A DISSERTATION ON

PROSPECTIVE STUDY ON CLINICAL OUTCOMES OF SPUTUM POSITIVE TUBERCULOSIS IN NEWLY DETECTED DIABETES PATIENTS IN COMPARISON TO NON DIABETIC PATIENTS

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LIST OF ABBREVIATIONS

TB: Tuberculosis

DM : Diabetes mellitus

WHO: World Health Organisation

AFB: Acid Fast Bacilli

CBNAAT :Catridge Based Nucleic Acid Amplification Test

HIV: Human Immunodeficiency Virus

IUAT : Internal Union Against Tuberculosis

ADA : American Diabetes Association

FBS: Fasting Blood Sugar

PPBS: Post Prandial Blood Sugar

ADR: Adverse Drug Reactions

GDM: Gestational Diabetes Mellitus

ATT: Anti Tuberculous Treatment

PCR: Polymerase Chain Reaction

ABSTRACT

BACKGROUND

The link between tuberculosis (TB) and diabetes mellitus (DM) has occupied the centre stage of discussion. Experts have raised concern about the merging epidemics of tuberculosis and diabetes particularly in the low to medium income countries like India and China that have the highest burden of TB in the world, and are experiencing the fastest increase in the prevalence of DM. The huge prevalence of DM in India, may be contributing to the increasing prevalence of TB. We discuss the epidemiology, clinical features, microbiology and radiology, and management and treatment outcomes of patients with tuberculosis and diabetes mellitus.

METHOD

Data were collected from 100 patients with sputum positive tuberculosis and were screened for presence of diabetes. Detailed history, chestX-rayand sputum analysis were done and patients were followed up until treatment

RESULTS

There was male preponderance and the mean age group among diabetics patients were 51.5 ± 9 years compared to 34.2 ±7 .26 years. Diabetic patients had more of chest pain, hemoptysis and dyspnoea compared to non-diabetics. Diabetic patients had more sputum positivity rates compared to non-diabetics.38 % of the diabetic patients had cavities in chest x-ray compared to 20 % amount non diabetics.48 % of the diabetic patients had lower zone infiltrates compared to 20 % in non-diabetics. Sputum conversion rates were84% in non-diabetic TB patients when compared to 70% in diabetic TB patients. Failure rates were high as 4% in diabetic patients but not statistically significant

CONCLUSION

All patients with pulmonary tuberculosis should be screened for diabetes mellitus and should be effectively treated for the same. Pulmonary Tuberculosis patients who have diabetes tend to have higher sputum positivity rates and delayed sputum conversion if glycemic levels are poorly controlled**..** Chest radiographs of such patients show multiple cavitations with predominant lower lobe involvement**.** The rates of treatment failures and treatment outcomes are adversely affected by the presence of diabetes.

INTRODUCTION

AIMS & OBJECTIVES

REVIEW OF LITERATURE

MATERIALS & METHODS

RESULTS

DISCUSSION

CONCLUSION

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ETHICAL COMMITTEE

APPROVAL

INTRODUCTION

The incidence of diabetes mellitus is on a rise in Indiawith an estimated 124 million to be affected by 2030.India tops the list in TBburden with 28 % of the global incidence in 2016.From the beginning of 20th centurythe bidirectional association of diabetes mellitus and tuberculosis has been a focus of interest[1].Diabetes can affect the clinical presentation and outcomes of tuberculosis and vice versa .In a developing and resource poor country likeIndia the steady increase inprevalence of diabetes has worsened the picture of tuberculosis. This comorbidity has become an alarming concern for treating clinicians.

Active tuberculosis and also latent tuberculosis infection have been known as a risk since long in diabetics. Recent studies have shown 3-5 times higher risk in acquiring tuberculosis for diabetic patients compared to non diabetics[2]. Subclinical diabetics surface due to stress of reigning infection. Tuberculosis also worsens the glycaemiccontrol .It reduces the efficacy of management of diabetes mellitus.[3]

The emerging epidemic of tuberculosis and diabetes mellitus has many impacts. Due to co existence of diabetes or underlying hyperglycaemiaalters the clinical presentation of tuberculosis. Patients may not be having the classical presentation of cough and breathlessness and hence may be an early diagnosis will be missed. For centuries

tuberculosis have been known to affect the lung apices due to a ventilation perfusion mismatch. In patient with hyperglycaemia ,an atypical in volvement of predominantly lower lung fields may confuse the physician in making diagnosis. The development of complications related to the tuberculosis and its treatment is worse in diabetic compared to non-diabetics. The sputum conversion is also delayed with lower rates of conversion in diabetic patients compared to non diabetics.[4-6]

The need to understand the dynamics of the emerging epidemic of tuberculosis and diabetes is more than ever. A better understanding will lead to early diagnosis, treatment and delay complications.

AIMS AND OBJECTIVES

- To screen the newly diagnosed tuberculosis patients registered under RNTCP for diabetes mellitus in GMKMCH SALEM during year 2016-2017
- Compare the measures of TB severity at clinical presentation (including lung cavitatory disease , sputum smear grade , and hemoptysis) in patients with and without DM.
- To note the response to treatment of Pulmonary Tuberculosis in diabetes with respect to sputum conversion.

TUBERCULOSIS : AN OVERVIEW

Background : Tuberculosis remains a leading cause of death globally . In 2014 there were an estimated 12.8 million new cases of tuberculosis worldwide[7]. Incidence of tuberculosis is greatest among those with conditions impairing immunity such as HIV infection and diabetes.[8]

History : Many terms were used to refer TB throughout history- consumption , phthisis , white plague ,Potts disease . Tuberculosis is caused by Mycobacteria. They are slender rods .Myco bacteria means fungus like bacteria. As they have filamentous branching forms. In this genus the first member to be identified was by Hansen. It was lepra bacillus in 1868.In 1882 the mammalian tubercle bacilli was isolated by Koch. He put forward the Koch's postulates. He made the result public on 24th march 1882 and hence the day is called world tuberculosis day .A purified protein derivative of the bacteria called tuberculin was developed by Koch in 1890.Till this day we are using tuberculin for immunisation against the disease. In 1908 another breakthrough discovery was made by Charles Mantoux.He developed intradermal test using tuberculin protein for diagnosing the disease.

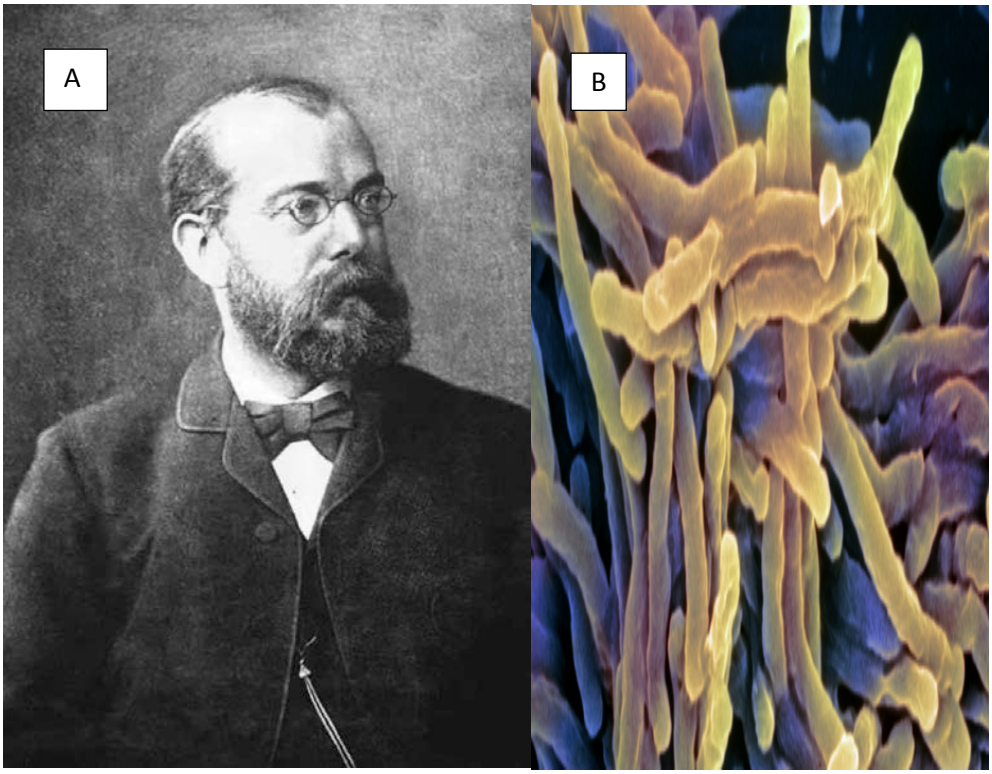


Figure 1 :

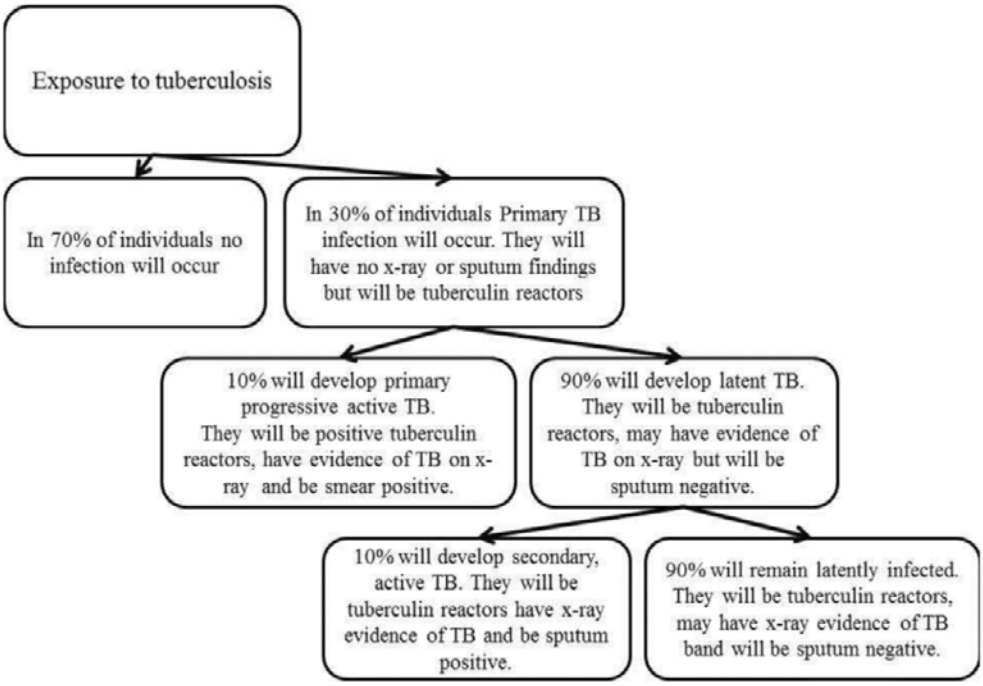
A) Robert Koch discovered TB bacilli

B) Mycobacteria tuberculosis under electron microscope

Morphology : M .tuberculosis are straight or curved rods. They occur singly ,in pair or rarely clumps. They are acid fast organisms due to presence of mycolic acids. The most common medium used for culture is Lowenstein Jenson medium. It is a solid medium. It is recommended by IUAT.It contains coagulated hens egg ,mineral salt solution, asparagine and malachite green. Malachite green acts as selective inhibiting agent. Liquid medium is used for testing sensitivity ,chemical analysis,. It is also used for preparation of vaccines and antigens. Liquid mediums are rarely used for cultures.

Mode of transmission : An infected host expels tiny aerosolised droplets of infected material into air. Infected material can be saliva ,sputum or phlegm. When an individual inhales this transmission of bacteria occurs. Now there are 3 possibilities for an individual who has acquired the bacteria. Either no disease state develops or latent TB or active TB infection ensues .

Latent TB is a disease state when viable bacteria is present inside the host but is not causing active disease.They remain dormant and can be reactivated at any time.Active TB is a disease state in which bacteria are continually replicating inside the host and the person shows symptoms and signs of the disease.The host may or may not be infectious.



PATHOGENESIS :

After uptake of the bacilli by the host ,a fraction reaches alveoli after evading upper respiratory tract and ciliated mucosal cells .Inactivated macrophages ingest the bacilli. Macrophage cell surface receptors are mannose receptors, complement receptors, immunoglobulin binding GFcy receptors and type A scavenger receptors. They help in adhering to the bacilli cell wall. Complement activation occurs.C3b opsonises the bacilli and phagocytosis is enhanced. Survival of the bacilli inside phagosome is dependent on reduced acidification this is due to lack of vesicular – ATP..Lipoarabino mannan inhibits the release of calcium inside the cell.Lipoarabinomannan is a complex glycolipid, which is a part of

bacilli cell wall . Hence calcium/calmodulin pathway comes to a standstill. It further also inhibits the PIP.PIP marks the bacilli phagosome for maturation ,membrane sorting and phagolysome formation. Bacteria also decelerates autophagy. Once phagosome maturation is stopped, bacilli will replicate inside profusely. Finally the phagosome will rupture and bacteria are released. Recruitment of other uninfected macrophages occurs.The infectious cycle is further continued and infection expands.

A specific virulence mechanism is used by the Mycobacterium tuberculosis to evade host defences. It also elicits early pro inflammatory reaction which in turn leads to granuloma formation. The epithelial cells that in contact with infected macrophages secrete MMP9.MMP(Matrix metallo proteinase) secretion is induced by ESAT-6, a mycobacterial protein.MMP9 helps in granuloma maturation and bacterial growth. Bacterial growth can be disrupted by inhibiting MMP9.There is an increase c-AMP,TNF- alpha and other chemoattractants.Their increase help the dendritic cells to catch the bacilli. They migrate to all the draining lymph nodes.T-lymphocytes are presented with mycobacterial antigens. Then cell mediated immunity and humoral immunity comes into play. During these initial stages host is asymptomatic.

Two host responses start developing after 2-4 weeks of the infection. A tissue damaging response and a macrophage activated cell mediated response. The mycobacterial antigens induce a delayed hypersensitivity reaction resulting tissue damaging response cells activate macrophages which in turn kill tubercle bacilli. Both mechanisms are essential in inhibiting bacterial growth. An equilibrium between these two response determines the outcome of the disease.

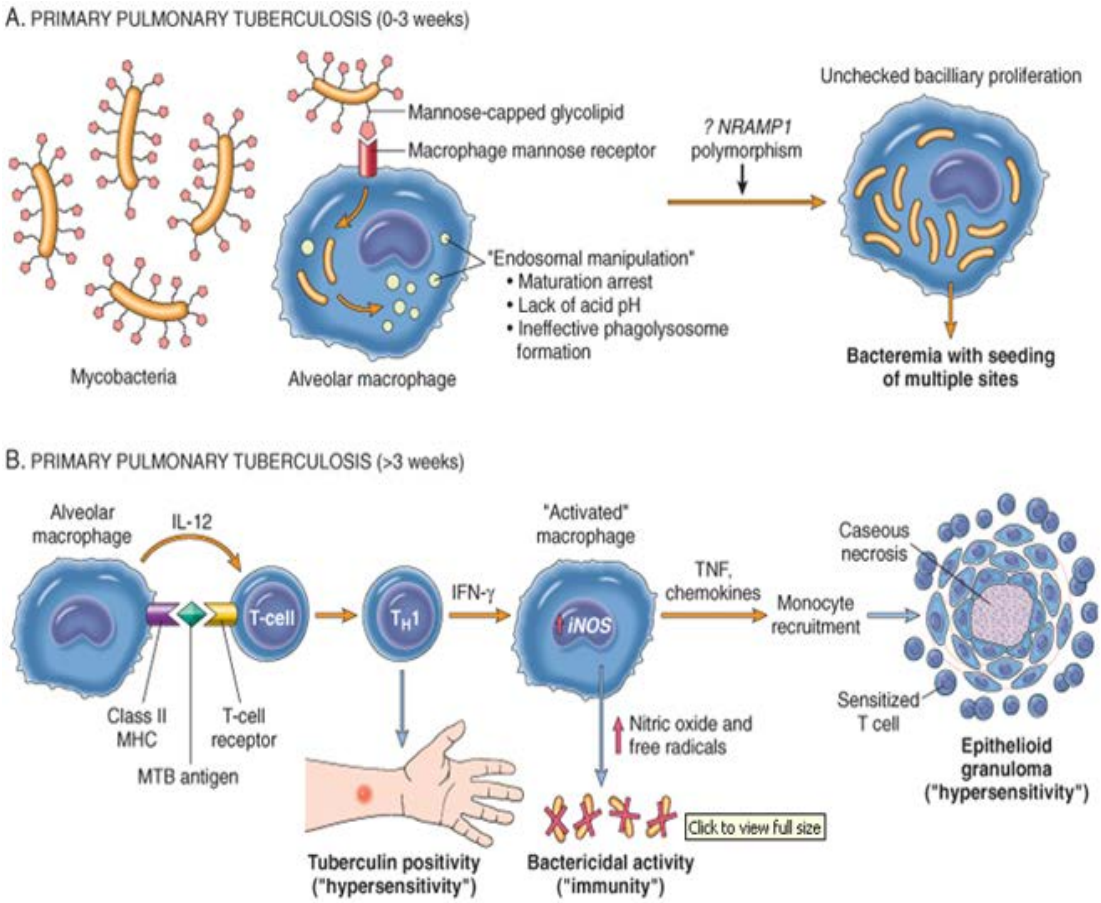


Figure 2: Pathogenesis of tuberculosis

Granulomatous tubercles develop in the area of primary lesion. This is due to specific immunity and accumulation of activated macrophages. Granulomas consist of lymphocytes and activated macrophages. These later progress into giant cells and epitheloid cells. Tissue damaging response kills inactivated macrophages and bacilli. It also causes caseating necrosis in the centre of the tubercle. Low oxygen tension and low pH inside the necrotic milieu deters the growth bacilli. Some lesions heal by fibrosis. Other lesion develop inflammation and necrosis. Subsequently calcification occurs.

Macrophage activating response :macrophages process mycobacterial antigens. They stimulate T lymphocytes.T lymphocytes release lymphokines.And local macrophages are activated. Activated ,macrophages ensemble in the centre of the lesion. They defuse tubercle bacilli. Further tissue destruction is not propagated.Caseous necrotic material is seen in the centre of the lesion. In healed lesions, viable bacteria may remain dormant for many years. It is mainly seen inside macrophages and necrotic material. Healed lesions later undergo calcification.

Delayed type hypersensitivity: Cell mediated immunity is sometimes weak. So body relies on intensified DTH reactions. Such

reactions result in tissue destruction. Lesion will propagate. Surrounding tissue is destroyed. Necrotic centre will liquefy. Surrounding structures like bronchial wall, vessels are destroyed. Cavities are formed. Cavities and bronchi contain liquefied caseous material. Bacteria multiply in these cavities. Infected material spill out into airways. During coughing and talking it gets expelled into environment. The bacilli migrate into central venous return from draining lymph nodes. They reinfect lungs and extrapulmonary vasculature. Children have poor natural immunity. They develop disseminated infection resulting in military TB and TB meningitis.

Clinical features : Of all type of infection pulmonary TB is of public importance. Before the HIV era, most of the TB was pulmonary. Now there is a drastic change in scenario.

Pulmonary TB :There are mainly 2 types – primary and post primary

Primary disease : There is formation of primary complex. It is also known as ghons complex. It is sub pleural in location and mostly seen in lower part of upper lobe or upper part of lower lobe. There is associated enlarged lymphnodes.More than 70% of the cases heal spontaneously. Any form of immunosuppression may lead to progressive disease. Clinical features may be acute or insidious.Fever,loss of appetite and weight, hemoptysis , chest pain ,

cough are the main symptoms. Allergic manifestations like phlycten and erythema nodosum may be seen in some patienst.Pleural effusion may be present or tuberculous pneumonia is seen. Physical examination may give clues of collapse, consolidation or cavity.

Post Primary Disease : There may be direct progression of primary lesion or reactivation of a dormant foci. Rarely haematogenous spread or reinfection can also occur. Upper lobes are commonly affected. There is early cavitation, fibrosis and healing. Patients who have resistance have a slow developing nodular form. If resistance is low a fibrocaseous cavity type disease is seen. The initial lesion is usually exudative pneumonia. Blood vessels may become thrombosed, aneurysmal and eventually rupture to produce hemoptysis.Patients have cough, evening rise in temperature,hemoptysis,chest pain breathlessness. Sputum is mucoid or mucoprulent.It is initially scanty and later copious. Patient becomes emaciated as disease progresses. On examination evidence of cavity,consolidations,effusions or pneumothorax is seen.

Complications :

Early complications include hemoptysis, pneumothorax, pleural effusion and poncet syndrome. Intermediate complications include secondary infection of cavities, massive hemoptysis,

progressive fibrosis, hemotogenous spread and non healing lesions. Late complications include bronchiectasis, fibrosis, aspergilloma, carcinoma and secondary amyloidosis.

INVESTIGATIONS

Sputum examination : the bacilli are demonstrated by Ziehl Nelson staining method. The amount of bacilli in sputum will affect the positivity of smears and cultures.100fields are examined for 10 mins before declaring it negative. Now PCR and CBNAAT studies are available which is more rapid and cost effective. Further confirmation is obtained by using cultures. Early morning sputum samples are preferred for smear examinations.

