroid function.
- Critically ill PTB patients

METHODS

- Patients who are coming to the Govt. KMCH and Otteri TB centre, who are detected as Sputum AFB positive for Pulmonary Tuberculosis are evaluated.
- The investigations done at the first visit to findout Euthyroid sick syndrome in sputum positive Tuberculosis includes fasting thyroid profile(done by CLIA –chemi luminescence immune assay method)
- They are followed up for sputum conversion at the end of intensive phase. So as to identify early development of Multi-Drug Resistant tuberculosis.
- For diagnosis of ESS is of three types.type1-Low T3 state. Type 2-combined low T3 and T4 state. Type 3-Low TSH state.

STUDY DESIGN



STATISTICAL ANALYSIS

Descriptive statistics was done for all data and suitable statistical tests of comparison were done.

Continuous variables were analysed with the Unpaired t-test and categorical variables were analysed with chi squared and Fisher Exact Test. Statistical significance was taken as $P < 0.05$. The data was analysed using SPSS Version 16. Microsoft Excel 2010.was used to generate charts.

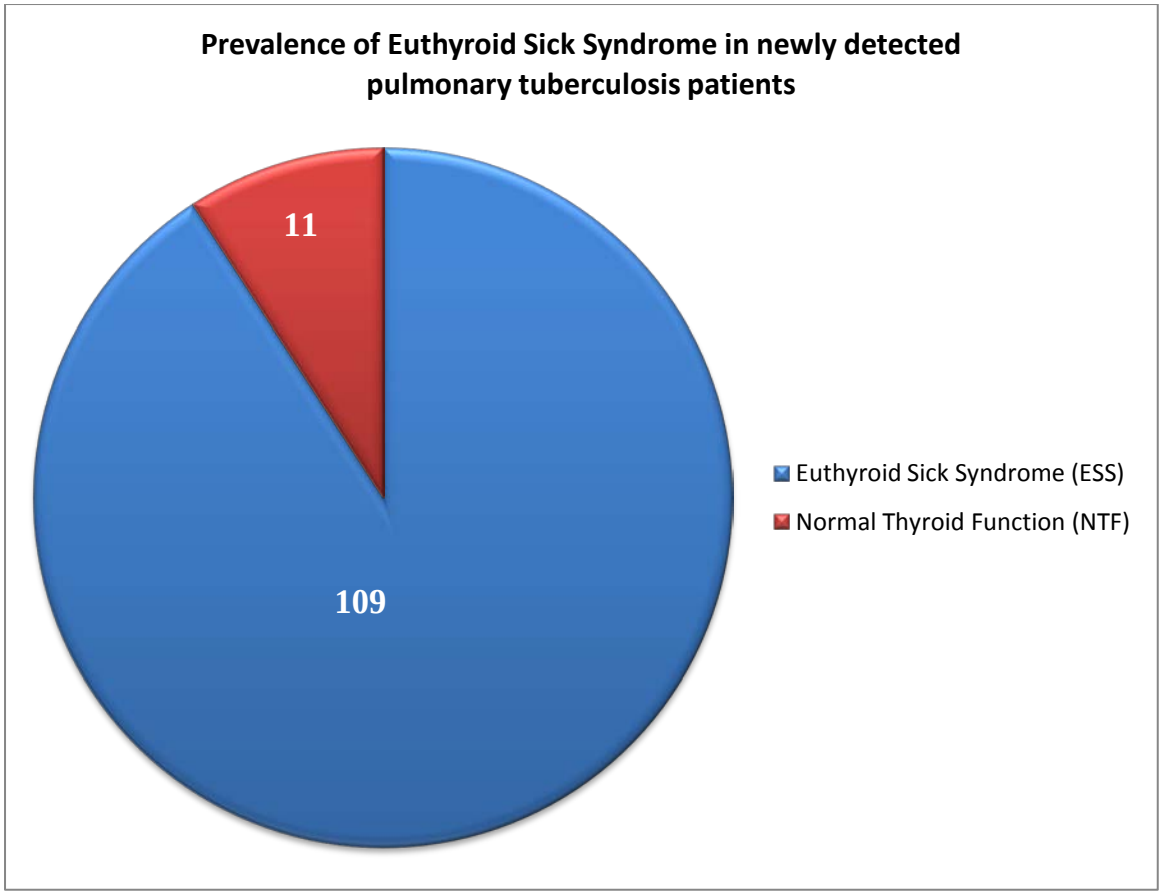
RESULTS AND ANALYSIS

Prevalence

Table1: Prevalence

Prevalence of Euthyroid Sick Syndrome in newly detected pulmonary tuberculosis patients	Number	%
Euthyroid Sick Syndrome (ESS)	109	90.83
Normal Thyroid Function (NTF)	11	9.17
Total	120	100.00

In this study, an analytical approach was adopted to assess the prevalence of euthyroid sick syndrome in newly detected pulmonary tuberculosis patients'. Data was collected from 120 selected subjects. For analysis purpose the study sample was internally compared (ESS and NTF groups), tabulated (Table:1), analysed and interpreted by using descriptive and inferential statistics in accordance to the objectives of the study.



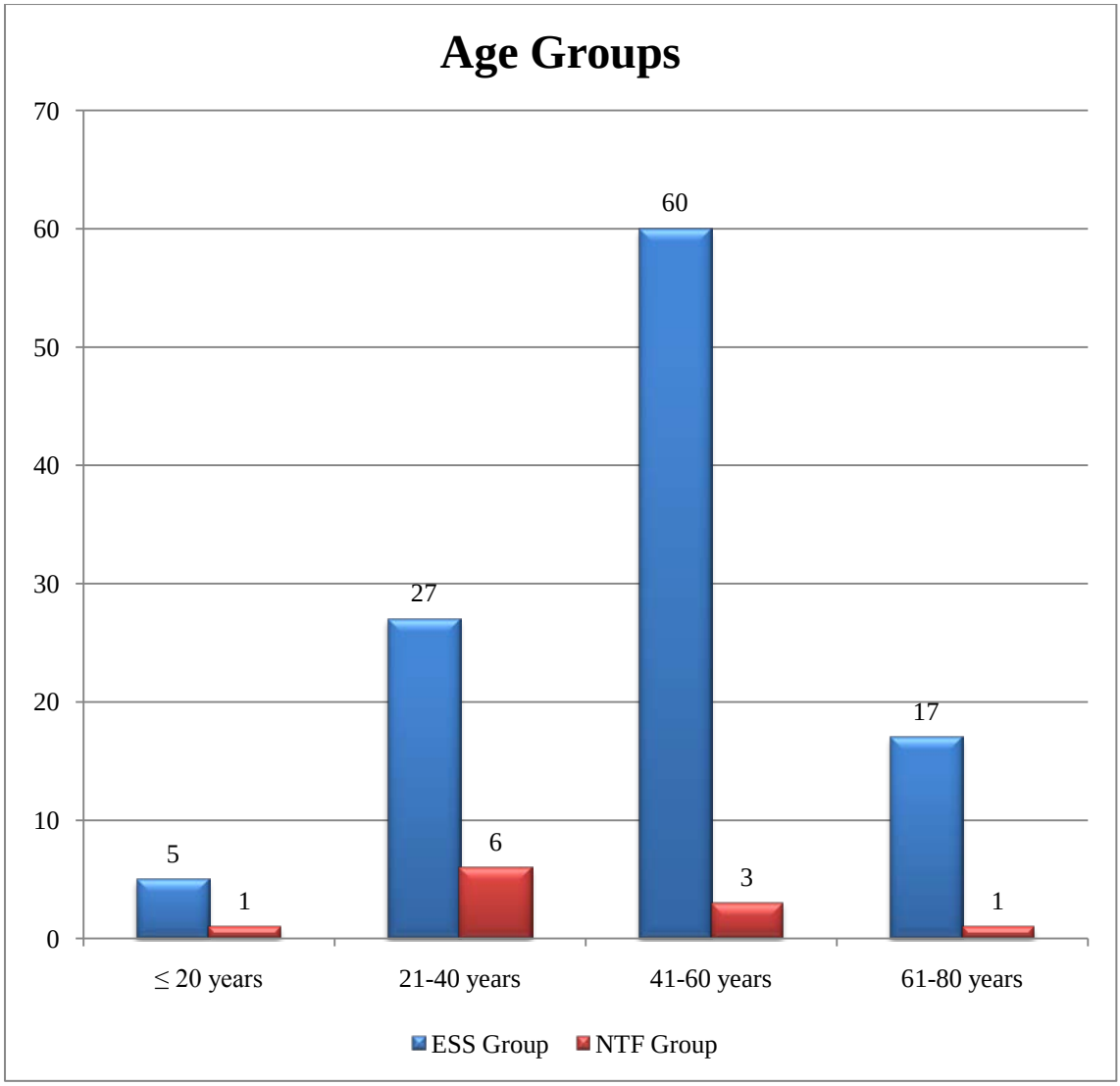
Age Distribution

Table 2: Age Distribution

Age Groups	ESS Group	%	NTF Group	%
≤ 20 years	5	4.59	1	9.09
21-40 years	27	24.77	6	54.55
41-60 years	60	55.05	3	27.27
61-80 years	17	15.60	1	9.09
Total	109	100.00	11	100.00

Age Distribution	ESS Group	NTF Group
Mean	47.18	39.09
SD	13.81	14.52
P value **Unpaired T Test**		**0.0677**

On analysis of age distribution, it was observed that majority in ESS group were in 41-60 years age group (55.05%) with a mean age of 47.18 years (Table:2). Similarly in NTF group majority were in 21-40 years age group (54.55%) with a mean age of 39.09 years. The data subjected to statistical unpaired t test reveals the existence of statistically insignificant association between age distribution and thyroid function both groups (p=0.0677).

