PREVALENCE OF CARDIOVASCULAR DISEASE AMONG TUBERCULOSIS PATIENTS AND TREATMENT OUTCOMES IN PENANG, MALAYSIA

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PREVALENCE OF CARDIOVASCULAR DISEASE AMONG TUBERCULOSIS PATIENTS AND TREATMENT OUTCOMES IN PENANG, MALAYSIA

by

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LIST OF ABBREVIATIONS

ACS	Acute Coronary Syndrome
AMI	Acute Myocardial Infarction
CAD	Coronary artery disease
COPD	Chronic Obstructive Pulmonary Disease
CRP	C - reactive protein
CVD	Cardiovascular disease
DR-TB	Drug-resistant Tuberculosis
HIV	Human Immunodeficiency Virus
ICAM-1	Intercellular adhesion molecule-1
IL-1	Interleukin-1
LDC	Low-Density Cholesterol
LTBI	Latent Tuberculosis Infection
LV	Left Ventricle
E. F	Ejection Fraction
LVEF	Lower Ventricle Ejection Fraction
MDR-TB	Multi drug-resistant Tuberculosis
XDR-TB	Extensively Drug-Resistant TB
NSTEMI	Non-ST Segment Elevation Myocardial Infarction
STEMI	ST-Segment Elevation Myocardial Infarction
TB	Tuberculosis
TNF-α	Tumor Necrosis Factor- α
UA	Unstable Angina
VCAM-1	Vascular cell adhesion molecule-1
ECG	Electro-Cardiogram
HIV	Human Immunodeficiency Virus
DM	Diabetes Mellitus

HTN	Hypertension
CVA	Cerebrovascular Accident (Stroke)
AIDS	Acquired Immune Deficiency Virus
IHD	Ischemic Heart Disease
CAS	Coronary Artery Stenosis
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
RDW	Red Cell Distribution Width
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
DST	Drug Sensitivity Testing
MTB	Mycobacterium Tuberculosis
INH	Isoniazid
PZA	Pyrazinamide
RIF	Rifampicin
ETH	Ethambutol
ATT	Anti-Tuberculosis Therapy
SM	Streptomycin
CHD	Coronary Heart Disease
LDL	Low-Density Lipid
HDL	High-Density Lipid
CAA	Coronary Artery Atherosclerosis
PAD	Peripheral Arterial Disease
PVD	Peripheral Vascular Disease
DVT	Deep Vein Thrombosis
AFB D/S	Acid Fast Bacilli Direct Smear
LPA	Line Probe Assay
AFB C/S	Acid Fast Bacilli Culture and Smear

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PREVALENS PENYAKIT KARDIOVASKULAR DALAM KALANGAN PESAKIT TUBERKULOSIS DAN HASIL RAWATAN DI PULAU PINANG, MALAYSIA

ABSTRAK

Beban tuberkulosis dan penyakit kardiovaskular (CVD) di seluruh dunia meluas di negara-negara membangun. Terdapat hubungan penyumbang antara jangkitan batuk kering dan penyakit CVD. Monosit atau makrofaj, limfosit, dan sitokin yang terlibat dalam tindak balas imun pengantaraan sel terhadap Mycobacterium tuberculosis juga merupakan pengendali utama aterosklerosis dalam arteri kardiovaskular. Kajian retrospektif ini, yang dijalankan di Hospital Besar Pulau Pinang, Malaysia dari Januari 2023 hingga Julai 2023, bertujuan untuk menilai kelaziman CVD dalam kalangan pesakit Tib, meneroka faktor risiko yang berkaitan, menilai hasil farmakoterapi dan menganalisis kadar kematian akibat CVD dalam populasi Tibi. Reka bentuk penyelidikan retrospektif dan deskriptif telah digunakan, memberi tumpuan kepada pesakit TB tanpa CVD yang sedia ada. Kajian ini dibahagikan kepada dua fasa. Fasa I melibatkan pensampelan mudah bagi 402 fail pesakit TB, manakala Fasa II menggunakan pensampelan bertujuan bagi 657 fail pesakit yang meninggal dunia dari 2015 hingga 2022. Penemuan fasa I mendedahkan kelaziman CVD yang ketara di kalangan pesakit TB, dengan 10.2% mengalami komplikasi kardiovaskular. Parameter klinikal, termasuk protein sensitiviti tinggi Troponin-T, protein C-reaktif, ECG, Eko-kardiogram, dan enzim jantung, telah digunakan untuk mengesan perkembangan CVD, sekunder kepada jangkitan Mycobacterium Tuberculosis. Analisis persatuan telah diterokai oleh model Regresi Chi-Square dan Logistik, mengekalkan selang keyakinan 95%. Kebarangkalian (nilai-P) 0.05 dianggap penting. Menurut penemuan analisis ujian persatuan Chi-Square, IVDU (P = 0.035, Chi-Square = 0.035), AKI (P = <0.001, Chi-Square = 18.524), anemia (P = <0.001 dan Chi-Square = 13.7) dan CRP (P = <0.001, Chi-Square =

41.590) mempunyai korelasi yang signifikan dengan perkembangan CVD di kalangan pesakit TB. Menurut Regresi Logistik Perduaan, korelasi yang ketara ditemui dengan IVDU (P = 0.017, OR = 2.541), anemia (P = 0.004, OR = 0.067), dan AKI (P = 0.004, OR = 0.035). Antara buah pinggang, hati, lipid, dan profil darah, tahap natrium yang rendah (P = 0.033, OR = 2.708), tahap klorida yang tinggi (P = 0.056, OR = 6.027), tahap kreatinin yang tinggi (P = 0.030, OR = 4.288), tahap albumin yang rendah (P = <0.001, OR = 10.233), tahap globulin yang tinggi (P = 0.029, OR = 0.339), tahap HDL yang rendah (P = 0.049, OR = 2.263), tahap LDL yang rendah (P = 0.019, OR = 3.401), kiraan RBC yang tinggi (P = 0.008, OR = 116.41), lebar taburan sel darah merah yang tinggi (P = 0.039, OR = 94.536), % limfosit rendah (P = 0.012, OR = 1.020), % monosit tinggi (P = 0.008, OR = 1.157) berkorelasi dengan ketara dengan perkembangan CVD dalam kalangan populasi TB. Pelbagai faktor menandakan kelaziman CVD yang lebih tinggi di kalangan lelaki (10.54%) berbanding wanita (8.98%) dan risiko yang lebih tinggi dikaitkan dengan hipertensi, DM, anemia, dan kecederaan buah pinggang akut. Ciri-ciri klinikal seperti tahap protein C-reaktif yang tinggi dan penemuan sinar-X dada yang teruk dikaitkan dengan CVD, menekankan peranan keradangan. Kes TB tahan ubat dikenal pasti dalam 6.5% pesakit, terutamanya tahan terhadap isoniazid (1.7%), rifampicin (1.7%) dan MDR (1.4%). Kekerapan hasil klinikal termasuk kehilangan susulan (5.5%), pesakit sembuh (41.5%), pesakit meninggal dunia (15.2%), dipindahkan keluar (14.9%), rawatan selesai (21.9%) dan rawatan gagal (0.7%). Dalam Fasa II, 12.5% pesakit TB yang meninggal dunia meninggal dunia akibat CVD, dengan sindrom koronari akut menjadi punca utama (8.37%). Faktor-faktor seperti anemia (p = 0.005) dan rintangan ubat (p = 0.004) menunjukkan hubungan yang ketara dengan kematian akibat CVD. Kesimpulannya, penyelidikan ini menyerlahkan hubungan kritikal antara TB dan CVD, menekankan kepentingan mengenal pasti faktor risiko seperti IVDU, anemia, dan AKI. Penemuan ini mencadangkan keperluan untuk meningkatkan pemantauan dan pengurusan kesihatan kardiovaskular di kalangan pesakit TB. Intervensi yang