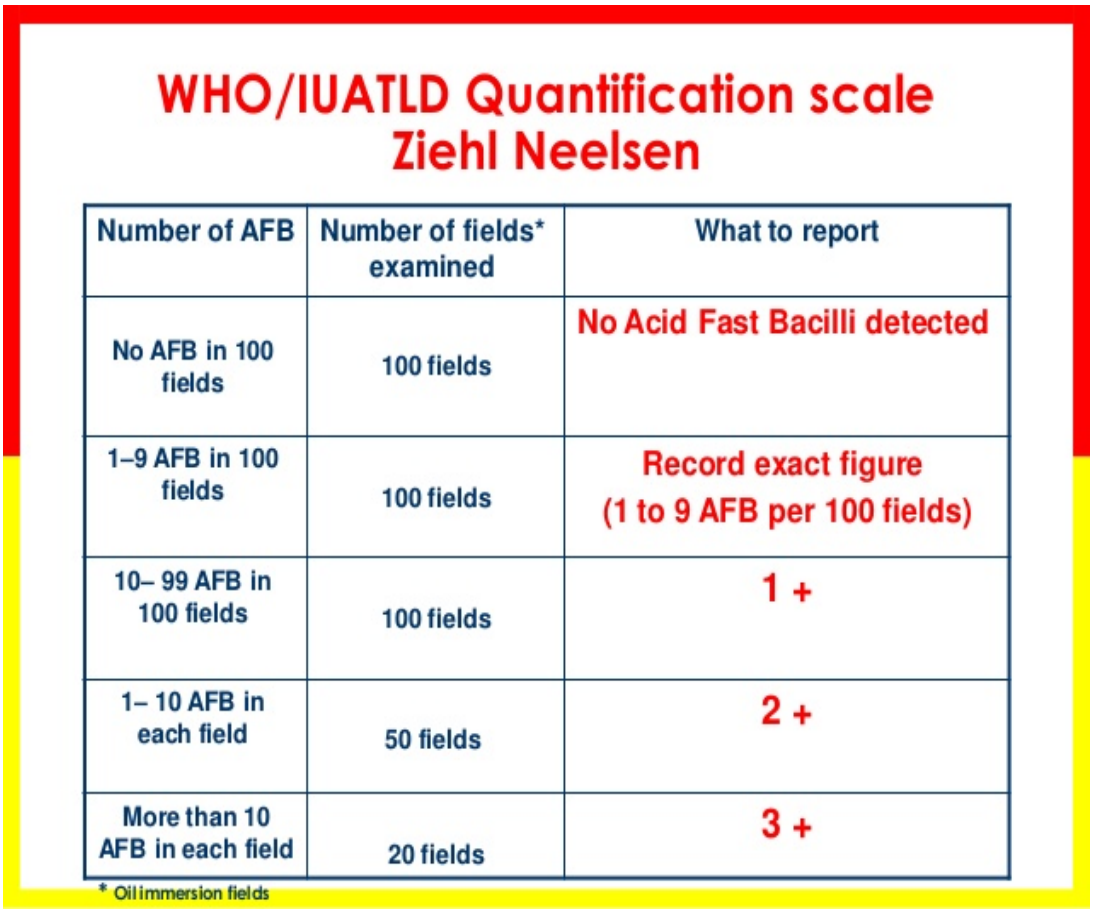


Figure 3 : Grading of smears for acid fast bacilli

Radiology : It is the most easiest and readily available diagnostic test.Primary Tb can affect upper and middle lobes. Progressive disease are seen in upper lobes with cavitatory lesions. Cavities are often thin walled, multiple and with intervening fibrosis. Bilateral lesions are almost always suggestive of tuberculosis. Once cavitation and fibrosis has set in lesion may not heal with treatment. In the long course there may be evidence of fibrosis, collapse and destroyed lung.

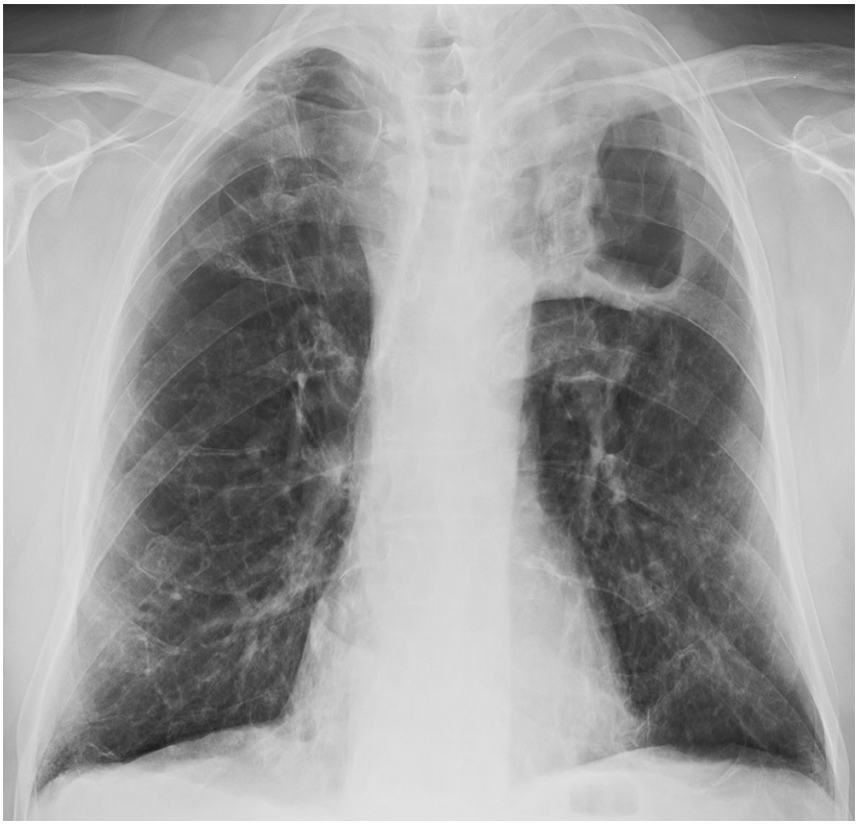


Figure 4 : Chest radiograph of patient showing upper lobe involvement with cavity

BLOOD INVESTIGATIONS : These include routine investigations.PCR testing is useful as it is highly sensitive and specific. Interferon release assays are taking an important role in diagnosing TB these days

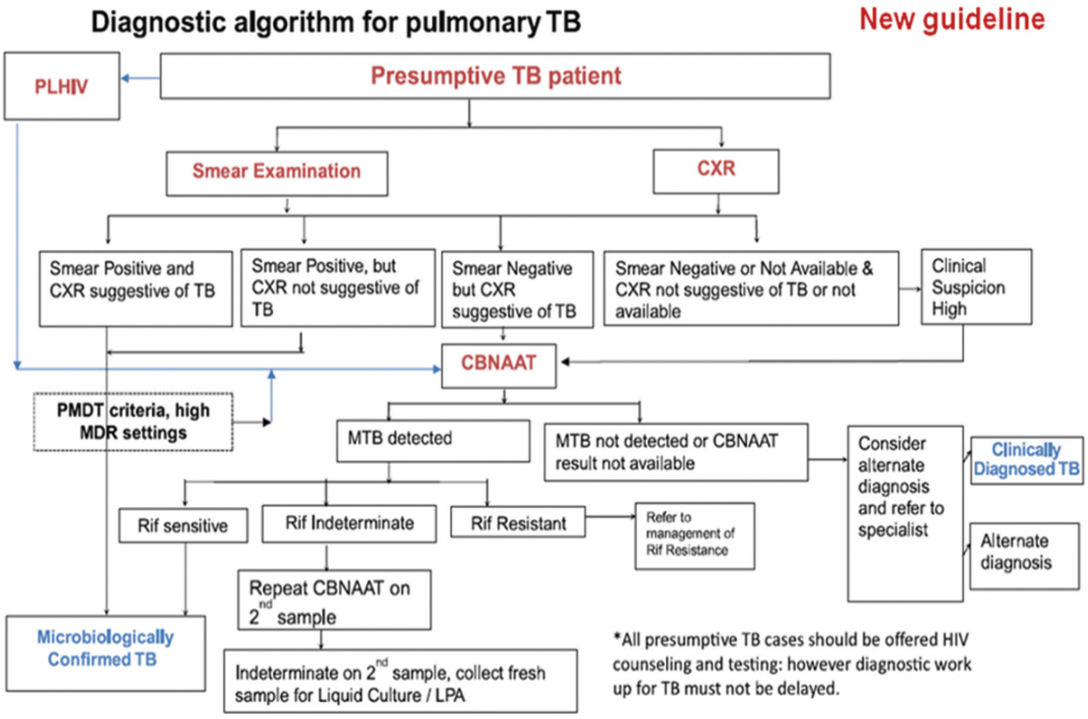


Figure 5 : Diagnostic Algorithm For Pulmonary TB

TREATMENT

The goals of treatment include ensuring cure without relapse, to prevent death, to prevent spread and to prevent development of resistance. Treatment consists of an active phase or intensive phase where all actively growing bacilli are killed. Also a proportion of dormant organisms are also killed. In continuation phase the remaining persisting bacilli are eliminated

Adequate chemotherapy administered without interruption is the cornerstone of success.

TABLE A **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)
Rifampin (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)

TABLE B **Recommended doses of second-line anti-TB 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	800–10000 mg
Levofloxacin	7.5–10	Oral	750-1000 mg
Moxifloxacin	7.5–10	Oral	400 mg

Figure 6 Recommended doses of anti Tuberculosis drugs

TREATMENT CATEGORIES AND REGIMEN

Treatment Groups	Type of Patient	Regimen	
		Intensive Phase (IP)	Continuation Phase (CP)
New (78 doses)	1. Sputum smear positive 2. Sputum smear negative 3. Extra-pulmonary	$2\ H^3\ R^3\ Z^3\ E^3$ (24 doses)	$4\ H^3\ R^3$ (54 doses)
Previously Treated (102 doses)	1. Sputum positive relapses 2. Sputum positive failure 3. Sputum positive treatment after default 4. Others	$2\ H^3\ R^3\ Z^3\ E^3\ S^3$ + $1\ H^3\ R^3\ Z^3\ E^3$ (24+12 doses)	$5\ H^3\ R^3\ E^3$ (66 doses)

TABLE 1 : TABLE SHOWING TREATMENT CATEGORIES IN TB

DIABETES MELLITUS

Background

Diabetes mellitus is a chronic disorder of metabolism. Chronic hyperglycaemia with or without glycosuria secondary to defects insulin secretion, action or resistance to insulin. There is disturbance of carbohydrate, protein and fat metabolism. It leads to both microvascular and macrovascular complications. Retinopathy with progressive blindness,neuropathy,neuropathy with renal failure, autonomic dysfunction and Charcot joints are micro vascular complications. Cerebrovacsular,peripheral occlusive vascular disease and cardiovascular disease are macrovascular disease.

History :In 1500 B.C the first mention of diabetes as a condition causing polyuria was first made in Papyrus Ebers at Luxor in Egypt. The word diabetes was first used by Aretaeus of Cappadocia in the second century AD.It comes from the Greek word meaning Siphon.

Prevalence :

Diabetes Mellitus is an epidemic disease seen throughout the world. It is more observed in developed countries. By 2030, the major burden will be shared by Asian and African countries. In

2014,according to ICMR there are 73.4 million diabetics and 86.2 million prediabetics in India. The prevalence is estimated to be 366 million worldwide by 2030.India will be having one third of the disease burden. Type 2 Diabetes mellitus amongst Indians occur a decade earlier when compared to western population. Indians have more abdominal obesity and waist hip ratio. Also urbanisation and changing lifestyle adds to it.

Classification of diabetes

In 1979a uniform terminology and a functional classification of diabetes was developed. It classifies diabetes into insulin dependent diabetes and non insulin dependent diabetes by the National Diabetic Data Group in USA.Modifications were later made by Who expert committee in 1980 and 1985.An International Expert Committee ,working under the sponsorship of ADA proposed the current classification and diagnostic criteria in 1997.This was later accepted by WHO.

Figure 7 : ETIOLOGICAL CLASSIFICATION OF DIABETES

1.Type 1 diabetes[a] (β-cell destruction, usually leading to absolute insulin deficiency)
- Immune mediated
- Idiopathic

2.Type 2 diabetes[a] (can range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)

3.Other specific types
- Genetic defects of β-cell function
  - Chromosome 20q, HNF-4α (MODY1)
  - Chromosome 7p, glucokinase (MODY2)
  - Chromosome 12q, HNF-1β (MODY3)
  - Chromosome 13q, insulin promoter factor (MODY4)
  - Chromosome 17q, HNF-1β (MODY5)
  - Chromosome 2q, neurogenic differentiation 1/b-cell e-box transactivator 2 (MODY6)
  - Mitochondrial DNA
  - Others
- Genetic defects in insulin action
  - Type 1 insulin resistance
  - Leprechaunism
  - Rabson-Mendenhall syndrome
  - Lipoatrophic diabetes
  - Others
- Diseases of the exocrine pancreas
  - Pancreatitis
  - Trauma/pancreatectomy
  - Neoplasia
  - Cystic fibrosis
  - Hemochromatosis
  - Fibrocalculous pancreatopathy
  - Others
- Endocrinopathies
  - Acromegaly
  - Cushing's syndrome
  - Glucagonoma
  - Pheochromocytoma
  - Hyperthyroidism
  - Somatostatinoma
  - Aldosteronoma
  - Others
- Drug- or chemical-induced
  - Vacor (pyriminil)
  - Pentamidine
  - Nicotinic acid
  - Glucocorticoids
  - Thyroid hormone
  - Diazoxide
  - β-Adrenergic agonists
  - Thiazides
  - Phenytoin
  - Interferon alpha
  - Others
- Infections
  - Congenital rubella
  - Cytomegalovirus
  - Others
- Uncommon forms of immune-mediated diabetes
  - "Stiff-man" syndrome
  - Anti-insulin receptor antibodies
  - Others
- Other genetic syndromes sometimes associated with diabetes
  - Down's syndrome
  - Klinefelter's syndrome
  - Turner's syndrome
  - Wolfram's syndrome
  - Friedreich's ataxia
  - Huntington's chorea
  - Laurence-Moon-Biedel syndrome
  - Myotonic dystrophy
  - Porphyria
  - Prader-Willi syndrome
  - Others

4. Gestational diabetes mellitus (GDM)

[a]Patients with any form of diabetes can require insulin treatment at some stage of their disease. Such use of insulin does not in itself classify the patient.

Adapted with permission from Report of the Expert Committee.[13]

DIABETES MELLITUS DIAGNOSIS

The American Diabetes Association criteria for the diagnosis of diabetes are the following for non pregnant patients

TABLE 2 : ADA DIAGNOSTIC CRITERIA FOR DIABETES

Test[a]	Threshold	Qualifier
Hemoglobin A_{1c} or	≥ 6.5%	Lab NGSP-certified, standardized DCCT assay
Fasting glucose or	≥ 126 mg/dL (7.0 mmol/L)	No caloric intake for at least 8 hours
2-hour glucose or	≥ 200 mg/dL (11.1 mmol/L)	After 75 g of anhydrous glucose
Random glucose	≥ 200 mg/dL (11.1 mmol/L)	Plus classic hyperglycemia symptoms or crisis

NGSP, National Glycohemoglobin Standardization Program; DCCT, Diabetes Control and Complications Trial.

[a] Results must be confirmed by repeated testing.

Diabetes mellitus type 1

It occurs due to absolute insulin deficiency. Positive family history is rare and ketonuria is common. The patients are dependent on exogenous insulin for metabolic control and survival.

It develops in people who are genetically predisposed. In addition the certain environmental triggers start the process of autoimmune destruction leading to complete beta cell destruction and insulopaenia.

Type 1 diabetes is associated with autoimmune antibodies. Markers of beta cell destruction include islet cellantibodies, antibodies to insulin, antibodies to GAD, antibodies to tyrosine phosphatase IA-2 and IA-2 B.It is presenting 80-90 % of the individuals.

The rate of beta cell destruction is variable is some individuals. Some have a rapid course like infants and children. Adults usually have a slow course. Diabetic ketoacidosis can be the first presentation in many patients especially children. These patients are at higher risk of developing other autoimmune diseases .

Diabetes Mellitus type 2

This type of diabetes , which accounts for 90% of patients is seen middle aged people but can occur in children and early adulthood also. It was previously referred to as non insulin dependent or adult onset

diabetes. It is caused by interaction of environmental triggers and genetic predisposition. It is a polygenic disorder. It is caused by a cluster of susceptibility genes. Type 2 diabetes patients have relative insulin deficiency secondary to insulin resistance.

Most of these patients are obese or have increased percentage of abdominal body fat and a high waist hip ratio. Diabetic ketoacidosis is not that common in this type of diabetes. It is usually precipitated by stress of another illness, most commonly infections. This type of diabetes goes undiagnosed for many years because the hyperglycemia develops gradually and at earlier stages is often not severe enough for the patient to notice the classical symptoms of the disease. Most of these patients develop micro vascular and macro vascular complications of the disease. Associated with insulin resistance, secretion is also defective to maintain metabolic control. Insulin resistance usually improves with weight reduction and glycemic control, It is seldom restored to normal. The risk of developing the disease increases with the age, obesity and lack of physical activity. It is associated with dyslipidemia, hypertension and women with prior GDM.

GESTATIONAL DIABETES MELLITUS

Glucose intolerance that develops during pregnancy and typically resolves with delivery, occurs in about 7 % of all

pregnancies. This occurs due to insulin resistance in pregnancy, overweight, obesity and genetic predisposition.

DIABETES MELLITUS SYMPTOMS.

The symptoms of uncontrolled diabetes are related to high blood glucose levels and loss of sugar in urine. Glycosuria causes increased urination leading to dehydration. It leads to increased thirst and increase in appetite. These patients have abrupt onset signs and symptoms of hyperglycemia.The inability to utilise glucose energy eventually leads to weight loss. Patients have polyuria, polydipsia ,polyphagia, weight loss and fatigue. Elevated glucose levels leads to lethargy and coma. Patients can develop diabetic ketoacidosis or hyperosmolar coma. They can develop symptoms of microvascular and macrovascular complications.

ASSOCIATION OF TUBERCULOSIS AND DIABETES MELLITUS

From the initial part of the 20th century ,an association between tuberculosis and diabetes have been noted by treating physicians.It was unclear at that point whether TB caused diabetes or whether diabetes caused TB. The coming decades showed clinicians taking active interest in this associations and studies being published about this emerging coepidemic.[9-13]

The last decade saw multiple observational studies been done on this coexistence and the association being proven beyond doubt.[14-18]McCornick and colleagues from the University of Texas school of Public Health did a study in 2007 .They surveyed the link between the two diseases .It was done in over 6000 TB patients on the two sides of the Rio Grande River. Using this retrospective data they established that the co morbidity of TB-DM exceeded that of TB-HIV. These patients were older. They had more chance of developing hemoptysis and chest cavities. They tend to be smear positive at diagnosis. They remain positive at the end of the first and second month of treatment.

In Mexicans and Hispanic Americans diabetes was found to be an important risk factors. These links raised concerns regarding

public health. There is likely immunological impairment in M.Th. significance of diabetic control in tuberculosis and incidence of infection in diabetes was of concern.

The public health significance of TB-DM comorbidity is high.TB is a leading killer in the developing countries and India has become the global capital for diabetes mellitus. Thus a systematic assessment of this coepidemic is absolutely necessary to combat the diseases and stratify the situation.

A recent journal in BMC cited that much of the tuberculosis burden in India can be accredited to diabetes. As much as 15.8% of pulmonary tuberculosis and 21.2% of smear-positive i.e. infectious tuberculosis is linked to this disease[19]. The scenario of tuberculosis is changing with an urban preponderance probably due to diabetes when compared to rural areas[20]. But poverty is an independent risk for TB. Patients in rural areas have delayed diagnosis of this coepidemic.

In India in 2010, there were an estimated 487,573,000 people over the age of 20 years[21]. Among these , 5.3% i.e. around 21,707,639 had diabetes .949,064 developed pulmonary tuberculosis. 575,900 were smear-positive and infectious. The recent studies predict that in India 17.4% (12.5% to 29.9%) of people with

pulmonary tuberculosis (both smear-positive and smear-negative) have diabetes .23.5% (12.1% to 44%) of patients in smear positive group has diabetes[22].

Once acquiring tubercle bacilli any person has a 10 % chance of acquiring infection in his lifetime. There is 5% chance in the first 2 years and another 5% chance in the entire lifetime. Impaired glucose tolerance has been detected in TB patients for a very long time[22]. This is due to the increase in stress hormones ,insulin resistance and also rarely tuberculosis of the pancreas. Different studies uses different diagnostic criteria and hence comparisons are difficult. Around half of these patients return back to normal glucose levels on completion of anti tuberculosis treatment.

At present one third of the population is affected with latent tuberculosis. To contain the infection is a challenge. With increasing prevalence of diabetes the amount of patients developing active disease is going to be high. India has very few studies on the risk factors associated with tuberculosis. Sikand and Parma carried out study in 1949.The incidence of tuberculosis in silicosis patients was 24.9 %[23]

Multiple theories have been put forward regarding the association of TB and DM. Hyper glycemia favours growth,

survival,viability and propagation of mycobacteria[22]. Increased glucose levels augments chance of infections and decreases the repair capacity of cells. There is electrolyte imbalance with local tissue acidosis. Certain study suggest that there is lowering of protective cytological function. Also presence of glycerol and nitrogenous waste products aids in growth of bacilli[24].

The possibility of pituitary dysfunction is being validated. There is increased production of ACTH leading to increased corticosteroids. Reduced defense mechanisms leads to exudative inflammation and less of granulation tissue. There is increased insulin resistance[25]. Hepatic dysfunction and ensuing hypovitaminosis of A and D may result in pulmonary involvement more than extrapulmonary involvement in diabetes.

There is decreased production of Th1 mediated cytokines and gamma interferons[26].The cytokines in diabetic people has reduced chemo taxis and less leucocyte bactericidal activity. There is decreased production of IL-2 , TNF and monocytes in blood[27]. The decrease in function is directly proportional to blood sugar and glycated haemoglobin levels.

CLINICAL FEATURES

Diabetic patients tend to have an aggressive course of disease[28]. The latent Tb is activated more. Patients are usually elderly and male. Experienced clinicians observe that patients with both diabetes and tuberculosis usually have a prolonged duration of fever and more significant weight loss with co-existent disease than with diabetes or pulmonary tuberculosis alone. Patients have prolonged fever ,weight loss ,hemoptysis and chest pain[30-31]. Any diabetic patients presenting with such symptoms should be evaluated for TB. Also all tuberculosis patients should undergo diabetic screening.