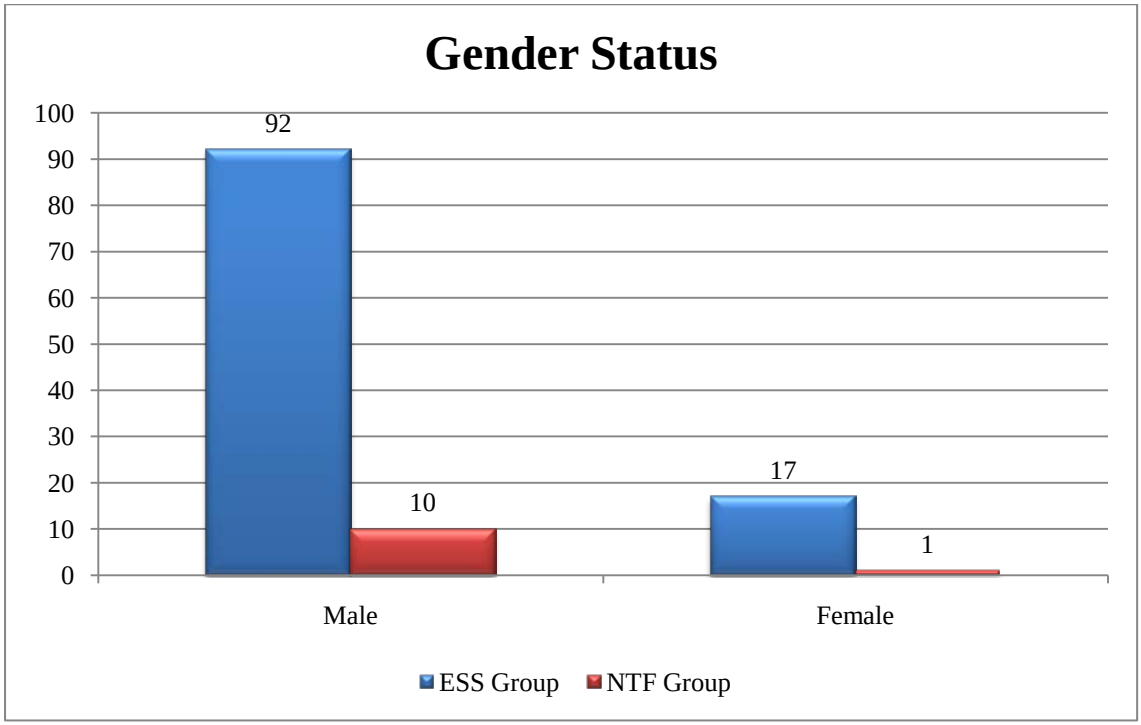

Age Groups
70
60
50
40
30
20
10
0
5
1
27
6
60
3
17
1
≤ 20 years
21-40 years
41-60 years
61-80 years
ESS Group
NTF Group

Gender Distribution

Table 3: Gender Distribution

Gender Status	ESS Group	%	NTF Group	%	P value Fishers Exact Test
Male	92	84.40	10	90.91	**>0.9999**
Female	17	15.60	1	9.09	
Total	109	100.00	11	100.00	

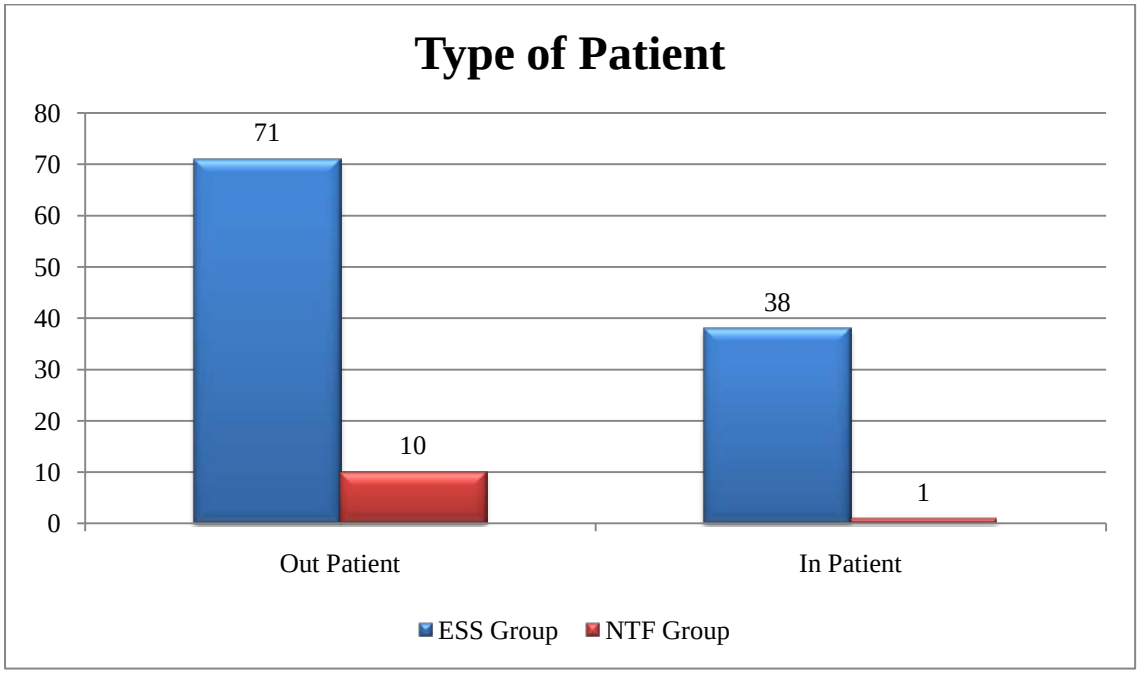
On analysis of gender status, it was observed that majority in ESS group were males (84.40%) and similarly in NTF group majority too were males (90.91%) (p= >0.9999) (Table: 3). The data subjected to statistical fishers exact test reveals the existence of statistically insignificant association between gender status and thyroid function both groups (p > 0.9999).



Type of Patient

Table 4: Type of patient

Type of Patient	ESS Group	%	NTF Group	%	P value Fishers Exact Test
Out Patient	71	65.14	10	90.91	0.1008
In Patient	38	34.86	1	9.09	
Total	109	100.00	11	100.00	



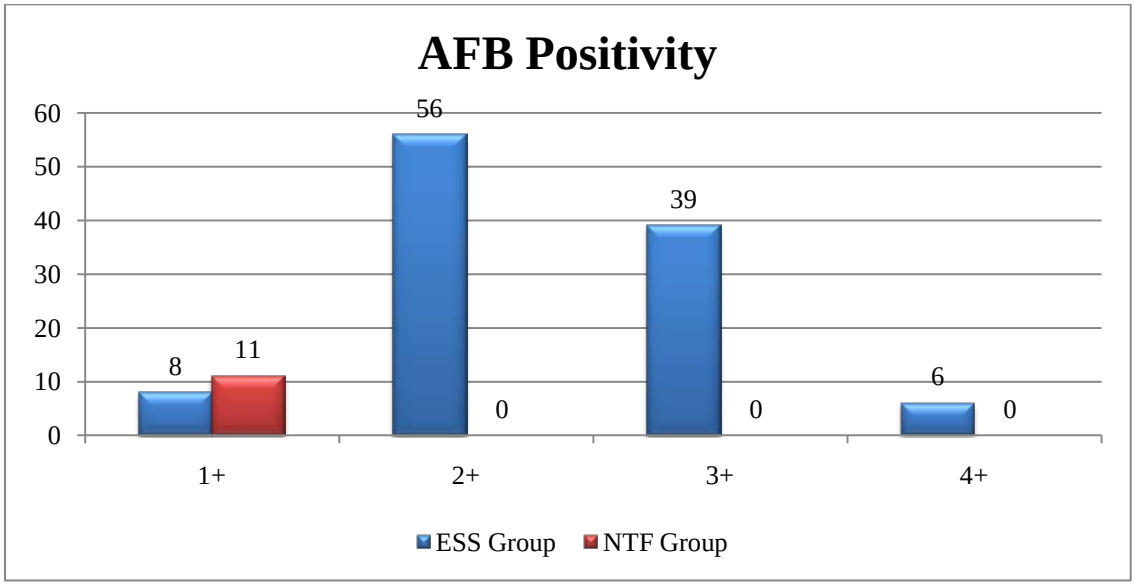
On analysis of type of patients, it was observed that majority in ESS group were from outpatient department (65.14%) and similarly in NTF group majority too were from outpatient department (90.91%) (p= 0.1008) (Table: 4). The data subjected to statistical fishers exact test reveals the existence of statistically insignificant association between type of patient status and ESS and NTF groups with a P value of 0.1008.

AFB Positivity

Table 5: AFB Positivity

AFB Positivity	ESS Group	%	NTF Group	%	P value Fishers Exact Test
1+	8	7.34	11	100.00	<0.0001
2+	56	51.38	0	0.00	
3+	39	35.78	0	0.00	
4+	6	5.50	0	0.00	
Total	109	100.00	11	100.00	

On analysis of AFB positivity status, it was observed that majority in ESS group were 2+ positive (51.38%) followed by 3+ positivity (35.78%). Similarly in NTF group majority were 1+ positivity (100%) (Table : 5). The data subjected to statistical fishers exact test reveals the existence of statistically significant association between AFB positivity status and thyroid function ESS groups (p= <0.0001)

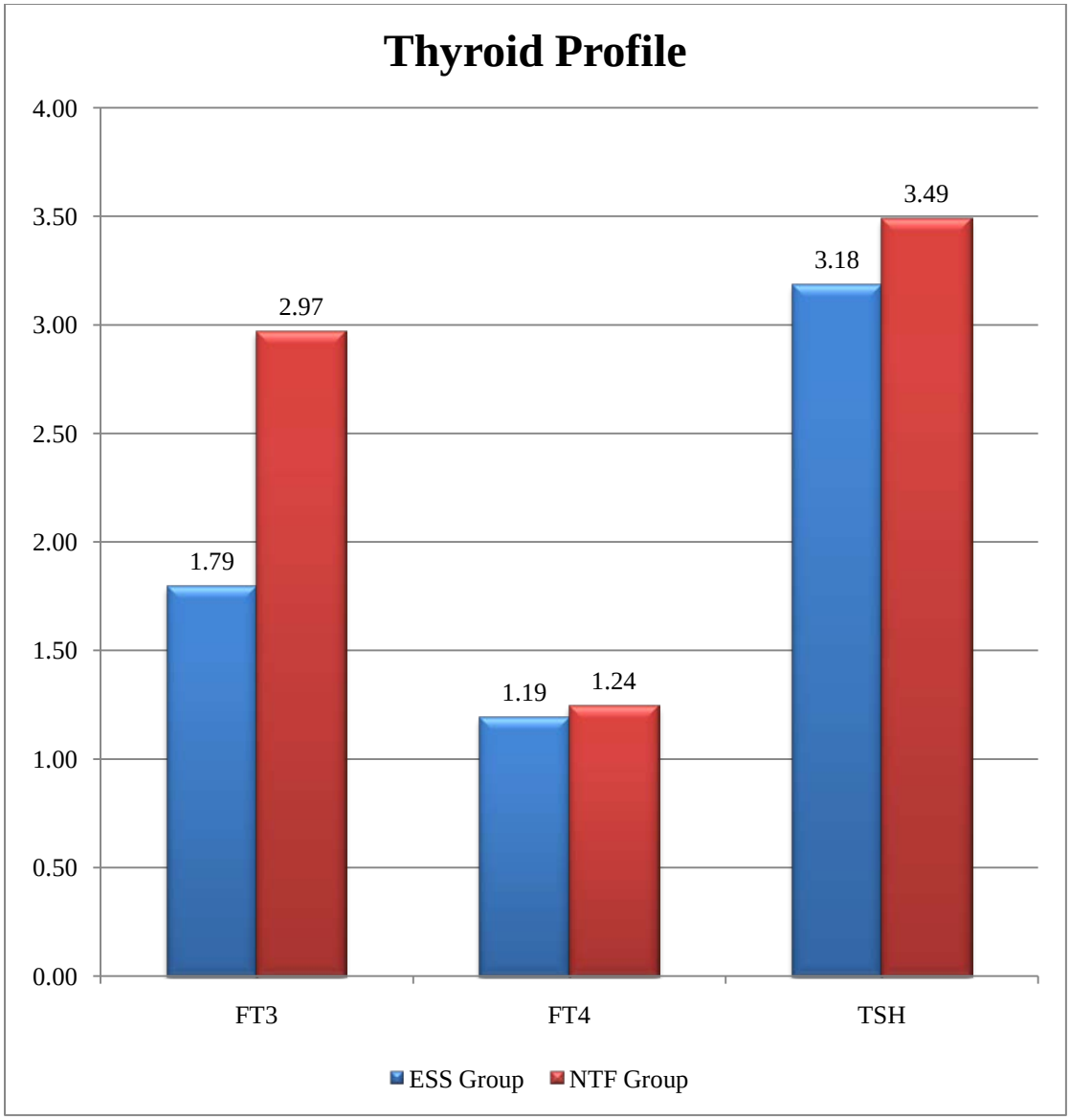


Thyroid Profile

Table 6: Thyroid Profile

Thyroid Profile		**FT3**	**FT4**	**TSH**
ESS Group	Mean	1.79	1.19	3.18
	SD	0.36	0.42	0.82
NTF Group	Mean	2.97	1.24	3.49
	SD	0.32	0.13	0.66
P value Unpaired T Test		<0.0001	0.6683	0.2356

On analysis of thyroid profile distribution, it was observed that in ESS group the mean values of FT3, FT4 and TSH were 1.79, 1.19 and 3.18. Similarly in NTF group the mean values of FT3, FT4 and TSH were 2.97, 1.24 and 3.49 respectively (p= <0.0001, 0.6683 and 0.2356) (Table: 6). The data subjected to statistical unpaired t-test reveals the existence of statistically significant association between FT3 distribution and thyroid function both groups ($p < 0.0001$) and existence of statistically insignificant association between FT4/TSH distribution and thyroid function both groups P=0.6683,0.2356.


