

DIFFERENCES IN CLINICAL AND LABORATORY PRESENTATIONS IN PEDIATRIC TUBERCULOSIS PATIENTS WITH AND WITHOUT HIV CO-INFECTION**Iffa Muthiah¹, Syandrez Prima Putra², Rinang Mariko³**¹Medicine, Faculty of Medicine, Andalas University, Padang, Indonesia²Department of Microbiology, Faculty of Medicine, Andalas University, Padang, Indonesia³Department of Pediatrics Faculty of Medicine Andalas University Padang, IndonesiaE-mail: iffamuthiah2001@gmail.com**INFO ARTIKEL****Riwayat Artikel:**

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Co-Infection**DOI:** <https://doi.org/10.62335>**ABSTRACT**

Tuberculosis (TB) remains one of the top 10 causes of death in children worldwide, particularly among those with HIV coinfection. This study aimed to determine differences in clinical and laboratory presentations between pediatric TB patients with and without HIV coinfection at Dr. M. Djamil Padang General Hospital. This cross-sectional observational study used secondary data from pediatric TB patients treated between 2017 and 2021. Clinical presentations (cough, fever, decreased appetite, weight loss, malnutrition, lymphadenopathy, dyspnea, oral candidiasis, diarrhea, and extrapulmonary TB) and laboratory parameters (hemoglobin, leukocyte count, platelet count, and differential leukocyte count) were analyzed. Among 106 patients, 20 (18.86%) had HIV coinfection. The most common clinical presentations were cough (93.4%), fever (86.6%), and malnutrition (74.5%). Anemia was found in 70.8% of patients. Significant differences in HIV-coinfected children included oral candidiasis (60%; $p<0.001$), lymphadenopathy (40%; $p=0.006$), diarrhea (45%; $p<0.001$), weight loss (75%; $p=0.001$), and anemia (95%; $p=0.018$). These findings suggest that clinical and laboratory presentations can help screen for HIV coinfection among pediatric TB patients in healthcare settings.

ABSTRAK

Tuberkulosis (TB) masih menjadi salah satu dari 10 penyebab utama kematian pada anak di seluruh dunia, terutama pada anak dengan koinfeksi HIV. Penelitian ini bertujuan mengetahui perbedaan gambaran klinis dan laboratorium pasien TB anak dengan dan tanpa koinfeksi HIV di RSUP Dr. M. Djamil Padang. Penelitian observasional dengan pendekatan potong lintang ini menggunakan data sekunder pasien TB anak periode 2017–2021. Variabel klinis meliputi batuk, demam, penurunan nafsu makan, penurunan berat badan, malnutrisi, pembesaran kelenjar getah bening, sesak napas, kandidiasis oral, diare, dan TB ekstraparu. Parameter laboratorium meliputi hemoglobin, jumlah leukosit, trombosit, dan hitung jenis leukosit. Dari 106 pasien, sebanyak 20 (18,86%) mengalami koinfeksi HIV. Gambaran klinis terbanyak adalah batuk (93,4%), demam (86,6%), dan malnutrisi (74,5%). Anemia ditemukan pada 70,8% pasien. Perbedaan bermakna pada pasien dengan koinfeksi HIV ditemukan pada kandidiasis oral (60%; $p < 0,001$), pembesaran kelenjar getah bening (40%; $p = 0,006$), diare (45%; $p < 0,001$), penurunan berat badan (75%; $p = 0,001$), dan anemia (95%; $p = 0,018$). Gambaran klinis dan laboratorium tersebut dapat membantu skrining koinfeksi HIV pada pasien TB anak di fasilitas pelayanan Kesehatan.