disasarkan boleh meningkatkan hasil pesakit dengan ketara dan mengurangkan kematian yang berkaitan dengan komplikasi kardiovaskular. Selain itu, menangani rintangan ubat adalah penting untuk pengurusan TB yang berkesan. Secara keseluruhan, penemuan ini menyumbang kepada pemahaman faktor risiko yang berpotensi, dan hasil rawatan, dan membuka jalan kepada intervensi yang disasarkan untuk meningkatkan penjagaan holistik pesakit TB.

PREVALENCE OF CARDIOVASCULAR DISEASE AMONG TUBERCULOSIS PATIENTS AND TREATMENT OUTCOMES IN PENANG, MALAYSIA

ABSTRACT

Worldwide load of tuberculosis and cardiovascular disease (CVD) is extensive in developing countries. There is a contributive relationship between tuberculosis infection and CVD disease. Monocytes or macrophages, lymphocytes, and cytokines involved in cellular-mediated immune responses against Mycobacterium tuberculosis are also the main operators of atherosclerosis in cardiovascular arteries. This retrospective study, conducted at Penang General Hospital, Malaysia from January 2023 to July 2023, aimed to assess the prevalence of CVD among TB patients, explore associated risk factors, evaluate pharmacotherapy outcomes, and analyze mortality rates due to CVD within the TB population. A retrospective and descriptive research design was employed, focusing on TB patients without pre-existing CVD. This study was divided into two phases. Phase I involved the convenient sampling of 402 TB patient files, while Phase II utilized the purposive sampling of 657 deceased patient files from 2015 to 2022. Phase I findings revealed a significant prevalence of CVD among TB patients, with 10.2% developing cardiovascular complications. Clinical parameters, including Troponin-T high sensitivity protein, C-reactive protein, ECG, Echo-cardiogram, and cardiac enzymes, were employed to detect CVD development, secondary to *Mycobacterium Tuberculosis* infection. Association analyses were explored by Chi-Square and Logistic Regression models, keeping a confidence interval of 95%. A Probability (P-value) of 0.05 was considered as significant. According to findings of Chi-Square association test analysis, IVDU (P = 0.035, Chi-Square = 0.035), AKI (P = <0.001, Chi-Square = 18.524), anaemia (P = <0.001 and Chi-Square = 13.7) and CRP (P = <0.001, Chi-Square = 41.590) had a significant correlation with

development of CVD among TB patients. According to Binary Logistic Regression, significant correlations were found with IVDU (P = 0.017, O.R = 2.541), anaemia (P = 0.004, O.R = 0.067), and AKI (P = 0.004, O.R = 0.035). Among renal, liver, lipid, and blood profiles, low level of sodium (P = 0.033, O.R =2.708), high level of chloride (P = 0.056, O.R =6.027), elevated level of creatinine (P = 0.030, O.R =4.288), low level of albumin (P = <0.001, O.R =10.233), high level of globulin (P = 0.029, O.R =0.339), low level of HDL (P = 0.049, O.R = 2.263), low level of LDL (P = 0.019, O.R = 3.401), high RBC count (P = 0.008, O.R = 116.41), high red cell distribution width (P = 0.039, O.R = 94.536), low lymphocyte % (P = 0.012, O.R = 1.020), high monocytes % (P = 0.008, O.R = 1.157) were significantly correlated with CVD development among TB population. Various factors marked a higher CVD prevalence among males (10.54%) than females (8.98%) and heightened risks were associated with hypertension, DM, anaemia, and acute kidney injury. Clinical characteristics such as high C-reactive protein levels and severe chest X-ray findings were associated with CVD, emphasizing the role of inflammation. Drug-resistant TB cases were identified in 6.5% of patients, mainly resistant to isoniazid (1.7%), rifampicin (1.7%) and MDR (1.4%). Frequency of clinical outcomes included loss to follow-up (5.5%), patient cured (41.5%), patient died (15.2%), transferred out (14.9%), treatment completed (21.9%) and treatment failed (0.7%). In Phase II, 12.5% of deceased TB patients succumbed to CVD, with acute coronary syndrome being the leading cause (8.37%). Factors such as anaemia (p = 0.005) and drug resistance (p = 0.004) demonstrated a significant association with mortality due to CVD. In conclusion, this research highlights the critical relationship between TB and CVD, emphasizing the importance of identifying risk factors such as IVDU, anaemia, and AKI. The findings suggest a need for enhanced monitoring and management of cardiovascular health among TB patients. Targeted interventions could significantly improve patient outcomes and reduce mortality associated with cardiovascular complications. Additionally, addressing drug resistance is vital for effective TB management. Overall, the findings contribute to

understanding potential risk factors, and treatment outcomes, and pave the way for targeted interventions to enhance the holistic care of TB patients.

CHAPTER 1

INTRODUCTION

1.1 Overview and Historical Background of Tuberculosis

Tuberculosis (TB) remains a global health problem, causing 1.3 million deaths in 2020; this number of deaths increased to 1.4 million in 2021 despite international efforts. Difficulties in diagnosing and treating tuberculosis during the COVID-19 pandemic have led to a decline, reversing years of progress in the field [1].

According to the World Health Organization's 2022 scenario, an estimated 10.6 million people got infected with tuberculosis in 2021 with immunocompromised patients accounting for about 7% of the total. Epidemiological data for the year 2021 shows that men were infected at a higher rate than women [2].

In 2022, TB claimed the lives of 1.3 million individuals, with 167,000 of them also affected by HIV. TB ranks as the second most fatal infectious disease globally, following COVID-19 and surpassing HIV/AIDS [3]. During the same year, approximately 10.6 million individuals worldwide contracted tuberculosis, comprising 5.8 million men, 3.5 million women, and 1.3 million children [4]. TB is present in all countries at any age group, but mostly in productive age. The available treatment for TB is curable and preventable [5].

Mycobacterium tuberculosis is the causative agent of tuberculosis (TB), a respiratory disease transmitted by aerosolized droplets from infected individuals. Tuberculosis is a serious respiratory disease that is a serious public health problem. Effective control of the disease worldwide requires the development of effective vaccines, improved diagnostics, and new, short-term treatments [6], [7].