Large number of studies has been made in radiological profiling of pulmonary tuberculosis patients with diabetes. Most of the clinicians find the findings atypical. There is involvement of lower lung fields and also evidence of multiple cavitations in most of the studies[32]. Lower lobe involvement with coexisting cavitations should raise the suspicion of TB-DM disease.

There is 5 to 6 higher risk of developing sputum positive pulmonary TB in diabetics[33]. Sputum conversion and smear positivity are methods to monitor to effective treatment. Patients with diabetes, radio logically extensive disease and cavities are delayed sputum conversion. Diabetes is considered an independent

risk factor for this. Also the amount of bacilli in oil immersion field is directly proportional to the blood glucose levels[34]. The suppression of immune system by diabetes may cause this high pre treatment bacillary load.

The mortality rates were high in diabetic patients with pulmonary tuberculosis when compared to non diabetic. Failures, relapserates and death were more seen in diabetes[32]. Although there are studies that show that diabetes do not alter the outcomes of treatment in TB patients. Diabetic patient were more to develop drug resistance tuberculosis. There is 8-9 times of risk of developing multi drug resistance tuberculosis[35]. This is mainly attributed to the hyperglycemia causing reduced drug absorption due to gastric paresis[36]. It also leads to impaired alveolar macrophage function and altered CD 4 function.

REVIEW OF PREVIOUS STUDIES

A multicentre case-control study was conducted in Guinee, Guinea Bissau and Gambia in West Africa. It was from January 1999 to March 2001. 846 newly detected sputum smear positive cases , 702 household controls and 828 community controls were recruited in the three countries. It showed that most of the patients were male, smokers and diabetes was an independent risk factor in development of tuberculosis[37].

Deshmukh et al studied 138 TB-DM patients . He established that 82.6% of the study population was above 45 years of age with a male preponderance. 43.4% of TB patients gave prior history of DM. 56.6% were detected further on the examination of urine and confirmed by blood sugar examination. Authors observed that, when a known case of diabetes presents with symptoms of general ill-health like fever, weakness, apathy, cough, haemoptysis, and chest pain; investigations may reveal the presence of tuberculosis[30].

Tripathi et al noted that TB patients with diabetes were underweight and above the age of 45 years[31].

Perenz-Guzman et al conducted a study on 192 TB-DM patients in Mexico TB patients as controls.TB-DM patients were found to be older (51.3 ± 0.9 vs. TB group 44.9 ± 1.8 years). They had a decreased frequency of upper (17% vs. 56%), and an increased involvement of lower (19% vs.7%) and upper and lower (64% vs. 36%) lung field lesions.TB-DM patients were prone for cavitations (82% vs. 59%) [38].They most often involved lower lung fields (29% vs. 3%). Cavities were often multiple in the TB-DM patients (25% vs. 2%).

The bacteriological profile of 737 patients were studied in turkey. These patients were hospitalized from 2000 to 2005 with pulmonary TB. Three hundred six (193 men and 113 women) patients with newly diagnosed pulmonary TB were studied[33]. Factors associated with both sputum smear and culture conversion time were investigated. Patients with DM, cavitary disease and radiologically extensive disease had longer sputum smear and culture conversion time when compared to the other groups.

692 smear-positive pulmonary TB patients in Riyadh, Saudi Arabia, were evaluated. The baseline characters of 187 patients with DM (TB-DM group) and 505 patients without DM (TB group) were compared. 65.2% of the patients in TB-DM group had numerous (>1 bacillus per oil

immersion field) AFB on smear examination compared to 54.1%

In a study by Ruslami et al the incidence of Diabetes and tuberculosis coepidemic was highest in India among 10 developing nations[39].

Sosman et al studied the radiological profile of pulmonary tuberculosis with diabetes and found that multilobular cavitatory TB is more common in diabetic people[40].

Wang et al studied self reported symptoms among TB patients with diabetes. He found that such patients had more of fever and hemoptysis[41].

MATERIALS AND METHODS

Study design :

Prospective non interventional case control study onclinical outcomes of sputum positive tuberculosis in newly detected diabetes patients in comparison to non diabetic patients.

Setting :

The study was carried at Government Mohan Kumaramangalam Medical College Hospital, Salem

Approval :

The study was approved by ethical committee of Government Mohan Kumaramangalam Medical College Hospital, Salem.

Study Population:

100 cases of newly diagnosed sputum positive pulmonary tuberculosis(50 diabetic and 50 non diabetic) fitting the inclusion criteria admitted over the period of 2 years from 2016-2017.Subjects were selected from medicine ward, pulmonology ward and Tuberculosis ward under DTC.The diagnosis of Pulmonary tuberculosis was made with clinical presentation and verification by detection of acid fast bacilli under microscope .

Inclusion Criteria :

- Age 18-75 Years
- Newly diagnosed sputum positive pulmonary tuberculosis cases.

Exclusion Criteria :

- Patients on steroids, thiazide diuretics
- HIV patients
- Sputum smear negative Pulmonary tuberculosis cases and extra pulmonary tuberculosis
- Patients not willing to participate.
- Pregnant women and women in postpartum period less than 6 weeks of delivery)
- Multi drug resistance Tuberculosis patients
- Known case of diabetes mellitus

Consent :

Patients were informed about the deatils of the tests performed and all investigations were collected with consent.

Measurement of glucose concentration :

All patients underwent fasting blood glucose testing at initiation of TB treatment. Any value above 110 mg/dl was considered abnormal. A 2 hour sample for plasma glucose was repeated after 75 grams OGTT.Values above or equal to 200 mg/dl was considered. Such patients were included in diabetic category. Diabetic patients were offered anti-diabetic medications at the diabetic clinic

Collection of other variables :

Detailed history with respect to age ,sex ,risk factors like smoking , alcohol and pan chewing were collected. The symptoms at the time of presentation and Chest X-Ray findings were recorded. Mycobacterial load was assessed and sputum cultures were done at 2 months and at end of treatment. Patients were regularly followed. Adverse drug reactions were monitored. Mainly 5 adverse drug reaction nausea and vomiting, peripheralneuropathy, liverinjury, hypoglycaemia and back pain were monitored. Liver injury was defined as clinical symptoms and signs of toxic hepatitis or elevation of enzymes more than 3 times normal.

Definition of TB treatment outcomes

Terms	Definitions
Cured	A PTB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion
Treatment completed	A TB patient who has completed treatment without evidence of failure but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable
Treatment failed	A TB patient whose sputum smear or culture is positive at month 5 or later during treatment
Died	A TB patient who dies for any reason before starting or during the course of treatment
Lost to follow-up	A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more
Not evaluated	A TB patient for whom no treatment outcome is assigned. This includes cases "transferred out" to another treatment unit as well as cases for which the treatment outcome is unknown to the reporting unit
Treatment success	The sum of *cured* and *treatment completed*

Statistical Methods:

Clinical presentation, severity, and treatment response to tuberculosis (sputum conversion at 2 months) were considered as primary outcome variables

Secondary outcome variable: ADR (Adverse Drug Reaction) (peripheral neuropathy, liver injury, hypoglycemia, back pain, nausea vomiting)

Primary explanatory variable: Diabetic status and glycemic control (as assessed by FBS and PPBS)

Other relevant variables: Age, gender, risk factors (alcohol, smoking, Pan chewing), etc. were considered as other explanatory variables.

Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. Data was also represented using appropriate diagrams like bar diagram, pie diagram and box plots.

The association between diabetic status, response to tuberculosis, ADR peripheral neuropathy, and quantitative explanatory parameters like, FBS, PPBS, sputum positivity, was assessed by comparing the mean values. The mean differences along with their 95% CI were presented. Independent sample t-test/ ANOVA.

The association between severity, response to tuberculosis and diabetic status was assessed by cross tabulation and comparison of percentages with 95% CI is presented. Chi square test was used to test statistical significance and represented using appropriate diagrams like stacked bar diagram

P value< 0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.(1)

OBSERVATION AND RESULTS

The results of the study are as follows

A total of 100 subjects were included in final analysis.

Table 3: Descriptive analysis of diabetic status in study population (N=100)

Diabetic status	Frequency	Percentage
Diabetics	50	50.00%
Non diabetics	50	50.00%

Among the study population , 50 (50%) were diabetics and 50 (50%) were non-diabetic.

Table 4: Descriptive analysis of gender in study population (N=100)

SEX	Frequency	Percentage
Male	56	56.00%
Female	44	44.00%

Among the study population , 56(56.00%) were male and 44(44.00%) were female.

CHART 1. : Pie chart showing sex distribution

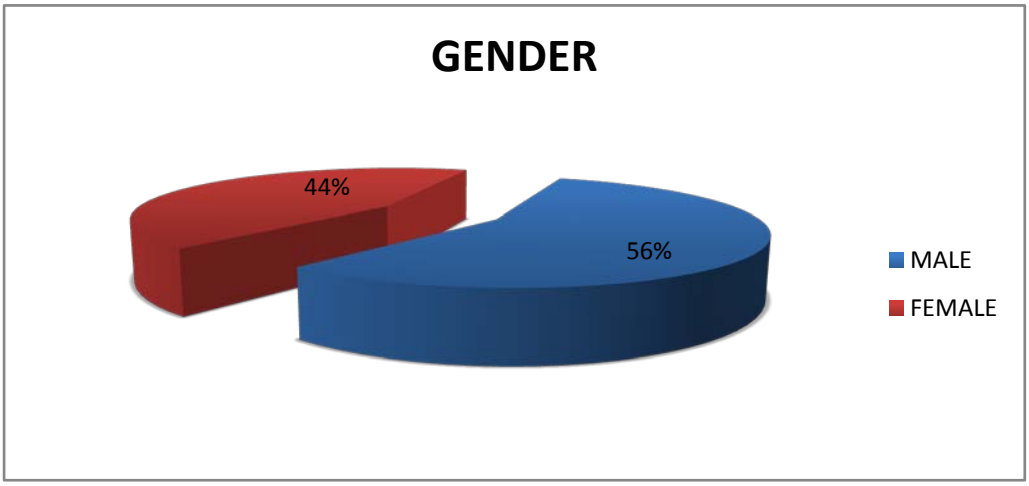


TABLE 5 :Frequency distribution of patients by age :

	FREQUENCY	PERCENTAGE
UPTO 20	1	1.0
21-30	13	13.0
31-40	28	28.0
41-50	37	37.0
51-60	11	11.0
61-70	8	8.0
ABOVE 70	2	2.0

CHART 2 : Bar diagram showing age distribution

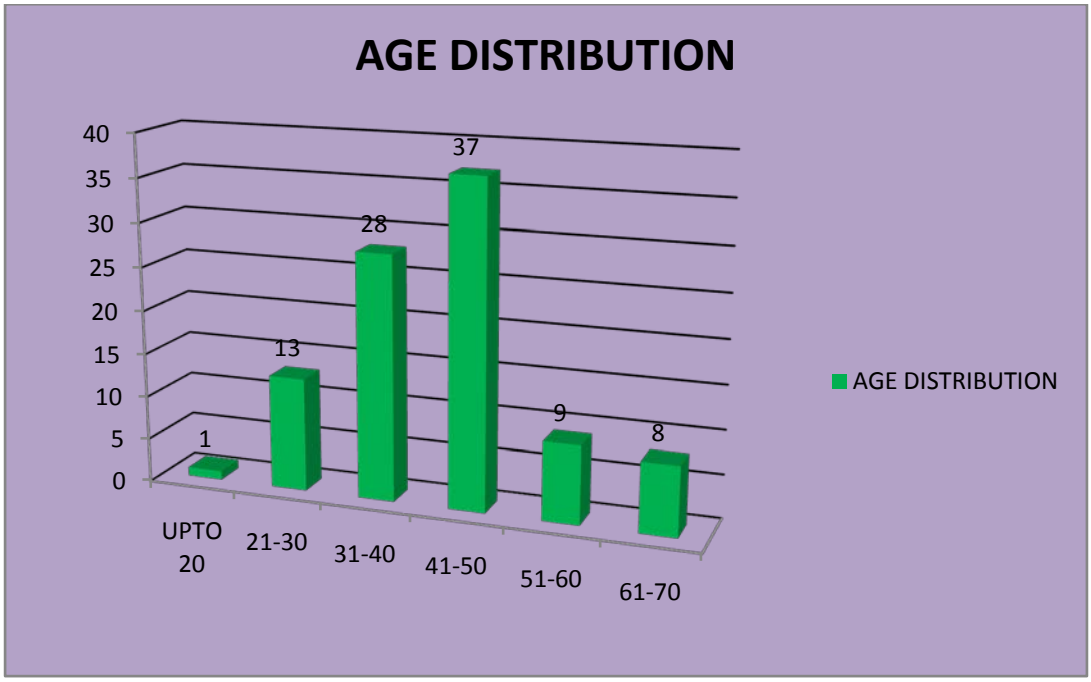


Table 6: Descriptive analysis for AGE in study population (N=100)

Parameter	Mean ±STD	Median	Min	Max	95% C.I. for EXP(B)	
					Lower	Upper
AGE	42.65 ± 11.76	42.50	19.00	72.00	40.32	44.98

The mean age was 42.65 ± 11.76 in the study population. Minimum years was 19 and maximum years was 72 in the study population (95% CI 40.32 to 44.98).

Table 7: Comparison of mean AGE across study groups (N=100)

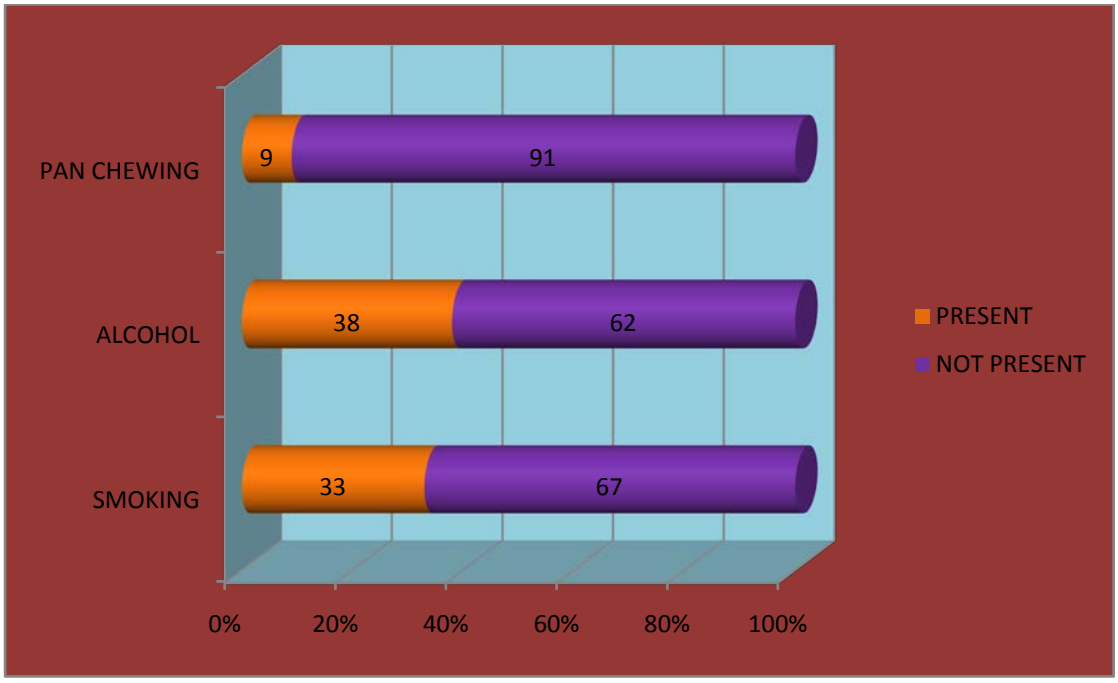
DIABETIC STATUS	**AGE Mean± STD**	**Mean difference**	**95% CI**		**P value**
			Lower	**Upper**	
Diabetics	51.1 ± 9	16.90	13.66	20.14	***<0.001***
Non diabetics	34.2 ± 7.26				

The mean age of diabetic status was 51.1 ± 9 and non-diabetic was 34.2 ± 7.26 , and the mean difference (16.90) between two groups was statistically significant (P value <0.001).

Table 8: Descriptive analysis of risk factors in study population (N=100)

Parameter	Frequency	Percent
Risk factors smoking		
Yes	33	33.00%
No	67	67.00%
Risk factors alcohol		
Yes	38	38.00%
No	62	62.00%
Pan chewing		
Yes	9	9.00%
No	91	91.00%

Chart 3: Horizontal bar diagram showing risk factors in study population

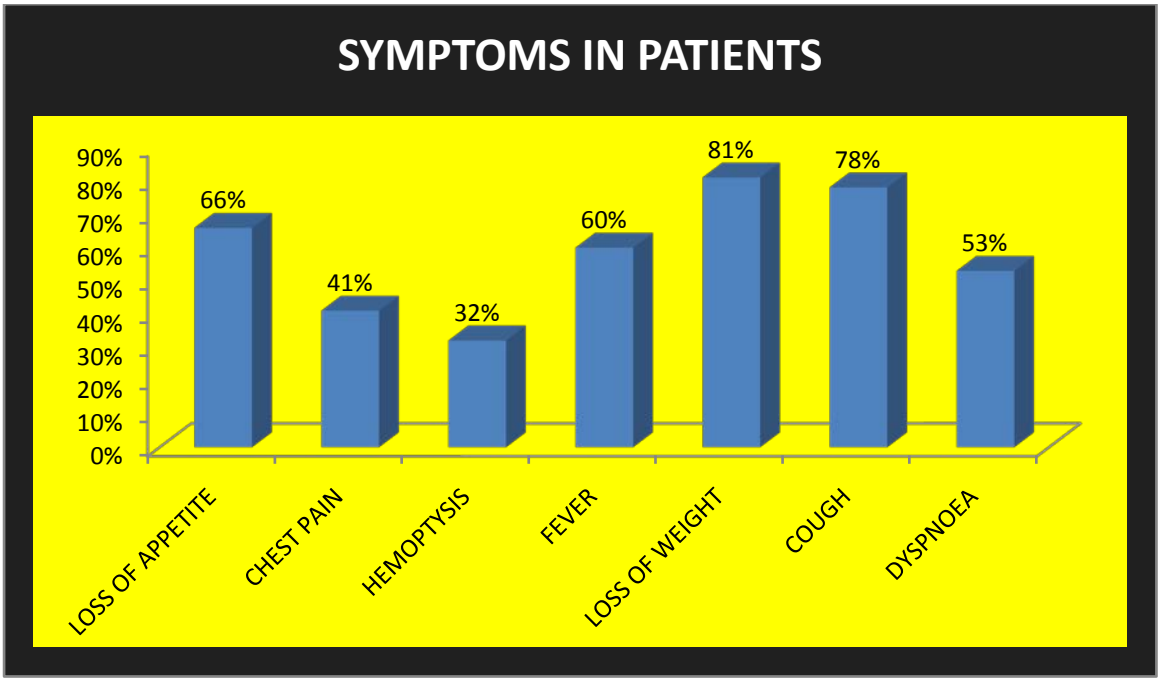


Among the study population 33(33.00%) were smokers , 38 (38.00%) were alcoholics and 9 (9.00%) were habituated to pan chewing.

Table 9: Descriptive analysis of symptoms in study population (N=100)

Parameter	Frequency	Percent
Dyspnoea		
Yes	53	53.00%
No	47	47.00%
Chest Pain		
Yes	41	41.00%
No	59	59.00%
Loss of appetite		
Yes	66	66.00%
No	34	34.00%
Evening rise of fever		
Yes	60	60.00%
No	40	40.00%
Loss of weight		
Yes	81	81.00%
No	19	19.00%
HEMOPTYSIS		
Yes	32	32.00%
No	68	68.00%
Cough		
Yes	78	78.00%
No	22	22.00%

CHART 4: bar diagram showing distribution of symptoms

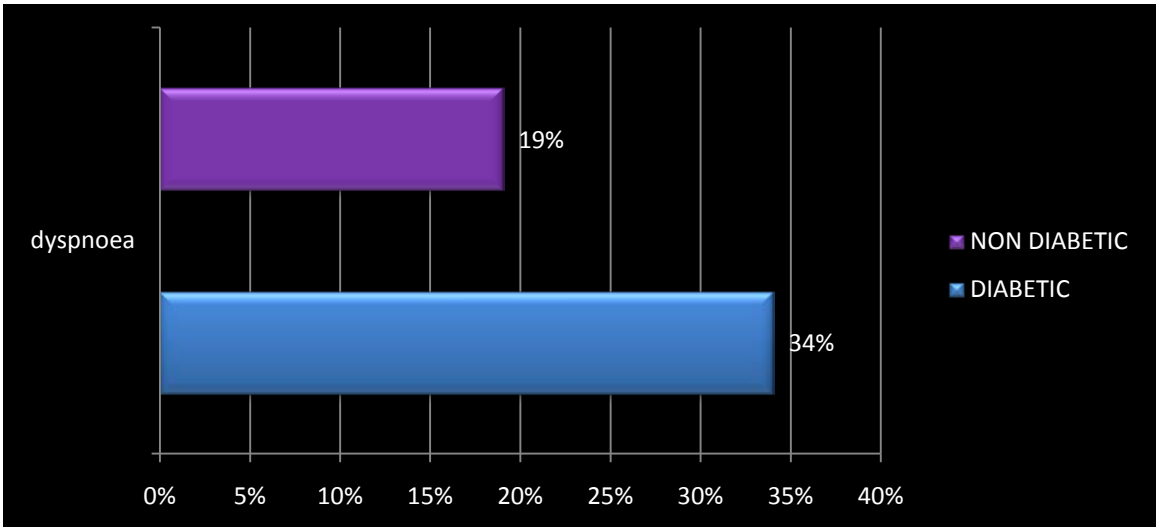


Among the study population, 53 (53.00%) had dyspnoea, 41 (41.00%) had chest pain, 66(66.00%) had loss of appetite , 60 (60.00%) had evening rise of temperature, 81(81.00%) had loss of weight, 32 (32.00%) had hemoptysis , 78 (78.00%) had cough.

