PROFILE OF HAEMATOLOGICAL INDICES AMONG PULMONARY TUBERCULOSIS PATIENTS ATTENDING KISII TEACHING AND REFERRAL HOSPITAL, KISII KENYA

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2024

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DEDICATION

I dedicate this special work to my dear wife Isabella Gesare, my children; Allan Ongwae and Derrick Ongwae God bless you all.

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ABSTRACT

Tuberculosis (TB) is as a result of Mycobacterium *tuberculosis* infection and contagious ailment primarily transmissible through inhalation of air-dispersed droplets from active TB patients. By 2021, the World Health Organization recorded ten (10) million TB cases and 1.4 million fatalities. Hematological abnormalities are common in TB patients and hold potential as prognostic indicators. This study evaluated hematological indices among TB confirmed patients attending Kisii Teaching and Referral Hospital between April to August 2022. It was a cross-sectional study design used to recruit participants from TB positive patients in KTRH whose venous blood sample were collected by venipuncture and placed in 4 ml Ethylene Diamine Tetra Acetic tubes for analysis. Simple random sampling technique used in recruitment of 210 participants, 105 patients and 105 negative controls. Flow cytometry technique was used for cell differential count. Erythrocyte Sedimentation Rate was set up by Westergren technique, thin blood film was prepared and examined morphologically. Statistical analysis for data analysis done using STATA version 23. Independent sampling for t-test was used to compare differences in mean values with a p-value of ≤ 0.05 was considered significant. Hematological abnormalities were observed in tuberculosis patients with mean values of hemoglobin level 11.93 ± 2.01 (P=0.001), hematocrit 37.96± 6.36 (P=0.001), mean corpuscular hemoglobin 27.80 ± 4.66 (P=0.028), mean corpuscular haemoglobin concentration 31.50g/dL (P=0.001), lymphocyte count of 1.81±0.85 $x10^3/\mu L$ (P =0.086) of pulmonary TB showed statistical decrements whereas total WBC 7.81 ±4.08 $x10^3/\mu L$ (P=0.018), platelet count 328.61±120.99 $x10^3/\mu L$ (P=0.009), neutrophil count 4.86 ±3.11 x $10^3/\mu L$ (P =0.044) and ESR 69.18 ± 22.86 mm/hr. (P =0.001) showed increased count. The blood film showed normocytic normochromic anemia in majority of PTB patients. In conclusion, Total WBC, Neutrophils, Lymphocytes, Monocytes count Hemoglobin, Hematocrit, MCH, MCHC, ESR, Platelets and blood film can be used for diagnosis and prognosis for PTB. This study recommends integrating hematological profiles for diagnosis, treating, monitoring, and clinically managing such patients.

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ABBREVIATIONS AND ACRONYMS

AFB	**:**	Acid Fast Bacillus
APC	**:**	Absolute platelet count
BCG	**:**	Bacille Chalmette-Guerin
CBC	**:**	Complete Blood Count
CD4	**:**	Helper T- Cells (Cell Differentiation no. 4)
DOTS	**:**	Directly Observed Treatment Short Courses
EDTA	**:**	Ethylene Diamine-Tetra-acetic Acid
ESR	**:**	Erythrocyte Sedimentation Rate
HCT	**:**	Hematocrit
HGB	**:**	Hemoglobin
HIV	**:**	Human Immune Deficiency Virus
MCV	**:**	Mean Corpuscular Volume
MCH	**:**	Mean Corpuscular Hemoglobin

MDRTB	**:**	Multidrug-Resistant Tuberculosis
MOH	**:**	Ministry of Health
PAS	**:**	Para-amino salicylic acid
PTB	**:**	Pulmonary Tuberculosis
PBF	**:**	Peripheral Blood Film
TB	**:**	Tuberculosis
TLC	**:**	Total Leukocyte Count
WHO	**:**	World Health Organization

OPERATIONAL DEFINITION OF TERMS

Extra-pulmonary TB cases: TB infection in other organs apart from the lungs

Hematological parameters: Blood indices tested like platelet counts, total and differential white cell counts, erythrocyte sedimentation rate (ESR), packed cell volume, and hemoglobin concentration

Mycobacterium tuberculosis: The causative agent for tuberculosis

Smear-negative: A patient not meeting the above criteria for smear examination and has no radiographic anomalies consistent with active pulmonary TB as determined by a physician.

Smear-positive: A patient with at least two positive results for AFB by direct microscopy and one culture positive or one positive AFB by direct microscopy and one culture positive and radiographic anomaly as determined by a physician.

Tuberculosis: A communicable disease caused by Mycobacterium tuberculosis.

CHAPTER ONE

INTRODUCTION

1.1 Background of the Study

Tuberculosis (TB) infection causes communicable disease when *Mycobacterium tuberculosis* is invested in the body. It is acquired through inhalation of air droplets from a person an infected with active TB disease (Krishnan et al., 2022). Other sources of TB infection include consumption of unpasteurized milk and meat infected with *M.tuberculii* (Téllez-Navarrete, et al., 2021). This infection normally affects the lungs (pulmonary TB) but it can also affect other body parts except the nails and hair (extra-pulmonary TB). Tuberculosis possesses a major public health burden in developing countries, especially due to HIV comorbidity and other socio-economic challenges such as overcrowding and multi-drug resistant strains of TB (MDRTB). During its early stages, TB presents with unclear symptoms making early diagnosis and treatment quite a challenge (Cannon, et al.,, 2021).

Globally, TB is among the top communicable killer disease. South-East Asia and Africa bear the greatest burden of the disease, 45% and 23% respectively (WHO, 2023). Notably, in 2021, eight countries were responsible for more than two-thirds of all TB cases: India recorded a 28%, TB cases, Indonesia (9.2%), China (7.4%), the Philippines (7.0%), Pakistan (5.8%), Nigeria (4.4%), Bangladesh (3.6%), and the Democratic Republic of Congo (2.9%) cases. Although some nations have made significant progress in reducing TB cases, others are experiencing a slow decline (Shringarpure et al., 2023). Countries such as China and Brazil are commendably

among the 22 nations that have sustained a downward trend in TB cases over the past two decades (Cortez, de Melo, Neves, Resende, & Camargos, 2021).

In 2020, Kenya reported a total of 558 per 100,000 TB cases with the highest burden was recorded between 25-34 age group having more cases than previously estimated. Kenya had a decline in TB from the 99,159 to 89,760(9.48%) cases in the year 2019 (Ministry of Health, 2019). Counties with the highest TB prevalence include Mombasa, Nairobi, and Homabay at 535, 490, and 426 cases per 100,000 respectively. In Kisii County, there were 1865 TB cases in 2019 with 8.4% cases reported among children (Ministry of Health, 2019). A survey carried out in 2016 identified 305 prevalent TB cases translating to a prevalence of 558 per 100,000 adult populations. The highest disease burden was reported among people aged 25-34 years and those who live in urban areas 760 (Enos et al., 2018).

Several studies have been done which stipulates that the hematological indices like white blood cells, red blood cells, platelet count, and body weight loss are useful indicators of the severity of tuberculosis (Urbán-Solano et al., 2022). Analysis of these indices from critical value of infections to normal levels after treatment is a good indication of disease control because they correlate with the absence of acid-fast bacilli in the sputum (Anayochukwu Ufelle et al., 2020). Hematological and biochemical abnormalities in pulmonary TB are common and may be valuable aids in diagnosis of Tb related diseases.

Sputum ZN staining, Gene Xpert, and culture are procedures in the techniques used to identify pulmonary tuberculosis (PTB) in Kisii. With ZN stain technique can

identify tuberculosis within hours, it is less accurate as compared with others(Amos, 2018). Gene-Xpert is a real-time PCR-based on molecular extraction for the identification of the bacilli. Early determination of the bacilli infection for tuberculosis in sputum negative patients increases prevention and the spread of TB. Hematological indices will aid in earliest detection as blood can be readily available for quick and urgent diagnosis. With the aforementioned county trend of TB cases in consideration, this study will be designed to examine the hematological parameters and in confirmed cases of pulmonary tuberculosis patients in the target area of Kisii Teaching and Referral Hospital.

1.2 Problem Statement

Tuberculosis cases are usually identified by mycobacterium tuberculosis confirmatory tests when they are at an advanced stage, which makes it challenging to institute intervention measures at an early stage of infection. Consequently, TB monitoring has been hampered by inefficient laboratory networks in the counties, inadequate trained health staff, and inadequate and expensive equipment like the GeneXpert and TB culture equipment (Migliori, Nardell, Yedilbayev, Ambrosio, et al., 2019). Microscopy has an accuracy of up to 60% and culture takes time before one gets results, this delays treatment making the bacteria continue spreading in the body (Deutsch-Feldman, Pratt, Price, Tsang, & Self, 2021). Lack of information on hematological indices among pulmonary tuberculosis patients may adversely affect tuberculosis management and control. Therefore, timely diagnostic, curative and preventive services are required to address TB and other risk factors that increase the

individual's susceptibility for TB (Paleckyte, Dissanayake, Mpagama, Lipman, & McHugh, 2021). As TB control and treatment gain pace in the country led by the counties, it is important to have studies undertaken on haematological indices among pulmonary tuberculosis patients in Kisii in order to establish changes which can aid in diagnosis. The referral hospital receives tuberculosis cases from surrounding counties which don't have capacity to diagnose and effectively manage the disease. This gives Kisii Teaching referral hospital the burden of dealing with many cases of TB. This research is key to bridge the knowledge gap with local figures and hematological changes of Tuberculosis patients. Tuberculosis is among the most significant cases of communicable diseases worldwide with high burden in Africa. World Health Organization declared tuberculosis as a global emergency in 1993 (Ainley& Kon, 2020). There are studies done in reference to tuberculosis but there is no sufficient information in regard to haematological indices analyzed in pulmonary tuberculosis patients in Kenya, and in Kisii region population. The present study describes the finding in haematological parameters variants in relation to disease severity for TB cases in respect to assigned control groups with predisposing factors associated with hematological profiles in the outcomes to help researchers to conclude the need to use such indicators.

This current research evaluated haematological profile among pulmonary tuberculosis confirmed patients attending Kisii Teaching and Referral Hospital.

1.3 Justification of the Study

Hematological testing maybe a good alternative method to supplement the routine methods currently used for tuberculosis diagnosis. Efficient and accurate methods lead to early diagnosis, treatment and follow-ups of TB disease. With accurate methods in place, we will have reduced transmission and enhance timely initiation of treatment, hence lowering the cost of treatment. This will create a healthy nation with a pool of manpower for the economic growth of the country. The current methods used have various challenges ranging from low sensitivity like ZN staining , expensive like blood culture which also takes a long time and sophisticated equipment like GeneXpert (Ainley & Kon, 2020). This study evaluated the use of hematological testing as an option screening method for TB and as an earlier indicator for TB infection. The haematological testing will be used as supplementary testing for TB testing. The disease is curable if detected earlier. Hospitals need to be advised on the use of hematological parameters as a differential diagnosis for early detection of TB, these can only be done through available empirical evidence hence the reason for the current study. The study will extend knowledge on diagnosis of TB as well as lead to the discovery of new diagnostic indicators hence saving life.

1.4 Objectives of this Study

1.4.1 Broad Objective

To profile haematological indices among pulmonary tuberculosis patients attended Kisii Teaching and Referral Hospital, Kenya.

1.4.2 Specific Objectives

1. To determine White Blood Cells (WBC) count among TB patients attended Kisii Teaching and Referral Hospital.
2. To establish red blood cell indices variations among tuberculosis patients attended Kisii Teaching and Referral Hospital.
3. To perform platelet, count in TB patients attended Kisii Teaching and Referral Hospital.
4. To establish morphological changes of blood cells on a Peripheral blood film among TB patients attended Kisii Teaching and Referral Hospital.

1.5 The Research Questions

1. What were the changes in White blood cell count among patients diagnosed with TB attended Kisii Teaching and Referral Hospital?
2. What were the red blood cell indices in TB infection among patients attended Kisii Teaching and Referral Hospital?
3. What were the platelet count in TB among patients attended Kisii Teaching and Referral Hospital?
4. What were the morphological changes in blood cells in Peripheral blood film among patients attended Kisii Teaching and Referral Hospital?

1.6 Study limitations

This study was based on hematological indices and their critical values in PTB patients. While these indicators offer valuable insights, to analyze confounding factors such as nutritional status, socioeconomic factors and other underlying health

conditions that might influence hematological parameters is another field for future. The study controlled for these variables to avoid spurious associations or mask potential causal relationships; however, a screening tool was adopted to ensure confounders were reduced.

Moreover, the use of a single hospital, Kisii Teaching and Referral Hospital, as the study site may limit the generalizability of findings to other settings however; regional variations in patient characteristics, healthcare access, and TB prevalence could impact the transferability of results to different populations.

CHAPTER TWO

LITERATURE REVIEW

With resource limitations, pulmonary tuberculosis (TB) infections have serious threats to world health burden (Ainley & Kon, 2020). *Mycobacterium tuberculosis*, is a bacillus that causes the TB disease, primarily affects lungs and other body parts. If it is not identified and treated early, it can cause significant morbidity and mortality (MacNeil et al., 2020). Kenya continues to struggle with the effects of TB as one of the high-burden nations, demanding a thorough grasp of the disease's many facets for efficient treatment and control measures (Paleckyte et al., 2021).

Hematological indices, which encompass a range of blood parameters related to cellular components and their characteristics, have gained recognition as valuable indicators of disease progression, severity, and treatment response in various clinical conditions, including infectious diseases. These indices provide insights into the body's physiological response to infections, inflammation, and other pathological processes (Sharma & Mohan, 2023). Consequently, studying the profile of hematological indices among pulmonary tuberculosis patients becomes a vital endeavor to elucidate the potential impact of TB on the hematological system and to explore its implications for patient care and management.

In the subsequent sections of this literature review, we delve into the existing body of research concerning the relationship between tuberculosis and hematological indices, exploring relevant findings, methodologies, and gaps in knowledge. Through this comprehensive review, this study aspires to establish a strong

foundation for the study in the context of pulmonary tuberculosis and its impact on hematological parameters.

2.1.1 Biology of Tuberculosis

Mycobacterium tuberculosis causes tuberculosis infections, sometimes referred to as "intake" historically beginning as a respiratory infection, but can spread to any part of the body, including the liver, bones, and brain.

Primary infection of tuberculosis is as a result of the bacilli when inhaled and engulfed by macrophages within the lung but the immune cells are unable to destroy the bacilli due to its waxy cell wall. The *Mycobacterium tuberculosis* grows within the macrophages in the lung (Simper et al., 2022). Some of the macrophages lyse and release the bacteria which are also engulfed by macrophages and other white blood cells like neutrophils but cannot destroy the *Mycobacterium tuberculosis* cells (McCaffrey et al., 2020). The area within the lungs is protected by the immune system in a fibrin-containing structure to contain the infection. The site of the tubercle bacilli form what is referred to as "caseous necrosis which is a cheesy consisting of the *Mycobacterium tuberculosis* infected tissue, and immune cells. Most *Mycobacterium tuberculosis* infections are halted by the formation of tubercles and the person remains asymptomatic (Kirwan, Chong, & Friedland, 2021).

In case of Secondary infection stage of *Mycobacterium tuberculosis,* and the patient has a weakened immune system, malnutrition or other disease, the tubercles can rupture and release the *Mycobacterium tuberculosis* which had been contained to become infective and new tubercles are formed. Although this is primarily in the

lungs, tubercles can have formed and attack any part of the body like bones and tissues. The tubercles and their rupture cause tissue damage and subsequently reduced lung function (and/or function of other organs/tissues containing tubercle Symptoms of active TB include: Coughing that lasts three or more weeks, Coughing up blood, Chest pain, or pain with breathing or coughing, Unintentional weight loss,Fatigue,Fever,Night sweats,Chills,Loss of appetite (Li et al., 2019).

2.1.2 Etiology of Tuberculosis

The transmission of tuberculosis (TB) takes place through the dissemination of air droplet for the nuclei which could harbor very fewer bacilli (Migliori, Nardell, Yedilbayev, D'Ambrosio, et al., 2019). People get exposure to TB typically through sharing the same breathing space with an infectious patient. Upon inhalation, these minuscule droplet nuclei find their way into the lung's terminal airspaces. Once encountered, macrophages, specialized immune cells, ingest and transport the bacteria towards nearby lymph nodes (de Martino, Lodi, Galli, & Chiappini, 2019)

The fate of these ingested bacilli rests on four potential outcomes: Firstly, they might succumb to the immune system's defense mechanisms and be neutralized. Secondly, they could proliferate, leading to the onset of primary TB infection. Alternatively, they could enter a dormant phase, remaining asymptomatic and inactive. Lastly, after a period of latency, they might undergo reactivation and resume proliferation, potentially resulting in a renewed disease episode. This reactivation disease could emerge subsequent to either the scenarios outlined in the second and third possibilities above (Jha & Rathish, 2023).