The *Mycobacterium* genus has a long history, dating back more than 150 million years ago [8]. Early studies suggested that all members of the *Mycobacterium tuberculosis* complex descended from a single common ancestor initiated by evolutionary events approximately 15,000 to 20,000 years ago [9].

With the invention of the stethoscope, Laennec elucidated the pathogenesis of tuberculosis and brought together information on whether the disease occurred in the lungs or elsewhere [10]. In 1882, Hermann Heinrich Robert Koch played an important role in changing the history of tuberculosis. He was the first to identify the bacillus that causes tuberculosis and named it *Mycobacterium tuberculosis*. Koch was awarded the Nobel Prize in Medicine or Physiology in 1905 for his significant contributions to bacteriology and elucidating the cause of tuberculosis. In 1890, Koch developed tuberculin, which was used for the first diagnosis of the disease [11].

In the 1920s, Assmann published his theory of "re-infection", which is still accepted by doctors today and showed that people could become infected again after treatment was completed. Many isolated hospitals and clinics were started for treatment to prevent future generations from the spread of tuberculosis [12].

1.2 Transmission of Disease

Mycobacterium tuberculosis is spread in the air by aerosolized droplet nuclei produced when patients with pulmonary or laryngeal tuberculosis cough sneeze, speak, and sing. These tiny bacteria, which carry one of three strains of M. tuberculosis, are small enough (1 to 5 μm) to remain in the air for long periods and can reach the alveoli when inhaled. Importantly, *Mycobacterium tuberculosis* is not transmitted from inanimate objects [13].

Many factors affect the likelihood that a person infected with M. tuberculosis will be exposed to *Mycobacterium tuberculosis*, including airborne pathogens, exposure, duration of exposure, and immune response. Members of the family, especially children and people in hospitals, nursing homes, and prisons are at greater risk of infection. People with weakened immune systems, such as HIV/AIDS patients or organ transplant recipients, are thought to be more likely to become infected with *Mycobacterium tuberculosis* than those who have normal immune function [14].

Some effective measures can be taken to reduce the spread of *Mycobacterium tuberculosis*. These include increasing room ventilation, aiming for 6 or more air changes per hour [14], using ultraviolet light, using a surgical face mask (e.g. N95 face mask), and treating patients with effective anti-tuberculosis therapy.

1.3 Pathophysiology of Tuberculosis

1.3.1 Causative Organism

Mycobacterium tuberculosis is the causative agent of Tuberculosis infection, a rod-shaped, non-spore-forming, aerobic, non-motile bacterium [15]. These mycobacteria are approximately 0.5 x 0.2 μm in size and are classified as acid-fast bacteria due to their unique cell wall structure. The cell wall contains large amounts of mycolic acid, a fatty acid that is covalently linked to the polysaccharide arabinogalactan by peptidoglycan bonds, forming a non-lipid barrier. This particular restriction is responsible for the immune system and subsequent defense mechanisms. *Mycobacterium tuberculosis* is an active aerobe that thrives in human tissues with the highest oxygen levels, such as the lungs, kidney parenchyma, and growing bones [16]. Another important feature is that MTB grows slowly. The presence of lipoarabinomannan (lipoglycan or glycolipid, a major virulence factor, and structural antigen) on the surface of the *Mycobacterium* body facilitates its survival

after phagocytosis by human macrophages. The Primary function of Lipoarabinomannan is to inactivate macrophages and scavenge oxidative radicals. The inactivation of macrophages allows for the dissemination of mycobacteria to other parts of the body [13].

1.3.2 Pathogenesis

Mycobacterium tuberculosis is spread by droplets released by tuberculosis patients when they cough, sneeze, talk, and sing. These droplets can remain airborne when inhaled. The upper respiratory tract contains mucus secretions, the primary defense mechanism that traps most bacilli [17]. Cilia on the surface of mucus-producing goblet cells then eliminate trapped bacilli along with the mucus, an important line of defense against infection in humans [18]. However, sometimes bacilli pass through the ciliary barrier and reach the alveoli, and are phagocytosed by alveolar macrophages. After phagocytosis by macrophages, an event begins that results in the destruction of bacteria; the development of latent TB, or the development of active TB [17]. These series of events are determined by the quality of the host's defense and the type of attacking *Mycobacterium* [19].

1.3.3 Drug Resistance to Mycobacterium Tuberculosis

Drug resistance arises when bacteria, viruses, fungi, and parasites change over time, reducing their susceptibility to drugs. This resistance complicates the treatment of diseases, heightening the risk of infection, severe illness, and mortality. Infections become challenging or uncontrollable as antibiotics and other medications lose their effectiveness against resistant strains [20].

The development of drug resistance in tuberculosis is not a recent phenomenon. It began shortly after the introduction of streptomycin for tuberculosis treatment in 1944, leading to the emergence of streptomycin-resistant strains of *M.*

tuberculosis. Genetic resistance to anti-TB drugs arises from chromosomal mutations at a relatively low frequency. Despite genetic resistance to antibiotics being less common, the rise in drug resistance is becoming a major concern. While such mutations are rare, the escalation or intensification of resistance is worrisome and is exacerbated by changes resulting from human error [21]. Human errors encompass scenarios like monotherapy, improper prescription practices by healthcare providers, and notably, patients' non-compliance with treatment regimens. Presently, drug resistance is categorized by distinguishing between drug resistance in new cases and those previously treated for TB (old cases), after treatment duration of at least one month [22].

1.3.4 Multi Drug-Resistant Tuberculosis (MDR-TB)

Multidrug-resistant tuberculosis (MDR-TB) is characterized by resistance to at least isoniazid and rifampicin. MDR-TB often occurs during TB treatment. It is commonly caused by inadequate or incomplete treatment or interruptions in the treatment regimen. Individuals with a history of defaulting on TB treatment (Defaulters) are particularly susceptible to developing MDR-TB [23].

1.3.5 Extensively Drug-Resistant TB (XDR-TB)

This refers to MDR-TB, characterized by resistance not only to any fluoroquinolone but also to at least one of the three injectable drugs commonly used in anti-TB therapy, namely Capreomycin, Kanamycin, and Amikacin [24].

The rise of multidrug-resistant tuberculosis (MDR-TB), extensively drug-resistant TB (XDR-TB), and the even more severe form, completely drug-resistant tuberculosis (XXDR-TB), has exacerbated the challenges associated with the disease. XXDR-TB, first identified in 2006, denotes a condition where patients not only exhibit resistance to rifampicin and isoniazid but also to fluoroquinolones and at

least one second-line injectable TB drug. The emergence of completely drug-resistant tuberculosis (XXDR-TB) signifies a troubling development where TB strains are impervious to both primary and secondary lines of treatment, rendering them nearly untreatable. This progression presents a notable obstacle in handling TB cases, as resistance to numerous drugs complicates treatment plans and raises the hurdle to achieving positive results. It highlights the pressing necessity for novel strategies to counter the dissemination of these extremely resistant strains and bolster global TB control endeavors [25].

