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Overview of pulmonary tuberculosis and extra pulmonary tuberculosis at the Siloam MRCCC Semanggi cancer hospital in 2018-2020

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Abstract

Clinical manifestations and results of investigations using imaging methods for pulmonary and extrapulmonary tuberculosis (TB) are often mistaken for malignancy, so TB is referred to as a "great imitator." This study aims to describe pulmonary TB and extrapulmonary TB patients at the Siloam MRCCC Semanggi Cancer Specialist Hospital in 2018-2020. A retrospective study design was used in the study with a sample of 71 patients according to the inclusion criteria. The research instrument used was the archives of the Anatomical Pathology Laboratory of the Siloam MRCCC Semanggi Cancer Special Hospital in 2018-2020. Pulmonary TB and extrapulmonary TB results were obtained in 2018 14 patients (19.7%), 31 patients (43.6%) in 2019, and 26 patients (36.7%) in 2020. Most TB occurred in the age range of 21-30 years (36.6%) and female sex (67.6%). Based on the location of the lesion, extrapulmonary TB was found in 64 patients (90.1%) and pulmonary TB in 7 patients (9.9%). Clinical diagnosis showed that 12 patients (17%) were suspected of malignancy, and 55 patients (77.4%) were not. After histopathological examination, 43 tuberculous lymphadenites (60.6%), seven bone and joint TB (9.9%), six lung TB (8.5%), four soft tissue TB (5.6%), 4 Genitourinary TB (5.6%), four gastrointestinal & peritoneal TB (5.6%), two cutaneous TB (2.8%), and one central nervous system TB (1.4%). Risk factors play an important role in the occurrence of pulmonary TB and extrapulmonary TB. Histopathological examination is important to exclude the possibility of malignancy in patients with pulmonary TB and extrapulmonary TB so that treatment can be carried out quickly and accurately.

Keywords: Tuberculosis; Malignancy; Histopathology; Indonesia

1. Introduction

In 2019 there was an increase in cases of 69%, namely 562,049 cases of tuberculosis (TB) [1]. The high increase in cases has ranked Indonesia 2nd with the most TB cases worldwide. Out of 34 provinces in Indonesia, DKI Jakarta is ranked first with 410 cases per 100,000 population [2]. Indonesia is ranked 3rd in 2020, namely, 8% of total TB cases worldwide, the decrease in the number of cases is caused by disruptions to the health system for diagnosing TB as a result of the Coronavirus disease 2019 (COVID-19) pandemic. Habits of life, socio-economic, and the environment also play a role in TB transmission [3; 4]. Research by Thomas B et al. found that 25% of pulmonary TB patients had smoking habits or smoking history [4]. Because men smoke more often than women, pulmonary TB is more common in men [5].

The hematogenous and lymphogenous spread of Tuberculosis (TB) results in the spread of infection to extrapulmonary organs or tissues [6]. Extrapulmonary spread is often associated with a low immune system [3; 6]. Extrapulmonary TB can occur in lymph nodes, pleura, genitourinary tract, bones, joints, meninges, gastrointestinal tract, eyes, skin, and pericardium [6]. Because TB can occur in various organs, the methods for diagnosing pulmonary TB and extrapulmonary TB also vary according to the location of the occurrence of tuberculosis [3; 5; 6].

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Research conducted by Singh G et al. found that most cases of extrapulmonary TB were found in the lymph nodes, with an incidence rate of 18% [7]. TB infection of the lymph nodes can resemble Malignant Lymphoma from the results of Positron Emission Tomography/Computed Tomography Fluorodeoxyglucose (F-18 FDG PET) imaging used to diagnose and determine the stage and the prognosis of malignancy before and after therapy [8; 9]. With this similarity, TB is a "great imitator," which is often misinterpreted as malignancy [9; 10].

2. Research Methodology

This type of research uses descriptive research methods with a retrospective approach. This study used secondary data from the archives of the Anatomical Pathology Laboratory of the Siloam MRCCC Semanggi Specialist Cancer Hospital in 2018-2020 to determine the description of patients with Pulmonary Tuberculosis and Extra Pulmonary Tuberculosis. The time for processing, collecting, and conducting the research was from April 2021 to November 2021. The sample in this study used the total sampling method, a data collection technique where the number of samples is the same as the population, with a total of 71 samples. All data obtained were entered into the SPSS (Statistical Package for the Social Science) computer application program. In this study, grouping data in the form of frequency distribution tables.

