A Study on Hematological Parameters of Tuberculosis Patients in Bangladesh.

A DISERTATION SUBMITTED TO BRAC UNIVERSITY IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF MS IN BIOTECHNOLOGY.

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November, 2018

Declaration by the Research Candidate

I am Mohammad Monirozzaman, hereby declare that the dissertation entitled "**A Study on Hematological Parameters of Tuberculosis Patients in Bangladesh.",** submitted by me to the Department of MNS, BRAC University, in partial fulfillment of the requirements for the award of the degree of Masters of Biotechnology(MS) is a complete record of original research work carried out by me under the supervision and guidance of **Dr. Mohammad Rafiqul Islam,** Associate Professor, Department of MNS, BRAC University and it has not formed the basis for the award of any other Degree/Diploma/ Fellowship or other similar title to any candidate of any University.

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ACKNOWLEGDEMENTS

In the Name of Allah, the Most Gracious, the Most Merciful. All praise of gratitude and thankfulness are due to the Almighty Allah, Who in His great kindness and benevolence has enabled me to undertake and complete this intellectual academic attempt.

I would like to express my sincere gratefulness to **Professor A F M Yusuf Haider**, Chairperson, Department of Mathematics and Natural Sciences for allowing me to continue my studies in this department.

Foremost, I wish to express my earnest gratitude to my research supervisor **Dr. Mohammad Rafiqul Islam,** Associate Professor, MNS Department, BRAC University, whose wholehearted support and untiring guidance have given me motivation to continue and complete this research project. His useful comments were truly a tremendous help at every stage.

My special thanks to **Dr. M. Mahboob Hossain**, Professor, MNS Department and **Dr. Aparna Islam**, Professor, MNS Department, BRAC University, for providing me with valuable insights regarding the technical aspects of this study.

I would like to thanks Shaheed Shorawardi Medical College and Hospital, Dhaka authorities for granting the permission to conduct the research work at the hospital and also the hospital stuffs for their support throughout the research project.

I am also thankful to my department faculty members for their assistance and inspiration. I express special gratitude to my caring parents for their love, support and guidance all through my life, including that for my research project. I am very grateful to my brother, sister and friends, who were involved enthusiastically in my research to bring this work to completion. It is because of the encouragement of the people around me that I have come all the way.

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List of Abbreviations

AFB	Acid Fast Bacillus
AIDS	Acquired Immunodeficiency Syndrome
BRACs	Bangladeshi Rural Advancement Committees
CBC	Complete Blood Count
DGHS	Directorate General of Health Services
DOTS	Directly Observed Treatment Short Course
E	Ethambutol
EPTB	Extra Pulmonary TB
ESR	Erythrocyte Sedimentation Rate
FDC	Fixed-Dose Combinations
GFATM	Global Fund for TB, AIDS and Malaria
Hb	Hemoglobin
HIV	Human Immunodeficiency Virus
MBDC	Mycobacterium Disease Control
MDR	Multidrug-Resistant
MoLGRDC	Ministry of Local government, rural development and cooperative
Mtb	*Mycobacterium tuberculosis*

NGO	Non Government Organization
NTP	National Tuberculosis Contro Program
PTB	Pulmonary Tuberculosis
R	Rifampicin
RBC	Red Blood Cell
S	Streptomycin
SS+	Sputum Smear Positive
SS-	Sputum Smear Negative
TB	Tuberculosis
TB Drugs	Tuberculosis Drugs
UHFPO	Upazila Health and Family Planning Officer
UPHCP	Urban Primary Health Care Project
USAID	United States Agency for International Development
WBC	White Blood Cell
WHO	World Health Organization
Z	Pyrazinamide

Abstract

Among all the infectious diseases, tuberculosis (TB) remains the deadliest. In 2017, the World Health Organization (WHO) ranked Bangladesh 6th among the world's 22 high-burden TB countries. In this study various hematological manifestations have been described in association with tuberculosis. In the present study an attempt has been made to study a complete hematological profile in tuberculosis patients. The prospective study was carried out among admitted patients in Shaeed Shohorawardi Medical College and Hospital, Dhaka city. A total of 290 TB cases were selected by simple random sampling technique. Patients who have been diagnosed with tuberculosis were considered for this study. The study showed that the incidence of TB occurs frequently among the age group of people 60 to 60 + years and high blood pressure were founded among TB patients. Weight loss and various clinical symptoms like cough with expectoration, fever, chest pain etc were found frequently among TB patients. In this study we found more male TB patients (58%) compared to female TB patients (42%). Among the various hematological profile of TB patients blood hemoglobin (Hb) level found low 75.6% in case of male TB patients and 83.6% in case of female TB patients. Blood RBC found low 77.4% in case of male TB patients and 72.1% in case of female TB patients. Blood platelet level showed low among 71.4% TB patients. On the other hand 91% TB patients showed high blood WBC. About 94.8% TB patients had high blood ESR. Serum creatinine level found high 68.5% in case of male TB patients and 77.5% in case of female TB patients. Blood glucose level found high among 62.2% TB patients.

Introduction

Tuberculosis (TB) is a chronic communicable bacterial disease that remains an important public health problem, especially in developing countries. TB is an airborne, infectious disease caused by bacteria which primarily affect the lungs. Approximately one third of the world's population carries the TB bacteria namely Mycobacterium TB (MTB). The World Health Organization (WHO) declared TB as a 'global emergence' in 1993 (Gupta et al., 2002). Every year almost two million people die worldwide due to TB and most deaths occur in low- and middle-income countries (World Health Organization [WHO] 2011). Although TB is a curable disease, it ranks as the second leading cause of death among infectious diseases worldwide, after the human immunodeficiency virus (HIV). TB takes advantage of individual's with weakened immune systems, which is why it is called an opportunistic infectious disease. Early case detection depends on patients' perception about their needs of seeking healthcare. Consequently, it is very important to make people understand when and where they should seek healthcare. Health knowledge allows individuals to assess symptoms, identify causes and transmission routes, and provide familiarity with the availability of treatment and cure. Likewise, knowledge and awareness of TB is very important among TB affected people. Increasing knowledge will lead to overcome some of the challenges to control TB. While people may have a general idea of what TB is and how it is treated, gaps in knowledge, such as transmission, treatment, and prevention causes diagnostic and treatment delays among many people living with TB. Delays in treatment occur for several reasons, such as, lack of knowledge, lack of awareness of the significance of symptoms, negative social attitudes or different combinations of these three factors (Koay 2004). Patients with low knowledge about symptoms are less likely to seek healthcare and get diagnosed. Patients with low knowledge are more likely to visit traditional healers and pharmacists rather than DOTs providers, which leads to delays in diagnosis and appropriate treatment.

Consequently, the risk of TB infection is higher among the people who are HIV positive (Mondal and Shitan 2013a, 2013b). Among 22 high burden countries (HBCs) Bangladesh has been ranked 6th where, the incidence rate for TB was 350 per 100,000 population and TB mortality rate was 36 per 100,000 population in 2017 (WHO 2018). To fight against TB, the Bangladesh National TB Control Program (NTP) has adopted the directly observed treatment

short course (DOTs) strategy since 1993 (Zafar Ullah et al., 2006). At present, Bangladesh has more than 165 million people, and is the seventh most populous country in the world. It is also one of the poorest nations, and faces great challenges in providing health care services including TB services for its citizens. People having symptoms of TB should be identified when they seek care at a general health facility, and referred to the specialized TB health care centers for diagnosis, treatment and case management. Given the challenges facing Bangladesh's health services infrastructure, this is often a difficult goal to achieve.

TB is the leading cause of death from an infectious disease worldwide. In 2017, there were estimated 9.6 million new TB cases globally and 1.5 million death due to TB. Tuberculosis is one of the major public health problem in Bangladesh with an estimated incidence about 360,000 per year. Every year, around 80,000 Bangladeshis die from tuberculosis (TB) and about 190,000 new cases occur. Every hour, nine people die from the disease, despite effective treatments being available. But diagnosis is not always easy, and treatment takes several months; in the meantime, loss of earnings for the sufferer may drive families into poverty, multiplying the burden of the disease. Most cases are drug-sensitive and respond well to standard treatment with a combination of drugs, but failure to complete a proper course of treatment encourages the development of multi-drug resistant TB (MDR-TB), which is difficult and costly to treat and has poorer outcomes. Because diagnosing active TB is quite complex, almost half of the cases in Bangladesh go unrecognized. The country relies on sufficiently skilled medical staff to diagnose patients who present with symptoms, but the strong community infrastructure is also mobilized via the network of community health workers and organizations such as the Bangladeshi Rural Advancement Committees (BRACs).

Objective of the Study

The objective of this study was to-

 Observe the hematological status of tuberculosis patients admitted in Shaheed Shorawardi Medical College and Hospital, Dhaka Bangladesh.

Literature Review

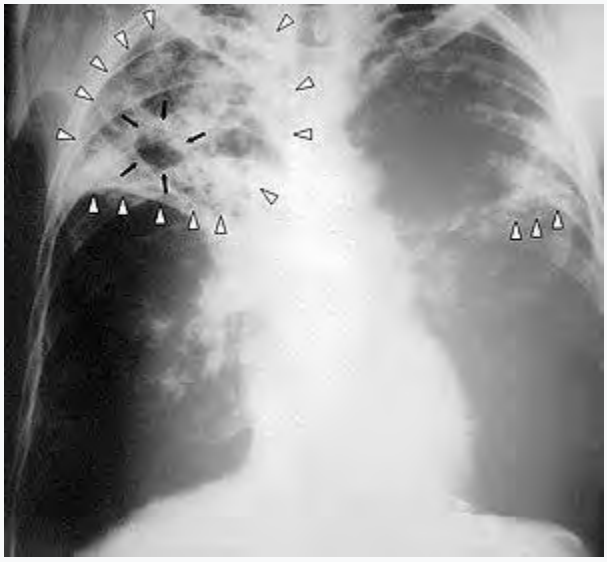
2.1 Tuberculosis

Tuberculosis (TB) continues to be an important health and socio-economic issue, especially in developing countries. Among all infectious diseases that afflict humans, tuberculosis remains the deadliest. The disease process itself produces no clear, typical clinical symptoms which make the infection more difficult to detect enabling it to freely disseminate and affect those in contact with a diseased individual. The development of TB is affected by social and economic factors more than any other disease. Epidemiological studies of these factors are fundamental, as they may influence TB frequency and distribution and interaction between people, as well as the course of treatment and its final outcome (Ilic *et al*., 2012; Stop, 2006).With the discovery in the late 1940s and early 1950s of antimicrobial drugs specific for tuberculosis, it became possible for the first time to discuss realistically the elimination of this communicable disease. Thoughts of eradication were exhilarating. A more realistic goal would be the elimination of tuberculosis as a public health problem and that is still the goal.