2.1.3 Pathology and pathogenesis of Tuberculosis

Approximately 90% of people affected with *Mycobacterium tuberculosis* experience latent TB infection (LTBI) which is asymptomatic, whereby there is a likelihood of progression an active TB disease for about 10% over a lifetime (Adams et al., 2019). Nevertheless, in the absence of treatment, the mortality rate among cases of active TB can surpasses 50%. The pathophysiology of *Mycobacterium tuberculosis* infection involves the penetration of mycobacteria bacilli into the lung alveoli where they infiltrate and reproduce in alveolar cells (Adigun & Singh, 2020). The primary infection by *Mycobacterium tuberculosis* when enters the lungs forms Ghon focus. Dendritic cells capture the bacteria and it inhibit replication, facilitating the transportation to local (mediastinal) lymph nodes. Wide dissemination occurs via the bloodstream, leading to the formation of secondary TB lesions in distant tissues and organs, such as lung abscess, lymph nodes, the kidneys, brain, and bone (Adigun & Singh, 2020). While various body parts can be affected by the disease, its impact on other parts of the body such as the heart, skeletal muscles, pancreas, and thyroid is rare but it can occur (Moule & Cirillo, 2020).

Tuberculosis belongs to the category of granulomatous inflammatory conditions forming granulomas being an aggregation of macrophages, lymphocytes and fibroblasts which encircles infected tissues. These granulomas not only restrict the spread of *Mycobacterium tuberculosis* but also establish a localized r immune cell interaction. T-lymphocytes with $CD4^+$ cells activate the secretion of cytokines like interferon gamma, which activates macrophages to eliminate the infected bacteria.

T-lymphocytes of class $CD8^+$ also directly engage in the destruction of infected cells (McCaffrey et al., 2020). This immune response does not eliminate the bacteria within granulomas but some become dormant, resulting in latent infections. Notably, human tuberculosis granulomas exhibit the occurrence of cell death, or necrosis, at the core of tubercles. This central area, resembling soft white cheese in texture, is termed gaseous necrosis (Adigun, Basit, & Murray, 2023).

Upon gaining access from damaged tissue regions to the bloodstream, TB bacteria disseminate throughout the body, giving rise to multiple infections, visually manifested as minute white tubercles in tissues. This severe manifestation, termed miliary tuberculosis, predominantly can affects infants and the elderly, with an associated fatality rate of around 20% despite intensive treatment (Sharma & Mohan, 2023). The progression of infection frequently displays variations, with healing and fibrosis counterbalancing tissue necrosis and destruction (McCaffrey et al., 2020). Affected tissue is replaced by scar tissue and voids filled with cheese-like white necrotic material. Some of these cavity's link with the bronchi during an active illness, allowing material containing live bacteria to be coughed up and aiding in the spread of the illness. Effective antibiotic treatment leads to bacterial elimination, fostering the process of healing. Following recovery, affected areas gradually undergo replacement by scar tissue (Urbanowski, Ordonez, Ruiz-Bedoya, Jain, & Bishai, 2020).

2.1.3 Clinical manifestations of tuberculosis

Pulmonary Tuberculosis (TB), a productive cough, a high body temperature, and gradual weight loss are all signs of pulmonary TB. Patients may occasionally get hemoptysis or chest pain. Systemic symptoms including anorexia, tiredness, and nocturnal sweating may also appear simultaneously (Luies & Preez, 2020).

Tuberculous Meningitis, Patients with tuberculous meningitis may first experience a headache for two to three weeks, either intermittently or consistently. In a few of days or weeks, subtle mental changes could progress to a comatose state. Fever could be mild or completely absent (Slane& Unakal, 2022).

Skeletal tuberculosis (TB) which primarily affects the spine (Pott's disease) sometimes precedes indications of back pain or stiffness'. Notably, a large percentage of patients with undiagnosed Pott's illness may develop lower extremity paralysis. The hip or knees are the joints most frequently affected by tuberculous arthritis, which normally affects a single joint. It affects other parts of the body such as the ankle, elbow, wrist, and shoulder. Pain may appear weeks or months before radiological changes (Slane& Unakal, 2022).

Genitourinary *Mycobacterium tuberculosis* infections can have symptoms like flank pain, dysuria, and increased frequency of urination, this is in contrast to how it can mimic pelvic inflammatory illness in women, genital infections may manifest in men along the epididymitis or at the scrotal lump. Around the world, *Mycobacterium tuberculosis* accounts for 10% of female infertility, while in developed nations, it accounts for 1% (Jha & Rathish, 2023).

Gastrointestinal *Mycobacterium tuberculosis*, can affect the parts of digestive system and it depends on the site of infection, clinical manifestations can include oral or anal ulcers that do not heal, dysphagia in cases of esophageal disease, abdominal pain that resembles peptic ulcer disease and involves the stomach or duodenum, malabsorption in cases of small intestine infection, and abdominal pain, diarrhea, or hematochezia in cases of colon infection (Jha & Rathish, 2023).

Mycobacterium tuberculosis can cause the enlargement of the lymph nodes (Scrofula) observed predominantly along the neck, the sternocleidomastoid muscle, tuberculous lymphadenitis typically appears unilaterally and is often devoid of substantial pain. Advanced cases can lead to suppuration and the development of a draining sinus (Bhandari & Thada, 2023).

Cutaneous TB, Direct mycobacterial exposure can cause ulceration or the development of wart-like lesions. The involvement of lymph node causes propagation of typically draining sinus. Hematogenous spread can cause tender nodules or abscesses in addition to a reddish-brown plaque on the face or extremities (lupus vulgaris)(Adigun & Singh, 2020).

2.1.4 Diagnosis of tuberculosis

A prospective diagnosis of tuberculosis (TB) necessitates the isolation from cultured sputum or aspiration of *Mycobacterium tuberculosis* microorganisms from the patients samples(Motallebirad, et al., 2018). While sputum remains the most common specimen type, alternate sources such as pus, cerebrospinal fluid (CSF), biopsied tissue, and others are also considered. Blood culture for the detection of

bacterial growth confirms the bacilli than microscopy and increases the number of TB sensitivity and isolation to 20–50%, depending on local incidence. Culture methods provide standardized diagnosis by establishing the viability and identity of the organisms by allowing the detection of other forms of drug resistance strains having more than 80 percent sensitivity rates.

Another method which has evolved is the GeneXpert with high sensitivity and specificity testing outcomes for *Mycobacterium tuberculosis* diagnosis using DNA sequences. This technique is specific for *Mycobacterium tuberculosis* and can detect rifampicin resistance gene in a sample of sputum.

Acid-fast bacilli smear and cultures are recommended when viable sputum sample is available. Fluorescence microscopy employing auramine-rhodamine staining is the preferred approach, exhibiting superior sensitivity compared to conventional Ziehl-Neelsen staining and this has been attributed to its sensitivity (Forbes et al., 2018). In Zn staining, the acidic part of the dye binds with the bacillus cell wall of the bacteria resulting in the selective staining of only those cells that have a high density of cell wall material for acid-fast bacteria.

Ziehl-Neelsen staining procedure allows the cell wall to be stained with a basic fuchsine solution, and subsequent incubation in an acid alcohol solution decolorizes all cells except for acid-fast cells, which retain the color and appeared as red. The mechanisms by which this color is produced through the interaction of the basic fuchsine with the cell wall components of bacteria creates a new molecular structure that is responsible for the color change. This method has sensitivity of 60 %.

When sputum production is constrained, different collection methods like the induction of sputum, and any other specimen can be obtained from genital warts, laryngeal swabs, bronchoalveolar lavage, or fine needle aspiration of pertinent collections. The Lowenstein-Jensen (LJ), Kirchner, or Middlebrooks (7H9, 7H10, and 7H11) have traditionally been used as historical culture media for growing these bacteria (Peng, Zhou et al., 2020).

Chest radiography can be used as a diagnostic tool for *Mycobacterium tuberculosis* (Creswell et al., 2019). In instances of active pulmonary *Mycobacterium tuberculosis*, radiographic imaging can reveal infiltrates, consolidations, and cavities predominantly within the upper lung regions. The presence of mediastinal lymphadenopathy, as well as tuberculous pleurisy with pleural effusions, can also be observed radiologically. It is notable in *Mycobacterium tuberculosis* associated lesions can manifest in any region of the lungs. Disseminated *Mycobacterium tuberculosis* is marked by a pattern of numerous minute nodules dispersed across the lung fields, a phenomenon termed miliary *Mycobacterium tuberculosis*. In immunosuppressed individuals with radiographic abnormality could potentially signify TB, or the chest X-ray may even exhibit a completely unremarkable appearance (Sharma, et al., 2023).

On the other hand, Tuberculin Skin Test have also been used in TB diagnosis (Adams et al., 2019). Two skin puncture, namely the Monteux and Heave tests, are employed for assessing tuberculin skin reactivity. The Mantoux skin test entails the intradermal injection of Purified Protein Derivative (PPD) tuberculin, followed by subsequent measurement and induration size within 48-72-hour interval. The size is measured

and reaction noted. This method assists in the evaluation of an individual's immune response to TB exposure.(Okoth,2017).

Fig 2.1 *Injecting a Monteux skin test. (source, google 2019)*

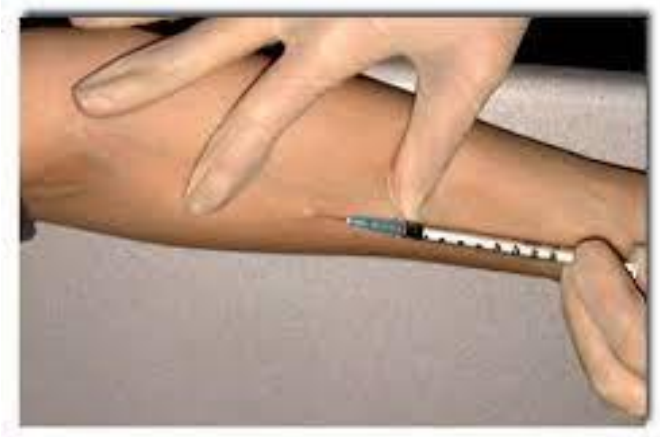


Fig 2.2 *Reading a Monteux after 48-72 hours. (source, google 2019)*

The Heaf test, also known as the Multiple Puncture Test (MPT), is one of the methods used for administering and evaluating the tuberculin skin test (Adams et al., 2019). It is named after its developer, Dr. Alan Heaf. Similar to the Monteux test, the Heaf

test is utilized to assess an individual's immune response to tuberculosis (TB) exposure by measuring the reaction of the skin to purified protein derivative (PPD) tuberculin, an extract derived from *Mycobacterium tuberculosis* (Adams et al., 2019) .

The Heaf test employs a multi-pronged instrument called a Heaf gun, which is designed to simultaneously introduce several calibrated needle prongs into the skin surface. These prongs are coated with a standardized amount of PPD tuberculin. Upon administration, the individual typically experiences minimal discomfort and the procedure is relatively quick. The Heaf test produces a pattern of small puncture wounds, each representing a separate introduction of PPD into the skin. The test is performed on the forearm, usually in a specific grid-like pattern, resulting in a distinctive configuration of punctures. The degree of skin reaction at each puncture site is assessed and graded according to a standardized system (Adams et al., 2019).

The results of the Heaf test is based on the individual puncture reactions, providing an overall score that aids in classifying the individual's tuberculin sensitivity. The Heaf test categorizes individuals into different groups or "grades" based on their cumulative skin reaction scores. These grades can range from 0 (no reaction) to 4 or more, with higher scores indicating stronger reactivity to PPD and potentially suggesting recent or significant exposure to TB (Adams et al., 2019).

While the Heaf test has been historically used in some settings, the Mantoux test is more commonly employed worldwide for tuberculin skin testing due to its simpler administration and clearer interpretation. The Heaf test's multiple punctures can lead

to variability in the depth of PPD delivery and subsequently, varying levels of skin reaction. As a result, the Heaf test's precision and reliability have been questioned, leading to its decreased use in favor of the Mantoux test or other more standardized methods of tuberculin testing (Adigun & Singh, 2020).

2.2 Haematological manifestations of Tuberculosis

Correlation with TB infection encompass a wide range of alterations in hematological indices such as the red blood cell counts, white blood cell counts, platelet counts, hemoglobin concentrations. Historically, the understanding of TB's effects on the hematological system was limited to the context of anemia, which has often been associated with chronic infections, including TB (Erhabor, Abubakar, Erhabor, & Mgbere, 2020). However, contemporary research is shedding light on a more intricate relationship between TB and hematological indices (Anayochukwu Ufelle et al., 2020). Beyond anemia, TB has been implicated in leukopenia, thrombocytosis, and various qualitative changes in blood cells' characteristics, including alterations in cell size, shape, and functionality (Dasaradhan et al., 2022).

The mechanisms underlying these hematological changes are multifactorial and complex. TB infection triggers a cascade of immune responses, involving both innate and adaptive immune components. The interaction between *Mycobacterium tuberculosis* and host immune cells can lead to the release of cytokines, chemokines, and other signaling molecules, influencing hematopoiesis and cell differentiation (Urbán-Solano et al., 2022). Additionally, the chronic inflammation associated with

TB infection can contribute to hematological alterations, further impacting the overall health of patients (Gil-Santana et al., 2019).

To understand hematological manifestations in TB diagnosis, there is growing recognition of their clinical significance. These changes can serve as potential indicators of disease severity, progression, and prognosis. Same phenomena can be expressed with hematological alterations to show co-existing conditions, such as anemia's impact on overall health and immunity.

2.2.1 White Blood Cells Differential Changes among Patients Diagnosed with TB

Researchers have indicated that alterations in WBC counts can serve as potential indicators of TB screening (Chedid et al., 2020). These are immune cells that triggers the defense against TB through activated responses of the body. The white blood cells, also known as leukocytes, are immune cells forming part of cellular components of the blood. Leukocytes are clustered as neutrophils, lymphocytes, monocytes, eosinophils, and basophils. There mode of action involves, inflammation, phagocytosis, and compliment activation are all diverse tasks performed by white blood cells (Chedid et al., 2020). These immune cells defend the body against pathogens and other undesired responses of the body by eliminating infectious agents. The action of cell immunity can be as a result of antibodies production to protect the body against disease.

Pluripotent stem cells produces leukocytes in a closed system that is controlled by growth factors and cytokines (Minardi et al., 2021). Granulocytes, which include

neutrophils, Eosinophils, and basophils, are the leucocytes that develop from CFU-GEMM. Lymphocytes, dendritic cells, and natural killer (NK) cells are another clone of immune cells that originates from CFU-Ls (McCaffrey et al., 2020). All these cells provide immunity to the body.

Rohini et al., (2016a) carried out a study on the assessment of hematological parameters among tuberculosis patients, he found that WBC count was increased in tuberculosis patients when compared with healthy controls. Another study by Ştefanescu et al., (2021) also found out that there was a decrease in immune cell count, neutrophils, monocytes, and other indicators like hemoglobin, platelets erythrocyte sedimentation rate (ESR) after anti-TB therapy compared to pretreatment in 70% of the patients who were culture negative.

Chedid et al.,2020) carried a study, in the assessment of treatment failure in relation with white blood cell, lymphocyte, and monocyte counts after TB treatment. The study showed that the likelihood of TB treatment failure is greatly increased by low WBC counts and low lymphocyte fractions.

In Ibadan, Nigeria, researchers looked at the hematological profiles of patients with pulmonary tuberculosis. Elevated erythrocyte sedimentation rate, anemia (occurred in 93.6% of patients), leukocytosis (occurred in 22.3%), neutrophilia (occurred in 45.2%), and Lymphopenia (occurred in 4.8%) were statistically significant hematologic abnormalities identified in the study. 12.9% of patients exhibited thrombocytosis, while 8% had thrombocytopenia. Only 8.4% of the patients exhibited lymphocytosis, and none had leucopoenia. (Erhabor et al., 2020). Mabrouk

et al from Sudan confirmed that the total and differential counts of white blood cells among tuberculosis patients who received treatment at Kenana Hospital had improved cell counts when TB patients' values were compared to those of healthy people, the results were highly significant. (Mabrouk, 2017).

2.2.2 Red Blood Cells Indices among TB Patients

Red blood cells (RBCs) hold an important role in the human body, being responsible for transporting oxygen and maintaining physiological equilibrium (Pretini et al., 2019). Significant changes of RBCs indices which include measurements of haemoglobin concentration, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration (Kahase et al.,2020a). These parameters provide crucial insights into the size and shape of RBCs, allowing us to have valuable information about various health conditions, which includes anemia, inflammation, and infections of tuberculosis (TB) (Kundrapu & Noguez, 2018).

In their mature form, human red blood cells assume a small, round, and biconcave shape, appearing as a dumbbell in profile. The remarkable flexibility of these cells allows them to transform into a bell shape as they navigate through minute blood vessels. Their lipid-protein membrane lacks a nucleus and encapsulates hemoglobin, an iron-rich protein binding oxygen (Pretini et al., 2019).

A study delved into the role of RBC indices in identifying iron deficiency among anemic pulmonary tuberculosis patients. The findings underscored the utility of RBC

indices in detecting iron deficiency in these patients, suggesting their potential clinical value (Barzegari, Afshari, Movahednia, & Moosazadeh, 2019).

However, within the context of tuberculosis, anemia has emerged as a prominent hematological alteration. This condition, characterized by decreased hemoglobin levels, has garnered substantial attention due to its prevalence among individuals affected by TB. Diverse studies across various geographical distribution and demographic grouping consistently reported high incidence of anemia among TB patients compared to the normal individuals (Abaynew et al.,2023). A study documented an anemia prevalence of approximately 65% among TB patients in an Indian tertiary care hospital. Furthermore, the severity of anemia in TB cohorts exhibits a wide spectrum, as observed in the research, spanning from mild to severe cases (Barzegari et al., 2019).

