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List of Abbreviations

AFB: Acid-Fast Bacilli.

ALP: Alkaline Phosphatase.

ALT: Alanine Aminotransferase (GPT).

ALT1: Alanine Aminotransferase, cytosolic isoenzyme.

ALT2: Alanine Aminotransferase, mitochondrial isoenzyme.

AMI: Acute Myocardial Infarction.

ANOVA: Analysis of Variance.

AST: Aspartate Aminotransferase (GOT).

AT-DILI: Anti-Tuberculosis Drug-Induced Liver Injury.

ATP: Adenosine Triphosphate.

BCG: Bacille Calmette-Guérin.

BPaLM: Bedaquiline, Pretomanid, Linezolid, Moxifloxacin (tuberculosis treatment regimen).

c-AST: Cytoplasmic Aspartate Aminotransferase.

CFP-10: Culture Filtrate Protein 10 (*Mycobacterium tuberculosis antigen*).

CI: Confidence Interval.

CNS: Central Nervous System.

COVID-19: Coronavirus Disease 2019.

CRP: C-Reactive Protein.

CT: Computed Tomography.

DNA: Deoxyribonucleic Acid.

DOTS: Directly Observed Treatment, Short-course.

DST: Drug Susceptibility Testing.

EPTB: Extrapulmonary Tuberculosis.

ESAT-6: Early Secreted Antigenic Target 6 kDa (*Mycobacterium tuberculosis antigen*).

FDA: Food and Drug Administration.

GGT: Gamma-Glutamyl Transferase.

GOT: Glutamate-Oxaloacetate Transaminase (AST old name).

GPT: Glutamate-Pyruvate Transaminase (ALT old name).

HBV: Hepatitis B Virus.

HCV: Hepatitis C Virus.

HIV: Human Immunodeficiency Virus.

ICT: Immunochromatographic Test.

IFN: Interferon.

INH: Isoniazid.

INSP: Institut National de Sante Publique (Algeria).

IU/L: International Units per Liter.

kDa: Kilodalton.

LPA: Line Probe Assay.

LTBI: Latent Tuberculosis Infection.

m-AST: Mitochondrial Aspartate Aminotransferase.

MPT-64: *Mycobacterium tuberculosis* Protein 64 (antigen used in rapid diagnostic tests).

MDR: Multidrug-Resistant.

MDR-TB: Multidrug-Resistant Tuberculosis.

MTBC: *Mycobacterium tuberculosis Complex.*

M. tuberculosis: *Mycobacterium tuberculosis.*

mg/L: Milligrams per Liter.

NAD^+: Nicotinamide Adenine Dinucleotide (oxidized form).

NADH: Nicotinamide Adenine Dinucleotide (reduced form).

NAFLD: Non-Alcoholic Fatty Liver Disease.

NAT2: N-Acetyltransferase 2.

ND1 / ND5: Mitochondrial genes encoding subunits of Complex I (NADH dehydrogenase) in the respiratory chain.

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs.

NTM: Non-Tuberculous Mycobacteria.

p: p-value (statistical significance).

PCR: Polymerase Chain Reaction.

PLP: Pyridoxal 5'-Phosphate.

PPAR-α: Peroxisome Proliferator-Activated Receptor alpha.

PPD: Purified Protein Derivative (tuberculin).

r: Correlation coefficient.

RIF: Rifampicin.

RNA: Ribonucleic Acid.

RR: Rifampicin-Resistant.

RR-TB: Rifampicin-Resistant Tuberculosis.

TB: Tuberculosis.

TB-LAMP: Tuberculosis Loop-Mediated Isothermal Amplification.

TCA cycle: Tricarboxylic Acid Cycle (Krebs cycle).

TDR-TB: Totally Drug-Resistant Tuberculosis.

TNF: Tumor Necrosis Factor.

TST: Tuberculin Skin Test.

U/L: Units per Liter.

UV: Ultraviolet.

WHO: World Health Organization.

XDR-TB: Extensively Drug-Resistant Tuberculosis.

ULN: Upper Limit of Normal.

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Introduction

Introduction

Tuberculosis remains, one of the most concerning infectious diseases on a global scale, despite the availability of effective diagnostic and therapeutic tools for several decades. Caused primarily by *Mycobacterium tuberculosis*, a bacillus identified by Robert Koch in 1882 **(Daniel, 2006; Prabhu & Singh, 2019),** this disease predominantly affects the lungs, but can also affect various organs, giving rise to diverse extrapulmonary forms **(Ramírez-Lapausa et al., 2015; WHO, 2025).** According to recent data from the World Health Organization, several million new cases of tuberculosis are recorded each year, and this infection remains among the leading causes of mortality due to a single infectious agent **(WHO, 2025).**

In Algeria, tuberculosis still represents a significant public health problem despite the efforts made within the national tuberculosis control program **(Bentata et al., 2025).** Recent epidemiological data show the persistence of tuberculosis cases in different regions of the country, requiring continuous strengthening of screening, early diagnosis, and therapeutic follow-up of patients **(Douba, 2025; INSP, 2025).**

The treatment of tuberculosis relies primarily on a combination of several antitubercular drugs, namely isoniazid, rifampicin, pyrazinamide, and ethambutol, administered over a prolonged period to ensure elimination of the bacillus and limit the emergence of resistance **(Suárez et al., 2019).** However, despite its effectiveness, this multidrug therapy can be responsible for several adverse effects, of which hepatotoxicity constitutes one of the most significant complications. Indeed, certain first-line antitubercular drugs can cause liver damage manifested by changes in biological parameters of hepatic function **(Motta et al., 2024).**

Biological monitoring of the liver therefore represents an essential step in the management of tuberculosis patients **(Suárez et al., 2019; Motta et al., 2024).** Among the biochemical markers used, serum transaminases hold a major place. Glutamate-pyruvate transaminase (GPT or ALAT) and glutamate-oxaloacetate transaminase (GOT or ASAT) are intracellular enzymes released into the bloodstream upon hepatocyte damage **(Huang et al., 2022).** Their measurement allows assessment of liver functional status and early detection of hepatic abnormalities related either to disease progression or to the toxicity of antitubercular treatments **(Vijaya Kumar et al., 2010 ; Motta et al., 2024).**

Thus, the study of GPT and GOT variations in tuberculosis patients provides a better understanding of the impact of tuberculous infection and antitubercular therapy on hepatic function. The present work aims to evaluate the variations in GPT and GOT levels in

tuberculosis patients before, during, and after treatment, as well as to highlight the importance of biological monitoring in the prevention of hepatic complications **(Motta et al., 2024 ; Suárez et al., 2019).**

The present study opens, in the first part, with an extensive bibliographic review on tuberculosis, covering its definition, the etiological agents responsible for the disease, its various clinical manifestations, and routes of transmission, followed by a discussion of the diagnostic approaches currently employed. Then, we also devoted to the study of GPT and GOT enzymes, addressing their definition, biological role, clinical significance, and variations in tuberculosis patients. As a second part, we presents the results obtained from our practical work and their discussion. The dissertation concludes with a general conclusion summarizing the main findings and future perspectives

Part one: Bibliographic synthe

Chapter I: Tuberculosis overview

1. Tuberculosis

Tuberculosis (TB) is a chronic, contagious infectious disease caused by *Mycobacterium tuberculosis*, an acid-fast bacillus that resists intracellular killing and persists within host phagocytes **(Khan et al., 2019).** The disease primarily affects the lungs, but can also involve other organs, forming characteristic lesions known as tubercles **(Cesur, 2023).** The transmission occurs through the airborne route, when infected individuals release contaminated droplets by coughing or sneezing **(Salim, 2020).** Following infection, the bacteria may remain dormant, causing latent TB, or progress to active disease with clinical symptoms **(Pai et al., 2016)**. Despite being preventable and treatable, TB continues to represent a major global public health burden, claiming approximately 1.23 million lives in 2024 alone, and ranking as the most fatal infectious disease attributable to a single pathogen worldwide **(WHO, 2025).**

1.1. Historical Background

Tuberculosis is one of humanity's oldest and most devastating diseases, with evidence suggesting that the genus *Mycobacterium* originated more than 150 million years ago **(Barberis et al., 2017)**. The earliest concrete proof dates back to Egyptian mummies from 2400 before Christ , while written records from India and China document its presence thousands of years ago **(Daniel, 2006)**.

In ancient greece, Hippocrates described the disease — known as *phthisis* — as striking predominantly young adults and being among the deadliest of his era **(Daniel, 2006)**. During the Middle Ages, its glandular form was known as the "king's evil", with the widespread belief that a royal touch alone could bring healing **(Barberis et al., 2017)**. A significant scientific milestone came in 1679, when Francis Sylvius provided the first precise anatomical description of the disease, followed by Benjamin Marten in 1720, who first proposed its infectious nature **(Barberis et al., 2017)**.

By the 18th century, TB had become a true epidemic with mortality rates reaching 900 deaths per 100,000 inhabitants, worsened by the industrial revolution's overcrowding and deteriorating living conditions **(Barberis et al., 2017).** In this context, Laennec unified the understanding of the disease in 1819 as a single entity whether pulmonary or extrapulmonary **(Daniel, 2006)**. Villemin then experimentally proved its transmissibility in 1865 **(Daniel, 2006).**

Robert Koch **(Fig. 01)** delivered the defining breakthrough on March 24, 1882, presenting *Die Aetiologie der Tuberculose* to the Berlin Physiological Society, identifying the tubercle

bacillus as the causative agent and establishing his famous postulates that remain a scientific reference to this day — an achievement that earned him the Nobel Prize in Medicine in 1905 **(Daniel, 2006)**.



Figure 1. Robert Koch **(Blevins & Bronze, 2010).**

On the therapeutic front, Brehmer pioneered the sanatorium concept in 1854, followed by Calmette and Guérin's introduction of the BCG vaccine in 1921 **(Daniel, 2006).** The true turning point, however, came with Waksman's discovery of streptomycin in 1943, followed by isoniazid in 1952 and rifamycins in 1957, marking the closure of sanatoria and the dawn of effective chemotherapy **(Prabhu & Singh, 2019; Daniel, 2006)**.

Despite significant advances in diagnosis, prevention, and treatment, tuberculosis (TB) remains a major global public health challenge, particularly with the emergence of multi-drug resistant tuberculosis (MDR-TB) and its more dangerous forms extensively drug-resistant tuberculosis (XDR-TB) and totally drug-resistant tuberculosis (TDR-TB). In response, the World Health Organization (WHO) launched its End TB Strategy in 2014, aiming to reduce deaths by 90% and new cases by 80% by 2030 **(Prabhu & Singh, 2019).**

2. Etiologic agents

2.1. Mycobacteria

2.1.1. Taxonomy and Classification

The genus *Mycobacterium* belongs to the phylum *Actinobacteria*, the order *Actinomycetales*, and the family *Mycobacteriaceae* **(Owens, 2024; La et al., 2025).** This genus comprises more than 200 recognized species, which are generally classified into three main groups based on their pathogenic potential **(La et al., 2025):**

- Species of the *Mycobacterium tuberculosis* complex (MTBC), responsible for tuberculosis

- Species causing leprosy: *Mycobacterium leprae* (M. leprae) and *Mycobacterium lepromatosis* (M. lepromatosis)
- Non-tuberculous Mycobacteria (NTM), also called atypical Mycobacteria, associated mainly with opportunistic infections in immunocompromised individuals

Most species of the genus are environmental saprophytes found in soil, natural water, and drinking water systems, where they may act as opportunistic pathogens under certain conditions **(Gunasingam, 2022)**. Clinically relevant species are grouped into MTBC and NTM, and are further classified according to their growth rate, pigmentation, and biochemical properties **(Owens, 2024).**

2.1.2. Morphological and Biological Characteristics

Mycobacteria are thin, straight or slightly curved, non-motile, non-spore-forming rod-shaped bacteria measuring 1–10 μm in length and 0.2–0.6 μm in width **(La et al., 2025).** They are aerobic organisms with complex metabolic pathways that allow them to survive in various environments, including soil, water, and host tissues **(Owens, 2024).**

The most characteristic feature of Mycobacteria is their lipid-rich cell wall, which contains high concentrations of mycolic acids — long-chain fatty acids of 60 to 90 carbon atoms — giving the bacteria strong hydrophobicity **(La et al., 2025).** This particular wall structure is responsible for three important properties **(Fig. 02) (La et al., 2025)**:

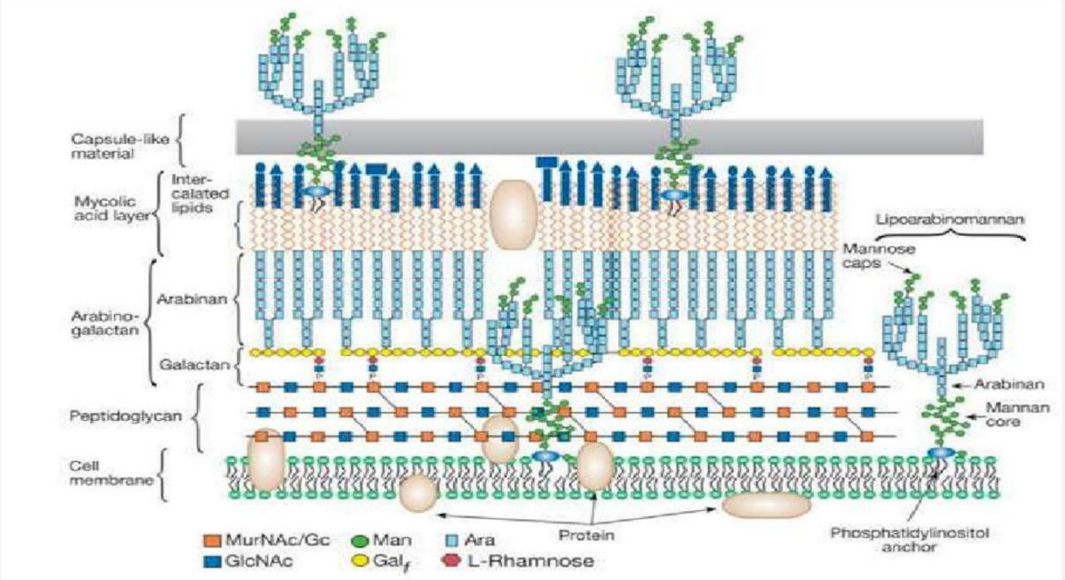


Figure 2. Structure of the cellular wall of Mycobacterium **(Schcolnik-Cabrera et al., 2017)**

- Acid-alcohol fastness (BAAR): after Ziehl–Neelsen staining, mycobacteria resist decolorization and appear as red-pink bacilli on a blue background **(Fig. 03) (Schcolnik-Cabrera et al., 2017)**
- Intrinsic resistance to many antibiotic families and antiseptic agents, due to the low permeability of the cell wall **(La et al., 2025)**
- Environmental resistance to acids, bases, and desiccation **(Schcolnik-Cabrera et al., 2017).**

Mycobacteria are also facultative intracellular pathogens that can survive inside host phagocytic cells, especially macrophages, where they escape immune defenses and cause persistent infections **(Owens, 2024).** This ability to survive intracellularly is a key factor in both their pathogenicity and their resistance to treatment **(Owens, 2024).**

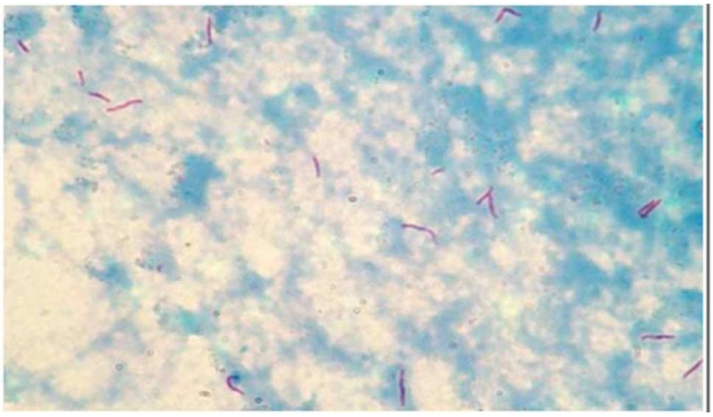


Figure 3. Ziehl–Neelsen stained sputum smear showing *Mycobacterium tuberculosis* bacilli **(Khutlang et al., 2010)**

2.2. *Mycobacterium tuberculosis*

M. tuberculosis is the most important member of the genus *Mycobacterium* from a clinical and public health standpoint, as it is the principal etiological agent of tuberculosis and one of the deadliest infectious agents known to mankind (**Koch & Mizrahi, 2018).**

2.2.1. Taxonomic Classification

M. tuberculosis, also known as Koch's bacillus after its discovery by Robert Koch in 1882 **(La et al., 2025)**, is classified as follows **(Table 1) (Koch & Mizrahi, 2018):**

Table 1. Taxonomic classification of *Mycobacterium tuberculosis* **(Koch & Mizrahi, 2018)**

Taxonomic Rank	**Classification**
Kingdom	*Bacteria*
Phylum	*Actinobacteria*
Order	*Actinomycetales*
Suborder	*Corynebacterineae*
Family	*Mycobacteriaceae*
Genus	*Mycobacterium*
Species	*Mycobacterium tuberculosis*

M. tuberculosis is neither Gram-positive nor Gram-negative. It is identified as an acid-fast bacillus (AFB**)** using Ziehl–Neelsen staining **(Koch & Mizrahi, 2018).**

2.2.2. The Mycobacterium tuberculosis Complex (MTBC)

M. tuberculosis is one of several species belonging to the *Mycobacterium tuberculosis* complex (MTBC), which comprises closely related species sharing more than 99% nucleotide sequence identity and identical 16S ribosomal RNA sequences **(La et al., 2025)**. Despite this genetic similarity, each species has distinct epidemiological characteristics and host preferences **(La et al., 2025)**.

The MTBC includes the following species **(Schcolnik-Cabrera et al., 2017; Gunasingam, 2022)**:

- *Mycobacterium tuberculosis* : the main cause of human tuberculosis, with no known animal reservoir
- *Mycobacterium africanum* : responsible for a small proportion of cases, mainly in West Africa
- *Mycobacterium bovis* : affects cattle and can be transmitted to humans via unpasteurized milk
- *Mycobacterium bovis* Bacille Calmette–Guérin (BCG): an attenuated strain used as a tuberculosis vaccine
- *Mycobacterium microti*, *Mycobacterium caprae*, *Mycobacterium pinnipedii*, *Mycobacterium canettii*: associated mainly with animal infections

In humans, TB is caused almost entirely by *M. tuberculosis*, and less commonly by *M. africanum*, both of which are obligate human pathogens with very limited survival outside the human host **(Schcolnik-Cabrera et al., 2017).**

2.2.3. Morphological and Physiological Characteristics

M. tuberculosis is a slightly curved rod measuring 1 to 4 μm in length and 0.3–0.6 μm in width **(Schcolnik-Cabrera et al., 2017).** Its main characteristics are summarized as follows **(Fig. 0**4**) (Koch & Mizrahi, 2018)**:

- Obligate aerobe, non-motile, and non-spore-forming

- Slow-growing, with a replication time of 12 to 24 hours and a generation time of about 20 hours in culture media — a feature that directly explains the chronic nature of the disease and the prolonged duration of treatment
- Classified as an acid-fast bacillus (AFB), poorly Gram-positive
- Prototrophic, able to synthesize all essential amino acids and cofactors independently
- Possesses a flexible metabolic capacity that allows adaptation to different host environments

The cell envelope is a major structural feature of *M. tuberculosis*, with lipids accounting for approximately 40% of the dry cell weight, contributing significantly to its virulence, antibiotic resistance, and ability to persist intracellularly **(Koch & Mizrahi, 2018).**

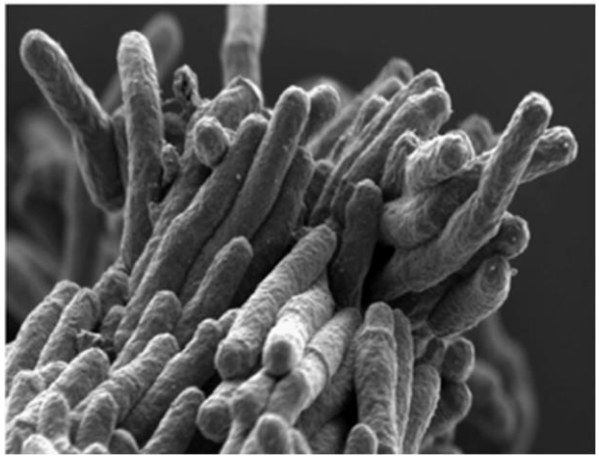


Figure 4. Scanning electron microscopy image of Mycobacterium tuberculosis **(Koch & Mizrahi, 2018)**

2.2.4. Genomic Characteristics

Mycobacterium tuberculosis (M. tuberculosis) has a single circular chromosome of about 4.4 Mb, with a high Guanine–Cytosine content (GC content) of 65.5% **(Koch & Mizrahi, 2018; Schcolnik-Cabrera et al., 2017**). Its genome contains approximately 4,000 genes, more than 200 of which are involved in lipid metabolism, reflecting its reliance on host-derived fatty acids as a primary carbon source during infection **(Schcolnik-Cabrera et al., 2017**). Several genomic features distinguish Mycobacterium tuberculosis (M. tuberculosis) from other bacteria **(Fig. 05) (Koch & Mizrahi, 2018):**

- Absence of plasmids and horizontal gene transfer, resulting in a highly stable and clonal genome
- Drug resistance arising exclusively from chromosomal mutations, with no acquisition of resistance genes from other organisms
- Approximately 10% of the genome consists of *Proline-Glutamate (PE)* and *Proline-Proline-Glutamate (PPE)* gene families, involved in immune evasion and pathogenesis.

From a phylogenetic perspective, nine major human lineages (L1 to L9) have been identified, each associated with specific geographic regions . Lineages 2 and 4 are the most widespread globally. Although these lineages were historically restricted to specific geographic regions, current human migration has significantly altered their distribution **(La et al., 2025).**

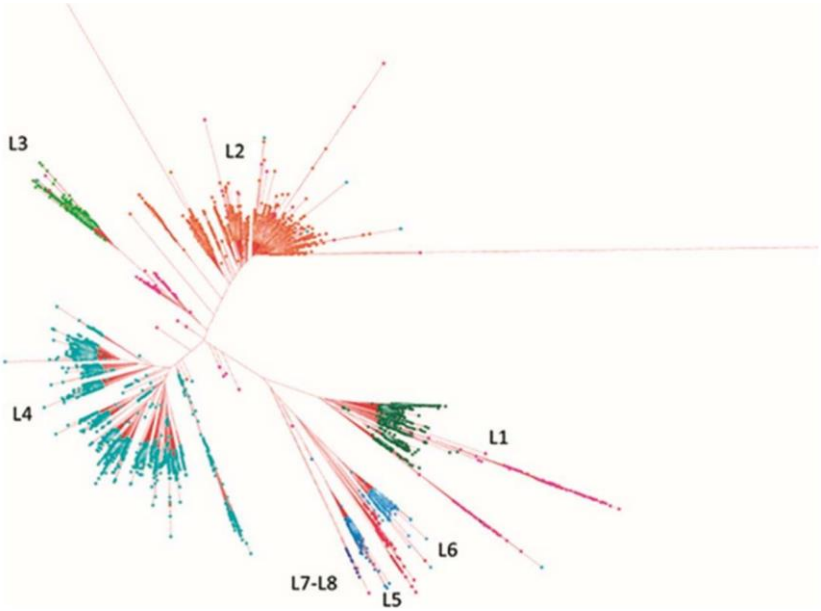


Figure 5. Unrooted phylogenetic tree of *Mycobacterium tuberculosis*, constructed using RAxML software on 15,901 MTB genome sequences, showing the main lineages L1 to L8. Pink: L1 (Indo-Oceanic); Blue: L2 (East Asian); Purple: L3 (East African); Red: L4 (Euro-American); Orange: L5 (*M. africanum*, West Africa I); Brown: L6 (*M. africanum*, West Africa II); Yellow: L7; Green: L8 **(La et al., 2025)**

3. Physiopathology of tuberculosis

3.1. Transmission and Initial Infection

Tuberculosis is transmitted exclusively via the airborne route through infectious droplet nuclei expelled by individuals with active pulmonary or laryngeal tuberculosis during coughing, sneezing, or speaking. These particles, measuring 1 to 5 micrometers in diameter,

can remain suspended in the air for prolonged periods, particularly in poorly ventilated enclosed environments. Several factors modulate transmission efficiency, including bacillary load, strain virulence, ultraviolet light exposure, and ambient ventilation **(Knechel, 2009).** High-risk settings include overcrowded households, correctional facilities, homeless shelters, and healthcare environments with inadequate infection control measures **(Fig. 06) (Kumar & Sharma, 2025).**

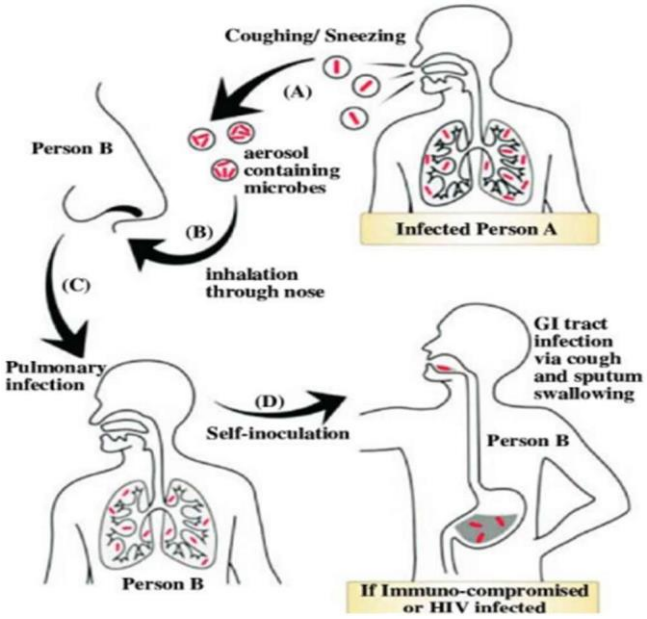


Figure 6. Modes of Tuberculosis Transmission and Progression in the Human Body **(Kumar & Sharma, 2025).**

Upon inhalation, the majority of droplet nuclei are intercepted by the mucociliary defense system of the upper respiratory tract. Only particles that successfully bypass this mechanical barrier reach the alveoli, where resident alveolar macrophages promptly phagocytose the bacilli, marking the initiation of the infectious process **(Fig. 07) (Knechel, 2009).**

3.2. Immune Response and Granuloma Formation

Following phagocytosis, *Mycobacterium tuberculosis* employs multiple immune evasion mechanisms to ensure intracellular survival. The bacterium inhibits phagosome-lysosome fusion, blocks phagosomal acidification, and alters host cell signaling pathways, thereby establishing a permissive intracellular environment that facilitates undetected replication **(Kumar & Sharma, 2025).**

The hallmark immunopathological structure of tuberculosis is the granuloma — an organized immune aggregate composed of infected macrophages, Langhans giant cells, epithelioid cells, and lymphocytes, enclosed within a fibrous capsule **(Fig. 07) (Kumar & Sharma, 2025).** Its primary function is to physically contain bacillary dissemination and restrict further bacterial replication **(Sikri & Tyagi, 2013).**

Within 2 to 3 weeks of granuloma establishment, the central core undergoes caseous necrosis — characterized by low oxygen tension, acidic pH, and nutrient depletion — conditions that effectively suppress active bacterial replication and establish a state of controlled containment **(Knechel, 2009).**