Thyroid Profile
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
1.79
2.97
1.19
1.24
3.18
3.49
FT3
FT4
TSH
ESS Group
NTF Group

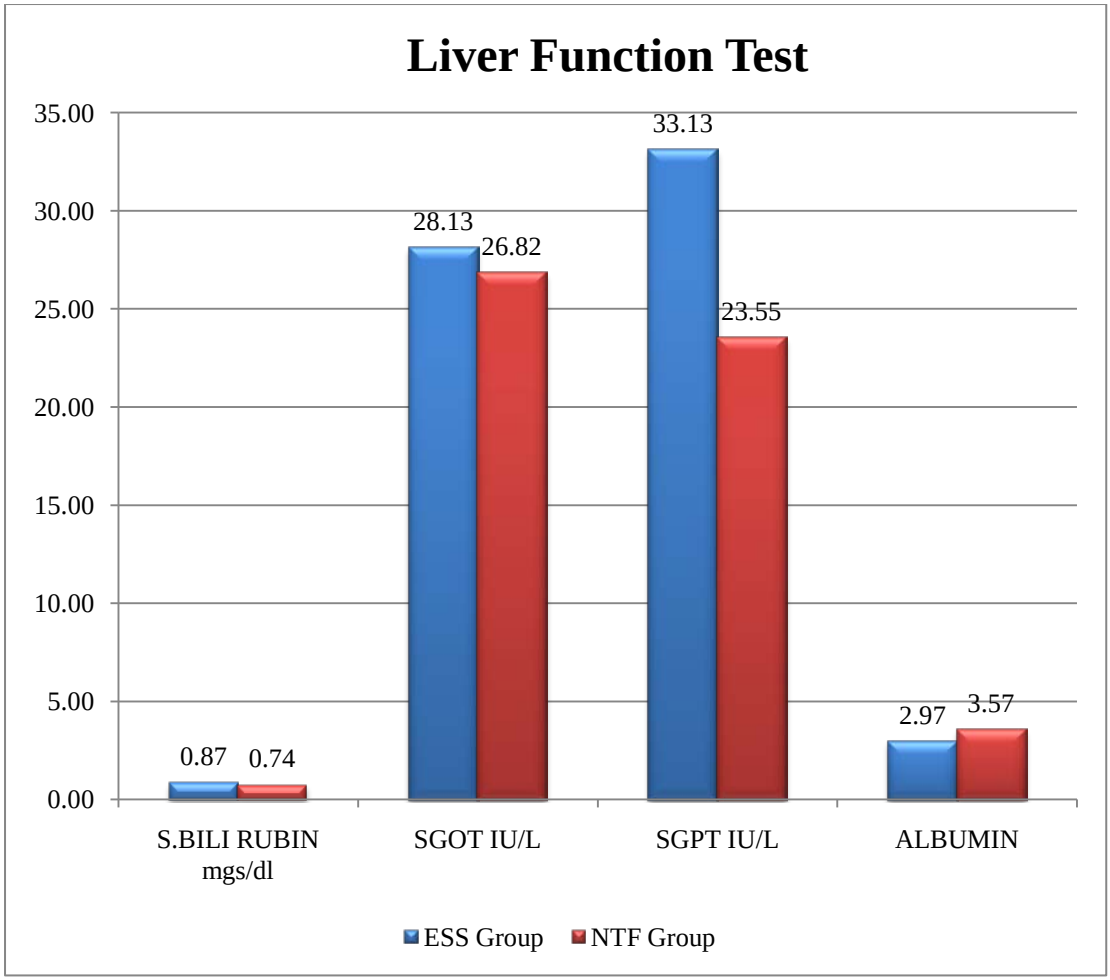
Liver Function Test(LFT)

Table 7: LFT

Lipid Profile		**S.BILI RUBIN mgs/dl**	**SGOT IU/L**	**SGPT IU/L**	**ALBUMIN**
ESS Group	**Mean**	0.87	28.13	33.13	2.97
	SD	0.41	8.18	41.74	0.87
NTF Group	**Mean**	0.74	26.82	23.55	3.57
	SD	0.15	7.57	8.59	0.89
P value Unpaired T Test		0.2819	0.6116	0.4505	0.0311

On analysis of liver function test, it was observed that in ESS group the mean values of bilirubin, SGOT, SGPT and albumin were 0.87, 28.13, 33.13 and 2.97. Similarly in NTF group the bilirubin, SGOT, SGPT and albumin were 0.74, 26.82, 23.55 and 3.57 respectively (p= 0.2819, 0.6116, 0.4505 and 0.0311) (Table :7).

The data subjected to statistical unpaired t test reveals the existence of statistically significant association between albumin distribution and thyroid function both groups (p = 0.0311) and existence of statistically insignificant association between bilirubin/SGOT/SGPT distribution and thyroid function both groups (p=0.2819,0.6116,0.4505).

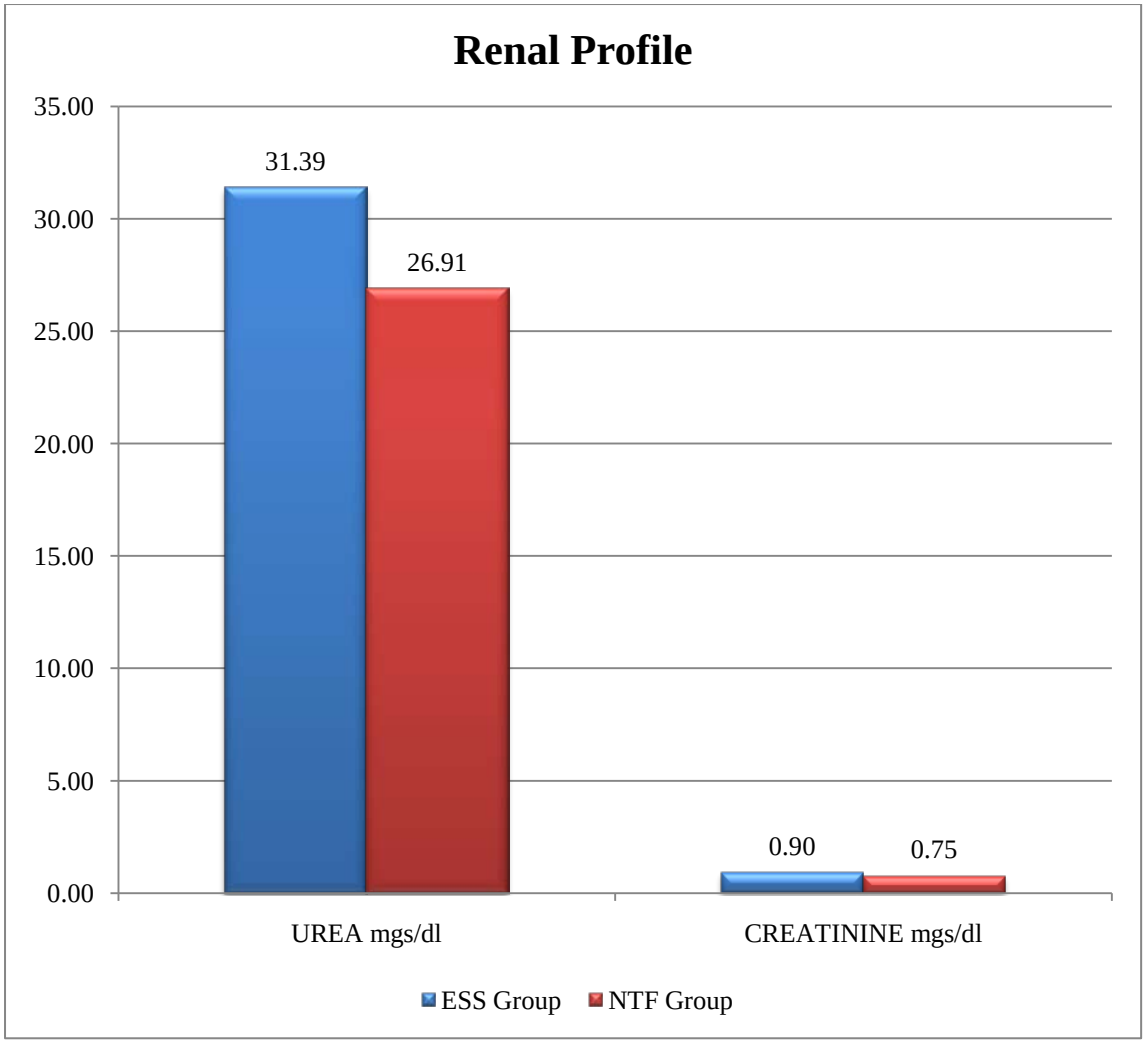

Liver Function Test
35.00
30.00
25.00
20.00
15.00
10.00
5.00
0.00
0.87
0.74
28.13
26.82
33.13
23.55
2.97
3.57
S.BILI RUBIN mgs/dl
SGOT IU/L
SGPT IU/L
ALBUMIN
ESS Group
NTF Group

Renal Profile

Table 8: Renal Profile

Renal Profile		UREA mgs/dl	CREATININE mgs/dl
ESS Group	**Mean**	31.39	0.90
	SD	11.79	0.19
NTF Group	**Mean**	26.91	0.75
	SD	18.68	0.11
P value Unpaired T Test		0.2609	0.0158

On analysis of renal profile distribution, it was observed that in ESS group the mean values of urea and creatinine were 31.39 and 0.90. Similarly in NTF group the mean values of urea and creatinine were 26.91 and 0.75 respectively (p= 0.2609 and 0.0158) (Table: 8). The data subjected to statistical unpaired t test reveals the existence of statistically significant association between creatinine distribution and thyroid function both groups (p=0.0158) and existence of statistically insignificant association between urea distribution and thyroid function both groups (p =0.2609).