Tuberculosis is an infectious disease mainly caused by *Mycobacterium tuberculosis*, which is an aerobic pathogenic bacterium that establishes its infection usually in the lungs. The infection is spread like a cold, mainly through airborne droplets breathed into the air by a person infected with TB. The bacteria causes formation of small tissue masses called tubercles. In the lungs these tubercles produce breathing impairment, coughing and release of sputum. TB may recur after long periods of latency if not treated adequately. Many variations of TB exist and are distinguished by the area of the body affected, degree of severity and affected population. Progression of TB infection is fundamentally regulated by hosts' immune system integrity (Davidson & Haslett, 2002). Most people who are exposed to TB never develop symptoms, because the bacteria can live in an inactive form in the body. But if the immune system weakens, such as in people with HIV or elderly adults, TB bacteria can become active. In their active state, TB bacteria cause death of tissue in the organs they infect. Active TB disease can be fatal if left untreated. This disease today is considered curable and preventable. Despite the first anti tuberculosis drugs being discovered more than 60 years ago, tuberculosis today still kills an estimated 1.7 million people each year (World Health Organization, 2011). Progress in the scaling up of tuberculosis diagnostic, treatment, and control efforts worldwide over the past

decade has been associated with improvements in tuberculosis control in many parts of the world. On the other hand, this progress has been substantially undermined by the HIV-1 epidemic, the growing challenge of drug resistance, and other increasingly important epidemiological factors that continue to stimulate the tuberculosis epidemic. Unfortunately the majority of these cases are likely to occur in the world's poorest nations, who struggle to cover the costs associated with management and control programmes (Ducati, Ruffino-Netto, Basso, & Santos, 2006).

2.2 Radiograph of TB patient



Chest X-ray of a person with advanced tuberculosis: Infection in both lungs is marked by white arrow-heads, and the formation of a cavity is marked by black arrows.

Figure 2.1:Radiograph of TB Patient

2.3 Global Epidemiology of TB

Figure 2.2: Global Scenario of TB Cases

In 2017, the number of cases of TB per 100,000 people was highest in sub-Saharan Africa, and was also relatively high in Asia.

Figure 2.3: Global death rate of TB Cases

Tuberculosis deaths per million persons in 2017
- 0–3
- 4–7
- 8–16
- 17–26
- 27–45

46–83
84–137
138–215
216–443
444-1,359

Roughly one-third of the world's population has been infected with *M. tuberculosis*, with new infections occurring in about 1% of the population each year. However, most infections with *M. tuberculosis* do not cause TB disease, and 90–95% of infections remain asymptomatic. In 2017, an estimated 8.6 million chronic cases were active. In 2016, 8.8 million new cases of TB were diagnosed, and 1.20–1.45 million deaths occurred, most of these occurring in developing countries. Of these 1.45 million deaths, about 0.35 million occur in those also infected with HIV.

Tuberculosis is the second-most common cause of death from infectious disease (after those due to HIV/AIDS). The total number of tuberculosis cases has been decreasing since 2005, while new cases have decreased since 2002. China has achieved particularly dramatic progress, with about an 80% reduction in its TB mortality rate between 1990 and 2016.The number of new cases has declined by 17% between 2004 and 2016. Tuberculosis is more common in developing countries; about 80% of the population in many Asian and African countries test positive in tuberculin tests, while only 5–10% of the US population test positive. Hopes of totally controlling the disease have been dramatically dampened because of a number of factors, including the difficulty of developing an effective vaccine, the expensive and time-consuming diagnostic process, the necessity of many months of treatment, the increase in HIV-associated tuberculosis, and the emergence of drug-resistant cases in the 1980s.

In 2017, the country with the highest estimated incidence rate of TB was Swaziland, with 1,200 cases per 100,000 people. India had the largest total incidence, with an estimated 2.0 million new cases. In developed countries, tuberculosis is less common and is found mainly in urban areas. Rates per 100,000 people in different areas of the world were: globally 178, Africa 332, the Americas 36, Eastern Mediterranean 173, Europe 63, Southeast Asia 278, and Western Pacific 139 in 2017. In Canada and Australia, tuberculosis is many times more common among the aboriginal peoples, especially in remote areas. In the United States Native Americans have a fivefold greater mortality from TB, and racial and ethnic minorities accounted for 84% of all reported TB cases.

The rates of TB varies with age. In Africa, it primarily affects adolescents and young adults. However, in countries where incidence rates have declined dramatically (such as the United States), TB is mainly a disease of older people and the immune compromised (risk factors are listed above). Worldwide, 22 "high-burden" states or countries together experience 80% of cases as well as 83% of deaths.

2.4 Present Status of TB in Bangladesh

While Bangladesh is making remarkable progress in achieving population health outcomes, tuberculosis (TB) persists as one of the major public health issues with high rates of incidence, prevalence, and death. Under the National Tuberculosis Control Program (NTP), and with partnership and support from BRAC, icddr,b and other non-government organizations which are implementing the DOTS programme, there has been considerable development in terms of an increase in the case notification rate from 31 in 100,000 in 1993 to 224 in 100,000 in 2016. In 2017, the estimated prevalence of people with TB was 314, incidence 350 and mortality rate 36 per 100,000 population.

2.5 Types of TB

2.5.1 Primary Tuberculosis

Primary tuberculosis refers to the infection process which eventually eliminates the pathogen or results in a stalemate between the *Mycobacteria* and the immune system. With most TB infections, the immune system is able to contain, although not eliminate, the *Mycobacteria* within the tubercle, preventing the spread of bacteria and progression of the disease. *M. tuberculosis* (Mtb) can remain in this impasse of dormant infection for many years (Davidson & Haslett, 2002).

2.5.2 Secondary or Reactivated Tuberculosis

The infection can become reactivated if the *Mycobacteria* are able to rupture the tubercle and spread through the lungs. This reactivation typically happens to those with a weakened or suppressed immune system.

2.5.3 Disseminated Tuberculosis

The spread of the disease within the body may result if infected macrophages moving through the blood and lymph transport the bacteria to other sites. Once infected, symptoms of disseminated TB correspond to the locations infected. The antiquated term "consumption" arose from the myriad of symptoms associated with disseminated tuberculosis, when those infected seemed to slowly waste away (Davidson & Haslett, 2002).

2.5.4 Osseous Tuberculosis

This form of TB can cripple the child for life. It presents itself in the spine, hips, knees and other bones. The joints swell and the person finds it difficult to walk and bend.

2.5.5 Laryngeal Tuberculosis

Laryngeal TB occurs when the bacterium attacks the throat's vocal chords. This highly uncommon pulmonary TB is frequently confused with other throat diseases like chronic laryngitis and laryngeal carcinoma.

2.5.6 Cavitary Tuberculosis

Cavitary TB infects a lung's upper lobes and slowly destroys them. Symptoms include a cough with sputum and possibly blood, night sweats, fever and weight loss. This type of TB is very contagious and can spread to other parts of the lung.

2.5.7 Miliary Tuberculosis

Similar to primary TB pneumonia, those with a weakened immune system are at greater risk for contracting this pulmonary form of the disease. In addition to a high fever, weight loss and night sweats, miliary TB is diagnosed when small granules appear in the lungs as seen on an x-ray (Davidson & Haslett, 2002).

2.5.8 Tuberculosis Pleurisy

Those who catch TB pleurisy will quickly show symptoms as the disease enters and ruptures the pleural space in the chest or the space between the lungs and the chest wall. Patients usually experience chest pain and difficulty breathing, and fluid is often present in the lungs. According to the pulmonarychannel.com website, close to two-thirds of patients with TB pleurisy develop other forms of pulmonary TB within five years (Davidson & Haslett, 2002).

2.5.9 Adrenal Tuberculosis

Adrenal TB is an extrapulmonary form of TB that affects the adrenal gland and the production of adrenal hormone. Patients with this form of TB often feel weak or faint due to insufficient adrenal gland production(Davidson & Haslett, 2002).

2.5.10 Lymph Node Tuberculosis

TB bacterium impacts the lymph nodes and causes them to become enlarged, lymph node disease is diagnosed. This extrapulmonary TB can even cause the lymph nodes to become so large they rupture through the skin if not diagnosed in time (Davidson & Haslett, 2002).

2.5.11 Cryptic tuberculosis

Cryptic tuberculosis is seen patients over sixty years of age. Patients undergo unexplained weight loss, general debility etc. Another feature is Negative tuberculin skin test. For diagnosis Normal chest X-ray is done. Confirmation by biopsy of liver or bone marrow is also performed (Davidson & Haslett, 2002).

2.6 Clinical Manifestation of TB

As the cellular processes occur, tuberculosis may develop differently in each patient, according to the status of the patient's immune system, stages include:

- Latency
- Primary disease
- Primary progressive disease
- Extra pulmonary disease

Each stage has different clinical manifestations as shown in Table 2.1

Table 2.1: Clinical Manifestation of Tuberculosis

Early infection	Early primary progressive (active)	Late primary progressive (active)	Latent
Immune system fights infection. Infection generally proceeds without signs or symptoms. Patients may have fever, paratracheal lymphadenopathy or dyspnea. Infection may be only subclinical and may not advance to active disease	Immune system does not control initial infection Inflammation of tissue ensues. Nonproductive cough develops. Diagnosis can be difficult: findings on chest radiographs may be normal and sputum smears may be negative for mycobacteria.	Cough becomes productive. More signs or symptoms as disease progresses. Patient experience progressive without weight loss, rales, anemia. Findings on chest radiographs are normal Diagnosis is via cultures of sputum	Mycobacteria persist in the body. No signs or symptoms occur Patients do not feel seek. Patients are susceptible to reactivation of disease. Granulomatous lesions calcify and become fibrotic, become apparent on chest radiographs. Infection can reappear when immune-suppression occurs

(Centers for Disease Control and Prevention, 2012)

2.6.1 Latent Tuberculosis

Mycobacterium tuberculosis organisms can be enclosed, but are difficult to completely eliminate. TB spreads through droplet infection. TB bacilli stay suspended in the air as droplets. Healthy people become infected with TB through inhalation of the droplets containing TB bacilli. Around 90% of the infected people do not progress to TB disease because of their immunity. Persons with latent tuberculosis have no signs or symptoms of the disease, do not feel sick, and are not infectious. However, viable bacilli can persist in the necrotic material for years or even a lifetime, and if the immune system later becomes compromised, as it does in many critically ill patients, the disease can be reactivated. Treatment of LTBI substantially reduces the risk that TB infection will progress to disease (Davidson & Haslett, 2002).