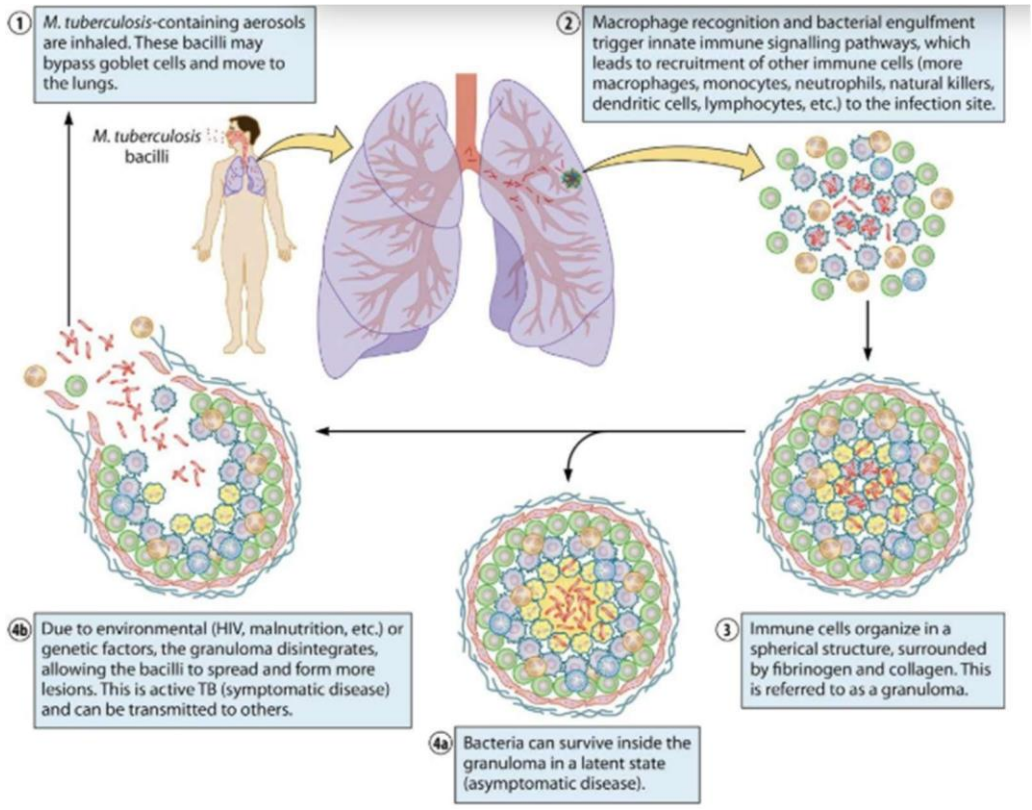


Figure 7. Pathophysiology of *Mycobacterium tuberculosis* infection. Following inhalation of M. tuberculosis bacilli, the bacteria reach the lungs and provoke a host immune response (macrophage recognition and engulfment), leading to granuloma formation, which typically suppresses the infection in its latent state. However, reactivation can occur under immunosuppressive conditions, resulting in active disease that can spread to other individuals **(Luies & du Preez, 2020).**

3.3. Latent versus Active Tuberculosis

The biological outcome of *M. tuberculosis* infection is fundamentally determined by the balance between bacterial virulence and host immune competence. Active tuberculosis develops in only 5% to 10% of immunocompetent individuals following exposure, while the remaining majority maintain successful granulomatous containment **(Knechel, 2009).**

In individuals where containment is successfully maintained, lesions undergo progressive fibrosis and calcification, and the bacteria enter a state of non-replicating persistence, defined as latent tuberculosis infection (LTBI), in which viable bacilli persist within the granuloma indefinitely without causing tissue damage or dissemination **(Fig. 08) (Knechel, 2009; Sikri & Tyagi, 2013).**

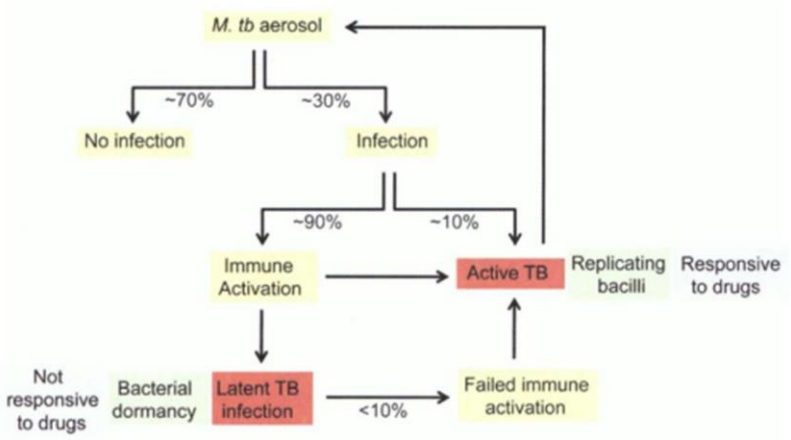


Figure 8. The dynamic state of tuberculosis infection **(Sikri & Tyagi, 2013)**.

This dormant state is maintained as long as host immune competence remains intact. However, when host immunity is compromised — whether by HIV co-infection, malnutrition, diabetes mellitus, or immunosuppressive therapies — the structural integrity of the granuloma deteriorates **(Fig. 09) (Kumar & Sharma, 2025).** The caseous core subsequently undergoes liquefaction, generating oxygen-rich necrotic cavities that provide optimal conditions for rapid extracellular bacterial proliferation **(Kumar & Sharma, 2025; Knechel, 2009).**

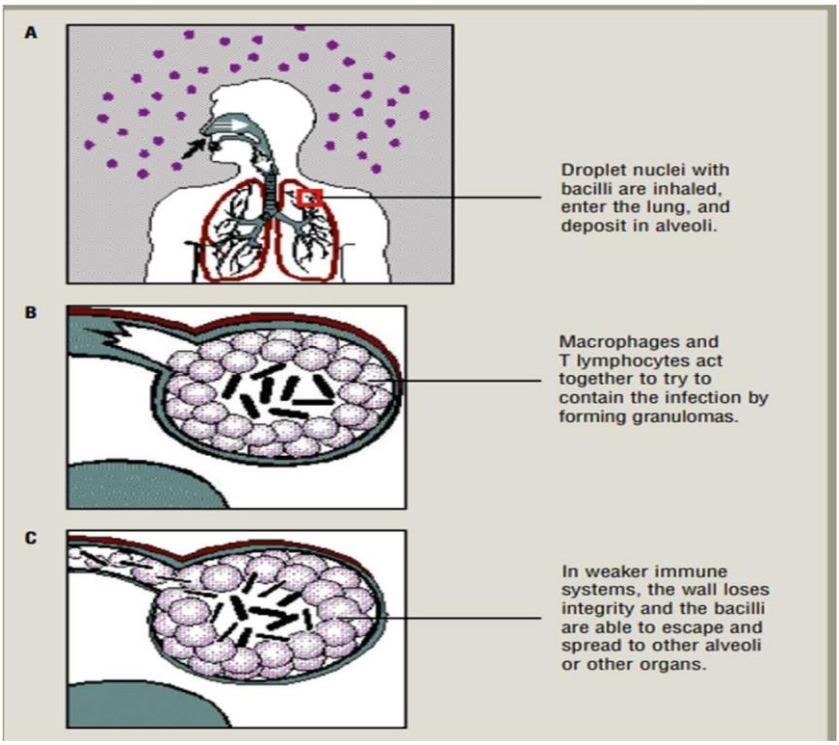


Figure 9. Pathophysiology of tuberculosis: inhalation of bacilli (A), containment in a granuloma (B), and breakdown of the granuloma in less immunocompetent individuals (C). (**Knechel, 2009)**

Progressive erosion of adjacent bronchiolar walls enables bacilli to disseminate into the airways, transitioning the infection from a contained latent state to active tuberculosis disease **(Knechel, 2009).** Should regional lymphatic containment fail, hematogenous dissemination can further seed distant organs, giving rise to extrapulmonary tuberculosis — including central nervous system involvement, skeletal tuberculosis, renal tuberculosis, and the disseminated miliary form **(Knechel, 2009; Kumar & Sharma, 2025).**

4. Risk factor of tuberculosis

Tuberculosis does not strike randomly. Behind every infection lies a combination of biological, behavioral, and social factors that together create the conditions for the disease to take hold and progress **(Narasimhan et al., 2013).**

4.1. Immunocompromising Conditions

HIV co-infection stands as the most potent driver of TB progression, elevating the annual reactivation risk to approximately 10% per year, compared to a lifetime risk of 5 to 10% in immunocompetent hosts **(Narasimhan et al., 2013)**. Individuals receiving immunosuppressive

therapies or suffering from chronic kidney disease face a similarly compromised immune response **(Davidson et al., 2024).**

4.2. Diabetes Mellitus

Diabetic patients carry roughly three times the risk of developing active TB (RR = 3.11; 95% CI: 2.27–4.26), with approximately 15% of global TB cases attributable to this metabolic condition. Poor glycemic control further amplifies this risk, as hyperglycemia directly impairs macrophage and T-cell function **(Silva et al., 2018).**

4.3. Malnutrition

Malnutrition impairs both innate and adaptive immunity, with malnourished individuals facing a six- to tenfold elevated hazard of TB disease. The relationship is bidirectional. Active TB itself drives nutritional deterioration, creating a self-reinforcing cycle of immune compromise **(Narasimhan et al., 2013).**

4.4. Behavioral Risk Factors

Tobacco smoking (RR = 2.3–2.7) and heavy alcohol use (RR = 2.94; 95% CI: 1.89–4.59) are well-established independent risk factors, both suppressing macrophage phagocytic function and cytokine production essential for mycobacterial containment **(Silva et al., 2018; Narasimhan et al., 2013).**

4.5. Socioeconomic and Demographic Factors

Overcrowding, poor ventilation, poverty, and limited healthcare access concentrate TB risk among the most marginalized populations**(Table 2)**. TB incidence peaks among young adults aged 15–44 years and disproportionately affects men due to occupational and behavioral exposures **(Davidson et al., 2024).**

Table 2. Relative risk and population attributable fraction of selected TB risk factors **(Narasimhan et al., 2013)**

Risk factor (reference)	Relative risk for active TB disease (range)[a]	Weighted prevalence, total population, 22 TB high burden countries[b]	Population attributable fraction (range)[c]
HIV infection	8.3 (6.1–10.8)	1.1%	7.3% (5.2–6.9)
Malnutrition	4.0 (2.0–6.0)	17.2%	34.1% (14.7–46.3)
Diabetes	3.0 (1.5–7.8)	3.4%	6.3% (1.6–18.6)
Alcohol use > 40 g/day	2.9 (1.9–4.6)	7.9%	13.1% (6.7–22.2)
Active smoking	2.6 (1.6–4.3)	18.2%	22.7% (9.9–37.4)
Indoor pollution	1.5 (1.2–3.2)	71.1%	26.2% (12.4–61.0)

5. Clinical Forms of Tuberculosis

Tuberculosis presents in a wide spectrum of clinical forms, broadly classified into pulmonary tuberculosis, extrapulmonary tuberculosis, and miliary tuberculosis, reflecting both the anatomical site of infection and the mode of disease progression **(Cesur, 2023).**

5.1. Pulmonary Tuberculosis

Pulmonary tuberculosis is the most common and contagious form of the disease, and is subdivided into two distinct clinical forms **(Coulon & Piette, 2001).**

5.1.1. Primary Pulmonary Tuberculosis

Primary pulmonary tuberculosis occurs following the initial infection with Mycobacterium tuberculosis, predominantly affecting children in endemic settings. In the majority of cases, the immune system successfully contains the infection and the disease resolves spontaneously, sometimes leaving behind a calcified pulmonary nodule and a calcified hilar lymph node, together forming the Ghon complex. In individuals with impaired immunity, such as infants, malnourished patients, or those co-infected with HIV, primary tuberculosis may progress toward severe disseminated forms including miliary tuberculosis and tuberculous meningitis **(Coulon & Piette, 2001).**

5.1.2. Post-primary Pulmonary Tuberculosis

Post-primary pulmonary tuberculosis, also referred to as reactivation tuberculosis, results either from endogenous reactivation of previously dormant bacilli or from exogenous reinfection in a previously sensitized individual. It predominantly affects adolescents and young adults. The upper lobes of the lungs are the preferential sites of involvement, with cavitation being a hallmark feature of advanced disease, associated with a high bacterial burden and significant contagiousness **(Coulon & Piette, 2001).**

5.2. Extrapulmonary Tuberculosis

Extrapulmonary tuberculosis (EPTB) is defined, according to WHO classification criteria, as infection by Mycobacterium tuberculosis affecting tissues and organs outside the pulmonary parenchyma. It represents between 20 and 25% of all tuberculosis cases, with a markedly higher proportion among HIV-positive patients **(Ramírez-Lapausa et al., 2015).** EPTB may develop through three main pathways: spread from superficial mucosal foci, direct spread from adjacent structures, or lymphohematogenous dissemination from an established focus **(Cesur, 2023).** The main clinical forms are described below.

5.2.1. Tuberculous Lymphadenitis

Tuberculous lymphadenitis**(Fig. 10)** is the most common form of EPTB, accounting for 30 to 40% of all extrapulmonary cases, predominantly affecting the cervical lymph node chain in 63 to 77% of cases **(Ramírez-Lapausa et al., 2015).** The affected nodes present as painless, firm, progressively enlarging masses that may eventually soften and form draining sinuses if untreated **(Vijaya Kumar et al., 2010).**



Figure 10. The subcutaneous nodules tuberculosis **(Vijaya Kumar et al., 2010).**

5.2.2. Pleural Tuberculosis

Pleural tuberculosis accounts for almost 20% of all EPTB cases and represents the most common cause of pleural effusion in high-burden settings, responsible for 30 to 60% of cases. The resulting effusion is characteristically unilateral, exudative, and lymphocyte-predominant, with lymphocytes comprising more than 80% of the cell count in two-thirds of cases **(Vijaya Kumar et al., 2010).**

5.2.3. Central nervous system (CNS Tuberculosis)

CNS is one of the most severe forms of EPTB, carrying mortality rates of 15 to 40% even with treatment, and leaving neurological sequelae in up to 25% of survivors. It encompasses tuberculous meningitis, intracranial tuberculomas, and cerebral vasculitis **(Ramírez-Lapausa et al., 2015**). Tuberculous meningitis follows a subacute course that progresses through three clinical stages: stage 1 with preserved consciousness and no focal neurological deficits; stage 2 with confusion and cranial nerve palsies; and stage 3 characterized by stupor, paraplegia, or hemiplegia **(Cesur, 2023).**

5.2.4. Genitourinary Tuberculosis

Genitourinary tuberculosis **(Fig. 11)** accounts for approximately 6.5% of all EPTB cases, more common in men than in women. Renal involvement may remain clinically silent for years, while in women, bilateral fallopian tube involvement occurs in up to 80% of cases and represents an important cause of infertility **(Ramírez-Lapausa et al., 2015).**



Figure 11. Plain abdominal radiograph in a male patient with genitourinary tuberculosis shows left renal, bladder, and seminal vesicle calcification**. (Vijaya Kumar et al., 2010).**

5.2.5. Abdominal Tuberculosis

Abdominal tuberculosis predominantly affects the ileocecal region in individuals between 25 and 45 years of age. The infection reaches the abdominal organs through hematogenous spread, ingestion of contaminated food, lymphatic dissemination, or direct extension from adjacent organs, with lymph node and peritoneal involvement possible independently **(Vijaya Kumar et al., 2010).**

5.2.6. Osteoarticular Tuberculosis

Osteoarticular tuberculosis **(Fig. 12)** accounts for approximately 11% of all EPTB cases, with the spine, hip, and knee being the most frequently involved sites **(Ramírez-Lapausa et al., 2015)**. Spinal tuberculosis, known as Pott's disease, represents 50% of all osteoarticular forms, characteristically beginning at the anterior vertebral endplates and spreading to the intervertebral disc and adjacent vertebral bodies **(Vijaya Kumar et al., 2010).**



Figure 12. Spinal tuberculosis **(Vijaya Kumar et al., 2010).**

5.2.7. Tuberculous Pericarditis

Tuberculous pericarditis develops most commonly through extension from mediastinal or hilar lymph nodes **(Cesur, 2023).** The disease evolves through four sequential stages: dry, effusive, absorptive, and constrictive, the last being marked by fibrous pericardial thickening and hemodynamic compromise **(Vijaya Kumar et al., 2010).**

5.2.8. Cutaneous Tuberculosis

Cutaneous tuberculosis is a rare manifestation accounting for 0.5 to 2% of EPTB cases in developed countries **(Ramírez-Lapausa et al., 2015).** Lupus vulgaris is the most common form in Western countries, while scrofuloderma predominates in developing nations **(Cesur, 2023).**

5.2.9. Ocular Tuberculosis

Ocular tuberculosis **(Fig. 13)** may manifest as choroidal tubercles, uveitis, iritis, or episcleritis, with choroidal involvement identified in 5 to 20% of patients during miliary tuberculosis in high-prevalence areas **(Cesur, 2023).**

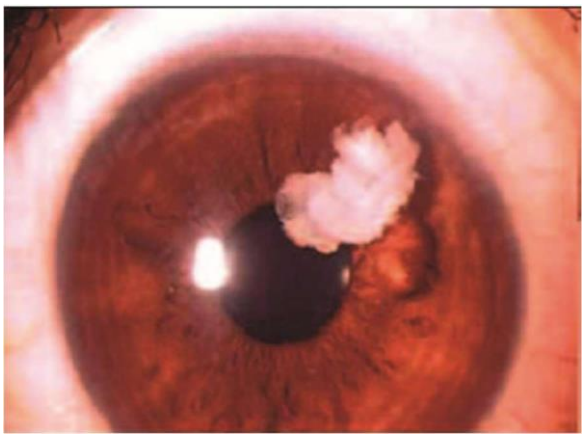


Figure 13. Ocular tuberculosis **(Vijaya Kumar et al., 2010).**

5.2.10. Laryngeal Tuberculosis

Laryngeal tuberculosis is a complication of pulmonary tuberculosis occurring in 12 to 45% of cases, manifesting through masses, ulcers, or nodules in the larynx and vocal cords, and is considered highly contagious due to its association with bacilliferous pulmonary disease **(Vijaya Kumar et al., 2010; Ramírez-Lapausa et al., 2015).**

5.3. Miliary Tuberculosis

Miliary tuberculosis **(Fig. 14)** is a severe disseminated form of the disease resulting from massive hematogenous spread of *Mycobacterium tuberculosis* to multiple organ systems simultaneously, accounting for approximately 1% of all tuberculosis cases **(Cesur, 2023).** The term derives from the characteristic pathological appearance of innumerable small nodules of 1 to 2 mm, resembling millet seeds, distributed throughout the affected organs **(Ramírez-Lapausa et al., 2015).**

The most frequently affected organs include the liver, spleen, lungs, lymph nodes, meninges, and bone marrow. It predominantly affects elderly, malnourished patients, and individuals with impaired cell-mediated immunity, such as those with HIV infection, chronic kidney disease, or patients on anti-TNF therapies **(Ramírez-Lapausa et al., 2015).**

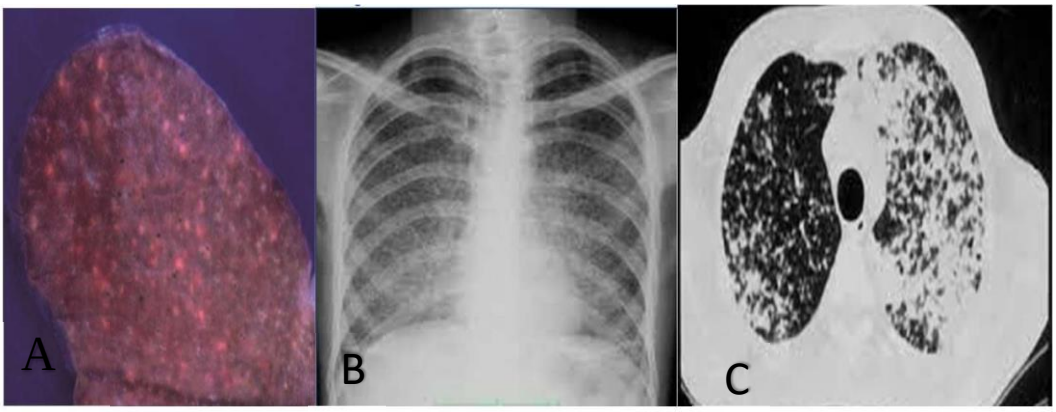


Figure 14. A) Miliary tuberculosis in lung **(Vijaya Kumar et al., 2010). B)** Micronodules on high-resolution lung CT (nodular infiltrative view showing patchy glass view in places on the right) **(Cesur, 2023). C)** Micronodules on high-resolution lung CT) **(Cesur, 2023).**

6. Clinical manifestations of tuberculosis

Tuberculosis is a complex infectious disease with a wide range of clinical manifestations that depend on the site of infection, disease extent, host immune status, and comorbidities. This variability makes it difficult to diagnose and allows it to progress silently before becoming clinically apparent.

6.1. Pulmonary Manifestations

The lungs represent the primary site of tuberculosis infection, with pulmonary tuberculosis being the most common clinical form. The hallmark symptom is a persistent cough lasting more than two weeks, often accompanied by sputum production that may be purulent or blood-stained. In addition to cough, patients frequently present with pleuritic chest pain, dyspnea, and wheezing, particularly when the infection involves the pleura or results in bronchial obstruction. In advanced stages, haemoptysis may occur, reflecting progressive damage to lung tissue **(Davidson et al., 2024; Alsayed & Gunosewoyo, 2023).**

6.2. Systemic Manifestations

Tuberculosis is not limited to the lungs but represents a systemic disease affecting the entire body. Patients with active tuberculosis commonly exhibit low-grade or intermittent fever, profuse night sweats (nocturnal hyperhidrosis), marked fatigue, and significant weight loss associated with loss of appetite and general malaise. These constitutional symptoms typically develop gradually, which may delay early recognition and highlights the need for careful clinical assessment **(Davidson et al., 2024; Alsayed & Gunosewoyo, 2023).**

6.3. Extrapulmonary Manifestations

When *Mycobacterium tuberculosis* disseminates beyond the lungs through the bloodstream, multiple organs may be affected. Extrapulmonary tuberculosis most frequently involves the lymph nodes, bones and joints, the central nervous system, and the genitourinary tract. Clinical presentation varies according to the affected site and may include localized pain and swelling, neurological impairments, or urinary disturbances. In severe cases, disseminated tuberculosis, known as miliary tuberculosis, affects multiple organ systems simultaneously and is associated with a high risk of mortality, particularly in immunocompromised individuals **(Davidson et al., 2024; Alsayed & Gunosewoyo, 2023).**

6.4. Pediatric manifestations

Tuberculosis in children often presents with clinical features that differ from those observed in adults. Instead of the typical respiratory manifestations, children may show nonspecific signs such as failure to thrive, poor weight gain, irritability, and developmental delay. Although respiratory symptoms such as cough, wheezing, and breathing difficulties may be present, extrapulmonary forms are more frequently observed in children, particularly involving the lymph nodes, bones, joints, and central nervous system **(Davidson et al., 2024).**

7. Microbiological diagnosis of tuberculosis

7.1. Specimen Collection

Prior to any microbiological examination, adequate specimen collection is essential. Respiratory secretions, whether spontaneous or induced sputum, are collected in the morning on 2 to 3 consecutive days, as MTB excretion is intermittent **(La et al., 2025).** According to the Centers for Disease Control and Prevention, 3 sputum specimens collected on consecutive mornings are recommended for detection of pulmonary tuberculosis **(Knechel, 2009).** For patients unable to expectorate, gastric lavage is an alternative, particularly in children. In cases of suspected extrapulmonary TB, additional specimens such as cerebrospinal fluid, pleural fluid, urine, or biopsy samples may be collected depending on the clinical presentation **(La et al., 2025**).

7.2. Microscopy

7.2.1. Ziehl-Neelsen Staining

Ziehl-Neelsen staining is the most widely used technique for direct microscopic examination of sputum. It exploits the acid-fast property of MTB, whereby the lipid-rich cell wall retains the fuchsin dye after decolorization, allowing bacilli to appear red under light microscopy **(Fig 15).** The technique is rapid, inexpensive, and accessible in resource-limited settings. However, its sensitivity is limited, ranging from 20% to 80%, and requires a bacterial concentration of at least 10^4 to 10^5 bacilli/ml to yield a positive result **(Huang et al., 2022; La et al., 2025).**

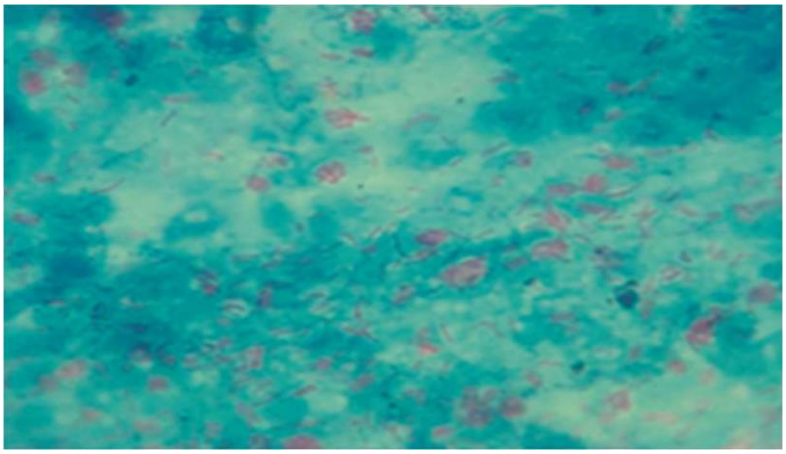


Figure 15. Ziehl-Neelsen staining under optical microscopy (×1000) **(La et al., 2025)**.

7.2.2. Fluorescence Microscopy

Fluorescence microscopy using auramine staining offers higher sensitivity than Ziehl-Neelsen, as bacilli appear as bright fluorescent structures under UV light **(Fig 16).** However, it carries a risk of false-positive results due to non-specific dye incorporation. The WHO recommends replacing conventional fluorescence microscopy with LED-based microscopy, which is more robust, sustainable, and practical for field settings **(Huang et al., 2022).**

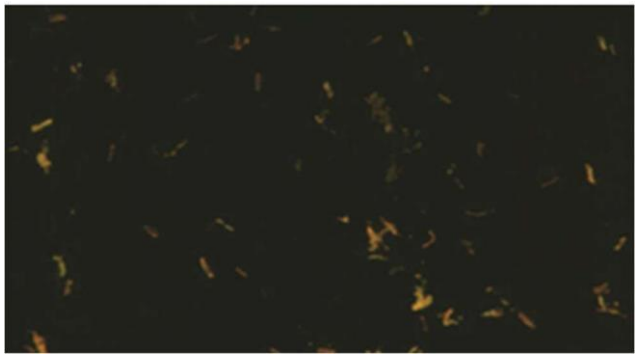


Figure 16. Auramine staining in fluorescence microscopy (×400) (La et al., 2025).

7.2.3. Fluorescein Diacetate (FDA) Staining

FDA staining selectively labels viable bacilli by converting non-fluorescent FDA into a green fluorescent product through enzymatic activity. This allows detection of viable MTB and prediction of quantitative culture results within one hour, useful for monitoring treatment response **(Huang et al., 2022).**

7.2.4. Limitations of Microscopy

A critical limitation of all microscopic methods is the inability to differentiate live from dead bacilli, or M. tuberculosis from nontuberculous mycobacteria (NTM) (Huang et al., 2022).