Renal Profile
35.00
30.00
25.00
20.00
15.00
10.00
5.00
0.00
31.39
26.91
0.90
0.75
UREA mgs/dl
CREATININE mgs/dl
ESS Group
NTF Group

Treatment outcomes Based on Sputum Grading at the end of two months

Table 9: Treatment outcomes Based on Sputum Grading –ESS group

Treat-ment out-comes Based on Sputum Grading - ESS Group	Negative	Positive	Not taken Tablet	Dropped Out	Dead/Defaulter	Negative (%)	Positive (%)	Not taken Tablet (%)	Dropped Out (%)	Dead/Defaulter (%)
1+	7	0	0	0	1	9.33	0.00	0.00	0.00	16.67
2+	49	1	1	4	1	65.33	5.56	100.00	44.44	16.67
3+	18	13	0	5	3	24.00	72.22	0.00	55.56	50.00
4+	1	4	0	0	1	1.33	22.22	0.00	0.00	16.67
Total	75	18	1	9	6	100.00	100.00	100.00	100.00	100.00
P value Chi Squared Test						<0.0001				

On analysis of treatment outcomes based on sputum grading in ESS group, it was observed that majority of sputum negative patients had 2+ grading (65.33%), sputum positive patients had 3+ grading (72.22%), not taken tablets patients had 2+ grading (100%), dropped out patients had 2+ and 3+ grading (100%) and dead/defaulter patients had ≥ 3+ grading (66.67%) (p= <0.0001) (Table:9).

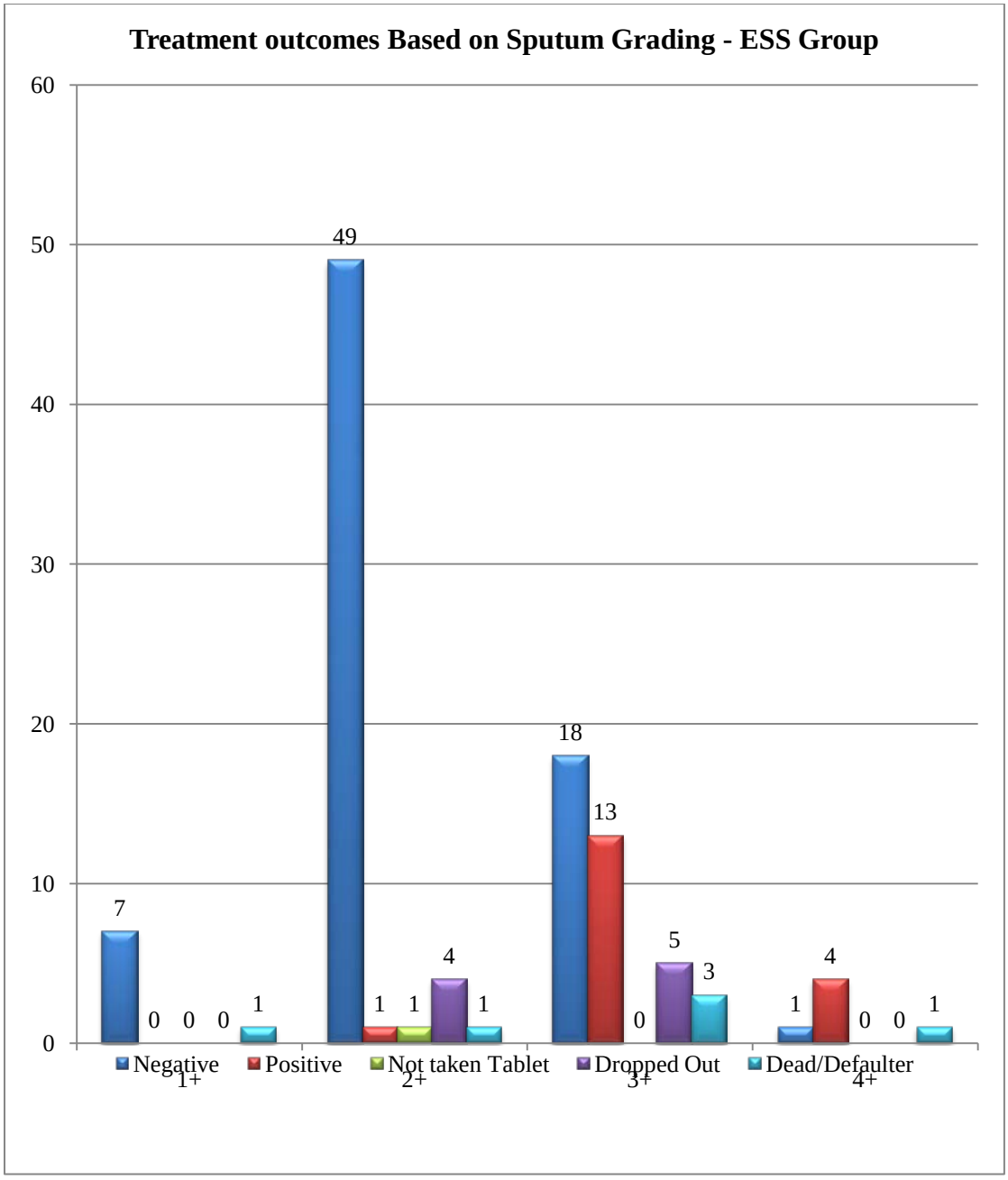
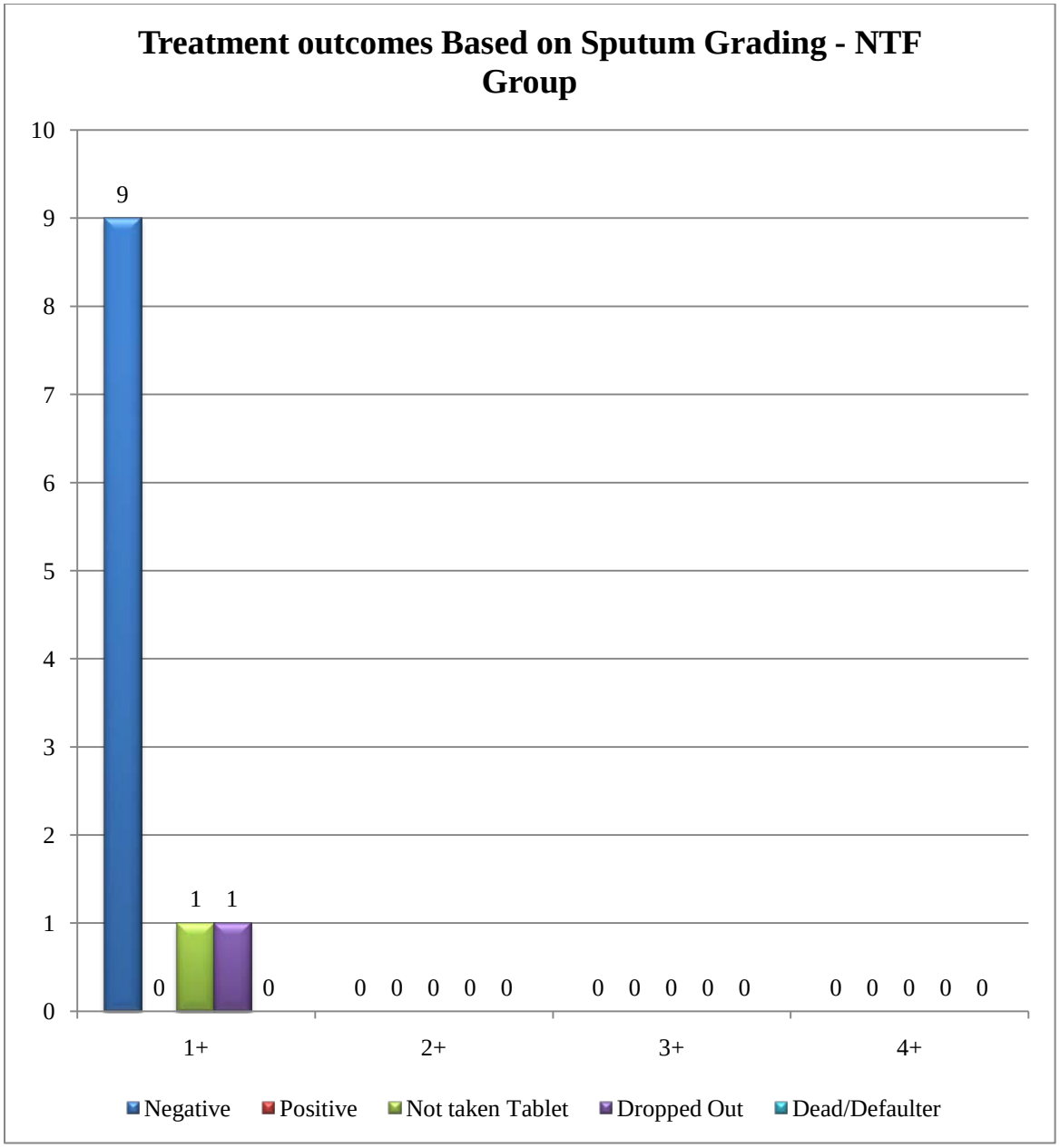

Treatment outcomes Based on Sputum Grading - ESS Group
60
50
40
30
20
10
0
49
18
13
7
0
0
0
1
1
1
4
1
0
5
3
1
4
0
0
1
Negative
Positive
Not taken Tablet
Dropped Out
Dead/Defaulter
1+
2+
3+
4+

Table 10: Treatment outcomes Based on Sputum Grading –NTF Group

Treatment outcomes Based on Sputum Grading - NTF Group	Negative	Positive	Not taken Tablet	Dropped Out	Dead/Defaulter	Negative (%)	Positive (%)	Not taken Tablet (%)	Dropped Out (%)	Dead/Defaulter (%)
1+	9	0	1	1	0	100.00	0.00	100.00	100.00	0.00
2+	0	0	0	0	0	0.00	0.00	0.00	0.00	0.00
3+	0	0	0	0	0	0.00	0.00	0.00	0.00	0.00
4+	0	0	0	0	0	0.00	0.00	0.00	0.00	0.00
Total	9	0	1	1	0	100.00	0.00	100.00	100.00	0.00
P value Chi Squared Test						>0.9999				

On analysis of treatment outcomes based on sputum grading in NTF group, it was observed that all sputum negative patients, not taken tablets patients had 1+ grading and dropped out patients had1+ grading (100%) (p= >0.9999) (Table:10).