INTRODUCTION

Tuberculosis (TB) is one of the 10 leading causes of death in children worldwide. Based on WHO data, TB causes 1.5 million deaths annually, and 230,000 of these deaths occur in children worldwide. (Sibuea et al., 2022) The highest mortality rate is found in children <5 years old and is strongly influenced by malnutrition. (UNICEF Indonesia, 2023) Deaths due to TB in Indonesia in 2021 are estimated to be around 144,000 or 52 per 100,000 population. Cases of TB in children and adolescents are often overlooked by health workers due to the difficulty in confirming the diagnosis, making it difficult to treat immediately. (World Health Organization, 2022) Although there are effective treatments available, there are still major challenges in diagnosing and treating TB. (Jaganath et al., 2022)

TB is still the leading cause of death after Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS).⁴ Based on WHO data, TB-HIV deaths amounted to 6,500 or 2.4 per 100,000 population. (Sulistyo & Kalinda, 2023) Of global TB deaths, 14% were children (<15 years) without HIV co-infection and 11% with HIV co-infection. (World Health Organization, 2022b) Co-infection of TB and HIV is a disease combination with a high mortality rate. HIV-infected individuals are more likely to suffer from opportunistic infections (IOs) during the disease. TB is one of the most

common IOs in people with HIV and may predate the onset of AIDS, but the two are often diagnosed together. People with HIV are 30 times more likely to be infected with TB than people without HIV. (Dafitri et al., 2020) HIV-infected children with significant immune decline are at 5 times higher risk of developing TB than children with milder immune decline. (Wijaya et al., 2021)

TB symptoms in children are divided into 2 categories, namely systemic/general complaints and complaints related to specific organs. Systemic complaints include malaise/fatigue, inactivity in play, fever, excessive night sweats, weight loss, and cough. (Asik et al., 2016) Typical TB symptoms often appear in individuals with HIV in the early stages, but those with advanced stages or severe immunocompromise show clinical symptoms that are not typical and vary, as a result, TB testing is often done late and may give negative results. Decreased immunity in HIV patients causes TB symptoms and clinical signs to be nonspecific, delaying TB diagnosis. (Wesmana & Putra, 2016) Although these symptoms are often considered atypical because they can occur in other diseases, TB has a special characteristic of being persistent for >2 weeks, even after receiving adequate therapy such as antibiotics or adequate nutrition to overcome weight problems. Clinical assessment of TB patients is very important for diagnosis so that when similar symptoms are found, patient treatment can be carried out more quickly.

If a person contracts TB, the body will experience an inflammatory process that can cause manifestations in the number of leukocytes. (Pratiwi et al., 2019) In TB patients before treatment there is an increase in the number of leukocytes which indicates the formation of many leukocytes to attack bacteria during the phagocytosis process. (Ainu'rohman et al., 2020) Previous studies have shown that TB-HIV patients have lower leukocyte counts than non-HIV patients. (Hanif et al., 2020) TB patients usually have high platelet counts associated with the severity of TB. (Kirwan et al., 2021) Although anemia is the most common complication of TB and HIV infection, other hematologic disorders are often reported, such as thrombocytosis. In advanced stages of HIV with high viremia, neutropenia may occur due to inadequate cell production resulting from bone marrow suppression by HIV infection. (Abay et al., 2018)

So far, there are not many studies that explain the differences in clinical appearance and laboratory counts in pediatric TB with and without HIV co-infection. Dr. M. Djamil Hospital Padang is a referral center for pediatric TB patients, both with and without HIV co-infection, in West Sumatra and surrounding areas. Therefore, researchers are interested in examining the differences in the clinical and laboratory appearance of TB patients in children with and without HIV co-infection at Dr. M. Djamil Hospital Padang.

METHODS

This type of research is observational with a cross-sectional design approach to analyze differences in clinical appearance and leukocyte counts between pediatric TB patients with and without HIV co-infection at Dr. M. Djamil Padang Hospital from

January 1, 2017-31 December 2021. The population of this study was all pediatric TB patients aged 0-18 years based on medical record data at Dr. M. Djamil Padang Hospital from January 1, 2017-December 31, 2021. The number of samples taken was all pediatric TB patients aged 0-18 years based on medical record data that met the inclusion criteria and exclusion criteria. The sample size of this study was calculated using a consecutive sampling technique. Based on the calculations made, a minimum sample size of 105 samples was obtained. Bivariate analysis was conducted to analyze the characteristics of the two groups to see whether there was a difference between clinical appearance and leukocyte count (dependent variable) between pediatric TB patients with and without HIV co-infection (independent variable). The type of statistical test in this study used the chi-square test for categorical data. The conclusion of the test is if the p-value is $p < 0.05$, then there is a significant difference between the variables studied.