3. Results and discussion

Mycobacterium tuberculosis (M. tuberculosis) is an acid-fast bacillus first identified by Robert Koch as the bacterium that causes tuberculosis (TB) [1]. The acidic stem nature of *Mycobacterium tuberculosis* is due to the high content of mycolic acid and lipoarabinomannan fatty acid (ManLAM) in its cell wall [6; 11]. The characteristics of *Mycobacterium tuberculosis* are resistance to several antibiotics, the ability to survive in extreme conditions (environments with extreme acidity or alkalinity, low oxygen situations), and intracellular survival (in macrophages) [12]. *Mycobacterium tuberculosis* takes a long time to divide, around 16-20 hours, and this division rate is much slower than other bacteria, which usually takes less than 1 hour [13].

Tuberculosis (TB) by aerosol spread occurs when individuals with active pulmonary TB or upper respiratory tract TB cough so that droplets with live bacilli are spread in the air. [13] In addition to coughing, TB can be spread when sneezing, singing, and talking. Droplets can dry quickly. Meanwhile, small droplets (<5-10 μm in diameter) can remain in the air for several hours and reach the airways when inhaled. Factors that affect transmission are the number of bacilli (bacillary load) from TB sufferers, contact with individuals with active TB, and duration of exposure [6]. The majority of individuals exposed to *Mycobacterium tuberculosis* do not develop the disease. An exposed person can fail to develop an infection, be infected but then clear the infection that occurred, successfully resist the infection but have bacilli without symptoms (latent TB infection), and develop progressive TB disease [13; 14].

Table 1 Frequency Distribution of Pulmonary Tuberculosis and Extra Pulmonary Tuberculosis Patients in 2018-2020

Year	Frequency	Percentage (%)
2018	14	19.7%
2019	31	43.6%
2020	26	36.7%
Total	71	100%

Of the 71 samples that met the inclusion criteria, in 2018, the number of patients diagnosed with pulmonary and extrapulmonary tuberculosis was 14 patients (19.7%). In 2019 there were 31 patients (43.6%), and in 2020 there were 26 patients (36,7%). The Global Tuberculosis Report the World Health Organization reports that since the Coronavirus disease 2019 (COVID-19) pandemic, there has been a change in TB rates worldwide. WHO stated that since 2020 there has been a decrease of 20% compared to 2019 in developing countries such as Indonesia, India, and the Philippines due to social restriction policies that make individuals suspected of tuberculosis reluctant to undergo examinations at health facilities [1]. The results obtained in the study decreased from 2019 to 2020, but the number of cases in 2020 did not decrease until it exceeded the cases in 2018.

Table 2 Frequency distribution of age groups of Pulmonary Tuberculosis and Extra Pulmonary Tuberculosis patients in 2018-2020

Age	Frequency	Percentage (%)
0-10	1	1.4
11-20	2	2.8
21-30	26	36.6
31-40	16	22.5
41-50	18	25.4
51-60	8	11.3
>60	0	0
Total	71	100

Based on the following table, the highest age group diagnosed histopathologically with pulmonary TB and extrapulmonary TB at the Siloam MRCCC Cancer Special Hospital Semanggi was the age group of 21-30 years 26 people (36.6%) out of a total of 71 people. The results follow research conducted by Tandirogang et al. that extrapulmonary TB in Indonesia is often found in productive age (15-64 years) [18]. The research was also conducted by Noviyani et al., who found that pulmonary TB in Indonesia was most often found in the age group of 25-34 years [35].

The risk factors can be divided into several factors, namely: Demographics: Older age and children are at the highest risk for developing TB. It happens because immunity is weak in old age and is not yet fully formed in children. However, the incidence of pulmonary TB and extrapulmonary TB is most often found in adolescents and young adults because they have social contacts that are much wider than outside the home [14; 15]. The study found that in Jakarta, the incidence of extrapulmonary TB was mostly found at the age < 35 years with a population of Betawi ethnicity [7].

The total population of Indonesia is dominated by productive age (15-64 years), which reaches 191.08 million people, which is 70.72% of the total population [36]. The productive age group is a group that works a lot and is in direct contact with the outside environment, and has a high level of mobility, so aerosol transmission of TB occurs more easily in this age group [18]. Diagnosis for children under five years is more advisable to use tuberculin skin testing (TST), while children over five years are more likely to use Interferon-Gamma Release Assays (IGRAs), so histopathological examination is not the main choice in diagnosis [28].