The relationship between tuberculosis and anemia, however, is characterized by complexity. Rooted in a multifaceted interplay of factors, the mechanisms driving this connection are far from simplistic. Chronic inflammation, a hallmark of TB, emerges as a central mechanism disrupting iron metabolism and availability, consequently impacting erythropoiesis. This disruption triggers a functional iron deficiency, ultimately influencing RBC production. In addition to the production of inflammatory cytokines like interleukin-6 and the tumor necrosis factor-alpha, play the role of inhibiting the production of erythropoietin—an essential hormone stimulating RBC formation (Barzegari et al., 2019).

The implications of anemia in tuberculosis extend beyond the realm of hematological parameters, exerting substantial influence on clinical outcomes and disease progression. Other studies have shown a clear association in anemia and TB severity. It indicated that individuals with severe anemia are more prone to experiencing advanced stages of TB (Dasaradhan et al., 2022). A study highlighted the likelihood of disseminated TB in individuals with severe anemia. Moreover, the impact of anemia extends to treatment response and patient survival, and thus TB patients with anemia exhibited delayed sputum conversion and prolonged hospital stays (Busti, Marchi, Ugolini, Castagna, & Girelli, 2018).

2.2.2.1 Hemoglobin Levels

Hemoglobin molecule is responsible for respiration by removing carbon dioxide gas produced in tissues and delivers it to the lungs for expiration while carries oxygen from the lungs to tissues (Ashenafi et al., 2022). *Mycobacterium tuberculosis* can cause an inflammatory response in TB patients that can affect the hemoglobin levels. Some Studies have shown that anemia frequently develops in TB patients due to low hemoglobin levels (Adams et al., 2019). Anemia is a frequent side effect of TB, and the severity of the condition can influence how the condition develops and how well therapy works (Luies& Preez, 2020).

Hemoglobin levels, central to assessing anemia, have also emerged as potential prognostic markers in TB. These levels, can serve as valuable indicators of disease severity, guiding clinicians in predicting clinical outcomes and tailoring treatment strategies. Reduced hemoglobin levels have been correlated with higher mortality

rates in TB patients, suggesting their utility as indicators of disease prognosis (Ashenafi et al., 2022).

Gil-Santana's research shows that TB patients have significantly reduction in hemoglobin levels than healthy individuals. Other authors hypothesized that mechanisms including decreased erythropoietin synthesis and shortened RBC lifespan could cause chronic inflammation in TB hence anemia (Gil-Santana et al., 2019).

2.2.2.2 Mean Corpuscular Volume (MCV)

The Mean Corpuscular Volume (MCV) measures the average red cell size, has shown promise as a diagnostic marker in various diseases. However, other factors that can cause increased MCV include alcoholism, liver disease, folic acid, Vitamin B12 and other pathologic issues. The normal adult range is 80 -95 fl there is potential utility of MCV in identifying haematological abnormalities associated with infections, inflammation, and anaemia. The altered immune milieu in TB patients triggers a cascade of responses that extend to haematological parameters, including RBC indices like MCV.Studies investigating MCV alterations in TB patients have demonstrated intriguing findings. The study examined MCV levels in TB patients seeking medication at the hospital facility and reported a statistically significant increase compared to healthy controls. This elevation in MCV values was postulated to be a reflection of the systemic inflammation characteristic of TB, influencing erythropoiesis and RBC characteristics (Fukushima et al., 2019).

Ashenafi et al.,2022, explored haematological profiles among TB patients who observed a significant increment of Mean Cell Volume compared with healthy individuals. Other authors attributed that this elevation in MCV might be associated with underlying micronutrient deficiencies, such as folate or vitamin B12 deficiency, which are common in TB patients and can contribute to macrocytic anemia (Ashenafi et al., 2022).

The mechanisms governing MCV alterations in TB infected patients are multifaceted and interlinked with the disease's immunopathology. Chronic inflammation, a hallmark of TB, triggers cytokine cascades that can disrupt erythropoiesis and influence RBC size. The work of (Maner et al., 2019) showed inflammations involving cytokines, interleukin-6 and tumor necrosis factor-alpha, can negatively impact erythroid precursor differentiation, potentially contributing to the observed changes in MCV (Simper et al., 2022).

Mean Corpuscular Volume (MCV) alterations have implications beyond mere RBC size, extending to disease severity and prognosis. A study carried by Abbey explored the correlation between MCV values and TB infections which suggested that increased MCV levels could potentially serve as a marker for more severe disease presentation. While the underlying mechanisms warrant further investigation, such findings could aid in risk stratification and treatment planning (Abay, Yalew, Shibabaw, & Enawgaw, 2018).

Understanding MCV dynamics during TB treatment is crucial. A study by Ye et al. monitored MCV levels in TB patients undergoing anti-TB therapy. The research

demonstrated that as treatment progressed, MCV values tended to normalize, suggesting a potential role for MCV as an indicator of treatment response (Ye et al., 2023). This finding confirmed importance of MCV not only as a diagnostic tool but also as a marker of disease progression and recovery.

2.2.2.3 Mean Corpuscular Haemoglobin and Mean Corpuscular Haemoglobin Concentration analysis.

The Mean corpuscular hemoglobin measures the red blood cell index for the average hemoglobin concentrations within individual erythrocytes (Kahase et al., 2020). The normal range for adults is 27 to 31 pg per cell. Decreased MCH values have been observed in various chronic inflammatory conditions, including TB. Studies suggest that decreased MCH might be linked to anemia of chronic disease and impaired iron metabolism (Lee et al., 2017). Monitoring MCH levels in TB patients could potentially aid in assessing disease progression and the efficacy of anti-TB therapies (Dasaradhan et al., 2022).

The Mean corpuscular hemoglobin concentration is the concentration is the average hemoglobin per a red blood cell. The reference range for MCHC is 32 g/dl to 36 g/dL. With researchers focusing on MCHC in TB patients was limited because of complexity of undertaking it alone, alterations in MCHC measures have been documented with chronic inflammatory diseases such as Rheumatoid arthritis and systemic lupus erythromatosus (Kornilu et al., 2019). Low MCHC values might indicate iron-deficiency anemia, whereas high values could be associated with conditions like hemolytic anemia (Lee et al., 2017). Investigating the relationship

between MCHC and TB could contribute to a more comprehensive understanding of the hematological profile of these patients. These indices can provide insights into the hemoglobin content and quality of RBCs (Lee et al., 2017).

A study conducted by Dasaradhan who investigated RBC indices with TB patients and found a significant decrease in MCH and MCHC compared to healthy persons. The authors hypothesized that this decrease might be attributed to the inflammatory response-induced alterations in iron metabolism and availability, affecting hemoglobin synthesis (Dasaradhan et al., 2022). A study by Hella et al. reported similar results, with decreased MCH and MCHC levels in TB patients compared to controls (Hella et al., 2018). Moreover, a study on TB in children observed that children with TB demonstrated a significant decrease in MCH and MCHC, reinforcing the notion that alterations in these indices might be a consistent hematological response to TB infection (Thomas, 2017).

Studies have indicated a decreased MCH and MCHC values in TB patients, suggesting the potential influence of the disease on hemoglobin content and concentration. In contrast others have found no significant differences in MCH and MCHC levels between TB patients and healthy controls (Kahase et al., 2020).

Reseachers have confirmed that MCH is reduced in levels among TB patients when compared with healthy individuals. The study also indicates that MCHC was considerably lower in TB infected patients with active disease compared to those with latent disease (Kahase, et al.,2020). Additionally, compared to TB active patients with high $CD4^+$ T cell counts, MCH and MCHC were significantly lower in

TB patients as well low $CD4^+$ T cell counts. MCH and MCHC may be helpful biomarkers for determining the severity of TB infection, according to some evidence (Mohammed et al.,2023).

Another study involving the effects of tuberculosis drugs on haematological profiles for the same patients in Northwest Ethiopia, it was found that MCH and MCHC were both significantly lower in TB infected patients who were treated than in those who were untreated (Minardi et al., 2021). This suggests that MCH and MCHC are very useful to monitoring the response to treatment in TB patients.

2.2.3 Platelet Indices among TB Patients

Small, non-nucleated cells called platelets, also referred to as thrombocytes, are produced by megakaryocytes in the bone marrow. They are essential to hemostasis because they help blood clots form to stop excessive bleeding. Additionally, platelets contribute to inflammation and interact with immune cells during the immunological response. Platelets are about 20% diameter of red blood cell (Wang et al., 2021). Due to their small size, platelets comprise of a small portion cellular component of blood, the average cell count is about 150,000–450,000 cells per microliter of blood. Platelets have been described using three indices; Mean Platelet Volume (MPV), Platelet Distribution Width (PDW), and Platelet-to-Lymphocyte Ratio (PLR) to shed light on the pathophysiology of disease, its diagnostic use, as well there prospective treatment targets (Ştefanescu et al., 2021).

2.2.3.1 Absolute Platelet Count (APC)

Absolute Platelet Count (APC), is a vital measure reflecting the concentration of platelets in a microliter of blood, plays a significant role in maintaining physiological hemostasis (Guo & Rondina.,et al 2019). The normal range of platelets is 150000-450000 cells per microliter of blood. Any outliers of platelet count serve as a potential indicator of immune activation and systemic alterations in various pathological conditions. Notably, several studies have documented notable changes in platelet count within the context of TB, suggesting potential perturbations in platelet production and consumption. For instance (Xu et al., 2021) conducted a study and reported a substantial decrease in platelet count among TB patients, implying possible immune dysregulation and platelet activation prompted by the infectious agent. This was attributed to the micro bacteria. Similarly, another study observed a low platelet count in TB patients than healthy individuals. This reduction was attributed to a phenomenon termed as splenic sequestration as an assumption to take place during the course of TB infection. Moreover, an immune response elicited by TB might lead to escalated platelet consumption and sequestration (Minardi et al., 2021).

Exploring the intricate mechanisms driving platelet count alterations in the context of TB unveils a multifaceted interplay between infection and host immune responses. Chronic inflammation, a hallmark of TB, emerges as a pivotal contributor to platelet activation and consumption (Korniluk et al., 2019). Additionally, the spleen could sequester platelets, thereby impacting platelet count and function. This interaction

underscores the systemic implications of TB on hematological indices (Kirwan et al., 2021).

Beyond the observation of platelet count changes, studies have also sought to establish correlations between platelet count and disease progression/severity. There is an established a link between reduced platelet counts and more severe forms of TB, implying the potential use of platelet count as a prognostic marker. This association underscores the intricate relationships between platelet dynamics and the systemic immune response mounted against TB (Kirwan et al., 2021).

Moreover, platelet count offers insights into TB management beyond diagnosis and prognosis. The dynamic nature of platelet count renders it valuable for monitoring treatment response. The effective anti-TB treatment led to a restoration of platelet count to near-normal levels. This observation highlights the potential utility of platelet count in tracking patient response to therapeutic interventions (Rees et al., 2020).

Thrombocytopenia is best characterized by a significant reduction in platelet count, emerges as a phenomenon observed in select TB infected patients. A study engaged in an investigation into the intricate interactions between TB and platelets, shedding light on potential immune-mediated mechanisms contributing to thrombocytopenia. This phenomenon underscores the broader systemic implications of TB on hematological indices (Cooper et al., 2021).

2.2.3.2 Mean Platelet Volume (MPV)

The Mean Platelet Volume (MPV), measures the average size of a platelet, stands as a valuable for the hematological index which indicates platelet activation status. The normal MPV is 8.9 ± 1.4 fL High MPV values often signify augmented platelet turnover and activation while a lower mpv is an indication of likely infection of bone marrow. Within the context of tuberculosis (TB), a globally significant infectious disease, emerging research has elucidated the potential significance of MPV as a dynamic parameter reflecting the intricate interplay between infection, inflammation, and the course of immune response. Tuberculosis (TB) induced inflammation and the ensuing immune responses have been linked to potential alterations in MPV (Xu et al., 2021). A study established that TB-induced infections may contribute to changes in MPV, signifying potential shifts in platelet dynamics. This elevation in MPV values could be attributed to heightened platelet activation and turnover in response to the immune response mounted against TB (Kirwan et al., 2021).

The mechanisms underlying MPV alterations in TB patients are multifaceted, encompassing the complex interplay between the infectious agent and the host's immune response. Chronic inflammation, a hallmark of TB, has the potential to contribute to platelet activation and perturbations in platelet production (Martino et al., 2019), had tried to describe the correlations between MPV change with inflammatory cytokines among TB patients, they indicated a potential relations in systemic inflammation and platelet dynamics (Xu et al., 2021).

MPV alterations in TB patients extend beyond mere hematological indicators, holding the promise of clinical significance. Recent studies have postulated correlations between MPV and disease severity among TB patients. Another report showed that elevated MPV levels were associated with more severe infections of TB, implying potential links between platelet activation and TB pathogenesis. This association suggests that MPV could serve as a dynamic indicator of disease progression and severity (Korniluk et al., 2019).

Moreover, MPV has demonstrated promise as a potential prognostic marker in TB patients. Studies exploring the relationship between MPV levels and treatment outcomes have shed light on its potential implications. A study revealed that higher baseline MPV levels were associated with poorer treatment responses and extended hospital stays among TB patients, emphasizing the potential role of MPV in predicting treatment outcomes (Chen et al., 2020).

Building upon these findings, Lee et al. (2019) further contributed to the understanding of MPV alterations in TB. Their study showcased elevated MPV levels among TB patients compared to normal healthy individuals. The authors postulated that this increase in MPV could be attributed to the inflammatory response in TB, leading to the activation and development abnormal and more reactive platelets in the bone marrow (Korniluk et al., 2019).

The implications of MPV as an indicator of platelet dynamics extend beyond diagnostics, traversing therapeutic considerations. Manipulating platelet activation and aggregation pathways could potentially influence TB outcomes. This potential

therapeutic avenue underscores the complexity of the interactions between platelet dynamics, inflammation, and immune responses in the context of TB.

2.2.3.3 Platelet Distribution Width (PDW)

The Distribution Width of Platelets is an extension for the Mean Platelet Volume (MPV), provides insights into platelet size variability within a blood sample, contributing to our understanding of platelet dynamics and activation status. Its assessment complements MPV by offering additional information on platelet heterogeneity, potentially reflecting intricate platelet activation and immune responses. The normal range is 8.3% to 56.6%. A study established PDW as an informative metric to assess platelet heterogeneity, contributing complementary insights to MPV. This parameter holds promise in unraveling platelet activation dynamics and immune responses, thereby enriching our comprehension of hematological alterations in TB (Ye et al., 2023).

Tzur et al. in their study contributed to the understanding of PDW in TB by investigating PDW levels in TB patients and observing significantly elevated values compared to healthy controls. The authors interpreted these heightened PDW values as indicative of platelet activation and an increased rate of platelet turnover, potentially driven by the inflammatory milieu and immune activation triggered by TB (Tzur et al., 2019).

Emerging research has accentuated PDW alterations among TB patients compared to healthy individuals. A study documented escalated PDW values in TB patients, underscoring potential platelet activation and concomitant immune responses. These

observations imply that PDW could serve as a valuable parameter to gauge platelet dynamics and their interplay with TB-related immune processes (Xu et al., 2021).

The complex mechanisms underpinning PDW changes in TB are multifaceted, shaped by the intricate interplay between TB infection, inflammation, and host immune responses. The hallmark chronic inflammation of TB contributes to platelet activation and modifications in platelet production. Studies have elucidated this association, linking PDW alterations to pro-inflammatory cytokines in TB patients. These findings underscore the potential interconnection between systemic inflammation and the dynamic nature of platelet heterogeneity (Guo & Rondina, 2019).

Beyond its role as a hematological marker, PDW alterations in TB patients hold clinical significance transcending traditional parameters. Studies have postulated potential correlations between elevated PDW levels and increased disease severity in TB patients, hinting at a plausible link between platelet activation and the pathogenesis of TB. This suggests that PDW could potentially serve as an adjunctive indicator in the disease progression and severity (Urbán-Solano et al., 2022).

Potentially prognostic utility of PDW in TB patients has garnered attention. Investigations into the relationship between PDW levels and treatment outcomes provide insights into its prognostic implications. A study done in Ethiopia reported that elevated baseline PDW levels were associated with prolonged hospital stays and treatment complications in TB patients, suggesting that PDW could be a predictor of treatment responses and clinical outcomes (Xu et al., 2021).

The exploration of PDW as an indicator of platelet dynamics introduces avenues for therapeutic considerations in TB management. While the manipulation of platelet activation pathways offers potential avenues for intervention, it necessitates meticulous research to establish safe and efficacious strategies.

2.2.3.4 Platelet verses Lymphocytic Ratio

The Platelet Verses Lymphocytic Ratio (PLR), is an equation of total platelet count and lymphocyte count. It was a marker for systemic inflammation and immune response. In a study in Romania, established that TB patients exhibited higher ratios compared to healthy controls. The authors suggested that the elevated ratio might be linked to the systemic inflammatory response associated with TB infection. This ratio was studied for potential marker in the disease pathogenicity and prognosis among TB patients (Ştefanescu et al., 2021).

A quantitative study of platelet indices was done among 82 patients with active tuberculosis and 87 who were asymptomatic TB infection individual in their study. They had also a radiological scope of Tb disease was determination among study subjects. Another study for PDW, MPV, and platelet ratios showed a significantly increased rate of active tuberculosis but dramatically decreased with anti-tuberculosis treatment. Platelets and erythrocyte sedimentation rate revealed a substantial link with the radiographic examinations of tuberculosis, while PDW and MPV indicated a significant but weaker correlation. Other PDW, MPV, and platelet levels were significantly lower than normal among the tuberculosis patients in a

subset of patients with pneumonia that can causes an acute phase reaction (Xu et al., 2021).

