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# APGHN

Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Volume 3 / No. 3

August 2024



[www.apghn.com](http://www.apghn.com)



Published by  
Indonesian Society of Pediatric Gastroenterology, Hepatology, and Nutrition

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Original Article

# Correlation Between Tuberculosis Type and Comorbidities with Nutritional Recovery Rates Post-Tuberculosis Treatment in Pediatric Patients

Safira Amelia<sup>1</sup>, Nastiti Kaswandani<sup>2</sup>

<sup>1</sup>Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

<sup>2</sup>Respirology Division, Departement of Child Health, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia



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e-ISSN: 2830-5442

**Corresponding author:**

Safira Amelia  
safiramelia02@gmail.com

**Published:**

31<sup>st</sup> August 2024

**DOI:**

<https://doi.org/10.58427/apghn.3.3.2024.1-11>

**Citation:**

Amelia S, Kaswandani N. Correlation Between Tuberculosis Type and Comorbidities with Nutritional Recovery Rates Post-Tuberculosis Treatment in Pediatric Patients. *Arch Pediatr Gastr Hepatol Nutr.* 2024;3(3):1-11.

**Abstract:**

**Background:** Tuberculosis remains a significant cause of mortality in children. Nutritional status is one of the major risk factors for tuberculosis severity. This study investigated the factors influencing nutritional status in tuberculosis patients.

**Methods:** This is a retrospective, cross-sectional study conducted in the tertiary national-referral hospital in Jakarta, Indonesia. Data were obtained from electronic health records from 2012-2018. This study included patients aged 0-18 years-old who were diagnosed and treated with anti-tuberculosis drugs. Patients who did not complete the therapy for minimum 2 months were excluded.

**Results:** A total of 207 patients were included in this study. The type of tuberculosis was associated with the nutritional status of children after 2 months of treatment ( $p$  value = 0.014; 95% CI = 0.422 - 0.914). Children with extrapulmonary TB showed better improvement in nutritional status compared to those with pulmonary TB. Comorbidities were also associated with nutritional status ( $p$ -value = 0.020; CI95% = 1.063 - 2.382). Patient without comorbidities experience better nutritional status improvement than those with comorbidities.

**Conclusion:** The nutritional status of tuberculosis patients improved after the 2-months of treatment. The type of tuberculosis and the presence of comorbidities influence the outcomes of nutritional status during anti-tuberculosis treatment.

**Keywords:** children, comorbidities, nutritional status, tuberculosis, types

## Introduction

Tuberculosis infection or TB is a disease caused by *Mycobacterium tuberculosis* bacteria. Tuberculosis remained the world's second leading cause of death in 2022 with 7.5 million people were newly diagnosed with TB, and 12% were children.<sup>1</sup> Reduction in appetite, macro and micronutrient malabsorption, as well as altered metabolism were observed and contributed to wasting in tuberculosis patients. Furthermore, protein and micronutrient deficiency in malnutrition increased vulnerability to infection and potentially exacerbate the disease progression.<sup>2</sup> Previous study revealed that undernutrition increased the risk of tuberculosis severity and adverse treatment outcomes such as delayed recovery, relapse, and mortality.<sup>3</sup> Study in Malawi also showed that patients with moderate-severe malnutrition exhibited higher mortality during the first four weeks treatment, compared to patients with normal nutritional status and mild malnutrition.<sup>4</sup> However, study had also shown that effective treatment of TB improved the nutritional status and subsequently the outcome of patients with TB.<sup>5</sup>

Several factors have been revealed to contribute in the occurrence of tuberculosis and the result of treatment in patient with tuberculosis. Tuberculosis is closely associated with both communicable diseases (CDs) such as diabetes and noncommunicable diseases (NCDs), including HIV/AIDS.<sup>6</sup> Other comorbidities, such as malignancy, heart disease, inflammatory bowel disease, and sickle cell disease have also been observed to increase patients' susceptibility to TB by compromising the immune system.<sup>7</sup> Presence of comorbid conditions were also seen to impact the outcome of TB. Comorbidities such as HIV and diabetes were reported to independently affect the result of TB treatment.<sup>8</sup> Previous studies have also shown that co-infection with HIV caused lower daily intake, nutrient deficiencies, malnutrition, wasting, and severe disease in patient with TB<sup>6,9</sup>