Treatment outcomes Based on Sputum Grading - NTF Group
10
9
8
7
6
5
4
3
2
1
0
9
0
1
1
0
0 0 0 0 0
0 0 0 0 0
0 0 0 0 0
1+
2+
3+
4+
Negative
Positive
Not taken Tablet
Dropped Out
Dead/Defaulter

Sputum Grading Among AFB Positive Patients with Low FT3 levels

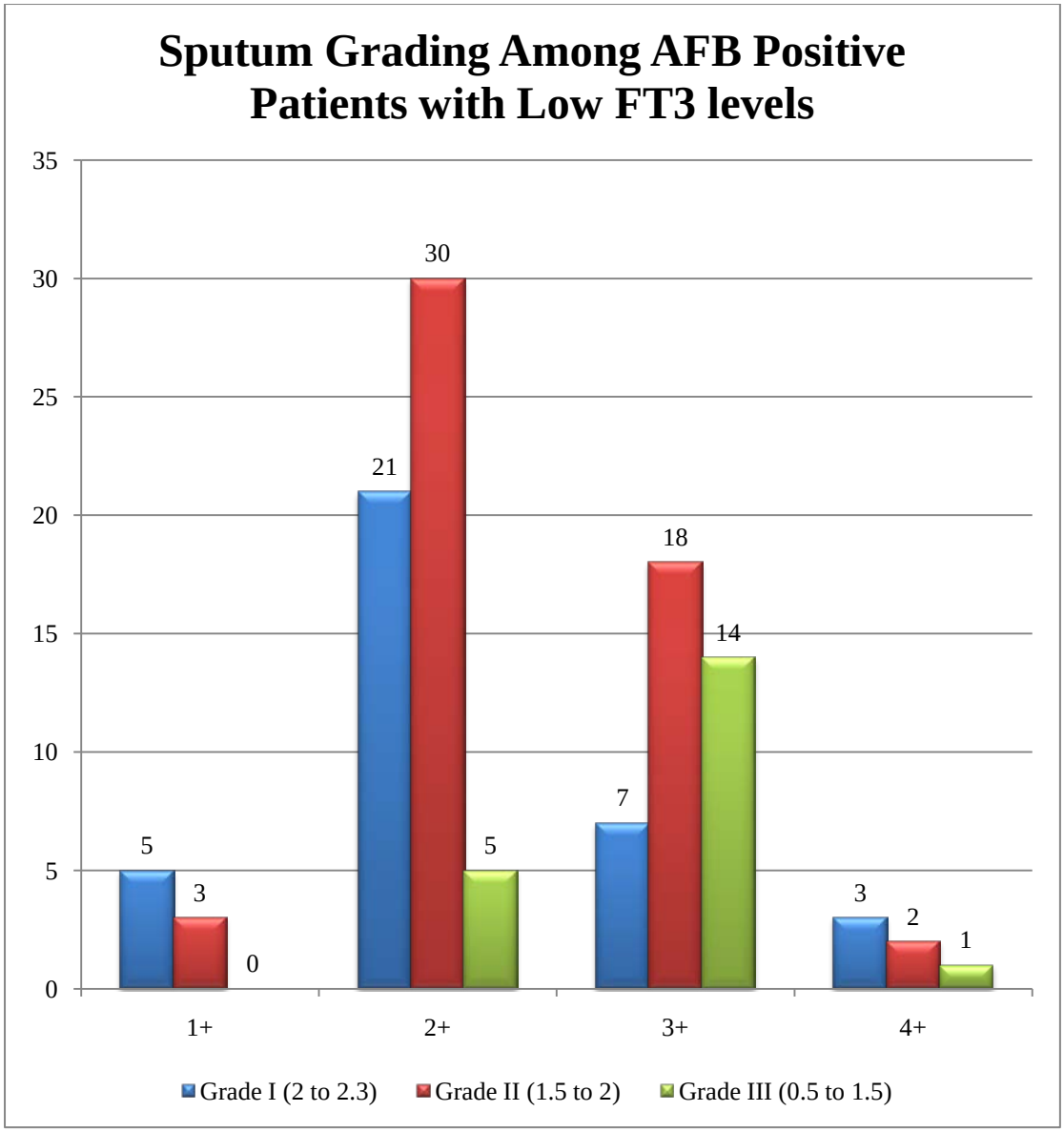
Table 11: Sputum Grading Among AFB

Positive Patients with Low FT3 levels

Sputum Grading Among AFB Positive Patients with Low FT3 levels	Grade I (2 to 2.3)	Grade II (1.5 to 2)	Grade III (0.5 to 1.5)	Grade I (%)	Grade II (%)	Grade III (%)
1+	5	3	0	13.89	5.66	0.00
2+	21	30	5	58.33	56.60	25.00
3+	7	18	14	19.44	33.96	70.00
4+	3	2	1	8.33	3.77	5.00
Total	36	53	20	100.00	100.00	100.00
P value Chi Squared Test				0.0092		

On analysis of sputum grading among AFB positive patients with low FT3 levels, it was observed that majority of grade I patients had 2+ grading (58.33%), grade II patients had 2+ grading (56.60%) and grade III patients had ≥ 3+ grading (75%) (p= 0.0092) (Table: 11).

The data subjected to statistical chi squared test reveals the existence of statistically significant association between sputum grading among AFB positive patients and low FT3 levels (p =0.0092).


Sputum Grading Among AFB Positive Patients with Low FT3 levels
35
30
25
20
15
10
5
0
5
3
0
21
30
5
7
18
14
3
2
1
1+
2+
3+
4+
Grade I (2 to 2.3)
Grade II (1.5 to 2)
Grade III (0.5 to 1.5)

DISCUSSION

In our study the AFB positivity status between the ESS and NTF groups was meaningfully significant.

This is evident by the increased 2+, 3+ and 4+sputum positivity rate in ESS group compared to NTF group (92.66 percentage points more, 93% more positivity) and the decreased 1+ positivity rate in ESS group compared to NTF group (92.66 percentage points less , 93% less positivity). Further, Cohen's effect size value (d = 0.93) suggested a very high practical significance (84% study subjects with euthyroid sick syndrome will have higher than 2+ AFB positivity as outcome).

In our study the FT3 distribution between the ESS and NTF groups was meaningfully significant. This is evident by the decreased mean FT3 in ESS group compared to NTF group (1.17 mean units less, 40% lower). Further, Cohen's effect size value (d = 3.45) suggested a very high practical significance (99% study subjects with euthyroid sick syndrome will have lower free T3 levels at presentation).

In our study the albumin distribution between the ESS and NTF groups was meaningfully significant.

This is evident by the decreased mean albumin levels in ESS group compared to NTF group (0.60 mean units less, 17% lower). Further, Cohen's effect size value (d = 0.68) suggested a high practical significance (75% study

subjects with euthyroid sick syndrome will have lower albumin levels at presentation).

In our study the creatine distribution between the ESS and NTF groups was meaningfully significant.

This is evident by the increased mean creatinine levels in ESS group compared to NTF group (0.14 mean units more, 16% higher). Further, Cohen's effect size value (d = 0.95) suggested a very high practical significance (84% study subjects with euthyroid sick syndrome will have higher creatinine levels at presentation).

In our study the of treatment outcomes based on sputum grading in ESS group was meaningfully significant. This is evident by the increased incidence of death in ≥3+ positivity rate in ESS group compared to < 3+ positivity rate in ESS group (33.33 percentage points more, 50% more positivity) Further, Cohen's effect size value (d = 0.50) suggested a moderate practical significance (69% study subjects with euthyroid sick syndrome with higher than 2+ AFB positivity will encounter death/defaulter as treatment outcome).

In our study the sputum grading among AFB positive patients and low FT3 levels were meaningfully significant. This is evident by the increased incidence of ≥3+ positivity rate in grade III group compared to grade II (37.26 percentage points more, 50% more positivity) and grade I groups (47.22) percentage points more, 63% more positivity). Further, Cohen's effect size value (d = 0.77) suggested a moderate practical significance (78% study subjects with low T3 will have greater AFB positivity as outcome).

In 1995 a prospective study conducted by chow et al[54]., titled as Euthyroid Sick Syndrome in Pulmonary Tuberculosis done by the Department of Medicine, Chinese University of Hong Kong, Prince of wales Hospital. The author of this study was Shatin,NT. In this study 40 patients over 50 years of age with newly diagnosed pulmonary tuberculosis were taken. For this patients blood samples were taken for serial thyroid function test at 1, 2 and 4 months interval. This study was conducted for 12 months. The Euthyroid Sick Syndrome occur in 63% of patients. Twelve of 25 ESS patients died as compared to 1 of 15 patients with normal thyroid function test. Among ESS patients those who died had significantly lower Free T3 concentration which reflects severity of illness and subsequent mortality.

In our study out of 120 patients who are sputum positive Tuberulosis, 109 patients were detected as ESS (90.83%). In this 109 patients, at the end of 2nd month 18 patients were remains sputum positive (16.15%) and 6 patients were died (5.50%). Those who remain sputum positive at the end of 2nd months, 13 out of 18 patients show 3 + grading of sputum (72.22%) at the time of initial diagnosis. The patients who died at the end of two months showed 3+ and 4+ grading of sputum at initial diagnosis itself (66.67%). In our study the Free T3 distribution between the ESS and NTF groups was meaningfully significant(<0.0001).Further Cohen's effect size value(d=3.45) suggested a very high practical significance (99% study subjects with euthyroid sick syndrome will have lower free T3 levels at presentation).

CONCLUSION

Euthyroid sick syndrome in TB patients will result in significantly heavy AFB staining (2+ to 4+) compared to patients with normal thyroid function. This suggests that TB patients with comorbid euthyroid sick syndrome will have enhanced degree of infectiousness.

Euthyroid sick syndrome in TB patients will result in significantly lower free T3 levels at presentation compared to patients with normal thyroid function. This suggests that TB patients with comorbid euthyroid sick syndrome presenting with lower free T3 levels will have enhanced severity of illness. It can also be used as a specific marker of euthyroid sick syndrome in TB patients.

Euthyroid sick syndrome in TB patients will result in significantly lower albumin levels at presentation compared to patients with normal thyroid function. This suggests that lower albumin levels at presentation can be used as a specific marker of euthyroid sick syndrome in TB patients and also signifies grave prognosis Euthyroid sick syndrome in TB patients will result in significantly higher creatinine levels compared to patients with normal thyroid function. This suggests that higher creatine levels can be used in TB patient with euthyroid sick syndrome as it signifies grave prognosis.

Euthyroid sick syndrome in TB patients with heavy AFB staining (2+ to 4+) will result in significantly more incidence of death or treatment default compared to patients with normal thyroid function. This suggests that TB

patients with comorbid euthyroid sick syndrome and heavy AFB load will have enhanced risk of death. This data suggests that heavy AFB load at presentation in euthyroid sick syndrome patients predicts a subsequent high mortality.

Low FT3 values in TB patients will result in significantly heavy AFB staining compared to patients with normal FT3.

To identify the prevalence of ESS in new sputum positive PTB patients and correlate with disease burden and failure of sputum conversion at the end of intensive phase treatment and it may necessitate the earlier identification of MDR strains among PTB patients with ESS.

To conclude those patients who are sputum positive Tuberculosis, thyroid profile has to be done the initial diagnosis itself. So Sputum Positive Tuberculosis Patients with Euthyroid sick Syndrome has to be closely monitored every month to identify earlierly Multi-Drug Resistant Tuberculosis. So that we can prevent mortality due to Multi-Drug Resistant Tuberculosis.

BIBLIOGRAPHY

1. Harrison’s Principles of Internal Medicine:19th Edition;2016

2. “WHO treatment guidelines for drug-resistant tuberculosis (2017 update)”, http://www.who.int/tb/areas-of-work/drug-resistant-tb/ treatment/ resources/en/

3. Euthyroid sick syndrome : Thyroid disorders : Merck Manual Professional. Retrieved 2009-23-29.

4. Saad T, Jyoti T, Wahid K & Jamal A 2014. Predisposing factors for pulmonary tuberculosis. J. Med.SciClin.Res., 2(5):949-957.

5. Drobniewski F, Caws M, Gibson A, Young D (2003). "Modern laboratory diagnosis of tuberculosis". Lancet Infect Dis. 3 (3): 141–7. PMID 12614730. doi:10.1016/S1473-3099(03)00544-9.

6. Moore D, Evans C, Gilman R, Caviedes L, Coronel J, Vivar A, Sanchez E, Piñedo Y, Saravia J, Salazar C, Oberhelman R, Hollm-Delgado M, LaChira D, Escombe A, Friedland J (2006). "Microscopic-observation drug-susceptibility assay for the diagnosis of TB". N Engl J Med. 355 (15): 1539–50. PMC 1780278. PMID 17035648. doi:10.1056/NEJMoa 055524. Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, Drobniewski F, Lalvani A (2007). "A systematic review of rapid diagnostic tests for the detection of tuberculosis infection". Health Technol Assess. 11 (3): 1–314. PMID 17266837. doi:10.3310/hta11030.