7.3. Culture

Culture remains the WHO-recommended gold standard for TB diagnosis, enabling both species identification and drug susceptibility testing (DST). Its detection threshold is significantly lower than microscopy, reaching 10 to 10^2 bacilli/ml **(La et al., 2025).** Both solid media such as Lowenstein-Jensen **(Fig . 17)** and liquid media such as Middlebrook 7H9 **(Fig .18**) are used; solid media are more economical and less prone to contamination, while liquid media offer faster and automated detection **(Huang et al., 2022).**

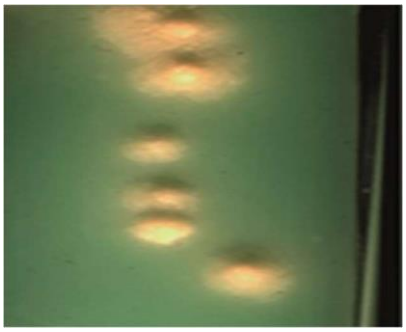


Figure 17. MTB colonies on Löwenstein–Jensen solid medium (La et al., 2025).



Figure 18. Positive 7H9 Middlebrook liquid medium for *Mycobacterium tuberculosis* with a UV fluorescent indicator **(La et al., 2025).**

For rapid identification from positive cultures, immunochromatographic (ICT) assays detecting MPT-64 antigen achieve sensitivity of 98.1–98.6% and specificity of 99.2–100% **(Huang et al., 2022).** However, culture requires 4–8 weeks for growth, additional time for DST, and biosafety level 3 facilities **(Fig. 19) (Huang et al., 2022; La et al., 2025).**

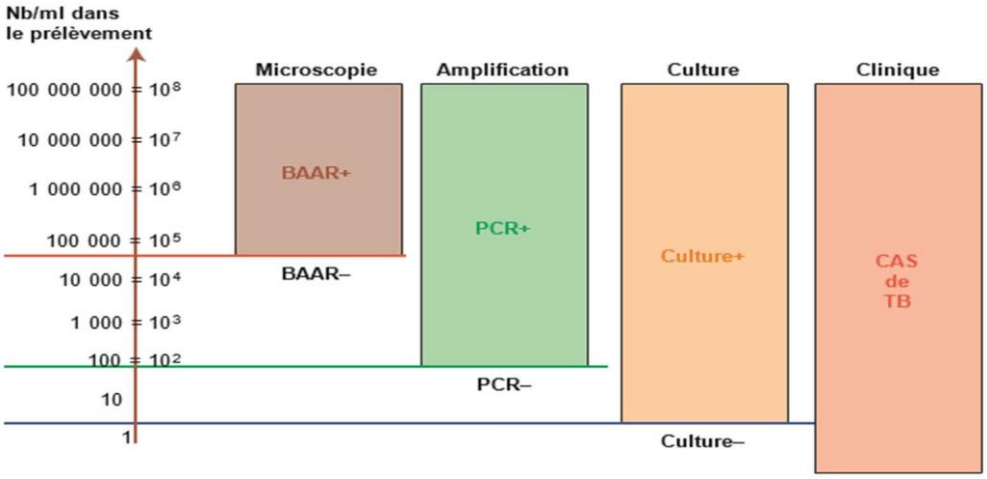


Figure 19. Sensitivity of biological and clinical tools for tuberculosis diagnosis according to the number of bacilli present per mL of sample. **AFB:** acid-fast bacilli; **PCR:** polymerase chain reaction; **TB:** tuberculosis. **(La et al., 2025).**

7.4. Molecular Tests

7.4.1. Xpert test for detection of *Mycobacterium tuberculosis* and rifampicin resistance.

Xpert MTB/RIF uses real-time PCR targeting the rpoB gene, providing results within 2 to 3 hours. Sensitivity is 99.8% for smear-positive and 90.2% for smear-negative cases, with specificity of 99.2% . A limitation is its inability to detect INH resistance. Xpert Ultra increases sensitivity from 83% to 88% and is WHO-recommended as the initial diagnostic test **(Huang et al., 2022).**

7.4.2. Tuberculosis Loop-Mediated Isothermal Amplification (TB-LAMP)

TB-LAMP amplifies DNA at constant temperature targeting gyrB and 16S rRNA genes. It has slightly lower sensitivity than Xpert but similar specificity and does not require advanced equipment, making it suitable for peripheral laboratories **(Huang et al., 2022).**

7.4.3. Line Probe Assay (LPA)

LPA combines PCR and reverse hybridization to detect M. tuberculosis and resistance mutations. MTBDRplus targets first-line drugs (INH, RIF), while MTBDRsl detects second-line resistance (fluoroquinolones and injectable drugs) **(Huang et al., 2022).**

7.4.4. Tuberculin Skin Test (TST)

TST is based on type IV hypersensitivity after intradermal PPD injection. Results are read at 72 hours **(Fig. 20)**. Induration ≥5 mm is considered positive depending on clinical context **(Table 3) (Huang et al2022; Knechel, 2009).**



Figure 20. Tuberculin test Positive test showing in duration >15 mm (left picture) and negative test without demonstrated in duration (right picture) (**Schcolnik-Cabrera et al., 2017).**

Table 3. Positive results in the tuberculin assay. The table shows the three possible positive results in the tuberculin assay b.y sub dermal application of PPD, according to the characteristics of each patient (**Schcolnik-Cabrera et al., 2017).**

Induration size	**Patients Positive for the Test**
> 5mm	Immunosuppressed patient with fibrotic changes demonstrated by thoracic radiography, consistent with previous tuberculous disease or in current contact with infective tuberculous cases
> 10mm	Subject that works or lives in high-risk areas; intravenous drug consumer; patient with concomitant diseases including silicosis, diabetes mellitus, chronic kidney failure, leukemia, lymphoma; patient with sudden and unexplainable weight loss ≥ 10%; subject with gastrectomy or yeyunoileal bypass; patient younger than 4 years of age
> 15mm	Any person, regardless the associated risk factors

7.4.5. Interferon-Gamma Release Assays (IGRAs)

IGRAs measure IFN-γ production in response to ESAT-6 and CFP-10 antigens. They are not affected by BCG vaccination and are more specific than TST **(Huang et al., 2022).** T-SPOT.TB counts producing cells, while QuantiFERON measures released IFN-γ. However, they cannot distinguish active from latent TB **(Table 4) (Suárez et al., 2019).**

Table 4. Comparison of the typical methods for diagnosis of TB disease (Huang et al., 2022).

	Microscopy	Xpert MTB/RIF	Culture	T-SPOT.TB
Price	**Low**	**High**	**Medium**	**High**
Procedure complexity	**Low**	**Low**	**High**	**High**
Sensitivity	**Low (for bacterial-positive TB)**	**High (for bacterial-positive TB)**	**High (for bacterial-positive TB)**	**Relatively high (for both bacterial-positive and bacterial-negative TB)**
Specificity	**High (in regions with a low incidence of NTM)**	**High**	**High**	**High (for diagnosis of Mtb infection), medium (for diagnosis of active TB in TB-endemic areas)**
Advantages	**Fast, simple, inexpensive**	**Fast, simple, low biosafety risk, detecting one drug resistance**	**Detecting all drug resistances**	**Detecting bacterial-negative TB, detecting latent TB infection**

	Microscopy	Xpert MTB/RIF	Culture	T-SPOT.TB
Shortcomings	**Low sensitivity, cannot differentiate between live and dead bacilli**	**Expensive, cannot differentiate between live and dead bacilli**	**High complexity, long turnaround time, high biosafety risk**	**Expensive, high complexit**

TB, tuberculosis; Mtb, *mycobacterium tuberculosis*; NTM, nontuberculous mycobacteria.

8. Epidemiology of tuberculosis

8.1. Tuberculosis in the World

8.1.1. Global WHO Figures (2024)

In 2024, tuberculosis (TB) caused an estimated 10.7 million new cases and 1.23 million deaths worldwide, maintaining its position as the leading infectious disease killer. The global incidence rate was 131 per 100,000 population per year, representing only a 12% reduction from the 2015 baseline — far below the End TB Strategy milestone of −50% by 2025**(Fig. 21) (WHO, 2025).**

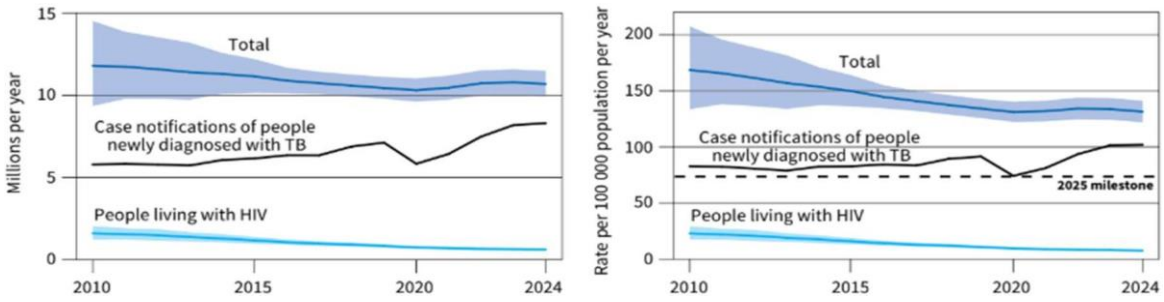


Figure 21. Global trends in the estimated number of incident TB cases (left) and the incidence rate (right),2010–2024 **(WHO, 2025)**

8.1.2. Most Affected Regions

The burden of TB is geographically concentrated. In 2024, three WHO regions accounted for 86% of all cases: South-East Asia (34%), the Western Pacific (27%), and Africa (25%). Eight countries alone represented 67% of global cases, with India leading at 25%, followed by Indonesia (10%), the Philippines (6.8%), China (6.5%), and Pakistan (6.3%)**(Fig. 22) (WHO, 2025).**

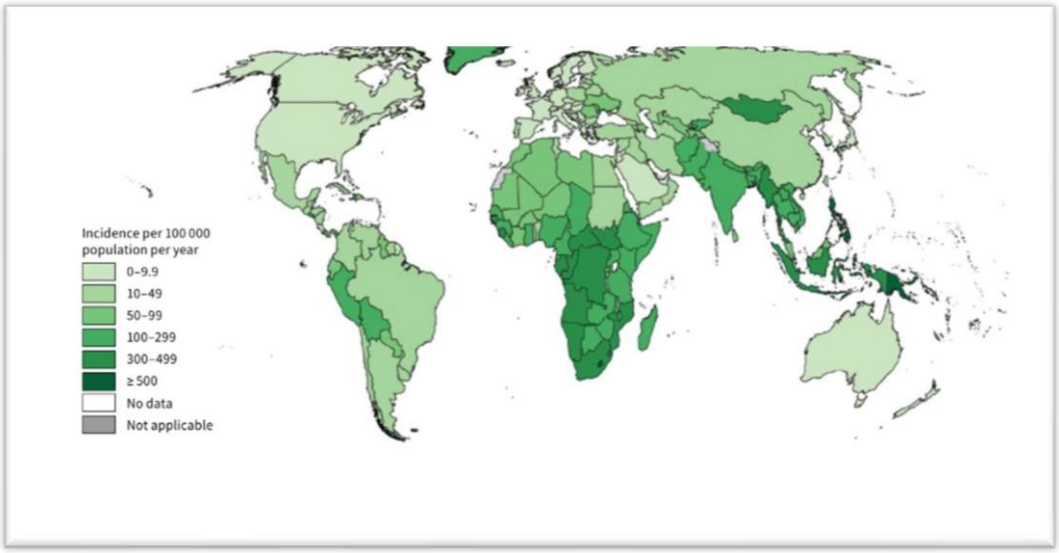


Figure 22. Estimated TB incidence rates at country level in 2024 **(WHO, 2025)**

The WHO African and European regions showed the strongest progress: between 2015 and 2024 they reduced their TB incidence rates by 28% and 39%, and their TB deaths by 46% and 49%, respectively. By contrast, the Region of the Americas recorded a 13% increase in incidence rate over the same period, partly attributable to COVID-19-related disruptions in 2020**(Fig. 23) (WHO, 2025).**

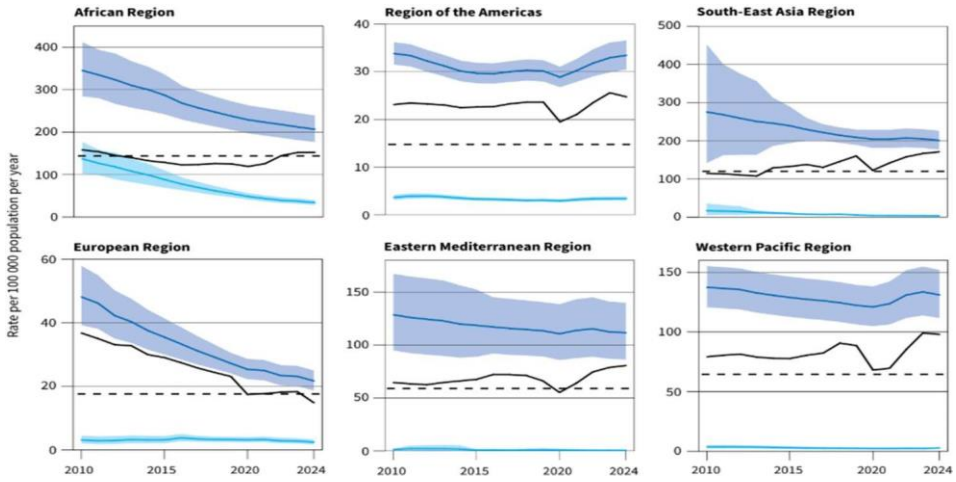


Figure 23. Trends in estimated TB incidence rates by WHO region, from 2010 to 2024 **(WHO, 2025)**

8.1.3. Drug-Resistant TB: MDR-TB and XDR-TB

Drug resistance represents one of the most critical threats to global TB control. In 2024, an estimated 390,000 people developed multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB). Among new TB cases, 3.2% had MDR/RR-TB; among previously treated cases, the proportion was 16%. Only 42% of estimated MDR/RR-TB patients were enrolled on treatment. XDR-TB — defined as resistance to rifampicin, any fluoroquinolone, and at least one of bedaquiline or linezolid — remains particularly difficult to treat, with high mortality **(Fig. 24) (WHO, 2025).**

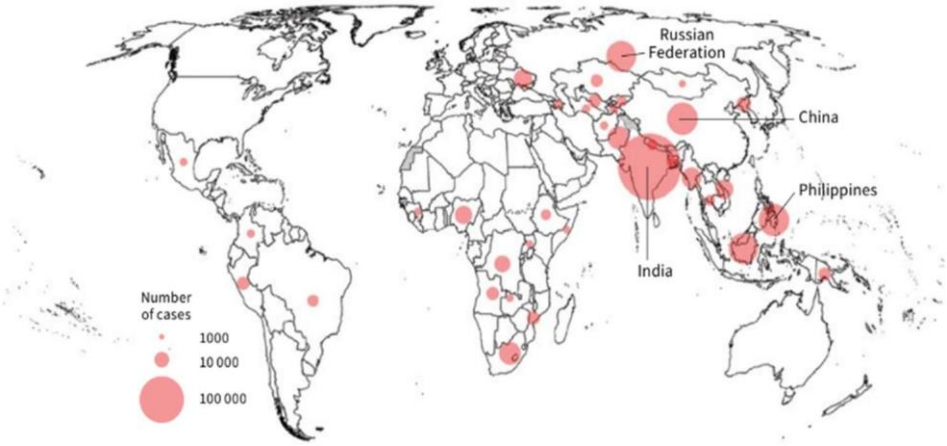


Figure 24. Estimated number of people who developed MDR/RR-TB (incident cases) for countries with at least 1000 incident cases, 2024 **(WHO, 2025).**

8.2. Tuberculosis in Algeria

In 2024, Algeria reported 18,857 tuberculosis cases, with an incidence of 39.88 per 100,000 inhabitants, marking a 2.9% decrease from 2023. Extra-pulmonary tuberculosis predominated (70.6%)**,** followed by pulmonary forms (28.3%), while other forms remained marginal**(Fig. 25)**. Lymph node involvement was the most frequent extra-pulmonary localization (62.4%), followed by pleural (11.0%) and other serous forms (8.4%), with bone (4.8%) and meningeal tuberculosis (0.7%) being less common **(Fig. 26) (INSP, 2025).**

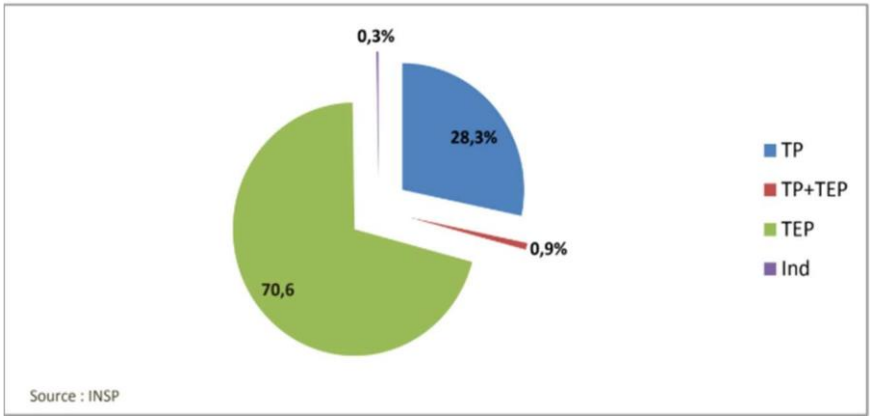


Figure 25. Distribution of tuberculosis cases by type in Algeria (2024) **(INSP, 2025).**

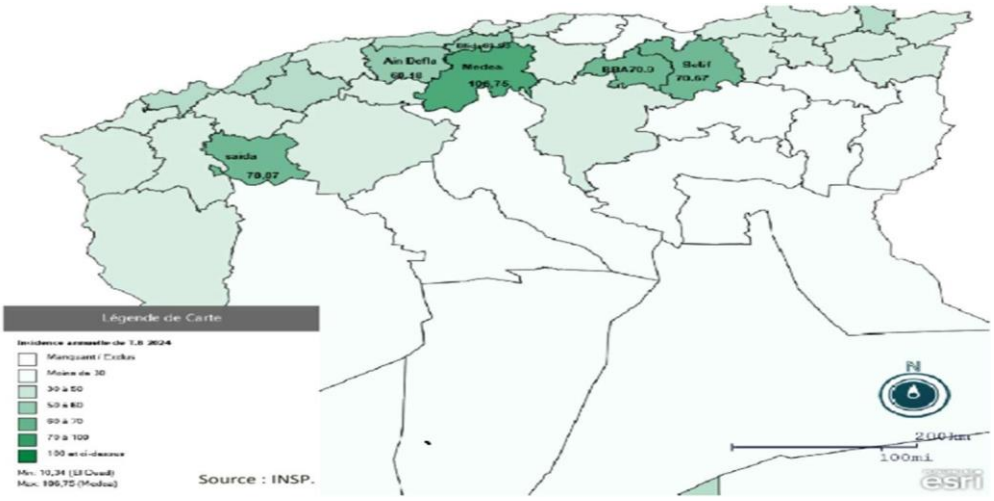


Figure 26. Distribution of tuberculosis incidence rates (all forms) by province (wilaya) in Algeria in 2024 **(INSP, 2025).**

Between 2014 and 2024, incidence declined by 30.5%, with reductions of 48.9% in pulmonary and 18.0% in extra-pulmonary tuberculosis. The lowest rate was observed in 2020 (36.74 per 100,000) due to disruptions caused by the COVID-19 pandemic. However, Algeria

has not yet reached the target set by the World Health Organization of a 50% reduction between 2015 and 2025, achieving only 32.4% **(Fig. 27) (INSP, 2025).**

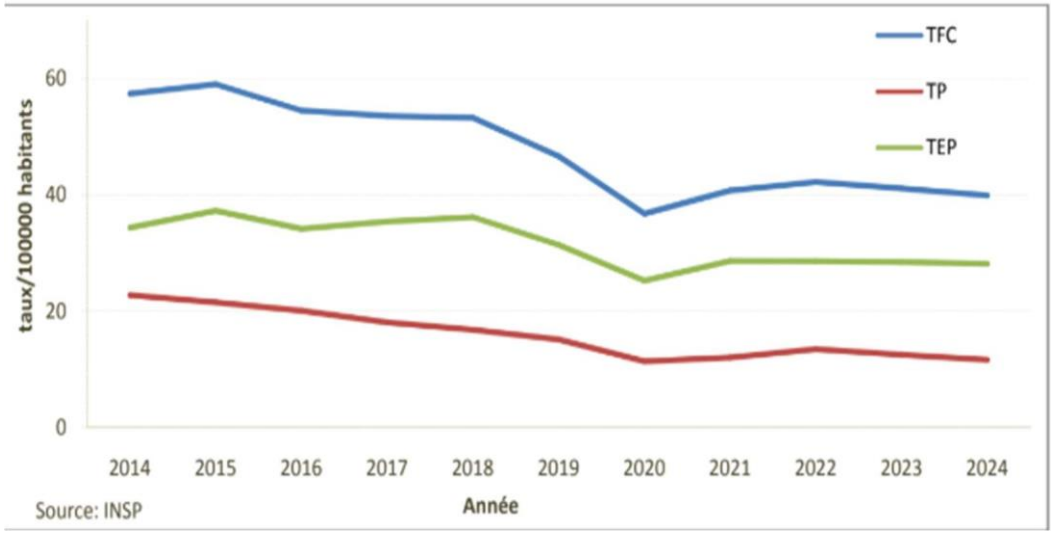


Figure 27. Evolution of incidence rates of tuberculosis, all forms (AF), pulmonary tuberculosis (PT), and extra-pulmonary tuberculosis (EPT) in Algeria between 2014 and 2024**(INSP, 2025).**

Tuberculosis control has relied on national programs since 1962, including standardized chemotherapy introduced in 1966 and widespread BCG vaccination with coverage reaching 90%, contributing to a reduced infection risk **(Bentata et al., 2025).** After a resurgence in the 1990s, the situation improved from the 2000s onwards, with pulmonary incidence falling below 17 per 100,000 by 2016 **(Bentata et al., 2025; Douba, 2025).**

In 2024, 82.57% of pulmonary cases were bacteriologically confirmed, remaining below the 85% target set by the World Health Organization. Children under 15 years represented 10.2% of cases, with extra-pulmonary forms predominating. A latent tuberculosis surveillance system introduced in 2021 reported 1,005 cases in 2024, primarily among close contacts and patients eligible for biotherapy **(INSP, 2025).**

Overall, tuberculosis in Algeria remains a public health concern despite a sustained decline, reflecting the ongoing epidemiological transition from infectious to chronic non-communicable diseases **(Douba, 2025).**

9. Treatment of Tuberculosis

9.1. Standard Treatment of Drug-Susceptible Tuberculosis

The treatment of tuberculosis relies on a well-established six-month regimen recommended by the World Health Organization (WHO). It is divided into two distinct phases: an intensive phase and a continuation phase **(Suárez et al., 2019; Motta et al., 2024).**

The intensive phase lasts two months and includes four first-line drugs: isoniazid, rifampicin, pyrazinamide, and ethambutol. This phase aims to rapidly reduce the bacterial load. The continuation phase lasts four months and includes only isoniazid and rifampicin, consolidating treatment and preventing relapse (**Table 5) (Suárezet al., 2019; Motta et al., 2024).**

Treatment duration may be extended in extrapulmonary forms of tuberculosis**(Table 6)**: six months for lymph node TB, nine months for osteoarticular TB, and up to twelvemonths for central nervous system TB **(Suárez et al., 2019).**

Table 5. Drug regimen for drug-sensitive TB for new and previously treated cases **(Natarajan et al., 2020)**

Type of TB cases	Intensive Phase (IP)	Continuation Phase (CP)
New	**(2) HRZE**	**(4) HRE**
Previously treated	**(2) HRZES + (1) HRZE**	**(5) HRE**
The CP may be extended by 12–24 weeks in treating EPTB (i.e. CNS TB, skeletal TB, disseminated TB etc) based on clinical assessment of treating physician.		