1.4 Clinical Manifestation of Tuberculosis

Tuberculosis (TB) may be regarded in two categories: active disease or latent infection.

1.4.1 Active TB

Active tuberculosis (TB) is a disease in which tuberculosis bacteria spread very quickly and enter many organs in the body. Symptoms of tuberculosis include cough, phlegm, chest pain, fatigue, weight loss, fever, chills, and night sweats. The most common form of active TB is a lung disease, but it may invade other organs also, so-called "extra-pulmonary TB" [26].

1.4.2 Latent TB

This is also called inactive tuberculosis. Many people with tuberculosis have no obvious symptoms and a chest X-ray will look normal. The only sign of exposure may be antibodies to the tuberculin skin test (TST) or interferon-gamma release test (IGRA). However, the risk of latent infection may lead to active infection. Other medical conditions, such as HIV or medications that weaken the immune system, may

increase the risk of developing active infection. As a preventive measure, prophylactic treatment or strategies to treat latent tuberculosis are needed [26].

1.4.3 Pulmonary Tuberculosis

TB affecting the Lungs of the Human Body is known as Pulmonary TB. The development of pulmonary tuberculosis is different depending on the immune system of each patient. Some stages of developing pulmonary tuberculosis include latent stage, primary TB, and extra-pulmonary TB (EPTB). The highest risk for developing active disease occurs in the first 2 years of infection [14] .

Physical or emotional stress can disrupt the balance between the immune system and infection, leading to disease. Some diseases, such as diabetes, silicosis, and diseases requiring immunosuppressive therapy (HIV/AIDS, corticosteroid use, and antiretroviral drugs), can reduce the host's ability to respond to pathogens and cause tuberculosis [27], [28]. People with HIV, especially those with low T cell counts, develop tuberculosis rapidly, with up to 50% developing tuberculosis within the first two years after infection. Other important risk factors for developing tuberculosis include gastrectomy, gastric bypass surgery, injection drug use, and high risk of infection in children less than 2 years of age [28], [29].

1.4.4 Extra Pulmonary Tuberculosis

Extra-pulmonary tuberculosis (EPTB) refers to tuberculosis that affects organs outside the lungs. EPTB covers many areas, including the pleura (tuberculous pleurisy), internal organs, stomach, intestines, genitals, skin, joints and bones, and brain [30].

Among these, central nervous system involvement, leading to meningitis, represents a severe and potentially fatal manifestation. Timely diagnosis is crucial for

individuals experiencing frequent headaches and mental status changes after potential exposure to the TB organism. Another life-threatening form is Miliary TB, characterized by *Mycobacterium tuberculosis* infecting the bloodstream. Lymphatic TB is the most common. Different types of EPTB present varied clinical signs and symptoms. For instance, Miliary TB exhibits symptoms like fevers, chills, and sweats, diagnosed through chest X-rays. Gastrointestinal TB may manifest with weight loss, fever, and abdominal pain, while spinal symptoms include fever, lower extremity weakness or paraplegia, and back pain. Radiographic evidence (X-ray, CT, or MRI) is useful in the diagnosis of spinal cord injury [31].

1.4.5 Disseminated Tuberculosis

Disseminated tuberculosis is a condition caused by mycobacterial infection where the bacteria travel from the lungs to various parts of the body via the bloodstream or lymphatic system. This form of TB can manifest relatively quickly after the initial infection. Its occurrence is often intertwined with the functioning of the immune system, frequently associated with conditions like AIDS [32].

1.4.6 Miliary Tuberculosis

Miliary tuberculosis (TB) belongs to the category of extra-pulmonary tuberculosis (EPTB) and disseminated tuberculosis. It involves the spread of *Mycobacterium tuberculosis* through hematogenous transmission, usually through blood. Classic miliary tuberculosis is confirmed by the presence of rice-like seeds of *Mycobacterium tuberculosis* in the lungs seen on chest X-ray. These TB infections can occur in a single organ (very few, <5%), in multiple organs, or throughout the body (>90%), including the brain. This disease is characterized by the presence of *Mycobacterium tuberculosis*, which can be difficult to diagnose and can be fatal if not treated quickly. Risk factors for tuberculosis include cancer, organ transplantation,

HIV infection, malnutrition, diabetes, silicosis, and immunocompromised conditions such as end-stage renal disease [33].

1.5 Diagnosis of Tuberculosis

Following are the laboratory tests and diagnostic tools and methods, which are performed for screening and confirmation of active Tuberculosis.

1.5.1 Tuberculin Skin Test (TST)

Tuberculin skin test (TST) is a widely used test to identify people with tuberculosis and people with latent tuberculosis. Among the various tuberculin skin tests, the Mantoux test is the most commonly used. In this procedure, graduated doses of tuberculin (purified protein derivative (PPD), which is made from an extract of inactivated cultures of *Mycobacterium tuberculosis* and is a combination of proteins that are used in the diagnosis of tuberculosis**)**, are injected intra-dermally into the forearm using a tuberculin syringe. The test works by saying that if the body encounters the tuberculosis virus; it will recognize this protein and the body will become immune. These reactions appear as bumps, bumps, or blisters at the injection site, indicating infection. Unfortunately, skin tests have poor sensitivity and specificity [34]. Susceptibility is particularly low and sometimes results in adverse outcomes if the person received the BCG vaccine early in life or if the immune system is weakened by other conditions or treatment [35]. For the Mantoux test, 0.1 ml of 5 TU PPD was injected intra-dermally into the forehead. Positive reactions are evaluated 48-72 hours after injection and appear as erythema and induration over 10 mm [30].

1.5.2 Sputum Smear Microscopy (SSM) / Acid Fast Bacilli Direct Smear

Sputum Smear Microscopy (SSM) has historically been the first diagnostic test for tuberculosis (PTB). SSM follows the Ziehl-Neelsen sputum direct smear microscopy diagnostic method [36]. Special properties of the *Mycobacterium tuberculosis* bacterial wall allow it to accumulate and persist initial staining with Carbol fuchsin and methylene blue even after exposure. During Ziehl-Neelsen staining using carbolic fuchsin and methylene blue, acid-fast bacteria appear scarlet or scarlet red when viewed under a microscope [37]. Although widely used, microscopy has limitations because it is not specific for the detection of acid-fast bacilli (AFB) in sputum and can only identify AFB at 60–70% of culture quality [38], [39]. Unlike previous pulmonary tuberculosis (PTB) tests, recent studies have shown that, in contrast to old practices for detection of PTB, examination of two sputum samples should be used to confirm TB [40].

1.5.3 Culture

Widespread use is made of cell culture techniques to identify *Mycobacterium tuberculosis* in pulmonary and extra-pulmonary cases. In addition to detecting bacteria, this method assesses the efficacy of specific antibiotics against bacterial infections, thereby offering valuable information regarding their performance. However, this may not always be possible, particularly in the case of extra-pulmonary tuberculosis, which could result in a reduced degree of evaluation control and the inability to obtain the bacteria in the sample. A drawback of this approach is the substantial time investment needed to achieve desired outcomes, estimated to be around six to eight weeks [39]. Nonetheless, there are also quicker and simpler methods of testing, including polymerase chain reaction (PCR) and Bactec. Nevertheless, these techniques are costly and might not be accessible in all laboratories [40] .