2.3 Epidemiology of TB

World Health Organization (WHO) indicates that 10.6 million TB cases and 1.6 million mortalities in the years 2020 were diagnosed. About 1.2 million TB incidences were among children and 140,000 deaths in 2020 (MacNeil et al., 2020).TB incidence is reducing globally on an average of 2% per year and cumulatively by 11% between 2015 and 2020. In 2015, one in three deaths among HIV patients was due to TB making the disease a top killer amongst people HIV/AIDS patients (WHO, 2020).

However, due to the public health measures taken globally with the intent of achieving the 3rd Millennium Development Goal, TB cases have reduced by an approximate rate of 1.5% per year since 2000. Mortality rate has also reduced by 47% between 1990 and 2015. In Kenya there has been a sharp reduction of TB cases. The country recorded an approximately 89,760 cases in 2013, indicating a 9.48% reduction from the 99,159 cases recorded in 2012. Part of this achievement is attributed to the improvement of TB diagnosis and treatment guidelines which has saved approximately 43 million lives between 2000 and 2014. Further success rate in TB management is will be achieved by 2030 with the adoption of Sustainable Development Goals (Dean et al., 2017)

There is a variability of TB incidence with age. In Africa TB is mainly common among the young adults. However, in countries where TB cases are low, TB mainly

affects the elderly or individuals with compromised immunity. About 15-25% of all new tuberculosis incidences in adults between 15 and 49 years are also HIV/AIDS co-infected (Enos et al., 2018).

Several studies have reported incidences among HIV related infection exacerbating rates of TB infections (Fernando et al., 2020). The prevalence rates among TB have shown to be high among the aged because of underreporting of TB cases among this group. Incidences of TB are also high among smokers, alcoholics, malnourished individuals, and immigrants. In the industrialized nations high TB cases is associated with inefficient TB management programs, overcrowding, and lack of funding (Hiramaet et al., 2020).

In other regions, TB infections (mainly *M. bovis*) have been linked to consumption of unpasteurized milk (Migliori, Nardell, Yedilbayev, D'Ambrosio, et al., 2019). Occupational exposure to environmental health hazards such as asbestos and silica dust has also been shown to predispose individuals to TB (Paleckyte et al., 2021). Nosocomial TB cases have also been reported in hospitals with poor infection control standards (Paleckyte et al., 2021). The link between body wasting and tuberculosis (TB) has been long observed. Malnutrition weakens an individual's immunity and predisposing him/her TB while TB itself can cause malnutrition (Téllez-Navarrete et al., 2021b).

2.4 Risk Factors among TB Related Index Case

2.4.1 The Bacillary Case Load

Tuberculosis smear-positive patients were more contagious than the other cases, this is so according to epidemiological studies done in early 20th century. Approximately ten individual can be infected per year when untreated sputum-positive patient are allowed to interact in the community, and each smear-positive case infect others with TB, this is possible because one is contagious (Deutsch-Feldman et al., 2021).

Tuberculosis infection rates is correlated with the quantity of bacilli present in their sputum sample collected from suspects. A prospective study of 803 household contacts with 174 index TB patients in the Dominican Republic, Espinal and other colleagues who examined the impact of HIV infection and Mycobacterium *tuberculosis* by giving the contacts 5 TU Tubersol PPD at baseline and then following them up at 2^{nd}, 8^{th}, and 14^{th} months. The positivity rate from contact individuals with an index case sputum smear grade of 1-10 (bacilli per field) and more than 10 (bacilli per field) were 1.98 and 5.88, respectively. This findings demonstrates that being in contact with TB positive patient in higher-grade bacilli is associated with chances of having a transmitted bacilli (Adams et al., 2019).

Although it is anticipated that smear negative individuals will have fewer bacilli than smear positive patients, investigations indicate that the infection of *M. tuberculosis* bacilli can be as low as one to ten bacilli. The prevalence rate of infection and disease is higher among contacts of smear positive cases than smear negative cases, according to epidemiological studies conducted in the USA, UK, and India have

confirmed that the prevalence and incidence rates, being higher among smear negative compared to the general population (Migliori, et al., 2019).

There was a research conducted by Behr, et al., on patients infected with the same strains for their molecular analysis in San Francisco, shows that cases of 183 secondary infection in those category; 17% contracted infection from smear negative individuals, with the percentage contracted from smear positive individuals (Pham et al., 2018). Similar studies done at the Greater Vancouver regional by Hernández-Garduo and other colleagues indicated that the episodes of transmission from smear negative individuals varied from 17.3 to 22.2% in the pulmonary group and 25 to 41% among extra pulmonary group (Ye et al., 2023). Amos Ogunde from Nigeria showed in his research that transmission from smear negative individuals was possible by 13% of the secondary cases even if the bacilli are not active but infective. This suggests that individuals with a sputum-positive result are more likely to be infectious, although smear-negative cases are still a significant source of transmission (Amos, 2018).

2.4.1.1 Proximity to an Infectious Patient

Research has indicated that household contacts, caregivers, and health care providers close to active TB patients are more likely to get *Mycobacterium tuberculosis* and develop primary active tuberculosis. Large epidemiological surveys and household contact investigations among TB patients from the early 20th century have proven the occurrence. (Sulaiman et al., 2019). A comprehensive review was carried out by Avalos and colleagues to ascertain the effectiveness of home contact research. With

other related studies carried out in 17countries i.e. 49% in Africa, 29% in Asia, and 22% in America. 4.5% of contacts studied had TB positive cases (including clinically and bacteriologically proven cases); 2.3% of contacts had cases with bacteriological confirmation. 51.4% of the contacts whose health was examined had latent TB infection stage. However, there were several conditions, that disease development and transmission happened without other evidence of organisms within the community, TB rates determination for the results are above the community detections. The majority of Sputum smear positive index case subgroup analysis revealed a pooled yield for Tb infections of 51.8% (Fernando et al., 2020).

A person without predisposing risk factors has a lower probability of developing TB illness than a person with LTBI (confirmed as TST positive). This has evidenced by several researched documents. When tuberculin skin tests were conducted among one thousand four hundred and seventy-two individuals of placebo groups of Ferebee's to assessed the efficacy of treating LTBI among contacts tracers of people with active TB and other patients in mental institutions which changed from negative to positive (Fernando et al., 2020). In the first year of follow-up among those whose tests; about 19 acquired illness which was 12.9 cases per 1000 person-years, as opposed to another 17 patients followed in the other seven years of follow-up (1.6 cases per 1,000 person-years) (Onyejepu et al., 2020). An inquiry of an epidemic aboard an airplane provided a convincing illustration of the impact of closeness to an infected patient. Within two cohort of the index TB patient, passengers had a higher likelihood of testing positive for tuberculin than those in the rest of the section (30.8% vs. 3.6%).

Therefore, contact tracing initiatives focuses on family members with TB cases based on the on familiar approach, with the likelihood of infection rising with closeness, the significance of community transmission of TB was disputed to have insignificant impact. The problem of determining contacts in a case and the emphasis on the necessity to broaden the concept of "contact" to include more people connected to each patient, suggesting that transmission happens outside of homes, were raised. The outcome of the risk and the population size of a given group determined the infection cases with exposure group defined by proximity to the source case. It appeared to be more cases of infection in very group of distant, low risk connections than in the other group of near, high-risk contacts, hence demonstrating the Rose axiom that "a large number of people at small risk may give rise to more cases than a small number of people at high risk." Only a fraction of infected contacts (20%) were identified by conventional contact tracing, which typically detected a high-risk connection. (Laghari et al., 2019).

With epidemiological studies showing that the young adults who had a positive TST had no trace contact within the source case and were thus likely to have contracted the disease in the community. According to Miglioriet in the year 2019 did a retrospective study of household in India, had 2% community infected individuals within households, 7% to suspect case households, and the remaining 91% of cases were non-case households. According to other authors, a case of an infectious disease had an impact on homes with 10 lots away (Migliori, et al., 2019).

The significance of incidental transmission in both high- and low-incidence situations has also been supported by molecular analysis to profile TB strains. (Msizi et al.,2017) demonstrated that there is widespread TB transmission taking place within the community of American. A total of 84 (46%) of the 182 individuals were detected using molecular procedures, with 58 (32%) being classified as having been recently transmitted. Epidemiological evidence of interactions was present in 20 (24%) of the 84 patients who were tested using DNA fingerprints. There were 64 (76%) cases without epidemiological connections and shared socio-environmental risk factors (young age, homelessness, alcohol, and drug use) for incidental exposure to infectious TB patients as well as demographic traits including spatial aggregation in an area with densely populated. The data suggest that TB infections can spread by unintentional recent transfer (Paleckyte et al., 2021).

These investigations demonstrate that TB may spread quickly through contact in unconventional settings, and that possibilities for such encounters are many in endemic settings with added risk factors such deprivation, crowding, and high infection pressure. Therefore, a crucial aspect of TB dynamics in endemic situations is casual transmission (Adams et al., 2019).

2.4.2 The Risk Factors Related TB infections

2.4.2.1 Immunosuppressive Conditions of a Patient

The risk factor for developing active TB illness is co-infection with HIV (Fernando et al…., 2020). Early before the HIV/AIDS infections, TB incidence was greatest in Southern Africa but it was manageable. Later TB case-reporting rates in the South

African nations with known HIV prevalence rates of had an upward trend to 20% when approximately 500 in 100,000 are co-infected patients were treated and followed same as in the USA were 5 per 100,000 infections. These statistics confirms that HIV co-infection significantly accelerates the course of TB infections or reinfection with increased likelihood of latent TB reactivating. Studies conducted in nations with high HIV prevalence have also revealed a considerable correlation between TB incidence and HIV prevalence have a geographical and temporal scales. Various studies confirmed that rising TB incidence with HIV infection in both high- and low-burden TB nations is becoming alarming(Adams, et al., 2019).

Immunocompromised patients having severe TB illness, indicates an upward spread HIV replication in afflicted organs such the pleura and lungs (Adigun & Singh, 2020). A key factor in the host's ability to prevent Extra PTB from spreading widely due to cell-mediated immunity. HIV development is sped up by TB as a result of enhanced systemic immunological activation. Therefore, co-infection accelerates the rate of disease progress and patient death for a variety of reasons (Fernando et al., 2020).

Other patients with known with immune-mediated inflammatory disorders (IMID) have a higher risk of contracting active tuberculosis (TB) with drug use especially after using tumor necrosis factor (TNF)—alpha inhibitors to treat a number of autoimmune diseases (Li et al., 2019) this drug affects cellular components of blood. Tumor Necrosis Factor (TNF) activates the host immune response in regulating a wide range of bacterial, fungal, parasitic, and mycobacterial infections in primates.

According to other studies, people are more likely to get severe illnesses of TB cases in places with a high background TB occurrence. As a result, testing for LTBI must be done in advance before starting TNF-alpha inhibitor medication. The use of TST and IGRAs are the best screening methods that can be used for LTBI, with IGRAs have greater specificity (Reeset al., 2020). De Leon et., al. assessed TST together with QFT responses to RA patients and health individuals in Peru, a country with a high TB prevalence, where 80% of participants had received the BCG vaccine in the past. Indicating that the IGRA was sensitive than TST in identifying LTBI, the proportion of patients testing positive for LTBI was substantially greater with QFT than with TST and more closely resembled that of the control group (Adams, et al., 2019). It is significant to highlight that neither test can reliably identify the subgroup that is at risk of developing disease; that is, neither test can discriminate between latent TB infection and active disease (Rees et al., 2020).

2.4.2.2 Malnutrition as a risk factor to develop Tuberculosis

Studies shows that due to a compromised immunological response, nutritional deficiency increases the risk of TB infections and up serge of the disease progress (Téllez-Navarrete et al., 2021). Due to decreased body activities and alterations in metabolism of the body, TB illness itself might result in malnutrition. With BCG vaccination program, studies conducted in the USA in the late 1960 on malnourished children confirmed that these children were twice as likely to get TB illness as their classmates who are receiving adequate nutrition and vaccinations, demonstrating that malnutrition and TB are interrelated in disease progress (Téllez-Navarrete et al.,

2021). Epidemiological Follow-up Study with the first National Health and Nutrition Examination (NHANES-1) performed in the USA in 1982 to 1984 among adults found that malnourished people had at high risk of tuberculosis (TB) that was six–to–ten times higher (Chandrasekaran et al., 2017). The risk factor associated with malnutrition still needs to be defined, according to Téllez-Navarrete et al. (2021)'s who reviewed the connection between malnutrition and tuberculosis using the ecological, epidemiological, and animal the researched in 2021.

2.4.2.3 Age as a risk factor of TB infections

Young age cohort are more likely to get TB illness and infection as compared to adults (Yang et al., 2020). This is true because of their share growth and immune responses to other body requirements. Studies done indicate that, sputum smear-positive source cases cause infection in 60–80% of those exposed, however sputum smear–negative tested cases can cause infection for about 30–40% of exposed cases due to latent TB. Children under 2 years old have demonstrated high rates of infection within are their household sources, but children beyond 2 years old are typically infected through the community because of contact traces to others in the area of living. The most common risk factor for children to develop TB infections is a household sputum positive contact case, which has a significant role in infection transmission even under ten years. The symptoms can appear during the first year of infection, because of pathogenesis of TB infections. Children with initial infection cohort of less than 2 years and those who are above 10 years are at high risks of infections with TB. Following first infection, the risk for TB-related death was

greatest in infancy as evidenced in other studies. The risk decreased to 1% under four years but subsequent increments do occur to more than 2% between under 25 years. These results provides the scientific foundation for traditional contact inquiry techniques, which concentrate on children under five years of age in the majority of low income countries and on all home contacts in the majority of developed nations (Yang et al., 2020).

2.4.2.4 Diabetes as a risk factor of TB infections

Diabetes disease is as a result of either the pancreas is not producing enough insulin or when body cannot effectively utilize insulin in the body (Silva et al., 2018). Studies indicate that diabetes condition of a patient accelerates the chance of developing active TB illness. Where by an estimates of 70% of diabetics cases who reside in low- and middle-income countries have increased rates of TB burden, these cases are evidenced in India and sub-Saharan Africa (Prada-Medina et al., 2017). Diabetes patients had a roughly twofold higher chance of having TB infections compared to those without diabetes, according to a systematic analysis of 13 researchers described the relationship between diabetes and TB (Hirama et al., 2020). Other studies have shown that diabetic individuals with TB co-infection had worse results, with high percentage of smear-positive cultures after treatment by 22.2% compared to 6.9% for those without diabetes (Prada-Medina et al., 2017). The risk of mortality has been shown to be 1.89 times higher in patients with diabetes and TB infections compared to those without diabetes, and after adjusting for relevant

confounders, the risk increased to higher levels for those with diabetes (Prada-Medina et al., 2017).

There are indications that diabetes directly inhibits innate and adaptive immune responses, speeding the spread of TB infections which is supported by biological data. Studies on animals revealed that diabetic mice that were experimentally infected with *M. tuberculosis* had a greater bacterial burden (Okoth, 2017). The likelihood of acquiring active TB in diabetic individuals is hypothesized to increase due to decreased IFN- and other cytokine production, lower T-cell immunity, and reduced neutrophil chemotaxis. There is evidence that TB infection can worsen glycaemia management in those with diabetes by increasing glucose intolerance. Future TB control efforts in India may be greatly hampered by rising diabetes prevalence in that country (Simper et al., 2022).

2.4.2.5 Healthcare Workers

Healthcare professionals (HCWs) are more likely to be exposed to TB. According to a review, the annual incidence of TB illness among native-born HCWs and the general population in high-income nations was respectively fewer than 10 and 25 per 100,000 people. The information in relation to incidence, prevalence of latent TB infection (LTBI) and illness among health care workers in low- and middle-income countries were compiled by Joshi and colleagues. The prevalence of LTBI among health care workers was 55%, with estimates of the yearly risk ranging from 0.5 to 14.3%, while the annual incidence of TB infections ranges from 69 to 5780 per

100,000 people, according to the authors' evaluation of 51 case studies (Laghari et al., 2019).

2.4.3 Socioeconomic and Behavioral Factors

It is having been demonstrated that socio-economic status of individuals and the rapid urbanization of a country have an impact on individual vulnerability to illness. The risk of contracting TB increases with decreasing socioeconomic status for any country. People with low SES are more likely to experience the risk factors for TB mentioned above, such as malnutrition, indoor air pollution, alcohol use, because they are more likely to be exposed to crowded, poorly ventilated environments and have less opportunities to practice safe living standards. Because of poor living circumstances, HIV coinfection, and injectable drug misuse, marginalized people, including prisoners, have an increased risk of contracting TB. Drug use, infections, and diabetes are not strongly connected with lower SES, despite the fact that smoking rates are greater among those from lower SES groups (Téllez-Navarrete et al., 2021a).

2.4.3 Tobacco Smoker

Several systematic reviews have described the connection between smoking and tuberculosis. There is high chance for smokers contracting TB infection and disease burden in any community(Korniluk et al., 2019). The relative risk of TB disease (RR = 2.3-2.7) is high among smokers compared to non-smokers. A comprehensive analysis and meta-analysis of 38 papers on the effects of indoor air pollution and smoking on tuberculosis was conducted by Lin et al. There was a pooled analysis for

latent TB infection (LTBI), whereby the findings for six studies that specifically looked at tuberculin reactivity in smokers were 2.08 (CI = 1.53-2.83) and 1.83 (1.49-2.23) at 5 and 10 mm TST cut-off points, and the effect of smoking on LTBI were confirmed after accounting for alcohol (OR = 1.76, CI = 1.43-2.16). These researchers also confirmed that there is a causal relationship between smoke exposure and Tb infection, with smoking having the main impact of increasing the risk of infection (Téllez-Navarrete et al., 2021).