RESULTS AND DISCUSSION

Clinical Features and Differences of Pediatric TB Patients with and Without HIV Co-infection

This study found pediatric TB patients with and without HIV co-infection in 2017-2021 who met the criteria as many as $n = 106$ people consisting of 20 pediatric TB patients with HIV co-infection and 86 pediatric TB patients without HIV co-infection. Bivariate analysis of differences in clinical appearance included cough, fever, decreased appetite, weight loss/weight gain, malnutrition, enlarged lymph node, shortness of breath, oral candidiasis, diarrhea, and extra-pulmonary TB as presented in Table 1.

Table 1. Differences in Clinical Appearance of Pediatric TB Patients with and Without HIV Co-infection

Clinical Appearance	Pediatric TB		Total	p-value
	With HIV co-infection	Without HIV co-infection	f (%)	
	f (%)	f (%)	n=106	
	n=20	n=86		
Cough	18 (90,0)	81 (94,2)	99 (93,4)	0,614
Fever	19 (95,0)	73 (84,9)	92 (86,8)	0,461
Decreased Appetite	12 (60,0)	36 (41,9)	48 (45,3)	0,223
Weight loss	15 (75,0)	28 (32,6)	43 (40,6)	0,001*
Malnutrition	13 (65,0)	66 (76,7)	79 (74,5)	0,423

Lymph node enlargement	8 (40,0)	10 (11,6)	18 (17,0)	0,006*
Shortness of breath	5 (25,0)	32 (37,2)	37 (34,9)	0,440
Oral Candidiasis	12 (60,0)	1 (1,2)	13 (12,3)	< 0,001*
Diarrhea	9 (45,0)	6 (7,0)	15 (14,2)	< 0,001*
Extra Pulmonary TB	5 (25,0)	29 (33,7)	34 (32,1)	0,626

Table 1 shows that the most common clinical features experienced by pediatric TB patients with and without HIV co-infection were cough 94.3%, fever 86.8%, and malnutrition 74.5%. Whereas in pediatric TB patients with HIV co-infection, the most common clinical appearances were weight loss 75.0%, malnutrition 65.0%, decreased appetite 60.0%, and oral candidiasis 60.0%. Based on the data in the table, the clinical appearance that shows a significant difference after being tested using the chi-square test is weight loss with a p-value = 0.001; Lymph node enlargement obtained a p-value = 0.006; oral candidiasis obtained p value = <0.001; and diarrhea with a p-value = <0.001.

Laboratory Features and Differences of Pediatric TB Patients with and Without HIV Co-infection

Table 2. Laboratory Differences in Pediatric TB Patients with and Without HIV Co-infection

Laboratory Result	Pediatric TB		Total f (%) n=106	p-value
	With HIV co- infection	Without HIV co-infection		
	f (%)	f (%)		
	n=20	n=86		

Hb (g/dL)

Anemia	19 (95,0)	56 (65,1)	75 (70,8)	0,018*
Tidak Anemia	1 (5,0)	30 (34,9)	31 (29,2)	

Leukocyte (mm3)

Leukopenia	7 (35,0)	2 (2,3)	9 (8,5)	< 0,001*
Normal	9 (45,0)	41 (47,7)	50 (47,2)	
Leukocytosis	4 (20,0)	43 (50,0)	47 (44,3)	
Thrombocyte (mm3)				
Thrombocytopenia	2 (10,0)	5 (5,8)	7 (6,6)	0,607
Normal	13 (65,0)	51 (59,3)	64 (60,4)	
Thrombocytosis	5 (25,0)	30 (34,9)	35 (33,0)	

Table 2 shows that anemia was mostly found in TB patients with and without co-infection 70.8%, but more experienced by pediatric TB patients with HIV co-infection and obtained a p-value = 0.018. Leukocyte counts in most of the two groups were found to be normal, but the distribution of leukopenia was found more in pediatric TB patients with HIV co-infection 35.0% and leukocytosis was found more in pediatric TB patients without HIV co-infection 50.0% which showed a significant difference with a p-value = <0.001 based on the chi-square test. Platelet counts in most of the two groups were also found to be normal, with more thrombocytopenia found in pediatric TB patients with HIV co-infection 10.0% and more thrombocytosis found in pediatric TB patients without HIV co-infection (34.9) which did not show a statistically significant difference based on the chi-square test.