1.5.4 Chest X-Ray

Chest X-ray is an important diagnostic tool for doctors and helps detect lung abnormalities in people showing symptoms of tuberculosis. However, a chest X-ray alone cannot detect TB, especially if the infection is not in the lungs or the smear test is negative [41]. Additionally, the chest X-ray exhibits limited efficacy in detecting infection during the early stages of the disease. In these initial phases, lung damage may not be pronounced enough to be identifiable through chest X-ray, potentially leading to a failure in identifying active TB cases, particularly among elderly or HIV/AIDS patients [13]. Moreover, scarring in the lungs persists even after a complete cure from previous TB, posing challenges in distinguishing between past cured TB and current active disease in chest x-rays.

1.5.5 GeneXpert

The World Health Organization consistently advocates for the utilization of the Xpert MTB/RIF, a diagnostic platform known as GeneXpert, as the primary test for diagnosing adults and children suspected of TB. This platform can simultaneously identify the presence of *Mycobacterium tuberculosis* and assess Rifampicin resistance, which serves as an indicator for MDR strains. The Xpert MTB/RIF demonstrates high sensitivity and specificity, even in smear-negative samples, and its ability to deliver results in a short time frame enhances its significance as a valuable tool in the battle against TB [42].

1.5.6 Line Probe Assay (LPA)

Line probe assays (LPAs) are molecular diagnostic tools capable of identifying M. tuberculosis and drug resistance. LPAs require a longer processing time compared to the Xpert MTB/RIF assay. They can detect isoniazid (INH) and rifampicin (RIF) resistance. This distinguishes them from GeneXpert, which only identifies

rifampicin resistance. LPA identifies RIF and INH resistance by identifying mutations in the rpoB, katG, and inhA genes, making it useful in field or laboratory settings [42].

1.5.7 Extra-Pulmonary Tuberculosis

The diagnosis of extra-pulmonary tuberculosis (EPTB) is often difficult. Challenges such as negative acid-fast bacillus smears and inability to culture the bacilli cause a poor diagnosis of EPTB [43]. Recognizing and understanding the findings in EPTB can reduce the difficulty of diagnosis [44]. Compared to pulmonary TB, diagnosis of EPTB is often difficult due to the lower sensitivity of traditional tests such as AFB smear, Mantoux, culture, and chest X-ray. The sensitivity of these applications generally varies between 25% and 39% [45].

1.6 Anti-Tuberculosis Therapy

Chemoprophylaxis and Bacillus Calmette-Guerin (BCG) immunization appear to be insufficient control methods for tuberculosis (TB); hence, anti-tubercular (anti-TB) medications were developed. Regrettably, throughout the last decade, there has been a dearth of novel anti-tubercular medications that correspond to treatment objectives namely, achieving relapse-free treatment, preventing fatalities, halting transmission, and circumventing the need for immunizations. Preventing the development of multi-drug-resistant tuberculosis requires that TB should not be treated with a single drug treatment and drugs having unsuccessful outcomes should be stopped and removed from the treatment regimen [46], [47].

Effective treatment regimens are structured into two phases: an initial or induction or intensive phase, where a combination of drugs is administered to eradicate the rapidly multiplying M. tuberculosis population and prevent drug resistance emergence. Typically, four drugs are given daily during this phase. This is

followed by the continuation phase, where sterilizing drugs are employed to eliminate the intermittently dividing population. In this phase, fewer drugs are administered intermittently [48].

Anti-tuberculosis therapy (ATT) drugs can be divided into first-line drugs, including isoniazid (INH), rifampicin (RIP), pyrazinamide (PZA), ethambutol and streptomycin (SM), and second-line drugs, including Para-amino salicylic acid (PAS), Kanamycin, Cycloserine (CS), Ethionamide (ETA), Amikacin, Capreomycin, Thioacetone and Fluoroquinolones. Moreover, antibiotics can be divided according to their specificity into specific tuberculosis drugs and general drugs (RIF, SM, kanamycin, amikacin, capreomycin, and fluoroquinolones). Resistance mechanisms to tuberculosis-specific drugs are specific to M. tuberculosis, whereas resistance mechanisms to broad-spectrum drugs are similar to those observed in other bacterial species such as E. coli [21], [49].

The World Health Organization (WHO) advises a standard anti-tuberculosis (ATT) regimen, consisting of a six-month course that includes Rifampicin and Isoniazid. Additionally, Pyrazinamide, along with Ethambutol or Streptomycin is recommended to use it during the first two months of treatment. Daily pyridoxine (vitamin B6) supplementation is often used to prevent isoniazid-induced neuropathy [50].

Streptomycin (SM) is an aminoglycoside antibiotic that disrupts bacterial protein synthesis. Typically administered intramuscularly, the daily dose is 15mg/kg of body weight [51]. This drug has drawbacks such as ototoxicity and the rapid emergence of resistance. Despite these limitations, Streptomycin remains a primary drug in the treatment of tuberculosis. It is commonly employed in combination with Isoniazid (INH) and Para-amino salicylic acid [52].

Rifampicin (RIF) functions primarily by impeding the transcription of RNA through inhibition of DNA-dependent RNA polymerase. The standard oral dosage for this drug is 10mg/kg per day. While Rifampicin can induce hepatotoxicity, its occurrence is lower compared to Isoniazid (INH). Additionally, intermittent hypersensitivity reactions, thrombocytopenia, renal failure, and flu-like symptoms have been documented as potential side effects [51].

Isoniazid (INH) works by inhibiting the synthesis of mycolic acids, an important component of the mycobacterial cell wall. Typically, it is administered orally at a dosage of 10mg/kg for adults and 5mg/kg for children [51]. INH treatment may result in an asymptomatic rise in serum transaminases beyond the levels observed in hepatitis, prompting the decision to halt the therapy [53].

Pyrazinamidase, an enzyme found in MTB, transforms PZA into Pyrazinoic acid, its active form, which accumulates within the bacilli. This accumulated Pyrazinoic acid disrupts the membrane potential of MTB, essential for its survival in the acidic environment of the infected site. PZA exhibits its highest activity in acidic conditions, particularly within macrophages. The recommended daily oral dosage of PZA is 15-30mg/kg. However, users may experience hypersensitivity reactions and gastrointestinal discomfort as potential side effects of this drug [51].

The potential implementation of secondary Tuberculostatic agents is considered when resistance develops to primary tuberculosis agents. Shockingly, tuberculous bacilli do not develop cross-resistance to Ethionamide, even though both Ethionamide and INH are generated from "Isonicotinic acid". Better tolerated than Ethionamide, Prothionamide is equivalent in potency [50]. With a reduced incidence of adverse effects, the quinolone medication class exhibits remarkable therapeutic effectiveness against *Mycobacterium TB*. Significantly, the effectiveness of novel quinolones, like Moxifloxacin, is augmented.[54], [55].