Increased susceptibility in pulmonary tuberculosis patients has been attributed to biological explanations such as impaired clearance of mucosal secretion, decreased phagocytic ability of alveolar macrophages, decrease in immune response, and/or $CD4^+$ Lymphopenia caused by nicotine in cigarettes (Torrelles et al., 2017). Laboratory animal experimentation demonstrated that exposing mice to cigarette smoke and then infecting them with *M. tuberculosis* causes a significant rise in the number of viable *M. tuberculosis* bacilli isolated from the lungs and spleen as well as a decline in the mice's adaptive immunity (Okoth et al., 2017).

2.4.3.1 Alcohol

There were molecular epidemiological studies that showed that alcohol is a significant risk factor also for tuberculosis (TB) disease and has been linked to high infections in both high- and low-incidence countries (OR = 2.6, CI = 2.13-3.3). According to a systematic evaluation of 3 cohort studies and 18 case-control studies, those who drunk more than 40 grams of alcohol per day and/or have an alcohol use problem had a significantly higher chance of developing active TB (RR = 2.94, 95%

CI = 1.89–4.59). Changes in the immune system, especially in the signaling molecules involved for cytokine production, are causes of the elevated risk when they have been suppressed (Silva et al., 2018).

2.4.3.2 In-door air pollution

More than 80% of solid fuels used for cooking in underdeveloped nations emit undesired fumes. Case control studies carried out in India and Brazil identified firewood or biomass fumes as a distinct risk factor for tuberculosis. However, animal studies have revealed that acute wood fumes decreased macrophage phagocytic activity, surface adherence, and bacterial clearance. There is scanty information on the mechanism through which biomass fumes promotes chronic lung illnesses. However, it has been demonstrated that biomass burning produces particulate matter (PM) including carbon monoxide (CO), nitrogen oxide, formaldehyde, and polyromantic hydrocarbons that can accumulate deeply inside the alveoli and cause significant harm (Kim et al., 2018).

2.4 Demographic (Ethnic) and Health Factors

2.4.1 Indigenous/Aboriginal Population

Indigenous people have greater chance of developing tuberculosis than migrants, this is true according to studies from Canada and Australia. Predisposing risk factors for TB, such as renal failure, diabetes, alcoholism, and smoking, are more common than usual among Aborigines. In addition, social issues including poverty and overcrowding are well-known sources of this burden.

A recent study, numerous Canadian aboriginals had gene deletions that may have increased their risk of contracting active tuberculosis. According to the study, endogenous reactivation will eventually contribute a growing amount to the overall burden of illness. There may be incidences of reactivation illness among aboriginal tribes due to the high prevalence of latent infection and higher risk of disease (Argan & Elq, 2018).

2.4.2 Health System Issues

According to studies carried in China, health systems have been strengthened through case notification using web-based reporting, which has improved the uptake of hospital referrals from 59% to 87% and a tripling of percentages for pulmonary TB cases that originate in the hospitals from 16% to 33%. On the other hand, problems with the healthcare system, turnaround time for diagnosis and treatment prolongs the period during which active patients are contagious that can cause the spread of TB. Delayed TB treatment causes household infection rates were positively correlated by Lin and colleagues in their cross-sectional investigation on the prevalence of TB infection in southern China. The DOTS program's current passive case discovery strategy is based on the idea that treating infectious patients as soon as possible will lessen the burden of infection and improve life without transmissions in the neighborhood. Delays in identification and treatment may hinder this and hasten the spread of the disease throughout the population (Li et al., 2019).

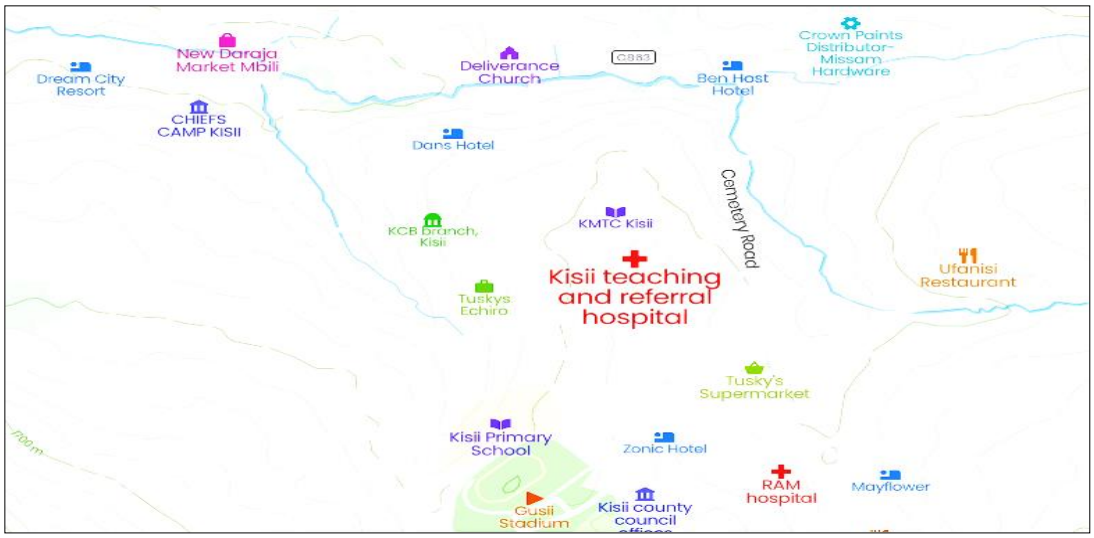
CHAPTER THREE

MATERIALS AND METHODS

3.1 The Study Site

The current study was conducted at Kisii Teaching and Referral Hospital in Kisii county, Kenya. This is the largest hospital facility in the area in terms of facilities and the hospital attends to approximately 500 patients each day. The hospital has 5 well equipped diagnostic laboratories. Microbiology laboratory, which tests TB has most advanced machines like GeneXpert, blood culture equipment and others. The laboratory attends to approximately 500TB patients a year. During the period of study which was from 1 April 2022 to 1st August 2022, the hospital attended to 142 patients, most of the cases are referred from other facilities and others by specialist within the hospital. The hematology laboratory is well equipped with latest analyzers. The hospital manages nine sub-county hospitals in addition to other neighboring counties including Nyamira, Homabay, Migori, and Bomet. It has Level 6 accreditation from the Ministry of Health. With 650 beds, the hospital offers complete inpatient treatments, including cancer, renal analysis, palliative care, and CT/MRI scanning. Due to its high patient activity level, given how well it is equipped and well trained staff, it is ideal for this study.

Figure 3. 1*: Kisii Teaching and Referral Hospital Locator Map(Source: Google maps, 2019)*



3.2 Research Design

It was a cross-sectional study design used to collect data among TB patients attending Kisii Teaching and Referral Hospital in Kisii county.

3.3 Target Population

The target population involved in the study were TB patients seeking services in the chest clinic at Kisii Teaching and Referral Hospital.

3.4 Sampling techniques

3.4.1 Determination of sample size

Yamane's (1967) formulae for sample size calculation was used to determine the sample size for this study.

$$n = \frac{N}{1 + N(e)^2}$$

Where;

N= population of TB patients at KTRH chest clinic, that is 142 TB patients

n=desired sample size

e=sampling error at 95% confidence level

The sample size was calculated as follows:

n = 142/1+142 $(0.05)^2 \approx 104.7 \approx 105$patients.

3.4.2 Sampling technique

It was a simple random sampling Technique used to obtain samples from TB patients who were confirmed to have tuberculosis infection attending KTRH during the study period between 1st April 2022 to 1st August 2022. The control subjects were selected based on eligibility and matched with the case group to ensure comparability. The recruitment of both patients and control allowed for a comprehensive analysis of the hematological profile among PTB patients and facilitated the comparison of results between the two groups. The controls were health individuals who were TB negative with inclusion criteria and exclusion criteria for the study and consented.

3.5 Inclusion and exclusion criteria

3.5.1 Inclusion criteria

The study recruited individuals who were not on anti-tuberculosis medication, had no history of any other chronic diseases, and were not pregnant; those who tested negative for HIV and individuals between the ages of 18 and 70 were recruited in this study.

3.5.2 Exclusion criteria

Those patients tested and were TB negative under the age of 18 years and those who were older than 70 years. Patients who had exhibited bleeding symptoms were excluded in this study. Also, endocrine problems, other organ dysfunction, systemic disorders, those with viral infection, Anaemic patients, Vit12 deficiency, folic acid deficiency or chronic inflammatory illness were not recruited in this study.

3.6 Blood Collection

The study participants were taken through what the research entailed and they consented. They were assessed and recruited following the WHO standardized tool adopted for collecting samples from confirmed TB patients attending KTRH. Eligible participants were then prepared for venous blood sample collection. A gauge 18 needle was inserted into the vein and the blood was collected in an airtight syringe. A 4-ml of blood was collected aseptically using the EDTA tube from each participant and correctly labeled with the patient's identification number.

3.7 Blood Samples Processing

Venous blood in an anticoagulant EDTA vacutainer tube was properly mixed and then complete blood count analysis of results using Cell Dyn 1800 hematology analyzer (Abay et al., 2018). In Erythrocyte sedimentation rate measurement was performed using Westergren method as used before(Ufelle et al., 2020).The test procedure for this research was done systematically with controls both internal and external for quality whereby Low, Medium and High specimens were used in quality assurance. Flow cytometry was used to measure the hematological indices as primary used (USEPA, 2017).

3.8 Hahematological Parameters among TB Patients

3.8.1 Hemoglobin (HGB)

An automated hematology analyzer that counts and gathers data on cell size and structure was used to do the hemoglobin test (Fukushima et al., 2019). Hemoglobin concentration was tested, noted, and printed out. Using the flow cytometry technique, which involves passing a single cell stream through a laser beam, the analyzer analyzed hemoglobin. Based on the linear relationship between the absorbance of light and the quantity of hemoglobin present, the optical density was measured against the scattered light was recorded at various angles to assess the cell structure singularly for the diameter, and cytoplasmic contents of the cell.

3.8.2 Total Leukocyte Count (TLC)

After appropriately mixing the sample blood in an anticoagulated EDTA tube, the tube was put at the aperture of an automated analyzer, which sufficiently sucked the specimen. Laser light from the interrogation point was scattered forward and at a 90-degree angle when the cell went through it. morphological characteristics of the cell, such as cell size, nuclear complexity, and cytoplasmic granularity, affected how much light was dispersed. These light scattering signals were collected by certain detectors, transformed into digital signals, and then shown as dot plots for study. The analyzer's computer system assisted in converting the optical display to a printed digital display (Chedid et al., 2020).

3.8.3 Differential Leucocyte Count

The blood sample was taken from the collection and put into a sucking aperture for examination. Automatic white cell counting with printed findings had the benefit of being more accurate.

3.8.4 Platelet Count, Hematocrit (HCT)

The same blood sample was used to determine platelet count, and the same analyzer was used to automatically calculate their value. The laser beams light was dispersed forward and at a 90-degree angle when the cell moved past the interrogation point. The physical characteristics of the platelets were examined, and the results were automatically recorded. The amount of light dispersed was depending on these findings. These light scattering signals were collected by certain detectors, translated

to digital data, and then shown as dot plots for platelet examination. The analyzer's computer system assisted in converting the optical display into a digital display that printed the platelet count results. Hematocrit levels were also determined using the analyzer, and the results were shown.

3.8.5 Mean Corpuscular Volume (MCV) and Mean Corpuscular Hemoglobin (MCH)

This result was achieved by multiplying a blood volume by the percentage of cellular blood and dividing the result by the absolute red blood cell count. MCV is a measure of the volume of red blood cells and can be represented in cubic microns (m3) or femtoliters (1015; fL). MCV has average values of 87 7 fl. Hemoglobin, hematocrit, and red blood cell count are used to calculate the red cell indices MCV, MCH, and MCHC using the rule of three (3). The analyzer analyzed the sample from the control group, and the results were computed as follows:

$$\text{MCV} = \frac{\text{Volume of packed cells/ 1000 ml of blood}}{\text{Red blood cell count in millions/ml}} \text{ fl or } \mu m^3$$

$$\text{MCH} = \frac{\text{Hemoglobin in g/ 1000 ml of blood}}{\text{RBC count in millions/ml}} \text{ pg/cell}$$

$$\text{MCHC} = \frac{\text{Hemoglobin in g/ 100 ml of blood} \times 100}{\text{Volume of packed cells/ 100 ml of blood}} \text{ g/dl or \%}$$

Source: (https://www.omnicalculator.com/health/rbc-indices).

3.8.6 Erythrocyte Sedimentation Rate (ESR)

Up to the 200 mm mark, blood was taken in a Westergren-Katz tube (Anayochukwu Ufelle et al., 2020). The tube is positioned vertically on a rack and kept at room temperature for an hour without being tilted. After an hour, the distance between the surface meniscus's lowest point and the red cell sediment's uppermost limit was measured. Erythrocyte sedimentation rate (ESR) is a measurement that indicates how far-red blood cells have moved over the course of one hour. The method was the same for the control group.

The ESR, a crucial clinical test used to identify inflammation or other disorders, may be evaluated with this technique. Red blood cells' size and shape, as well as blood substances that may cause the cells to clump together, all have an impact on the ESR.

3.8.8 Peripheral Blood Smears (PS)

A thin blood smear was made by dropping a little quantity of blood and spreading it on a microscopic glass slide. Leishman stain was applied and coated it. For 7 minutes, it was diluted with buffer, followed by a de-ionized water wash and drying. The discolored blood smear was finally seen with an oil immersion objective. There were several different sorts of cells, and there may also be anomalies.

3.9 Quality Assurance

The use of standard operating procedures (SOPs) and manufacturer's instruction for both hematological tests were applied to validate equipment. Before running the

patient's sample, the hematology analyzer's quality performance was examined by executing normal, low, and high blood controls.

3.10 Data Analysis

Data obtained was analyzed with the use of Stata Version 23 origin to obtain the Means and P-values for the independent samples t-test. The independent samples t-test was used to determine statistics of value for the hematological profiles among Tb patient and the controlled Tb negative patients. The results were tabulated in tables and figures.

3.11 Ethical consideration

The study obtained ethical approval from the University of East African, Baraton University Ethical Committee **(UEAB/REC/12/10/2021) (**Appendix 6) and permission was sought from Kisii University, NACOSTI (**NACOSTI/P/22/15517**) (Appendix 7) and Kisii Teaching and Referral Hospital. A written consent was sought from the patients who participated in this study from December 2021 to February 2022. Patients were explained every procedure to be performed and why the test was to be done.

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CHAPTER FOUR

RESULTS

4.1 Haematological parameters of the study participants

The mean standard deviation of total white blood cell count for cases was (7.81 ±4.08 $x10^3/\mu L$) and for controls (6.03± 2.67 $x10^3/\mu L$) (P=0.018). Absolute neutrophil counts (mean± SD) for cases was (4.86 ±3.11 x $10^3/\mu L$) while for controls, the neutrophil count was (3.66 ± 2.33$x10^3/\mu L$) (P=0.044). The mean ± SD of platelet count for cases was(328.61±120.99 $x10^3/\mu L$) while for controls was (272.77±69.23 $x10^3/\mu L$) (P=0.009). The mean ± SD of erythrocyte sedimentation rate for cases was (69.18 ± 22.86 mm/hr.) while for controls was (14.34 ± 4.38 mm/hr.) (P=0.001) (Table 2).

Table:4.1 Tabulation for Hematological Profiles in Patients and Controls from April to August 2022

Parameter	Cases mean± SD (n=105)	Controlsmean± SD(n=105)	P-value
RBC(10^3/uL)	4.37 ± .85	5.10 ± .82	0.001*
HGB(g/dL)	11.93 ± 2.01	14.60 ± 2.15	0.001*
HCT (%)	37.96± 6.36	44.02 ±5.35	0.001*
MCV(fL)	87.95 ±10.45	87.97± 5.50	0.991
MCH(pg)	27.80 ± 4.66	29.57 ± 2.46	0.028*
MCHC(g/dL)	31.50± 2.19	33.41 ± 1.83	0.001*
ESR (mm/hr)	69.18±22.86	14.34 ±4.38	0.001*
Platelet(10^3/µL)	328.61±120.99	272.77±69.23	0.009*
TWBC(10^3/µL)	7.81 ±4.08	6.03 ± 2.67	0.018*
Neutrophil(10^3/µl)	4.86 ± 3.11	3.66 ± 2.33	0.044*
Monocytes (10^3/µl)	0.56 ± .28	0.54 ± .32	0.041*
Lymphocyte(x10^3/µl)	1.81±0.85	2.49±2.46	0.086

4.2.1Total White Blood Cells Count

The PTB patients had a mean ± SD total WBC count of (7.81 ± 4.08 x 10^3/µL), while the controls had a mean ± SD of (6.03 ± 2.67 x 10^3/µL). Among the PTB patients, 20.5% had a total leukocyte count below the normal range (< 4.0 x 10^3/µL), while 63.6% of the participants had normal total leukocyte count, and 15.9% had a count above the normal range (> 11.0 x 10^3/µL). In the control group, 22.7% had a

leukocyte count below the normal range, 72.7% had a normal range count, and 4.5% had a count above the normal range.