Table 6. Drug treatment of tuberculosis: Dosages and durations **(Schaberg et al., 2019)**

Drug	Duration of treatment (months)	Dosage (mg/kg BW/d)	Minimum/maximum dose (mg) *
Isoniazid (INH)	**6**	**5**	**200/300**
Rifampicin (RMP)	**6**	**10**	**450/600**
Pyrazinamide (PZA)	**2**	**25**	**1500/2500**
Ethambutol (EMB)	**2**	**15**	**800/1600**

9.2. Adverse Effects of Anti-Tuberculosis Therapy

Although highly effective, first-line anti-TB therapy is associated with a range of adverse effects. Severe reactions requiring treatment modification occur in a minority of patients. The most clinically significant toxicity is hepatotoxicity, characterized by elevated liver enzymes, which may necessitate temporary discontinuation of treatment **(Suárez et al., 2019).**

Other notable adverse effects include:

- Optic neuritis, associated with ethambutol use
- Peripheral neuropathy, linked to isoniazid administration
- Hyperuricemia, caused by pyrazinamide
- Gastrointestinal and cutaneous reactions **(Suárez et al., 2019)**

Pyridoxine (vitamin B6) supplementation is recommended to prevent isoniazid-induced peripheral neuropathy, particularly in high-risk populations such as pregnant women, malnourished patients, and individuals with diabetes or HIV infection **(Suárez et al., 2019).**

9.3. Drug-Resistant Tuberculosis and Management

Multidrug-resistant tuberculosis (MDR-TB) is defined as resistance to at least isoniazid and rifampicin, the two most potent first-line anti-TB drugs. It represents a major global health challenge due to limited treatment options, prolonged therapy duration, and greater toxicity profiles compared to drug-susceptible TB **(Motta et al., 2024).**

Recent advances have introduced all-oral regimens, replacing injectable-based treatments that were previously standard. The BPaLM regimen, comprising bedaquiline, pretomanid, linezolid, and moxifloxacin, has demonstrated high efficacy and an improved safety profile in MDR/RR-TB cases **(Motta et al., 2024).**

For pre-extensively drug-resistant TB (pre-XDR-TB), the BPaL regimen (bedaquiline, pretomanid, and linezolid) has shown high treatment success rates, although toxicity associated with linezolid remains a clinical concern requiring close monitoring **(Motta et al., 2024).**

Figure (**Fig .28)** shows the global increase in the diagnosis of drug-resistant tuberculosis cases and the initiation of treatment between 2007 and 2017, reflecting the improvement in diagnostic capabilities **(Natarajan et al., 2020).**

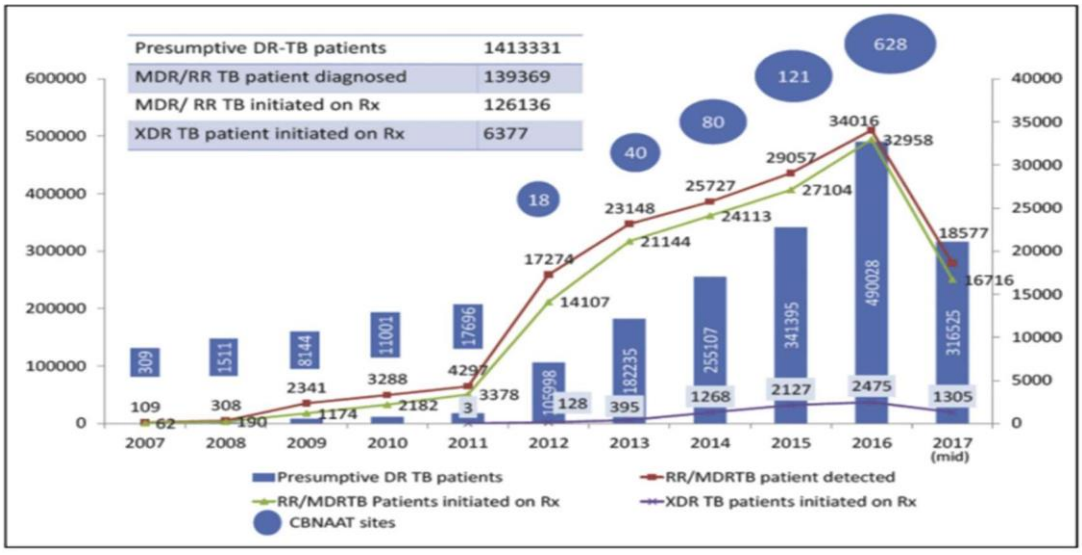


Figure 28. Drug-resistant TB cases and treatment initiation from 2007 to 2017 **(Natarajan et al., 2020).**

9.4. Recent Advances in Shorter Treatment Regimens

Recent clinical trials have explored the feasibility of shortening treatment duration for drug-susceptible TB. A four-month regimen incorporating rifapentine, isoniazid, pyrazinamide, and moxifloxacin has been demonstrated to be non-inferior to the standard six-month treatment in adults **(Motta et al., 2024).** In pediatric populations, shorter regimens of approximately 16 weeks have also demonstrated effectiveness in non-severe cases, supporting the development of more individualized and patient-centered therapeutic strategies **(Motta et al., 2024).**

9.5. Preventive Treatment of Latent Tuberculosis Infection

Preventive therapy for latent tuberculosis infection (LTBI) aims to eliminate dormant bacilli and reduce the risk of progression to active disease. Before initiating preventive treatment, active TB must be systematically excluded through clinical evaluation and chest radiography **(Suárez et al., 2019).**

Preventive therapy is recommended for high-risk populations, including individuals with HIV infection and patients receiving immunosuppressive treatments such as tumor necrosis factor-alpha (TNF-α) inhibitors. Early identification and treatment of LTBI in these groups is a critical component of global TB elimination strategies **(Suárez et al., 2019; WHO, 2022).**

Chapter II: Glutamate-Pyruvate Transaminase and Glutamate-Oxaloacetate Transaminase in tuberculosis

1. Glutamate-Pyruvate Transaminase (GPT/ALT)

Glutamate-Pyruvate Transaminase, more commonly known as Alanine Aminotransferase (ALT) or GPT, is one of the most clinically significant enzymes in the human body **(Kamil et al., 2024).** It belongs to the aminotransferase family and plays a central role in both amino acid metabolism and energy homeostasis **(McGill, 2016).** Understanding its biochemical nature, physiological functions, and clinical implications is essential for any thorough investigation of liver health and hepatic injury **(Liu et al., 2014).**

1.1. Biochemical Structure and Characteristics

At the molecular level, ALT is a cytosolic enzyme predominantly concentrated within hepatocytes. It is composed of 496 amino acids and is encoded by the ALT gene located on the long arm of chromosome 8 **(Fig. 29 and 30) (Liu et al., 2014**). One of its most distinguishing features is its remarkably high intracellular concentration; the activity of ALT within hepatic cells is approximately 3,000 times greater than what is normally detected in serum. This steep concentration gradient between the intracellular and extracellular compartments makes ALT an exceptionally sensitive indicator of hepatocyte integrity **(Liu et al., 2014; Youssef & Wu, 2024).**

Length 496 **Last updated** 2007-01-23 v3
Mass (Da) 54,637 **MD5 Checksum**[i] 01237F91D83EE77BFA8E1CEFFC1E0BE3

```
        10         20         30         40         50         60         70         80         90        100        110
MASSTGDRSQ AVRHGLRAKV LTLDGMNPRV RRVEYAVRGP IVQRALELEQ ELRQGVKKPF TEVIRANIGD AQAMGQRPIT FLRQVLALCV NPDLLSSPNF PDDAKKRAER

       120        130        140        150        160        170        180        190        200        210        220
ILQACGGHSL GAYSVSSGIQ LIREDVARYI ERRDGGIPAD PNNVFLSTGA SDAIVTVLKL LVAGEGHTRT GVLIPIPQYP LYSATLAELG AVQVDYYLDE ERAWALDVAE

       230        240        250        260        270        280        290        300        310        320        330
LHRALGQARD HCRPRALCVI NPGNPTGQVQ TRECIEAVIR FAFEERLFLL ADEVYQDNVY AAGSQFHSFK KVLMEMGPPY AGQQELASFH STSKGYMGEC GFRGGYVEVV

       340        350        360        370        380        390        400        410        420        430        440
NMDAAVQQQM LKLMSVRLCP PVPGQALLDL VVSPPAPTDP SFAQFQAEKQ AVLAELAAKA KLTEQVFNEA PGISCNPVQG AMYSFPRVQL PPRAVERAQE LGLAPDMFFC

       450        460        470        480        490
LRLLEETGIC VVPGSGFGQR EGTYHFRMTI LPPLEKLRLL LEKLSRFHAK FTLEYS
```

Figure 29. Primary amino acid sequence of human Alanine Aminotransferase (496 residues) **(UniProt Consortium, 2024).**

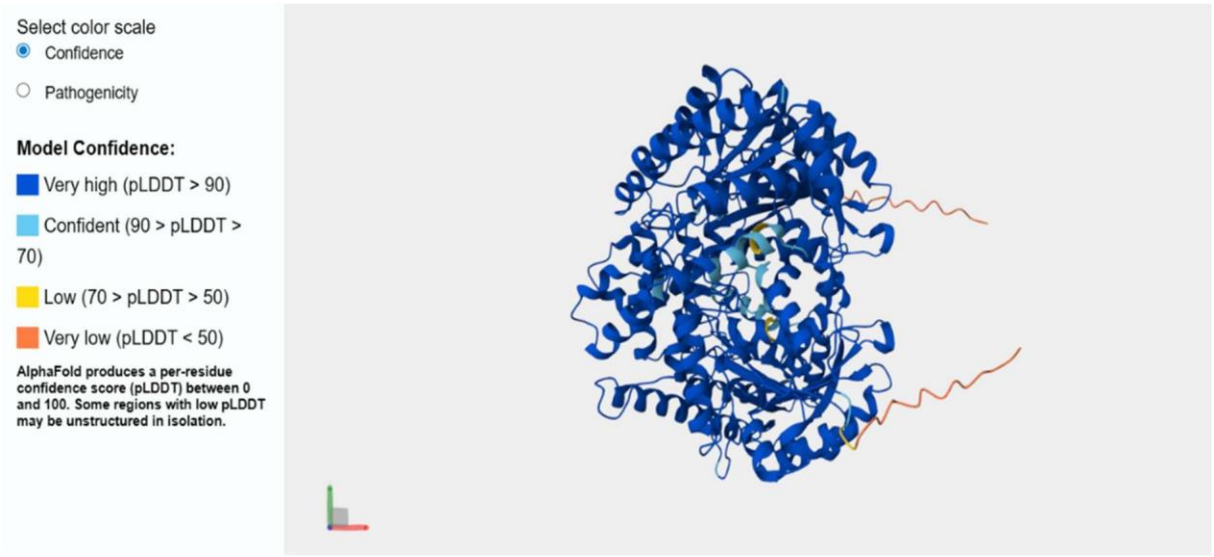


Figure 30. Predicted three-dimensional structure of human Alanine Aminotransferase 1 (GPT/ALT1, UniProt P24298) generated by AlphaFold2, showing the homodimeric assembly colored by per-residue confidence score (pLDDT): dark blue (pLDDT > 90) = very high confidence; cyan (70–90) = confident; orange (< 50) = disordered regions **(UniProt Consortium, 2024).**

In terms of its catalytic mechanism, ALT facilitates the reversible transfer of an amino group from L-alanine to α-ketoglutarate, yielding L-glutamate and pyruvate as reaction products (**Fig. 31**) **(Kamil et al., 2024)**. This transamination reaction is critically dependent on pyridoxal 5'-phosphate (PLP), a biologically active derivative of vitamin B6, which serves as an indispensable coenzyme **(McGill, 2016).** The reversibility of this reaction allows ALT to participate in multiple metabolic pathways simultaneously, underlining its biochemical versatility **(Liu et al., 2014).**

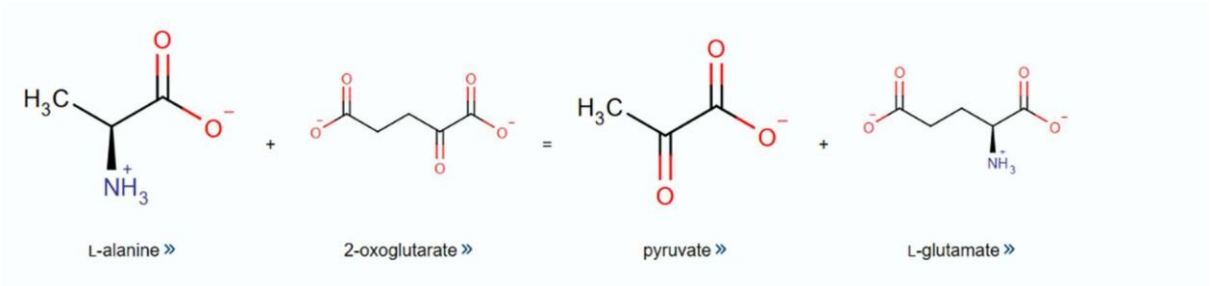


Figure 31. Chemical reaction of L-alanine transamination catalyzed by ALT **(UniProt Consortium, 2024).**

The plasma half-life of ALT has been reported to be approximately 47 ± 10 hours, which is notably longer than that of AST, whose mean plasma half-life is only around 17 hours **(Kamil et al., 2024; Thakur et al., 2024).** This relatively extended half-life means that elevations in serum ALT can persist for a considerable period following hepatocellular injury, making it a valuable marker for monitoring both the progression and the resolution of liver damage over time **(Kamil et al., 2024).**

1.2. Physiological functions

Beyond its well-known role as a liver injury biomarker, ALT performs several indispensable physiological functions **(McGill, 2016).** Its most prominent metabolic role lies within the glucose-alanine cycle, a sophisticated inter-organ metabolic pathway that links muscle tissue and the liver **(McGill, 2016; Youssef & Wu, 2024).** During periods of physiological stress — such as fasting or intense physical exercise — ALT within muscle cells converts pyruvate into alanine by transferring an amino group derived from glutamate **(McGill, 2016).** This alanine is subsequently released into the bloodstream and transported to the liver, where hepatic ALT reverses the reaction, regenerating pyruvate that can then be utilized for gluconeogenesis **(McGill, 2016; Youssef & Wu, 2024).**

While ALT is predominantly a cytosolic enzyme in the liver, it is not exclusively confined to hepatocytes **(Liu et al., 2014).** Smaller quantities of ALT are also found in skeletal muscle, adipose tissue, the intestines, the colon, the prostate, and the brain. However, its concentration in these tissues is considerably lower than in the liver, which is precisely why ALT is regarded as more liver-specific than AST **(McGill, 2016; Youssef & Wu, 2024).**

1.3. Clinical significance and causes of elevation

Under normal physiological conditions, serum ALT levels are maintained at relatively low concentrations, typically below 30 IU/L in healthy individuals. When hepatocyte membrane integrity is compromised — whether through necrosis, toxic injury, or inflammation — intracellular ALT is released into the bloodstream, leading to measurable elevations in serum activity **(Kamil et al., 2024**). It is important to emphasize that the absolute peak of ALT elevation does not correlate with the extent of liver cell damage **(Gowda et al., 2009).**

Among hepatic causes, viral hepatitis caused by HBV and HCV represents one of the most frequent triggers of ALT elevation worldwide **(Liu et al., 2014; Thakur et al., 2024).** In acute injury, ALT levels may exceed 500 U/L **(Gowda et al., 2009),** and can reach up to 50 times the normal range in severe cases (Huang et al., 2006). Non-Alcoholic Fatty Liver Disease (NAFLD)

is currently considered one of the most common causes of unexplained mild-to-moderate ALT elevation in asymptomatic individuals **(Liu et al., 2014; Thakur et al., 2024).** Among extrahepatic causes, conditions such as celiac disease, skeletal muscle injuries, thyroid disorders, and hereditary hemochromatosis have all been documented to produce elevated serum ALT levels **(Kamil et al., 2024).**

Drug-induced liver injury represents another clinically important cause of ALT elevation that deserves particular attention. A wide range of medications — including non-steroidal anti-inflammatory drugs, antipsychotics, antibiotics, and oral contraceptives — are known to induce hepatotoxic reactions of varying severity. First-line anti-tuberculosis drugs — notably isoniazid, rifampicin, and pyrazinamide — are established hepatotoxic agents that may lead to pronounced elevations in serum ALT levels. This form of drug-induced hepatotoxicity, commonly referred to as anti-tuberculosis drug-induced liver injury (AT-DILI), represents one of the most serious complications encountered during tuberculosis treatment, and the monitoring of ALT levels is therefore considered an essential component of patient management throughout the course of anti-tuberculosis therapy **(Thakur et al., 2024).**

Demographic variables also modulate baseline Alanine Aminotransferase ALT levels. Males tend to exhibit higher values than females due to hormonal influences, and peak ALT levels are typically observed in middle-aged adults, followed by a progressive decline in older populations. Ethnic variation in ALT reference ranges has also been reported, suggesting that a single universal threshold may not be appropriate for all populations **(Liu et al., 2014).**

2. Glutamate-Oxaloacetate Transaminase (GOT/AST)

Glutamate-Oxaloacetate Transaminase, widely referred to as Aspartate Aminotransferase (AST) or GOT, is another pivotal enzyme of the aminotransferase family **(Kamil et al., 2024).** Like ALT, it plays an essential role in amino acid metabolism, but its broader tissue distribution and distinct subcellular localization give it a somewhat different clinical profile **(Gowda et al., 2009).** Together with ALT, AST constitutes one of the two cornerstone biomarkers of hepatocellular injury in both clinical practice and biomedical research **(McGill, 2016).**

2.1. Biochemical structure and isoenzymes

AST depends on pyridoxal 5'-phosphate (PLP) for its catalytic activity and facilitates the reversible transamination between aspartic acid and α-ketoglutarate, yielding oxaloacetic acid and glutamic acid as products **(Fig. 32**).

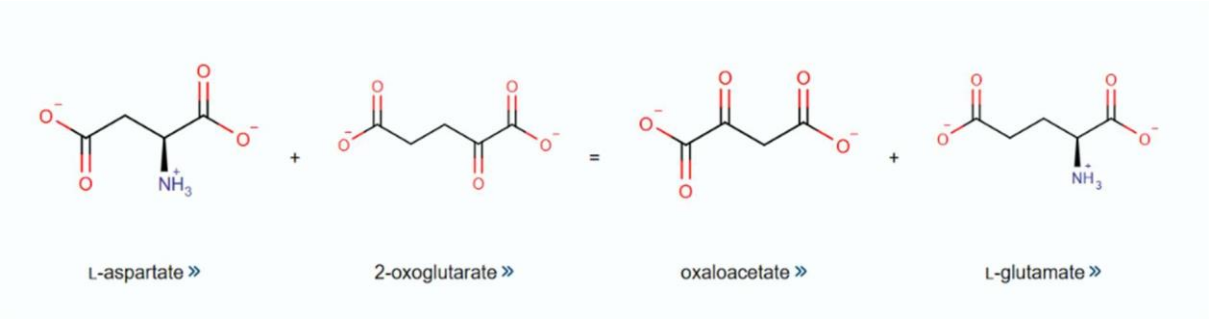


Figure 32. Chemical reaction of L-aspartate transamination catalyzed by AST **(UniProt Consortium, 2024).**

Structurally, AST exists as a homodimer composed of two symmetrical subunits, each consisting of a large domain and a small domain. The cytoplasmic AST monomer is made up of 413 amino acid residues **(Fig. 33)** with a molecular weight of approximately 45 kilodaltons, exhibiting a secondary structure rich in α-helices and β-strands **(Fig. 34) (Kamil et al., 2024).**