1.7 Vaccination

In 1888, Robert Koch observed that guinea pigs injected with live bacilli developed non-healing skin ulcers, with the disease spreading widely and proving fatal in some cases. However, some animals survived the infection with healed ulcers and recovery. Upon a second injection of live *M. tuberculosis* into these survivors, an intense local reaction occurred, followed by an abscess that drained and eventually healed. All these animals survived. Koch's discovery revealed that the initial infection had provided cellular-level immunity against a second infection [56]. This immune response forms the basis for BCG vaccination and diagnostic tests like Mantoux. Since 1922, BCG (Bacillus Calmette-Guerin) has played a crucial role in immunization against TB.

1.8 Adverse Drug Reactions (ADRs) due to Anti-Tubercular Drugs

Adverse reactions to the primary anti-tubercular drugs are observed in both HIV-infected and uninfected patients, but they are more prevalent in those with HIV infection. Significant issues include skin reactions and Steven-Johnsons syndrome. Research indicated that the incidence of thioacetone toxicity is 18 times higher in HIV-infected individuals compared to HIV-uninfected individuals [57].

Significant interactions can occur between Rifampicin and antiretroviral drugs; these include protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Rifampicin induces cytochrome CYP450 enzymes in the liver and affects the metabolism of other drugs. In such situations, it is recommended to consider stopping antiretroviral treatment to use Rifampicin for TB treatment or substituting Rifabutin, a less potent alternative. Additionally, continuing antiretroviral drugs can be part of the management strategy [58].

Isoniazid (INH) can result in toxic neuritis and toxic hepatitis. Toxic hepatitis is observed in 1 to 2% of cases, typically occurring after two months of treatment. Rifampicin (RIF) may induce gastrointestinal intolerance and exacerbate INH-related liver toxicity. Pyrazinamide (PZA) is also associated with hepatotoxicity. Ethionamide (ETH) has the potential to cause optic neuritis, particularly at higher doses, while the use of Streptomycin (SM) is linked to otovestibular toxicity [59].

1.9 Effect of Tuberculosis Infection on Cardiovascular Disease

The worldwide impact of tuberculosis and cardiovascular disease (CVD) is significant, with the potential for these conditions to coincide and mutually affect each other's risk. Factors contributing to CVD risk in tuberculosis could involve direct impacts of *Mycobacterium tuberculosis* on the heart muscle and coronary arteries, heightened immune activation leading to increased cytokine production, and the potential cross-reactivity of antibodies targeting mycobacterial elements against cardiovascular tissues [60], [61].

Fabricant, Litrenta, and Minick provided the first evidence of linking some infections to cardiovascular disease (CVD) in 1978. Their research showed that chickens infected with an avian herpesvirus (Marek's disease), caused the development of atherosclerotic plaques in arteries [62], [63].

In 1992, Shor et al. in South Africa found Chlamydia pneumonia in the fatty streaks of coronary artery plaques [64]. Subsequent experiments in animal models supported a pathogenic role of C. pneumonia in atheroma formation [65], [66], [67]. Besides this, Helicobacter pylori inhabit atherosclerotic plaques and their elimination from the body is associated with an increase in coronary artery lumen size and a decrease in cardiovascular events [68], [69].

Influenza Virus is associated with acute myocardial infarction (AMI) and rapid development of early plaques [70], [71], [72]. Human immunodeficiency virus (HIV) is also associated with CVD, with a 1.5- to 2-fold increased risk of cardiovascular disease after adjusting for CVD events [73]. Recent studies have highlighted the association between latent tuberculosis infection (LTBI) and chronic disease and suggested an association between LTBI and CVD [74], [75].

A recent investigation revealed that those who have either pulmonary or extra-pulmonary tuberculosis are at a higher risk of experiencing acute myocardial infarction (AMI) and unstable angina in the future. Remarkably, the risk of cardiovascular disease (CVD) remained high even several years after the initial diagnosis of *Mycobacterium Tuberculosis.* This indicates that tuberculosis sickness may have both short-term and long-term consequences for CVD. Alternatively, the development of tuberculosis disease may simply indicate faulty immune responses in susceptible hosts, as these are the same abnormal responses that make patients more likely to acquire tuberculosis and also increase the risk of cardiovascular disease (CVD) [76].

The concept that tuberculosis is associated with cardiovascular disease (CVD) is supported by both individual case studies demonstrating tuberculosis-induced cardiovascular death and population-based research indicating an elevated risk of cardiovascular events. The occurrence of tuberculous granuloma development in the coronary arteries has been documented as an uncommon factor leading to myocardial infarction in young patients [75],[76].

Dummer et al. conducted research that supports the notion that infection may increase the likelihood of cardiovascular disease (CVD) at a young age. They discovered an association between cytomegalovirus (CMV) infection and the development of coronary atherosclerosis in the hearts of young patients who had

undergone heart transplantation. Tuberculosis may potentially be a contributing factor to early cardiovascular mortality in regions with a high prevalence of tuberculosis [77].

A large population-based retrospective cohort study conducted in Taiwan goes beyond these individual clinical observations to look at baseline CVD risk elevation in patients who had tuberculosis disease. The researchers looked at 10,168 patients with a history of tuberculosis disease and 40,672 control patients without a history of tuberculosis disease. Selected TB patients aged ⩾20 years with newly diagnosed TB from 1997 to 2010 (14 years database) who had received medical care at least three times, including outpatient visits and/or hospitalizations. After adjusting for important comorbidities, the tuberculosis group had a 40% increased risk of unstable angina and AMI compared to the non-tuberculosis group. This heightened risk remained consistent throughout the whole duration of the study, which spanned up to 14 years [78].

The possible impacts of tuberculosis extend beyond coronary heart disease (CHD) and also include other vascular disorders mediated by atherosclerosis, such as stroke. A study conducted in Taiwan tracked patients who had previously been diagnosed with non-meningeal TB disease but had no prior history of stroke. The study also included a group of control patients for comparison. After a 3-year follow-up, the researchers discovered a 50% higher likelihood of ischemic stroke in the tuberculosis group. This study also demonstrated an elevated susceptibility to coronary heart disease (CHD) in individuals with tuberculosis [79].

The recent research has specifically examined systemic disease markers in Indian individuals with tuberculosis (TB), latent TB infection (LTBI), individuals who have previously had TB, and healthy individuals serving as controls. The study determined that LTBI patients exhibit higher levels of monocyte/macrophage activation and inflammatory mediators, including CD14, CXCL3, CCL2, and CCL8, as

compared to healthy controls. This indicates a transition from a dominant involvement of neutrophils to a dominant involvement of monocytes/macrophages in the immune response of individuals infected with latent tuberculosis. Evidence indicates that latent tuberculosis infection (LTBI) can induce long-lasting and continuous inflammation, even in the absence of active tuberculosis [79].