7. Lalvani A (2003). "Spotting latent infection: the path to better tuberculosis control". Thorax. 58 (11): 916–8. PMC 1746498. PMID 14586040. doi:10.1136/thorax.58.11.916. Kang YA, Lee HW, Hwang SS, et al. (2007). "Usefulness of Whole-Blood Interferon-γ Assay and Interferon-γ Enzyme-Linked Immunospot Assay in the Diagnosis of Active Pulmonary Tuberculosis". Chest. 132 (3): 959–65. PMID 17505029. doi:10.1378/chest.06-2805.

8. Arbex MA, Varella MCL, Siqueira HR, Mello FAF.Antituberculosis drugs: Drug interactions, adverse effects, and use in special situations. Part 2: Second-linedrugs.J Bras Pneumol.2010; 36 (5):641-656.http://dx.doi.org/10.1590/S1806-37132010000500017

9. World Health Organization (WHO) (2012) Global Tuberculosis Report 2012. (WHO/HTM/TB/2012.6).Geneva.Caminero JA, Sotgiu G, Zumla A, Migliori GB. Best drug treatment for multidrug-resistant and extensively drug-resistant tuberculosis. Lancet Infect Disnfection 2010; 10:621-doi: 10.1016/S1473-3099(10)70139-0.

10. Gillespie SH (2002). "Evolution of drug resistance in Mycobacterium tuberculosis: clinical and molecular perspective". Antimicrob Agents Chemother. 46 (2): 267–74. PMC 127054. PMID 11796329. doi:10.1128/AAC.46.2.267-274.2002 Sadler.

11. Gray's Anatomy- The Anatomical basis of clinical practice,40th Edition, 2008, pp. 462–4.

12. Langman's Medical Embryology (13th ed.). pp. 285–6,293. ISBN 978-1-4511-9164-6

13. Larsen, William J. (2001). Human embryology (3. ed.). Philadelphia, Pa.: Churchill Livingstone. pp. 372–374. ISBN 0-443-06583-7

14. Guyton & Hall Text book of Medical Physiology, 13th Edition, 2011, p. 932.

15. Melmed, S; Polonsky, KS; Larsen, PR; Kronenberg, HM (2011). Williams Textbook of Endocrinology (12th ed.). Saunders. p. 331. ISBN 978-1-4377-0324-5.

16. Kaptein EM: Clinical relevance of thyroid hormone alterations in nonthyroidal illness, Thyroid International 4:22–25, 1997.

17. Wartofsky L, Burman KD: Alterations in thyroid function in patients with systemic illnesses: the “Euthyroid Sick Syndrome”, Endocrine Rev 3:164–217, 1982.

18. J.Chopra: Euthyroid sick syndrome: is it a misnomer?Journal of Clinical Endocrinology and Metabolism 1997,82; 329-334.

19. Vinayak K Patki;Alteration of Thyroid function test in critically ill children. Journal of paediatric critical care, P-229.Vol-1,No-4,October 2014.

20. Csako G, Zweig MH, Benson C, et al: On the albumin-dependence of the measurement of free thyroxine. II. Patients with nonthyroidal illness, Clin Chem 33:87–92, 198Vierhapper H, Laggner A, Waldhausl W, et al: Impaired secretion of TSH in critically ill patients with “low T4-syndrome”. Acta Endocrinol 101:542–549, 1982.

21. Hamdy, Roland. "The thyroid glands: a brief historical perspective". www.medscape.com. Retrieved 2016-11-13. Kaptein EM, Robinson WJ, Grieb DA, et al: Peripheral serum thyroxine, triiodothyronine and reverse triiodothyronine kinetics in the low thyroxine state of acute nonthyroidal illnesses. A noncompartmental analysis, J Clin Invest 69:526–535, 1982. Van den Berghe G, de Zegher F, Bouillon R: Acute and prolonged critical illness as different neuroendocrine paradigms, J Clin Endocrinol Metab 83:1827–1834, 1998.

22. Post FA, Soule SG,Wilcox PA, et al.The spectrum of endocrine dysfunction in active pulmonary tuberculosis.Clin Endocrinology (OXF)1994;367-71.

23. Di Napoli M,Reda G, Zannoni G, et al. The euthyroid sick syndrome .Its incidence and clinical significance in an internal medicine department.Minerva Med 1994;85:161-5.

24. Endocrine dysfunction among adult patients with tuberculosis:An African experience:Dr.Davis Kibirige, Indian Journal of Endocrinology and Metabolism.2014 May-Jun;18(3):288-294.

25. "Thyroid History Timeline – American Thyroid Association". www.thyroid.org. Retrieved 13 November 2016.

26. Niazi, Asfandyar Khan; Kalra, Sanjay; Irfan, Awais; Islam, Aliya (2016-11-13). "Thyroidology over the ages". Indian Journal of Endocrinology and Metabolism. 15 (Suppl2): S121–S126. ISSN 2230-8210. PMC 3169859 . PMID 21966648. doi:10.4103/2230-8210.83347

27. Anderson, D.M. (2000). Dorland's illustrated medical dictionary (29th edition). Philadelphia/London/Toronto/Montreal/Sydney/Tokyo: W.B. Saunders Company.

28. Magner, James (2014). "Historical Note: Many Steps Led to the 'Discovery' of Thyroid-Stimulating Hormone". European Thyroid Journal. doi:10.1159/000360534.

29. Ellis, Harold; Susan Standring; Gray, Henry David (2005). Gray's anatomy: the anatomical basis of clinical practice. St. Louis, Mo: Elsevier Churchill Livingstone. pp. 538–539. ISBN 0-443-07168-3. Camacho PM, DwarKanathan AA. Sick euthyroid syndrome. What do we do when thyroid function tests are abnormal in critically ill patients? Postgrad Med 1999;105(4): 215-219.doi:10.3810/pgm.1999.04.694.

30. Aatif S, Qamar R, Ahmed I, Imran K. Sick euthyroid syndrome: Thyroid function abnormalities in patients with non-thyroid illness JLUMHS 2008; 7 (2): 83-86.

31. Maldonado LS, Murata GH, Hershman JM, Braun-stein GD. Do thyroid function test independently predicthe survival in the critically ill?Thyroid1992; 2 (2): 119-123. doi:10.1089/thy.1992.2.119.

32. Sharma SK, Mohan A. Multidrug-resistance tuberculosis: a menace that threatens to destabilize tuberculosis control.Chest2006; 130 (1): 261-272. doi: 10.1378/chest.130.1.261

33. Andries A, Isaakidis P, Das M, Khan S, Paryani R,Desai C et al. High rate of hypothyroidism in multidrug-resistant tuberculosis patients co-infected with HIV inMumbai, India. PLoS One 2013; 8 (10):78313.PubMed edoi:10.1371/journal.pone.0078313.

34. Sajid KM, Parveen R, Sabih DE, Mahmood R. Thyroid function in pulmonary tuberculosis.J Coll Physicians Surg Pak 2006; 16 (10): 633-636. PMID 17007749

35. DeGroot LJ: “Non-thyroidal illness syndrome” is functional central hypothyroidism, and if severe, hormone replacement is appropriate in light of present knowledge, J Endocrinol Invest 26:1163–1170, 2003.

36. Stathatos N, Wartofsky L: The euthyroid sick syndrome: is there a physiologic rationale for thyroid hormone treatment? J Endocrinol Invest 26:1174–1179, 2003.

37. Hennemann G, Docter R, Krenning EP: Causes and effects of the low T3 syndrome during caloric deprivation and non-thyroidal illness: an overview, Acta Med Kaust 15:42–45, 1988.

38. Phillips RH, Valente WA, Caplan ES, et al: Circulating thyroid hormone changes in acute trauma: prognostic implications for clinical outcome, J Trauma 24:116–119, 1984.

39. Vardarli I, Schmidt R, Wdowinski JM, et al: The hypothalamo-hypophyseal-thyroid axis, plasma protein concentrations and the hypophyseogonadal axis in low T3 syndrome following acute myocardial infarct, Klin Wochenschrift 65:129–133, 1987.

40. Eber B, Schumacher M, Langsteger W, et al: Changes in thyroid hormone parameters after acute myocardial infarction, Cardiology 86:152–156, 1995.

41. Holland FW, Brown PS, Weintraub BD, et al: Cardiopulmonary bypass and thyroid function: a “euthyroid sick syndrome.” Ann Thorac Surg 52:46–50, 1991.

42. Docter R, Krenning EP, de Jong M, et al: The sick euthyroid syndrome: changes in thyroid hormone serum parameters and hormone metabolism, Clin Endocrinol 39:499–518, 1993.

43. Schilling JU, Zimmermann T, Albrecht S, et al: Low T3 syndrome in multiple trauma patients – a phenomenon or important pathogenetic factor? Medizinische Klinik 3:66–69, 1999.

44. Wartofsky L, Burman KD: Alterations in thyroid function in patients with systemic illnesses: the “Euthyroid Sick Syndrome”, Endocrine Rev 3:164–217, 1982.

45. Docter R, Krenning EP, de Jong M, et al: The sick euthyroid syndrome: changes in thyroid hormone serum parameters and hormone metabolism, Clin Endocrinol 39:499–518, 1993.

46. Chopra IJ, Taing P, Mikus L: Direct determination of free triiodothyronine (T3) in undiluted serum by equilibrium dialysis/radioimmunoassay, Thyroid 6:255–259, 1996.

47. Chopra IJ: Simultaneous measurement of free thyroxine and free 3,5,3’-triiodothyronine in undiluted serum by direct equilibrium dialysis/radioimmunoassay: evidence that free triiodothyronine and free thyroxine are normal in many patients with the low triiodothyronine syndrome, 1998.

48. Faber J, Kirkegaard C, Rasmussen B, et al: Pituitary-thyroid axis in critical illness, J Clin Endocrinol Metab 65(2):315–320, 1987 Aug.

49. Arem R, Deppe S: Fatal nonthyroidal illness may impair nocturnal thyrotropin levels, Am J Med 88:258–262, 1990.

50. Mohan A ,Sharma SK.. In : Sharma SK, Mohan A, editors. Tuberculosis. 2nd ed.New Delhi:Jaypee Brothers Medical Publishers;2011. 751-768.

51. Rubin SA. Tuberculosis. Captain of all these men of death.Radiolclin North Am 1995;33:619-39.

52. Sakula A.Robert Koch:centenary of the discovery of the tubercle bacillus, 1882.Thorax 1982; 37 : 246-51.

53. Sharma SK, Mohan A. Multidrug-resistanttuberculosis.Indian J Med Res2004;120:354-76.

54. Chow CC, Mak TW,Chan, Cockram CS.Euthyroid sick syndrome in pulmonary tuberculosis before and after treatment.Ann Clinn Biochem.1995; 32(385-391)

PROFORMA

- Name:
- Age:
- Sex:
- OP No:
- Department:
- Hospital:
- Address:
- Contact No:
- Occupation:

Chief complaints

- H/O Cough with expectoration
- H/O Fever
- H/O LOW/LOA
- H/O Breathing difficulty
- H/O Fatigue
- H/O Weight gain
- H/O Hoarseness of voice
- H/O Intolerance to cold
- H/O Menstrual abnormalities
- H/O Palpitation
- H/O Weight loss inspite of good apptite.