Many people who have latent TB infection never develop TB disease. Some people develop TB disease soon after becoming infected like within weeks before their immune system can fight the TB bacteria. Other people may get sick years later when their immune system becomes weak for another reason. For people whose immune systems are weak, especially those with HIV infection, the risk of developing TB disease is much higher than for people with normal immune systems (Centers for Disease Control and Prevention, 2012).

Table 2.2: TB Infection vs. TB Disease

TB Infection	TB Disease
Tubercle bacilli in the body	Tubercle bacilli in the body
Tuberculin skin test reaction usually positive	Tuberculin skin test reaction usually positive
Chest X-ray usually normal	Chest X-ray usually abnormal
Sputum smears and culture negative	Sputum smears and cultures positive
No symptoms	Symptoms such as cough, fever, weight loss
Not infectious	Often infectious before treatment
Not a case of TB	A case of TB

(Mori et al., 2004)

Although co-infection with human immunodeficiency virus is the most notable cause for progression to active disease, other factors, such as uncontrolled diabetes mellitus, sepsis, renal failure, malnutrition, smoking, chemotherapy, organ transplantation, and long-term corticosteroid usage that can trigger reactivation of a remote infection are more common in the critical care setting. Additionally, persons 65 years or older have a disproportionately higher rate of disease than any does other age group, often because of diminishing immunity and reactivation of disease (Centers for Disease Control and Prevention, 2012).

Tuberculosis Disease

Tuberculosis disease means tuberculosis infection plus presence of signs and symptoms of TB. Around 10% of the people infected with TB bacilli may progress to TB disease in their lifetime. TB bacilli multiply in their lungs or other organs and produce the symptoms and signs. Around 5% of the infected people develop TB disease within months or years and the remaining in their old age that is known as reactivation of the disease (Kaufmann, 2001).

There are three potential outcomes of infection of the human host in *Mycobacterium tuberculosis*:

i. The frequency of abortive infection resulting in spontaneous healing is unknown, but is assumed to be minute.

ii. In the immuno-compromised host, disease can develop directly after infection.

iii. In most cases, mycobacteria are initially contained and disease develops later as a result of reactivation.

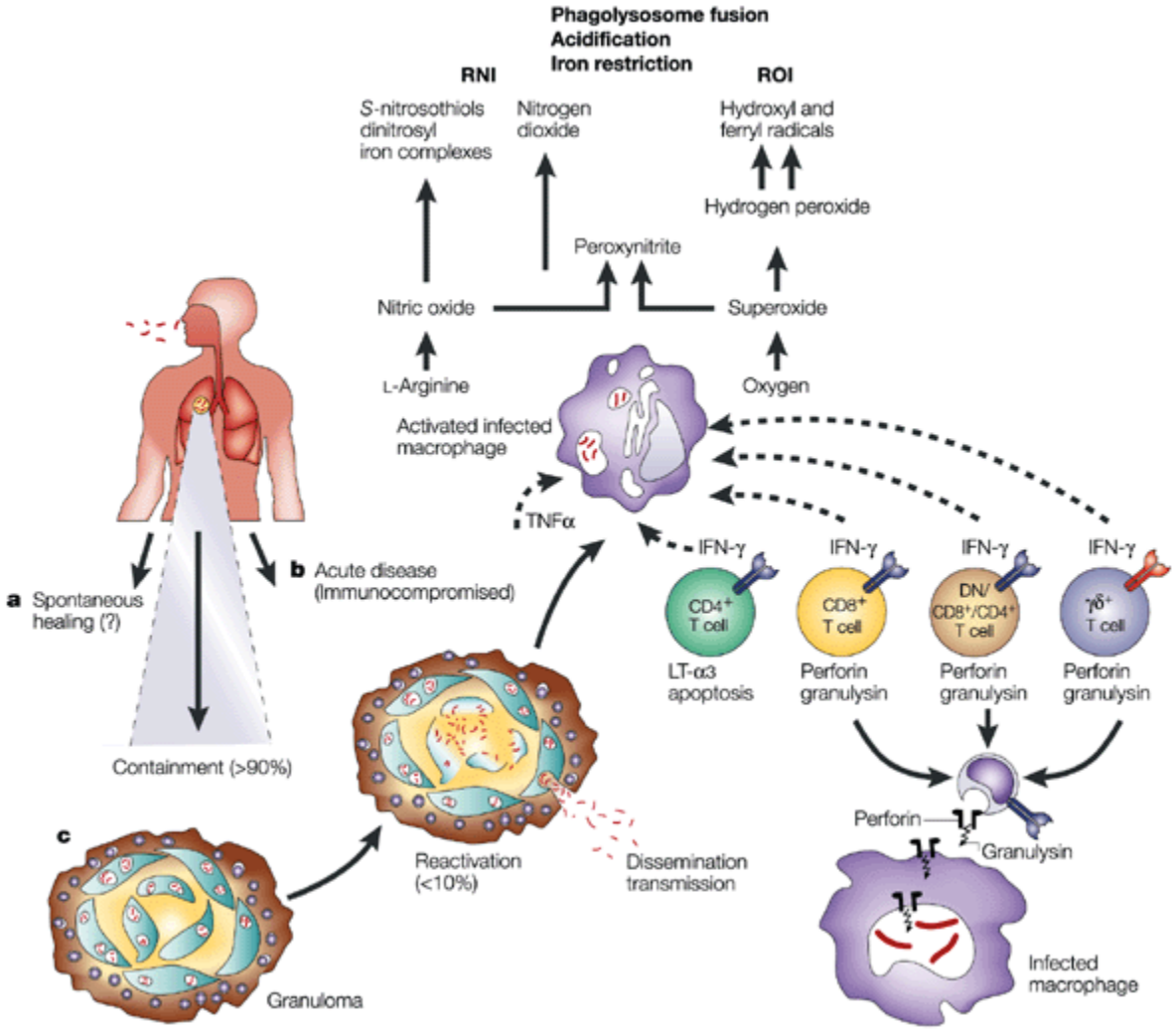


Figure 2.4: Main features of tuberculosis: from infection to host defense (Kaufmann, 2001).

The granuloma is the site of infection, persistence, pathology and protection. Effector T cells (including conventional CD4+ and CD8+ T cells, and unconventional T cells, such as γδ T cells) and macrophages participate in the control of tuberculosis. Interferon-γ (IFN-γ) and tumour-necrosis factor-α (TNF-α), produced by T cells, are important macrophage activators. Macrophage activation permits phagosomal maturation and the production of antimicrobial molecules such as reactive nitrogen intermediates (RNI) and reactive oxygen intermediates (ROI) (Kaufmann, 2001).

2.7 Sign and Symptoms of TB patient

Tuberculosis may infect any part of the body, but most commonly occurs in the lungs (known as pulmonary tuberculosis). Extrapulmonary TB occurs when tuberculosis develops outside of the lungs, although extrapulmonary TB may coexist with pulmonary TB.(Dolin et al,.2010) General signs and symptoms include fever, chills, coughs with blood, loss of appetite, night sweating, breathlessness, fatique, swelling, chest pain, abdominal pain, body ace etc

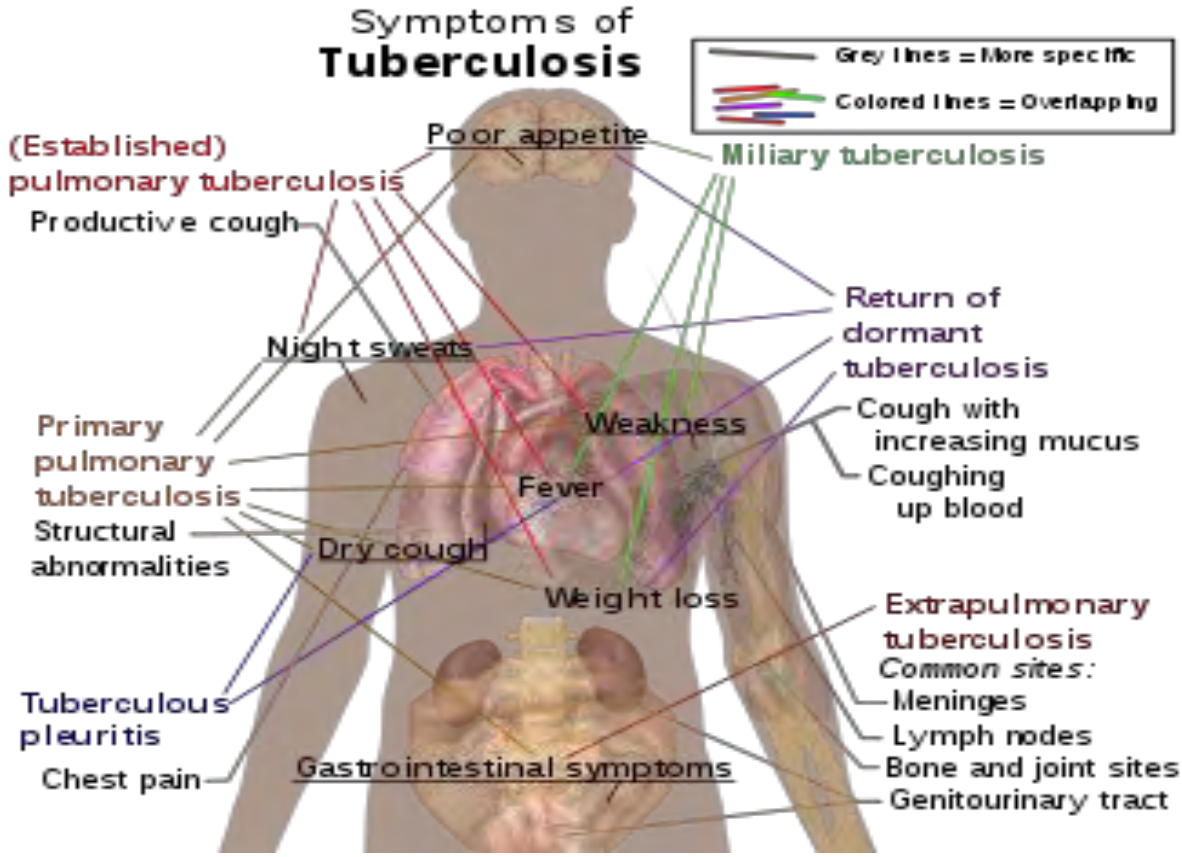


Figure 2.5: Sign and Symptoms of TB patient

The main symptoms of variants and stages of tuberculosis are given,with many symptoms overlapping with other variants, while others are more (but not entirely) specific for certain variants. Multiple variants may be present simultaneously.