Interestingly, similar signs of monocyte/macrophage activation have been observed in individuals previously treated for TB and this may explain the AMI and immune system dysfunction that was observed years after TB relapse in the previously discussed Taiwanese cohort study [80]. Although not all studies examining LTBI and inflammation markers show positive associations, it is important to conduct further research to elucidate the role of LTBI in cardiovascular disease which must have an international impact [81].

1.10 Mechanism of Development of Cardiovascular Disease in Tuberculosis

Two primary theories elucidate the mechanism, linking tuberculosis infection and cardiovascular disease:

1. Autoimmune disorder
2. Elevated inflammation causing the development and rupture of coronary artery plaques.

It is acknowledged that pathogens infiltrate developing atherosclerotic plaques, inducing direct damage to the vasculature [82]. Atherosclerosis is commonly recognized as a persistent inflammatory condition triggered by diverse vascular and extravascular factors [83]. Numerous epidemiological studies have confirmed the connection between various 'inflammatory' factors and coronary artery disease (CAD). As a result, several systemic inflammation markers have been scrutinized and correlated to identify individuals at risk of developing cardiovascular disease (CVD).

Tuberculosis triggers an immunological response in the lung through the activation of the body's innate immune system. This response triggers a significant increase in phagocytic cells, which also serve as a host for *Mycobacterium Tuberculosis* [83],[84]. During the response, the immune system persistently infiltrates the lungs, providing more cells to the bacteria and ultimately creating granulomas. The creation of granulomas is contingent upon the presence of inflammatory chemical mediators that attract more immune cells to gather at the site of infection [85]. Following the first immune reaction within the body, the adaptive response subsequently generates immunity. Upon activation of the adaptive response, CD4+ T cells activate and release several cytokines to regulate the immune system's response to M. tuberculosis. TNF-α and IFN-γ are crucial in the inflammatory response linked to cardiovascular disease (CVD) and have a significant impact [86].

For infectious diseases to cause serious illness through cardiovascular disease (CVD), the infection must stimulate the immune system, similar to the process seen in atheroma formation. Plaque in the coronary arteries begins with a mild inflammatory process that manifests as the accumulation of fat in sections of the artery [85]. Endothelial cells are activated in response to the secretion of phospholipids and other stimuli. This activation upregulates the expression of surface adhesion molecules, including intercellular adhesion molecule-1 (ICAM-1), and enhances the expression of surface adhesion molecules on monocytes, lymphocytes, and other cell types. It facilitates the attachment of immune cells, such as circulating monocytes, lymphocytes, and other types. [86].

Host receptors, including Toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), and C-type lectins, recognize *Mycobacterium tuberculosis* and its products [87]. The interaction between M. tuberculosis ligands and TLRs leads to the activation of inflammatory mediators and

the production of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-12, chemokines (CXC) and nitric oxide (NO)[88] .

Accumulation of cells in the lungs will lead to granuloma formation, thus promoting granuloma formation, which relies on inflammatory chemical mediators to bring other immune cells to the site of infection [89]. Once the immune system is initiated in the body, the state of immunological equilibrium is reached through an adaptive response. Once an adaptive response is established, activated CD4 + T cells secrete a series of cytokines to modulate the immune system against *M. tuberculosis* [90].

In tuberculosis patients, IL-1, IL-2, and IL-6 levels are increased and total T cells are decreased. Stimulation of Th1 cells with mycobacterial antigens immediately produces interferon-γ (IFN-γ), IL-17, and IL-22. Th1 inflammation positively reflects the inflammatory properties of plaque formation. Th1 inflammation is very similar to the inflammatory profile of plaque formation [74]. Therefore, tuberculosis may play an important role in the development of CVD by promoting atherogenesis and causing atherosclerosis by exploiting the immune system.

According to Autoimmune theory, mycobacterial HSP65 shows homology to human HSP60 [91]. Antibodies made against all mycobacterial heat shock protein (HSP65) cross-react with human heat shock protein HSP60 [92]. When antibodies are targeted to specific epitopes of mycobacterial heat shock protein (HSP65), a cross-reaction occurs with human heat shock protein (HSP60). Injection of mycobacterial heat shock protein HSP65 induced arteriosclerosis in rabbits having normal and increased cholesterol levels [84].

A significant association between anti-heat shock protein antibodies (Mycobacterial heat shock protein-HSP65) and carotid artery atherosclerosis has been demonstrated in humans [84], [93]. These findings suggest that lung disease

may contribute to CVD pathogenesis through anti-HSP65 antibody-mediated molecular mimicry and autoimmunity.