Length 413 **Last updated** 2007-01-23 v3
Mass (Da) 46,248 **MD5 Checksum** 67F099236B8364EB70E266B2A3B16ABC

```
MAPPSVFAEV PQAQPVLVFK LTADFREDPD PRKVNLGVGA YRTDDCHPWV LPVVKKVEQK IANDNSLNHE YLPILGLAEF RSCASRLALG DDSPALKEKR VGGVQSLGGT
GALRIGADFL ARWYNGTNNK NTPVYVSSPT WENHNAVFSA AGFKDIRSYR YWDAEKRGLD LQGFLNDLEN APEFSIVVLH ACAHNPTGID PTPEQWKQIA SVMKHRFLFP
FFDSAYQGFA SGNLERDAWA IRYFVSEGFE FFCAQSFSKN FGLYNERVGN LTVVGKEPES ILQVLSQMEK IVRITWSNPP AQGARIVAST LSNPELFEEW TGNVKTMADR
ILTMRSELRA RLEALKTPGT WNHITDQIGM FSFTGLNPKQ VEYLVNEKHI YLLPSGRINV SGLTTKNLDY VATSIHEAVT KIQ
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Figure 33. Primary protein sequence of human cytoplasmic Aspartate Aminotransferase (Length: 413 amino acids) **(UniProt Consortium, 2024).**

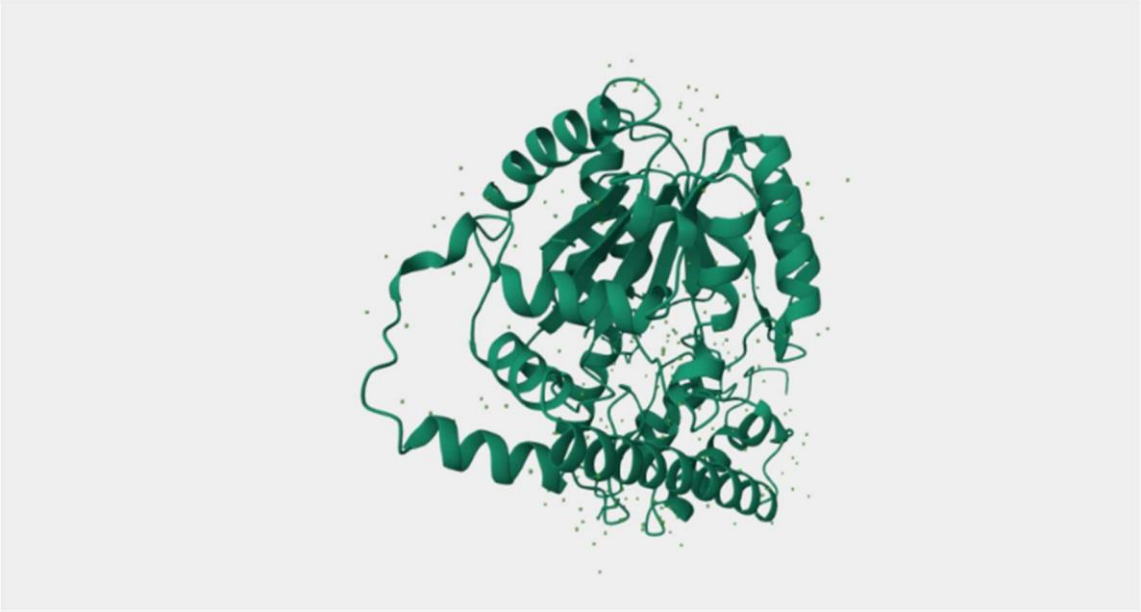


Figure 34. Three-dimensional structure of human cytoplasmic Aspartate Aminotransferase (GOT/c-AST, UniProt P17174) in ribbon representation, illustrating the homodimeric assembly with the characteristic large and small domain architecture of class-I pyridoxal-phosphate-dependent aminotransferases **(UniProt Consortium, 2024).**

A particularly important feature of Aspartate Aminotransferase (AST) is its existence as two genetically and immunologically distinct isoenzymes: the cytoplasmic isoform (c-AST) and the mitochondrial isoform (m-AST) **(Youssef & Wu, 2024; Kamil et al., 2024).** Although both isoforms catalyze the same transamination reaction, they differ in their kinetic properties and share only approximately 45% sequence homology **(Youssef & Wu, 2024).** In the liver, approximately 80% of total AST activity is attributable to the mitochondrial isoform, while the remaining 20% resides in the cytoplasm. In cardiac tissue, mitochondrial AST accounts for roughly 65% of total activity **(Kamil et al., 2024).**

The mean plasma half-life of total Aspartate Aminotransferase (AST) is approximately 17 hours, whereas the mitochondrial isoform (m-AST) has a notably longer half-life of around 87 hours (**Kamil et al., 2024).** The appearance of mitochondrial Aspartate Aminotransferase (AST) in circulation is therefore generally indicative of more severe cellular injury involving mitochondrial disruption, as opposed to the superficial cytoplasmic leakage characterizing milder hepatocellular damage **(McGill, 2016).** Unlike Alanine Aminotransferase (ALT), which is exclusively cytoplasmic, Aspartate Aminotransferase (AST) is present in both the cytoplasm and the mitochondria **(Youssef & Wu, 2024).**

2.2. Physiological functions

One of AST's most critical functions is the maintenance of the intracellular NAD^+/NADH ratio through its participation in the malate-aspartate shuttle, a mechanism that transfers reducing equivalents from the cytosol into the mitochondrial matrix **(McGill, 2016; Youssef & Wu, 2024).** This shuttle supports both glycolysis and oxidative phosphorylation, ensuring adequate ATP production under aerobic conditions **(McGill, 2016).** The products of the AST-catalyzed reaction (alpha-ketoglutarate and oxaloacetate) also replenish key intermediates of the Krebs cycle, contributing indirectly to the biosynthesis of purines, pyrimidines, glucose, urea, and various proteins **(Thakur et al., 2024).**

Unlike ALT, AST is not organ-specific. Its activity has been detected in virtually all human tissues, with particularly high concentrations in the heart, liver, skeletal muscle, kidney, and brain. Notably, AST activity in cardiac tissue exceeds that found in the liver **(Gowda et al., 2009; Kamil et al., 2024),** which explains why acute myocardial infarction can produce significant AST elevations independently of hepatic involvement **(Kamil et al., 2024).**

2.3. Clinical significance and causes of elevation

Serum AST reference ranges are generally reported between 0–35 U/L, although some studies consider 40 U/L as the upper normal limit. These differences are mainly attributed to variations in laboratory methods and reference populations. **(Gowda et al., 2009; Huang et al., 2006).** In severe tissue injury, AST levels can rise 10 to 20 times above the normal range **(Huang et al., 2006).** Elevated AST is associated with viral hepatitis, alcoholic liver disease, cirrhosis, drug-induced hepatotoxicity, myocardial infarction, skeletal muscle injury, hemolysis, and septic shock **(Kamil et al., 2024; Thakur et al., 2024).**

The AST/ALT ratio, known as the De Ritis ratio, carries important diagnostic value. A ratio exceeding 2 is characteristically observed in alcoholic hepatitis, while a ratio greater than 1 suggests advanced liver fibrosis or chronic hepatitis C infection **(Gowda et al., 2009).** This pattern reflects the preferential mitochondrial damage caused by alcohol, which promotes release of the mitochondrial AST isoform **(Youssef & Wu, 2024).**

Monitoring serum AST and ALT levels is fundamental during anti-tuberculosis therapy for the early recognition of drug-induced hepatotoxicity. The hepatotoxic potential of first-line anti-tuberculosis agents, particularly isoniazid, rifampicin, and pyrazinamide, is well established, and elevated AST levels during treatment may signal the onset of serious liver injury requiring clinical intervention **(Thakur et al., 2024).** Given that AST reflects both cytoplasmic and

mitochondrial hepatocellular damage, its elevation in the context of anti-tuberculosis drug-induced liver injury may indicate a more profound degree of hepatic insult than ALT elevation alone **(Kamil et al., 2024; Thakur et al., 2024).**

Regarding release mechanisms, plasma membrane disruption during oncotic necrosis represents the most common pathway. However, membrane blebs forming during ischemia-reperfusion injury can also release cytosolic AST without complete cell death **(McGill, 2016).** In fulminant hepatic failure, massive hepatocyte loss paradoxically leads to declining AST levels despite ongoing injury, as insufficient viable liver tissue remains to release the enzyme a clinical trap that must not be misinterpreted as improvement **(Youssef & Wu, 2024).**

Table 7. Comparative Overview of GPT/ALT and GOT/AST: Biochemical, Physiological, and Clinical Characteristics**. (Kamil et al., 2024; Gowda et al., 2009; Liu et al., 2014)**

Feature	GPT / ALT	GOT / AST
Full name	Alanine Aminotransferase	Aspartate Aminotransferase
Amino acid substrate	L-Alanine	L-Aspartate
Reaction product	Pyruvate	Oxaloacetate
Coenzyme	Pyridoxal 5'-phosphate (PLP)	Pyridoxal 5'-phosphate (PLP)
Amino acid composition	496 amino acids	413 amino acids (cytoplasmic monomer)
Molecular weight	Not reported	~45 kDa
Subcellular localization	Cytoplasm only	Cytoplasm + Mitochondria
Isoenzymes	ALT1 (cytosolic), ALT2 (mitochondrial)	c-AST (cytoplasmic), m-AST (mitochondrial)

Plasma half-life	~47 ± 10 hours	~17 h (total); ~87 h (m-AST)
Primary tissue	Liver (highly specific)	Liver, heart, muscle, kidney, brain
Organ specificity	High (liver-specific)	Low (multi-organ)
Normal serum range	< 30 IU/L	0–35 U/L (up to 40 U/L)
Elevation in severe injury	Up to 50× normal	10–20× normal
Main physiological role	Glucose-alanine cycle	Malate-aspartate shuttle / NAD^+/NADH ratio
Best marker for	Hepatocellular injury	Alcoholic liver disease / multi-organ injury
De Ritis ratio (AST/ALT)	—	>2 alcoholic hepatitis; >1 fibrosis/HCV

3. Association of GPT and GOT in tuberculosis patients

Alanine aminotransferase (ALT/GPT) and aspartate aminotransferase (AST/GOT) are two key hepatic enzymes whose levels in tuberculosis patients are affected by both *Mycobacterium tuberculosis* infection and its pharmacological treatment **(Sales et al., 2023; Thakur et al., 2024).** A prospective Brazilian study found that newly diagnosed TB patients already presented with significantly elevated ALT and AST compared to healthy controls before any drug exposure, indicating that hepatic involvement is a feature of active tuberculosis and not solely a drug-induced phenomenon **(Sales et al., 2023**). This baseline elevation underlines the importance of pre-treatment liver function assessment as a mandatory clinical reference point **(Sales et al., 2023).**

3.1. Biochemical basis of co-elevation

ALT and AST are released into the bloodstream when hepatocytes undergo necrosis or inflammatory damage, and their simultaneous rise indicates the extent of liver damage. The two enzymes differ in tissue distribution. ALT is more liver-specific, with higher activity in hepatic tissue than in other organs. AST is found across multiple tissues, including cardiac muscle, skeletal muscle, and the brain,which reduces its specificity for liver injury when considered alone **(Thakur et al., 2024).**

This difference gives the AST/ALT ratio clinical value. A disproportionate AST rise may suggest extrahepatic sources of injury, while a predominant ALT elevation more reliably points to the liver. Their plasma half-lives also differ: ALT persists for approximately 47 hours, while AST clears in around 17 hours, meaning that serial measurements can indicate whether liver impairment is ongoing or resolving **(Thakur et al., 2024)**. The De Ritis ratio (AST/ALT) adds further diagnostic value — a ratio exceeding 2 is generally associated with severe mitochondrial injury, while values between 1 and 2 may suggest drug-induced hepatocellular damage **(Gowda et al., 2009).**

3.2. Correlation between ALT and AST in TB patients

In TB patients with documented liver disease who developed AT-DILI, both ALT and AST showed strong positive correlations with injury occurrence. Baseline ALT and AST correlated with AT-DILI at $r = 0.947$ and $r = 0.963$ respectively ($p < 0.001$), suggesting that their co-elevation is a meaningful signal of hepatic dysfunction **(Wu et al., 2025).**

Longitudinal data from a Congolese cohort further illustrate this association. Average AST (Aspartate Aminotransferase) and ALT (Alanine Aminotransferase) values during the first two months of directly observed therapy (DOTS) were 19.2 ± 7.8 U/L (Units per liter) and 14.8 ± 8.9 U/L (Units per liter) respectively, with both rising significantly across the observation period. Both remained within the normal reference range in most patients without adverse reactions, highlighting that co-elevation does not automatically indicate Anti-Tuberculosis Drug-Induced Liver Injury (AT-DILI). The magnitude and trajectory of change must be interpreted against the upper limit of normal (ULN) (Upper Limit of Normal) — the highest enzyme value expected in a healthy individual (Mokondjimobe et al., 2012).

3.3. Drug-specific modulation of the ALT–AST association

The ALT–AST association is also shaped by which drug is responsible for hepatic stress. A Taiwanese case-control study found that patients with isoniazid-induced AT-DILI carried more mitochondrial DNA variants in the ND1 and ND5 genes — components of oxidative phosphorylation complex I — suggesting possible mitochondrial involvement in their co-elevation **(Lee et al., 2019).** Both ALT and AST are linked to mitochondrial energy metabolism through their roles in the malate-aspartate shuttle **(Thakur et al., 2024).** Patients with rifampicin- or pyrazinamide-induced AT-DILI showed no significant association with mitochondrial DNA variants, suggesting that the elevation pattern varies by drug **(Lee et al., 2019).**

4. Variations of ALT and AST in tuberculosis patients

ALT and AST levels change throughout the course of tuberculosis and its treatment in a time-dependent manner **(Mokondjimobe et al., 2012; Zhong et al., 2021).** Monitoring these variations is important for detecting AT-DILI and for distinguishing pathological changes from the normal fluctuations expected during treatment **(Wu et al., 2025).**

4.1. Pre-treatment baseline variations

ALT and AST are often abnormal before anti-TB therapy begins. In a Brazilian cohort, TB patients showed higher median values of both enzymes compared to healthy controls at diagnosis, before any drug exposure. Nearly half of the patients already had elevated ALP and GGT, and all had elevated CRP at presentation. This indicates that hepatic inflammation may be present at the time of TB diagnosis, independent of treatment **(Sales et al., 2023).**

In patients with pre-existing liver disease, baseline values are predictably higher. TB patients who later developed AT-DILI had baseline ALT of 80.24 ± 10.83 U/L and AST of 70.08 ± 8.38 U/L, compared to 30.37 ± 5.38 U/L and 25.27 ± 3.46 U/L in non-AT-DILI patients ($p < 0.001$). These findings suggest that pre-treatment enzyme levels may help identify patients at higher risk of developing AT-DILI **(Wu et al., 2025).**

4.2. Variations during Anti-TB treatment

The first two months of anti-TB therapy represent the period of greatest enzyme variation. In a Congolese cohort, both AST and ALT rose significantly across the 60-day intensive phase (ANOVA, $p < 0.0001$), peaking at day 30 before partially stabilizing by day 60. Most patients

remained within the normal range, suggesting a pharmacological response rather than overt liver damage **(Mokondjimobe et al., 2012).**

In a Taiwanese cohort, mean time to peak ALT was 33.8 ± 23.6 days, reaching 12.5 × ULN in AT-DILI patients. This level of elevation meets the clinical threshold of AT-DILI, defined as ALT ≥ 5× ULN, or ALT ≥ 3× ULN combined with total bilirubin ≥ 2× ULN **(Lee et al., 2019).** As treatment duration increases, the risk of enzyme elevation also increases, suggesting a progressive accumulation of hepatotoxic drug metabolites **(Zhong et al., 2021).**

4.3. Variations according to the causative drug

4.3.1. Isoniazid

Isoniazid-induced AT-DILI is associated with the most distinctive ALT and AST elevation profile. Affected patients carried a higher burden of nonsynonymous substitutions in the mitochondrial ND5 gene, suggesting possible mitochondrial complex I involvement. Hydrazine — the toxic isoniazid metabolite — may further inhibit complex II, potentially contributing to enzyme elevation through impaired hepatocyte energy metabolism **(Lee et al., 2019).**

4.3.2. Rifampicin and Pyrazinamide

Rifampicin-induced AT-DILI showed no association with mitochondrial DNA variants, and its mechanism may involve lipid accumulation and oxidative stress. Pyrazinamide-induced AT-DILI was the most frequent among the three drugs in the studied cohort, also unlinked to mitochondrial variants, with PPAR-α downregulation and enhanced oxidative stress proposed as possible mechanisms **(Lee et al., 2019).**

4.3.3. Combined regimens

Rifampicin induces INH hydrolase activity, accelerating hydrazine production from isoniazid and amplifying its hepatotoxic potential. Patients on combined anti-TB regimens showed a significantly higher risk of developing AT-DILI compared to those on monotherapy. Plasma isoniazid above 2 mg/L was independently associated with ALT and AST elevation **(El Bouazzi et al., 2016).**

4.4. Genetic susceptibility and post-treatment normalization

4.4.1. Genetic susceptibility

Genetic background also influences ALT and AST variation during anti-TB therapy. The NAT2 slow acetylator genotype impairs isoniazid metabolism and prolongs its plasma half-life, leading to higher drug concentrations and greater hepatic enzyme responses. In Morocco, 72.39% of individuals carry this phenotype, which is considered a contributing factor to the elevated AT-DILI incidence observed in that population **(El Bouazzi et al., 2016).**

At the mitochondrial level, the cumulative burden of genetic variants appears to drive ALT and AST elevation in isoniazid-treated patients. Mean ND5 variant count was higher in isoniazid-induced AT-DILI patients (3.5 per person) than in non-AT-DILI controls (2.0 per person, $p = 0.005$), and nonsynonymous substitutions in ND5 were also elevated ($p = 0.033$) **(Lee et al., 2019).**

4.4.2. Post-treatment normalization

When the offending drug is withdrawn, ALT and AST typically return to normal levels **(El Bouazzi et al., 2016; Mokondjimobe et al., 2012).** In the Moroccan cohort, median normalization time was 18 days (range: 10–30 days) **(El Bouazzi et al., 2016).** Post-treatment values in a Congolese cohort — measured at 15 and 45 days after the continuation phase — were not significantly different from pre-treatment baseline values ($p > 0.05$), suggesting that enzyme variations are reversible in patients without structural liver damage **(Mokondjimobe et al., 2012).** This reversibility underlines the importance of early detection and prompt drug withdrawal in the management of AT-DILI **(El Bouazzi et al., 2016).**

4.4.3. Objectives of the Study

This study aims to evaluate the variations of Glutamate-Pyruvate Transaminase (GPT/ALT) and Glutamate-Oxaloacetate Transaminase (GOT/AST) in patients with different forms tuberculosis, and to assess their clinical significance as biomarkers of liver function during the disease progression and anti-tuberculosis treatment**.**

More specifically, this work also aimed to:

- Analyzing the baseline variations of GPT and GOT in newly diagnosed tuberculosis patients;
- Monitoring the dynamic changes of these enzymes during anti-tuberculosis therapy;
- Investigating the relationship between anti-tuberculous drugs and hepatic enzyme alterations;
- Evaluating the potential of GPT and GOT as early indicators of anti-tuberculosis drug-induced liver injury (AT-DILI);

Emphasizing the importance of regular biochemical monitoring for the prevention and early detection of hepatic complications in tuberculosis patients

Part two: Practical part

Chapter III: Materiel and Method

1. Study Design and Duration

As part of academic training, a descriptive, analytical, and retrospective study was conducted, aiming to analyze the clinical data and their correlation with GPT an GOT variation from patients diagnosed with tuberculosis from various regions of Mila Province. This study was carried out during the field training period, which extended from February 15 to April 20, 2026.

2. Study Location

This study was conducted in four public health institutions distributed across various municipalities of Mila Province. The study was carried out in these healthcare facilities with the aim of covering a broad geographical and representative range, in order to accurately reflect the epidemiological situation within the province.

2.1. Study Area

Mila Province is located in the northeastern part of Algeria. It is bordered to the north by Jijel Province, to the northeast by Skikda, to the east by Constantine, to the southeast by Oum El Bouaghi, to the south by Batna, and to the west by Sétif. The province covers an area of 9,375 km² and is administratively divided into 13 districts (daïras) comprising 32 municipalities, including Zgaiya, Redjas, Rouached, Ahmed Rachedi, Beni Guecha, Ferdjioua, Grarem Gouga, Shigara, Outemania, Tassala, Chlghoum- Laïd among others. According to the 2008 census, Mila Province had a total population of 766,886, resulting in a population density of approximately 225 inhabitants per km². These demographic and geographic indicators provide an essential basis for understanding the population distribution and territorial structure of the studied area.

2.2. Presentation of Internship Locations

2.2.1. The Public Primary Healthcare Institution – Chelghoum Laïd

2.2.1.1. Clinic Location

The “18 Février” Multi-Service Clinic is located in the city of Chelghoum Laïd, Mila Province, Algeria. The clinic is strategically situated within the urban area of the city, near several public facilities, which facilitates access for the inhabitants of Chelghoum Laïd and neighboring districts. Its strategic location contributes to ensuring the delivery of primary healthcare services to citizens, as it represents one of the main healthcare structures affiliated with the Public Establishment of Local Healthcare of Chelghoum Laïd **(Fig. 35)**.

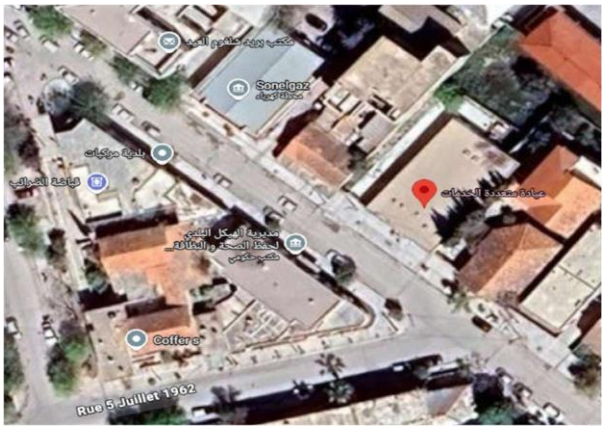




Figure 35. The Public Primary Healthcare Institution – Chelghoum Laïd **(ref, google map).**

2.2.1.2. Clinic Overview

The "18 Février" Multi-Service Clinic is one of the primary local healthcare institutions dedicated to providing preventive and curative healthcare services for the local population, within the framework of strengthening primary healthcare and improving the quality of medical services delivered.

The clinic includes several integrated healthcare units and departments, namely:

• General Medical Consultation Unit: Provides daily medical consultations and examinations, ensuring primary medical follow-up and diagnosis of various health conditions.

• Dental Care Unit: Offers preventive and therapeutic dental services, supported by modern medical equipment.

• Community Healthcare Unit: Aims to promote preventive healthcare services, vaccination programs, and primary healthcare management for the population.

• Vaccination Unit: Oversees the implementation of national vaccination programs, including childhood immunization campaigns against poliomyelitis and other infectious diseases.

• Mother and Child Healthcare Unit: Ensures the follow-up of pregnant women, maternal and child healthcare, and monitoring of children's healthy growth.

• School Health Unit: Includes screening and monitoring units (UDS) within educational institutions and aims to supervise school health and ensure early disease detection.

• Health Programs Unit: Responsible for the follow-up of chronic diseases, in addition to tuberculosis prevention and monitoring programs.

• Administrative and Digitalization Services: Manage medical records and appointment organization, while adopting digitalization in consultation offices to improve the quality of healthcare services.

This integrated organization allows the clinic to ensure effective and sustainable healthcare services, while contributing to reducing pressure on major hospital institutions and strengthening public health in Mila Province.

2.2.2. The Public Primary Healthcare Facility – Bouarroudj, Mila

2.2.2.1. Clinic Location

The public primary health care center is located in the city of Mila, located in eastern Algeria. Its strategic location in a densely populated urban area makes it a key hub for providing basic health services to the city's residents and its suburbs. The center is easily accessible by various means of transportation that enhances its ability to respond quickly to citizens' daily health needs **(Fig. 36).**

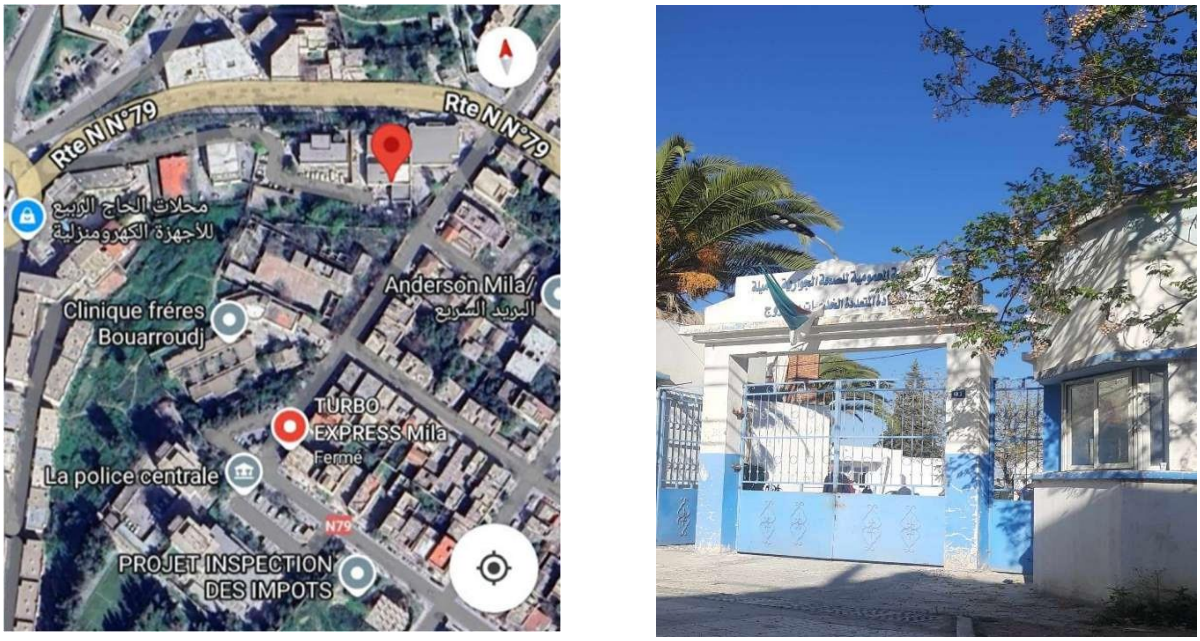


Figure 36. The Public Primary Healthcare Facility – Bouarroudj, Mila **(google map)**

2.2.2.2. Clinic Overview

In accordance with the joint ministerial decree dated December 20, 2009, which defines the internal structure of public primary healthcare institutions, the Mila Primary Healthcare Center is designed to provide comprehensive services in prevention, diagnosis, treatment, and health education.

The center is organized into several essential units:

- General Medicine Unit: Provides daily medical consultations, diagnoses common conditions, and refers patients to specialists when necessary.
- Maternal and Child Health Unit: Focuses on prenatal care, postnatal follow-up, and child immunization as per the national vaccination program.
- Dental Care Unit: Offers preventive and restorative dental services, including routine check-ups and basic treatments.
- Emergency Unit: Manages minor emergencies, providing first aid and stabilizing patients for referral to higher-level hospitals if needed.
- Chronic Disease Follow-Up Unit: Ensures continuous care for patients with chronic conditions such as diabetes, hypertension, and asthma.
- Preventive and Immunization Unit: Organizes vaccination campaigns and conducts health awareness programs in schools and neighbourhoods.
- Radiology Room: Equipped to provide basic imaging services to support clinical diagnosis.
- Pharmacy: Responsible for ensuring the availability and proper dispensing of essential medications as prescribed by healthcare providers.
- Administrative Services: Manages patient records, appointment scheduling, and coordination with other healthcare institutions in the province.

This center is a cornerstone of the healthcare system in Mila Province, playing a crucial role in providing quality, accessible, and comprehensive healthcare services. It contributes significantly to early intervention, preventive care, and the overall health promotion efforts in the region.