2.8 Causative agent of TB

Mycobacteria

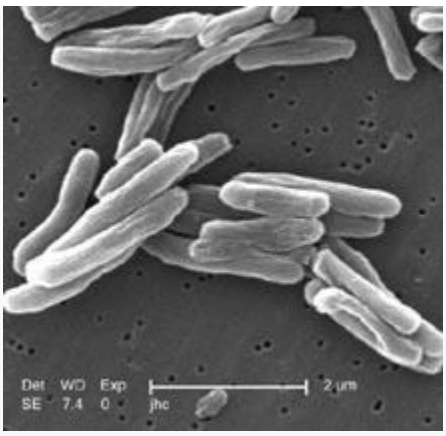


Figure 2.6: Scanning electron micrograph of *M. tuberculosis*

The main cause of TB is *Mycobacterium tuberculosis* (MTB), a small, aerobic, nonmotile bacillus.The high lipid content of this pathogenaccounts for many of its unique clinical characteristics. It divides every 16 to 20 hours, which is an extremely slow rate compared with other bacteria, which usually divide in less than an hour.]Mycobacteria have an outer membrane lipid bilayer. If a Gram stain is performed, MTB either stains very weakly "Gram-positive" or does not retain dye as a result of the high lipid and mycolic acid content of its cell wall.MTB can withstand weak disinfectants and survive in a dry state for weeks. In nature, the bacterium can grow only within the cells of a host organism, but *M. tuberculosis* can be cultured in the laboratory.

Using histological stains on expectorated samples from phlegm (also called "sputum"), scientists can identify MTB under a microscope. Since MTB retains certain stains even after being treated with acidic solution, it is classified as an acid-fast bacillus.The most common acid-fast staining techniques are the Ziehl–Neelsen stain and the Kinyoun stain, which dye acid-fast bacilli a bright red that stands out against a blue background. Auramine-rhodamine staining and fluorescence microscopy are also used. The *M. tuberculosis* complex (MTBC) includes four other TB-causing mycobacteria: *M. bovis*, *M. africanum*, *M. canetti*, and *M. microti*.*M. africanum* is not widespread, but it is a significant cause of tuberculosis in parts of Africa*M. bovis* was once a common cause of tuberculosis, but the introduction of pasteurized milk has almost completely

eliminated this as a public health problem in developed countries*M. canetti* is rare and seems to be limited to the Horn of Africa, although a few cases have been seen in African emigrants.*M. microti* is also rare and is seen almost only in immunodeficient people, although its prevalence may be significantly underestimated. (Orcau, CaylÄ, & MartÃnez, 2011).

Other known pathogenic mycobacteria include *M. leprae*, *M. avium*, and *M. kansasii*. The latter two species are classified as "nontuberculous mycobacteria" (NTM). NTM cause neither TB nor leprosy, but they do cause lung diseases that resemble TB.Mycobacterial infections are intracellular and, generally, result in the formation of slow-growing granulomatous lesions that are responsible for major tissue destruction (Orcau *et al*., 2011).

2.9 Pathophysiology

Once inhaled, the infectious droplets settle throughout the airways. The majority of the bacilli are trapped in the upper parts of the airways where the mucus-secreting goblet cells exist. The mucus produced catches foreign substances, and the cilia on the surface of the cells constantly beat the mucus and its entrapped particles upward for removal (Freiden, Sterling, Munsiff, Watt, & Dye, 2003). This system provides the body with an initial physical defensethat prevents infection in most persons exposed to tuberculosis (Jensen, Centers for Disease, Prevention, National Center for Hiv, & Prevention, 2005). Bacteria in droplets that by pass the mucociliary system and reach the alveoli are quickly surrounded and engulfed by alveolar macrophages (Freiden *et al.*, 2003),the most abundant immune effector cells present in alveolar spaces (Korf *et al.*, 2006). These macrophages, the next line of host defense, are part of the innate immune system and provide an opportunity for the body to destroy the invading mycobacteria and prevent infection (van Crevel, Ottenhoff, & van der Meer, 2002). Macrophages are readily available phagocytic cells that combat many pathogens without requiring previous exposure to the pathogens. Several mechanisms and macrophage receptors are involved in uptake of the mycobacteria (Nicod, 2007). The mycobacterial lipoarabinomannan is a key ligand for a macrophage receptor (Nicod, 2007).

The complement system also plays a role in the phagocytosis of the bacteria (Li, Petrofsky, & Bermudez, 2002). The complement protein C3 binds to the cell wall and enhances recognition of themycobacteria by macrophages. Opsonization by C3 is rapid, even in the air spaces of a host

with no previous exposure to M tuberculosis (Ferguson, Weis, Martin, & Schlesinger, 2004). The subsequent phagocytosis by macrophages initiate cascade of events that results in either successful control of the infection, followed by latent tuberculosis, or progression to active disease, called primary progressive tuberculosis (Freiden *et al.*, 2003). The outcome is essentially determined by the quality of the host defenses and the balance that occurs between host defenses and the invading mycobacteria (Guyot-Revol, Innes, Hackforth, Hinks, & Lalvani, 2006; van Crevel *et al.*, 2002). After being ingested by macrophages, the mycobacteria continue to multiply slowly, with bacterial cell division occurring every 25 to 32 hours (Freiden *et al.*, 2003). Regardless of whether the infection becomes controlled or progresses, initial development involves production of proteolytic enzymes and cytokines by macrophages in an attempt to degrade the bacteria (Nicod, 2007; van Crevel *et al.*, 2002). Released cytokines attract T lymphocytes to the site, the cells that constitute cell-mediated immunity.

Macrophages then present mycobacterial antigens on their surface to the T cells (van Crevel *et al*., 2002). This initial immune process continues for 2 to 12 weeks; the microorganisms continue to grow until they reach sufficient numbers to fully elicit the cell-mediated immune response, which can be detected by a skin test (Freiden *et al.*, 2003). For persons with intact

cell mediated immunity, the next defensive step is formation of granulomas around the *M. tuberculosis* organisms (Guyot-Revol *et al.*, 2006). These nodular-type lesions form from an accumulation of activated T lymphocytes and macrophages, which creates a microenvironment that limits replication and the spread of the mycobacteria (Freiden *et al.*, 2003).

This environment destroys macro phages and produces early solid necrosis at the center of the lesion; however, the bacilli are able to adapt to survive (Dheda *et al.*, 2005). In fact, *M tuberculosis* organisms can change their phenotypic expression, such as protein regulation, to enhance survival (Li *et al.*, 2002). By 2 or 3 weeks, the necrotic environment resembles soft cheese, often referred to caseous necrosis, and is characterized by low oxygen levels, low pH, and limited nutrients. For less immune competent persons, granuloma formation is initiated yet ultimately is unsuccessful in containing the bacilli. The necrotic tissue undergoes liquefaction, and the fibrous wall loses structural integrity. The semi-liquid necrotic material can then drain into a bronchus or nearby blood vessel, leaving an air-filled cavity at the original site. In patients infected with *M. tuberculosis,* droplets can be coughed up from the bronchus and infect other

persons. If discharge into a vessel occurs, occurrence of extrapulmonary tuberculosis is likely. Bacilli can also drain into the lymphatic system and collect in the tracheobronchial lymph nodes of the affected lung, where the organisms can form new caseous granulomas (Dheda*et al.*, 2005).

Macrophases and T lymphocytes act together to try to contain the infection by forming granulomas (Raqib *et al.,* 2004**)**.In weaker immune systems, the wall loses integrity and the bacilli are able to escape and spread to other alveoli or other organs. Pathophysiology of tuberculosis: inhalation of bacilli (A), containment in a granuloma (B), and breakdown of the granuloma in less immune-competent individuals (C) (Centers for Disease Control and Prevention, 2012).