Table 3. Laboratory Differences in Leukocyte Counts of Pediatric TB Patients with and Without HIV Co-infection

Laboratory Result	Pediatric TB		Total	p-value
WBC Count (%)	With HIV co- infection f (%) n=20	Without HIV co-infection f (%) n=86	f (%) n=106	
Basophil				
Low	0 (0)	0 (0)		-
Normal	20 (100,0)	86 (100,0)	106 (100,0)	
High	0 (0)	0 (0)		
Eosinophil				
Low	11 (55,0)	37 (43,0)	48 (45,3)	0,156
Normal	3 (15,0)	32 (37,2)	35 (33,0)	
High	6 (30,0)	17 (19,8)	23 (21,7)	
Rod Neutrophil				
Low	7 (35,0)	51 (59,3)	58 (54,7)	0,010*
Normal	13 (65,0)	26 (30,2)	39 (36,8)	
High	0 (0)	9 (10,5)	9 (8,5)	
Segment Neutrophil				
Low	0 (0)	3 (3,5)	3 (2,8)	0,392
Normal	13 (65,5)	43 (50,0)	56 (52,8)	

High	7 (35,0)	40 (46,5)	47 (44,3)	
Lymphocyte				
Low	8 (40,0)	30 (34,9)	38 (35,8)	0,911
Normal	8 (40,0)	37 (43,0)	45 (42,5)	
High	4 (20,0)	19 (22,1)	23 (21,7)	
Monocyte				
Low	3 (15,0)	23 (26,7)	26 (24,5)	0,345
Normal	13 (65,0)	54 (62,8)	67 (63,2)	
High	4 (20,0)	9 (10,5)	13 (12,3)	

Table 3 shows that the number of low rod neutrophils is more experienced by pediatric TB patients without HIV co-infection at 59.3%, while in pediatric TB with HIV co-infection more rod neutrophils are found in a normal state of 65.0%, with a p-value = 0.010 based on the chi-square test which indicates a significant difference. Based on the chi-square test there is no significant difference in the number of eosinophils, segment neutrophils, lymphocytes, and monocytes in pediatric TB patients with and without HIV co-infection, while in the number of basophils, because all pediatric TB patients with and without HIV co-infection have normal numbers, it cannot be tested using chi-square.

Overview and Differences in Clinical Appearance of Pediatric TB Patients with and without HIV Co-Infection

This study found that the most common clinical appearance found in pediatric TB with and without HIV co-infection was cough (93.4%), based on the chi-square test there was no significant difference between the two groups (p-value = 0.614). This is by research conducted by Agatha et al. on pediatric TB patients without HIV co-infection which found that cough (71.8%) was the most common of all samples. (Ginting et al., 2022) This study is also in line with research conducted by Widyaningsih et al. on pediatric TB patients with HIV co-infection found that the most common clinical appearance was cough (96.2%) of all samples. (Widyaningsih et al., 2011) Based on these findings, cough is the most dominant sign in children with or without HIV co-infection. This is due to Mtb bacteria that irritate the bronchi so coughing is a pulmonary mechanism for self-defense and clearing foreign bodies in the respiratory tract. Initially, a dry cough then becomes a productive cough that produces sputum after inflammation

or can become a cough of blood that occurs due to rupture of blood vessels. (Armika, 2020)

Fever was also among the most common clinical appearances found in pediatric TB with and without HIV co-infection (86.8%), there was no significant difference between the two groups (p -value = 0.461). This is in line with the literature review conducted by Yogi which found that the most common primary symptoms in pediatric tuberculosis are cough and fever ≥ 2 weeks with a fever that is usually not high. (Pratama, 2021) The results of this study are also in line with research conducted by Hardini et al. who found that all samples of pediatric tuberculosis experienced a clinical appearance of fever (100%). (Intan et al., 2008) Research conducted by Widyaningsih et al. also found that all samples of pediatric tuberculosis with HIV co-infection experienced a long fever. (Widyaningsih et al., 2011) The fever experienced is usually not high and often disappears so that the child never seems to recover from the fever. (Armika, 2020) This suggests that the presence or absence of HIV co-infection is not associated with the clinical appearance of fever.