Table 10: Association of diabetic status with dyspnoea of study population (N=100)

Dyspnoea	DIABETIC STATUS		Chi square	P-value
	Diabetics (N=50)	Non diabetics(N=50)		
Yes	34 (68%)	19 (38%)	9.033	***0.003***
No	16 (32%)	31 (62%)		

Chart 5: horizontal bar diagram showing dyspnoea symptom in diabetic and non diabetic patients.

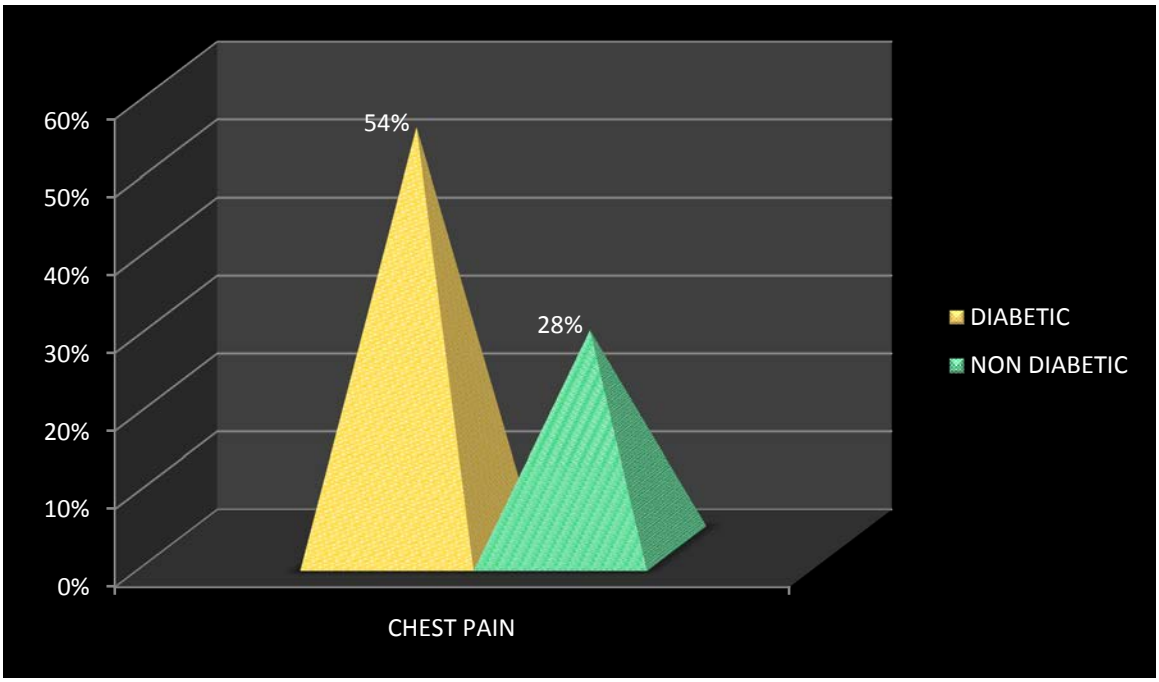


Among the diabetic, 34 (68%) had dyspnoea. Among the non-diabetic, 19 (38%) had dyspnoea.The difference in the proportion of diabetic status between dyspnoea was statistically significant (P value 0.003)

Table 11: Association of diabetic status with chest pain of study population (N=100)

Chest Pain	DIABETIC STATUS		Chi square	P-value
	Diabetics	Non diabetics		
Yes	27 (54%)	14 (28%)	6.986	***0.008***
No	23 (46%)	36 (72%)		

CHART 6 : Pyramid showing percentage of chest pain among diabetic and non diabetic

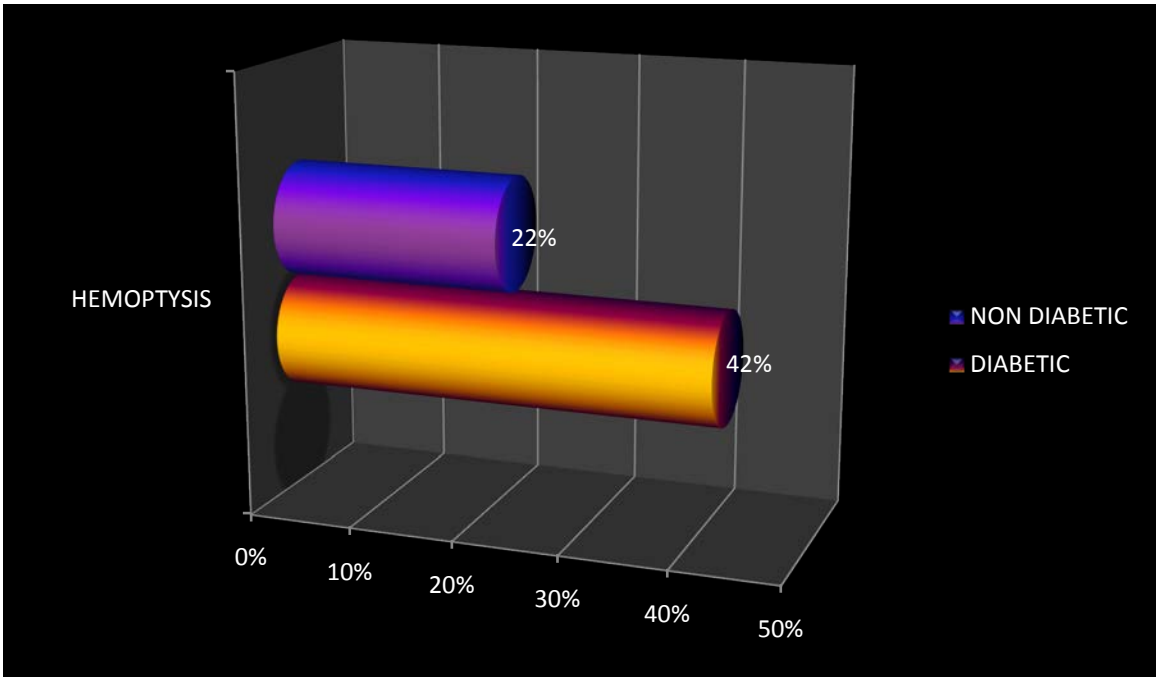


Among the diabetic, 27 (54%) had chest pain. Among the non-diabetic, 14 (28%) had chest pain.The difference in the proportion of diabetic status between chest pain was statistically significant (P value 0.008)

Table 12: Association of diabetic status with hemoptysis of study population (N=100)

HEMOPTYSIS	DIABETIC STATUS		Chi square	P-value
	Diabetics	Non diabetics		
Yes	21 (42%)	11 (22%)	4.596	***0.032***
No	29 (58%)	39 (78%)		

CHART 7: horizontal bar diagram showing hemoptysis in diabetic and non diabetic patients



Among the diabetic, 21 (42%) had hemoptysis. Among the non-diabetic, 11 (22%) had hemoptysis.The difference in the proportion of diabetic status between hemoptysis was statistically significant (P value 0.032)

Table 13: Association of diabetic status with cough of study population (N=100)

COUGH	**DIABETIC STATUS**		**Chi square**	**P-value**
	Diabetics	**Non diabetics**		
Yes	36 (72%)	42 (84%)	2.098	0.148
No	14 (28%)	8 (16%)		

Among the diabetic,36 (72%) had cough. Among the non-diabetic,42 (84%) had cough. The difference in the proportion of diabetic status between cough was statistically not significant (P value 0.148)

Table 14: Association of diabetic status with loss of weight of study population (N=100)

Loss of weight	DIABETIC STATUS		Chi square	P-value
	Diabetics	Non diabetics		
Yes	39 (78%)	42 (84%)	0.585	0.444
No	11 (22%)	8 (16%)		

Among the diabetic, 39 (78%) had loss of weight. Among the non-diabetic 42 (84%) had loss of weight. The difference in the proportion of diabetic status between loss of weight was statistically not significant (P value 0.444)

Table 15: Association of diabetic status with loss of appetite of study population (N=100)

Loss of appetite	DIABETIC STATUS		Chi square	P-value
	Diabetics	Non diabetics		
Yes	29 (58%)	37 (74%)	2.852	0.091
No	21 (42%)	13 (26%)		

Among the diabetic, 29 (58%) had loos of appetite. Among the non-diabetic 37 (74%) had loss of appetite. The difference in the proportion of diabetic status between loss of appetite was statistically not significant (P value 0.091) (Table 46)

Chart 8: bar diagram showing symptoms analysis in diabetic and non diabetic patients

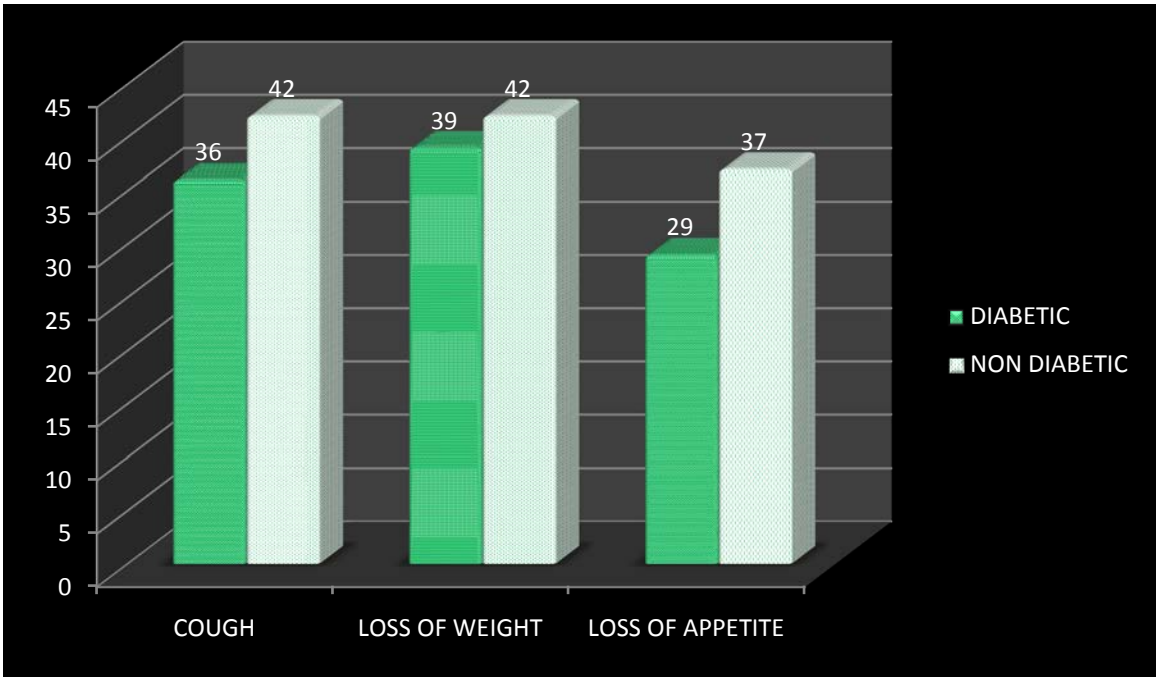
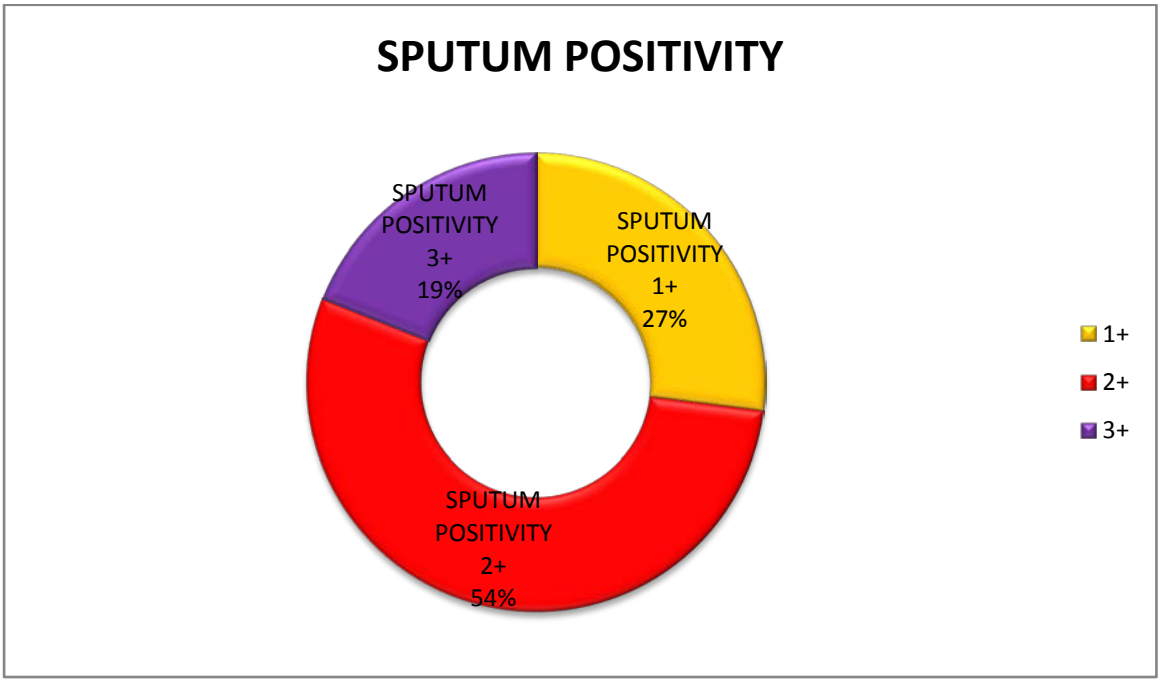


Table 16: Descriptive analysis of sputum positivity in study population (N=100)

Sputum positivity	Frequency	Percentages
1+	27	27.00%
2+	54	54.00%
3+	19	19.00%

CHART 9: Doughnut diagram showing sputum positivity rates in study population

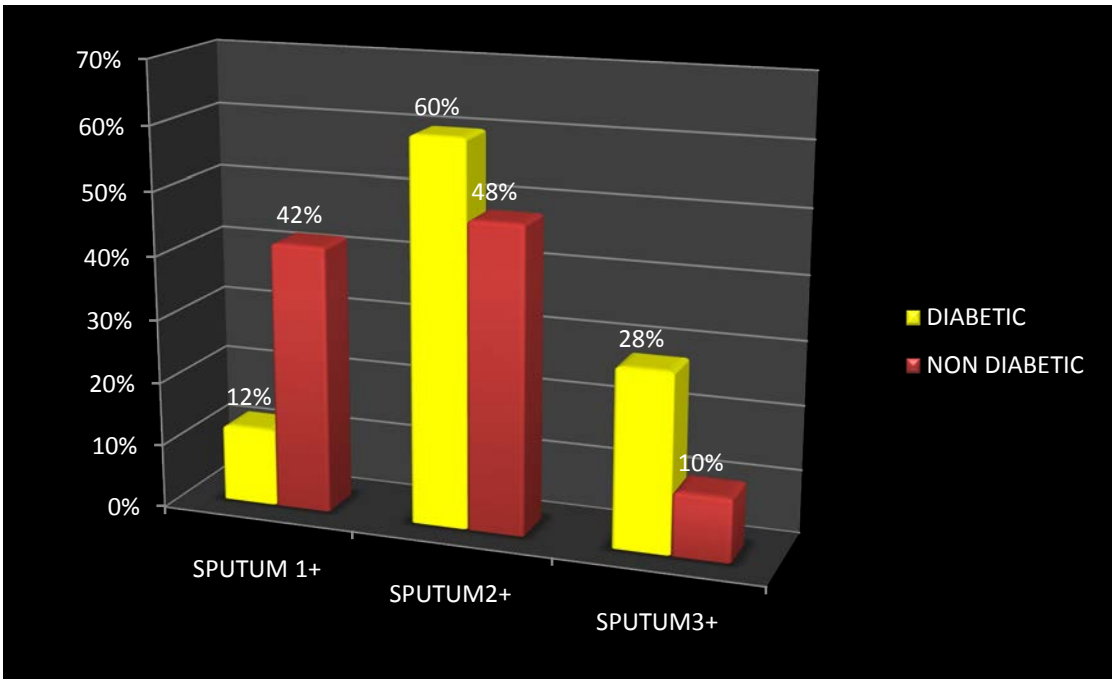


Among the study population of sputum positivity was 1+ , 2+ and 3+ in 27 (27.00%), 54 (54.00%) and 19 (19.00%) subjects respectively .

Table 17: Association of diabetic status with sputum positivity of study population (N=100)

Sputum Positivity	**Diabetic Status**		**Chi square**	**P-value**
	Diabetics (N=50)	**Non diabetics (N=50)**		
1+	6 (12%)	21 (42%)	13.263	***0.001***
2+	30 (60%)	24 (48%)		
3+	14 (28%)	5 (10%)		

CHART 10 : Bar diagram showing sputum positivity rates among diabetics and non diabetics

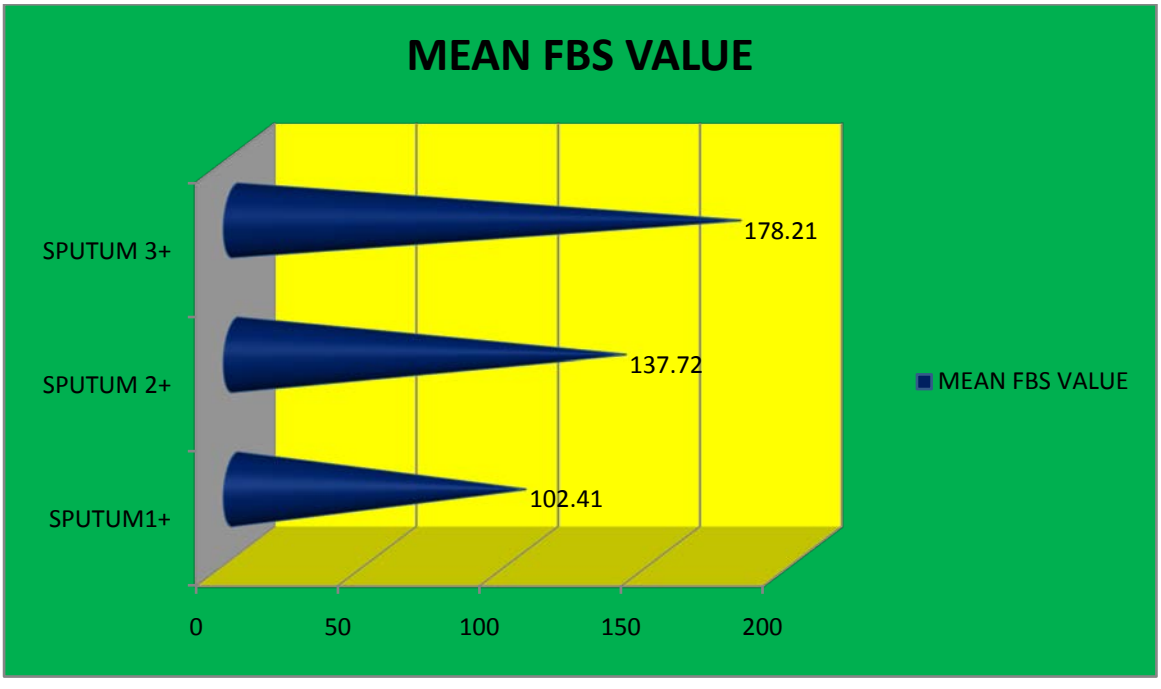


Among the diabetic , 6 (12%) had positivity 1, 30 (60%) had positivity 2 , and 14 (28%) had positivity 3.Among the non-diabetic , 21 (42%) had positivity 1, 24 (48%) had positivity 2, and 5 (10%) had positivity 3.The difference in the proportion of diabetic status between sputum positivity was statistically significant (P value 0.001).

Table 18: Comparison of mean FBS across study groups (N=100)

Sputum Positivity	Mean ± S. D	Mean difference	95% Confidence Interval for Mean		P value
			Lower Bound	Upper Bound	
1+	102.41 ± 20.32				
2+	137.72 ± 44.22	35.315	15.38	55.25	***<0.001***
3+	178.21 ± 58.58	75.803	50.48	101.13	***<0.001***

CHART 11 : Diagram showing mean FBS value in each sputum positivity groups



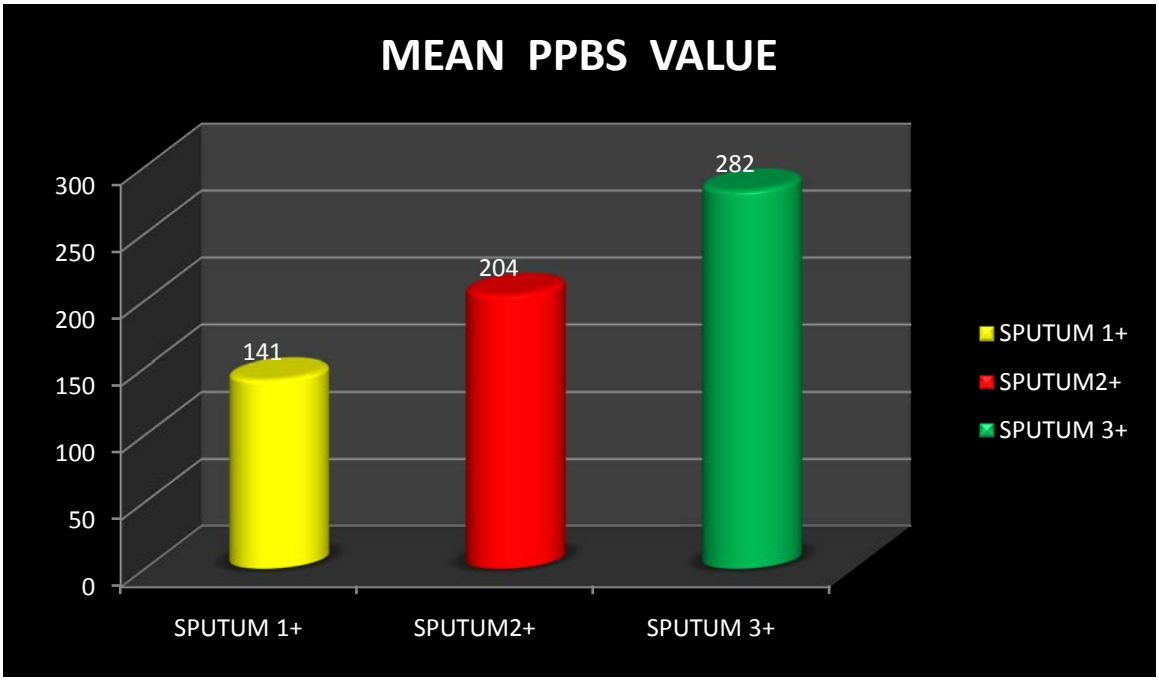
The mean FBShad positivity 1 was 102.41 ± 20.32, 137.72 ± 44.22 had positivity 2 and 178.21 ± 58.58 had positivity 3. Considering sputum

positivity 1 as base line, the mean difference of FBS(35.315) in positivity 2 was statistically significant (P value <0.001) and also positivity 3 (75.803) was statistically significant (P value <0.001).