Examination

- **General Examination**:

Built and nourishment, pallor, icteric, cyanosis, clubbing, lymphadenopathy, pedal edema.

- **Systemic Examination**: CVS, ABDOMEN, CNS.
- **Examination of Respiratory system**: Inspection, Palpation, Percussion, Auscultation.

Investigations

- Free T3, Free T4, TSH
- CXR-PA View
- Sputum AFB
- Others:
    - Complete Hemogram,
    - Renal Function Test,
    - Liver Function Test,
    - Blood Sugar,
    - Lipid Profile.

Treatment

- **CAT-1 ATT Treatment**
- **Follow up- end of 2 months**

PATIENT CONSENT FORM

STUDY DETAIL: "**PREVALENCE OF EUTHYROID SICKSYNDROME IN NEWLY DETECTED PTB PATIENTS AND THE CORRELATION OF THE SAME WITH FAILURE AT THE END OF INITIATION PHASE"**

STUDY CENTRE: KILPAUK MEDICALCOLLEGE, CHENNAI

PATIENTS NAME:

PATIENTS AGE:

IDENTIFICATION NUMBER :

PATIENT MAY CHECK ( ) THESE BOXES

☐ I CONFIRM THAT I.HAVE UNDERSTOOD THE PURPOSE OF PROCEDURE FOR THE ABOVE STUDY. I HAVE THE OPPORTUNITY TO ÀSK QUESTION AND ALL MY QUESTIONS AND DOUBTS HAVE BEEN ANSWERED TO MY COMPLETE SATISFACTION.

☐ I UNDERSTAND THAT MY PARTICIPATION IN THE STUDY IS VOLUNTARY AND THAT I AM FREE TO WITHDRAW AT ANY TIME WITHOUT GIVING REASON, WITHOUT MY LEGAL RIGHTS BEING AFFECTED.

☐ I UNDERSTAND THAT SPONSOR OF THE CLINICAL STUDY, OTHERS WORKING ON THE SPONSOR'S BEHALF, THE ETHICAL COMMITTEE AND THE REGULATORY AUTHORITIES WILL NOT NEED MY PERMISSION TO LOOK AT MY HEALTH RECORDS, BOTH IN RESPECT OF CURRENT STUDY AND ANY FURTHER RESEARCH THAT MAY BE CONDUCTED IN RELATION TO IT, EVEN IF I WITHDRAW FROM THE STUDY I AGREE TO THIS ACCESS. HOWEVER, I UNDERSTAND THAT MY IDENTITY WILL NOT BE REVEALED IN ANY INFORMATION RELEASED TO THIRD PARTIES OR PUBLISHED, UNLESS AS REQUIRED UNDER THE LAW. I AGREE NOT TO RESTRICT THE USE OF ANY DATA OR RESULTS THAT ARISE FROM THIS STUDY.

☐ I AGREE TO TAKE PART IN THE ABOVE STUDY AND TO COMPLY WITH THE INSTRUCTIONS GIVEN DURING THE STUDY AND FAITHFULLY COOPERATE WITH THE STUDY TEAM AND TO IMMEDIATELY INFORM THE STUDY STAFF IF I SUFFER FROM ANY DETERIORATION IN MY HEALTH OR WELL-BEING OR ANY UNEXPECTED OR UNUSUAL SYMPTOMS.

☐ I HEREBY CONSENT TO PARTICIPATE IN THIS STUDY.

☐ I HEREBY GIVE PERMISSION TO UNDERGO COMPLETE CLINICAL EXAMINATION AND DIAGNOSTIC TESTS INCLUDING HEMATOLOGICAL, BIOCHEMICAL, RADIOLOGICAL TESTS.

SIGNATURE/THUMB IMPRESSION:

PATIENTS NAME AND ADDRESS: PLACE DATE

SIGNATUPE OF INVESTIGATOR:

STUDY INVESTIGATOR'S NAME: PLACE DATE

சுய ஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு :

"சளியில் காசநோய் கிருமியால் பாதிக்கப்பட்டவர்களுக்கு இரத்தத்தில் தைராய்டு ஹார்மோன்களின் தன்மை அறிதல் பற்றிய ஆய்வு".

இடம் : பொது மருத்துவத்துறை
அரசு கீழ்பாக்கம் மருத்துவக்கல்லூரி மருத்துவமனை
சென்னை 600 010.

பங்கு பெறுபவரின் பெயர் :

பங்கு பெறுபவரின் வயது :

பங்கு பெறுபவரின் எண். :

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. நான் இவ்வாய்வில் தன்னிச்சையாக பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகிக் கொள்ளலாம் என்றும் அறிந்து கொண்டேன்.

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்து மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்கு பெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்துக் கொள்கிறேன். இந்த ஆய்வின் மூலம் கிடைக்கும் தகவலையோ, முடிவையோ பயன்படுத்திக் கொள்ள மறுக்கமாட்டேன்.

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக் கொள்கிறேன். இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதியளிக்கிறேன்.

பங்கேற்பவரின் கையொப்பம் ஆய்வாளரின் கையொப்பம்.

இடம் :
தேதி :

S.No	NAME	AGE	SEX	OP/IP	SPUTUM AFB POSITIVE 1+2+3+	FT3	FT4	TSH	S.BILIRUBIN mgs/dl	SGOT IU/L	SGPT IU/L	ALBUMIN	UREA mgs/dl	CREATININE mgs/dl	SPUTUM CONVERSION AT THE END OF 2 MONTH POSITIVE/NEGATIVE
1	SANDHIYA	25	F	OP	3+POSITIVE	1.86	0.92	2.76	0.7	30	32	2.8	22	0.8	NEGATIVE
2	ANTONY	37	M	OP	3+POSITIVE	1.3	1.2	3.722	1	28	22	3	46	0.8	NEGATIVE
3	SRINIVASAN	57	M	OP	2+POSITIVE	1.68	0.98	4.601	1	32	28	2.6	28	0.7	**DROPPED OUT**
4	ADHAVAN	36	M	OP	3+	2.12	1.22	3.012	0.6	26	30	2	36	1	NEGATIVE
5	DIVYA	14	F	OP	1+	2.96	1.2	4.21	0.8	40	32	2.4	80	0.7	NEGATIVE
6	KRISHNAMOORTHI	49	M	OP	3+	0.92	0.61	1.261	0.6	26	30	2.8	32	1	**POSITIVE 2+**
7	SHAM BAHAOHVR	51	M	OP	4+	2.01	1.62	2.766	0.6	28	36	4.8	80	0.8	**POSITIVE 2+**
8	KESAVAN	48	M	OP	3+	1.82	1.12	3.16	0.7	36	32	4.1	24	0.7	**DEAD/DEFAULTER**
9	KARTHICK	24	M	IP	3+	1.02	1.22	4.412	0.6	30	25	2.1	36	1.2	**POSITIVE 1+**
10	DURAISAMY	50	M	IP	2+	1.81	1.26	4.21	0.8	32	36	3.6	30	1.1	NEGATIVE
11	KRISHNAN	62	M	IP	4+	1.68		3.692	1.1	32	36	3	18	0.8	**POSITIVE 4+**
12	RAGAVAN	50	M	IP	3+	1.22	0.94	2.731	0.8	26	24	2.2	32	1.2	**POSITIVE 2+**
13	JAYARANI	52	F	OP	2+	1.92	1.2	4.112	0.7	30	36	3.8	26	0.7	NEGATIVE
14	SUBRAMANI	45	M	OP	3+	0.85	1.01	3.421	0.8	36	34	2.1	40	1.1	**POSITIVE 2+**
15	RATHINAM	70	M	IP	4+	1.18	1.23	1.161	0.8	28	32	2.8	20	0.6	NEGATIVE
16	MURALIMHOEN	59	M	OP	2+	2.18	0.91	2.664	1	32	36	2.9	28	1.1	NEGATIVE
17	CHANDRAN	21	M	IP	2+	2.01	1.04	2.821	1	32	28	3.8	18	0.8	NEGATIVE
18	PADMANABHAN	70	M	IP	3+	2.02	1.02	3.161	0.6	34	28	2.7	38	1.4	NEGATIVE
19	RAJI	40	M	OP	1+	3.01	1.26	4.012	0.6	28	21	4	16	0.8	NEGATIVE
20	BARATHI	22	M	OP	3+	1.21	1.07	3.186	0.8	38	28	2.4	32	1	NEGATIVE
21	SETHU	37	M	OP	2+	0.62	1.12	3.212	1	25	30	2.6	18	0.6	NEGATIVE
22	KUMARAN	41	M	IP	2+	1.61	1.61	4.211	0.8	22	18	4.2	20	0.8	NEGATIVE
23	GUNA SUNDHARI	50	F	IP	3+	1.81	1.06	3.123	0.6	24	20	3	22	0.7	**DROPPED OUT**
24	RAJKUMAR	20	M	OP	2+	2.12	1.06	4.123	0.8	22	18	2.8	28	0.8	NEGATIVE
25	MOHENRAJ	21	M	OP	2+	2.01	0.98	2.761	1	26	21	2.5	22	1	NEGATIVE
26	NAGARAJ	65	M	OP	3+	1.21	1.31	4.022	3.7	30	26	2.1	52	0.8	**POSITIVE 3+**
27	KAYALVIZHI	17	F	OP	2+	1.92	1.22	3.621	0.8	22	28	3	18	1	NEGATIVE
28	RICKY	22	M	OP	1+	3.04	1.28	3.761	0.9	26	24	4.8	16	0.8	NEGATIVE