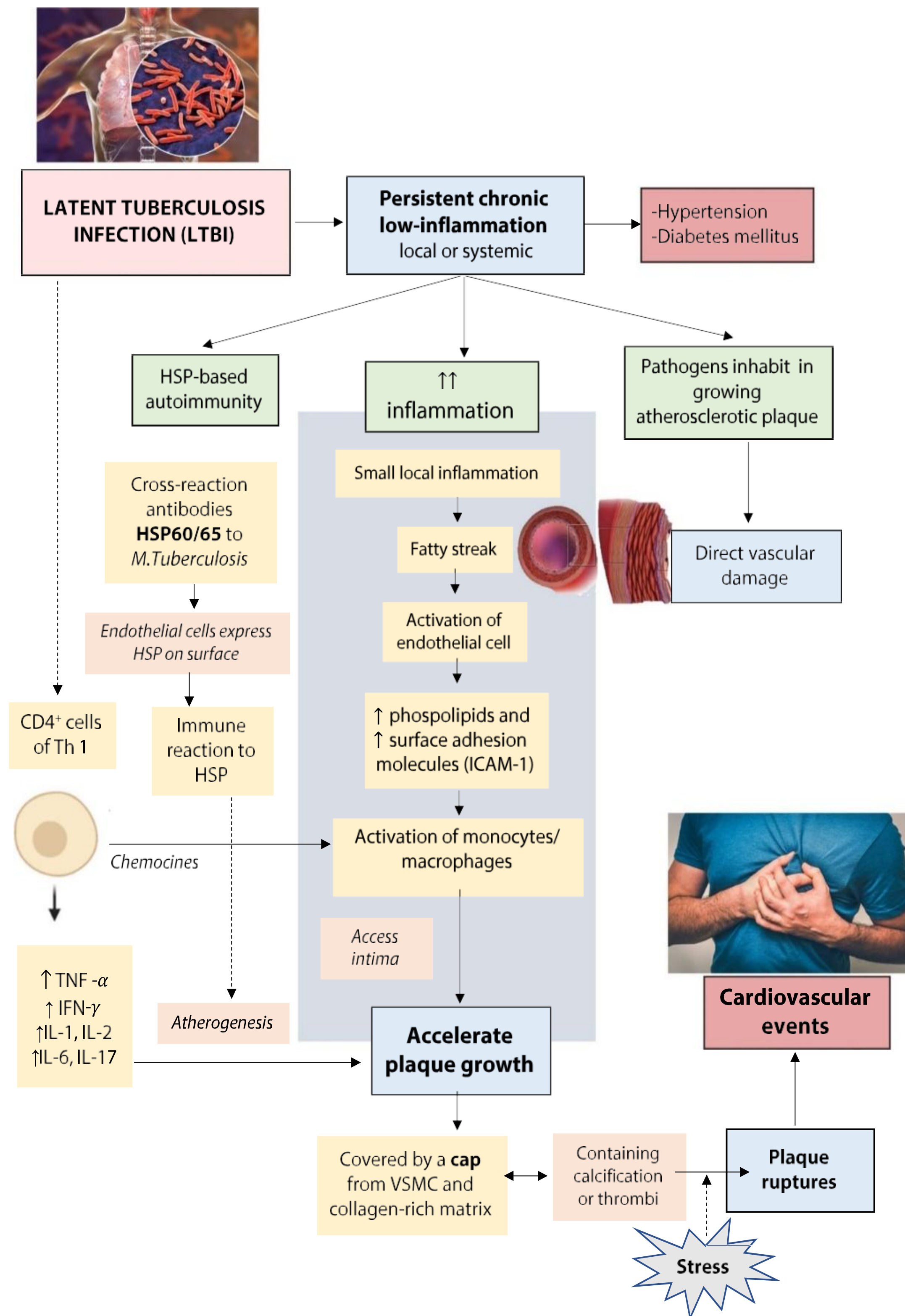

Figure 1.1 Mechanism of the association of LTBI and other factors with the occurrence of cardiovascular events [94]

1.11 Role of Tuberculosis Infection in Atherosclerosis (Inflammatory Process)

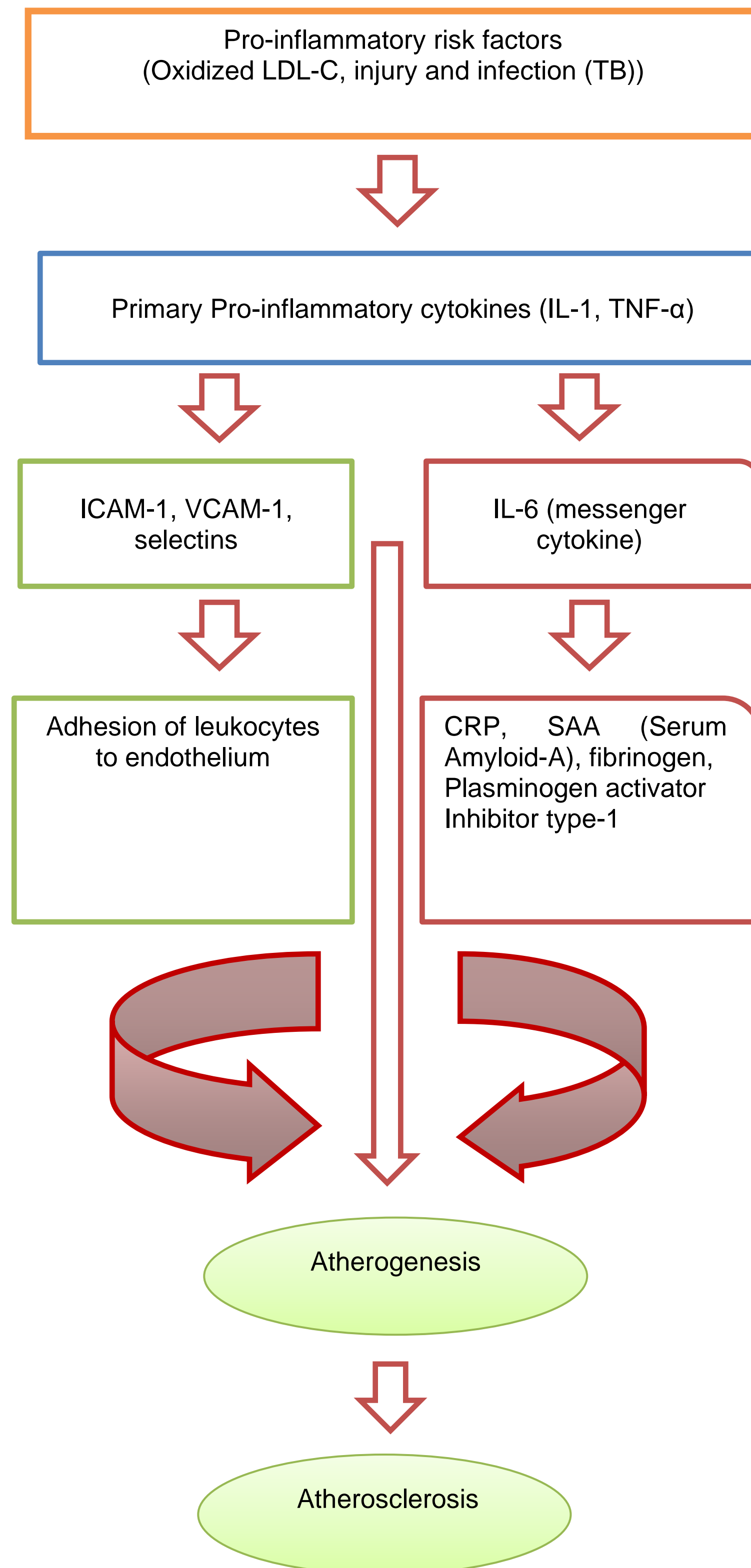

Figure 1.2 Role of Tuberculosis Infection in Atherosclerosis (Inflammatory Process)

1.12 Problem Statement and Study Rationale

Mounting evidence shows that tuberculosis (TB) can increase the risk of non-communicable diseases (NCDs) by affecting the body's metabolism [76], [95], [96]. In particular, most people with tuberculosis are living in low and middle-income countries, where non-communicable diseases such as type 2 diabetes, acute myocardial infarction (AMI), and stroke pose threats to public health [97] .

A sub-category of cardiovascular diseases represents a group of symptoms attributed to sudden reduced blood flow in the coronary arteries. This category includes life-threatening conditions which include unstable angina and myocardial infarction. Despite advances in treatment, these diseases still carry serious morbidity and mortality risks. Additionally, complications of myocardial infarction can lead to heart failure, arrhythmias, and even stroke [98].

There are clinical studies in the literature showing that, in addition to traditional or normal conventional risk factors such as hypertension, diabetes, dyslipidemia, and obesity; *Mycobacterium tuberculosis* (MTB) also plays a role in promoting atherosclerosis via its pronounced inflammatory effect, thus indirectly contributing to the development and progression of cardiovascular disease [82], [99], [100], [101]. Considering the risk of tuberculosis, research studies have questioned the potential impact of tuberculosis on cardiovascular diseases.

The impact of tuberculosis is not only limited to coronary heart disease (CHD) but also includes other vascular diseases mediated by atherosclerosis, including stroke. One study examined tuberculosis patients to assess the risk of ischemic stroke over a 3-year follow-up period. Research showed that people with tuberculosis have a 50% higher risk of ischemic stroke and heart disease [76] .

The relationship between tuberculosis and cardiovascular disease is increasingly recognized, with research indicating that TB can elevate the risk of CVD