Table 19: Comparison of mean PPBS across study groups (N=100)

Sputum Positivity	**Mean ± S. D**	**Mean difference**	**95% Confidence Interval for Mean**		**P value**
			Lower Bound	**Upper Bound**	
1+	141.11 ± 40.69				
2+	204.04 ± 80.73	62.926	26.29	99.56	***<0.001***
3+	282.16 ± 107.11	141.047	94.50	187.59	***<0.001***

CHART 12 : Bar diagram showing mean PPBS value in sputum positivity groups

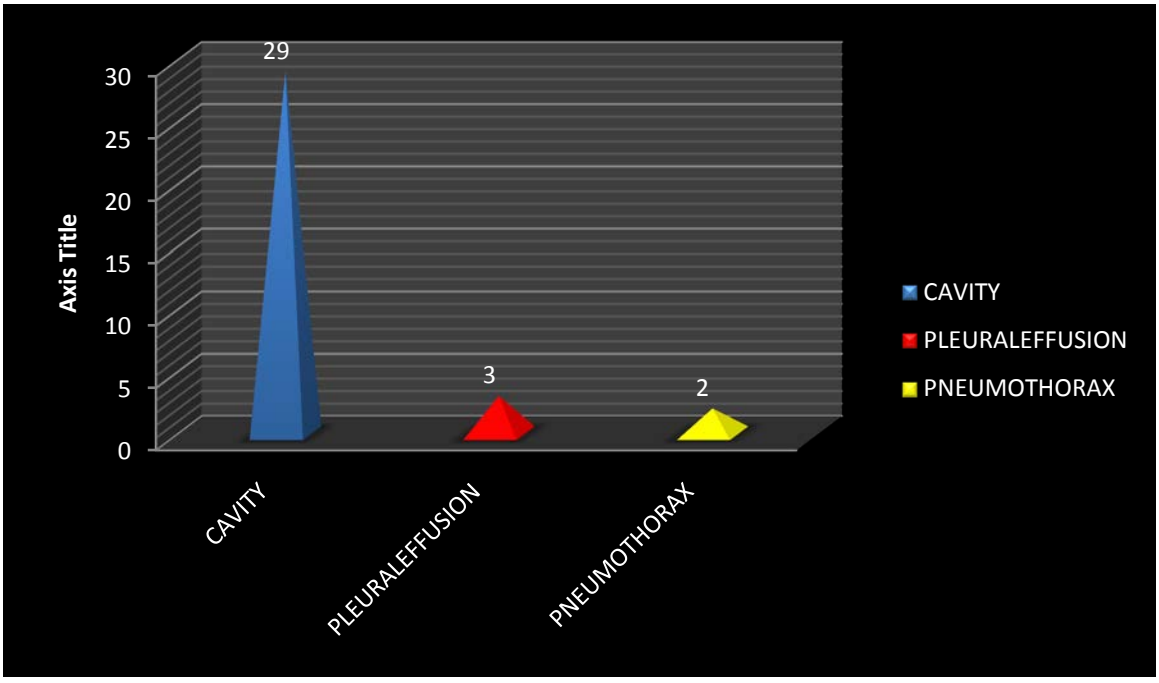


The mean PPBShad positivity 1 was 141.11 ± 40.69, 204.04 ± 80.73 had positivity 2 and 282.16 ± 107.11 had positivity 3. Considering sputum positivity 1 as base line, the mean difference of PPBS(62.926) in positivity 2 was statistically significant (P value <0.001) and also positivity 3 (94.50) was statistically significant (P value <0.001).

Table 20: Descriptive analysis of Chest x-ray cavity in study population (N=100)

Chest x-ray cavity	Frequency	Percentage
CAVITY	29	29.00%
NO	66	66.00%
PLEURAL EFFUSION	3	3.00%
PNEUMOTHORAX	2	2.00%

CHART 13 : bar diagram showing x ray findings in study population

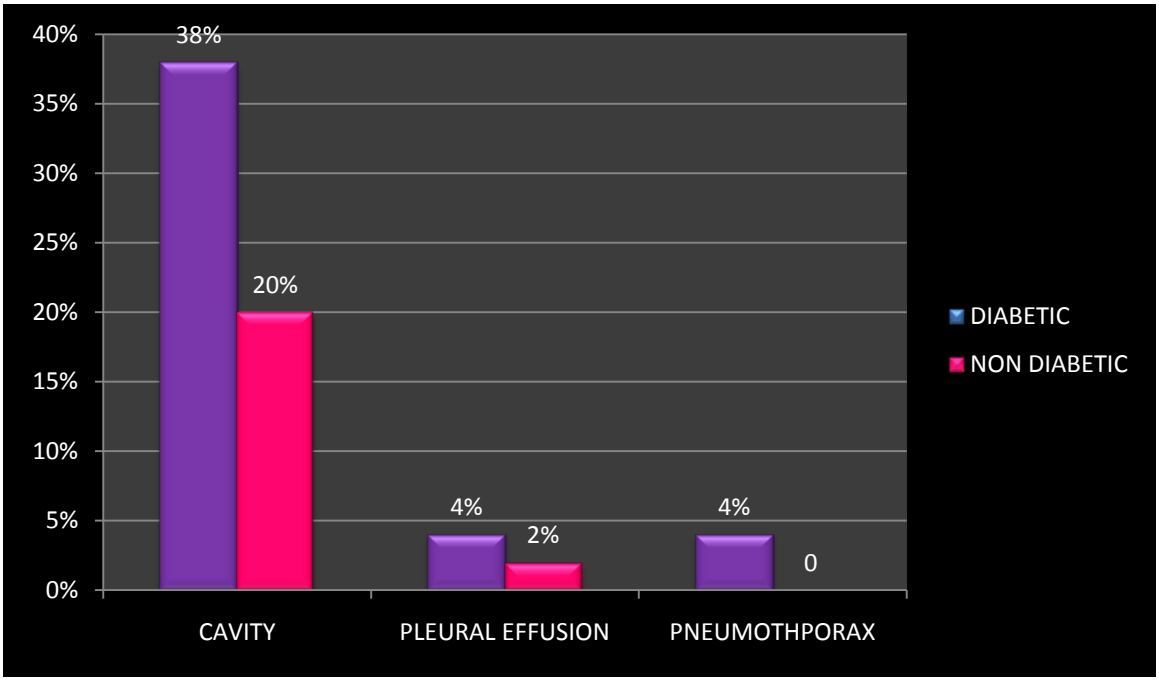


Among the study population, 29(29.00%) had cavity in chest X-ray, 3 (3.00%) had pleural effusion and 2 (2.00%) had pneumothorax.

Table 21: Association of diabetic status with Chest X-ray CAVITY of study population (N=100)

Chest X-ray CAVITY	**DIABETIC STATUS**		**Chi square**	**P-value**
	Diabetics(N=50)	**Non diabetics(N=50)**		
CAVITY	19 (38%)	10 (20%)	3.934	0.047
NO	27 (54%)	39 (78%)		
PLEURAL EFFUSION	2 (4%)	1 (2%)		
PNEUMOTHORAX	2 (4%)	0 (0%)		

CHART 14: bar diagram showing chest X ray findings in each study group



Among the diabetic, 19 (38%) had cavity, 27 (54%) had no cavity, 2 (4%) had pleural effusion, and 2(4%) had pneumothorax. Among the non-diabetic, 10(20%) had cavity, 39 (78%) had no cavity, 1 (2%) had pleural effusion. The difference in the proportion of diabetic status between chest X-ray cavity was statistically significant.

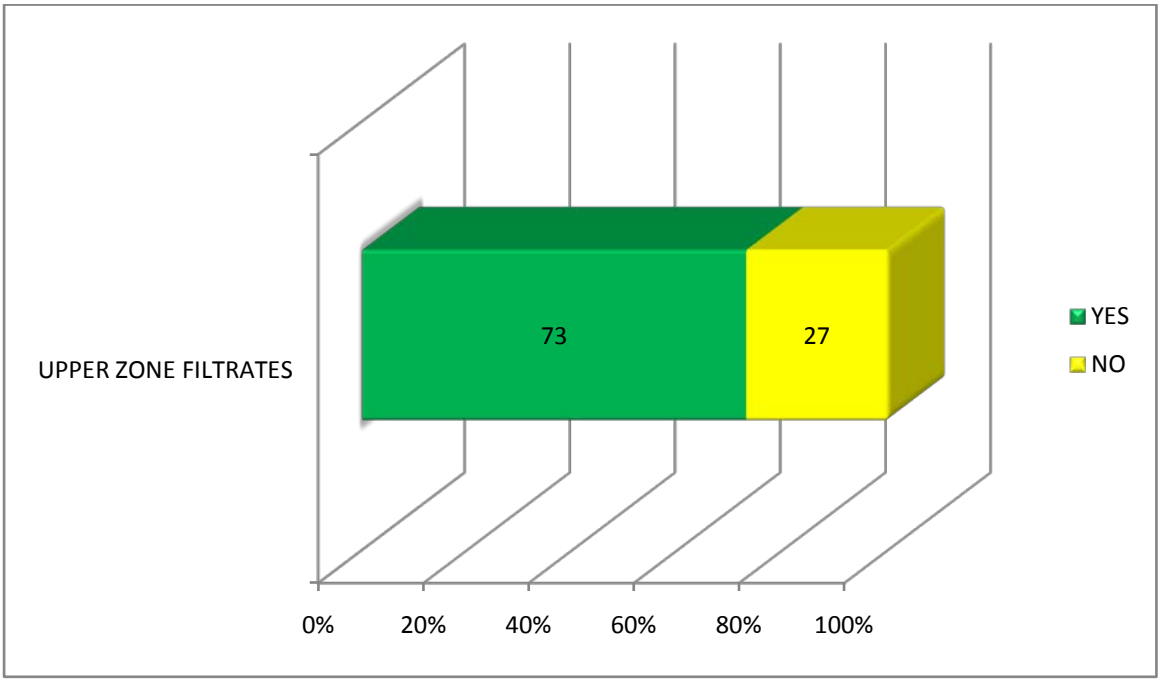
Table 22: Descriptive analysis of upper zone infiltrates in study population (N=100)

Upper zone infiltrates	Frequency	Percentage
Yes(bilateral)	16	16.00%
Yes(left)	33	33.00%
Yes(right)	24	24.00%
No	27	27.00%

Table 23 : Descriptive analysis of upper zone infiltrates category in study population (N=100)

Upper zone infiltrates category	Frequency	Percentage
Yes	73	73.00%
No	27	27.00%

CHART 15: horizontal bar diagram showing percentage of upper zone infiltrates in study population.

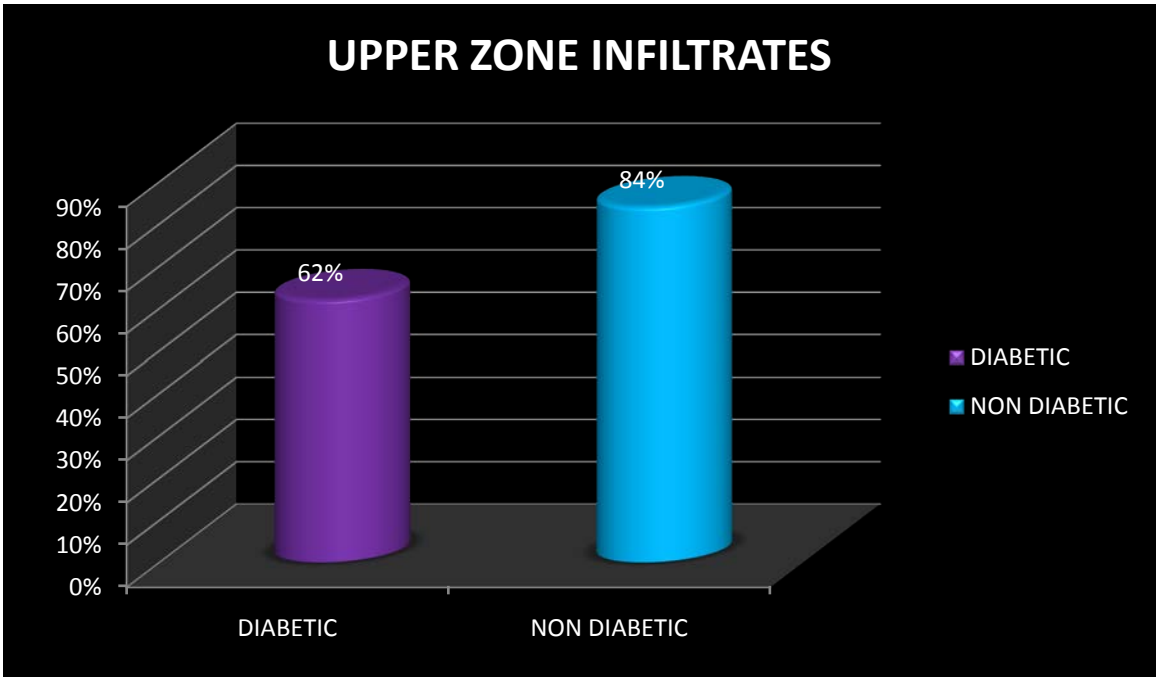


Among the study population, 73 (73.00%) had upper zone infiltrates.

Table 24: Association of diabetic status with upper zone infiltrates category of study population (N=100)

Upper zone infiltrates category	DIABETIC STATUS		Chi square	P-value
	Diabetics (N=50)	Non diabetics (N=50)		
Yes	31 (62%)	42 (84%)	6.139	***0.013***
No	19 (38%)	8 (16%)		

CHART 16 : bar diagram showing upper zone infiltrates in chest x-ray in diabetic and non diabetic patients



Among the diabetic, 31 (62%) were upper zone infiltrates. Among the non-diabetic, 42 (84%) were upper zone infiltrates.The difference in the proportion of diabetic status between upper zone infiltrates was statistically significant (P value 0.013)

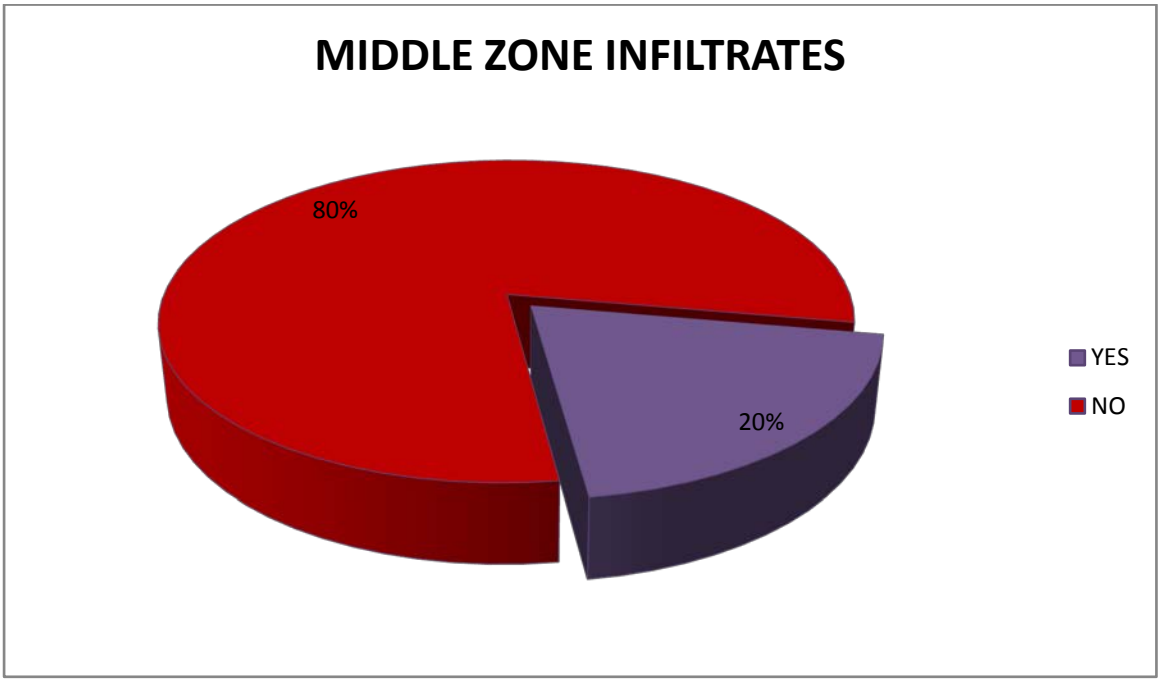
Table 25: Descriptive analysis of middle zone infiltrates in study population (N=100)

Middle zone infiltrates	Frequency	Percentage
Yes(bilateral)	7	7.00%
Yes(left)	8	8.00%
Yes(right)	5	5.00%
No	80	80.00%

Table 26: Descriptive analysis of Middle zone infiltrates category in study population (N=100)

Middle zone infiltrates category	Frequency	Percentage
Yes	20	20.00%
No	80	80.00%

CHART 17 : figure showing middle zone infiltrates in chest x-ray in study population

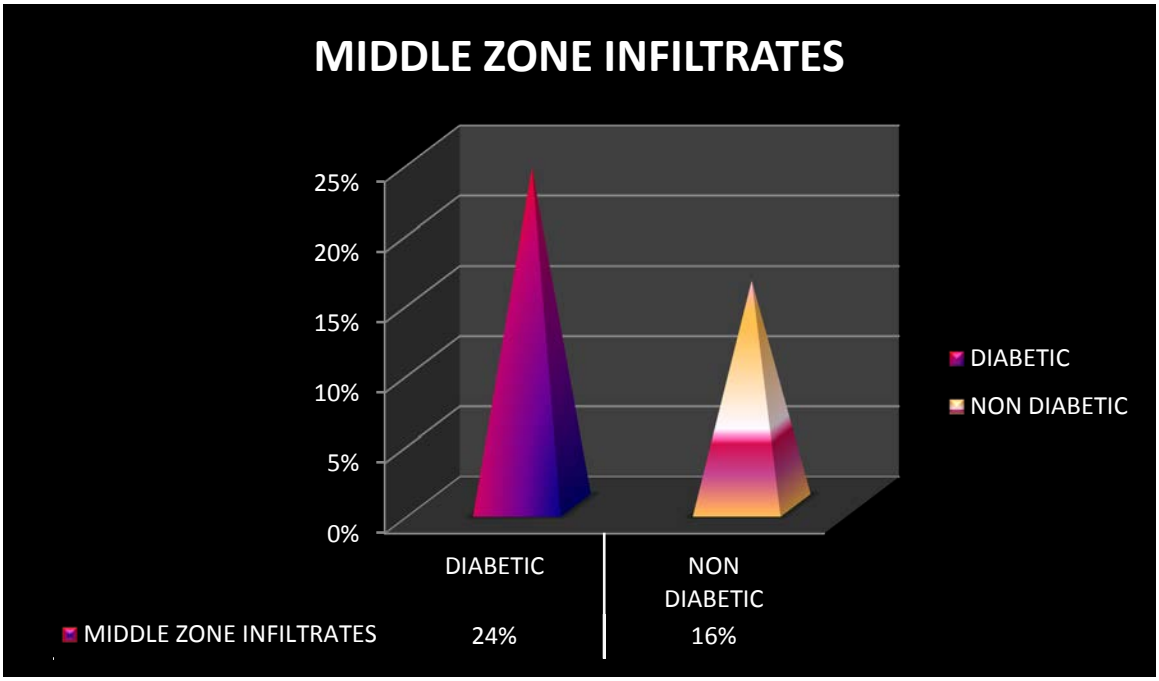


Among the study population, 20 (20.00%) had middle zone infiltrates.