Table 3 Gender Frequency Distribution of Patients Undergoing Histopathological Examination

Gender	Frequency	Percentage (%)
Male	23	32.4
Female	48	67.6
Total	71	100

Women are the largest population diagnosed with pulmonary TB and extrapulmonary TB, namely 67.6%, and in men, as much as 32.4%. , Mehraj et al. also showed the same results and found that extrapulmonary TB in Southeast Asia was more common in women [37]. Studies say that protein intake is lower and less energy in women, so it can reduce immunity and make infections easier. Insufficient protein intake and insufficient energy are still found in many women in Indonesia, so they can reduce immunity which plays a role in fighting TB infection [38]. The high level of women's awareness about health means that more women have their health checked at health facilities so that the diagnosis of pulmonary TB and extrapulmonary TB can be carried out quickly [18]. Hormonal and genetic factors are thought to influence the development of extrapulmonary TB in women. Extrapulmonary TB in women often occurs in the urogenital organs [16; 17; 18].

Social, Economic, and Educational Status: Low income with a high population increase is often found in developing countries, so the choice of place to live tends to be in a dense environment which triggers TB transmission [19]. Low socioeconomic status increases the risk of malnutrition, resulting in decreased immunity so that TB can be easily contracted [20; 21]. Nutritional Status: The relationship between TB and malnutrition is bidirectional. TB causes individuals to experience malnutrition, increasing the risk of developing active TB by 6-10 times. Micronutrients can maintain a healthy gut microbiota to maintain homeostasis in the body's immune system. Poor nutritional status also influences response to anti-TB drugs and is associated with an increased risk of TB recurrence [22]. Immunity Status: The close relationship between HIV infection and pulmonary TB and extrapulmonary TB is possible because CD4+ T cells are deficient in individuals with HIV, so the main role of controlling *Mycobacterium tuberculosis* infection cannot work optimally [23; 24].

Smoking: Tobacco smoke from cigarettes can harm the health of active and passive smokers. Smoking affects both innate and adaptive immunity. Smokers are at higher risk of developing pulmonary TB and extrapulmonary TB. Poor TB treatment outcomes are also affected by smoking [25]. Alcohol: The production of monocyte cytokines that regulate inflammation will be limited by alcohol consumption so that the ability of macrophages to respond to these cytokines and present *Mycobacterium tuberculosis* antigens to lymphocytes is also reduced. Alcohol consumption facilitates gathering people in social environments such as bars, thereby making TB transmission easier [6; 26]. Genetics: Studies conducted in populations in West Africa suggest that the NRAMP1 (Natural Resistance Associated Macrophage Protein 1) gene mapped to chromosome 2q may play a role in susceptibility to *Mycobacterium tuberculosis* infection [6].

The attachment of *Mycobacterium tuberculosis* to macrophages occurs due to the binding of the bacterial cell wall to various macrophage surface receptors, namely the mannose-binding leptin receptor, the complement receptor, the GFcγ immunoglobulin receptor, and the type A scavenger receptor [3; 6]. *Mycobacterium tuberculosis* can inhibit the normal microbicidal response by inhibiting phagosome maturation and preventing lysosome fusion with phagocytic vacuoles [6].

Alveolar macrophages, dendritic cells, and other immune cells recognize *Mycobacterium tuberculosis* structures through pathogen-associated molecular patterns (PAMPs) such as ManLAM, PI3P, and heat shock proteins (Hsp65 and Hsp70) by Toll-Like Receptors (TLR2) [3]. Interaction with TLRs activates signaling pathways for pro-inflammatory cytokines TNF, IL-1B, IL-12, and Nitric Oxide [6]. The T-helper (TH1) response appears three weeks after infection and activates macrophages so that they are bactericidal [6; 21]. The TH1 response begins when *Mycobacterium tuberculosis* antigen enters the lymph nodes and is displayed on naive T cells in regional lymph nodes [6]. TH1 differentiation depends on IL-12, produced by Antigen-Presenting Cells (APC), which has met with *Mycobacterium tuberculosis* [21].

Macrophages activated by IFN-γ differentiate into "epitheloid histiocytes," which can aggregate to form granulomas or tuberculomas [24]. Several epithelioid cells coalesce into giant cells called Datia Langhans cells [1; 2]. Granuloma formulation and caseous necrosis formation are regulated by T-helper (TH1) [24]. Granulomas that form may be observed in other conditions, such as neoplasms [6]. The tissue damage that occurs results from delayed-type hypersensitivity to *Mycobacterium tuberculosis* antigens [6]. Delayed hypersensitivity damages inactive macrophages where bacilli multiply but also form caseous necrosis. *Mycobacterium tuberculosis* is commonly found in the peripheral area of caseous necrosis in the center of the granuloma [3; 21]. The manifestations of tuberculosis are:

Primary Pulmonary Tuberculosis: *Mycobacterium tuberculosis*'s first contact with the host manifests as primary Tuberculosis (TB). Most of the inspired air is distributed to the middle and lower portions of the lung, so these are the areas most frequently involved in primary TB. Lesions that develop after the initial infection are called Ghon foci, usually peripheral and accompanied by hilar or paratracheal lymphadenopathy [3; 6]. A chest X-ray examination cannot show any abnormalities in this phase. The lesions heal spontaneously and become small calcified nodules in most cases.