2.2.3. Public Primary Healthcare Institution of Ferdjioua

2.2.3.1. Clinic Location

The Ferdjioua Public Neighbourhood Health Institution is located in the Ferdjioua municipality, Mila Province, Algeria. The institution enjoys a strategic location in a densely populated area, directly below the Madah Hospital, making it easily accessible to the residents of Ferdjioua and the surrounding rural areas. Its location enhances its role as a major provider of primary healthcare services, serving as the first point of contact for patients seeking medical assistance after completing their hospitalization **(Fig. 37).**



Figure 37. Public Primary Healthcare Institution of Ferdjioua **(Ref, google map).**

2.2.3.2. Clinic Overview

In accordance with the Joint Ministerial Decree of December 20, 2009, which establishes the regulatory framework for public community health institutions in Algeria, the Ferjioua Institution is designed to ensure the efficient and effective delivery of a wide range of primary healthcare services. The institution consists of several basic units designed to meet both preventive and curative healthcare needs:

- General Medicine Unit: Provides general consultations, diagnostics, and outpatient care, forming the basis of primary medical services.
- Maternal and Child Health Unit: Provides comprehensive maternal care, prenatal and postnatal services, child immunizations, and growth monitoring.

- Dental Care Unit: Performs preventive and restorative dental procedures, focusing on oral health at the community level.
- Chronic Diseases Unit: Focuses on long-term follow-up and management of non-communicable diseases, including diabetes, hypertension, and cardiovascular disease.
- Preventive Care and Immunization Unit: Implements national immunization programs and leads health awareness campaigns throughout the community.
- Radiology Room: Facilitates initial diagnostic imaging to meet the needs of local patients.
- Pharmacy Unit: Ensures the availability, controlled storage, and distribution of essential prescription medications within the facility.
- Administrative Services: Manages patient records, scheduling, coordination with external healthcare providers, and internal operations.

This integrated, community-focused structure enables the Ferjioua Neighborhood Public Health Foundation to provide responsive, equitable, and sustainable healthcare services. It plays a pivotal role in supporting the health system of the Mila Province by addressing local health challenges and improving health outcomes.

2.2.4. Public Primary Healthcare Institution of Ouled Achour

2.2.4.1. Clinic Location

The Public Primary Healthcare Institution of Hammam Ouled Achour is located in the municipality of Ain Beida Ahriche, Mila Province, Algeria, in a rural area along a main road connecting several neighboring municipalities, which makes it easily accessible for residents of the region and surrounding rural communities **(Fig. 38)**.

This location also strengthens its role as a specialized healthcare center for the follow-up and treatment of tuberculosis patients, as it receives patients for regular medical monitoring, assessment of disease progression, and distribution of anti-tuberculosis treatment within the framework of the National Tuberculosis and Respiratory Diseases Control Program.





Figure 38. Public Primary Healthcare Institution of Ouled Achour (Google Maps).

2.2.4.2. Clinic Overview

This healthcare structure operates as a specialized unit for the control and follow-up of tuberculosis and respiratory diseases (SCTMR: Structure de Contrôle de la Tuberculose et des Maladies Respiratoires). Its activities are mainly focused on the monitoring and management of tuberculosis patients within the framework of the national tuberculosis control program.

The clinic ensures regular medical follow-up of patients undergoing anti-tuberculosis treatment and supervises treatment adherence in order to improve recovery rates and reduce disease transmission. It also provides anti-tuberculosis medications and maintains medical records for patient monitoring and case registration.

In addition, the structure performs tuberculin skin testing (TST) for suspected tuberculosis cases as part of the diagnostic orientation and screening process. Health education and awareness activities concerning tuberculosis prevention, transmission, and treatment compliance are also carried out to support public health efforts within the local community.

3. Methodology

3.1. Data Collection and Investigation

As part of our study, we collected and analysed clinical data of tuberculosis patients who diagnosed and monitored for treatment in public health institutions, covering a ten-year period (from 2016 to 2025).

Our analysis focused on patients who had performed a GPT and GOT rates at the beginning of their treatment and also performed several other measures of these two parameters at several times during their treatment period in order to follow the variation of these two

parameters with treatment duration. Along with these two parameters' rates, a range of clinical variables, including gender, age, geographic area of residence, general health condition, presence of comorbidities, type of tuberculosis, treatment regimens, and treatment outcomes. In addition, several biological and laboratory parameters were also evaluated.

3.2. Selection Criteria

3.2.1. Inclusion Criteria

In the context of this study, specific and well-defined inclusion criteria were applied. The selected sample consisted of patients with confirmed tuberculosis, regardless of their age or gender. This included individuals who were either hospitalized or monitored at various public health facilities.

Diagnosis confirmation was based on several diagnostic methods, primarily the presence of characteristic radiological signs on chest computed tomography (CT) scans, or positive microscopic detection of *Mycobacterium tuberculosis* in sputum or respiratory secretions.

Bacteriological confirmation was also obtained through culture of clinical samples on appropriate media. In addition, molecular techniques such as PCR (polymerase chain reaction) were used for the genetic identification of the pathogen. For extrapulmonary tuberculosis, diagnosis was confirmed through biopsy of the affected tissue followed by laboratory identification of the causative agent.

3.2.2. Exclusion Criteria

All cases in which tuberculosis infection was not clearly confirmed using standard diagnostic methods—such as radiological imaging, microscopic examination, or bacteriological culture—were excluded from the study. Additionally, patients whose medical records lacked essential clinical or biological data required for statistical analysis—such as age, gender, place of residence, type of tuberculosis, treatment initiation and completion dates, duration of treatment, and other relevant variables—were also excluded. Furthermore, cases that had been diagnosed with tuberculosis but did not undergo regular medical follow-up, whether in hospitals or public health institutions, were excluded due to the potential impact on the reliability and validity of the study findings.

3.3. Study Population

Our study included a sample of 521patients who were diagnosed and followed up in various public health institutions across the Wilaya of Mila during the period from 2016 to 2025. Tuberculosis infection was confirmed using standard diagnostic methods, including radiological imaging, microscopic examination, bacteriological culture, and, in some cases, molecular testing such as PCR, particularly in cases requiring greater diagnostic precision.

Clinical data were collected from official medical records maintained by the relevant health services, with the aim of analyzing and studying the information according to established scientific and statistical standards. The treatment outcomes of tuberculosis patients were classified based on their response to therapy as follows:

Cured: Patients who completed the full course of treatment and were confirmed bacteriologically negative at the end of therapy.

Completed: Refers to patients who adhered to and completed the treatment regimen, although no final laboratory confirmation of recovery was available.

Treatment failed: Applies to patients who, despite adhering to the prescribed treatment, remained bacteriologically positive after five months of therapy.

Treatment Default: Includes patients who began treatment but discontinued it for a prolonged period, while the disease remained active.

Died: Encompasses patients who died from any cause during the course of tuberculosis treatment.

Transfer-out patients: Refers to patients whose treatment outcomes could not be determined due to transfer to another healthcare facility or district.

Relapse: It is the condition in which a patient is considered cured of the disease, but after a period of stopping treatment, the symptoms return again.

According to the World Health Organization standards, tuberculosis treatment outcomes are classified into two main categories:

- **Successful Treatment Outcome:** Refers to cases in which patients have completed the full course of treatment, achieved clinical recovery with resolution of symptoms, and obtained negative results on smear microscopy at the end of treatment.

Unsuccessful Treatment Outcome: Includes patients who did not exhibit an effective response to therapy, resulting in treatment failure, those who died during the course of treatment, as well as patients who experienced a relapse after initial recovery

3.4. Clinical and Biological Data Analysis

The clinical data and biological parameters were compiled into Excel sheets to create a dedicated database, which will later be used for result interpretation. Initially, the clinical data were analysed in a comprehensive manner, followed by comparisons across different categories based on gender, mortality rates, and other relevant variables identified according to the study objectives. These analyses will be used to draw conclusions regarding the impact of various factors on patient outcomes.

3.5. Statistical Data Analysis

Statistical analysis was performed using the IBM SPSS. Descriptive statistics were presented in the form of frequencies or means ± standard deviation. Categorical variables were compared using the $\chi 2$ test, while continuous variables were compared using the One-way ANOVA. A *P*-value of less than 0.05 was considered statistically significant. Graphical analyses were conducted using GraphPad Prism Statistics software.

Chapter IV: Results and discussion

In the framework of this study, was a comprehensive analysis based on the evaluation variations of Alanine Aminotransferase (ALAT) (also called Glutamate-Pyruvate Transaminase (GPT)) and Aspartate Aminotransferase (ASAT) (also called Glutamate-Oxaloacetate Transaminase (GOT)) in tuberculosis patients, with the aim of evaluating the impact of anti-tuberculosis treatment on liver enzyme levels among TB patients treated and followed in the public health institutions. In addition, the study assessed the prevalence of comorbidities and monitored changes in biological parameters, particularly liver function markers, throughout the course of treatment. Furthermore, the progression of tuberculosis was analyzed over a nine-year period (2016–2025), with particular attention to temporal trends in disease incidence.

Additionally, a comparative analysis was performed to evaluate differences in GPT and GOT variations between female and male patients, in order to investigate the potential influence of gender on hepatic response during tuberculosis treatment. Finally, enzyme variations were compared between patients who successfully completed treatment and achieved recovery and those who experienced treatment failure, in order to identify possible associations between liver enzyme fluctuations and treatment outcomes.

1. Overview on clinical patient's characteristics

The present study involved 521 patients diagnosed with different clinical forms of tuberculosis. For appropriate statistical processing and interpretation, the collected clinical variables were presented either as frequencies or as mean values accompanied by standard deviations (mean ± SD). The dataset obtained in this work served as a key foundation for assessing the changes in ALAT and ASAT levels among tuberculosis patients throughout anti-tuberculosis treatment and during follow-up.

1.1. Global overview and sex distribution

The study included a total of 521 tuberculosis patients. Women represented the majority of cases, representing 68% (n=355) of our patients, whereas men accounted for 32% (n=166) (**Fig. 39)**.

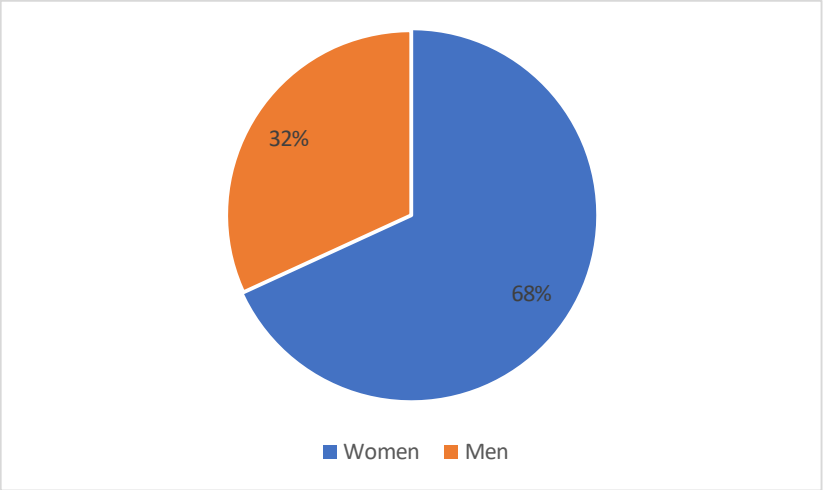


Figure 39. Distribution of patients by gender.

The women predominance observed in our cohort is consistent with previous reports documenting a higher frequency of extrapulmonary tuberculosis among females across multiple geographic settings **(Dabitao and Bishai 2023; Baya et al. 2023).** In contrast, Yu et al. (2024) reported a male predominance in their Chinese cohort (male-to- female ratio were 2.03:1) explained by a pattern attributed to non-biological gender-related factors such as higher rates of tobacco use, occupational exposure, and reduced health-seeking behavior among males. The reversal of this ratio in our study may be related to the predominance of extrapulmonary forms (64%), which are known to disproportionately affect women. This pattern may partly be explained by hormonal and immunological differences between sexes, although the exact mechanisms remain incompletely understood **(Dabitao and Bishai 2023).**

1.2. Age distribution according to gender

Our results showed that ages of patients ranged from 18 to 96 years, with a mean of 46.51 ± 19.57 years. When stratified by gender, women predominated in all age groups. Among women, the highest number of cases was observed in the 18 to 29 years age group (98 cases), followed by groups that include the 30 to 39 years and women aged more than 70 years, with 70 cases each. Among men, the greatest numbers were recorded in the 30 to 39 years (36 cases) and 18 to 29 years (34 cases) groups **(Fig. 40).** Dong et al. (2022) reported a peak in TB incidence among individuals aged 20–24 years, whose likelihood of developing tuberculosis was 1.73 to 3.03 times greater than that of the reference group. Likewise, Abiot et al. (2023) identified the 25–34-year age group as having the highest incidence rate, corroborating our findings that young adults constitute the population most susceptible to tuberculosis. Zhenguo et al. (2025) demonstrated that tuberculosis incidence is disproportionately higher among the

elderly population, particularly in the 70–79-year age group, which represented 49.79% of the participants. This elevated incidence was associated with immunosenescence and the higher prevalence of comorbid conditions in older individuals, factors that increase vulnerability to infection.

The predominance of females across all age groups in our study aligns with previous findings and may reflect sex-related biological and anatomical factors that influence susceptibility to the disease. Baya et al. (2023) reported that lymph node and abdominal tuberculosis were significantly more frequent in females (p=0.004 and p=0.015, respectively), whereas pleural tuberculosis predominated in males. A finding that mirrors the distribution observed in our own cohort and suggests that the sex-specific pattern may be largely driven by site-specific rather than global biological differences. As for the male age distribution, the concentration of cases in the 18–29 and 30–39 years groups is consistent with the pattern described by Yu et al. (2024) and Dabitao and Bishai (2023), in which tuberculosis in males peaks during working age, a trend commonly attributed to greater occupational exposure, tobacco and alcohol use, and reduced health-seeking behavior which though the relative contribution of each factor may vary depending on the local context.

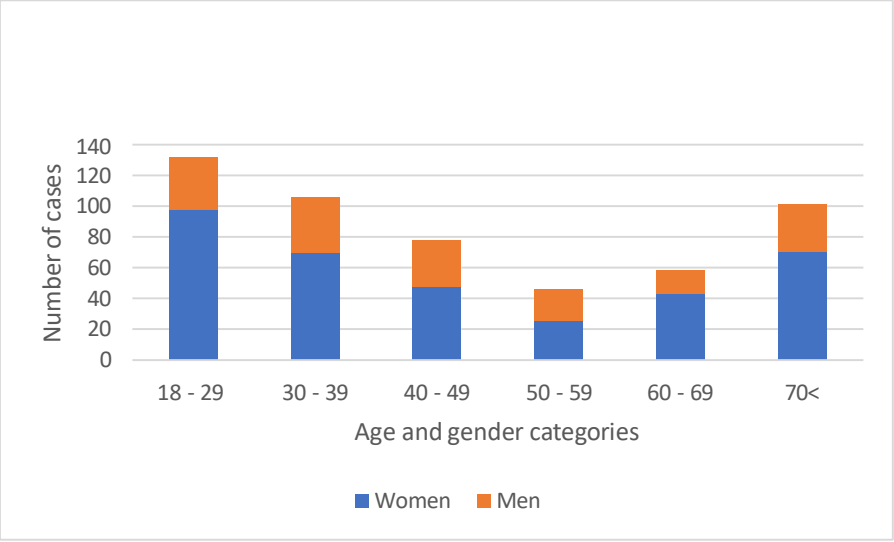


Figure 40. Distribution of the age group of patients by gender

1.3. Comorbidities

Of the 521 patients included in this study, 150 (28.8%) presented at least one comorbid condition, while the remaining 371 patients (71.2%) had no notable medical history **(Table 8).** Of comorbidities, cardiovascular diseases constituted the most frequently observed in 69 patients (13.3%). Within this category, blood hypertension predominated (present among 50

patients, 9.6%), followed by cardiopathy in 15 patients (2.9%) and other cardiovascular conditions, including pulmonary embolism and pericardial effusion, in 4 patients (0.8%). Diabetes mellitus represented the second most common comorbidity, identified in 41 patients (7.9%). Among diabetic patients, the type was not specified in the medical records for 21 patients (4.0%), while type 2 diabetes was documented in 17 patients (3.3%) and type 1 diabetes in 3 patients (0.6%). Other comorbidities were recorded with lower frequency. Respiratory disease affected 23 patients (4.4%), miscellaneous conditions 17 patients (3.3%), and thyroid disease 14 patients (2.7%). Skin and autoimmune disorders were noted in 10 patients (1.9%), gastrointestinal disease in 9 patients (1.7%), endocrine/metabolic disease in 8 patients (1.5%), blood disease and anemia in 8 patients (1.5%), and neurological disease or stroke in 6 patients (1.2%).

The distribution of comorbidities observed among TB patients in this study reflects a pattern increasingly reported in the literature. Cardiovascular disease emerged as the most prevalent comorbidity, with hypertension representing its predominant manifestation. This pattern is well-documented, as Wang et al. (2024) similarly identified hypertensive diseases as the leading comorbidity among PTB patients, and attributed this association to the role of systemic inflammation as a shared pathophysiological mechanism linking cardiovascular conditions and tuberculosis infection. Furthermore, the same authors demonstrated that chronic ischemic heart disease was significantly associated with an increased risk of developing PTB (aOR 1.58, 95% CI 1.31–1.90), reinforcing the notion that circulatory system diseases and tuberculosis share a complex and clinically relevant interplay.

Diabetes mellitus ranked as the second most frequent comorbidity. This finding is strongly supported by Wang et al., who demonstrated that diabetic individuals were twice as likely to develop PTB compared to non-diabetic counterparts (aOR 2.07, 95% CI 1.76–2.44), and by Stubbs et al. (2021), who confirmed this association across 48 low- and middle-income countries (OR 1.63, 95% CI 1.16–2.32). Both studies underline the bidirectional nature of the TB-diabetes relationship, whereby diabetes impairs immune defenses against mycobacterial infection, while TB itself may aggravate glycemic control, creating a mutually reinforcing cycle of disease burden.

Regarding respiratory diseases, Wang et al. identified chronic lower respiratory diseases as one of the strongest comorbid risk factors for PTB (aOR 7.25, 95% CI 5.98–8.80), suggesting that pre-existing pulmonary damage significantly compromises local defense mechanisms against *Mycobacterium tuberculosis*. Thyroid and endocrine/metabolic disorders were also

found to be significantly associated with PTB risk (aOR 1.89 and 1.56 respectively), with Wang et al. classifying these conditions within the same comorbidity cluster, reflecting their shared metabolic and immunological pathways.

Concerning skin and autoimmune disorders, Wang et al. described connective tissue diseases as carrying one of the highest comorbid risks for PTB (aOR 3.62, 95% CI 1.87–7.00). This strong association is explained by the inherent immune dysregulation characterizing autoimmune conditions, as well as the potential immunosuppressive effect of their treatment. In a similar way, gastrointestinal diseases were linked to PTB development through a significant association with noninfective enteritis and colitis (aOR 1.82, 95% CI 1.13–2.93).

Concerning blood diseases and anemia, Wang et al. identified them as a strong predictor of PTB, particularly among middle-aged patients (aOR 5.68, 95% CI 1.92–16.78). As for neurological diseases and stroke, cerebrovascular diseases showed a significant though moderate association with PTB (aOR 1.28, 95% CI 1.05–1.57).

Taken together, these findings align with the broader conclusions of both Wang et al. (2024) and Stubbs et al. (2021), who demonstrated that the risk of developing PTB increases incrementally with the number of concurrent comorbidities, and that diseases spanning the respiratory, circulatory, endocrine/metabolic, and immune systems tend to co-occur and cluster in TB patients. These observations highlight the importance of systematic NCD screening within TB care programs, particularly in high-burden settings where integrated management remains a clinical and public health priority.

Table 8. clinical characteristics of the TB patients

Comorbidities	Frequency or (%)
Cardiovascular Diseases	69 (13.3 %)
hypertension	50 (9,6%)
cardiopathy	15 (2,9%)
Other	4 (0,8%)
Diabetes	41 (7,9)
Diabetes Mellitus Unspecified	21 (4 %)

Diabetes Mellitus Type 2	17 (3,3 %)
Diabetes Mellitus Type 1	3 (0,6 %)
Respiratory Diseases	23 (4,4 %)
Miscellaneous Conditions	17 (3,3 %)
Thyroid Diseases	14 (2,7 %)
Skin/Autoimmune Diseases	10 (1,9 %)
Gastrointestinal Diseases	9 (1,7%)
Endocrine/Metabolic Diseases	8 (1,5%)
Blood Diseases and Anemia	8 (1.5 %)
Neurological Diseases/Stroke	6 (1,2 %)

1.4. Clinical forms of tuberculosis

The distribution of tuberculosis according to its clinical presentation indicated a predominance of extrapulmonary forms. Extrapulmonary tuberculosis represented 334 cases (64%), while pulmonary tuberculosis accounted for 181 cases (35%). Mixed pulmonary–pleural forms were uncommon and represented only 6 cases (1%) **(Fig. 41)**. The predominance of extrapulmonary forms in our cohort (64%) considerably exceeds global WHO estimates, which placed the proportion of EPTB at 16% of the 7.1 million notified incident cases in 2019 (World Health Organization, 2020), and also surpasses the 49.4% reported by Sunnetcioglu et al. (2015) in Turkey. Furthermore, Yu et al. (2024) documented that 52.04% of their EPTB patients presented concurrent pulmonary involvement, compared to only 1% of mixed forms in our series. This high proportion of extrapulmonary tuberculosis in our cohort may reflect local epidemiological characteristics, as well as the preferential referral of severe or atypical cases to the specialized institutions included in this study.

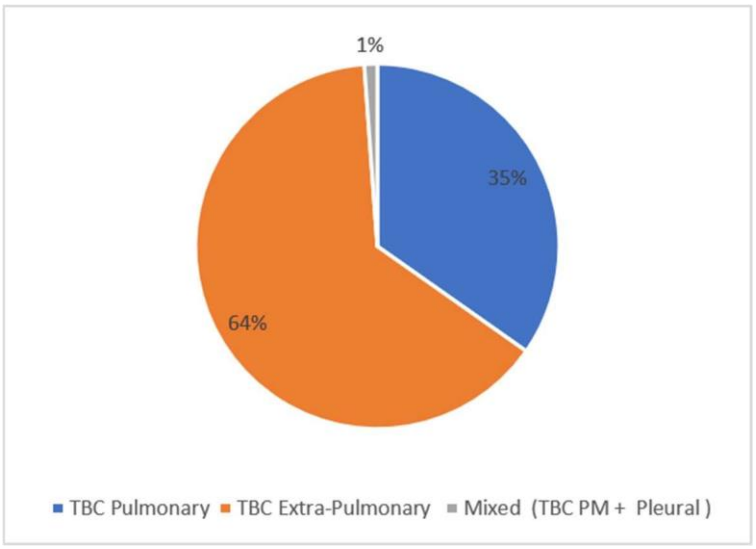


Figure 41. Distribution of Pulmonary vs Extra-Pulmonary Tuberculosis Cases

1.5. Anatomical localization of tuberculosis

A marked heterogeneity was observed among the different tuberculosis localizations. Lymph node tuberculosis was the most frequently reported form, with 214 cases, followed by pulmonary tuberculosis with 181 cases. Pleural and peritoneal tuberculosis occupied intermediate positions with 39 and 31 cases, respectively. Osteoarticular tuberculosis and breast tuberculosis were each represented by 14 cases. Lower frequencies were observed for urogenital tuberculosis and musculo-cutaneous tuberculosis, with 5 cases each, whereas intestinal tuberculosis, meningeal tuberculosis, mixed forms, and other localizations were only occasionally recorded **(Fig. 42).**. The predominance of lymph node tuberculosis in our patients is consistent with findings reported across diverse geographic settings. Yu et al. (2024) identified lymphatic tuberculosis as the most prevalent extrapulmonary subtype in a Chinese cohort of 1,324 patients (29.83%), and Baya et al. (2023) similarly ranked it among the four dominant forms in Mali. This convergence across different epidemiological contexts may reflect shared pathophysiological mechanisms underlying lymph node involvement in tuberculosis, regardless of the geographic or demographic context. The relatively high proportion of this form in our cohort could also be associated with the demographic profile of our patients, given that lymph node tuberculosis tends to predominate in young adults and females — both characteristics that define our study population **(Baya et al. 2023; Yu et al. 2024).** Regarding pleural tuberculosis, the male predominance observed in our study aligns with Baya et al. (2023), who reported 51% higher odds in males (OR: 1.51; 95% CI [1.16–1.98]), and might reflect the anatomical proximity of the pleura to the pulmonary parenchyma, positioning pleural disease as a transitional form between pulmonary and extrapulmonary