Table 27: Association of diabetic status with middle zone infiltrates category of study population (N=100)

Middle zone infiltrates category	DIABETIC STATUS		Chi square	P-value
	Diabetics (N=50)	Non diabetics (N=50)		
Yes	12 (24%)	8 (16%)	1.000	0.317
No	38 (76%)	42 (84%)		

CHART 18: Diagram showing middle zone infiltrates in chest x-ray in diabetic vs. non diabetic group



Among the diabetic, 12 (24%) were middle zone infiltrates. Among the non-diabetic, 8 (16%) were middle zone infiltrates.The difference in the proportion of diabetic status between middle zone infiltrates was statistically not significant (P value 0.317)

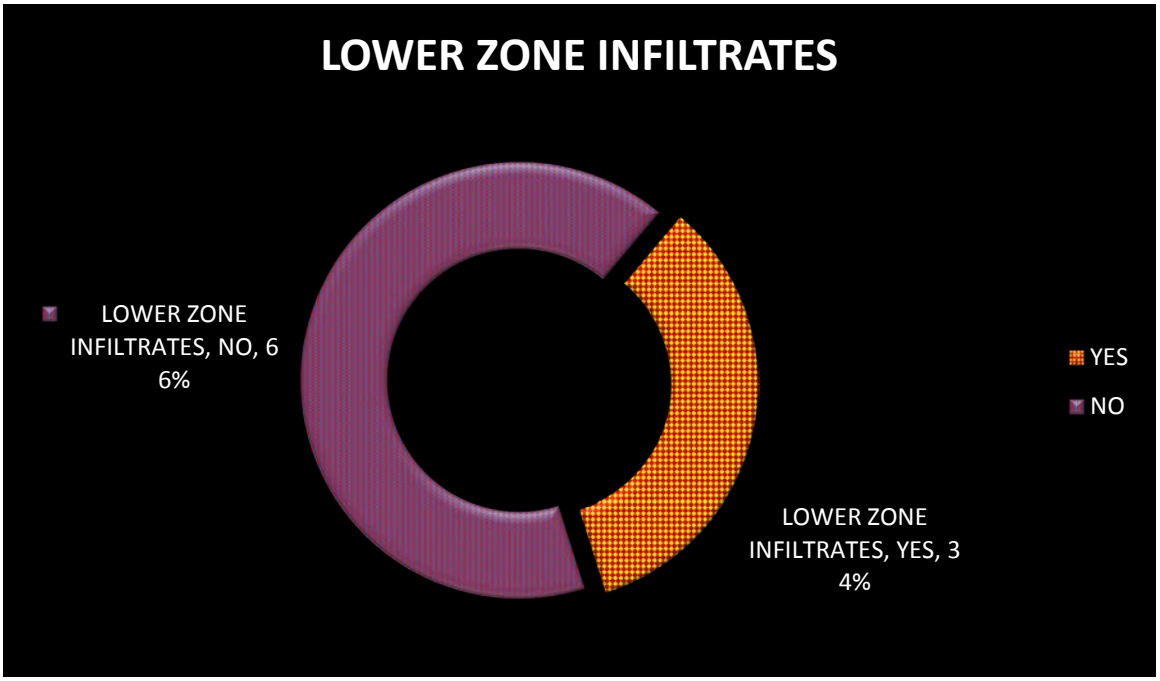
Table.28: Descriptive analysis of lower zone infiltrations in study population (N=100)

Lower zone infiltrations	Frequency	Percentages
Yes (bilateral)	12	12.00%
Yes(left)	13	13.00%
Yes(right)	9	9.00%
No	66	66.00%

Table 29: Descriptive analysis of Lower zone infiltrations category in study population (N=100)

Lower zone infiltrations category	Frequency	Percentage
Yes	34	34.00%
No	66	66.00%

CHART 19: Pie chart showing lower zone infiltrates in study population

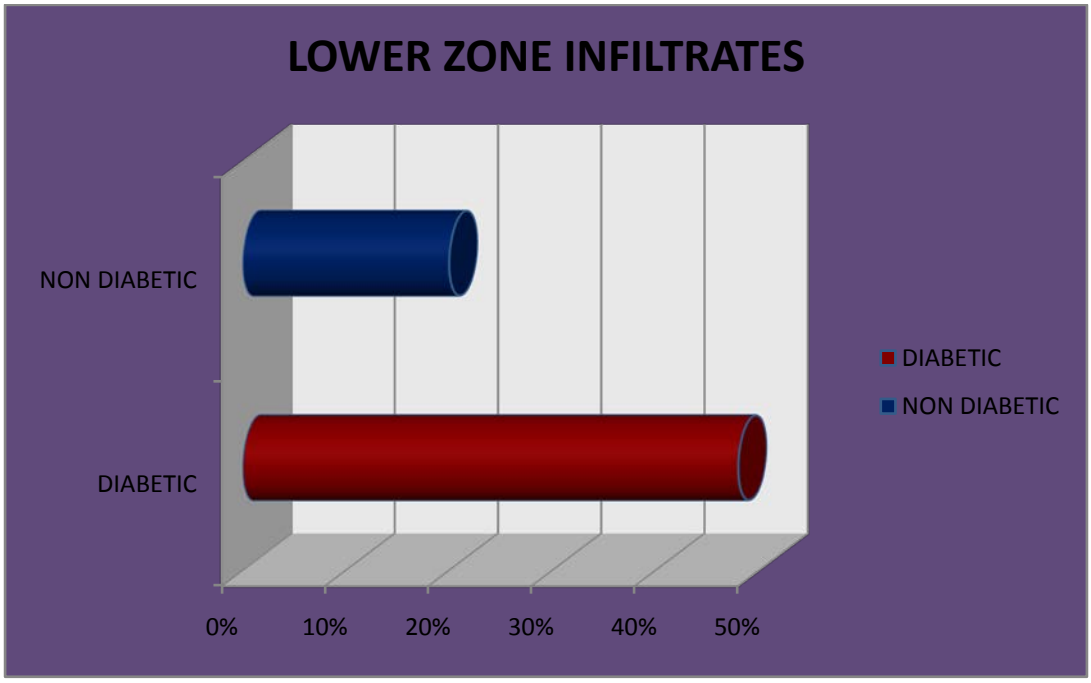


Among the study population, 34 (34.00%) had lower zone infiltrates.

Table 30: Association of diabetic status with lower zone infiltrations category of study population (N=100)

Lower zone infiltrations category	DIABETIC STATUS		Chi square	P-value
	Diabetics (N=50)	Non diabetics (N=50)		
Yes	24 (48%)	10 (20%)	8.734	***0.003***
No	26 (52%)	40 (80%)		

CHART 20: bar diagram showing lower zone infiltrates in x-ray in diabetic and non diabetic patients



Among the diabetic, 24 (48%) were lower zone infiltrates. Among the non-diabetic, 10 (20%) were lower zone infiltrates.The difference in the proportion of diabetic status between lower zone infiltrates was statistically significant (P value 0.003)

Table 31: Descriptive analysis of Sputum status at 2 months after initiation of treatment in study population (N=100)

Sputum status at 2 months after initiation of treatment	**Frequency**	**Percentage**
Positive	23	23.00%
Negative	77	77.00%

Among the study population, sputum status at 2 months after initiation oftreatment was 23 (23.00%) had positive and 77(77.00%) had negative.

CHART 21: Pie chart of Sputum status at 2 months after initiation of treatment distribution in study population (N=100)

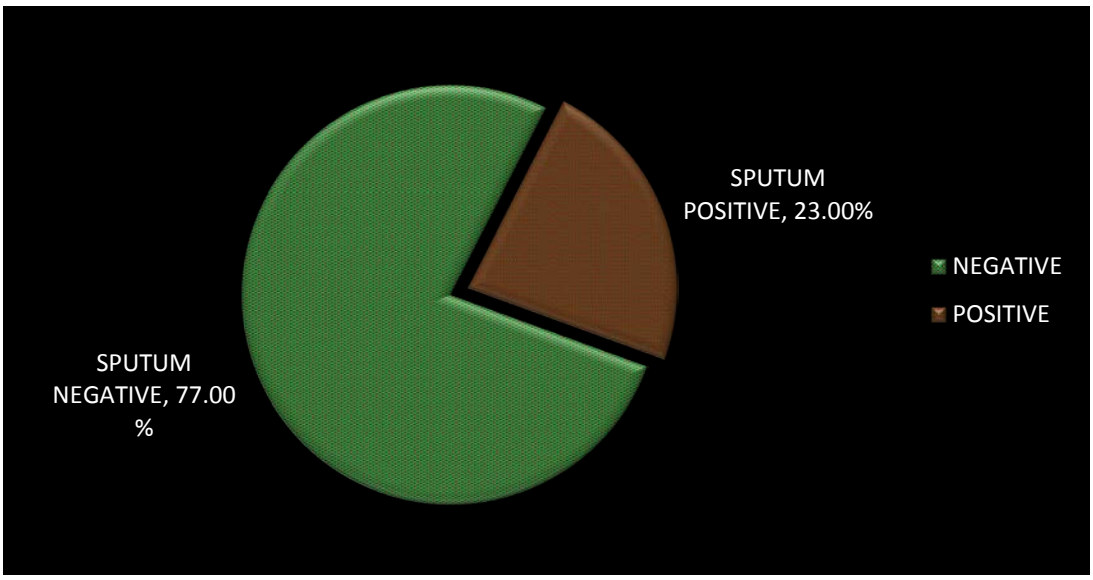


Table 32: Association of diabetic status with sputum status at 2 months after initiation of of treatment in study population (N=100)

Sputum status at 2 months after initiation of treatment	DIABETIC STATUS		Chi square	P-value
	Diabetics (N=50)	Non diabetics (N=50)		
Positive	15 (30%)	8 (16%)	2.767	0.096
Negative	35 (70%)	42 (84%)		

Among the diabetic, 15 (30%) had positive, and 35 (70%) had negative.Among the non-diabetic, 8 (16%) had positive, and 42 (84%) had negative.The difference in the proportion of diabetic status between sputum status at 2 months was statistically not significant (P value 0.096)

CHART 22: Stacked bar chart of association of diabetic status with sputum status at 2 months after initiation of treatment initiation of study population (N=100)

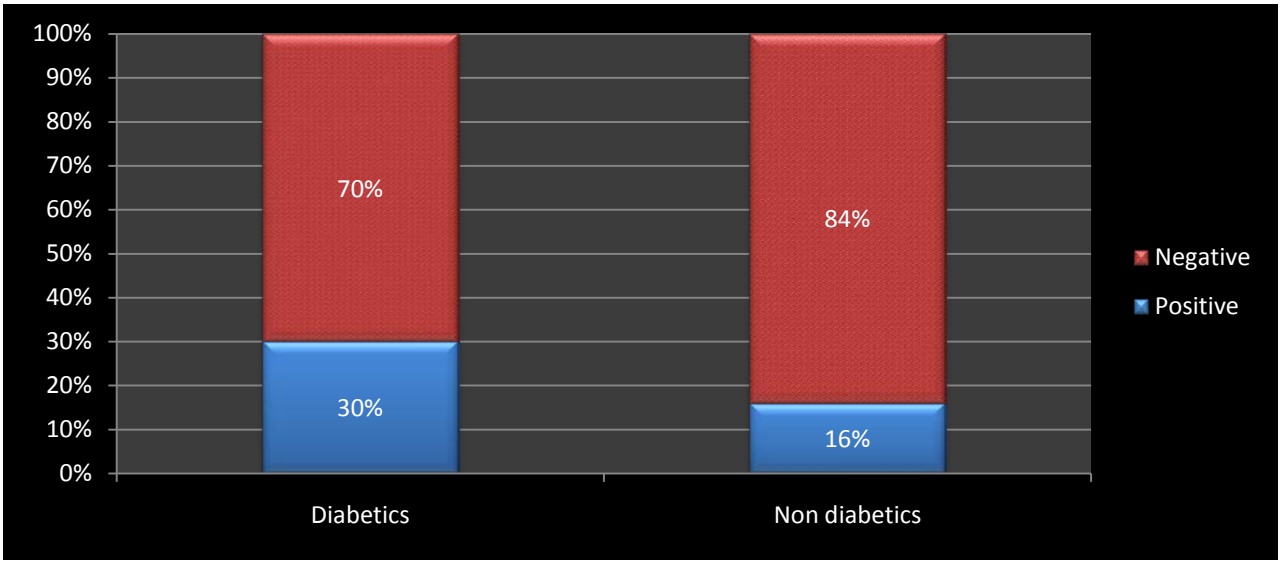


Table 33: Comparison of mean FBS across study groups (N=100)

SPUTUM STATUS AT 2 MONTHS AFTER TREATMENT INITIATION	FBS Mean± STD	Mean difference	95% CI		P value
			Lower	Upper	
Positive	149.91 ± 50.86	18.22	-4.85	41.30	0.120
Negative	131.69 ± 48.37				

The mean FBSof sputum status positive at 2 months was 149.91 ± 50.86 and negative was 131.69 ± 48.37, and the mean difference (18.22) between two groups was statistically not significant (P value <0.120).

Table 34: Comparison of mean PPBS across study groups (N=100)

SPUTUM STATUS AT 2 MONTHS I1	PPBS Mean± STD	Mean difference	95% CI		P value
			Lower	Upper	
Positive	228.35 ± 90.67	34.36	-8.15	76.87	0.112
Negative	193.99 ± 90				

The mean PPBSof sputum status at 2 months was 228.35 ± 90.67 and negative was 193.99 ± 90, and the mean difference (34.36) between two groups was statistically not significant (P value <0.112).

CHART 23: bar diagram showing mean FBS and PPBS levels in sputum positive and negative patients

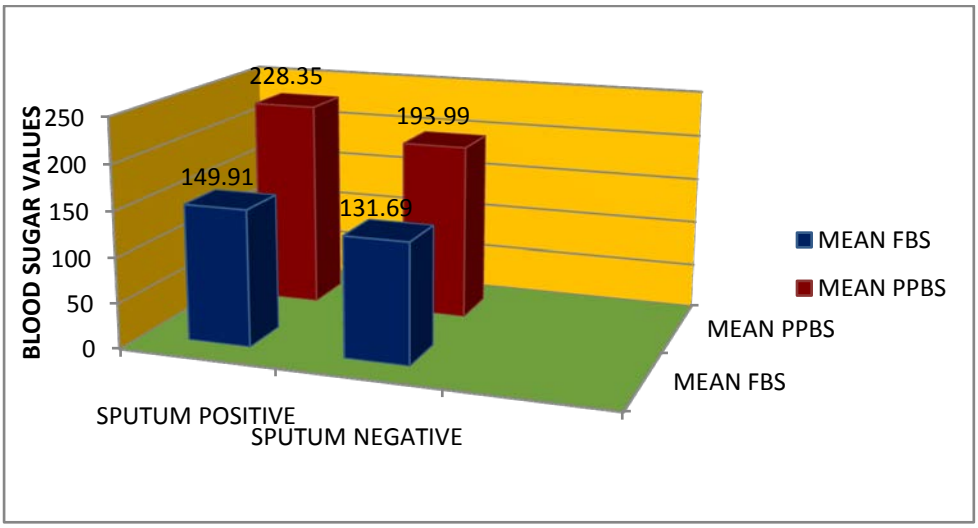
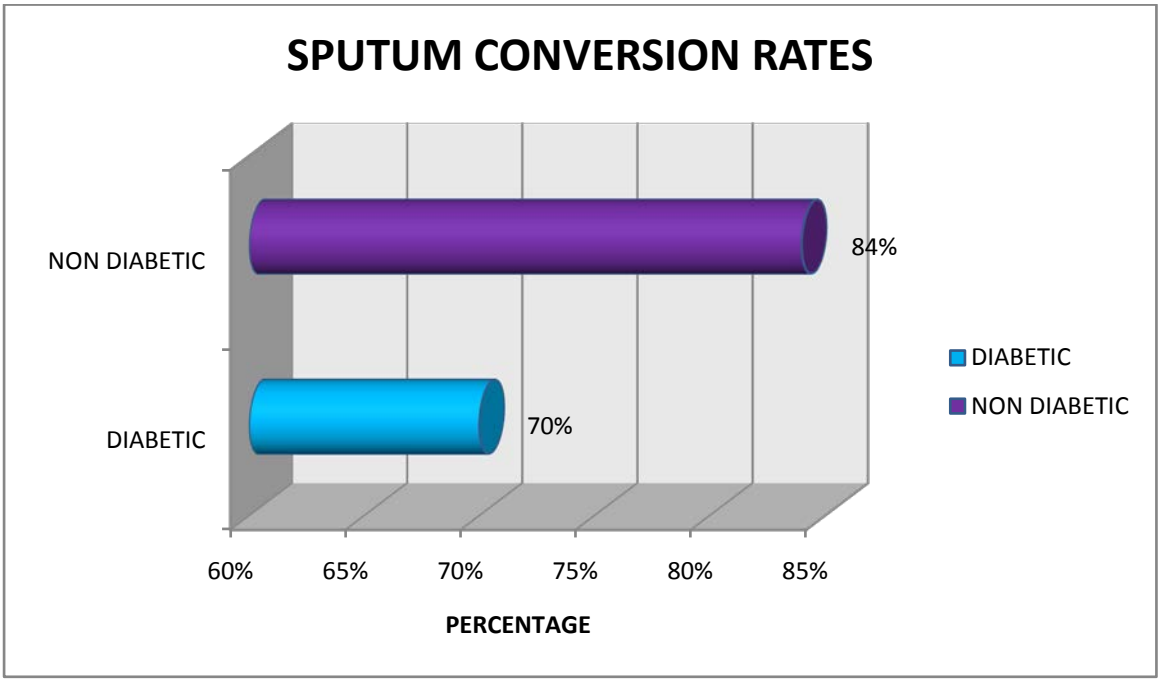


Table 35: Comparison of sputum conversion rate between two groups

Sputum status at 2 months after treatment initiation	DIABETIC STATUS		Chi square	P-value
	Diabetics	Non diabetics		
Sputum conversion rate	35 (70%)	42 (84%)	2.767	0.096

CHART 23: horizontal bar diagram showing sputum conversion rates in diabetic and non diabetic patients



The sputum conversion rate is 70 % in diabetic patients while it is 84% in non diabetic patients. Even though sputum conversion rates are less in diabetics it is not statistically significant.

Table 36: Descriptive analysis of treatment outcomes in study population (N=100)

Treatment outcomes	Frequency	Percentages
Completed	91	91.00%
Defaulter	4	4.00%
Failure	5	5.00%

Among the study population, 91(91.00%) have completed the treatment, 4 (4.00%) were defaulter the treatment, and remaining 5(5.00%) were treatment failures. (Table 13 & Fig 2)

CHART 24: Pie chart of treatment outcomes distribution in study population (N=100)

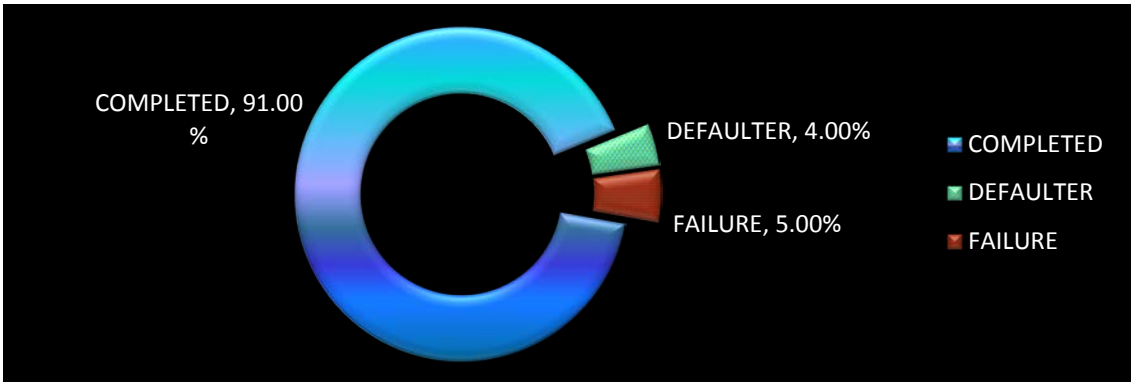


Table 37: Association of diabetic status with treatment outcomes of study population (N=100)

Treatment outcomes	DIABETIC STATUS		Chi square	P-value
	Diabetics	Non diabetics		
Completed	44 (88%)	47 (94%)	1.899	0.387
Defaulter	2 (4%)	2 (4%)		
Failure	4 (8%)	1 (2%)		

Among the diabetic, 44 (88%) have treatment completed, 2 (4%) were treatment defaulter, and 4 (8%) were treatment failure.Among the non-diabetic, 47 (94%) have treatment completed, 2 (4%) were treatment defaulter, and 1 (2%) were treatment failure.The difference in the proportion of diabetic status between treatment outcomes was statistically not significant (P value 0.387)

CHART 25: Stacked bar chart of association of diabetic status with treatment outcomes of study population (N=100)