Secondary Pulmonary Tuberculosis: Endogenous reactivation of latent TB or new infection (primary infection or reinfection) is the cause of secondary TB. The location of the lesion was found in the apical segment (Simon's focus) and the superior posterior lobe, which has a much higher mean oxygen tension than the inferior lobe. This much higher oxygen pressure supports the growth of *Mycobacterium tuberculosis* which is an obligate aerobic bacterium [6; 21]. Diurnal fever and night sweat with fever, weight loss, anorexia, malaise, and weakness are non-specific but common signs and symptoms. In 90% of cases, the cough will be productive with the production of purulent sputum and may be accompanied by hemoptysis resulting from erosion of dilated vessels within the cavity (Rasmussen's aneurysm) [6; 27].

Extrapulmonary tuberculosis (TB) is TB that can occur in any organ and can be found in immunocompetent and immunocompromised individuals. Individuals with Human Immunodeficiency Virus (HIV) infection and Tuberculosis are more likely to have extrapulmonary TB. Extrapulmonary TB occurs in about 20-25% of all TB cases [6; 28].

Hematogenous and lymphogenous spread contributes to extrapulmonary TB. Extrapulmonary spread begins when *Mycobacterium tuberculosis* invades out of the lung parenchyma and produces nonspecific clinical findings that appear slowly [28]. Based on the spread of extrapulmonary TB, which spreads lymphogen and hematogen, it is most often found in the lymph nodes, and direct spread from the lungs to other organs, the most common direct spread is pleural TB [6].

Table 4 Frequency Distribution of Tuberculosis Locations

Location	Frequency	Percentage (%)
Extra Pulmonary	64	90.1
Lung	7	9.9
Total	71	100

Extrapulmonary tuberculosis (TB) dominated as much as 90.1% of events, with 64 of 71 samples. Histopathological examination is one of the most recommended examinations for extrapulmonary TB [6]. This examination was also carried out because of suspicions of malignancy in the samples examined [27].

Table 5 Description of TB Lesion Locations

TB lesion location	Frequency	Percentage (%)
Neck Lymph Nodes	26	36.6
Lungs	7	9.9
Axillary Lymph Nodes	6	8.5
Supraclavicular Lymph Nodes	6	8.5
Inguinal Lymph Nodes	2	2.8
Ovarian Tube	2	2.8
Thoracic Vertebrae 7	2	2.8
Genu	2	2.8
Appendix	1	1.4
Appendices Epiploica Sigmoid	1	1.4
Ascending Colon	1	1.4
Thoracic Wall	1	1.4
Distal Forearm and Part of the Ulnar Nerve	1	1.4
Ankle	1	1.4
Cervical and Axillary Lymph Nodes	1	1.4
Mesocolic Lymph Nodes	1	1.4
Para-aortic Lymph Nodes	1	1.4
Parotid Lymph Nodes	1	1.4
Pelvic Lymph Nodes	1	1.4
Mediastinum	1	1.4
Pelvis	1	1.4
Perianal	1	1.4
Peritoneum	1	1.4

Cerebrum	1	1.4
Sternum	1	1.4
Uterus	1	1.4
Total	71	100

Mycobacterium tuberculosis infection of the lymph nodes results in the formation of granulomas either in separate or fused foci [3]. These foci of granulomas that form damage the anatomical structure of the lymph nodes [20]. Tuberculous lymphadenitis refers to painless swelling of the lymph nodes resulting from *Mycobacterium tuberculosis* infection. Lymph nodes that are initially discrete slowly develop into a hard mass and may form fistula tracts that secrete caseous material, usually in the cervical region (scrofula) [6; 29]. Diagnosis is made by Fine Needle Aspiration Biopsy (FNAB) or surgical excision biopsy to rule out differential diagnoses such as lymphoma, metastatic carcinoma, Kikuchi's disease, Kimura's disease, and Castleman's disease [6; 29; 30].

Pleural tuberculosis (TB) is often the result of spread originating in the lung parenchyma. Pleural effusion is often present in primary infection; fluid accumulation in the pleura indicates a hypersensitivity response to *Mycobacterium tuberculosis* antigen [2]. Tuberculous empyema is a complication that can occur in pulmonary tuberculosis. It occurs due to the rupture of the pulmonary cavity with the spread of germs to the pleura [27; 31].