4.2.2 Absolute Neutrophil Count (A.N.C)

The PTB patients had a mean ± SD A.N.C of (4.86 ± 3.11 x 10^3/µL), while the controls had a mean ± SD of (3.66 ± 2.33 x 10^3/µL). Among the PTB patients, 13.6% had an A.N.C below normal range (< 2 x 10^3/µL), 68.2% of these patients had a normal A.N.C, about 18.2% had an A.N.C above the normal range (> 7 x 10^3/µL). In the control group, 15.9% had an A.N.C below the normal range, 75% had a normal range A.N.C, and the remaining 9.1% had an A.N.C above the normal range (fig: 2).

4.2.3 Total Lymphocyte and Monocyte Counts

The mean ± SD total lymphocyte count for pulmonary tuberculosis cases was (1.81 ± 0.85 x 10^3/µL), while for the control group it was (2.49 ± 2.46 x 10^3/µL). Among PTB patients, 13.6% had an ALC below (1 x 10^3/uL), 79.5% had a normal ALC, and 6.8% had an ALC above 3 x 10^3/µL. In the control group, 4.5% had an ALC below the normal range, 86.1% had a normal ALC, and 9.4% had an ALC above the normal range. The mean ± SD absolute monocyte count for PTB cases was (0.56 ± 0.28 x 10^3/µL), while for the control group it was (0.54 ± 0.32 x 10^3/µL).

4.3 Red Blood Cell Parameters

TB patients had significantly lower red blood cell counts (4.37 ± 0.85 x 103/uL) compared to the controls (5.10 ± 0.82 x 10^3/uL) (P = 0.001). With a significant difference in mean cell hemoglobin concentration between cases (31.50 ± 2.19 g/dL)

and controls (33.41 ± 1.83 g/dL) *(P* = 0.001). Similarly, the mean cell hemoglobin was significantly lower in TB patients (27.80 ± 4.66 pg) compared to controls (29.57 ± 2.46 pg). However, there was no significant difference in mean cell volume between cases (87.95 ± 10.45 fL) and controls (87.97 ± 5.50 fL) (*P* = 0.991). With TB patients, normocytic anemia was common (50%), followed by microcytic anemia (26.6%) and macrocytic anemia (23.4%).

4.3.1 Hemoglobin and Hematocrit

The mean hemoglobin was lower in TB patients (11.93 ± 2.01 g/dL) compared to controls (14.60 ± 2.15 g/dL). The hematocrit percentage was also lower in TB patients (37.96% ± 6.36) compared to controls (44.02% ± 5.35). Anemia was present in 68.2% of TB patients at the time of diagnosis. Among the TB patients, 18.2% had moderate anemia, 47.7% had mild anemia, and 2.3% had severe anemia. In the control group, 29.5% had mild anemia, while the remaining 70.5% had normal hemoglobin levels (fig 1).

***Figure 4.1**: Severity of Anemia Stratification by Hemoglobin Concentration among Tb patients*

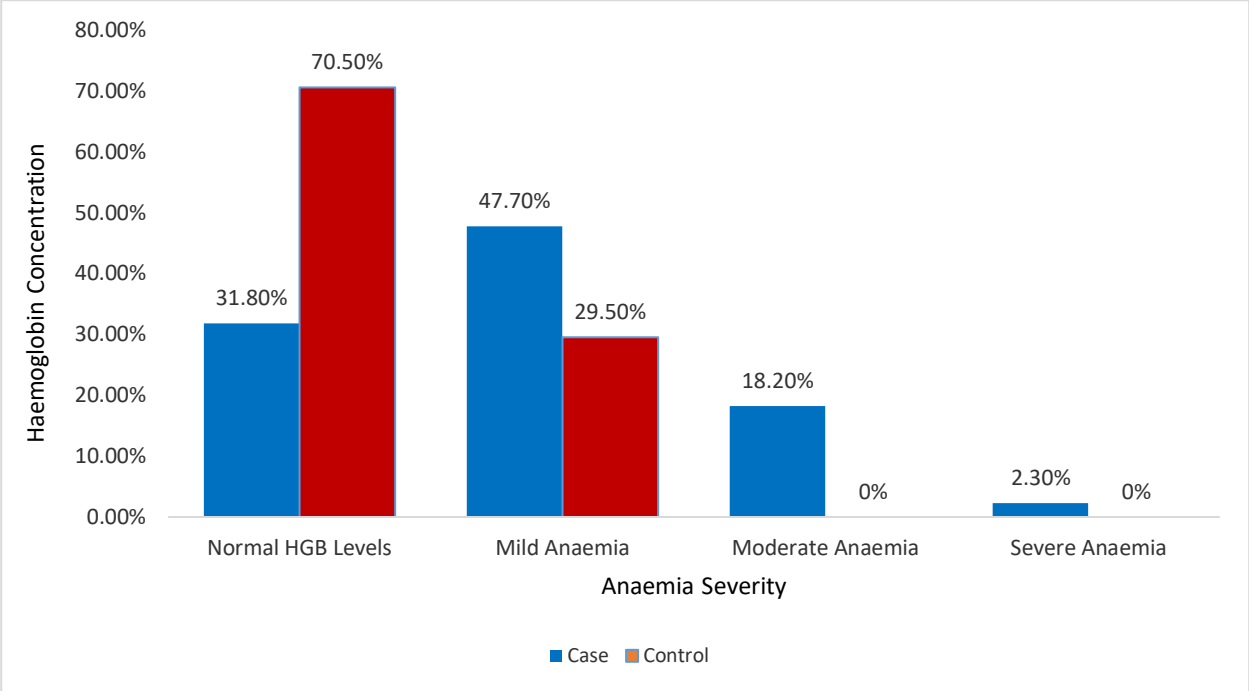
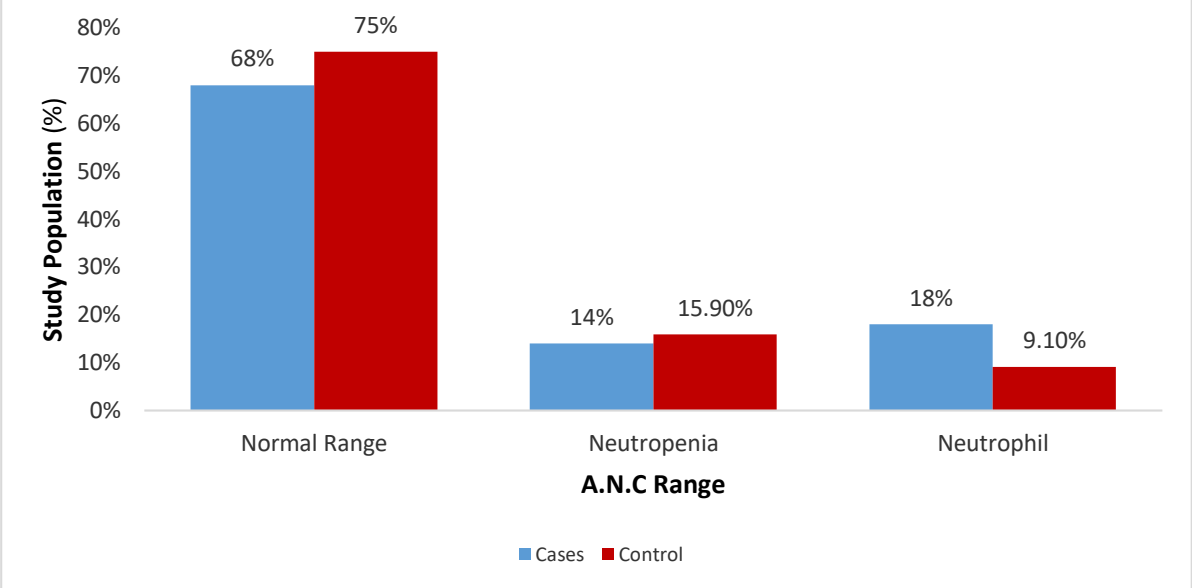


***Figure 4.2:** Total Neutrophil Count among Tb patients*



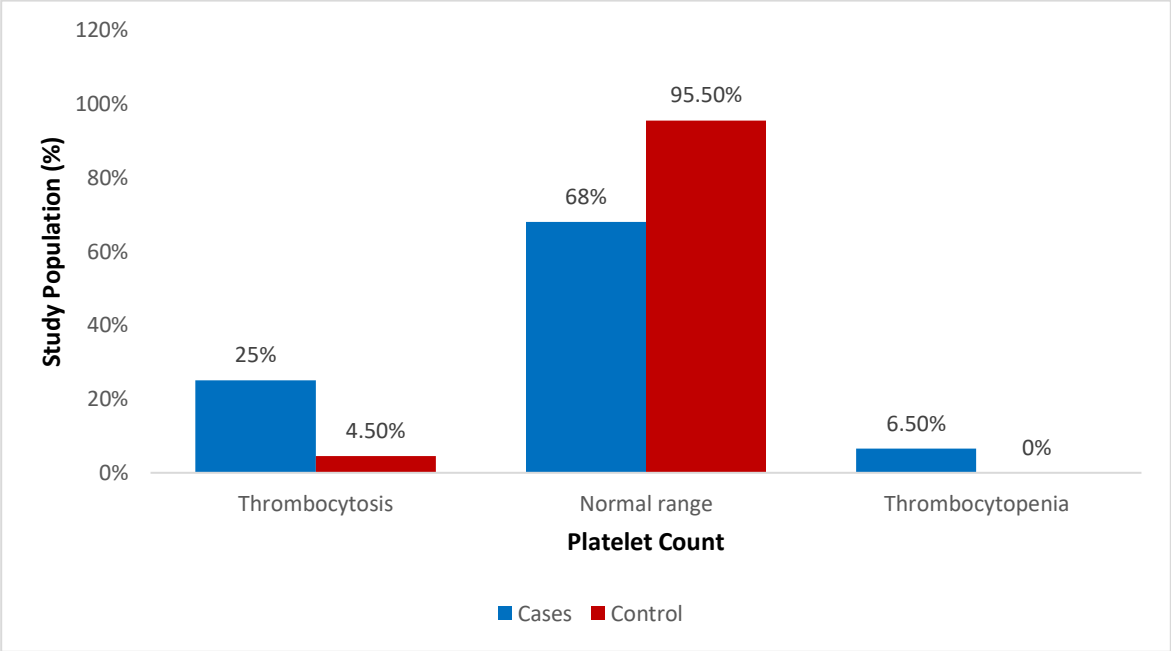
4.3.2 Erythrocyte Sedimentation Rate

The mean ± SD of erythrocyte sedimentation rate for pulmonary tuberculosis cases was (69.18 ± 22.86 mm/hr.), while for the control group it was (14.34 ± 4.38 mm/hr.). Erythrocyte Sedimentation Rate was significantly higher among PTB cases compared to the control group.

4.4 Platelet Count

The mean ± SD platelet count for pulmonary tuberculosis cases was (328.61 ± 120.99 x 10^3/µL), while for the control group it was (272.77 ± 69.23 x 10^3/µL). Among PTB patients, 6.8% had a platelet count below (150 x 10^3/µL), 68.2% were normal in platelet count and 25% had a platelet count above (400 x 10^3/µL). In the control group, only 4.5% had a platelet count above the normal range, while the remaining 95.5% had a normal range of thrombocytes (fig 3).

Figure 4.3: *Platelet Count among PTB patients*



4.5 Morphological Changes seen in Peripheral Blood Film

Normochromic anemia was a common hematological indicator among pulmonary TB patients accounting for 55% of the other anemias. Other types of anemia included microcytic hypochromic (20%), normocytic hypochromic (10%), macrocytic normochromic (5%), and macrocytic hyperchromic (5%). Anemia disorders were observed in 68.2% Among PTB patients under study, with 18.2% having moderate anemia, 47.7% had mild anemia, and only 2.3% experiencing severe anemia. Toxic granulation was present in 65% of patients with TB infections, while 25% showed the band form of neutrophils and 10% had normal WBC morphology. Most patients (95%) exhibited normal platelet morphology, while 5% had giant platelets. Thrombocytosis was indicated by higher platelet counts in PTB patients compared

to the control group that is, (328.61±120.99 $x10^3/\mu L$ for cases and 272.77±69.23 $x10^3/\mu L$ for controls).

CHAPTER FIVE

DISCUSSION

5.1 Introduction

The rate of Tuberculosis as a communicable disease in the world has a major public health problem in Kenya. It has been declared by WHO as a global emergency in 1993(WHO, 2020). Various studies have described the association hematological indices with tuberculosis(Li et al., 2019). There is insufficient literature in regard to hematological indices and parameters in pulmonary tuberculosis patients in Kenya, and Kisii as well and its environment. However, this study addressed the variants of the hematological profiles of TB patients in respect to control groups and factors associated with these parameters.

5.1.1 Total White Blood Cells Count (TWBC)

The study showed a significant elevation of the mean total white blood cell (TWBC) count among pulmonary tuberculosis (PTB) patients in comparison to the control group. This elevation in TWBC count corresponds with a concurrent state of neutrophil, more than 70 percent of total cells, which manifests as an augmented neutrophil count. Distinct from prior studies that have documented a spectrum of hematological aberrations in PTB patients, encompassing leukocytosis, neutrophilia, neutropenia, lymphocytosis and Monocytosis (Reta et al., 2023). the current study illuminates a particular and consistent pattern of hematological alteration.

The documented occurrence of leukocytosis, evident in approximately 20.5% of the PTB patients, imparts a noteworthy dimension to the hematological profile within

the context of PTB. This observation resonates with the work of other researchers who have similarly noted the presence of leukocytopenia in tuberculosis patients (Kim et al., 2018). Furthermore, it is imperative to underscore that a substantial proportion (63.6%) of the PTB patients under investigation exhibited leukocyte counts within the normal range. This variability underscores the heterogeneity of hematological parameters among individuals grappling with PTB. Such heterogeneity could potentially be attributed to multifaceted variables including disease progression stage, infection severity, idiosyncratic immune responses, and the confluence of co-morbidities (Abaynew et al., 2023).

The identification of leukocytosis in 15.9% of the PTB patients adds a novel facet to the study's findings. Leukocytosis, typified by an anomalously high white blood cell count, has been documented across diverse infectious and inflammatory scenarios (Batool, Pervaiz, Arooj, & Fatima, 2022). Its emergence within a subgroup of PTB patients alludes to the intricate interplay between the immune response and the pathogenic agent. This phenomenon may conceivably be linked to the orchestrated recruitment and activation of immune cell cohorts as a responsive countermeasure against the mycobacterial incursion.

In light of these findings, juxtaposing the current study's outcomes against antecedent research endeavors, notably those conducted by (Mohamed, Sabry, Razek, & Ahmed, 2019). accentuates the inherently dynamic trajectory characterizing hematological variations within the PTB patient demographic. Such comparative analyses underscore the evolving nature of scientific inquiry and contribute to a

nuanced comprehension of the intricate hematological dynamics that underlie pulmonary tuberculosis manifestations.

5.1.2 Absolute Neutrophil Count (A.N.C)

The study's results indicate a notable elevation in the Absolute Neutrophil Count (A.N.C) among TB patients as compared to the control group. This variation aligns with another study conducted by (Mohamed et al.,2019), which reported similar findings. Such consistency across studies underscores the robustness of the observed hematological change and suggests that it might be a recurring phenomenon in the context of pulmonary tuberculosis. The increase in A.N.C holds significant implications beyond its immediate numerical value, as it is often considered a reflection of the immune response in various disease conditions.

The rise in A.N.C is not just an isolated phenomenon; it is linked to a broader immune response against the Mycobacterium tuberculosis bacteria. This immune reaction involved various cytokines, such as interferon-gamma (IFN-γ), interleukin-1β (IL-1β), and interleukin-18 (IL-18), which play a role though not investigated in this research , orchestrating the immune defense against the invading pathogen (Mohamed et al., 2019). These cytokines activate the production of neutrophils and other immune cells to the site of infection. Consequently, the increase in neutrophils observed in this study was attributed to the heightened immune activity triggered by the cytokine cascade (Urbán-Solano et al., 2022).

Interestingly, the elevation in A.N.C could have implications beyond its role as an immune response marker. The study suggests that this increase might serve as a

potential prognostic factor for various diseases. While the specific implications of A.N.C elevation as a potential prognostic marker were not detailed in the present study, there is profound clinical significance. Prognostic markers can aid healthcare providers to determine the course of the disease, assessing its severity, and determining the treatment strategies.

Comparing these findings with the broader body of research on hematological changes in TB patients enriches our understanding in multifaceted defense of the body in response to unfolds during tuberculosis infection. The immune mediations against TB is a complex with of various immune cells, cytokines, and molecular pathways. Adigun, in his study observed the increase in the number of neutrophils in patients with Tuberculosis, he attributed this to the fact that as among first cells to reach the site of infection are neutrophils (Adigun & Singh, 2020). The elevation in A.N.C, reflecting an increase in neutrophils, aligns with the immune mechanism involved in containing and combating the mycobacterial infection. Moreover, the interconnectedness between different immune cells becomes evident when considering the concurrent relative increase in monocytes alongside neutrophil elevation. This intricate immune orchestration signifies the dynamic changes of the host-pathogen interaction among tuberculosis infected patients.