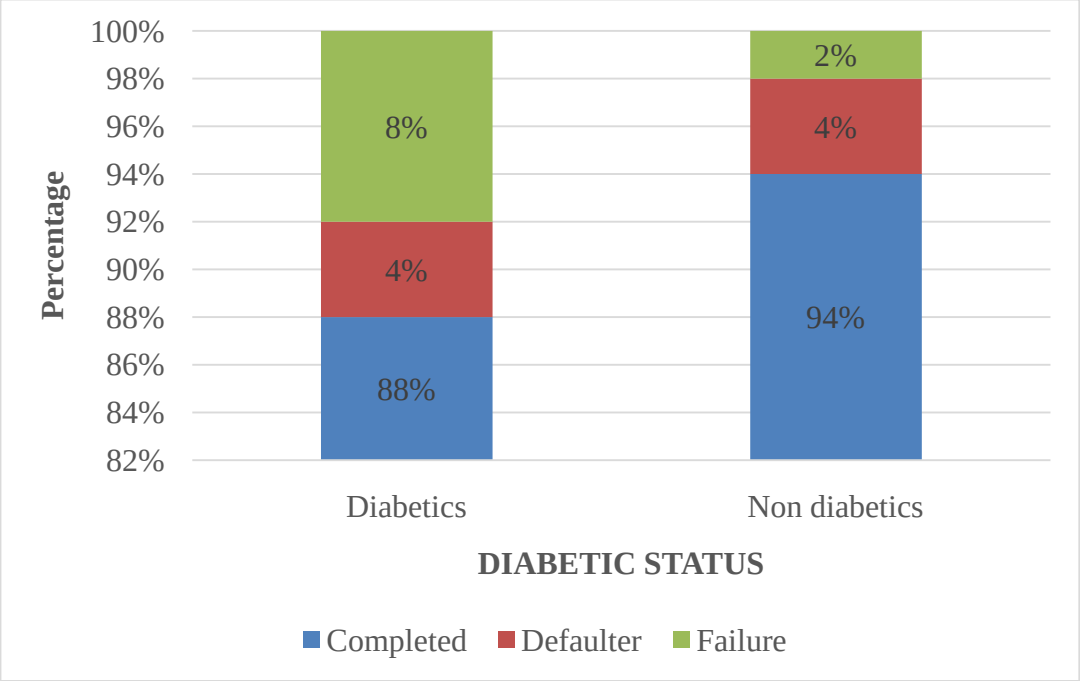
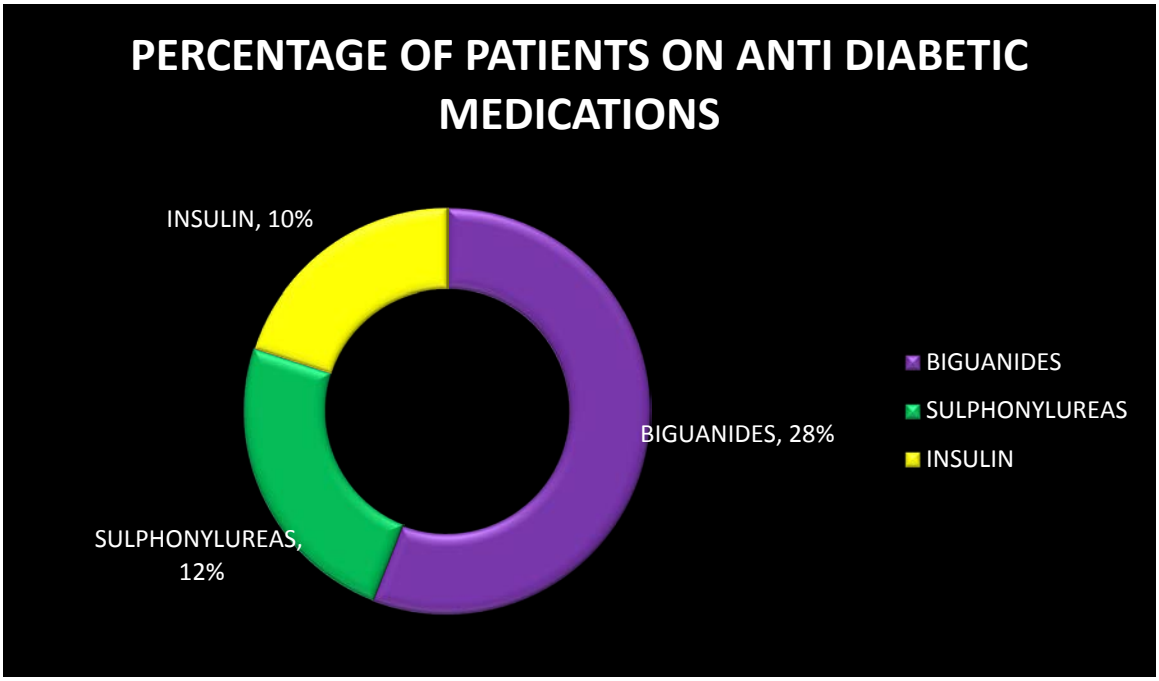


Table 38: Descriptive analysis of drugs for diabetic mellitus in study population (N=50)

Drugs for diabetic mellitus	Frequency	Percentage
Biguanides	28	56.00%
Insulin	10	20.00%
Sulphonylureas	12	24.00%

CHART 26: diagram showing percentage of patients on various anti diabetic medications

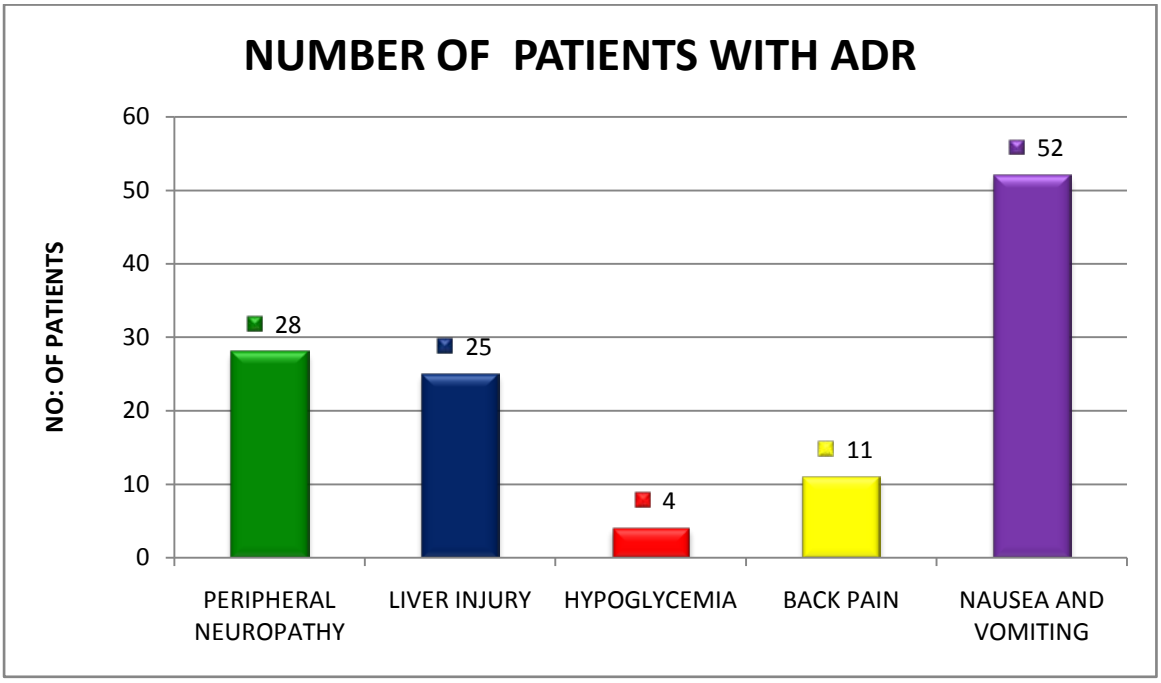


Among the diabetic population, 28 (28.00%) were receiving biguanides, 10 (10.00%) were receiving insulin, and 12 (12.00%) were receiving sulphonylureas.

Table 39: Descriptive analysis of ADR (Adverse Drug Reaction) in study population (N=100)

ADR	**Frequency**	**Percentage**
ADR peripheral neuropathy	28	28.00%
Liver injury	25	25.00%
Hypoglycemia	4	4.00%
Back pain	11	11.00%
Nausea vomiting	52	52.00%

CHART 27 : bar diagram showing frequency distribution of ADR in study population



Among the study population, 28 (28.00%) hadperipheral neuropathy, 25 (25.00%) had liver injury, 4 (4.00%) had hypoglycemia, 11 (11.00%) had back pain, and 52 (52.00%) had nausea vomiting.

Table 40: Association of diabetic status with ADR peripheral neuropathy of study population (N= 100)

ADR PERIPHERAL NEUROPATHY	DIABETIC STATUS		Chi square	P-value
	Diabetics	Non diabetics		
YES	19 (38%)	9 (18%)	4.960	***0.026***
NO	31 (62%)	41 (82%)		

Among the diabetic, 19 (38%) had peripheral neuropathy. Among the non diabetic, 9 (18%) had peripheral neuropathy.The difference in the proportion of diabetic status between ADR peripheral neuropathy was statistically significant (P value 0.026)

Table 41: Comparison of mean FBS across study groups (N=100)

ADR PERIPHERAL NEUROPATHY	**FBS Mean± STD**	**Mean difference**	**95% CI**		**P value**
			Lower	**Upper**	
Yes	163.5 ± 60.26	38.36	17.86	58.87	***<0.001***
No	125.14 ± 39.87				

The mean FBSof peripheral neuropathy was 163.5 ± 60.26 and without peripheral neuropathy was 125.14 ± 39.87, and the mean difference (38.36) between two groups was statistically significant (P value <0.001).

Table 42: Comparison of mean PPBS across study groups (N=100)

ADR PERIPHERAL NEUROPATHY	PPBS Mean± STD	Mean difference	95% CI		P value
			Lower	Upper	
Yes	241.18 ± 104.81	54.57	15.71	93.42	***0.006***
No	186.61 ± 80.55				

The mean PPBSof peripheral neuropathy was 241.18 ± 104.81 and without peripheral neuropathy was 186.61 ± 80.55, and the mean difference (54.57) between two groups was statistically significant (P value 0.006).

Table 43: Association of diabetic status with liver injury of study population (N=100)

LIVER INJURY	DIABETIC STATUS		Chi square	P-value
	Diabetics	Non diabetics		
YES	15 (30%)	10 (20%)	1.333	0.248
NO	35 (70%)	40 (80%)		

Among the diabetic, 15 (30%) had liver injury. Among the non-diabetic, 10 (20%) had liver injury.The difference in the proportion of diabetic status between liver injury was statistically not significant (P value 0.248)

Table 44: Association of alcohol with liver injury of study population (N=100)

LIVER INJURY	ALCOHOL		Chi square	P-value
	Yes	No		
Yes	18 (47.37%)	7 (11.29%)	16.355	***<0.001***
No	20 (52.63%)	55 (88.71%)		

Among the people using alcohol, 18 (47.37%) had liver injury. Among the people never using alcohol 7 (11.29%) had liver injury. The difference in the proportion of alcohol between liver injury was statistically significant (P value <0.001)

Table 45: Association of diabetic status with hypoglycemia of study population (N=100)

HYPOGLYCEMIA	**DIABETIC STATUS**	
	Diabetics	**Non diabetics**
Yes	4 (8%)	0 (0%)
No	46 (92%)	50 (100%)

**No statistical test was applied- due to 0 subjects in the cells.*

Among the diabetic, 4 (8%) had hypoglycemia.

Table 46: Association of diabetic status with back pain of study population (N=100)

BACK PAIN	**DIABETIC STATUS**		**Chi square**	**P-value**
	Diabetics	**Non diabetics**		
Yes	8 (16%)	3 (6%)	2.554	0.110
No	42 (84%)	47 (94%)		

Among the diabetic, 8 (16%) had back pain. Among the non-diabetic, 3 (6%) had back pain.The difference in the proportion of diabetic status between back pain was statistically not significant (P value 0.110)

Table 47: Association of diabetic status with nausea vomiting of study population (N=100)

NAUSEA VOMITING	**DIABETIC STATUS**		**Chi square**	**P-value**
	Diabetics	**Non diabetics**		
Yes	16 (32%)	36 (72%)	16.026	***<0.001***
No	34 (68%)	14 (28%)		

Among the diabetic, 8 (16%) had back pain. Among the non-diabetic, 3 (6%) had back pain.The difference in the proportion of diabetic status between nausea vomiting was statistically significant (P value <0.001)

DISCUSSION

Despite a concurrent increase in coexistence of diabetes and tuberculosis in India, limited data is available in south India. The Union /World diabetes foundation has acknowledged the need for more epidemiological research to determine TB burden attributed to Diabetes.

Our study included newly diagnosed diabetic patients with sputum positive pulmonary tuberculosis. In previous literature a wide prevalence of 1.9- 35% of diabetes has been reported in active TB patients. Studies from Indonesia and Tanzania has reported 73% and 61% of newly diagnosed diabetes among TB patients respectively. This confers the need of expanded medical attention in screening of TB patients for diabetes and its effective management.

Our results showed that diabetic patients were more likely to be male and of older age group when compared to non diabetics. In diabetic patients the proportion of TB appears to increase with age. Case series by Deshmukh et al [30] with 138 TB – DM patients revealed that 82.6% of the study population was above 45 years and there was a male preponderance. Patients were having risk factors of smoking , alcohol

consumption and pan chewing. A multicentre case-control study was conducted in Guinee , Guinea Bissau and Gambia in West Africa , from January 1999 to March 2001, wherein 846 newly detected sputum smear positive cases , 702 household controls and 828 community controls were recruited in the three countries[37]. It showed smoking , alcohol and other environmental factors resulted in development of tuberculosis.

Analysing symptoms associated with tuberculosis , we found that dyspnoea , hemoptysis and chest pain were more among diabetics when compared to non diabetics. Weight loss is thought to be more frequent in Tb with diabetes. However in our study weight loss was seen more in non diabetic patients. In a study by Alisjahbana et al [42]it showed more weight loss among diabetic patients. Few authors have suggested that there is not much difference in clinical presentation of Tb among diabetics and non diabetics. Low grade fever and productive cough were the most common symptoms and were observed with almost equal frequency in both groups.

In our study we observed higher rates of sputum 3+ positive and sputum 2+ positive patients among diabetics. Study by

Alisjahbana et al reported higher frequency of sputum negative smears in diabetic patients. Few studies show no association between sputum positivity and diabetic status. Another study looked at the effect of diabetes on the presentation of pulmonary TB patients. 46 Records of 692 smear-positive pulmonary TB patients admitted to a referral hospital in Riyadh , Saudi Arabia , were reviewed retrospectively. The baseline characteristics of 187 patients with DM (TB-DM group) were compared to 505 patients without DM (TB group). In the TB-DM group , 65.2 % of the patients had numerous (>1 bacillus per oil immersion field) AFB on the sputum smear examination compared to 54.1% in the control group. They established that TB-DM patients have an elevated pre-treatment bacillary load.DM was an independent risk factor associated with numerous AFB on sputum smear examination. They explained that the immune suppression induced by DM could be responsible for the high bacillary load in TB patients with DM.

In our study we notice that diabetic patients had more cavities in chest X-Ray. In our study diabetic patients had more of infiltrates in the lower zone when compared to non diabetic patients. Comparative studies of chest X-ray findings in diabetics with tuberculosis have yielded contrasting results. In a lot of published

articles chest radiograph images from patients have been described as ‘atypical’. This is because they often involve the lower lung fields, mostly with cavities.

The largest study done by Perenz-Guzman et al in Mexico[38]. It compared the radiological findings of pulmonary tuberculosis in 192 diabetic patients with a control group of patients with pulmonary tuberculosis alone. It showed that both the groups had a similar progression time of tuberculosis , around two years. In this study the TB-DM patients were older (51.3 ± 0.9 vs. TB group 44.9 ± 1.8 years).They had a lower frequency of upper (17% vs. 56%) , and an higher frequency of lower (19% vs. 7%) and upper and lower (64% vs. 36%) lung field lesions. TB-DM patients developed cavitations (82% vs. 59%) more commonly in the lower lung fields (29% vs. 3%). Cavities were more often multiple in the TB-DM patients (25% vs. 2%). Statistical analysis showed that being a diabetic patient was the most important factor determining lower lung field lesions and cavities. Thus this study , along with earlier studies confirmed that chest radiograph images considerably sally forth from the typical presentation. Other authors have been unable to find differences in the chest x-ray patterns of pulmonary tuberculosis in diabetics and non- diabetic patients.

The sputum status at 2 month after initiation of treatment was studied.It showed higher rates of sputum positive patients with low levels of sputum conversion among diabetic patients when compared to non diabetic patients. Few studies did not reveal any relation between sputum conversion rates and diabetic status. Poor diabetic control probably lead to sputum positive status at the end of intensive phase. Patients with higher value of blood sugar at the beginning of treatment tend to remain sputum positive after intensive phase, according to our study. In a study from Turkey [36], the bacteriological profile of 737 patients from 2000 to 2005 with pulmonary TB was studied. Three hundred six (193 men and 113 women) patients newly diagnosed with pulmonary TB and HIV negative were evaluated. Factors associated with both sputum smear and culture conversion time were studied. It was found that patients with DM , cavitary disease and radio logically extensive disease tend to have longer sputum smear and culture conversion time than the other groups.

In our study we had very few defaulters and failures. The failures were all diabetic patients but it was not statistically significant. There is scarcity of data regarding the outcome of treatment of TB patients with coexisting diabetes. Some studies

suggest adverse effects of hyperglycemia on the treatment outcome of TB patients. There is an increased rate of failures , deaths , defaults and relapse. Mortality rates in such patients are stated to be quite high when compared to non-diabetic pulmonary TB patients. Studies have also pointed out that , In well- controlled diabetes the course of pulmonary tuberculosis is not different from that in patients without diabetes.

In our study the incidence of adverse reactions to anti tuberculosis drugs were variable. Diabetics had more incidences of peripheral neuropathy and liver injury. Presence of diabetes influences the adverse drug reactions. This is mostly attributed to the anti diabetic medications[43-46]. No large studies exist regarding evaluation of adverse drug reactions to ATT in diabetic patients.

CONCLUSION

- All patients with pulmonary tuberculosis should be screened for diabetes mellitus and should be effectively treated for the same.
- Pulmonary Tuberculosis patients who have diabetes tend to have higher sputum positivity rates and delayed sputum conversion if glycemic levels are poorly controlled
- Patients with coexisting pulmonary tuberculosis and diabetes mellitus have atypical presentations. Chest radiographs of such patients show multiple cavitations with predominant lower lobe involvement
- The rates of treatment failures and treatment outcomes are adversely affected by the presence of diabetes.

SUMMARY

Our study conducted with a sample size of 100 patients sputum positive tuberculosis in our hospital from January- 2016 to June 2017.50 patients with newly detected diabetes mellitus and 50 patients without diabetes were compared and studied. There was male preponderance. The mean age group of pulmonary tuberculosis with diabetes was higher when compared to non diabetics.

Symptom analysis showed that pulmonary tuberculosis with diabetes had variable symptoms and signs with atypical presentations. Patients with diabetes and TB had more of hemoptysis chest pain and dyspnoea. The rate of sputum positivity were seen more in diabetic patients. The blood sugar values were directly proportional to the sputum positivity rates. There was delayed sputum conversion in TB patients with associated diabetes mellitus.

Chest radiographs of pulmonary tuberculosis patients having diabetes showed cavitations mainly involving the lower lobes. The treatment failure rates were high among patients with diabetes and pulmonary tuberculosis. The pattern of adverse drug reactions were more specific for patients with TB and DM coinfection