Many diseases and conditions can cause pleural effusion, such as lung or breast malignancy, congestive heart failure, pneumonia, liver abscess, inflammatory diseases (rheumatoid arthritis, Wegener's granulomatosis, and Churg-Strauss syndrome), and lymphatic disorders. Pleural fluid analysis can be performed to diagnose pleural TB [6; 27]. Symptoms found were hoarseness, dysphonia, dysphagia, and chronic productive cough. Examination of acid-resistant rods (BTA) showed positive results, but a tissue biopsy can also be done to rule out a differential diagnosis of laryngeal carcinoma, which has the same signs but without pain [6; 27]. Urogenital TB is a disease that can be transmitted and can cause infertility. Urogenital TB is an infection of *Mycobacterium tuberculosis* in every urogenital organ (kidneys, urinary tract, male and female genital organs) [27]. Polyuria, dysuria, nocturia, hematuria, and flank or abdominal pain are the most common clinical manifestations of urogenital tuberculosis (TB). Individuals who are infected initially do not feel symptoms, so genitourinary TB is often diagnosed after severe kidney damage. Chronic urinary tract inflammation, obstructive uropathy, infertility, and masses in the kidney or testicles can all contribute to urothelial cancer [6; 28].

The most common location for extrapulmonary TB was the lymph node in 45 samples, with the neck lymph nodes being the most common location for extrapulmonary TB lesions. In theory, the spread of extrapulmonary TB can be lymphogenous, which can explain extrapulmonary TB is most commonly found in the lymph nodes [6]. Hematogenous spread also plays a role as a pathway for extrapulmonary TB spread so that it can occur anatomically far from the lungs, such as the genitourinary organs, bones, and gastrointestinal tract [27].

In women, urogenital TB can occur in the fallopian tubes and endometrium, which can cause infertility, pelvic pain, and abnormal menstruation. In men, genitourinary TB can occur in the epididymis, prostate, seminal vesicles, and penis with the manifestation of a soft mass. Diagnosis of genitourinary TB requires a biopsy or culture specimen, Polymerase Chain Reaction (PCR), Intravenous Pyelography (IVP), ultrasonography (USG), and Computed Tomography (CT) [27]. The pathogenesis of tuberculosis (TB) of the bone is related to the reactivation of a hematogenous focus or spread via paravertebral lymph nodes. Weight-bearing joints such as the spine, hips, and knees are often affected by bone TB. Spinal TB, also called Pott's disease/TB spondylitis, often involves two or more corpus vertebrae bones next to each other [6; 27].

Not infrequently, *Mycobacterium tuberculosis* germs spread from the lungs to the spine along Batson's paravertebral venous plexus or through lymphatic drainage to the para-aortic lymph nodes [27]. The radiographic appearance is usually 2–5 months after the onset of the disease. The classic triad of tuberculous tenosynovitis and arthritis (Phemister's triad) is juxticular osteoporosis, peripheral bone erosions, and gradual narrowing of the intraarticular space on radiology. Magnetic resonance imaging (MRI) and computed tomography (CT) are useful for further identification of disease TB of the bone that responds to chemotherapy treatment, but in severe cases, surgery is required [27; 28].

Tuberculous meningitis results from the hematogenous spread of primary pulmonary tuberculosis (TB) or rupture of the subependymal tubercles into the subarachnoid space. Symptoms may include low-grade fever, malaise, anorexia, and irritability. Because of the involvement of the meninges, which are also present at the base of the brain, cranial

nerve paresis is common [3; 27]. Lumbar puncture is required for diagnosis. Examination of the cerebrospinal fluid, which dominates is mononuclear (MN), but in the early stages, it is dominated by polymorphonuclear (PMN), increased protein, and decreased glucose [27]. Tuberculoma is an uncommon manifestation of the central nervous system (CNS), these space-occupying lesions of the CNS often cause seizures and focal signs. CT and MRI show contrast-enhanced ring lesions, but a biopsy is needed to confirm the diagnosis [6; 32].

Tuberculosis (TB) in the gastrointestinal tract includes the esophagus, stomach, small intestine, ileocaecal, colon, and anorectal. The terminal ileum and caecum are the most common sites for gastrointestinal TB. Abdominal pain similar to appendicitis, swelling, obstruction, hematochezia, and a palpable mass on the abdomen are common in cases of gastrointestinal TB. In addition, fever, specific weight loss, anorexia, ascites, and night sweats may also be found [6; 27; 28]. As a "Great Imitator," the clinical presentation of gastrointestinal TB is highly non-specific and varies depending on the disease's specific site and the host's immune status. It can present inflammatory bowel disease, gastrointestinal infections such as amebiasis, enteric fever, and gastrointestinal tract malignancies or other abdominal and pelvic organs [27; 24].