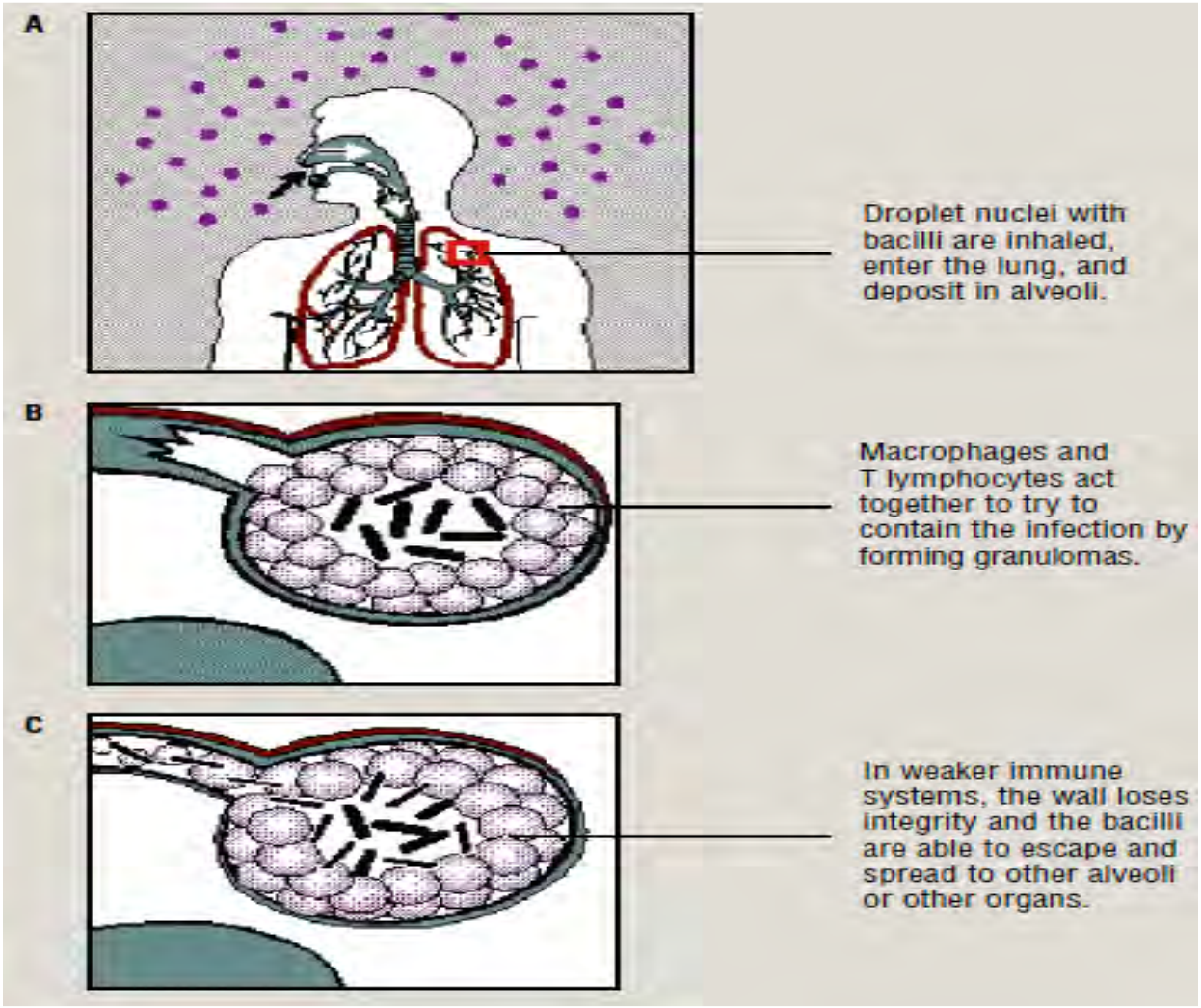


Figure 2.7: Pathophysiology of tuberculosis (Dheda *et al.*, 2005)

This condition restricts further growth and establishes latency. Lesions in persons with an adequate immune system generally undergo fibrosis and calcification, successfully controlling the infection so that the bacilli are contained in the dormant, healed lesions.18 Lesions in persons with less effective immune systems progress to primary progressive tuberculosis (Dheda *et al.*, 2005; Li *et al.*, 2002).

2.9.1 Post-primary Pulmonary Tuberculosis

Pulmonary TB is the most frequent form of post-primary disease. The onset is typically insidious and develops slowly over several weeks. Systemic symptoms include fever, night sweats, malaise, loss of appetite and weight, and are accompanied by progressive pulmonary symptoms. The earliest radiographical change is typically an ill-defined opacity situated in one of the upper lobes. Disease often involves two or more areas of lung and may be bilateral. As disease progresses, consolidation, collapse and cavitation develop to varying degrees. The presence of a miliary pattern or cavitation indicates active disease although there is a wide differential. In extensive disease, collapse may be marked and result in significant displacement of the trachea and mediastinum. Occasionally, a caseous lymph node may drain into an adjoining bronchus, resulting in tuberculosis pneumonia (Rekha *et al.* 2011).

2.9.2 Extra-pulmonary Tuberculosis

Although the pulmonary system is the most common location for tuberculosis, extra pulmonary disease occurs in more than 20% of immune competent patients, and the risk for extra-pulmonary disease increases with immunosuppression. The most serious location is the central nervous system, where infection may result in meningitis or space occupying tuberculomas. If not treated, tubercular meningitis is fatal in most cases, making rapid detection of the mycobacteria essential. Headaches and change in mental status after possible exposure to tuberculosis or in high risk groups should prompt consideration of this disease as a differential diagnosis. Another fatal form of extra-pulmonary tuberculosis is infection of the bloodstream by mycobacterium; this form of the disease is called disseminated or miliary tuberculosis. The bacilli can then spread throughout the body, leading to multi organ involvement. Miliary tuberculosis progresses rapidly and can be difficult to diagnose because of its systemic and

nonspecific signs and symptoms, such as fever, weight loss, and weakness. Lymphatic tuberculosis is the most common extra-pulmonary tuberculosis and cervical adenopathy occurs most often. Other possible locations include bones, joints, pleura, and genitourinary system (Davidson & Haslett, 2002).

2.10 Diagnosis of TB:

2.10.1 Tools for diagnosis of TB

Because active TB disease can be difficult to diagnose, especially in children and those who have weakened immune systems, additional tests beyond medical examinations are required. To determine if a patient has active TB disease, the following tests may be used:

Sputum Smear Examination (AFB Microscopy)

The most cost-effective tool for screening pulmonary TB suspects is microscopy examination of their sputum by the Ziehl-Neelsen method. Over 65% of pulmonary TB patients are smear-positive and will be detected by this method. In the remaining pulmonary TB patients, the number of bacilli in their sputum is too low to be detected through this method. Sputum examination is the most reliable procedure for diagnosis of TB.

Radiological (X-ray) Examination of the Lungs

Chest X-Ray findings do not specifically indicate pulmonary tuberculosis because there are other chest diseases which may show the same changes on X-ray. Chest X-ray findings suggestive of pulmonary tuberculosis in patients with smear-negative microscopy should always be supported by clinical findings. A qualified physician should decide on the diagnosis of TB.

Tuberculin Skin Test (Mantaux Test)

This test is only used for supporting TB diagnosis in young children. In populations with a high TB prevalence, the tuberculin skin test is of little value in the diagnosis of TB disease in adults. A positive tuberculin skin test does not by itself differentiate *M. tuberculosis* infection from TB disease. Previous exposure to environmental mycobacteria may also result in a false-positive test result. With increasing age an increasing percentage of the population willhave been infected with *M. tuberculosis* (almost 100% at the age of 40-50 years) and 90% of them will not have

developed TB disease. Hence, diagnosis of TB based on Mantoux test will lead to over-diagnosis of many patients. Conversely, the tuberculin skin test result may be negative, even when the patient has TB

Table 2.3 Diagnostic Test for identifying Tuberculosis

Variable	Sputum smear	Sputum culture	Polymerase chain reaction	Tuberculin skin test	Quanti FERON-TB test	Chest radiography
Purpose of test or study	Detect acid-fast bacilli	Identify *My cobacterium tuberculosis*	Identify *My cobacterium tuberculois*	Detect exposure to my cobact eria	Measure immune reactivity to *M. tuberculosis*	Visualize lobar infiltrates with cavitation
Time required for result	<24 hours	3-6 weeks with solid media, 4-14 days with high pressure liquid chromato graphy	Hours	48-72 hours	12-24 hours	Minutes

Culture of TB Bacilli

Culture is more sensitive than smear microscopy, detecting a higher proportion of patients among suspects. If resources permit and adequate, quality-assured laboratory facilities are available, culture should be included in the algorithm for evaluating patients with negative sputum smears. However, it takes about six weeks to provide a definite result, and is not accessible to most patients. Therefore, it is unsuitable as routine procedure. The probability of finding acid-fast bacilli in sputum smears by microscopy is directly related to the concentrations of bacilli in the sputum. Sputum microscopy is likely to be positive when there are at least 10 000 organisms per ml of sputum. At concentrations below 1000 organisms per ml of the sputum, the chance of observing acid-fast bacilli in a smear is less than 10%. In contrast, a properly

performed culture can detect organism even concentrations below 100 organisms per ml (WHO Country Office for Bangladesh, 2009).

FNAC and Biopsy

FNAC stands for fine needle aspiration cytology. It is a diagnostic procedure sometimes used to investigate superficial lumps or masses. These are special tests performed to confirm extra pulmonary TB to be referred to concerned specialists. Fine needle aspiration biopsies are very safe, minor surgical procedures. Often, a major surgical biopsy can be avoided by performing a needle aspiration biopsy instead. In 1981, the first fine needle aspiration biopsy in the United States of America was done at Maimonides Medical Center, eliminating the need for surgery and hospitalization. Today, this procedure is widely used in the diagnosis of cancer (WHO Country Office for Bangladesh, 2009).

Blood Tests

Recently developed blood Tests (e.g., The T-SPOT, TB Test)are testing for both active disease and latent TB infections (College of Physicians & Surgeons of Saskatchewan, 2012). A blood sample is needed to run this test which is performed in the laboratory. The results are available to the doctor the next day. The T-SPOT, TB test holds several major advantages over the tuberculin skin test in that it does not require a second visit, it is not affected by BCG vaccination and it is very reliable--even in patients with weakened immune systems (College of Physicians & Surgeons of Saskatchewan, 2012; Peters *et al.*, 2008).

2.10.2 Hematological Indices

Apart from the diagnostic tests specific for diagnosis of tuberculosis, some common routine tests are done such as:

- CBC with ESR
- Biochemical analysis(blood glucose, blood urea, Serum creatinine etc.)

Complete Blood Count (CBC)

A complete blood count is a diagnostic test that uses a blood sample to estimate the values of various components found in human blood and is conducted as a routine test in almost every medical condition. The complete blood count is usually the first test conducted on a patient when the patient has symptoms of a disease or infection and also when the patient is admitted to hospital. The complete blood count test is conducted on a sample of blood, usually drawn from a vein in the upper forearm of the patient. The blood is responsible for transporting nutrition, oxygen, hormones and many other substances around the body. The heart creates pressure which allows the blood to move continuously around the body. The blood is measured for its components because it carries so many different components that are diagnostically relevant. The most important components when it comes to a complete blood count are the red blood cells, the white blood cells, the platelet count and the hemoglobin levels. Many common conditions are diagnosed using these parameters (College of Physicians & Surgeons of Saskatchewan, 2012; Peters *et al.*, 2008).

Erythrocyte Sedimentation Rate

ESR stands for erythrocyte sedimentation rate and is also known as sedimentation rate or Westergren ESR. It is the rate at which red blood cells sediment in a period of 1 hour. It is a common hematology test, and is a non-specific measure of inflammation. The ESR is a commonly ordered test for the assessment of inflammation and is not meant to be used to screen an asymptomatic person for disease. It is a test that indirectly measures how much inflammation is in the body. It is a test that is conducted to check the speed at which the red blood cells precipitate over a period of time. The results are measured as millimeters per hour. Typically, the complete blood count with ESR is conducted as the first test on a patient suspected to have a disease or infection. The results of the ESR test are useful to plan further testing and to commence treatment depending on the condition that is suspected (College of Physicians & Surgeons of Saskatchewan, 2012; Peters *et al.*, 2008).