Another factor that might contribute to tuberculosis and the treatment result is the type of tuberculosis. Studies show that extrapulmonary TB presents a higher mortality rate due to severe forms like miliary or disseminated TB and the higher HIV prevalence.<sup>10</sup> Additionally, study by Kumar et al. revealed that patient with extrapulmonary tuberculosis is associated with successful treatment of tuberculosis.<sup>11</sup> However, study on the success rate of tuberculosis treatment between types of tuberculosis and the relation with nutritional status is still scarce. Considering the potential relationship between nutritional status and factors influencing the success of tuberculosis therapy, this study aimed to examine the relationship between the level of improvement in nutritional status post-treatment with factors affecting the success of tuberculosis therapy in children, particularly on the type of tuberculosis and comorbid conditions.

## Methods

This is a retrospective, cross-sectional study conducted in the tertiary national-referral teaching hospital in Jakarta, Indonesia. This study was approved by The Ethics Committee, with the approval number: 0489/UN2.F1.D1/KBK/PDP.01/2018. All data were collected from electronic medical health record. Patient aged 0-18 years old, who were diagnosed and treated with anti-tuberculosis drugs in 2012-2018, were included in this study. Meanwhile, patient with incomplete record of body weight and height, and patient who did not complete the anti-tuberculosis therapy for minimum 2 months were excluded.

Operational definitions of this study were as followed. Pulmonary tuberculosis was defined tuberculosis infection affecting the lung parenchyma, excluding the pleural and lymph nodes of the lung hilum. Extrapulmonary tuberculosis was characterized by tuberculosis infection in organs other than the lungs, including pleura, meninges, pericardium, lymph nodes, bones, joints, skin, intestines, kidneys, and urinary tract. Comorbid conditions were diseases that accompanied the diagnosis of tuberculosis and limited to diseases that impaired the immune system (including HIV/AIDS), autoimmune diseases, heart, lung, liver, and kidney diseases, malignancies, and other conditions that could potentially compromise the patient's nutritional status. Furthermore, this study used weight-per-length for children aged < 2 years old and weight-per-height for children aged > 2 years old, as the indicator for growth and development. The indicators were plotted using WHO chart for children aged up to 5 years old and CDC curve chart for children above 5 years of age. Nutritional status was interpreted by calculating and plotting the percentage of ideal body weight (%IBW) according to the relevant WHO or CDC charts based on the patients' age. The percentage of ideal body weight was calculated using the formula: percentage actual body weight divided by percentage of ideal body weight. An improvement in nutritional status was defined as an increase of 5% or more, while a decrease or smaller increase was categorized as no improvement.

Statistical analysis were conducted using SPSS ver. 24. Chi square test was used to conduct the bivariate analysis, with  $p < 0.05$  considered as significant.

## Results

A total of 207 pediatric patients were included in this study. Participants were subsequently categorized into 2 different groups based on the type of tuberculosis and the presence of comorbidities. Based on the type of tuberculosis, 109 patients were diagnosed with pulmonary tuberculosis, while 98 were classified as having extrapulmonary tuberculosis. Among the extrapulmonary cases, lymphadenitis tuberculosis was the most common, followed by tuberculosis related to the central

nervous system (e.g., meningitis and meningoencephalitis) and skeletal tuberculosis (e.g., coxitis and spondylitis). Furthermore, 96 out of the 207 patients were found to have comorbidities alongside their tuberculosis diagnosis, with HIV, malignancies, and congenital heart disease being the most prevalent. The demographic characteristics of the study population are presented in **Table 1**.