Tuberculous granuloma of the liver is most often found in the periportal area. The clinical picture of hepatobiliary TB is usually the patient complaining of a fever of unknown origin. Anorexia, weight loss, and abdominal pain localized to the right upper quadrant are also included in the clinical picture. Hepatomegaly is the most common finding resembling an isolated tumor or liver abscess. In half of the cases, hepatic TB has the same clinical picture as the neoplasm [6; 27]. Clinical findings suggest acute cholecystitis or biliary colic may manifest in isolated biliary TB. The presence of jaundice suggests biliary involvement, and also the results of biochemical tests may mimic extrahepatic biliary obstruction. Isolated pancreatic tuberculosis may present with clinical manifestations similar to pancreatic neoplasms [27].

Direct extension of mediastinal or hilar lymph nodes adjacent to the pericardium and hematogenous spread is the pathogenesis of tuberculous pericarditis. Weight loss, cough, dyspnea, orthopnea, chest pain, night sweats, fever, tachycardia, cardiomegaly, and pleural effusion are clinical signs that can be found in TB pericarditis [6; 28]. Classification of Tuberculosis (TB) cutis is divided into three categories, namely: exogenous inoculation, endogenous infection, and hematogenous spread [27; 28; 29; 30; 31; 32]. Ocular TB is usually unilateral and asymmetric. It can affect the ocular surface, lids, conjunctiva, cornea, sclera, uvea, choroid, retina, orbit, lacrimal gland, and optic nerves, which extend to the central nervous system. Clinical manifestations of ocular TB include uveitis, retinitis, optic neuropathy, endophthalmitis, choroidal tubercle, tuberculous conjunctivitis, scleritis, and Eales' disease [34].

Miliary tuberculosis (TB) is the hematogenous spread of the tubercle bacilli. The lesions are yellowish granulomas with a diameter of 1-2 mm, which form millet seeds. Clinical manifestations are nonspecific and vary, depending on the primary site involved. Fever, night sweats, anorexia, weakness, and significant weight loss can be found as the main symptoms in cases of miliary TB [6; 33]. The *Mycobacterium tuberculosis* nucleic acid amplification test is available as a first-line diagnostic test. This test is progressively replacing microscopic smear examination because it can quickly confirm all types of TB with high specificity and sensitivity. These assays are Xpert MTB/RIF and Xpert MTB/RIF Ultra assay (Ultra), which detect TB and resistance to Rifampicin in less than 2 hours [6]. WHO recommends using Xpert MTB/RIF worldwide as a first-line TB diagnostic test in children and adults with signs or symptoms of active TB and individuals with HIV infection who are suspected of having TB [32]?

Table 6 Frequency Distribution of Clinical Diagnosis

Clinical Diagnosis	Frequency	Percentage (%)
Malignancy	12	17
Not Malignancy	55	77.4
No Clinical Diagnosis (N/A)	4	5.6
Total	71	100

N/A: Not Available (No Data)

Clinical diagnosis indicating malignancy was 17%, not malignancy as much as 77.4%, and 5.6% had no clinical diagnosis. TB is a "great imitator" that can resemble malignancy in clinical symptoms and investigations with imaging methods [5].

Table 7 Description of Clinical Diagnosis

Description of Clinical Diagnosis	Frequency	Percentage (%)
Axillary Lymphadenopathy	13	18.3
Tuberculous Lymphadenitis	4	5.6
N/A	4	5.6
Lymphoma	3	4.2
Ovarian Carcinoma	2	2.8
Lung Carcinoma	2	2.8
Neck Lymphadenitis	2	2.8
Supraclavicular Lymphadenopathy	2	2.8
Glandular Tuberculosis	2	2.8
Left Neck Tumor	2	2.8
Axillary Abscess Spondylitis	2	2.8
Tuberculosis abscess	1	1.4
Appendicitis	1	1.4
Duodenal Carcinoma	1	1.4
Lung Metastatic Carcinoma	1	1.4
Lung Metastatic Nasopharyngeal Carcinoma	1	1.4
Ulcerative Colitis	1	1.4
Complex Anal Fistula	1	1.4
Tuberculous Gonitis	1	1.4
Ovarian Cyst	1	1.4
Axillary Lymphadenitis	1	1.4
Neck Lymphadenitis and Axillary Lymphadenitis	1	1.4
Axillary Lymphadenopathy	1	1.4
Cutaneous Lymphadenopathy and Tumors	1	1.4
Tuberculous Lymphadenopathy	1	1.4
Malignant Lymphoma	1	1.4
Low-Grade Lymphoma	1	1.4
Lung Mass	1	1.4
Meningioma	1	1.4
Meningitis TB	1	1.4
Multiple Limfadenopati Colli	1	1.4
Axillary Abscess	1	1.4
Spontaneous Pneumothorax	1	1.4
Nontoxic Nodosa Struma	1	1.4
Ankle Tuberculosis	1	1.4