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MASTER CHART

S. No.	DIABETIC STATUS	AGE	SEX	RISK FACTORS SMOKING	RISK FACTORS-ALCOHOL	PAN CHEWING	FBS	PPBS	SPUTUM POSITIVITY	CXR-CAVITY	UPPER ZONE INFILTRATES	MIDDLE ZONE INFILTRATES	LOWER ZONE INFILTRATIONS	SPUTUM STATUS AT 2 MONTHS+I1	TREATMENT OUTCOMES	DYSPNOEA	CHEST PAIN	LOSS OF APPETITE	EVENING RISE OF FEVER	LOSS OF WEIGHT	HEMOPTYSIS
1	1	44	FEMALE	NO	NO	NO	240	312	3+	CAVITY	NO	NO	YES (BILATERAL)	POSITIVE	COMPLETED	YES	YES	YES	NO	YES	YES
2	1	56	MALE	YES	YES	NO	140	210	2+	NO	YES(LEFT)	NO	NO	NEGATIVE	COMPLETED	YES	NO	NO	YES	NO	NO
3	1	45	MALE	YES	YES	NO	142	276	2+	NO	YES(BILATERAL)	NO	NO	NEGATIVE	COMPLETED	YES	NO	YES	YES	YES	NO
4	1	72	MALE	YES	YES	NO	178	319	3+	NO	NO	NO	YES(LEFT)	NEGATIVE	DEFAULTER	YES	NO	NO	NO	NO	NO
5	1	54	MALE	NO	YES	NO	159	263	2+	CAVITY	YES(BILATERAL)	NO	NO	POSITIVE	COMPLETED	YES	YES	NO	YES	YES	YES
6	1	48	FEMALE	NO	NO	NO	162	294	2+	NO	YES(LEFT)	NO	NO	NEGATIVE	COMPLETED	YES	NO	NO	NO	NO	NO
7	1	38	MALE	NO	YES	NO	132	216	2+	NO	YES(RIGHT)	NO	NO	NEGATIVE	DEFAULTER	YES	NO	YES	NO	YES	NO
8	1	63	FEMALE	NO	NO	NO	189	315	3+	PNEUMOTHORAX	NO	YES(LEFT)	YES(LEFT)	NEGATIVE	COMPLETED	YES	YES	YES	NO	NO	NO
9	1	70	MALE	NO	YES	NO	151	218	2+	NO	NO	NO	YES(LEFT)	NEGATIVE	COMPLETED	NO	YES	NO	YES	YES	NO
10	1	49	MALE	YES	NO	NO	143	253	2+	NO	YES(BILATERAL)	YES(BILATERAL)	YES(BILATERAL)	POSITIVE	FAILURE	YES	YES	YES	NO	YES	NO
11	1	48	MALE	YES	YES	NO	212	359	3+	CAVITY	YES(BILATERAL)	YES(BILATERAL)	YES(BILATERAL)	POSITIVE	COMPLETED	YES	YES	NO	YES	YES	YES
12	1	42	FEMALE	NO	NO	NO	190	278	2+	CAVITY	YES(LEFT)	NO	NO	NEGATIVE	COMPLETED	YES	YES	NO	YES	NO	YES
13	1	40	FEMALE	NO	NO	NO	278	398	3+	CAVITY	NO	NO	YES(BILATERAL)	NEGATIVE	COMPLETED	YES	YES	YES	NO	YES	YES
14	1	52	FEMALE	NO	NO	YES	245	402	3+	PNEUMOTHORAX	YES(BILATERAL)	YES(BILATERAL)	YES(BILATERAL)	POSITIVE	FAILURE	YES	YES	YES	YES	YES	YES
15	1	51	MALE	YES	YES	NO	196	368	3+	CAVITY	NO	NO	YES(LEFT)	NEGATIVE	COMPLETED	YES	YES	YES	NO	YES	YES
16	1	47	MALE	YES	YES	NO	204	324	3+	NO	YES(BILATERAL)	YES(BILATERAL)	YES(BILATERAL)	POSITIVE	COMPLETED	YES	NO	YES	YES	YES	NO
17	1	56	MALE	YES	YES	NO	179	246	3+	CAVITY	NO	NO	YES(LEFT)	NEGATIVE	COMPLETED	NO	YES	NO	YES	YES	YES
18	1	64	MALE	YES	YES	NO	137	198	1+	NO	YES(LEFT)	NO	NO	POSITIVE	COMPLETED	YES	NO	NO	NO	NO	NO
19	1	49	MALE	YES	YES	NO	129	232	1+	CAVITY	YES(LEFT)	NO	NO	NEGATIVE	COMPLETED	YES	YES	YES	YES	YES	NO
20	1	43	FEMALE	NO	NO	NO	158	269	2+	NO	NO	NO	YES(RIGHT)	NEGATIVE	COMPLETED	YES	NO	NO	NO	NO	NO
21	1	42	FEMALE	NO	NO	NO	149	312	2+	CAVITY	YES(LEFT)	NO	NO	NEGATIVE	COMPLETED	NO	YES	YES	YES	YES	YES
22	1	44	MALE	YES	NO	NO	186	257	2+	NO	YES(BILATERAL)	NO	NO	NEGATIVE	COMPLETED	YES	NO	NO	YES	NO	NO
23	1	41	MALE	YES	YES	NO	175	298	2+	CAVITY	YES(LEFT)	NO	NO	POSITIVE	COMPLETED	YES	YES	NO	YES	YES	YES
24	1	47	MALE	NO	YES	NO	141	231	1+	NO	YES(LEFT)	NO	NO	NEGATIVE	COMPLETED	NO	NO	NO	NO	NO	NO
25	1	45	MALE	YES	NO	NO	169	251	2+	PLEURAL EFFUSION	YES(RIGHT)	NO	NO	NEGATIVE	COMPLETED	YES	NO	NO	YES	NO	NO
26	1	49	FEMALE	YES	NO	NO	192	237	2+	NO	YES(LEFT)	NO	NO	POSITIVE	COMPLETED	YES	NO	YES	NO	YES	NO
27	1	51	FEMALE	NO	NO	NO	201	273	2+	NO	NO	NO	YES(RIGHT)	NEGATIVE	COMPLETED	NO	YES	YES	YES	YES	NO
28	1	69	FEMALE	NO	NO	YES	183	254	2+	NO	NO	YES(LEFT)	YES(LEFT)	POSITIVE	COMPLETED	NO	YES	NO	NO	NO	NO
29	1	50	MALE	YES	YES	NO	146	267	2+	NO	YES(LEFT)	NO	NO	NEGATIVE	COMPLETED	NO	NO	YES	NO	YES	NO
30	1	48	MALE	NO	NO	NO	195	329	2+	CAVITY	NO	NO	YES(RIGHT)	NEGATIVE	COMPLETED	YES	YES	YES	NO	YES	YES
31	1	46	MALE	YES	YES	NO	136	214	1+	NO	YES(BILATERAL)	NO	NO	POSITIVE	COMPLETED	YES	NO	YES	NO	YES	NO
32	1	42	MALE	YES	YES	NO	167	243	2+	NO	NO	NO	YES(RIGHT)	NEGATIVE	COMPLETED	YES	NO	YES	NO	YES	YES
33	1	53	MALE	NO	NO	NO	234	398	3+	CAVITY	YES(RIGHT)	NO	NO	NEGATIVE	COMPLETED	YES	YES	YES	YES	YES	YES
34	1	50	MALE	NO	YES	NO	246	364	2+	NO	NO	NO	YES(LEFT)	NEGATIVE	COMPLETED	NO	YES	YES	YES	YES	YES
35	1	39	FEMALE	NO	NO	NO	194	299	2+	NO	YES(BILATERAL)	NO	NO	NEGATIVE	COMPLETED	YES	NO	YES	YES	YES	NO
36	1	47	FEMALE	NO	NO	NO	177	278	2+	PLEURAL EFFUSION	NO	NO	YES(LEFT)	NEGATIVE	COMPLETED	YES	NO	YES	NO	YES	NO
37	1	44	FEMALE	NO	NO	NO	132	205	1+	NO	YES(LEFT)	YES(LEFT)	NO	NEGATIVE	COMPLETED	YES	NO	YES	YES	YES	NO
38	1	62	FEMALE	NO	NO	YES	194	329	2+	CAVITY	YES(RIGHT)	YES(RIGHT)	NO	NEGATIVE	COMPLETED	NO	YES	YES	YES	YES	YES
39	1	48	MALE	YES	YES	NO	187	345	3+	CAVITY	NO	YES(LEFT)	YES(LEFT)	POSITIVE	FAILURE	NO	YES	YES	NO	YES	YES
40	1	72	FEMALE	NO	NO	YES	179	297	2+	NO	YES(BILATERAL)	YES(BILATERAL)	YES(BILATERAL)	POSITIVE	COMPLETED	YES	NO	YES	NO	YES	NO
41	1	68	MALE	YES	YES	NO	214	378	3+	CAVITY	YES(RIGHT)	NO	NO	NEGATIVE	COMPLETED	NO	YES	YES	NO	YES	YES
42	1	51	FEMALE	NO	NO	NO	198	342	2+	CAVITY	YES(LEFT)	NO	NO	NEGATIVE	COMPLETED	NO	YES	YES	NO	YES	NO
43	1	48	FEMALE	NO	NO	NO	178	267	2+	NO	YES(RIGHT)	NO	NO	NEGATIVE	COMPLETED	YES	NO	YES	NO	YES	NO
44	1	46	FEMALE	NO	NO	NO	149	194	1+	NO	YES(RIGHT)	YES(RIGHT)	NO	NEGATIVE	COMPLETED	YES	NO	NO	NO	YES	NO
45	1	61	MALE	YES	YES	NO	198	308	3+	CAVITY	YES(RIGHT)	NO	NO	NEGATIVE	COMPLETED	NO	YES	YES	NO	YES	YES
46	1	65	FEMALE	NO	NO	YES	176	268	2+	CAVITY	NO	NO	YES(LEFT)	NEGATIVE	COMPLETED	NO	YES	NO	YES	YES	YES

47	1	52	FEMALE	NO	NO	NO	182	219	2+	NO	YES(LEFT)	NO	NO	NEGATIVE	COMPLETED	YES	NO	NO	YES	YES	NO
48	1	54	FEMALE	NO	NO	NO	165	289	3+	CAVITY	NO	YES(RIGHT)	YES(RIGHT)	POSITIVE	FAILURE	NO	YES	NO	NO	YES	YES
49	1	48	MALE	YES	NO	NO	148	212	2+	NO	NO	NO	YES(RIGHT)	POSITIVE	COMPLETED	YES	YES	NO	NO	YES	YES
50	1	42	FEMALE	NO	NO	NO	184	245	2+	NO	NO	NO	YES(BILATERAL)	NEGATIVE	COMPLETED	NO	NO	NO	NO	YES	NO
51	2	43	MALE	NO	YES	NO	100	124	2+	NO	YES(LEFT)	NO	NO	NEGATIVE	COMPLETED	YES	NO	YES	YES	YES	NO
52	2	30	FEMALE	NO	NO	NO	96	126	2+	CAVITY	YES(BILATERAL)	NO	NO	POSITIVE	COMPLETED	YES	YES	YES	YES	YES	YES
53	2	32	MALE	YES	YES	NN	84	132	1+	NO	YES(LEFT)	NO	NO	NEGATIVE	COMPLETED	NO	NO	NO	NO	YES	NO
54	2	44	FEMALE	NO	NO	YES	108	132	1+	NO	YES(RIGHT)	NO	NO	NEGATIVE	COMPLETED	NO	NO	YES	YES	YES	NO
55	2	45	MALE	YES	YES	NO	86	128	1+	NO	YES(LEFT)	NO	NO	NEGATIVE	COMPLETED	NO	NO	YES	YES	YES	NO
56	2	34	MALE	NO	YES	NO	92	120	1+	NO	NO	NO	YES(LEFT)	NEGATIVE	COMPLETED	YES	NO	YES	YES	NO	NO
57	2	38	MALE	NO	YES	NO	107	120	2+	CAVITY	NO	NO	YES(RIGHT)	POSITIVE	COMPLETED	YES	YES	NO	YES	YES	YES
58	2	39	FEMALE	NO	NO	NO	100	130	2+	NO	YES(RIGHT)	NO	NO	NEGATIVE	COMPLETED	YES	NO	YES	YES	YES	NO
59	2	21	MALE	NO	NO	NO	101	120	3+	NO	YES(BILATERAL)	YES(BILATERAL)	YES(BILATERAL)	POSITIVE	COMPLETED	YES	NO	YES	YES	YES	NO
60	2	31	MALE	NO	YES	NO	94	118	1+	NO	YES(LEFT)	NO	NO	NEGATIVE	COMPLETED	NO	NO	YES	NO	NO	NO
61	2	24	MALE	NO	NO	NO	87	120	2+	NO	YES(RIGHT)	YES(RIGHT)	NO	NEGATIVE	DEFAULTER	NO	NO	YES	YES	YES	NO
62	2	36	FEMALE	NO	NO	NO	90	115	1+	NO	YES(LEFT)	NO	NO	NEGATIVE	COMPLETED	NO	YES	NO	NO	NO	NO
63	2	32	MALE	NO	YES	NO	92	119	1+	NO	YES(LEFT)	NO	NO	NEGATIVE	COMPLETED	YES	NO	YES	YES	YES	NO
64	2	37	MALE	NO	YES	YES	96	120	1+	NO	YES(RIGHT)	NO	NO	NEGATIVE	COMPLETED	NO	NO	YES	YES	YES	NO
65	2	39	MALE	NO	YES	NO	83	109	2+	NO	YES(BILATERAL)	NO	NO	NEGATIVE	COMPLETED	NO	NO	NO	NO	NO	NO
66	2	48	FEMALE	NO	NO	NO	88	122	2+	CAVITY	NO	NO	YES(LEFT)	POSITIVE	FAILURE	YES	YES	YES	YES	YES	YES
67	2	43	MALE	YES	NO	NO	99	126	1+	NO	YES(LEFT)	NO	NO	NEGATIVE	COMPLETED	NO	NO	YES	YES	YES	NO
68	2	46	FEMALE	NO	NO	YES	108	139	1+	CAVITY	NO	NO	YES(BILATERAL)	NEGATIVE	COMPLETED	YES	YES	NO	YES	YES	YES
69	2	28	MALE	NO	NO	NO	102	116	2+	NO	YES(LEFT)	YES(LEFT)	NO	NEGATIVE	COMPLETED	NO	NO	YES	YES	YES	NO
70	2	31	MALE	NO	YES	NO	92	134	3+	CAVITY	YES(BILATERAL)	YES(BILATERAL)	YES(BILATERAL)	POSITIVE	COMPLETED	YES	YES	YES	YES	YES	YES
71	2	34	MALE	YES	YES	NO	95	129	2+	NO	YES(RIGHT)	NO	NO	NEGATIVE	COMPLETED	NO	NO	NO	YES	YES	NO
72	2	29	MALE	NO	NO	NO	85	117	2+	NO	YES(RIGHT)	NO	NO	NEGATIVE	COMPLETED	NO	NO	YES	NO	YES	NO
73	2	30	MALE	YES	YES	NO	80	119	3+	NO	YES(LEFT)	NO	NO	POSITIVE	COMPLETED	YES	YES	YES	YES	YES	YES
74	2	34	FEMALE	NO	NO	NO	87	110	2+	NO	NO	NO	YES(BILATERAL)	NEGATIVE	COMPLETED	NO	NO	NO	NO	NO	NO
75	2	31	MALE	YES	YES	NO	100	110	2+	NO	YES(LEFT)	NO	NO	NEGATIVE	DEFAULTER	NO	NO	YES	YES	YES	NO
76	2	38	FEMALE	NO	NO	NO	81	130	1+	CAVITY	YES(BILATERAL)	NO	NO	NEGATIVE	COMPLETED	YES	YES	YES	YES	YES	YES
77	2	41	MALE	YES	NO	NO	84	120	1+	NO	NO	YES(LEFT)	YES(LEFT)	NEGATIVE	COMPLETED	NO	NO	YES	YES	YES	NO
78	2	42	MALE	YES	YES	NO	96	114	2+	NO	YES(RIGHT)	NO	NO	NEGATIVE	COMPLETED	YES	YES	NO	YES	YES	NO
79	2	23	MALE	NO	NO	NO	94	118	3+	NO	YES(RIGHT)	NO	NO	NEGATIVE	COMPLETED	NO	NO	YES	YES	YES	NO
80	2	46	FEMALE	NO	NO	YES	109	128	2+	NO	YES(LEFT)	YES(LEFT)	NO	NEGATIVE	COMPLETED	NO	NO	YES	YES	YES	NO
81	2	19	MALE	NO	NO	NO	92	108	1+	NO	YES(LEFT)	NO	NO	NEGATIVE	COMPLETED	NO	NO	YES	NO	NO	NO
82	2	22	MALE	NO	NO	NO	93	136	1+	NO	YES(RIGHT)	NO	NO	NEGATIVE	COMPLETED	YES	NO	NO	YES	YES	NO
83	2	42	MALE	YES	YES	NO	90	129	2+	NO	NO	NO	YES(RIGHT)	NEGATIVE	COMPLETED	NO	NO	YES	NO	YES	NO
84	2	43	FEMALE	NO	NO	NO	87	122	2+	CAVITY	YES(LEFT)	NO	NO	POSITIVE	COMPLETED	YES	YES	YES	YES	YES	YES
85	2	25	MALE	NO	YES	NO	88	110	1+	NO	YES(RIGHT)	NO	NO	NEGATIVE	COMPLETED	NO	NO	YES	YES	YES	NO
86	2	26	FEMALE	NO	NO	NO	84	127	1+	NO	YES(RIGHT)	NO	NO	NEGATIVE	COMPLETED	NO	NO	YES	YES	YES	NO
87	2	23	FEMALE	NO	NO	NO	83	112	2+	NO	YES(BILATERAL)	NO	NO	NEGATIVE	COMPLETED	NO	NO	YES	NO	NO	NO
88	2	34	MALE	YES	YES	NO	80	118	2+	NO	YES(LEFT)	NO	NO	NEGATIVE	COMPLETED	NO	YES	YES	YES	YES	NO
89	2	33	FEMALE	NO	NO	NO	100	109	3+	NO	YES(LEFT)	NO	NO	NEGATIVE	COMPLETED	NO	NO	NO	YES	YES	NO
90	2	37	FEMALE	NO	NO	NO	86	102	2+	PLEURAL EFFUSION	YES(LEFT)	NO	NO	NEGATIVE	COMPLETED	NO	NO	NO	YES	YES	NO
91	2	40	MALE	YES	NO	NO	87	104	1+	NO	YES(RIGHT)	NO	NO	NEGATIVE	COMPLETED	NO	NO	NO	YES	YES	NO
92	2	31	FEMALE	NO	NO	NO	98	100	1+	NO	YES(LEFT)	NO	NO	NEGATIVE	COMPLETED	NO	NO	NO	YES	YES	NO
93	2	32	MALE	NO	NO	NO	92	132	2+	CAVITY	NO	YES(RIGHT)	YES(RIGHT)	POSITIVE	COMPLETED	YES	YES	YES	NO	YES	YES
94	2	26	FEMALE	NO	NO	NO	99	128	2+	NO	YES(LEFT)	NO	NO	NEGATIVE	COMPLETED	NO	NO	YES	YES	YES	NO
95	2	31	FEMALE	NO	NO	NO	104	119	2+	NO	YES(LEFT)	NO	NO	NEGATIVE	COMPLETED	NO	NO	YES	YES	YES	NO
96	2	30	MALE	YES	NO	NO	100	130	1+	CAVITY	YES(RIGHT)	NO	NO	NEGATIVE	COMPLETED	YES	YES	YES	NO	NO	YES
97	2	33	FEMALE	NO	NO	NO	92	122	1+	NO	YES(RIGHT)	NO	NO	NEGATIVE	COMPLETED	NO	NO	YES	YES	YES	NO
98	2	35	FEMALE	NO	NO	NO	93	100	1+	CAVITY	YES(RIGHT)	NO	NO	NEGATIVE	COMPLETED	YES	YES	YES	YES	YES	YES
99	2	40	FEMALE	NO	NO	NO	103	139	2+	NO	YES(RIGHT)	NO	NO	NEGATIVE	COMPLETED	YES	NO	YES	NO	YES	NO
100	2	39	FEMALE	NO	NO	NO	82	124	2+	NO	YES(LEFT)	YES(LEFT)	NO	NEGATIVE	COMPLETED	NO	NO	YES	YES	YES	NO

COUGH	DRUGS FOR DM	ADR-PERIPHERAL NEUROPATHY	LIVER INJURY	HYPOGLYCEMIA	BACKPAIN	NAUSEA VOMITING
YES	INSULIN	YES	NO	NO	NO	NO
YES	BIGUANIDES	NO	YES	NO	NO	NO
YES	BIGUANIDES	NO	YES	NO	NO	NO
YES	INSULIN	YES	NO	YES	NO	NO
YES	BIGUANIDES	NO	YES	NO	NO	NO
YES		NO	YES	NO	NO	NO
YES	SULPHONYLUREAS	YES	YES	NO	NO	NO
YES	BIGUANIDES	NO	NO	NO	YES	YES
YES	SULPHONYLUREAS	NO	NO	NO	NO	NO
YES	BIGUANIDES	NO	NO	NO	NO	NO
YES	INSULIN	YES	NO	NO	NO	YES
NO	BIGUANIDES	NO	NO	NO	YES	NO
YES	INSULIN	YES	NO	YES	NO	NO
YES	INSULIN	YES	NO	YES	NO	YES
YES	INSULIN	NO	NO	NO	NO	NO
YES	INSULIN	YES	NO	NO	YES	NO
NO	BIGUANIDES	YES	YES	NO	NO	YES
YES	SULPHONYLUREAS	NO	NO	NO	NO	NO
NO	BIGUANIDES	NO	YES	NO	NO	NO
YES	SULPHONYLUREAS	NO	NO	NO	NO	YES
NO	BIGUANIDES	NO	YES	NO	NO	NO
YES	SULPHONYLUREAS	YES	NO	NO	YES	NO
NO	BIGUANIDES	NO	YES	NO	NO	YES
YES	BIGUANIDES	YES	YES	NO	NO	NO
YES	SULPHONYLUREAS	NO	NO	NO	NO	NO
YES	BIGUANIDES	YES	NO	NO	NO	YES
YES	SULPHONYLUREAS	NO	NO	NO	NO	NO
YES	BIGUANIDES	YES	NO	NO	YES	NO
YES	BIGUANIDES	NO	YES	NO	NO	NO
YES	SULPHONYLUREAS	YES	NO	NO	NO	YES
YES	BIGUANIDES	NO	YES	NO	NO	NO
NO	BIGUANIDES	NO	NO	NO	YES	YES
NO	INSULIN	YES	NO	NO	NO	NO
NO	INSULIN	YES	NO	YES	NO	NO
YES	BIGUANIDES	NO	NO	NO	NO	YES
YES	BIGUANIDES	NO	YES	NO	NO	YES
YES	BIGUANIDES	NO	NO	NO	YES	NO
NO	SULPHONYLUREAS	NO	NO	NO	NO	NO
NO	BIGUANIDES	NO	YES	NO	NO	NO
YES	BIGUANIDES	NO	NO	NO	NO	YES
NO	INSULIN	YES	NO	NO	NO	NO
YES	SULPHONYLUREAS	NO	NO	NO	NO	NO
YES	BIGUANIDES	YES	NO	NO	NO	NO
YES	SULPHONYLUREAS	NO	NO	NO	NO	YES
NO	BIGUANIDES	NO	NO	NO	NO	YES
YES	BIGUANIDES	NO	NO	NO	NO	YES

YES	SULPHONYLUREAS	YES	NO	NO	NO	NO
NO	BIGUANIDES	NO	NO	NO	NO	NO
NO	BIGUANIDES	YES	YES	NO	YES	NO
YES	BIGUANIDES	NO	NO	NO	NO	YES
YES		NO	NO	NO	NO	NO
YES		NO	NO	NO	NO	YES
YES		NO	NO	NO	NO	NO
YES		NO	YES	NO	NO	YES
YES		YES	NO	NO	NO	YES
YES		NO	NO	NO	NO	NO
YES		NO	YES	NO	NO	YES
NO		NO	NO	NO	NO	YES
YES		NO	NO	NO	NO	YES
YES		YES	YES	NO	YES	YES
YES		NO	NO	NO	NO	YES
YES		NO	NO	NO	NO	NO
YES		NO	NO	NO	YES	YES
YES		NO	YES	NO	NO	YES
YES		NO	NO	NO	NO	YES
YES		YES	NO	NO	NO	YES
YES		NO	NO	NO	NO	YES
NO		NO	NO	NO	NO	NO
YES		NO	NO	NO	NO	YES
YES		NO	YES	NO	NO	YES
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YES		NO	YES	NO	NO	YES
YES		NO	YES	NO	NO	YES
YES		NO	NO	NO	NO	YES
YES		NO	NO	NO	NO	NO
NO		NO	NO	NO	NO	YES
YES		YES	NO	NO	NO	YES
YES		NO	NO	NO	NO	NO
YES		NO	NO	NO	NO	NO
YES		NO	NO	NO	NO	YES
YES		YES	NO	NO	NO	YES
YES		NO	NO	NO	NO	YES
YES		NO	YES	NO	NO	YES
YES		YES	NO	NO	NO	YES
NO		NO	NO	NO	NO	NO
YES		NO	NO	NO	NO	YES
YES		NO	NO	NO	NO	NO
YES		NO	YES	NO	NO	YES
YES		YES	NO	NO	NO	YES
NO		NO	NO	NO	YES	YES
YES		YES	NO	NO	NO	YES
YES		NO	NO	NO	NO	NO
YES		NO	NO	NO	NO	YES
YES		NO	YES	NO	NO	YES
NO		NO	NO	NO	NO	NO
YES		NO	NO	NO	NO	YES
YES		NO	NO	NO	NO	YES
YES		YES	NO	NO	NO	YES
YES		NO	NO	NO	NO	YES
NO		NO	NO	NO	NO	NO