5.1.3 Absolute Monocyte Count

The study revealed higher levels of monocytes in tuberculosis patients compared to controls, suggesting their role in infection control or inflammation. Monocytes, a type of white blood cell, are known for their role in the immune system as precursors

to macrophages and dendritic cells (Liu, et al., 2017). Macrophages are central players in the immune defense against TB, as they engulf and attempt to eliminate the *Mycobacterium tuberculosis* bacteria (Simper et al., 2022). An increased levels of monocytes tested among TB patients was indicative of an intensified immune reaction against the infection.

Intriguingly, the elevated monocyte count might serve dual roles in the context of tuberculosis. Firstly, monocytes are mobilized to the site of infection as part of the immune response, suggesting their role in infection control. Secondly, their increase may be linked to the inflammatory nature of tuberculosis. Inflammation is a reaction of the body's response to infection, and an elevated monocyte count can reflect the activation of the immune system's activation in an attempt to combat the invading pathogen (Netea et al., 2020).

This study's findings agree with another study by Wang et al., 2019, who observed an elevated monocyte-to-lymphocyte ratio in tuberculosis patients. This ratio was calculated by dividing the monocyte count and the lymphocyte count to garner attention for potential diagnostic and prognostic marker in various diseases, including tuberculosis. The elevation of this ratio in TB patients suggests a skewed immune response with a prevalence of monocytes, potentially reflecting the immune system's attempt to mount a robust response against the infection. Wang et al further proposed the utilization of this ratio for diagnosis and monitoring of therapeutic efficacy (Wang et al., 2019). These highlights the clinical significance for monocyte alterations in TB and the potential of this parameter as the diagnostic tool.

Moreover, considering the interaction between monocytes and other hematological parameters provides a more comprehensive understanding of their role in tuberculosis infection. When combined with other blood parameters, such as neutrophil, lymphocyte and even the monocyte-to-lymphocyte ratio, the absolute monocyte count could serve as a valuable tool for indicating the presence of tuberculosis infection (Rees et al., 2020). This multi-parameter approach could enhance the accuracy of diagnosis and provide clinicians with a broader picture of the patient's immune response. The interplay between various immune cells, cytokines, and molecular pathways orchestrates complex stimulus between the host and the pathogen. The elevation of monocytes observed in this study can be seen as a part of this intricate relationship, with the immune system striving to control the infection while simultaneously managing the inflammatory response. Just like wang observed that monocytes are crucial and get elevated when the mycobacteria tuberculosis attacks because the cells are baseline when infection occurs.

5.1.4 Absolute Lymphocyte Count

This study depicts a significant reduction of lymphocytes count among TB patients compared to the control group. The observation made raises intriguing questions about the interplay between various immune cell populations in the context of tuberculosis infection. Lymphocytes are central players in the immune response, responsible for recognizing and eliminating pathogens. The decrease in lymphocyte count, as observed in this study, suggest an altered immune response in TB patients, potentially weakening the body's ability to combat infection (Martino et al., 2019).

My study agrees with another research done by Martino on reduction of lymphocytes on TB patients.

A plausible reason for the lower lymphocyte counts in TB patients lies in the correlation with the higher neutrophil count and the associated inflammation. Neutrophils clusters of white blood cell provide crucial role in the initial defense against infections. However, their presence is often indicative of a more intense inflammatory response, which can sometimes lead to tissue damage. The higher neutrophil count observed in TB patients, as noted in the study, signify a heightened inflammatory environment. This inflammation may, in turn, influence the lymphocyte population, leading to a decrement in their numbers (Chedid et al., 2020).

Interestingly, this decrement in lymphocyte count aligns with previous studies, including Kahase et al. (2020). Kahase also documented a reduction in lymphocyte count in TB patients, establishing a consistency across studies in different settings (Kahase et al., 2020). The concurrence of findings lends weight to the observation that decreased lymphocyte counts could be a hallmark of TB severity. This correlation between lymphocyte counts and disease severity indicates the potential significance in assessing progression and prognosis in tuberculosis infections.

Delving further into the immunological implications, lymphocytes are key components of the adaptive immune response, responsible for producing specific antibodies and orchestrating targeted attacks against pathogens. Their role in combating infections, including TB, is pivotal. The decrease in lymphocyte count, as

demonstrated in this study, might compromise an immune response to an effective defense against *Mycobacterium tuberculosis*. This could lead to prolonged or recurrent infections, potentially contributing to the chronic phases of tuberculosis.

The association between reduced lymphocyte count and increased risk of tuberculosis raises an important question. Could lymphocyte levels be used as a predictive marker for tuberculosis susceptibility? If individuals with lower baseline lymphocyte counts are indeed more susceptible to TB, this could have significant implications for screening and preventive strategies. Identifying individuals at higher risk based on their lymphocyte counts could enable targeted interventions to prevent the onset of active TB.

This study indicates that intricate relationship between different immune cell populations and their roles in TB pathogenesis. The heightened inflammation associated with the increased neutrophil count could play a dual role in tuberculosis. While inflammation is an essential component of the immune response, an excessive or uncontrolled inflammatory environment can contribute to tissue damage. This damage, in turn, can facilitate the spread and persistence of the TB infection. Thus, the correlation between the lower lymphocyte counts and heightened inflammation adds nuance to our understanding of the immune dynamics in tuberculosis.

5.2.1 Red Blood Cell and its Indices

The study's outcomes shed light on the reduction of Red Blood Cells count (RBCs) in patients with pulmonary TB compared to the control group. This finding provokes a reconsideration of the hematological alterations that accompany TB infection. The

observed decrease in RBC count could be attributed to multiple factors, including suppressed erythropoiesis, a process critical for RBC production. Inflammatory mediators, which are frequently elevated during infections, can negatively impact the bone marrow's ability to produce RBCs, contributing to a diminished RBC count. Furthermore, anemia of chronic disease, characterized by impaired iron utilization, could also contribute to the reduced RBC levels.

Interestingly, the study's results find consonance with earlier investigations conducted by (Kahase et al., 2020b) . Kahase et al.'s study showed a significant reductions of RBC count and other RBC indices, such as the Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), and Mean Corpuscular Hemoglobin Concentration (MCHC) among TB patients (Kahase et al., 2020b). The consistency between these studies underscores the robustness of the observed hematological changes. The concurrent reduction in RBC indices in these studies suggests a complex web of interactions between the immune response, inflammation, and hematopoiesis in TB patients.

Adding depth to this observation, Ashkenazi et al(2022) discovered decreased serum hemoglobin levels and RBC counts in TB patients compared to healthy control (Ashenafi et al., 2022). This aligns with the current study's findings of reduced RBC levels and underscores the potential clinical significance of RBC alterations in TB. Hemoglobin, the protein in RBCs responsible for oxygen transport, serves as a vital parameter for assessing anemia and overall health status. The decrease in hemoglobin

and RBC count among TB patients might contribute to the fatigue and weakness often reported by individuals with active tuberculosis.

However, the interpretation of RBC indices as diagnostic markers for TB is not without debate. Abay et al. (2018) emphasized the insignificance of Mean Corpuscular Volume (MCV) as a diagnostic indicator for TB. MCV, a measure of the average volume of RBCs, is often used to classify anemias (Abay et al., 2018). Abay's findings resonate with studies conducted by (Maner& Moosavi, 2019) and Baker which showed no significant reduction in MCV for newly diagnosed pulmonary TB patients compared to controls. These contrasting results highlight the complexities of using specific RBC indices as sole diagnostic markers for TB. Hematological alterations in TB patients are influenced by a multitude of factors, and the interpretation of these changes requires a comprehensive understanding of their underlying mechanisms.

It's noteworthy that the reduced RBC count, as highlighted by this study, could potentially serve as an indicator of TB infection. This concept was in line with the findings of (Batool et al., 2022), who recognized a potential for reduced RBC count as a diagnostic parameter for TB. The interplay between inflammation which was not done though in this research, hematopoiesis, and RBC levels offers a unique avenue for identifying individuals at risk or those already infected with TB. Integrating hematological markers, including RBC count, with other diagnostic tools could enhance the accuracy of TB diagnosis and contribute to more informed clinical decision-making.

5.2.2 Hemoglobin (HGB) and Hematocrit (HCT)

The current study confirms an underscore of a significant decrease of Hemoglobin (HGB) and Hematocrit (HCT) levels diagnosed patients with pulmonary TB, when compared with the control group. These findings prompt an exploration of the intricate relationship between TB infection and the hematological profile. Hemoglobin, a protein within red blood cells, plays a critical role in oxygen transport throughout the body (Fukushima et al., 2019). Hematocrit, on the other hand, calculates the proportion of red blood cells within the total blood volume (Reta et al., 2023). The decrease in HGB and HCT levels suggested a disruption of oxygen-carrying capacity of the blood and overall blood volume, possibly influenced by the immune response and inflammation triggered by TB infection.

The agreement between this study's findings and the work of Gil- Santana (Gil-Santana et al., 2019) adds credence to the robustness of the observed hematological changes Gil-Santana et al.'s study reported significant reductions in both HGB and hematocrit levels in TB patients, mirroring the current study's findings (Anayochukwu Ufelle et al., 2020). The consistency between these studies points to a recurring pattern of hematological alterations in TB patients, emphasizing the clinical relevance of these changes. The congruence between the studies underscores the potential for HGB and HCT as diagnostic markers for TB.

Furthermore, (Anayochukwu et al., 2020) noted an upward trajectory prevalence of anemia among patients diagnosed with active pulmonary TB. Anemia, characterized by a deficiency in red blood cells or hemoglobin, was attributed to various factors,

including nutritional deficiencies, chronic inflammation, and anemia of chronic diseases (Abaynew et al., 2023). The latter mechanism is particularly application in the context of TB infections. Chronic inflammation, often seen in infections like TB, can disrupt the body's iron utilization, impacting erythropoiesis and causing anemia (Busti et al., 2018). These findings align with the same mechanism, as the reduction in HGB and HCT values could be reflective of the anemia of chronic disease associated with TB infection.

Interestingly, (Ufelle et al., 2020) also associated the reduction in HGB and hematocrit levels with increased levels of interleukin-6 (IL-6), which is a pro-inflammatory cytokine. IL-6 is also known to have pleiotropic effects, including the potential to induce anemia and expand plasma volume. This plasma volume expansion, while haemodilution and concentration of blood cells causes lowered HGB as well as HCT values. A correlation between increased IL-6 levels and anemia underscores the intricate relationship between inflammation and hematological alterations of TB patients(Hella et al., 2018).

Clinical implications for the findings are noteworthy. Anemia, even when attributed to the anemia of chronic disease, can exacerbate the health status of individuals with active TB. Decreased oxygen-carrying capacity can lead to fatigue, weakness, and impaired physical activity (Fukushima et al., 2019). Moreover, the interplay between inflammation and anemia can create a vicious cycle, where inflammation contributes to anemia and anemia, in turn, can perpetuate inflammation. Addressing anemia in TB patients becomes crucial for holistic patient care and optimal treatment outcomes.

5.2.3 Erythrocyte Sedimentation Rate (ESR)

The study's outcomes depict a substantial increase in Erythrocyte Sedimentation Rate (ESR) among individuals with PTB compared to the control group. This finding points towards an elevated level of inflammation in TB patients, as indicated by the accelerated sedimentation of red blood cells. ESR is a well-established index for the acute phase of infection, a nonspecific systemic reaction to inflammation, infection, or tissue injury (Abay et al., 2018). The correlation between elevated ESR and inflammation aligns with the known pathophysiology of tuberculosis, wherein the immune system mounts an inflammatory response against *Mycobacterium tuberculosis* (Ufelle et al., 2020)

This study finds resonance with the findings of Ufelle et al.,2020) who reported elevated Erythrocyte Sedimentation Rate in newly diagnosed TB patients. Ufelle et al.'s did a similar study, recognized the potential of ESR index for inflammation among TB patients. Moreover, Ufelle noted a decrease in ESR during treatment, highlighting the dynamic nature of this parameter as inflammation subsides with effective treatment (Ufelle et al., 2020). The alignment between these studies reinforces the consistency in the observed hematological changes in TB patients and emphasizes the clinical significance of elevated ESR as an indicator of the disease. The study confirms that ESR is an important test which can be used in TB prognosis.

The utility of ESR as a routine parameter for tuberculosis checkups is a noteworthy aspect discussed in this study. The heightened ESR levels observed in tuberculosis patients underscore the value of this simple and cost-effective test as an indicator of

chronic infection. Routine monitoring of ESR could offer a reliable and accessible method to track disease progression and treatment response in resource-constrained healthcare settings. The ESR test, which requires minimal equipment and training, could potentially aid in identifying individuals who may require further diagnostic assessments or adjustments in treatment plans. This will help in predicting outcome of the disease.

Furthermore, the elevated ESR levels in tuberculosis patients highlight the intricate relationship between inflammation and the stimulation of immune response against *Mycobacterium tuberculosis*. As the body responds to the invading pathogen, the resulting inflammation can be detected through markers of ESR index. The persistent inflammation contributes to the characteristic tissue damage seen in TB and can lead to a variety of clinical manifestations. Recognizing the connection between inflammation and TB infection requires a holistic approach to manage disease that encompasses both antimicrobial treatment and the modulation of the inflammatory response.

5.3.1 Platelets

The study findings reveal that patients with TB had higher platelet counts compared to healthy controls. This observation, suggesting an elevation in platelet count among TB patients, introduces a novel dimension to our understanding of the hematological changes associated with TB infection. The concordance of this finding with the work of (Mohamed et al., 2019) enhances its robustness and implies that the elevation in platelet count might indeed be a consistent characteristic of TB patients.

However, the study's results diverge from studies conducted in Pakistan, such as the one by (Kirwan et al., 2021), which reported lower platelet counts in TB patients. This discrepancy underscores the complexity of hematological alterations in TB and emphasizes the influence of various factors, including population differences, co-morbidities, and treatment regimens, that can contribute to divergent findings across studies.

The underlying mechanisms driving the observed increase in platelet count among TB patients warrant extra exploration. One plausible explanation lies in the role of interleukin especially (IL-6), which is a pro-inflammatory cytokine that is often elevated during infections (Urbán-Solano et al., 2022). IL-6 is a marker that promotes megakaryocytopoiesis, the process by which platelets are produced from precursor cells in the bone marrow. During the acute phase of infection, elevated IL-6 levels could lead to an increased production of platelets, contributing to the higher platelet count observed in TB patients (Xu et al., 2021).

Interestingly, the elevation in platelet count among TB patients, as seen in this study, has potential diagnostic and prognostic implications. The platelet count's responsiveness to IL-6 and its correlation with TB infection could position it as a valuable marker for prognosis and monitoring the disease. A consistently higher platelet counts in TB patients, as indicated by the findings, could serve as an indicator for TB infection. Furthermore, the association between platelet count and disease progression or treatment response could be could be effectively used for prognosis of tuberculosis and these offer great significance in its detection.

Considering the broader immunological context, the relationship between platelet count and TB prompts reflection on the immune response mechanisms in TB patients. Platelets are among the cells involved in hemostasis and play a role in the immune response. They interact with immune cells, release cytokines, and contribute to the formation of thrombi during inflammation. The elevation in platelet count observed among TB patients could be linked to the immune response dynamics against the mycobacterial infection as was proved in the results compared with negative controls.

Moreover, the findings regarding platelet count hint at the interplay between various hematological parameters in TB patients. The elevation in platelet counts and its potential connection to inflammation might intersect with other hematological changes, such as leukocyte alterations and erythrocyte changes. Investigating these interconnections provides a comprehensive picture of the immune response and its implications for TB pathogenesis.

The use of platelet counts as a potential diagnostic and prognostic marker for TB presents both opportunities and challenges. While the elevation in platelet count is consistent with certain studies and aligns with immune response dynamics, it's essential to consider the variability in platelet counts among individuals. Therefore, the interpretation of platelet count should be should be considered alongside other clinical and laboratory findings.

5.4.1 Morphological Changes of Blood Cells in Peripheral Blood Film

The study's results indicate that normochromic anemia, particularly of the normocytic normochromic type, was the most prevalent form of anemia among PTB patients. Normocytic normochromic anemia, characterized by a decrease in hemoglobin levels without significant changes in red blood cell size or color, is often indicative of chronic inflammation or underlying chronic diseases. The concordance of this finding with the work of (Laghari, Sulaiman, Khan, & Memon, 2019) adds robustness to the observed prevalence of normochromic anemia among PTB patients. The consistency across studies shows the clinical relevance of this hematological alteration in cases of TB infection.

Especially, the isolation of toxic granulation in a significant proportion of white blood cells among PTB patients provides a window into the underlying inflammatory processes in TB. Toxic granulation, characterized by the presence of cytoplasmic granules within white blood cells, is often a reflection of heightened immune activity and inflammation. With TB infection, the presence of toxic granulation aligns with the immune response dynamics triggered by Mycobacterium tuberculosis. The immune system mounts an inflammatory response to contain the infection, which is reflected in the morphological changes observed in white blood cells. This observation corroborates the presence of inflammation caused by TB infection and underscores the intricate interplay between the immune response and hematological alterations which alters cell morphologies.

The presence of thrombocytosis, characterized by increased platelet counts, among PTB patients compared to the control group is another intriguing finding of this study. Thrombocytosis is often a reactive response to various conditions, including infections and inflammation. The elevation in platelet counts, as noted in this study, aligns with research by (Abay et al., 2018) that has reported reactive thrombocytosis in infectious diseases, including PTB. The immune response mounted against the mycobacterial infection can stimulate the production of various cytokines, which, in turn, can influence platelet production and result in thrombocytosis (Batool et al., 2022). The presence of thrombocytosis among PTB patients suggests a dynamic interplay between immune response and hematological alterations in TB infection.