Intestinal Tuberculosis	1	1.4
Timoma	1	1.4
Pulmonary Tuberculosis	1	1.4
Sigmoid Epiploica Appendix Tumor	1	1.4
Axillary Tumor	1	1.4
Dextra Neck Tumor	1	1.4
Ulnar Nerve Area Tumor	1	1.4
Gene Tumor	1	1.4
Parotid Tumor	1	1.4
Total	71	100

N/A: Not Available (No Data)

Based on the description of the clinical diagnosis in table 8, the clinical diagnosis of extrapulmonary TB, similar to malignancy, most closely resembles lymphoma. KGB enlargement (lymphadenopathy), significant weight loss, fever, and respiratory symptoms are clinical symptoms that can be found in TB and lymphoma [38]. Imaging features such as plain chest radiographs, contrast-enhanced computed tomography (CT) scans, and Positron Emission Tomography/Computed Tomography Fluorodeoxyglucose (F-18 FDG PET) is a modality used for cancer patients can give TB a picture resembling malignancy [5; 9; 39]. There is also a clinical diagnosis in patients diagnosed with nasopharyngeal carcinoma with clinical manifestations suspected of metastasizing to the lungs, but after histopathological examination, the result is pulmonary TB.

Microscopic Examination of Acid Resistant Stems (BTA). Examination of Acid Resistant Stem (BTA) requires sputum or tissue biopsy specimens. Traditional methods using Ziehl-Neelsen or Kinyoun Gabbet stains will produce microscopic images of red stems against a bluish background. Individuals with signs or symptoms of pulmonary TB should collect sputum three times in the morning, or sputum can be collected at any time in the morning [33]. Mycobacterium culture using the Mycobacterium Growth Indicator Tube (MGIT) recommended by WHO as a culture standard [2]. Egg- or agar-based media such as Lowenstein-Jensen can also be used as culture; *Mycobacterium tuberculosis* grows slowly and requires 4-8 weeks on these conventional culture media [37; 40].

Chest X-ray is one of the most widely used tests for pulmonary TB. Manifestations of chest X-rays of pulmonary TB depend on the stage of infection. During primary TB, granuloma formation may lead to persistent focal scarring or parenchymal nodules (Ghon focus). The classic chest radiograph in TB is an upper lobe abnormality of the lung with infiltrates and cavities. The best X-ray positions are anteroposterior (AP), lateral, and apex. Chest X-rays are generally used to evaluate pulmonary TB [2; 16]. Computed Tomography (CT) is used to clarify questionable chest X-rays findings and diagnose extrapulmonary TB, such as Pott's disease. MRI is useful in the diagnosis of intracranial TB.

Positron emission tomography (PET) combined with CT can detect subclinical diseases that may develop into TB that spreads throughout the body in HIV-infected individuals [2; 12; 16]. The skin test with tuberculin is the most widely used in screening for latent TB. This test can measure the response to antigen stimulation by T cells in the skin. IFN-γ Release Assays (IGRA) is a test that can measure the response of circulating memory T cells in reservoir parts in the spleen, bone marrow, and lymph nodes to bacilli antigens. IGRA is reported to be more specific than the tuberculin test in diagnosing latent TB but cannot differentiate between active and latent TB [2].

Tuberculosis (TB) is called the "Great Imitator," so it is important to do a histopathological examination to avoid mistakes in diagnosis [14]. Pulmonary TB and extrapulmonary TB that have clinical or imaging features that suggest a malignancy in the lungs or extrapulmonary organs can be examined by histopathology. Positron Emission Tomography/Computed Tomography Fluorodeoxyglucose (F-18 FDG PET) imaging results in tuberculosis give a picture similar to pulmonary and extrapulmonary malignancies [15; 16].