The nutritional status of the all participants are illustrated in **Table 2** and **Table 3**. Overall, there is a declining trend in the number of patients with malnourished and undernourished nutritional status after 2 months of treatment. Similar trends were also observed regardless of tuberculosis type or the presence of comorbidities, as there was a consistent reduction in the number of malnourished and undernourished patients accompanied with an increase in the number of patients with normal nutritional status after two months of treatment in all groups. Based on the percentage of ideal body weight before and after 2 months of intensive antituberculosis therapy, the average increase in nutritional status after 2 months of treatment was 1.54% in the pulmonary TB group and 4.02% in the extrapulmonary TB group. Patients with extrapulmonary tuberculosis exhibited a 2.5-fold greater increase of %IBW compared to patients with pulmonary TB. Furthermore, the average increase in nutritional status after therapy in groups with or without comorbidities were 1.64% and 3.85%, respectively. Patients without any comorbidities showed a 2.3-fold greater improvement in nutritional status compared to patients with comorbidities.

**Table 4** exhibited the association between type of tuberculosis and presence of comorbidities with nutritional status after treatment. The analysis showed a significant difference in the proportion of patient with improved nutritional status between the two groups, with the p-value of 0.014 and 0.020, respectively.

## Discussion

The proportion of gender between tuberculosis patient in this study were nearly equal, with 55.1% of the patient were male and 44.9% were female. This aligns with previous studies, which revealed that the prevalence of pediatric tuberculosis was not significantly different between genders. Furthermore, our study reported higher prevalence of pediatric tuberculosis in children above 5 years old. This contrasts with earlier studies that reported a higher prevalence of TB in children under 5 years of age. However, a recent systematic review by Siddalingaiah et al. indicated that tuberculosis is more commonly reported in patients over 5 years of age.<sup>12</sup> This discrepancy could be attributed to the difficulty in obtaining sputum samples from young children, which may impede the diagnostic process in this age group. Moreover, young children often present with non-specific clinical and radiological findings, further complicating the diagnosis in this population.

**Table 1.** Characteristics of the Participants

| <b>Characteristics</b>                  | <b>Frequency (n (%))</b> |
|---|--------------------------|
| <b>Age (years)*</b>                     | 6.0 (0.3-18.0)           |
| < 5 years old                           | 83 (40.1)                |
| ≥ 5 years old                           | 124 (59.9)               |
| <b>Gender</b>                           |                          |
| Male                                    | 114 (55.1)               |
| Female                                  | 93 (44.9)                |
| <b>Tuberculosis</b>                     |                          |
| Pulmonary                               | 109 (52.7)               |
| Extrapulmonary                          | 98 (47.3)                |
| <b>Extrapulmonary Tuberculosis</b>      |                          |
| Lymphadenitis                           | 27 (27.6)                |
| Central Nervous System                  | 19 (19.4)                |
| Skeletal                                | 18 (18.7)                |
| Miliary                                 | 13 (13.3)                |
| Pleural                                 | 9 (9.2)                  |
| Abdominal                               | 7 (7.1)                  |
| Ocular                                  | 6 (6.1)                  |
| Cutaneous                               | 4 (4.1)                  |
| Pericarditis                            | 4 (4.1)                  |
| Laryngeal                               | 1 (1.0)                  |
| Orchitis                                | 1 (1.0)                  |
| <b>Comorbidities</b>                    |                          |
| Yes                                     | 111 (53.6)               |
| No                                      | 96 (46.4)                |
| <b>Types of Comorbidities</b>           |                          |
| HIV                                     | 21 (21.9)                |
| Malignancy                              | 13 (13,5)                |
| Heart disease                           | 13 (13,5)                |
| GERD                                    | 11 (11,5)                |
| Thalassemia                             | 10 (10,4)                |
| Epilepsy                                | 9 (9,4)                  |
| Autoimmune disease                      | 7 (7,3)                  |
| Kidney disease                          | 6 (6,3)                  |
| Mental retardation                      | 4 (4,2)                  |
| Developmental delay                     | 4 (4,2)                  |
| Cerebral Palsy                          | 4 (4,2)                  |
| Congenital Digestive Tract Malformation | 3 (3,1)                  |
| Anemia                                  | 2 (2,1)                  |
| Type 1 Diabetes Mellitus                | 1 (1,0)                  |
| Empyema                                 | 1 (1,0)                  |
| Bell's Palsy                            |                          |