This study found undernutrition in the majority of pediatric TB patients with and without HIV co-infection (74.5%), and there was no significant difference between the appearance of nutritional status in the two groups. Based on these findings, it can be observed that HIV co-infection is not associated with the appearance of nutritional status in children with TB. In line with a study conducted by Widyaningsih et al. on pediatric TB patients with HIV co-infection and obtained poor and poor nutrition (92.5%). (Widyaningsih et al., 2011) In a study by Nurwitasari et al. obtained the results of children with poor nutritional status in pediatric TB patients without HIV co-infection as much as 79.2% which showed a relationship between nutritional status and the incidence of childhood TB. (Nurwitasari & Wahyuni, 2015) Poor nutritional status can reduce the immune system, increasing the risk of children being infected with TB. In addition to being a risk factor, TB also affects nutritional status because being infected with TB will interfere with the absorption of nutrients in the body. (Rita et al., 2020)

Lymph node enlargement was found more in children with TB with HIV co-infection than without HIV co-infection (40% vs 11.6%) which showed a significant difference between the two groups with p -value = 0.006. These results are in line with the research conducted by Hardini et al. in pediatric tuberculosis without HIV co-infection where 10% of children experienced lymph node enlargement. (Intan et al., 2008) In line with research conducted by Nastiti et al. in pediatric tuberculosis with HIV co-infection, 45.8% of samples experienced lymph node enlargement. (Kaswandani et al., 2021) Lymph node enlargement was found to be more dominant in children with HIV co-infection, possibly due to other opportunistic infections. Lymph node in TB infection is more commonly found in the Colli region.

This study found that shortness of breath was experienced by a small proportion of TB children with and without HIV co-infection (34.9%). In line with the results of research conducted by Hardini et al. get shortness of breath (24%), because shortness of

breath does not often occur except in severe and acute conditions such as miliary tuberculosis and pleural effusion. (Intan et al., 2008)

In this study, oral candidiasis was found to be more common in pediatric TB with HIV co-infection than without HIV co-infection (60% vs 1.2%), with p-value = <0.001 indicating a significant difference between the two groups. These results are in line with research conducted by Radithia et al. stating that TB patients rarely find oral lesions and reported incidence rates <0.5-1% of all TB patients. (Radithia et al., 2020) Oral candidiasis is one of the main opportunistic infections that often occur in 50-90% of HIV patients. The presence of oral candidiasis is an indicator that the CD4+ cell count in HIV patients has dropped below 200 cells/mm³ and poor nutrition is also associated with an increased incidence of oral candidiasis. (Sipayung, 2022)

In this study, diarrhea was found more in children with TB with HIV co-infection than without HIV co-infection (45% vs 7%), with p-value = <0.001 indicating a significant difference between the two groups. In line with research conducted by Widyaningsih et al. on pediatric tuberculosis with HIV co-infection, diarrhea was 96.3%. In line with research conducted by Mahayani et al., it was found that 44.9% of HIV children suffered from diarrhea, this could occur because diarrhea is one of the opportunistic infections that are often found in children suffering from HIV / AIDS. The cause of diarrhea in children with HIV is due to the disruption of immune function so children will be more susceptible to infection by bacteria, viruses, protozoa, fungi, and worms. (Mahayani et al., 2013)

The clinical appearance of extra-pulmonary TB was found in only 32.1% of all pediatric TB samples with and without HIV co-infection. As the disease progresses, TB can spread to other organs through the circulatory or lymphatic system or even through blood transfusions. About 80% of TB-causing germs invade the lungs and only a small proportion invade organs other than the lungs, usually more common in groups with weakened immune systems. (Suhariani & Wibisono, 2015)

Laboratory Differences in Pediatric TB Patients with and Without HIV Co-infection