tuberculosis. The low frequencies of meningeal, urogenital, and mixed forms are in line with the known epidemiology of these presentations, which tend to occur at the extremes of age or in immunocompromised patients— groups less represented in our cohort **(Dabitao and Bishai, 2023).**

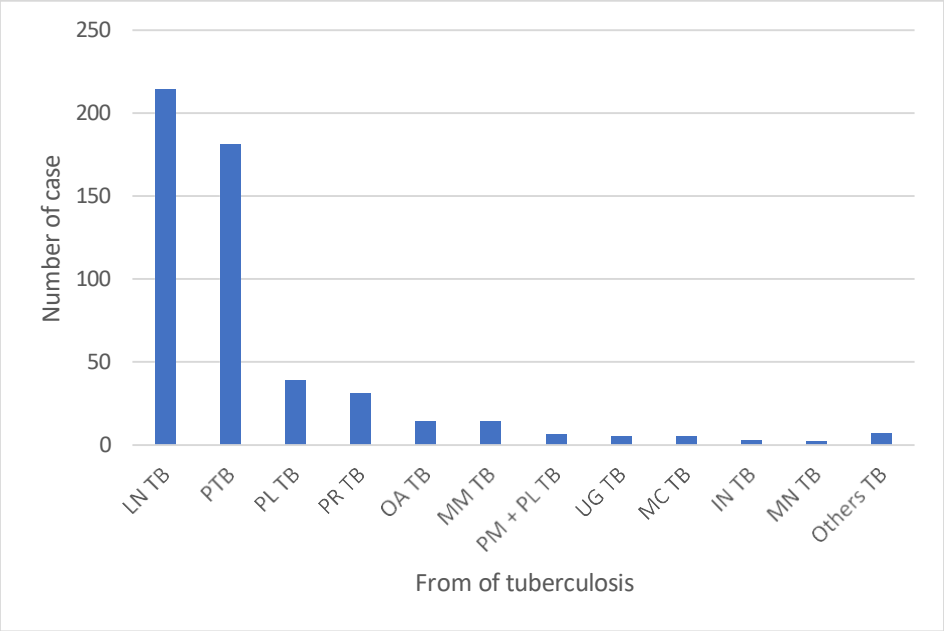


Figure 42. Cases number of each type of tuberculosis.**PTB:** Pulmonary TB, **LN TB**: Lymph node TB, **PL**. **TB:** Pleural TB, **PR TB:** Peritoneal TB, **MN TB:** Meningitis TB, **MM TB:** Mammary TB, **IN TB:** Intestinal TB, **CU TB:** Cutaneous TB, **UG TB:** Urogenital TB, **OA TB:** Osteoarticular TB, **PTB+ PL TB:** Pulmonary TB + Pleural TB

1.6. ALAT and ASAT rates among TB patients

Our results showed that the majority of patients had normal values (≤ 40 IU/L), with 464 cases for ALAT and 465 cases for ASAT whereases 56 patients exhibited high abnormal rates (> 40 IU/L) for both ALAT and ASAT. Of these, Mild elevations (×1–2 ULN) were the most frequent, accounting for 44 cases for each enzyme. Moderate elevations (×2–3 ULN) were observed in 8 cases for ALAT and 4 cases for ASAT. Severe elevations (×3–4 ULN) were noted in 4 cases for ASAT only. Very severe elevations (×4–5 ULN) were limited to 2 cases for ALAT, while levels exceeding ×5 ULN were found in 2 cases for ALAT and 4 cases for ASAT.

Table 9 presents the distribution of liver enzyme levels (ALAT and ASAT) among the study population, classified according to the Upper Limit of Normal (ULN = 40 IU/L) **(Table 9)**.

The distribution of liver ALAT and ASAT enzyme levels in the study population showed that the majority of patients-maintained values within the normal range (464 for ALAT and 465 for ASAT), consistent with evidence that most patients tolerate first-line anti-TB therapy without clinically significant hepatocellular injury (Tweed et al., 2018). Among those with elevated levels, mild elevations (×1–2 ULN) were the most frequent for both enzymes, reflecting the well-documented phenomenon of hepatic adaptation, whereby transient asymptomatic transaminase rises occur in up to 20% of isoniazid-treated patients and typically resolve spontaneously without treatment discontinuation **(Saukkonen et al., 2006; Ramappa & Aithal, 2013).**

Higher-grade elevations were considerably less common, with levels exceeding ×5 ULN detected in only 2 cases for ALAT and 4 for ASAT. Although rare, such elevations carry clinical significance, as they meet the ATS threshold for mandatory treatment interruption **(Saukkonen et al., 2006).** The overall pattern observed is broadly comparable to published data from North African and Middle Eastern cohorts, where AT-DILI incidence tends to be higher than in Western settings, partly attributable to the greater prevalence of slow NAT2 acetylators, which increases susceptibility to isoniazid-induced hepatotoxicity **(El Bouazzi et al., 2016; Abbaspour et al., 2024).**

Table 9. Distribution of patients according to ALAT and ASAT levels, graded by multiples of the upper limit of normal (ULN).

	ALAT	ASAT
Normal rate (40 IU/L)	464	465
ULN (> 40 IU/L)	56	56
(1-2) x ULN	44	44
(2-3) x ULN	8	4
(3-4) x ULN	0	4
(4-5) ULN x	2	0
x 5 > ULN	2	4

ULN, upper limit of normal.

Furthermore, to investigate whether ALAT and ASAT levels varied according to the anti-tuberculosis treatment regimen, we compared the changes in these enzymes during the first two months of therapy, when patients were receiving the four-drug regimen (RHZE), with those observed during the subsequent four-month period, when treatment consisted of the two-drug regimen (RH). Table shows the comparison of ALAT and ASAT levels before and after two months of treatment, stratified by treatment outcome (successful vs unsuccessful) **(Table 10).**

Regarding ALAT levels, no statistically significant difference was observed between the two groups at baseline (24.68 ± 40.71 vs 24.82 ± 30.66, P = 0.9837). However, after two months, a statistically significant difference was found between the successful and unsuccessful groups (29.35 ± 34.45 vs 14.62 ± 8.5, P = 0.0005), corresponding to a percentage change of -50.19%.

Regarding ASAT levels, no significant difference was noted at baseline between the two groups (28.97 ± 36.84 vs 29.44 ± 20.30, P = 0.9200). After two months, the difference between the groups did not reach statistical significance (35.04 ± 33.23 vs 25.21 ± 14.90, P = 0.0910), with a percentage change of -28.05%.

At baseline, no statistically significant difference in ALT or AST levels was observed between successful and unsuccessful patients (P = 0.9837 and P = 0.9200, respectively), indicating comparable hepatic status at treatment initiation. After two months, a significant divergence emerged for ALT, with unsuccessful patients showing markedly lower values than successful ones (14.62 ± 8.5 vs 29.35 ± 34.45, P = 0.0005). This paradoxical finding may reflect reduced drug exposure due to early discontinuation rather than better hepatic tolerance, a pattern consistent with observations by Perwitasari et al. (2025), who linked enzyme fluctuations during treatment to medication adherence. The difference in AST did not reach statistical significance (P = 0.0910), which may be attributable to the greater sensitivity of ALT over AST in detecting hepatocellular injury, as emphasized by Saukkonen et al. (2006). These findings underscore the importance of systematic enzyme monitoring during the first two months of anti-TB treatment, a window identified by Tweed et al. (2018) as capturing approximately 75% of peak liver enzyme elevations.

Table 10. Comparison of ALAT and ASAT levels before and after 2 months according to treatment outcome (successful vs unsuccessful).

	ALAT		P-value	Percentage of change (%)
	Successful	Unsuccessful		
Before 2 Months	24,68 ± 40,71	24,82 ± 30.66	0.9837	0.56
After 2 Months	29,35 ± 34,45	14,62 ± 8,5	0.0005	-50,19
	ASAT			
	Successful	Unsuccessful		
Before 2 Months	28,97 ± 36,84	29,44 ± 20,30	0.9200	1.62
After 2 Months	35,04 ± 33,23	25,21 ± 14,90	0.0910	-28,05

Mean ALAT levels varied across the different treatment outcome categories both before treatment initiation and after two months of anti-tuberculosis therapy **(Fig. 43)**. At baseline, the highest mean ALAT value was recorded in the treatment discontinued group (54.42 IU/L),

followed by the lost to follow-up (32.60 IU/L), cured (24.63 IU/L), and completed (24.02 IU/L) groups. Lower values were observed in the dead (18.40 IU/L), treatment failure (13.65 IU/L), and relapsed (8.00 IU/L) groups. After two months, ALAT levels increased in the completed (31.73 IU/L), cured (28.56 IU/L), and relapsed (13.00 IU/L) groups, whereas decreases were observed in the dead (13.00 IU/L), treatment failure (12.00 IU/L), and treatment discontinued (20.47 IU/L) groups. No follow-up value was available for the lost to follow-up category. Except for the baseline value in the treatment discontinued group, all mean ALAT values remained below the threshold of 40 IU/L

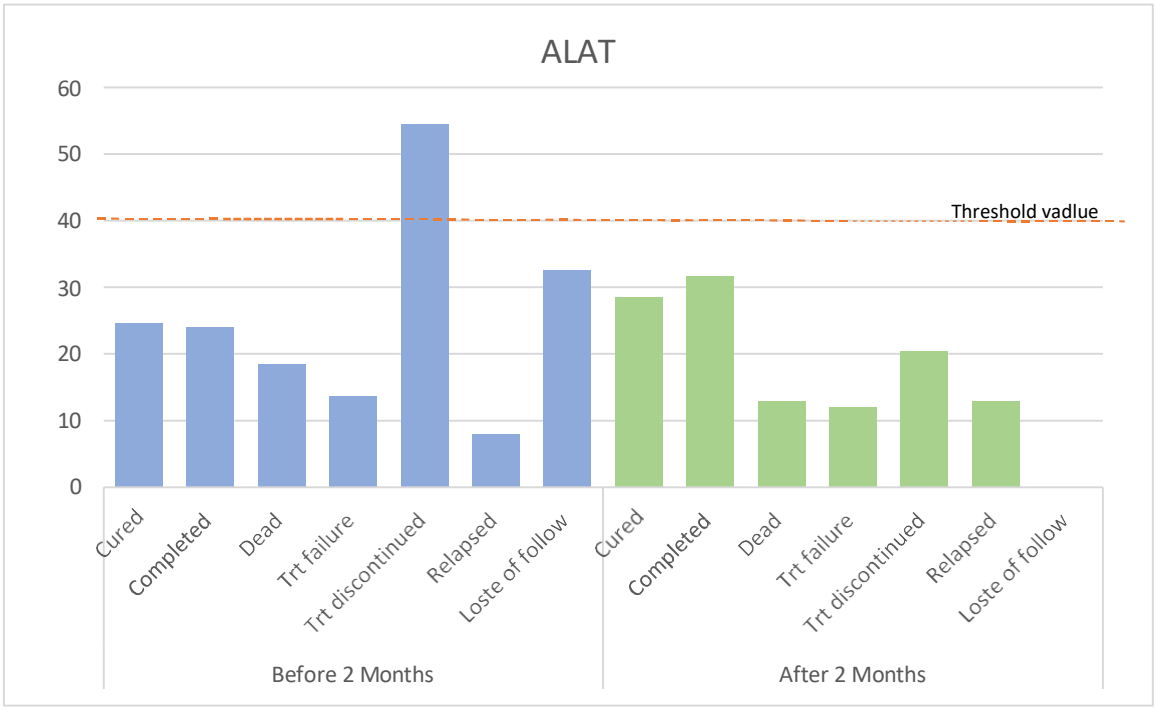


Figure 43. Mean ALAT levels before and after 2 months by treatment outcome category

Mean ASAT levels also showed variations between baseline and the second month of treatment according to treatment outcome **(Fig. 44)**. Before treatment, the highest mean ASAT value was observed in the lost to follow-up group (40.40 IU/L), followed by the treatment discontinued (37.78 IU/L), completed (29.30 IU/L), cured (28.70 IU/L), dead (28.02 IU/L), treatment failure (25.09 IU/L), and relapsed (12.50 IU/L) groups. After two months, ASAT levels increased in the completed (37.94 IU/L), cured (34.14 IU/L), and relapsed (22.00 IU/L) groups, while decreases were recorded in the dead (28.00 IU/L), treatment failure (21.00 IU/L), and treatment discontinued (25.82 IU/L) groups. No follow-up measurement was available for patients lost to follow-up. Overall, all mean ASAT values remained below the threshold value of 40 IU/L.

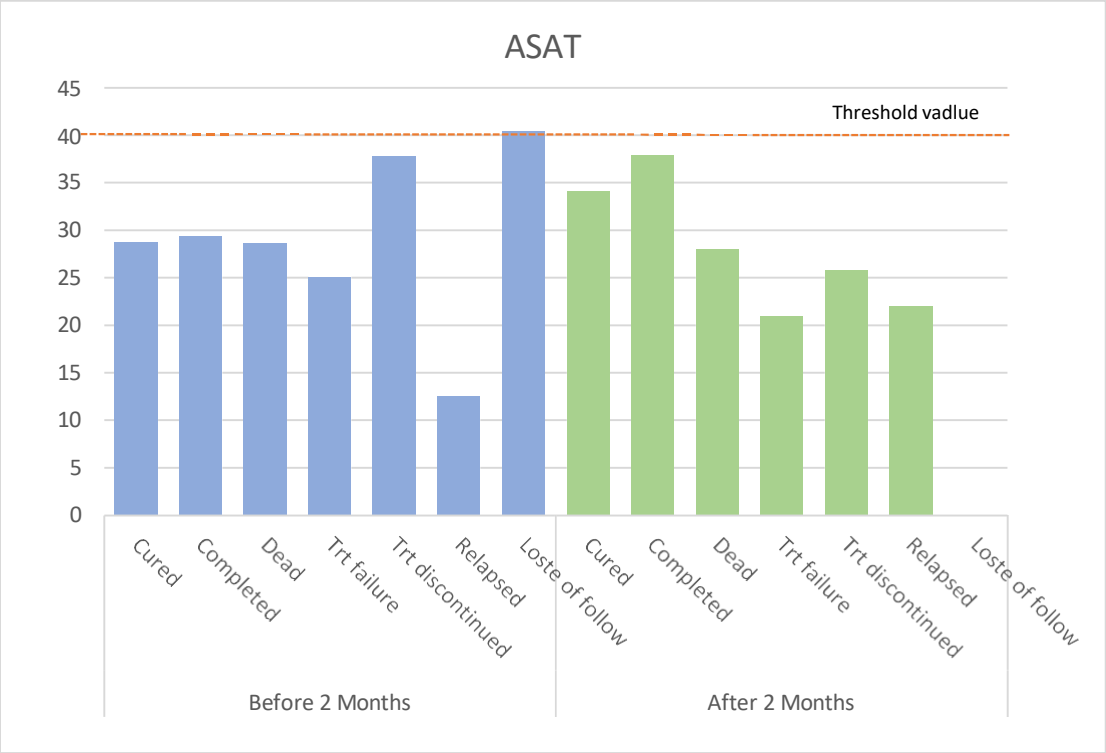


Figure 44. Mean ASAT levels before and after 2 months by treatment outcome category

Table 11 summarizes the evolution of ALAT and ASAT levels before treatment and after two months according to treatment outcome. For ALAT, mean values increased by 15.96% in cured patients and by 32.10% in patients who completed treatment, whereas decreases were observed in the dead (-29.35%), treatment failure (-12.09%), and treatment discontinued (-62.39%) groups. The relapsed group showed an increase of 62.50%, while no post-treatment measurement was available for the lost to follow-up group. None of the ALAT changes reached statistical significance (all $P > 0.05$). Regarding ASAT, increases were observed in the cured (+18.95%), completed (+29.18%), and relapsed (+76.00%) groups, whereas decreases occurred in the dead (-2.17%), treatment failure (-16.30%), and treatment discontinued (-31.66%) groups. Among all comparisons, only the increase observed in the cured group reached statistical significance ($P = 0.0431$), while the remaining changes were not statistically significant ($P > 0.05$).

Table 11. Evolution of ALAT and ASAT levels before and after 2 months according to treatment outcome category

	ALAT		P-value	Percentage of change(%)
	Before 2 Months	After 2 Months		
	Mean ± SD			
Cured	24,63 ± 40,21	28,56 ± 33,82	0.1687	15,96
Completed	24,02 ± 37,84	31,73 ± 36,33	0.1615	32,10
Dead	18,4 ± 12,92	13 ± 9,03	0.3408	-29,35
Trt failure	13,65 ± 11,31	12 ± 2,65		-12,09
Trt discontinued	54,42 ± 56,36	20,47 ± 12,54	0.5584	-62,39
Relapsed	8,00 ± 00,00	13 ± 00,00		62,50
Lost of follow	32,6 ± 34,99	ND		
	ASAT			
	Before 2 Months	After 2 Months		
	Mean ± SD			
Cured	28,7 ± 36,27	34,14 ± 32,12	0.0431	18,95
Completed	29,3 ± 38,09	37,94 ± 37,42	0.1236	29,18
Dead	28,62 ± 20,46	28 ± 22,84	0.9561	-2,17
Trt failure	25,09 ± 9,46	21 ± 3,61		-16,30
Trt discontinued	37,78 ± 15,51	25,82 ± 10,61	0.5696	-31,66
Relapsed	12,5 ± 2,12	22 ± 00,00		76,00
Lost of follow	40,4 ± 41,6			

the highest mean ALAT level that was observed in the treatment-discontinued group is likely attributable to the hepatotoxic potential of first-line anti-tuberculosis drugs, particularly isoniazid, rifampicin, and pyrazinamide, which are well known to induce transient elevations in liver enzymes during the intensive phase of treatment **(Saukkonen et al., 2006; Tostmann et al., 2008; Chang et al., 2007).** The exceptionally high baseline ALAT level observed in the treatment-discontinued group may indicate pre-existing liver dysfunction before the initiation of therapy. Elevated baseline liver enzymes have been identified as a major risk factor for the development of anti-tuberculosis drug-induced hepatotoxicity (ATDH) and are associated with an increased likelihood of treatment interruption or discontinuation **(Sharma et al., 2002; Saukkonen et al., 2006).** Other factors that may contribute to elevated baseline ALAT include chronic viral hepatitis, alcohol consumption, malnutrition, HIV co-infection, and concomitant use of hepatotoxic medications **(Tostmann et al., 2008).**

Nevertheless, the mean ALAT values in the other groups remained below the threshold of clinical concern, suggesting that the observed elevations were generally mild and did not significantly compromise treatment outcomes, as mild and transient increases in liver enzymes are frequently observed during anti-tuberculosis therapy and often resolve without requiring treatment discontinuation **(Yee et al., 2003; Nahid et al., 2016).**

1.7. Time variation of ALAT and ASAT variations during tuberculosis treatment:

Mean serum ALAT levels increased progressively from baseline (20.48 ± 21.11 IU/L) to 22.48 ± 29.06 IU/L at 1 month and 27.66 ± 44.13 IU/L at 2 months, reaching a peak of 47.09 ± 78.34 IU/L at 3 months. Values subsequently declined to 26.99 ± 30.29 IU/L at 4 months and remained relatively stable at 25.57 ± 25.53 IU/L and 24.05 ± 23.96 IU/L at 5 and 6 months, respectively, before rising again to 29.99 ± 30.63 IU/L beyond 6 months. Statistically significant differences compared to baseline were observed at 2 months ($p=0.0238$), 3 months ($p<0.0001$), and beyond 6 months ($p=0.0088$) **(Fig. 45).** This early rise can be explained by the intensive hepatic metabolism of isoniazid, rifampicin, and pyrazinamide, which produce reactive metabolites such as hydrazine capable of causing transient liver stress during the first months of treatment **(Tostmann et al., 2008).** This also matches the fact that most cases of antituberculous drug-induced hepatotoxicity occur early, within the first month of treatment **(Lee et al., 2016).** The decline and stabilization seen at 4 to 6 months reflects hepatic adaptation, a protective mechanism allowing the liver to tolerate the drugs better over time **(Saukkonen et al., 2006),** and this overall pattern of temporary elevation followed by normalization is

consistent with what was observed in most patients completing standard treatment without major liver injury **(Tweed et al., 2018).**

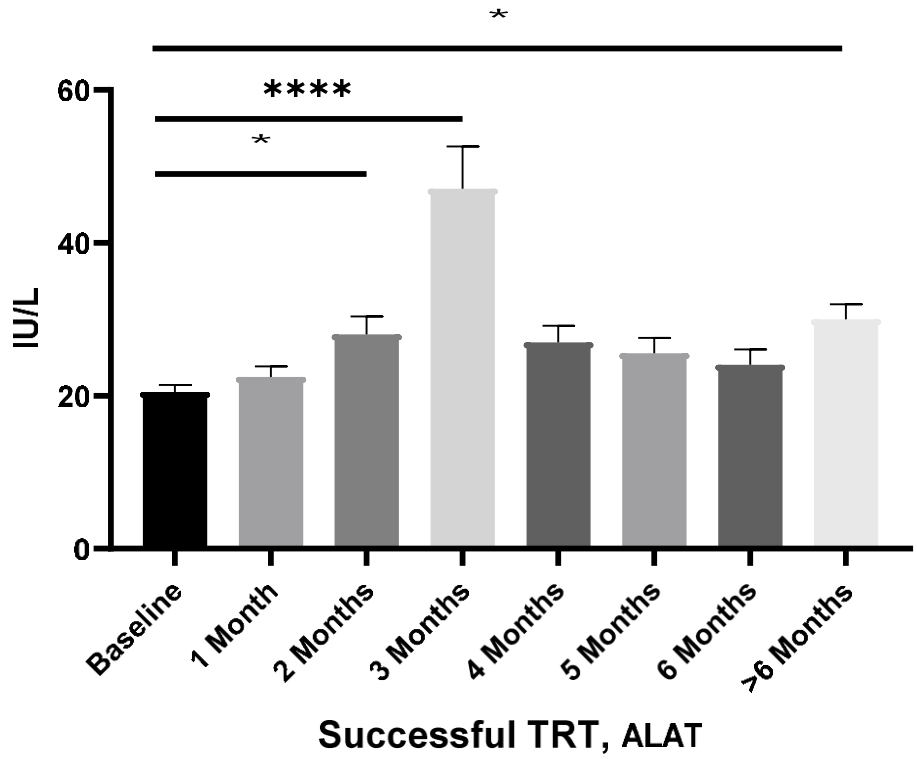


Figure 45. ALAT variations during successful tuberculosis treatment

Mean serum ASAT levels rose from 25.93 ± 27.85 U/L at baseline to 27.13 ± 22.6 U/L at 1 month and 31.9 ± 46.11 U/L at 2 months, reaching a maximum of 46.36 ± 61.89 U/L at 3 months. Levels then decreased to 30.36 ± 26.21 U/L at 4 months, remained relatively stable at 31.78 ± 22.42 U/L and 28.3 ± 21.25 U/L at 5 and 6 months, respectively, and increased again to 41.16 ± 41.95 U/L beyond 6 months. Significant differences relative to baseline were noted at 2 months ($p=0.0143$), 3 months ($p<0.0001$), and beyond 6 months ($p=0.0003$) **(Fig. 46)**. The fact that ASAT follows the same pattern as ALAT is expected, since both enzymes usually rise together during drug-induced liver stress **(Saukkonen et al., 2006),** and a similar close agreement between ALT and AST elevations was reported during standard tuberculosis treatment (**Tweed et al., 2018).** The late increase beyond 6 months may suggest cumulative drug exposure in patients with prolonged treatment, although this should be interpreted carefully, since liver enzymes were generally found to decrease, not increase, after completion of anti-tuberculosis therapy **(Mirlohi et al., 2016).**

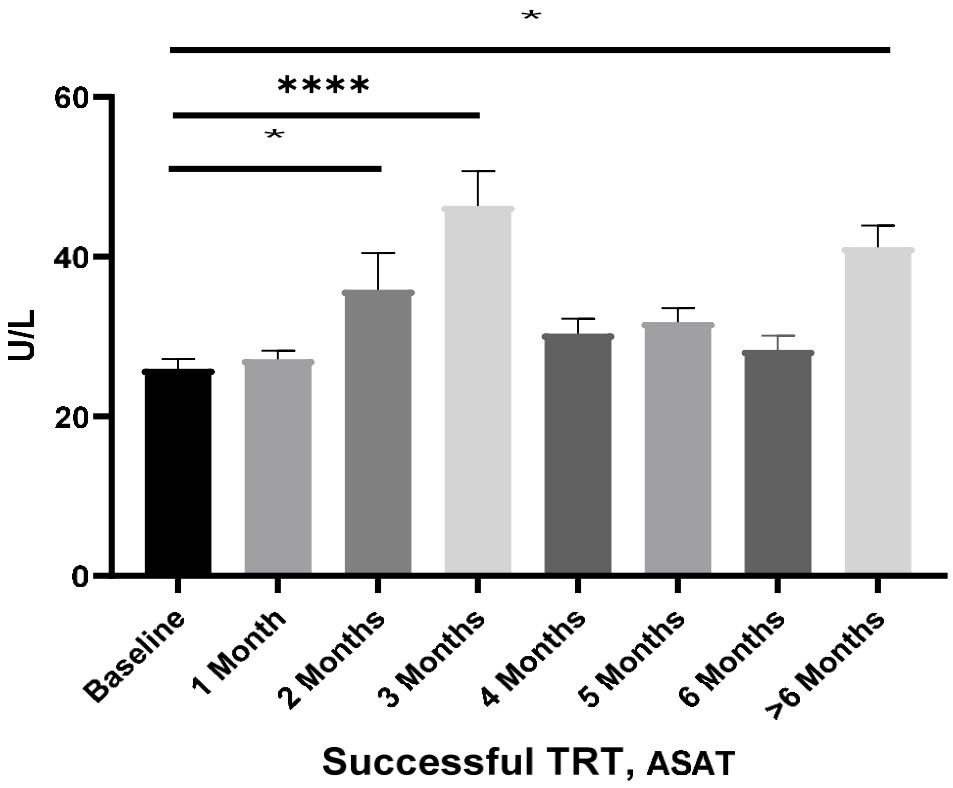


Figure 46. ASAT variations during successful tuberculosis treatment

Mean serum ALAT levels declined progressively from 26.72 ± 42.76 IU/L at baseline to 25.08 ± 22.22 IU/L at 1 month, 22.18 ± 21.58 IU/L at 2 months, and 19.41 ± 10.09 IU/L at 3 months, reaching the lowest value of 6.12 ± 4.48 IU/L at 4 months. Levels subsequently increased to 16.5 ± 2.12 IU/L at 6 months and decreased slightly to 13.5 ± 0.71 IU/L beyond 6 months. No statistically significant differences were observed at any follow-up time point compared to baseline (**Fig. 47).** This absence of the expected early peak, unlike what is normally seen during the first months of treatment **(Lee et al., 2016; Tweed et al., 2018),** suggests that these patients may not have been regularly exposed to the drugs, since the hepatic stress caused by isoniazid, rifampicin, and pyrazinamide could not develop without consistent intake **(Tostmann et al., 2008).** A relationship between liver enzyme levels and treatment adherence was also reported in tuberculosis patients, although in that case non-adherence was linked to higher, not lower, enzyme levels **(Perwitasari et al., 2025),** which suggests that the pattern observed here may instead reflect a more complete interruption of treatment rather than partial non-adherence. However, this explanation remains a hypothesis rather than a confirmed finding, as adherence was not directly assessed in the present study, and the declining enzyme pattern could equally be related to other factors affecting drug metabolism that were not evaluated here.

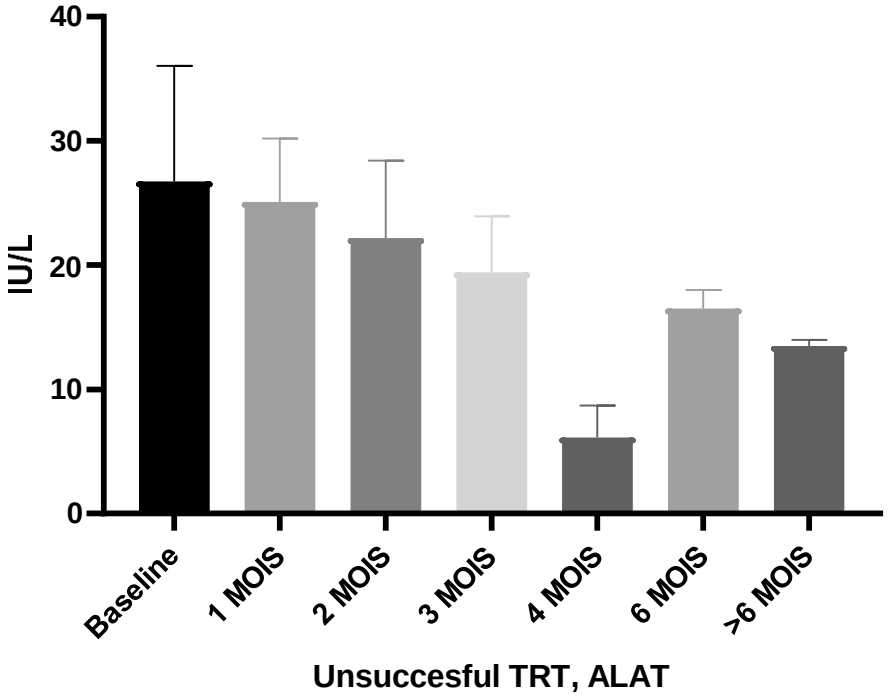


Figure 47. ALAT variations during unsuccessful tuberculosis treatment

Mean serum ASAT levels increased slightly from 27.24 ± 21.9 U/L at baseline to 27.63 ± 12.8 U/L at 1 month, then rose to 36.5 ± 26.97 U/L at 2 months and 33.5 ± 19.54 U/L at 3 months. Values then decreased to 18.32 ± 10.49 U/L at 4 months, increased to 20.5 ± 9.19 U/L at 6 months, and remained close to this level (19.5 ± 3.54 U/L) beyond 6 months. No statistically significant differences were detected across the follow-up period(**Fig. 48).** This irregular pattern, without a clear peak as seen in the successful group, reflects the difficulty of interpreting liver enzyme changes when treatment adherence and actual drug exposure are uncertain **(Saukkonen et al., 2006).** The lack of a defined early rise around 2 to 3 months supports the idea, already discussed for ALAT in this group, that these patients were not consistently exposed to the standard anti-tuberculosis regimen.

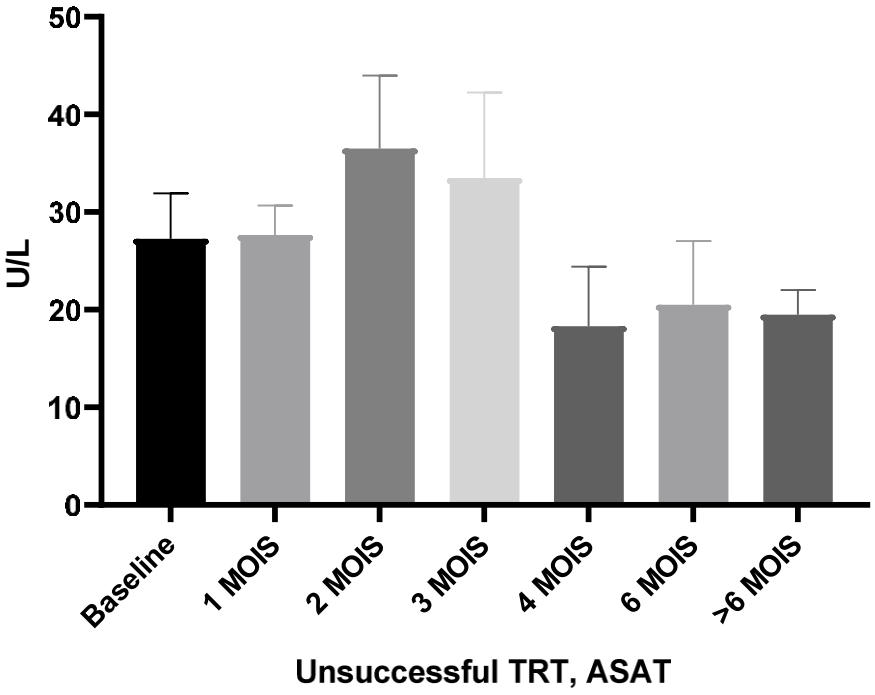


Figure 48. ASAT variations during unsuccessful tuberculosis treatment

Table 13 reports the mean ± standard deviation values of ALAT and ASAT, along with their corresponding p-values, at baseline and at each follow-up time point in both the successful and unsuccessful TRT groups. In the successful TRT group, both ALAT and ASAT values increased markedly between baseline and 3 months, with statistically significant differences recorded at 2 months, 3 months, and beyond 6 months. In the unsuccessful TRT group, both enzymes showed an overall decline, reaching their lowest values at 4 months, with no statistically significant differences observed at any time point **(Table. 12)**. This statistical contrast confirms the patterns already described in Figures 1 to 4. The significant, time-dependent enzyme variation observed in the successful group reflects sustained hepatic exposure to first-line anti-tuberculosis drugs **(Tostmann et al., 2008; Tweed et al., 2018),** while the complete absence of significant variation in the unsuccessful group reflects irregular or interrupted drug intake throughout treatment (**Perwitasari et al., 2025).**

Table 12. Comparison of ALAT and ASAT Levels (Mean ± SD) according to treatment duration in successful versus unsuccessful treatment outcome.

	Successful TRT outcome		Unsuccessful TRT outcome	
TRT Duration	ALAT	ASAT	ALAT	ASAT
TRT Start	20,48 ± 21,11	25,93 ± 27,85	26,72 ± 42,76	27,24 ± 21,9
1 Month	22,48 ± 29,06 P 0,9636	27,13 ± 22,6 P 0,9995	25,08 ± 22,22 P 0,9998	27,63 ± 12,8, P 0,9999
2 Months	27,66 ± 44,13 **P 0,0238**	31,9 ± 46,11 **P 0,0143**	22,18 ± 21,58 P 0,998	36,5 ± 26,97 P 0,6921
3 Months	47,09 ± 78,34 **P <0,0001**	46,36 ± 61,89 **P <0,0001**	19,41 ± 10,09 P 0,9957	33,5 ± 19,54 P 0,9862
4 Months	26,99 ± 30,29 P 0,2155	30,36 ± 26,21 P 0,8387	6,12 ± 4,48 P 0,821	18,32 ± 10,49 P 0,9725
5 Months	25,57 ± 25,53 P 0,5823	31,78 ± 22,42 P 0,6656	ND	ND
6 Months	24,05 ± 23,96 P 0,9037	28,3 ± 21,25 P 0,9969	16,5 ± 2,12 P 0,9969	20,5 ± 9,19 P 0,9975
< 6 Months	29,99 ± 30,63 **P 0,0088**	41,16 ± 41,95 **P 0,0003**	13,5 ± 0,71 P 0,9895	19,5 ± 3,54 P 0,9947

General Conclusion

General Conclusion

This study investigated the variations of liver enzymes, namely alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT), among tuberculosis patients undergoing anti-tuberculosis treatment, with the aim of assessing the hepatic impact of therapy and its possible association with treatment outcomes. The study population was characterized by a predominance of females and a high proportion of extrapulmonary tuberculosis, particularly lymph node tuberculosis, highlighting the specific epidemiological profile of tuberculosis in our region. A substantial proportion of patients also presented comorbidities, mainly cardiovascular diseases and diabetes mellitus, emphasizing the need for integrated management of tuberculosis and non-communicable diseases. Although elevated transaminase levels were observed in a minority of patients, most ALAT and ASAT values remained within the normal range throughout treatment. Mild and transient increases in liver enzymes were the most frequent abnormalities and were generally not associated with adverse clinical outcomes. The highest baseline ALAT levels were observed in the treatment-discontinued group, suggesting that pre-existing liver dysfunction may constitute an important risk factor for treatment interruption and drug-induced hepatotoxicity.

Longitudinal analysis revealed that both ALAT and ASAT levels increased during the intensive phase of treatment, reaching their highest values around the third month before progressively declining and stabilizing. This pattern is consistent with the known hepatotoxic effects of first-line anti-tuberculosis drugs, particularly isoniazid, rifampicin, and pyrazinamide, and reflects a process of hepatic adaptation in most patients. In contrast, patients with unsuccessful treatment outcomes exhibited irregular and generally declining enzyme profiles, which may indicate inconsistent drug exposure or treatment interruption. Importantly, significant enzyme variations were primarily observed in patients who successfully completed treatment, whereas no significant changes were detected in patients with unsuccessful outcomes. These findings suggest that fluctuations in transaminase levels may partly reflect treatment adherence and sustained exposure to anti-tuberculosis medications rather than clinically significant liver injury.

Overall, the present study demonstrates that anti-tuberculosis therapy is generally well tolerated from a hepatic perspective, with severe hepatotoxicity remaining relatively uncommon. Nevertheless, systematic monitoring of liver function, particularly during the first three months of treatment and among patients with elevated baseline liver enzymes or comorbid

conditions, remains essential to ensure early detection and appropriate management of hepatotoxicity.

Future studies involving larger multicenter cohorts and incorporating additional risk factors, such as viral hepatitis status, alcohol consumption, genetic polymorphisms, and adherence measurements, are warranted to further elucidate the determinants of liver enzyme variations and improve the safety of anti-tuberculosis treatment.

Bibliographic References

List of References

1. Alsayed, S. S. R., & Gunosewoyo, H. (2023). Tuberculosis: Pathogenesis, current treatment regimens and new drug targets. *International Journal of Molecular Sciences, 24*(6), 5202. https://doi.org/10.3390/ijms24065202
2. Barberis, I., Bragazzi, N. L., Galluzzo, L., & Martini, M. (2017). The history of tuberculosis: from the first historical records to the isolation of Koch's bacillus. *Journal of Preventive Medicine and Hygiene, 58*, E9–E12.
3. Bentata, K., Alihalassa, S., Gharnaout, M., Bennani, M. A., & Berrabah, Y. (2025). Algerian tuberculosis control program: 60 years of successful experience. *Cureus, 17*(6), e86357. https://doi.org/10.7759/cureus.86357
4. Bentata, K., Alihalassa, S., Gharnaout, M., Bennani, M. A., & Berrabah, Y. (2025). *Algerian tuberculosis control program: 60 years of successful experience*. *Cureus, 17*(6), e86357. https://doi.org/10.7759/cureus.86357
5. Blevins, S. M., & Bronze, M. S. (2010). *Robert Koch and the "golden age" of bacteriology*. *International Journal of Infectious Diseases, 14*, e744–e751. https://doi.org/10.1016/j.ijid.2009.12.003
6. **Cesur, S. (2023).** Clinical forms and diagnosis of tuberculosis. *Journal of Pulmonology and Intensive Care, 1*(1), 13-19.
7. Cesur, S. (2023). Clinical forms and diagnosis of tuberculosis. Journal of Pulmonology and Intensive Care, 1(1), 13–19. https://doi.org/10.51271/JOPIC-0004
8. Coulon, J. P., & Piette, E. (2001). Tuberculose. Encyclopédie Médico-Chirurgicale, Stomatologie, 22-047-A-10. Editions Scientifiques et Médicales Elsevier SAS.
9. Daniel, T. M. (2006). The history of tuberculosis. *Respiratory Medicine, 100*(11), 1862–1870. https://doi.org/10.1016/j.rmed.2006.08.006
10. Daniel, T. M. (2006). The history of tuberculosis. *Respiratory Medicine, 100*(11), 1862–1870. https://doi.org/10.1016/j.rmed.2006.08.006