Significantly these hematological changes extend beyond mere observations, as they have potential diagnostic and clinical implications. The identification of normochromic anemia, toxic granulation, and thrombocytosis in PTB patients' peripheral blood films offers a window into the disease's pathophysiology. These morphological changes serve as indicators of the underlying immune response, inflammation, and hematopoietic alterations triggered by TB infection. Incorporating these observations into the diagnostic process and treatment monitoring could provide a more comprehensive understanding of individual patient profiles. The findings regarding hematological alterations in PTB patients' peripheral blood films also emphasize the interconnected nature of the various hematological parameters. The presence of normochromic anemia, toxic granulation, and thrombocytosis collectively underscores the systemic impact of TB infection on the body's hematological profile. These changes are not isolated events but rather a reflection

of the intricate immune response and inflammatory dynamics that occur during TB infection.

CHAPTER SIX

CONCLUSION AND RECOMMENDATION

6.1: Conclusion

There were increased total white blood cell count especially the neutrophil count which suggested that an immune response occurs against *Mycobacterium tuberculosis*. There was a reduced red blood cell count, hemoglobin, and hematocrit levels which is an indicative of suppressed erythropoiesis and inflammation-mediated iron restriction. The higher erythrocyte sedimentation rate supports the presence of inflammation in PTB patients. Additionally, Elevated platelet counts also support presence of inflammation in PTB patients while the identification of toxic granulation among patients provides a window into underlying inflammatory processes in Tuberculosis.

6.2: Recommendations

Based on this study, healthcare professionals should consider incorporating White blood cell count, Total and differential parameters into the diagnostic and monitoring protocols for pulmonary tuberculosis patients. It is important to make use of total red blood cell indices including Erythrocyte sedimentation rate in the prognosis and treatment of pulmonary Tuberculosis. The platelet count should be an important indicator in diagnosis while the peripheral blood film morphological changes will aid in the diagnosis. Integrating these hematological parameters into clinical practice can contribute to more comprehensive management of pulmonary tuberculosis

patients. Further studies are ideally recommended to confirm the role of PTB in leukocyte alteration and its effect on other biochemical tests.

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APPENDICES

APPENDIX I: INFORMATION SHEET

Research Thesis: Evaluation of Hematological Parameters among Tuberculosis Patients attending Kisii Teaching and Referral Hospital.

Sponsorship: Medical Laboratory Sciences department in the School of Health Sciences, Kisii University.

Principal Investigator: Jared Mekenye Ongwae [MSc. Biomedical Science (Hematology and Blood Transfusion) Candidate].

Supervisors: Stanslaus Musyoki PhD and Dr. Samuel Mong'are PhD.

Introduction

Dear participants, I wish to invite you as a participate in this research voluntary. Before proceeding, I request you to read and understand the information provided to allow you participate voluntarily in study by answering the questions asked correctly as done by the investigator during the interview.

Research Objectives

The objective of the study is to collect and analyze data by the principal investigator and the supervisors of Kisii University to evaluate hematological parameters among tuberculosis participants.

Procedure

The use of developed and adopted standard operational procedures suitable for Kisii Teaching and Referral Hospital will be applied during the phlebotomy procedures

that are involved in this study. Each process will be critically evaluated to ensure the results are precise and accurately determined to achieve the goal standards of this study.

Risks and Benefits to Participants

There is a slight discomfort you may encounter when drawing the sample of blood same as that of routine examination with slight pain. There may be a change in color of your skin following the blood drawing occur transiently done by health care professionals carefully. You will not be provided with direct incentives for you to participate in this research.

But the cost for the medical examination will be covered by the project and based on the results outcome, you will be linked accordingly to care and management when necessary. Therefore, the result of this study will be beneficial to you in quality management of tuberculosis than before. Hence, you are indirectly benefiting other patients and the society in this aspect.

Confidentiality

The information obtained will be kept confidential. Log books used in the laboratory will have no names but bar coded. The information sheet that links the coded number to patient name shall be kept save under key and lock. You have full rights to withdraw from participating in this study at any time before and after consent even without explaining the reason. Your decision will not affect your right to get health service you are supposed to get otherwise.

Contact Person:

Jared Mekenye Ongwae 0723245075

APPENDIX II: UNIVERSITY INTRODUCTION LETTER

Telephone : +254 786826826
Facsimile : 020 2491131
Email: tabbymugo@kisiiuniversity.ac.ke

KISII UNIVERSITY

DEPARTMENT OF APPLIED HEALTH SCIENCES

P. O. Box 408-40200
KISII, KENYA.
www.kisiiuniversity.ac.ke

SCHOOL OF HEALTH SCIENCES

To: whom it may concern, 12th May 2021

Re: JARED MEKENYE ONGWAE

This is to inform you that **Jared Mekenye Ongwae** Reg. No. **MHS12/40026/14** is a Bonafide student of **Kisii University** Department of Applied Health Sciences. **Jared Mekenye Ongwae** is currently pursuing his **Masters Degree in Biomedical Sciences (Haematology and Blood Transfusion)**.

He has successfully defended his proposal entitled "**Characteristics of Haematological Indices of Tuberculosis patients attending Kisii Teaching and Referral Hospital.**

This Letter is to request your office to facilitate the processing of **his research permit**. Kindly contact the undersigned in case you have questions.

Thanks in advance.

Sincerely,

KISII UNIVERSITY
SCHOOL OF APPLIED HEALTH SCIENCES
12 MAY 2021
KENYA

Tabitha Wanjau, PhD
Post graduate Coordinator School of Health Sciences

KISII UNIVERSITY IS ISO 9001:2008 CERTIFIED

APPENDIX III: CONSENT

Department of Medical Laboratory Sciences, School of Health Sciences, Kisii University, Consent form for the participation of the study participants in their search project.

Name of the participant……

Patient unique number…..……

I am fully informed about the research project that will evaluate and correlate hematological parameters among tuberculosis patients. The objective of this research project has been correctly explained to me with the impact of the results obtained from me. I have been informed about the confidentiality of this research project and well informed of my right to keep hold of information, decline to cooperate and make myself withdraw from the study. Therefore, with full understanding of the importance of the study, I agreed voluntarily to provide the requested samples and my benefit will be only from the free laboratory investigation results.

I_____hereby consent for participating in this research project.

Signature:_____Date

_____

APPENDIX IV: STUDY PARTICIPANTS INFORMATION

Code Number_____

Socio-Demographic Characteristics

1. Gender

Male ( )

Female ( )

2. Age

16 – 30 ( )

31 – 45 ( )

46 – 60 ( )

3.Marital Status

Single ( )

Married ( )

Divorced/Widow ( )

4. Occupation

Civil Servants ( )

Housewives ( )

Farmers ( )

Self Employed ( )

Students ( )

Others ( )

5. **Education level**

No Education ( )

Primary ( )

Secondary ( )

Tertiary ( )

Assessment of the health conditions of the study participants

- Do you have any underlying chronic condition apart TB? (Yes/No)
- Are you currently under any medical treatment apart from TB treatment? (Yes/No)
- In the last six months, have you been treated for any chronic infection apart from TB(Yes/No)
- Have you been transfused in the last 6 months? (Yes/No)
- Do you have sufficient food? (Able to afford three meals in a day) (Yes/No)

APPENDIX V: STANDARD OPERATING PROCEDURE (SOP)

Procedure for Venous blood

Blood was collected using safety precautions to ensure test results were reliable, reproducible and validated. Laboratory staff were adequately trained and supervised during venipuncture procedures. For infants, pathologist was involved to obtain substantial amount of blood as follows:

1. Introduction and identification of the patient.
2. Washing of hands and wear gloves
3. Prepare the equipment
4. Prepare the patient
5. Apply the tourniquet in case of venous blood
6. Choose the vein or femoral and jugular in case of infants.
7. Disinfect the draw site with 70% alcohol swab
8. Insert the needle and draw the required amount of blood
9. Draw the Vacutainer tube in a correct order and mix well
10. Exit the vein and apply pressure to arrest bleeding
11. Discard the needle in the safety box
12. Label the sample before the patient leaves the phlebotomy room

Wash your hands and allow to the patient to leave phlebotomy room

APPENDIX VI: STANDARD OPERATING PROCEDURE FOR SERUM PREPARATION

Aim: This is important to prepare blood components

Purpose: To standardize component preparations

1. Collect blood in a plain tube.
2. Allow the blood to clot for 30-60 min
3. Samples should be at room temperature.
4. Release the clot from the wall of the tube
5. Use applicator stick to remove the clot.
6. Centrifuge at 2500 rpm for 10 min.
7. The liquid portion at the top is the serum and is used in other biochemistry studies.

Preparation of serum without centrifugation

i. Collect the blood in a clean test tube without anticoagulant.

ii. Allow the blood to clot at room temperature for an hour.

iii. Separate the serum after an hour with the help of a Pasteur pipette.

APPENDIX VII: ETHICAL APPROVAL LETTER

OFFICE OF THE DIRECTOR OF GRADUATE STUDIES AND RESEARCH
UNIVERSITY OF EASTERN AFRICA, BARATON
P.O Box 2500-30100, Eldoret, Kenya, East Africa

B1648132021 **October 12, 2021**

TO: **Jared Mekenye Ongwae**
Department of Applied Health Sciences
Kisii University

Dear Jared,

RE: Characteristics of Haematological Indices of Tuberculosis patients attending Kisii Teaching and Referral Hospital

This is to inform you that the Research Ethics Committee (REC) of the University of Eastern Africa Baraton has reviewed and approved your above research proposal. Your application approval number is UEAB/REC/12/10/2021. The approval period is 12th October, 2021 – 12th October, 2022.
This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used.
ii. All changes including (ammendments, deviations and violations) are submitted for review and approval by the Research Ethics Committee (REC) of the University of Eastern Africa Baraton.
iii. Death and life threatening problems and serious events or unexpected adverse events whether related or unrelated to the study must be reported to the Research Ethics Committee (REC) of University of Eastern Africa Baraton within 72 hours of notification.
iv. Any changes anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to the Research Ethics Committee (REC) of the University of Eastern Africa Baraton within 72 hours.
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. Submissions of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii. Submission of an executive summary report within 90 days upon completion of the study to the Research Ethics Committee (REC) to the University of Eastern Africa Baraton.

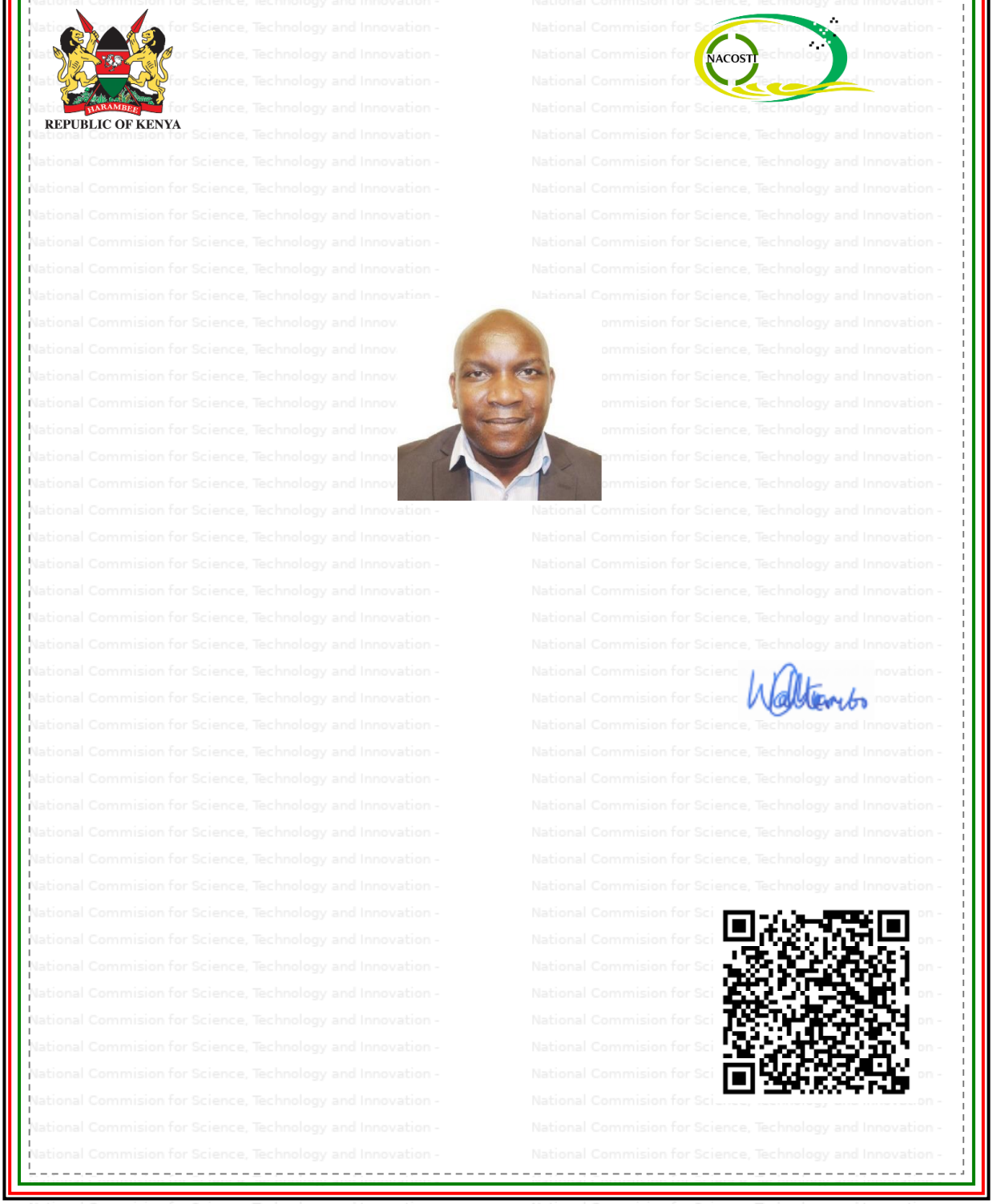
Prior to commencing your study, you will be expected to obtain a research licence from National Commission for Science, Technology and Innovation (NACOSTI) https://oris.nacosti.go.ke and also obtain other clearances needed.

Sincerely Yours,

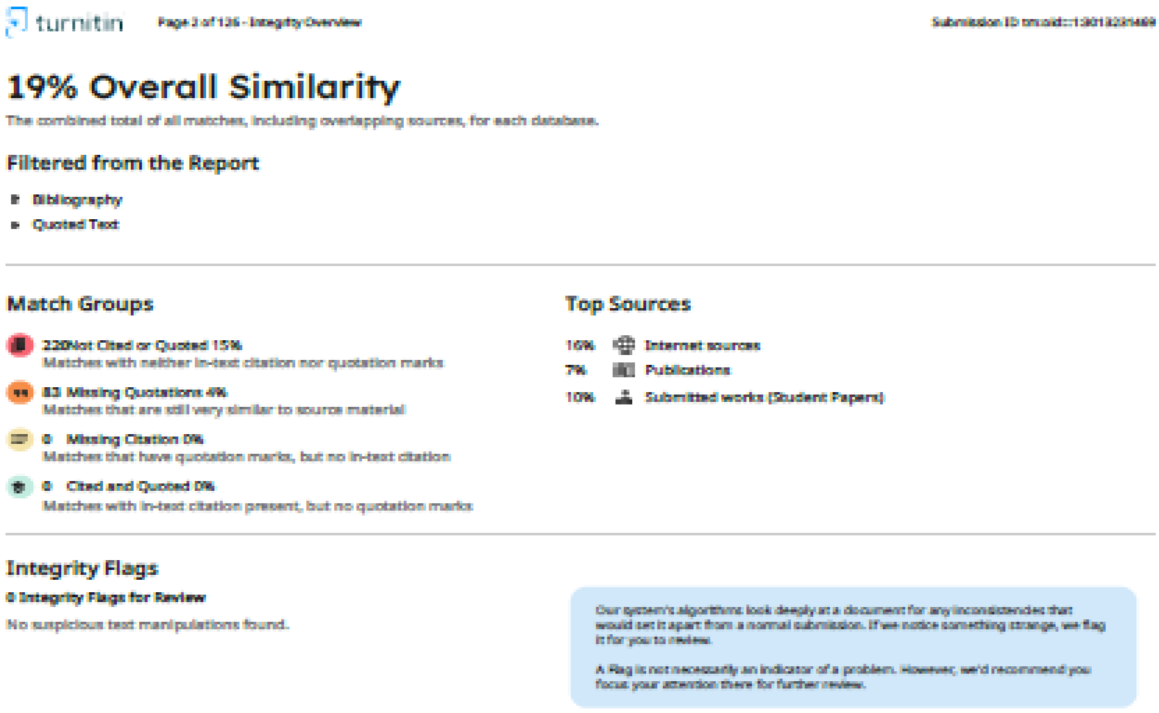
Prof. Jackie Kpeinzeh Obey, Phd
Chairperson, Research Ethics Committee

University of Eastern Africa, Baraton
12 OCT 2021
P.O Box 2500-30100
ELDORET
Research Ethics Committee

APPENDIX VIII: NACOSTI RESEARCH PERMIT



APPENDIX IX: PLAGIARISM REPORT



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