Once a diagnosis has been made, this test may be used to monitor whether the illness is becoming more active or flaring up. It is a screening test, which means it cannot be used to diagnose a specific disorder. However, it is useful for detecting and monitoring:

 Autoimmune disorders

 Certain forms of arthritis

 Inflammatory diseases that cause vague symptoms

 Tissue death

 Tuberculosis

An increased ESR rate may be due to some infections, including:

 Body-wide (systemic) infection

 Tuberculosis

 Bone infections

 Infection of the heart or heart valves

 Rheumatic fever

 Severe skin infections, such as erysipelas

An increased ESR rate may be due to:

 Anemia

 Cancers such as lymphoma or multiple myeloma

 Kidney disease

 Pregnancy

 Thyroid disease

The immune system helps protect the body against harmful substances. In autoimmune disorder is a condition that occurs when the immune system mistakenly attacks and destroys healthy body tissue. ESR is often higher than normal in people with an autoimmune disorder (College of Physicians & Surgeons of Saskatchewan, 2012).

2.11 Factors increasing the risk of TB

2.11.1 Patient Related

 Age (children > young adults < elderly)

 First-generation immigrants from high-prevalence countries

 Close contacts of patients with smear-positive pulmonary tuberculosis

 Overcrowding: prisons, collective dormitories

 Chest radiographic evidence of self-healed tuberculosis

 Primary infection < 1 year previously

2.11.2 Associated diseases

 Immunosuppression-HIV, infliximab, high-dose corticosteroids, cytotoxic agents

 Malignancy (especially lymphoma and leukaemia)

 Type 1 diabetes mellitus

 Chronic renal failure

 Silicosis

 Gastrointestinal disease associated with malnutrition (gastrectomy, jejuno-ileal bypass, cancer of the pancreas, malabsorption)

 Deficiency of vitamin D

2.12 Treatment of Tuberculosis

Treating tuberculosis as well as other mycobacterial infections presents therapeutic problems. The organism grows slowly; thus, are difficult to culture and may have to be treated for 6 months to 2 years. Resistant organisms readily emerge, particularly in patients who have had prior therapy or who fail to adhere to the treatment protocol.

Aims of treatment

The aims of treating TB are:

 To cure the patient of TB

 To prevent death from active TB or its late effects

 To prevent relapse of TB

 To decrease transmission of TB to others

 To prevent the development of acquired drug resistance

The basic principles of good TB treatment are:

i. Right combination of drugs to kill different bacterial populations

ii. Drugs are given for the right duration (several months) to kill the bacilli

iii. Drugs are given in the right dosage to achieve therapeutic but not toxic effect

Effective chemotherapy consists of two phases (WHO Country Office for Bangladesh, 2009):
i. The initial or intensive phase administered daily for two months in new cases and three months in re-treatment cases. The aim of this phase is to rapidly reduce and eliminate the multiplying bacilli without allowing the development of acquired resistance to the prescribed drugs. During the intensive phase, the tubercle bacilli are killed rapidly. The infectious patients quickly become non-infectious (within approximately two weeks).

ii. The continuation phase is essential to eliminate the remaining bacterial population. Drugs administered daily for the rest of the treatment duration according to category.

2.12.1 Commonly used Drugs

There are five key anti-tuberculosis drugs:
 Isoniazid
 Rifampicin
 Pyrazinamide
 Streptomycin
 Ethambutol
Second line drugs:
 Aminoglycosides: Amikacin, Kanamycin
 Polypeptides: Caprcomycin
 Quinolones: Ciprofioxacin, Ofioxacin
 Thioamides: Ethionamide&Prothionamide
 Paraminosalicyclic acid (PAS): Cycloserine

2.12.2 Strategies for Addressing Drug Resistance

Strains of *M. tuberculosis* that are resistant to a particular agent emerge during treatment with a single drug. For example, resistance rapidly develops in patients given only streptomycin. Therefore, multidrug therapy is employed when treating tuberculosis in an effort to delay or prevent the emergence of resistant strains. Isoniazid, rifampin, ethambutol, and pyrazinamide are the principal or so-called "first-line" drugs because of their efficacy and acceptable degree of toxicity. Today, however, because of poor patient compliance and other factors, the number of multidrug-resistant organisms has risen. Some bacteria have been identified that are resistant to as many as seven anti-tubercular agents. Therefore, although treatment regimens vary in duration and in the agents employed, they always include a minimum of two drugs, preferably with both being bactericidal. The combination of drugs should prevent the emergence of resistant strains. The multidrug regimen is continued well beyond the disappearance of clinical disease to eradicate any persistent organisms. For example, the initial short-course chemotherapy for tuberculosis includes isoniazid, rifampin, ethambutol, and pyrazinamide for 2 months and then isoniazid and rifampin for the next 4 months. Before susceptibility data are available, more drugs may be added to the first-line agents for patients who have previously had tuberculosis or those in whom multidrug-resistant tuberculosis is suspected. The added drugs normally include an aminoglycoside (streptomycin, kanamycin, or amikacin) or capreomycin (injectable agents), a fluoroquinolone, and perhaps a second-line antituberculosis agent such as cycloserine, ethionamide, or p-aminosalicylic acid. Once susceptibility data are available, the drug regimen can be individually tailored to the patient. Patient compliance is often low when multidrug schedule last for 6 months or longer. One successful strategy for achieving better treatment completion rates is "directly observed therapy," also known as DOT, in which patients take their medication while being supervised and observed. DOT has been shown to decrease drug resistance as well as relapse and mortality rates and to improve cure rates. Most local and state health departments offer DOT services (Harvey, 2008).

2.12.3 The Role of Treatment in the Control of Tuberculosis

Treatment and cure of infectious cases of tuberculosis will interrupt transmission of TB infection in the community. Therefore, successful completion of treatment is the most effective way of prevention of TB (WHO Country Office for Bangladesh, 2009).

2.13 Vaccine Development

The search for a vaccine against tuberculosis began 110 years ago with great expectations. Only 8 years after discovering the tubercle bacillus in 1882, Robert Koch devised a subunit vaccine for the treatment of tuberculosis, a disease that constituted the worst threat to mankind at the time. This therapeutic vaccine completely failed. The second attempt was initiated 10 years later by the French scientists Calmette and Guérin. After more than 200 passages, they obtained an attenuated strain of *M. bovis*, the etiological agent of cattle tuberculosis, which can, though rarely, cause tuberculosis in humans. This attenuated vaccine, now termed BCG (from Bacille Calmette–Guérin) proved more successful. After more than 3 billion administrations, it is still in use today. However, it did not match the expectations it evoked. Although BCG prevents disseminated tuberculosis in newborns, it fails to protect against the most common form of the disease, pulmonary tuberculosis in adults. The Bacille Calmette-Guérin (BCG) vaccine is recommended as soon as possible after birth. The vaccine is known to prevent the more severe types of TB such as TB meningitis and miliary TB. However, the efficacy of the vaccine in general ranges from 0% to 80%. The reasons for this variability are: different types of BCG used in different countries, differences in the strains of *M tuberculosis* prevailing in different regions, different levels of exposure, etc. Revaccination offers no added protection, and is therefore not recommended (WHO Country Office for Bangladesh, 2009).

Satisfactory control of tuberculosis can only be achieved using a highly efficacious vaccine. Tuberculosis is particularly challenging for the immune system. The intracellular location of the pathogen shields it from antibodies, and a variety of T-cell subpopulations must be activated to challenge the bacterium's resistance to antibacterial defense mechanisms. The combined information from recent studies of natural infection with *M. tuberculosis* and vaccination with BCG, combined with information from the *M. tuberculosis* genome, transcriptome and proteome, offer good prospects for the development of an efficacious new vaccine (Kaufmann, 2001).

2.14 TB control in Bangladesh

In the pre-DOTS era, TB control in Bangladesh was vertical and based in a limited number of large hospitals in different districts of the country. Chest x-ray and longterm therapy was the mainstay of diagnosis and treatment. In 1993, the government of Bangladesh adopted the DOTS strategy for TB control and started to implement its components throughout the country. This occurred initially in rural areas and was only from 2003 onwards scaled-up to the urban areas. One important feature in expanding TB services was including NGOs in TB-control activities from the beginning. The government commitment continued with subsequent annual development plans. TB-control activities were further strengthened with the availability of funding support from Global Fund for TB, AIDS and Malaria (GFATM) since 2003.

2.14.1 The National TB Control Programme

The services of the National Tuberculosis Control Programme (NTP) are organized under a sub directorate called Mycobacterium Disease Control (MBDC) which reports directly under the governance of the Directorate General of Health Services (DGHS). At the district level, the Civil Surgeon (CS) heads the health administration, and at the Upazila or sub-district level, the Upazila Health and Family Planning Officer (UHFPO) is responsible for TB services. This latter is the basic unit for diagnosis and management of TB patients. Every Upazila has a central centre where microscopy for TB diagnosis is performed and other DOTS-activities General introductionare implemented. This centre is run by government or NGO staff. Additional DOTS services are provided at lower level facilities by Health Assistants, and occasionally by trained village doctors. The TB services are organized slightly different in urban areas. They are provided under the Urban Primary Health Care Project (UPHCP) which falls under the Ministry of Local government, rural development and cooperative (MoLGRDC). In addition to the 460 Upazila Health Complexes of the country, free TB series are also available through 44 chest diseases clinics at district levels, 11 chest disease hospitals, all 64 districts and all medical college hospitals, 264 urban health centres, prisons and in many garments factory work places.

Materials and Methods

3.1 Method

This study was done on tuberculosis patients admitted in Shaheed Shorawardi Medical College and Hospital, Dhaka Bangladesh. All the wards of the hospital were visited for this purpose. Patient's hematological data was be collected from medical reports along with CBC with ESR test report. Each of the patients was debriefed appropriately. Support from the hospital stuff was taken. Proper protection was taken e.g., both patients and researcher wore masks.

3.2 Study place

The study was conducted at Shaheed Shorawardi Medical College and Hospital, is a govt. hospital situated at Sher E Bangla Nagar, Dhaka, Bangladesh.

3.3 Research approach

After having approval of the research proposal from the respected research supervisor, permission was obtained from Hospital Director, Shaheed Shorawardi Medical College and Hospital, Dhaka Bangladesh.

3.4 Inclusion criteria

 Male and female patients diagnosed with TB

 Patients within the age of 10-85 years.

 Patients who were admitted in Shaheed Shorawardi Medical College and Hospital, i.e., indoor patients

3.5 Study type

It is a prospective study.

3.6 Sample size

The sample size for the study was 290 TB patients both pulmonary and extra-pulmonary.