This study found that the most common laboratory in children with and without HIV co-infection was anemia (70.8%), whereas anemia cases were significantly more common in children with TB with HIV co-infection (95.0% vs 65.1%, p-value = 0.018). These results are in line with research conducted by Abay et al. found more anemic patients with TB with HIV co-infection than TB without HIV co-infection (60% vs 46%). This can be caused by the effects of proinflammatory cytokines such as IL-6 and TNF- α , which can reduce erythropoietin production, suppress the bone marrow response to erythropoietin, and affect iron metabolism which results in the process of red blood cell formation (erythropoiesis) can be disrupted. (Abay et al., 2018) This finding is different from the research of Hanif et al., which found the number of anemic patients in TB without HIV co-infection (59.1%) more than TB with HIV co-infection (40.9%). (Hanif et al., 2020)

In addition to hemoglobin, significant differences were observed in leukocyte cell counts. In the pediatric TB group with HIV co-infection, there were more cases of leukopenia than without HIV co-infection (35.0% vs 2.3%, p -value = <0.001). This result is directly proportional to the study of Hanif et al. where leukopenia was more common in TB with HIV co-infection (100% vs 0%). (Hanif et al., 2020) The same thing was also found in the study of Abay et al. leukopenia was more dominant in TB cases with HIV co-infection (14% vs 6%). Leukopenia is usually associated with disease progression in HIV patients. This may occur due to decreased production of granulocyte progenitor cells in the bone marrow of HIV-infected patients. (Abay et al., 2018) Leukopenia is often associated with disease progression in HIV-infected patients. An absolute decrease in the number of CD4+ T lymphocytes occurs as one of the earliest immunologic disorders in HIV infection and is an important indicator of the risk of developing opportunistic infections. (Hanif et al., 2020) From the results of leukocyte counts, leukocytosis was more common in pediatric TB cases without HIV co-infection (50% vs 20%, p -value <0.001). This reflects the patient's systemic response to ongoing inflammation.

Based on platelet counts, there was no significant difference between the groups of pediatric TB with and without HIV co-infection, and platelet counts in both groups were mostly normal. However, in terms of percentage, thrombocytopenia was more common in children with HIV co-infection (10.0% vs 5.8%) and thrombocytosis was more common in children without HIV co-infection (34.9% vs 25.0%). Similar results were also obtained in Lasut et al.'s study, where the percentage of normal platelets from 67 TB patients was (74.62%), followed by thrombocytosis (19.40%) and thrombocytopenia (5.97%). (Lasut et al., 2016) The results of the study are also in line with research conducted by Abay et al. which shows that thrombocytopenia is more common in TB with HIV co-infection. (Abay et al., 2018) In contrast to the research of Hanif et al. who found that thrombocytopenia was more common in TB without HIV co-infection. (Hanif et al., 2020) In some cases of infection, reactive thrombocytosis often occurs with an increase in thrombotic factors such as IL-6 released by inflamed cells in response to inflammation. (Lasut et al., 2016)

Based on the results of leukocyte counts in general, there were no significant differences between pediatric TB patients with and without HIV co-infection, except for the number of rod neutrophils. Rod neutrophils in pediatric TB without HIV co-infection decreased more than in pediatric TB with HIV co-infection (59.3 vs 35.0%, p -value = 0.010). Meanwhile, to the best of the researchers' knowledge, no study explicitly examines the difference in the number of rod and segment neutrophils in pediatric TB patients with and without HIV co-infection. However, Abay et al. found that neutropenia was more prevalent in HIV co-infected TB. Neutropenia can be caused by a combination of the effects of hypersplenism and granulopoiesis failure by the bone marrow under the influence of various cytokines and malnutrition. (Abay et al., 2018).

CONCLUSION

This study found significant differences in clinical and laboratory presentations between pediatric tuberculosis (TB) patients with and without HIV coinfection. Clinical manifestations significantly associated with HIV coinfection included weight loss, lymph node enlargement, oral candidiasis, and diarrhea. Laboratory findings showed significant differences in anemia, leukocyte counts, and band neutrophil counts, with anemia and leukopenia more frequently observed in children with HIV coinfection. However, no significant differences were found in platelet counts or most other differential leukocyte parameters. These findings indicate that specific clinical manifestations and hematological abnormalities may help identify HIV coinfection among pediatric TB patients. Therefore, healthcare providers should consider these clinical and laboratory findings as screening indicators to support early recognition and appropriate management of TB-HIV coinfection in children. Further studies with larger samples are needed to validate these findings and improve screening strategies in pediatric healthcare settings.

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