11. Davidson, G., Davidson, D. U., Okoye, O. K., Mensah, L. S., Ukaegbu, E. C., Arrey Agbor, D. B., Adegbola, M. O., Eneyo, U. S., Osuluku, B. A., Dinyain, T. O., Okeke, A. A., Okah, M. J., Owulu, A. I., Peterson, J. C., Onyekweli, S. O., Omoruyi, G. O., Adebiyi, O. S., Atoyebi, F. A., Omeje, A. C., Ogbueli, O. J., Odobulu, O. B., & Uche, C. J. (2024).

Overview of tuberculosis: Causes, symptoms and risk factors. *Asian Journal of Research in Infectious Diseases, 15*(9), 8–19. https://doi.org/10.9734/ajrid/2024/v15i9370

12. Douba, S. (2025). The dynamics of epidemiological transition in Algeria: From communicable diseases to the burden of chronic diseases. *Algerian Review of Human Security, 11*(1), 747–765.
13. Douba, S. (2025). *The dynamics of epidemiological transition in Algeria: From communicable diseases to the burden of chronic diseases*. *Algerian Review of Human Security, 11*(1), 747–765.
14. El Bouazzi, O., Hammi, S., Bourkadi, J. E., Tebaa, A., Soussi Tanani, D., Soulaymani-Bencheikh, R., Badrane, N., & Bengueddour, R. (2016). First line anti-tuberculosis induced hepatotoxicity: incidence and risk factors. *Pan African Medical Journal, 25*, 167. https://doi.org/10.11604/pamj.2016.25.167.10060
15. El Bouazzi, O., Hammi, S., Bourkadi, J. E., Tebaa, A., Soussi Tanani, D., Soulaymani-Bencheikh, R., Badrane, N., & Bengueddour, R. (2016). First line anti-tuberculosis induced hepatotoxicity: incidence and risk factors. *Pan African Medical Journal, 25*, 167. https://doi.org/10.11604/pamj.2016.25.167.10060
16. Gowda, S., Desai, P. B., Hull, V. V., Math, A. A. K., Vernekar, S. N., & Kulkarni, S. S. (2009). A review on laboratory liver function tests. *Pan African Medical Journal, 3*, 17. https://doi.org/10.4314/pamj.v3i1.46839
17. Gowda, S., Desai, P. B., Hull, V. V., Math, A. A. K., Vernekar, S. N., & Kulkarni, S. S. (2009). A review on laboratory liver function tests. *Pan African Medical Journal, 3*, 17. https://doi.org/10.4314/pamj.v3i1.46839
18. Gunasingam, N. (2022). Morphology and pathological characteristics of mycobacteria. *Mycobacterial Diseases, 12*(S4), 005. https://doi.org/10.35248/2161-1068.22.S4.005
19. Huang, X. J., Choi, Y. K., Im, H. S., Yarimaga, O., Yoon, E., & Kim, H. S. (2006). Aspartate aminotransferase (AST/GOT) and alanine aminotransferase (ALT/GPT) detection techniques. *Sensors, 6*(7), 756–782. https://doi.org/10.3390/s6070756
20. Huang, X. J., Choi, Y. K., Im, H. S., Yarimaga, O., Yoon, E., & Kim, H. S. (2006). Aspartate aminotransferase (AST/GOT) and alanine aminotransferase (ALT/GPT) detection techniques. *Sensors, 6*(7), 756–782. https://doi.org/10.3390/s6070756

21. Huang, Y., Ai, L., Wang, X., Sun, Z., & Wang, F. (2022). Review and updates on the diagnosis of tuberculosis. *Journal of Clinical Medicine, 11*(19), 5826. https://doi.org/10.3390/jcm11195826

22. Huang, Y., Ai, L., Wang, X., Sun, Z., & Wang, F. (2022). Review and updates on the diagnosis of tuberculosis. *Journal of Clinical Medicine*, 11(19), 5826. https://doi.org/10.3390/jcm11195826

23. Institut National de Santé Publique (INSP). (2025). *Situation épidémiologique de la tuberculose en Algérie, année 2024*. Alger: INSP.

24. Institut National de Santé Publique (INSP). (2025). *Situation épidémiologique de la tuberculose en Algérie, année 2024.* Alger : INSP.

25. Kamil, R. M., Albadry, M. A. Z., Yaseen, I. I., & Al-fahham, A. A. (2024). Aminotransaminases: Structures, functions and clinical significance. *International Journal of Health & Medical Research*, *3*(6), 409–413. https://doi.org/10.58806/ijhmr.2024.v3i06n25

26. Kamil, R. M., Albadry, M. A. Z., Yaseen, I. I., & Al-fahham, A. A. (2024). Aminotransaminases: Structures, functions and clinical significance. *International Journal of Health & Medical Research*, *3*(6), 409–413. https://doi.org/10.58806/ijhmr.2024.v3i06n25

27. Khan, M. K., Islam, M. N., Ferdous, J., & Alam, M. M. (2019). An overview on epidemiology of tuberculosis. *Mymensingh Medical Journal, 28*(1).

28. Khutlang, R., Krishnan, S., Dendere, R., Whitelaw, A., Veropoulos, K., Learmonth, G., & Douglas, T. S. (2010). Classification of *Mycobacterium tuberculosis* in images of ZN-stained sputum smears. *IEEE Transactions on Information Technology in Biomedicine*, *14*(4), 949–957. https://doi.org/10.1109/TITB.2009.2028339

29. Klindt, C., Fuchs, A., Behnke, K., Dröge, C., Eberhardt, K. A., Orth, H. C., Pfäfflin, F., Schönfeld, A., Nordmann, T., Mesfun, M. G., Keitel, V., Luedde, T., Tufa, T. B., Jensen, B.-E. O., & Feldt, T. (2025). Genetic and clinical risk factors for anti-tuberculosis drug-induced liver injury: insights from a prospective cohort study in central Ethiopia. *Infection*, *53*, 2833–2846. https://doi.org/10.1007/s15010-025-02632-7

30. Klindt, C., Fuchs, A., Behnke, K., Dröge, C., Eberhardt, K. A., Orth, H. C., Pfäfflin, F., Schönfeld, A., Nordmann, T., Mesfun, M. G., Keitel, V., Luedde, T., Tufa, T. B., Jensen,

B.-E. O., & Feldt, T. (2025). Genetic and clinical risk factors for anti-tuberculosis drug-induced liver injury: insights from a prospective cohort study in central Ethiopia. *Infection*, *53*, 2833–2846. https://doi.org/10.1007/s15010-025-02632-7

31. Knechel, N. A. (2009). Tuberculosis: Pathophysiology, clinical features, and diagnosis. *Critical Care Nurse, 29*(2), 34–43. https://doi.org/10.4037/ccn2009968

32. Knechel, N. A. (2009). Tuberculosis: Pathophysiology, clinical features, and diagnosis. *Critical Care Nurse*, 29(2), 34–43. https://doi.org/10.4037/ccn2009968

33. Koch, A., & Mizrahi, V. (2018). *Mycobacterium tuberculosis*. *Trends in Microbiology*, *26*(6). https://doi.org/10.1016/j.tim.2018.02.012

34. Kumar, R., & Sharma, S. (2025). A comprehensive review of tuberculosis: Epidemiology, diagnosis, treatment, prevention, and research. *International Journal of Scientific Research in Science, Engineering and Technology, 12*(4), 129–154. https://doi.org/10.32628/IJSRSET2512405

35. Lee, L.-N., Huang, C.-T., Hsu, C.-L., Chang, H.-C., Jan, I.-S., Liu, J.-L., Sheu, J.-C., Wang, J.-T., Liu, W.-L., Wu, H.-S., Chang, C.-N., & Wang, J.-Y. (2019). Mitochondrial DNA variants in patients with liver injury due to anti-tuberculosis drugs. *Journal of Clinical Medicine*, *8*(8), 1207. https://doi.org/10.3390/jcm8081207

36. Lee, L.-N., Huang, C.-T., Hsu, C.-L., Chang, H.-C., Jan, I.-S., Liu, J.-L., Sheu, J.-C., Wang, J.-T., Liu, W.-L., Wu, H.-S., Chang, C.-N., & Wang, J.-Y. (2019). Mitochondrial DNA variants in patients with liver injury due to anti-tuberculosis drugs. *Journal of Clinical Medicine*, *8*(8), 1207. https://doi.org/10.3390/jcm8081207

37. Liu, Z., Que, S., Xu, J., & Peng, T. (2014). Alanine aminotransferase-old biomarker and new concept: A review. *International Journal of Medical Sciences*, *11*(9), 925–935. https://doi.org/10.7150/ijms.8951

38. Liu, Z., Que, S., Xu, J., & Peng, T. (2014). Alanine aminotransferase-old biomarker and new concept: A review. *International Journal of Medical Sciences*, *11*(9), 925–935. https://doi.org/10.7150/ijms.8951

39. Luies, L., & du Preez, I. (2020). The echo of pulmonary tuberculosis: Mechanisms of clinical symptoms and other disease-induced systemic complications. *Clinical Microbiology Reviews*, *33*(4), e00036-20. https://doi.org/10.1128/CMR.00036-20

40. Luies, L., & du Preez, I. (2020). The echo of pulmonary tuberculosis: Mechanisms of clinical symptoms and other disease-induced systemic complications. *Clinical Microbiology Reviews*, *33*(4), e00036-20. https://doi.org/10.1128/CMR.00036-20

41. McGill, M. R. (2016). The past and present of serum aminotransferases and the future of liver injury biomarkers. *EXCLI Journal*, *15*, 817–828. https://doi.org/10.17179/excli2016-800

42. McGill, M. R. (2016). The past and present of serum aminotransferases and the future of liver injury biomarkers. *EXCLI Journal*, *15*, 817–828. https://doi.org/10.17179/excli2016-800

43. Mokondjimobe, E., Longo-Mbenza, B., Akiana, J., Ndalla, U. O., Dossou-Yovo, R., Mboussa, J., & Parra, H.-J. (2012). Biomarkers of oxidative stress and personalized treatment of pulmonary tuberculosis: emerging role of gamma-glutamyltransferase. *Advances in Pharmacological Sciences, 2012*, 465634. https://doi.org/10.1155/2012/465634

44. Mokondjimobe, E., Longo-Mbenza, B., Akiana, J., Ndalla, U. O., Dossou-Yovo, R., Mboussa, J., & Parra, H.-J. (2012). Biomarkers of oxidative stress and personalized treatment of pulmonary tuberculosis: emerging role of gamma-glutamyltransferase. *Advances in Pharmacological Sciences, 2012*, 465634. https://doi.org/10.1155/2012/465634

45. Motta, I., Boeree, M., Chesov, D., Dheda, K., Günther, G., Horsburgh, C. R., Jr., Kherabi, Y., Lange, C., Lienhardt, C., McIlleron, H. M., Paton, N. I., Stagg, H. R., Thwaites, G., Udwadia, Z., Van Crevel, R., Velasquez, G. E., Wilkinson, R. J., & Guglielmetti, L. (2024). Recent advances in the treatment of tuberculosis. *Clinical Microbiology and Infection, 30*(9), 1107–1114. https://doi.org/10.1016/j.cmi.2023.07.013

46. Motta, I., Boeree, M., Chesov, D., Dheda, K., Günther, G., Horsburgh, C. R., Jr., Kherabi, Y., Lange, C., Lienhardt, C., McIlleron, H. M., Paton, N. I., Stagg, H. R., Thwaites, G., Udwadia, Z., Van Crevel, R., Velasquez, G. E., Wilkinson, R. J., & Guglielmetti, L. (2024). Recent advances in the treatment of tuberculosis. *Clinical Microbiology and Infection, 30*(9), 1107–1114. https://doi.org/10.1016/j.cmi.2023.07.013

47. Narasimhan, P., Wood, J., MacIntyre, C. R., & Mathai, D. (2013). Risk factors for tuberculosis. *Pulmonary Medicine, 2013*, Article 828939. https://doi.org/10.1155/2013/828939

48. Natarajan, A., Beena, P. M., Devnikar, A. V., & Mali, S. (2020). A systemic review on tuberculosis. *Indian Journal of Tuberculosis, 67*(2), 295 https://doi.org/10.1016/j.ijtb.2020.02.005

49. Owens, K. (2024). Diversity and significance of *Mycobacterium*: Overview of genus. *Mycobacterial Diseases, 14*, 435. https://doi.org/10.35248/2161-1068.24.14.435

50. Pai, M., Behr, M. A., Dowdy, D., Dheda, K., Divangahi, M., Boehme, C. C., Ginsberg, A., Swaminathan, S., Spigelman, M., Getahun, H., Menzies, D., & Raviglione, M. (2016). Tuberculosis. *Nature Reviews Disease Primers, 2*, 16076. https://doi.org/10.1038/nrdp.2016.76

51. Prabhu, R., & Singh, V. (2019). The history of tuberculosis: Past, present, and future. *Advances in Microbiology, 9*(11), 931–942. https://doi.org/10.4236/aim.2019.911059

52. Prabhu, R., & Singh, V. (2019). The history of tuberculosis: Past, present, and future. *Advances in Microbiology, 9*(11), 931–942. https://doi.org/10.4236/aim.2019.911059

53. Ramírez-Lapausa, M., Menéndez-Saldaña, A., & Noguerado-Asensio, A. (2015). Extrapulmonary tuberculosis: an overview. *Revista Española de Sanidad Penitenciaria, 17*, 3–11.

54. Ramírez-Lapausa, M., Menéndez-Saldaña, A., & Noguerado-Asensio, A. (2015). Extrapulmonary tuberculosis: an overview. Revista Española de Sanidad Penitenciaria, 17, 3–11.

55. Sakamoto, K. (2012). The pathology of *Mycobacterium tuberculosis* infection. *Veterinary Pathology*, 49(3), 423–439. https://doi.org/10.1177/0300985811429313

56. Sales, A. C. d. S., Lopes, L. A., Vale, M. C. d. S., Costa, M. F., Lima, J. V. d. S., Silva, J. G. M. d., Ferreira, B. S. d. C., Nascimento, V. A. d., Flor, S. E. d. S., Sousa, E. L. C. d., Paz, B. K. B., Garcia, R. A. d. S., Sousa, E. M. d., Santos, A. F. d., Silva, L. C. N. d., & Zagmignan, A. (2023). Clinical features, biochemical parameters, and treatment adherence of individuals who started the treatment for active pulmonary tuberculosis during the pandemic period. *Journal of Clinical Medicine, 12*(14), 4843. https://doi.org/10.3390/jcm12144843

57. Sales, A. C. d. S., Lopes, L. A., Vale, M. C. d. S., Costa, M. F., Lima, J. V. d. S., Silva, J. G. M. d., Ferreira, B. S. d. C., Nascimento, V. A. d., Flor, S. E. d. S., Sousa, E. L. C. d.,

Paz, B. K. B., Garcia, R. A. d. S., Sousa, E. M. d., Santos, A. F. d., Silva, L. C. N. d., & Zagmignan, A. (2023). Clinical features, biochemical parameters, and treatment adherence of individuals who started the treatment for active pulmonary tuberculosis during the pandemic period. *Journal of Clinical Medicine*, *12*(14), 4843. https://doi.org/10.3390/jcm12144843

58. Salim, S. (2020). Prevalence, types and treatment of tuberculosis: A review. *Scientific Inquiry and Review, 4*(4), 63-87. https://doi.org/10.32350/sir.44.05

59. Salim, S. (2020). Prevalence, types and treatment of tuberculosis: A review. *Scientific Inquiry and Review, 4*(4), 63–87. https://doi.org/10.32350/sir.44.05

60. Schaberg, T., Bauer, T., Castell, S., Dalhoff, K., Detjen, A., Diel, R., ... & Ziegler, R. (2019). The diagnosis and treatment of tuberculosis. *Deutsches Ärzteblatt International*, *116*(43), 729–735. https://doi.org/10.3238/arztebl.2019.0729

61. Schcolnik-Cabrera, A., Orduna, P., Ponce de Leon, S., & Lopez-Vidal, Y. (2017). Tuberculosis: Basic and clinical relevant aspects. *International Journal of Pulmonary & Respiratory Sciences*, *1*(3), 42–69. https://doi.org/10.19080/IJOPRS.2017.01.555561

62. Sikri, K., & Tyagi, J. S. (2013). The evolution of *Mycobacterium tuberculosis* dormancy models. *Current Science*, 105(5), 607–616. https://www.jstor.org/stable/24097932

63. Sikri, K., & Tyagi, J. S. (2013). The evolution of *Mycobacterium tuberculosis* dormancy models. *Current Science*, *105*(5), 607–616. https://www.jstor.org/stable/24097932

64. Silva, D. R., Muñoz-Torrico, M., Duarte, R., Galvão, T., Bonini, E. H., Arbex, F. F., Arbex, M. A., Augusto, V. M., Rabahi, M. F., & Mello, F. C. Q. (2018). Risk factors for tuberculosis: Diabetes, smoking, alcohol use, and the use of other drugs. *Jornal Brasileiro de Pneumologia*, *44*(2), 145–152. https://doi.org/10.1590/S1806-37562017000000443

65. Suárez, I., Fünger, S. M., Kröger, S., Rademacher, J., Fätkenheuer, G., & Rybniker, J. (2019). The diagnosis and treatment of tuberculosis. *Deutsches Ärzteblatt International, 116*(43), 729–735. https://doi.org/10.3238/arztebl.2019.0729

66. Suárez, I., Fünger, S. M., Kröger, S., Rademacher, J., Fätkenheuer, G., & Rybniker, J. (2019). The diagnosis and treatment of tuberculosis. *Deutsches Ärzteblatt International, 116*(43), 729–735. https://doi.org/10.3238/arztebl.2019.0729

67. Thakur, S., Kumar, V., Das, R., Sharma, V., & Mehta, D. K. (2024). Biomarkers of hepatic toxicity: an overview. *Current Therapeutic Research*, *100*, 100737. https://doi.org/10.1016/j.curtheres.2024.100737

68. Thakur, S., Kumar, V., Das, R., Sharma, V., & Mehta, D. K. (2024). Biomarkers of hepatic toxicity: an overview. *Current Therapeutic Research*, *100*, 100737. https://doi.org/10.1016/j.curtheres.2024.100737

69. Thakur, S., Kumar, V., Das, R., Sharma, V., & Mehta, D. K. (2024). Biomarkers of hepatic toxicity: an overview. *Current Therapeutic Research*, *100*, 100737. https://doi.org/10.1016/j.curtheres.2024.100737

70. Thakur, S., Kumar, V., Das, R., Sharma, V., & Mehta, D. K. (2024). Biomarkers of hepatic toxicity: an overview. *Current Therapeutic Research*, *100*, 100737. https://doi.org/10.1016/j.curtheres.2024.100737

71. UniProt Consortium. (2024). UniProt: The universal protein knowledgebase in 2024. *Nucleic Acids Research*, *52*(D1), D609–D617. https://doi.org/10.1093/nar/gkad1052

72. UniProt Consortium. (2024). UniProt: The universal protein knowledgebase in 2024. *Nucleic Acids Research*, *52*(D1), D609–D617. https://doi.org/10.1093/nar/gkad1052

73. Vijaya Kumar, S., Deka, M. K., Bagga, M., Sasi Kala, M., & Gauthaman, K. (2010). A systematic review of different type of tuberculosis. *European Review for Medical and Pharmacological Sciences, 14*, 831–843.

74. Vijaya Kumar, S., Deka, M. K., Bagga, M., Sasi Kala, M., & Gauthaman, K. (2010). A systematic review of different type of tuberculosis. European Review for Medical and Pharmacological Sciences, 14, 831–843.

75. World Health Organization. (2022). *WHO consolidated guidelines on tuberculosis*. https://www.who.int/publications/i/item/9789241550529

76. World Health Organization. (2025). *Global tuberculosis report 2025*. World Health Organization. https://iris.who.int/handle/10665/379339

77. World Health Organization. (2025). *Global tuberculosis report 2025*. World Health Organization. https://iris.who.int/handle/10665/379339

78. Wu, S., Yang, Q., Li, H., & Li, Y. (2025). The feasibility of using liver function indices and FibroScan in combination to predict the occurrence of anti-tuberculosis drug-induced

liver injury in patients with liver disease. *Journal of Medical Biochemistry*, *44*(1), 17–23. https://doi.org/10.5937/jomb0-50878

79. Wu, S., Yang, Q., Li, H., & Li, Y. (2025). The feasibility of using liver function indices and FibroScan in combination to predict the occurrence of anti-tuberculosis drug-induced liver injury in patients with liver disease. *Journal of Medical Biochemistry*, *44*(1), 17–23. https://doi.org/10.5937/jomb0-50878

80. Youssef, E. M., & Wu, G. Y. (2024). Subnormal serum liver enzyme levels: A review of pathophysiology and clinical significance. *Journal of Clinical and Translational Hepatology*, *12*(4), 428–435. https://doi.org/10.14218/JCTH.2023.00446

81. Youssef, E. M., & Wu, G. Y. (2024). Subnormal serum liver enzyme levels: A review of pathophysiology and clinical significance. *Journal of Clinical and Translational Hepatology*, *12*(4), 428–435. https://doi.org/10.14218/JCTH.2023.00446

82. Zhong, T., Fan, Y., Dong, X.-L., Guo, X., Wong, K. H., Wong, W.-T., He, D., & Liu, S. (2021). An investigation of the risk factors associated with anti-tuberculosis drug-induced liver injury or abnormal liver functioning in 757 patients with pulmonary tuberculosis. *Frontiers in Pharmacology*, *12*, 708522. https://doi.org/10.3389/fphar.2021.708522

83. Zhong, T., Fan, Y., Dong, X.-L., Guo, X., Wong, K. H., Wong, W.-T., He, D., & Liu, S. (2021). An investigation of the risk factors associated with anti-tuberculosis drug-induced liver injury or abnormal liver functioning in 757 patients with pulmonary tuberculosis. *Frontiers in Pharmacology*, *12*, 708522. https://doi.org/10.3389/fphar.2021.708522

Abstract:

Tuberculosis is one of the most widespread infectious diseases worldwide and remains a major public health concern. It is caused by *Mycobacterium tuberculosis*, which primarily affects the respiratory system but may also involve other organs. Tuberculosis treatment mainly relies on a combination of anti-tuberculosis drugs administered regularly over a defined period. However, these medications may cause adverse effects, particularly hepatotoxicity, which can negatively affect treatment outcomes. In this context, an analytical study was conducted on the clinical data of 521 tuberculosis patients recruited from four public health institutions in Mila Province: Ain Beida Harriche, Mila, Ferdjioua, and Chelghoum Laïd. The results showed that tuberculosis was more frequent among women than men, and that lymph node tuberculosis was the most common form among extrapulmonary cases. Extrapulmonary tuberculosis accounted for the majority of cases, and differences in infection rates were observed among age groups, with young adults being the most affected category. In addition, a considerable proportion of patients presented with chronic comorbidities, particularly cardiovascular diseases and diabetes mellitus.

Regarding liver enzyme levels, most patients maintained normal ALT and AST values throughout treatment. Mild and transient elevations were the most common abnormalities, suggesting hepatic adaptation rather than clinically significant liver injury. Temporal analysis showed that both enzymes increased during the intensive phase of treatment, reached their peak around the third month, and then gradually declined. Significant variations in enzyme levels were observed among patients who successfully completed treatment, whereas irregular patterns were more common in patients with unfavorable treatment outcomes.

In conclusion, this study highlights the importance of regular monitoring of liver function during anti-tuberculosis therapy, especially during the first three months and in patients with comorbidities. Such monitoring may contribute to the early detection of hepatic complications and improve treatment effectiveness in Algeria.

Keywords: Tuberculosis, *Mycobacterium tuberculosis*, glutamate Pyruvate Transaminase (GPT/ALAT), Glutamate Oxaloacetate Transaminase (GOT/ASAT), hepatotoxicity, liver function, anti-tuberculosis therapy.

Résumé

La tuberculose est l'une des maladies infectieuses les plus répandues dans le monde et demeure un important problème de santé publique. Elle est causée par *Mycobacterium tuberculosis*, qui atteint principalement le système respiratoire, mais peut également toucher d'autres organes. Le traitement de la tuberculose repose principalement sur une association de médicaments antituberculeux administrés régulièrement pendant une durée déterminée. Cependant, ces médicaments peuvent provoquer des effets indésirables, notamment une hépatotoxicité susceptible d'altérer les résultats du traitement. Dans ce contexte, une étude analytique a été menée sur les données cliniques de 521 patients tuberculeux recrutés dans quatre établissements publics de santé de la wilaya de Mila : Aïn Beïda Harriche, Mila, Ferdjioua et Chelghoum Laïd. Les résultats ont montré que la fréquence de la tuberculose était plus élevée chez les femmes que chez les hommes et que la tuberculose ganglionnaire constituait la forme la plus fréquente parmi les cas extrapulmonaires. Les formes extrapulmonaires représentaient la majorité des cas, et des différences de fréquence ont été observées entre les différentes classes d'âge, les jeunes adultes étant les plus touchés. En outre, une proportion importante des patients présentait des comorbidités chroniques, notamment les maladies cardiovasculaires et le diabète.

Concernant les enzymes hépatiques, la majorité des patients ont conservé des valeurs normales d'ALAT et d'ASAT tout au long du traitement. Les augmentations légères et transitoires constituaient les anomalies les plus fréquentes, traduisant davantage une adaptation hépatique qu'une atteinte hépatique cliniquement significative. L'analyse temporelle a montré que les deux enzymes augmentaient pendant la phase intensive du traitement, atteignaient leur pic vers le troisième mois, puis diminuaient progressivement. Des variations significatives des taux enzymatiques ont été observées chez les patients ayant achevé leur traitement avec succès, tandis que des profils irréguliers étaient plus fréquemment associés aux issues thérapeutiques défavorables.

En conclusion, cette étude souligne l'importance d'une surveillance régulière de la fonction hépatique au cours du traitement antituberculeux, en particulier durant les trois premiers mois et chez les patients présentant des comorbidités. Cette surveillance pourrait contribuer à la détection précoce des complications hépatiques et à l'amélioration de l'efficacité du traitement en Algérie.

ملخص

يُعتبر السل من أكثر الأمراض المعدية انتشارًا في العالم، وينتج عن بكتيريا *Mycobacterium tuberculosis* التي تصيب أساسًا الجهاز التنفسي وقد تمتد إلى أعضاء أخرى. يعتمد علاج السل على مجموعة من الأدوية المضادة للسل، إلا أن هذه الأدوية قد تسبب آثارًا جانبية أهمها السمية الكبدية.

أُجريت هذه الدراسة على 521 مريضًا بالسل موزعين على أربع مؤسسات صحية بولاية ميلة: عين البيضاء حريش، ميلة، فرجيوة، وشلغوم العيد، بهدف تقييم تأثير العلاج المضاد للسل على وظائف الكبد.

أظهرت النتائج أن نسبة الإصابة كانت أعلى لدى النساء مقارنة بالرجال، وأن السل العقدي اللمفاوي كان الشكل الأكثر شيوعًا من السل خارج الرئة. كما مثّلت الأشكال خارج الرئوية غالبية الحالات، وكانت فئة الشباب الأكثر تأثرًا بالمرض. بالإضافة إلى ذلك، لوحظ انتشار بعض الأمراض المزمنة المصاحبة، خاصة أمراض القلب والأوعية الدموية وداء السكري.

فيما يخص وظائف الكبد، حافظ معظم المرضى على مستويات طبيعية لإنزيمي ALT و AST خلال فترة العلاج، بينما كانت الارتفاعات الطفيفة والعابرة هي الأكثر شيوعًا. كما سُجل ارتفاع في مستويات الإنزيمين خلال المرحلة المكثفة من العلاج، مع بلوغ الذروة حوالي الشهر الثالث، ثم انخفاضها تدريجيًا بعد ذلك. وظهرت تغيرات أكثر انتظامًا لدى المرضى الذين أتموا العلاج بنجاح، في حين كانت الاضطرابات أوضح لدى المرضى ذوي النتائج العلاجية غير المواتية.

وفي الختام، تؤكد الدراسة أهمية المتابعة المنتظمة لوظائف الكبد أثناء العلاج المضاد للسل، خاصة خلال الأشهر الثلاثة الأولى ولدى المرضى المصابين بأمراض مزمنة، لما لذلك من دور في الكشف المبكر عن المضاعفات الكبدية وتحسين فعالية العلاج.