3.7 Sampling technique

It was a Simple Random Sampling. A semi structured questionnaire was used for the purpose of data collection.

3.8 Data analysis

A collection of data, all data was checked. Data was analyzed with the help of Microsoft excel and SPSS to compute frequency distribution. Data sets were presented in both in tabular form and graphically using pie chart, histogram etc.

Results and Discussion

Hematological and biochemical abnormalities in tuberculosis are common and may be valuable aids in diagnosis. Various studies have shown anemia to be one of the commonest manifestation of TB. (Choi CW et al.,2004) and (Ania BJ et al.,1994).

4.1 Distribution of the TB Patients based on gender

Data of two hundred ninety (290) patients were studied. Among them one hundred sixty eight (168) were male and the remaining one hundred twenty two (122) were female.

Table 4.1: Frequency table of distribution of TB patients based on gender

Gender	Frequency	Percentage (%)
Male	**168**	**58**
Female	**122**	**42**
Total	**290**	**100**

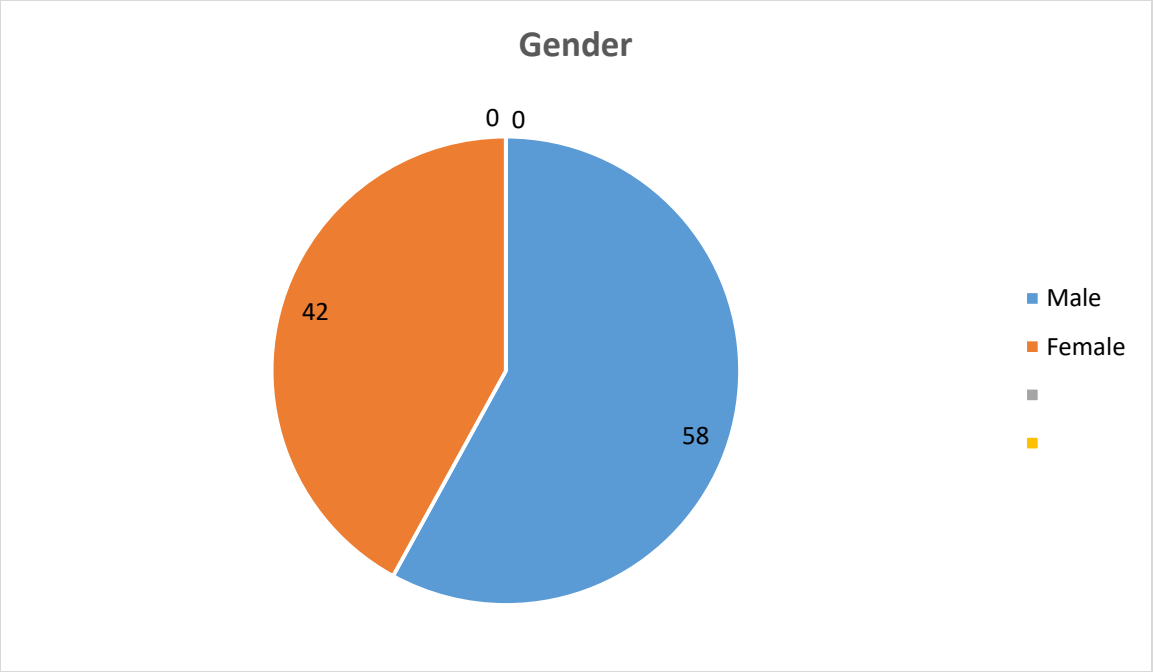


Figure 4.1: Distribution of the TB Patients based on gender

It was observed in the study that the prevalence of TB disease is higher in males. From a total of 290 patients 58% is male and 42% is female.

4.2 Distribution of the TB Patients based on PTB/EPTB

Table 4.2: Frequency Table of Distribution of TB Patients based on PTB and EPTB

PTB and EPTB	Frequency	Percentage (%)
PTB	**170**	**58.6**
EPTB	**120**	**41.4**
Total	**290**	**100**

This shows that pulmonary tuberculosis (PTB) is more common than extra-pulmonary tuberculosis (EPTB). Out of 290 TB patients 170 TB patients had PTB with 58.6% and 120 TB patients had EPTB with 41.4%.

4.3 Distribution of the PTB and EPTB based on Gender

Table 4.3: Cross table analysis between gender of the TB patients and their PTB/EPTB group.

PTB/EPTB	Gender				Total
	Male	Percentage (%)	Female	Percentage (%)	
PTB	118	70	52	42.6	170
EPTB	50	30	70	51.4	120
TOTAL	168	100	122	100	290

TB was classified as pulmonary or extra-pulmonary as per WHO guidelines. World Health Organization (2006 a).

In this analysis out of 168 male TB patients 118 male TB patients had PTB with 70% and 50 male TB patients had EPTB with 30% and out of 122 female TB patients 52 female TB patients had PTB with 42.6% and 70 female TB patients had EPTB with 51.4%. So this study shows that pulmonary TB (PTB) is more common in men than women.

4.4 Distribution of the TB Patients based on Clinical Symptoms.

Table 4.4: Frequency Table of Distribution of TB Patients based on Clinical Symptoms.

Clinical Symptoms	Frequency	Percentage(%)
Coughs with expectoration	254	87.5
Loss of appetite	195	67.2
Fever	183	63.1
Sweating	171	59
Breathlessness	163	56.2
Chills	130	45
Fatique	127	44
Swelling	115	39.6
Weight loss	112	38.6
Chest pain	102	35.1
Abdominal pain	98	33.7
Body ache	87	30

It is observed that from this table among those TB clinical symptoms Coughs with expectoration has highest frequency 254 TB patients out of 290 TB patients with 87.5%.

4.5 Distribution of the TB Patients based on age range.

Table 4.5: Frequency Table of Distribution of TB Patients based on age range.

Age (Year)	Frequency	Percentage (%)
10-19	**53**	**18.3**
20-29	**45**	**15.5**
30-39	**43**	**14.8**
40-49	**53**	**18.3**
50-59	**19**	**6.5**
60 and 60+	**77**	**26.6**
Total	**290**	**100**

All the patients fall in the age range of 10 to 60+. out of total number of patients age group of 10 to years had 53 patients, 20 to 29 had 45 patients, 30 to 39 had 43 patients, 40 to 49 had 53 patients, 50 to 59 had 19 patients and remaining 77 patients were 60 and above 60 years old.

It was observed from the study the highest number of TB patients fall in the group of 60 and above 60 years. The percentage of TB patients based on the age groups are found as follows, 10 to 19 years (18.3%), 20 to 29 years (15.5%), 30-39 years (14.8%), 40 to 49 years (18.3%), 50 to 59 years (6.5%) and 60 and above 60 years (26.6%).

4.6 Distribution of Age Range of the TB patients based on Gender

It was identified that the most critical age range for the occurrence of TB disease is 60 and above 60 years.

Table 4.6: Cross table analysis between gender of the TB patients and their age range.

Age	Gender				Total
	Male	Percentage (%)	Female	Percentage (%)	
10-19	29	17.2	24	19.7	53
20-29	26	15.5	19	15.6	45
30-39	25	14.9	18	14.7	43
40-49	38	22.6	15	12.3	53
50-59	11	6.5	8	6.5	19
60 and Above60	39	23.3	38	31.2	77
Total	168	100	122	100	290

Among the 168 male TB patients, age group of 10-19 years had 17.2% patients, 20-29 years had 15.5% patients, 30-39 years had 14.9% patients, 40-49 years had 22.6% patients, 50-59 years had 6.5% patients, and 60 to above 60 years had 23.3% patients.

On the other hand, out of 122 female TB patients, age group of 10-19 years had 19.7% patients, 20-29 years had 15.6% patients, 30-39 years had 14.7% patients, 40-49 years had 12.3% patients, 50-59 years had 6.5% patients and 60 to above 60years had 31.2% patients.

It can be observed that in both male and female patients, most of the patients are from age range of 60 to above 60 years and the next critical age range is 40 to 49 years and 10 to 19 years.

4.7 Distribution of the TB Patients based on blood pressure (Systolic).

Most of the TB patients had an irregular blood pressure and they were suffering from hypertension. Moreover, systolic blood pressure of the patients was randomly measured. The majority of the patients had a high systolic blood pressure.

Table 4.7: Frequency Table of Distribution of TB Patients based on Blood Pressure (systolic).

Systolic BP (mmHg)	Frequency	Percentage (%)
<120	71	24.5
120(Normal Range)	85	29.1
>120	134	42.2
Total	290	100

From the data assembly, it can be observed that 24.5% TB patients had low systolic blood pressure, 29.1% TB patients had normal systolic blood pressure and 42.2% TB patients had high systolic blood pressure.

4.8 Distribution of the TB Patients based on blood pressure (Diastolic).

Most of the TB patients had an irregular blood pressure and they were suffering from hypertension. Moreover, diastolic blood pressure of the patients was randomly measured. The majority of the patients had a high diastolic blood pressure.

Table 4.8: Frequency Table of Distribution of TB Patients based on Blood Pressure (diastolic).

Diastolic BP(mmHg)	Frequency	Percentage (%)
<80	56	19.3
80 (Normal Range)	102	35.2
>80	132	45.5
Total	290	100

From the data assembly, it can be observed that 19.3% TB patients had low diastolic blood pressure, 35.2% TB patients had normal diastolic blood pressure, and 45.5% TB patients had high diastolic blood pressure.

4.9 Distribution of the TB Patients based on weight range.

Table 4.9: Frequency Table of Distribution of TB Patients based on weight range.

Weight (kg)	Frequency	Percentage
19-28	**6**	**2**
29-38	**38**	**13.1**
39-48	**120**	**41.4**
49-58	**86**	**29.6**
Above58	**40**	**13.9**
Total	**290**	**100**

It can be observed from the table that most of patients (41.4%) fall in weight group of 39 to 48 kg. other weight group 19 to 28 kg had 2% patients, 29 to 38kg had 13.1%, 49 to 58 kg had 29.6% and above 58 had 13.9% TB patients.

4.10 Distribution of the TB Patients based on blood group.

Table 4.10: Frequency Table of Distribution of TB Patients based on Blood Group.