29	KRISHANAN	53	M	OP	3+	1.44	0.36	2.861	1	36	40	2.3	62	1.1	**POSITIVE 2+**
30	SRIDHAR	37	M	OP	3+	1.96	1.41	3.741	0.8	32	34	2.6	32	1	NEGATIVE
31	SUMATHI	44	F	OP	3+	1.91	0.98	2.812	1.2	24	30	4	22	0.9	NEGATIVE
32	RAJENDRAN	55	M	IP	2+	2.02	1.2	1.681	1	30	24	4.6	36	1	NEGATIVE
33	MARI	58	M	IP	2+	2.16	1.51	2.642	0.8	24	20	4.2	18	0.8	**DROPPED OUT**
34	MAHESHIWARI	53	F	OP	1+	1.86	1.26	3.201	0.9	28	32	0.8	32	0.9	NEGATIVE
35	MURUGHAN	53	M	IP	3+	1.82	1.1	3.618	3	30	34	2.1	40	1.1	**DEAD**
36	SIVA	30	M	OP	1+	3.68	0.9	2.121	0.7	24	18	4.5	18	0.7	**NOT TAKEN TABLET**
37	SHARIKA	15	F	IP	2+	2.06	1.53	3.68	0.8	28	22	2.3	16	0.6	NEGATIVE
38	KUMARESAN	36	M	IP	2+	2.14	1.18	3.417	1.1	30	28	3.6	20	0.8	NEGATIVE
39	SUBRAMANI	55	M	OP	2+	2.13	0.97	4.012	0.9	21	16	2.4	38	1.4	NEGATIVE
40	VARADHAN	75	M	IP	2+	1.14	1.06	2.821	0.8	14	18	2.8	44	0.8	NEGATIVE
41	RAJESH	38	M	IP	3+	1.16	1.23	2.681	1	42	36	2.6	42	1	**POSITIVE 1+**
42	MOHAN	55	M	OP	1+	2.64	1.38	3.414	0.8	14	22	4	38	0.7	NEGATIVE
43	RAMESH	50	M	OP	2+	2.05	0.98	3.792	1.3	26	18	3.8	22	0.8	NEGATIVE
44	JAYAKUMAR	49	M	IP	1+	1.96	1.24	4.061	0.7	18	22	4.6	26	0.8	NEGATIVE
45	MOHAN	50	M	OP	4+	2.1	1.26	3.816	0.8	22	28	0.7	34	1	**DEAD**
46	KARAN BAHODUR	40	M	OP	2+	1.98	1.26	3.921	1	32	28	2.4	38	1.4	**NOT TAKEN TABLET**
47	MANI	46	M	OP	3+	1.1	1.61	2.81	0.8	38	455	2.1	44	1.2	NEGATIVE
48	KUMAR	48	M	OP	2+	1.91	0.96	4.211	1.1	45	46	2.7	40	1.1	NEGATIVE
49	KUPPUSAMY	55	M	OP	3+	1.88	1.34	3.121	1	24	22	2.3	64	1	NEGATIVE
50	SETHU	70	M	IP	2+	1.66	0.91	2.861	0.8	30	28	2.5	36	1	**POSITIVE 2+**
51	MANI	52	M	OP	3+	2.17	0.96	3.162	0.5	16	14	3.8	24	0.8	NEGATIVE
52	VENKATESAN	52	M	OP	2+	1.86	0.92	2.862	0.7	38	28	4.8	26	1	NEGATIVE
53	SHAHIRA	20	F	IP	3+	0.96	1.14	4.061	0.5	28	36	5.2	38	0.8	NEGATIVE
54	GANESHKUMAR	38	M	OP	1+	2.01	0.96	3.723	0.4	26	24	3.4	16	0.7	NEGATIVE
55	CHINNAPAN	58	M	OP	4+	1.61	0.98	3.681	0.9	28	36	5.1	13	0.7	**POSITIVE 3+**
56	GUNASEKAR	35	M	IP	1+	2.78	1.41	4.26	0.6	30	18	3.6	18	0.6	NEGATIVE
57	DHATCHAYANI	40	F	IP	2+	1.97	1.28	3.781	0.6	21	30	2.1	30	0.9	NEGATIVE
58	GANESAN	57	M	IP	2+	2.16	1.64	3.881	1.1	32	32	2.2	43	1.3	NEGATIVE
59	ANAND	24	M	OP	2+	1.92	1.07	3.181	0.5	26	30	2.8	46	1.1	NEGATIVE
60	PANEERSELVAM	40	M	IP	3+	2.21	1.42	3.863	0.6	20	31	3	28	0.7	**DROPPED OUT**
61	SHNMUGHAM	40	M	OP	2+	1.83	1.62	2.81	1.5	30	26	3	27	0.9	NEGATIVE

62	SELVAM	37	M	OP	1+	3.06	1.22	3.822	1	22	14	4.1	26	0.8	NEGATIVE
63	RAMAN	56	M	OP	2+	2.18	0.98	3.681	0.8	25	28	3.8	24	0.7	**DROPPED OUT**
64	MANIMEGHALAI	40	F	OP	4+	2.06	1.37	2.463	0.7	21	18	4	30	0.6	**POSITIVE 1+**
65	AMUDHAVANI	40	F	OP	2+	2.12	0.91	4.516	0.9	22	20	3.8	28	0.7	NEGATIVE
66	SEKAR	54	M	OP	2+	1.85	1.06	1.762	1	18	16	2.7	42	0.9	NEGATIVE
67	PONNUSAMY	41	M	OP	1+	1.98	1.56	2.792	0.8	20	22	4.1	16	0.7	NEGATIVE
68	ARUMUGHAM	56	M	OP	3+	2.16	1.02	3.686	0.7	24	31	3.7	29	0.8	NEGATIVE
69	YAMINI	30	F	OP	2+	2.05	0.84	3.012	0.9	46	51	2.8	34	1	NEGATIVE
70	UMASHANKAR	41	M	OP	2+	1.96	0.64	2.76	0.6	44	36	2.5	30	1.1	NEGATIVE
71	MAHALAKSHMI	52	F	OP	3+	1.87	1.23	2.614	0.5	44	20	2.8	26	1	**DROPPED OUT**
72	MANOHARAN	62	M	OP	2+	1.46	0.7	2.461	0.5	30	26	2.6	42	1.2	NEGATIVE
73	PRATHAP	48	M	OP	2+	1.95	1.21	1.861	1.2	22	20	2.6	36	1	NEGATIVE
74	RAMESH	50	M	OP	3+	1.68	4.42	2.817	1	36	38	3	22	0.8	**DROPPED OUT**
75	JAYGANESH	49	M	OP	2+	1.61	1.61	3.012	0.8	44	50	3.2	26	0.7	NEGATIVE
76	SEETHARAMAN	56	M	OP	2+	1.85	1.05	1.475	0.6	52	40	2.6	38	1	NEGATIVE
77	RAJASEKARAN	62	M	OP	3+	1.92	1.28	1.871	0.5	26	34	2.2	21	0.7	NEGATIVE
78	KANDHASAMY	58	M	OP	2+	2.1	1.64	2.812	0.8	22	28	4	36	0.8	NEGATIVE
79	KAMALAKANNAN	44	M	OP	3+	2.2	1.4	2.716	0.7	20	18	4.2	18	0.6	NEGATIVE
80	RAMASAMY	71	M	IP	3+	1.28	0.86	0.326	0.9	26	18	2.1	60	1.2	**POSITIVE 3+**
81	SANKAR	56	M	IP	2+	1.92	1.21	2.871	1.9	30	32	2.3	36	1.1	NEGATIVE
82	MANI	47	M	OP	3+	2.01	1.26	3.16	1.1	20	21	2.7	26	1	NEGATIVE
83	RAMDASS	36	M	OP	2+	1.96	1.06	2.812	0.4	30	18	2.2	18	0.8	NEGATIVE
84	BALAKRISHNAN	66	M	OP	2+	2.11	1.28	3.862	0.6	30	32	2.8	22	0.74	NEGATIVE
85	SAMBATH	48	M	OP	3+	1.76	1.26	2.761	0.9	40	35	2.1	46	0.8	**POSITIVE 1+**
86	NILAVARASU	39	M	OP	1+	3.1	1.24	3.121	0.5	25	22	2.4	22	1	NEGATIVE
87	CHINNANAN	67	M	IP	2+	2.1	0.98	2.922	0.6	26	26	3.5	38	1.1	NEGATIVE
88	DHAYALAN	51	M	IP	2+	1.85	0.98	3.612	1	14	22	4.2	24	0.7	NEGATIVE
89	PONNUSAMY	51	M	IP	3+	1.96	0.98	3.612	1	14	22	4.2	24	0.7	**DROPPED OUT**
90	SUBRAYAN	66	M	OP	1+	2.41	1.22	3.112	0.6	36	32	2.5	18	0.6	NEGATIVE
91	KARMEGHAM	71	M	IP	2+	1.72	1.1	2.861	0.6	32	36	3.6	62	1	NEGATIVE
92	SUBRAMANI	44	M	OP	1+	2.86	1.32	2.721	0.8	18	14	4.2	22	0.8	NEGATIVE
93	KASI	41	M	OP	2+	2.1	1.23	3.421	0.9	20	14	4.4	30	0.7	NEGATIVE
94	PANDISAMY	66	M	OP	3+	1.82	0.96	3.112	1	28	44	4	36	0.8	NEGATIVE

95	KUMAR	42	M	OP	2+	1.81	1.62	1.812	0.6	14	18	4.8	32	0.9	NEGATIVE
96	RANGHARAJAN	68	M	IP	2+	1.9	1.71	2.762	0.7	22	30	2	40	0.8	NEGATIVE
97	SAMYNATHAN	59	M	OP	2+	1.62	0.68	2.816	1	52	46	2.2	46	1	NEGATIVE
98	SOLAIYAPPAN	70	M	IP	3+	1.96	1.22	3.187	0.6	24	26	2.4	40	0.8	**POSITIVE 2+**
99	ASOKAN	56	M	OP	2+	2.12	1.26	2.712	0.7	18	24	4	22	0.8	NEGATIVE
100	CHINNARAJ	46	M	OP	2+	1.81	0.92	3.827	0.8	46	36	2.7	51	1.4	NEGATIVE
101	LOGIDASAN	68	M	IP	2+	1.86	0.64	0.21	0.8	28	32	3	18	0.7	**DEAD**
102	ANBHALAGAN	56	M	IP	3+	1.2	0.98	3.681	0.7	18	42	2.1	22	0.9	**POSITIVE 1+**
103	VINOTHVISVAS	40	M	OP	2+	1.87	1.12	4.21	0.9	26	36	3.2	24	0.8	NEGATIVE
104	DHANALAKSHMI	27	F	OP	2+	1.86	1.41	3.112	0.8	21	28	3.5	18	0.7	NEGATIVE
105	DEVARAJ	45	M	OP	3+	1.76	1.21	2.812	0.9	38	36	2	38	1.1	**POSITIVE 1+**
106	GOPINATH	41	M	OP	3+	1.92	1.4	3.812	0.8	32	46	2.1	28	0.9	NEGATIVE
107	SELVARAJ	52	M	IP	1+	2.11	1.7	4.61	0.7	18	22	3	18	0.8	NEGATIVE
108	SIVAKUMAR	30	M	OP	2+	2.1	1.01	3.761	0.8	26	42	2.1	22	0.9	NEGATIVE
109	SELVARAJ	47	M	IP	1+	2.02	0.64	4.218	1	28	22	3	18	0.7	**DEAD**
110	CHITRA	23	F	OP	1+	2.01	1.22	3.512	0.7	18	28	2.9	21	0.8	NEGATIVE
111	NIRAIMATHI	20	F	OP	3+	1.12	1.6	3.912	0.9	28	32	2.1	28	1	NEGATIVE
112	DEVARAJ	48	M	OP	1+	3.1	1.26	3.812	0.8	32	42	2.8	22	0.8	**DROPPED OUT**
113	CHITRA	32	F	OP	2+	1.86	1.21	4.21	0.8	18	26	2.6	28	0.7	NEGATIVE
114	PONNUSAMY	67	M	OP	2+	1.12	1.28	4.126	0.9	32	41	2.5	22	1	NEGATIVE
115	ARUMUGHAM	30	M	IP	2+	2.07	1.63	2.781	0.7	21	28	2.6	28	0.8	NEGATIVE
116	VEDIYAPPAN	42	M	IP	1+	2.16	1.11	3.811	0.8	32	47	2.4	30	1	NEGATIVE
117	SAKTHIVEL	42	M	OP	3+	1.81	1.28	2.812	1.1	46	64	2.1	38	1	**POSITIVE 2+**
118	SARAVANAN	45	M	IP	2+	1.91	1.41	3.286	0.8	22	18	2.4	26	0.6	NEGATIVE
119	MURALI	50	M	IP	3+	1.82	0.38	3.681	0.8	28	18	2.1	48	0.8	**DEAD**
120	MUNUSAMY	55	M	OP	2+	0.81	1.54	3.126	0.7	18	25	2.8	32	0.9	**DROPPED OUT**