The choice of diagnostic procedure depends on the organs involved in extrapulmonary TB. Various methods can be used to collect small, medium, or large tissue samples, including needle biopsy, excision, endoscopy, laparoscopy, ultrasound, and ultrasound/CT-guided biopsy [2]. The characteristic feature of TB on histopathological examination is a central

granular caseation surrounded by giant, multinucleated epithelioid cells. However, TB granulomas may not show central caseation [1; 28].

Table 8 Frequency Distribution of Histopathological Diagnoses

Histopathological Diagnosis	Frequency	Percentage (%)
Tuberculous Lymphadenitis	43	60.6
Bone and Joint Tuberculosis	7	9.9
Pulmonary Tuberculosis	6	8.5
Soft Tissue Tuberculosis	4	5.6
Genitourinary Tuberculosis	4	5.6
Gastrointestinal & Peritoneal Tuberculosis	4	5.6
Tuberculosis Cutis	2	2.8
Central Nervous System Tuberculosis	1	1.4
Total	71	100

Histopathological diagnosis of pulmonary TB and extrapulmonary TB at the MRCCC Siloam Semanggi Cancer Hospital in 2018-2020 found TB lymphadenitis the most case of extrapulmonary TB, followed by pulmonary TB as the 2nd most common. This result differs from data from the World Health Organization (WHO), which states that Indonesia is included in the world's top 10 most pulmonary TB [1]. Examination for pulmonary TB is recommended to use nucleic acid amplification such as Xpert MTB/RIF or Ziehl Neelsen/Kinyoun Gabbet Acid Resistant Basil (BTA) staining so that a histopathological examination is rarely an option for pulmonary TB examination except in certain cases which show imaging results or clinical signs of pulmonary tuberculosis resembling lung cancer [27].

Table 9 Description of Histopathological Diagnosis

Description of Histopathological Diagnosis	Frequency	Percentage (%)
Tuberculous Lymphadenitis	43	60.6
Pulmonary Tuberculosis	6	8.5
Soft Tissue Tuberculosis	3	4.2
Tuberculous Spondylitis	2	2.8
Tuberculosis Cutis	2	2.8
Tuberculous Gonitis	2	2.8
Tuberculous salpingitis	2	2.8
Tuberculous Osteomyelitis	1	1.4
Tuberculosis Inflammation	1	1.4
Tuberculous Colitis	1	1.4
Tuberculous Cervicitis, Tuberculous Endometritis	1	1.4
Anal tuberculosis	1	1.4
Thoracic Wall Tuberculosis	1	1.4
Soft Tissue Tuberculosis	1	1.4
Omental Tuberculosis	1	1.4
Pelvic Tuberculosis	1	1.4

Peritoneal Tuberculosis	1	1.4
Cerebral Tuberculosis	1	1.4
Total	71	100

This study has the same results as the study of Singh G et al., who found that 18% of the incidence of extrapulmonary TB at Cipto Mangunkusumo Hospital was tuberculous lymphadenitis [19]. Extrapulmonary TB is more often carried out by histopathological examination by sampling methods with various biopsy methods [6].

The stages of TB treatment consist of the initial stage, which is given every day for two months to eradicate germs. Generally, transmission begins to decrease during the first two weeks of treatment. The advanced stage is carried out to kill the remaining germs with a treatment duration of 4 months [6; 32]. In the early stages, the treatment uses Rifampicin (R), Isoniazid (H), Pyrazinamide (Z), and Ethambutol (E). Then in the advanced stage, given the drug Isoniazid and Rifampicin for four months. The initial and advanced regimens are also referred to as 2RHZE/4RH by WHO.

4. Conclusion

The number of patients diagnosed histopathologically with pulmonary tuberculosis, and extrapulmonary tuberculosis was the highest in 2019 and decreased during the COVID-19 pandemic compared to before the pandemic. Of the 71 study samples, the largest age group diagnosed with histopathologically pulmonary tuberculosis and extrapulmonary tuberculosis was the productive age, namely the age group of 21-30 years. Women are the largest population diagnosed histopathologically with pulmonary tuberculosis and extrapulmonary tuberculosis.

The location of the most extrapulmonary organs diagnosed histopathologically with tuberculosis is the lymph nodes. Most initial clinical diagnoses in tuberculosis cases are not included in malignancy. The initial clinical diagnosis, which includes the most common malignancy, is Lymphoma. The most common histopathological diagnosis in tuberculosis cases is tuberculous lymphadenitis and extrapulmonary tuberculosis.

Compliance with ethical standards

Disclosure of conflict of interest

The authors (Marliana Nurprilinda, Fajar Lamhot Gultom, Kurniyanto and Praisela Syania H Nelwan) declare no conflict of interest.

Statement of informed consent

All necessary information provided and voluntarily signed consent form.

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