Blood Group	Frequency	Percentage (%)
A-(ve)	12	4.1
A+(ve)	19	6.5
AB-(ve)	20	6.8
AB+(ve)	36	12.3
B-(ve)	10	3.4
B+(ve)	163	55.8
O-(ve)	20	6.8
O+(ve)	12	4.1
Total	292	100.0

From all the 290 patients 4.1%TB patients had A-(ve) 6.5%TB patients had A+(ve), 6.8%TB patients had AB-(ve), 12.3%TB patients had AB+(ve) 3.4%TB patients had B-(ve), 55.8%TB patients had B+(ve), 6.8%TB patients had O-(ve), 4.1%TB patients had O+(ve).

It can be observed that majority of patients had B+(ve) blood group.

4.11 Distribution of the TB Patients based on blood glucose level

Table 4.11: Frequency Table of Distribution of TB Patients based on Blood Glucose Level.

Blood Glucose (mmol/l)	Frequency	Percentage(%)
0-4.3	4	1.4
4.4-7.8(Normal Range)	105	36.4
7.9 and above	181	62.2
Total	290	100

From the table 1.4% patients had low blood glucose level and 36.4% patients had normal blood glucose level and 62.2% patients had high blood glucose level. It can predict that TB patients has higher blood glucose level.

4.12 Distribution of the TB Patients based on blood hemoglobin (Hb) level.

In some previous studies reported decreased level of hemoglobin in most of tuberculosis patients. (Charles M et al.,1989) and (Lombard EH et al.,1993).

Table 4.12: Frequency Table of Distribution of male TB Patients based on Blood Hemoglobin (Hb) Level.

Blood Hemoglobin (g/dl)	Frequency	Percentage(%)
0-13.4	127	75.6
13.5-17.5(Normal Range)	41	24.4
Above 17.5	0	0
Total	168	100

Normal range of blood hemoglobin is different in male and female. The normal range of blood hemoglobin (Hb) level in male is (13.5 to 17.5)g/dl. (medicine.com,2017)

From the total 168 male patients only 75.6% patients had 0 to 13.4 g/dl blood hemoglobin level, 24.4% patients had 13.5 to 17.5 g/dl (Normal Range) blood hemoglobin level and no patients had 17.5 to above g/dl blood hemoglobin level. It can be predict that male TB patients had lower blood hemoglobin level.

Table 4.13: Frequency Table of Distribution of female TB Patients based on Blood Hemoglobin (Hb) Level

Blood Hemoglobin(g/dl)	Frequency	Percentage(%)
0-11.9	**102**	**83.6**
12-15.5(Normal Range)	**20**	**16.4**
Above 15.5	**0**	**0**
Total	**122**	**100**

Normal range of blood hemoglobin level is different in male and female. The normal range of blood hemoglobin (Hb) level in female is (12 to 15.5) g/dl. (medicine.com,2017)

From the total 122 female patients 83.6% patients had 0 to 11.9 g/dl blood hemoglobin level, 16.4% patients had 12 to 15.5 g/dl (Normal Range) blood hemoglobin level and no patients had 15.5 to above g/dl blood hemoglobin level .It can be predict that female TB patients had lower blood hemoglobin level.

This rise in hemoglobin levels can be used as a markers reflecting response to treatment. (Al-omar I et al.,2009)

4.14 Distribution of the TB Patients based on blood RBC count.

It has been reported that the lower RBC values may be associated with a deficiency of iron which may be acquired through extrinsic factors. For example malnutrition (Wessels et al.,1999).

Table 4.14: Frequency Table of Distribution of male TB Patients based on Blood RBC Count.

Blood RBC (10^6/microliter)	Frequency	Percentage (%)
0-4.6	130	77.4
4.7-6.1(Normal Range)	38	22.6
Above 6.1	0	0
Total	168	100

Normal range of blood RBC is different in male and female. The normal range of blood RBC in male is (4.7 to 6.1) 10^6/microlitre. (medicine.com,2017)

From the total 168 male patients only 77.4% patients had 0 to 4.6 (10^6/microliter) blood RBC, 22.6% patients had 4.7 to 6.1 (10^6/microliter) blood RBC and no patients had 6.1 to above 10^6/microliter blood RBC. It can be predict that male TB patients had lower blood RBC.

Table 4.15: Frequency Table of Distribution of female TB Patients based on Blood RBC Count.

Blood RBC (10^6/microliter)	Frequency	Percentage (%)
0-4.1	88	72.1
4.2-5.4 (Normal Range)	34	27.9
Above 5.4	0	0
Total	122	100

Normal range of blood RBC is different in male and female. The normal range of blood RBC in female is (4.2 to 5.4) 10^6/microlitre. (medicine.com,2017)

From the total 122 female patients only 72.1% patients had 0 to 4.1 (10*6/microliter) blood RBC, 27.9% patients had 4.2 to 5.4 (10^6/microliter) blood RBC, and no patients had 5.4 to above 10^6/microliter Blood RBC. It can be predict that female TB patients had lower blood RBC.

4.15 Distribution of the TB Patients based on serum creatinine level.

Table 4.16: Frequency Table of Distribution of male TB Patients based on Serum Creatinine Level.

Serum Creatinine(mg/dl)	Frequency	Percentage(%)
0-0.8	5	3
0.9-1.3 (Normal Range)	48	28.5
1.4 and Above	115	68.5
Total	168	100

Normal range of serum creatinine is different in male and female. The normal range of serum creatinine in male is (0.9 to 1.3) mg/dl. (medicine.com,2017)

From the total 168 male patients only 3% patients had 0 to .8 mg/dl serum creatinine level, 28.5% patients had 0.9 to 1.3 mg/dl (Normal Range) serum creatinine level and 68.5% patients had 1.4 to above mg/dl serum creatinine level. It can be predict that male TB patients had higher serum creatinine level.

Table 17:Frequency Table of Distribution of Female TB Patients based on Serum Creatinine Level.

Serum Creatinine(mg/dl)	Frequency	Percentage(%)
0-0.5	10	8.2
0.6-1 (Normal Range)	24	14.3
1.1 and Above	88	77.5
Total	122	100

Normal range of serum creatinine is different in male and female. The normal range of serum creatinine in female is (0.6 to 1) mg/dl. (medicine.com,2017)

From the total 122 female patients only 8.2% patients had 0 to .5 mg/dl serum creatinine level, 14.3% patients had 0.6 to 1 mg/dl (Normal Range) serum creatinine level and 77.5% patients had 1.1 to above mg/dl serum creatinine level. It can be predict that female TB patients had higher serum creatinine level.

4.16 Distribution of the TB Patients based on Blood Platelet level

Table 18: Frequency Table of Distribution of TB Patients based on Blood Platelet Count.

Blood Platelet (10^8/microliter)	Frequency	Percentage(%)
0-1.9	207	71.4
2-2.5(Normal Range)	83	28.6
Above 2.5	0	0
Total	290	100

The normal range of blood Platelet level is (2-2.5) 10^8/ml. (medicine.com,2017)

From the total 290 patients no patients had 0 to 1.9 (10^8/ml) blood platelet level, 71.4% patients had 2 to 2.5 (10^8/ml) (Normal Range) blood platelet level and no patients had 2.5 to above (10^8/ml) blood Platelet level. It can be predict that TB patients had lower blood Platelet level.

4.17 Distribution of the TB Patients based on Blood WBC Count.

The total WBC count was reported significantly higher in TB patients. (Amilo GI et al.,2013).

Table 19: Frequency Table of Distribution of TB Patients based on Blood WBC Count

Blood WBC(10^9/L)	Frequency	Percentage(%)
0-4.4	**0**	**0**
4.5-11(Normal Range)	**26**	**9**
Above 11	**264**	**91**
Total	**290**	**100**

The normal range of blood WBC is (4.5 to 11) 10^9/L. (medicine.com,2017)

From the total 290 patients no patients had 0 to 4.4 10^9/L blood WBC, 9% patients had 4.5 to 1.3 10^9/L (Normal Range) blood WBC and 91% patients had 11 to above 10^9/L serum blood WBC. It can be predict that TB patients had higher blood WBC.

4.18 Distribution of the TB Patients based on Blood ESR

ESR is regarded as test of activity in tuberculosis. Elevated ESR to different level is one of the indicators of severity of disease and a prognostic tool, was evident in our study. It elevates in those patients with increase in sputum positivity. In earlier studies the elevated ESR is also reported by different scientists in tuberculosis patients.(Chakraborti AK et al.,1995) and (Deodhare SG et al.,2001)

Table 20: Frequency Table of Distribution of TB Patients based on Blood ESR

Blood ESR(mm/h)	Frequency	Percentage (%)
0-4.4	0	0
4.5-10(Normal Range)	21	7.2
Avobe10	269	94.8
Total	290	100

This table shows that almost every TB patients had higher blood ESR than normal range.

Several studies demonstrated that the hemoglobin level , white blood cell count , red blood parameters, erythrocyte sedimentation rate, high platelet count and body weight loss are useful indices of severity in tuberculosis, and the return of these indices to normal level is a good indication of disease control in that they correlate with sputum conversion to acid-fast bacilli negative (Morris .,1989 ; Olaniyi and Akenova .,2003 ; Muzaffar etal.,2008) . Hematological and biochemical abnormalities in pulmonary TB are common and may be valuable aids in diagnosis.

Conclusion

One-third of the world's population, or two billion people, carry the TB bacteria, more than 9 million of whom become sick each year with active TB which can be spread to others. TB disproportionately affects people in resource-poor settings, particularly those in Bangladesh. More than 90% of new TB cases and deaths occur in developing countries, posing significant challenges to the livelihoods of individuals and developing economies as TB primarily affects people during their most productive years. DOTS aims to decrease TB-related morbidity, prevent TB deaths, and decrease TB transmission. These efforts have shown some promising signs. Hematological and biochemical abnormalities in tuberculosis are common and may be valuable aids in diagnosis. There was elevated level of ESR in all the patients to substantial level whereas Hemoglobin (Hb) was lower in most of the patients presenting anemic situation. The WBC found high among TB patients. The platelet count was lower than normal in most of the patients. Some hematological abnormalities are quite common in patients with TB and physicians must maintain a high index of suspicion for diagnosis of TB in patients with these abnormalities. We suggest the differential diagnosis of tuberculosis should be entertained in patients with varied hematological disorders and effective awareness program should be launched to minimize the chances of spread of the disease. Moreover, around one-third of the cases of tuberculosis go undetected, resulting in a larger number of undiagnosed and untreated cases that spread the disease further. Present study showed hematological indicators could be used as a diagnostic marker for the diagnosis of tuberculosis by correlating the hematological value to this infectious disease. With judicious case detection and implementing appropriate measures, TB incidence, prevalence and morbidity can be minimized to a greater extent.

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