**Table 2.** Nutritional Status Among Pediatric TB Patients Before and After Therapy

| Nutritional Status | Total Participant  |                   |
|--------------------|--------------------|-------------------|
|                    | Before Therapy (%) | After Therapy (%) |
| Malnutrition       | 22 (10.6)          | 16 (7.7)          |
| Underweight        | 72 (34.8)          | 57 (27.5)         |
| Normal             | 96 (46.4)          | 111 (53.6)        |
| Overweight         | 9 (4.3)            | 13 (4.8)          |
| Obese              | 8 (3.9)            | 10 (4.8)          |

**Table 3.** Nutritional Status Among Pediatric TB Patients Before and After Therapy Based on Types of TB and Presence of Comorbidities

| Nutritional Status | Types of Tuberculosis |           |                |           | Presence of Comorbidities |           |            |           |
|--------------------|-----------------------|-----------|----------------|-----------|---------------------------|-----------|------------|-----------|
|                    | Pulmonary             |           | Extrapulmonary |           | Yes                       |           | No         |           |
|                    | Before (%)            | After (%) | Before (%)     | After (%) | Before (%)                | After (%) | Before (%) | After (%) |
| Malnutrition       | 19 (17.4)             | 15 (13.8) | 3 (3.31)       | 1 (1.0)   | 9 (8.1)                   | 6 (5.4)   | 13 (13.5)  | 10 (10.4) |
| Underweight        | 37 (33.9)             | 28 (25.7) | 35 (35.7)      | 29 (29.6) | 43 (38.7)                 | 30 (27.0) | 33 (34.4)  | 27 (28.1) |
| Normal             | 56 (42.4)             | 58 (63.2) | 50 (51.0)      | 53 (54.1) | 50 (45.0)                 | 61 (55.0) | 43 (44.8)  | 51 (53.1) |
| Overweight         | 6 (5.5)               | 5 (4.6)   | 3 (3.1)        | 8 (8.2)   | 3 (2.7)                   | 8 (7.2)   | 5 (5.2)    | 5 (5.2)   |
| Obese              | 1 (0.9)               | 3 (2.8)   | 7 (7.1)        | 7 (7.1)   | 6 (5.4)                   | 6 (5.4)   | 2 (2.1)    | 3 (3.1)   |

**Table 4.** Association between Type of Tuberculosis and Presence of Comorbidities with Improvement in Nutritional Status

| Parameters                | Nutritional Status |              | RR (95% CI)           | p     |
|---------------------------|--------------------|--------------|-----------------------|-------|
|                           | Improved           | Not Improved |                       |       |
| Type of Tuberculosis      |                    |              | 0.621 (0.422 - 0.914) | 0.014 |
| Pulmonary                 | 29 (26.6)          | 80 (73.4)    |                       |       |
| Extrapulmonary            | 42 (42.9)          | 56 (57.1)    |                       |       |
| Presence of Comorbidities |                    |              |                       | 0.020 |
| Yes                       | 46 (41.4)          | 65 (58.6)    | 1.591 (1.063 - 2.382) |       |
| No                        | 25 (26.0)          | 71 (74.0)    |                       |       |

Malnutrition and tuberculosis form a vicious cycle. Malnutrition weakens the immune system and increases the risk of tuberculosis progression, while the inflammatory response in tuberculosis further worsens the nutritional status.<sup>13</sup> Tuberculosis patients often experience anabolic block caused by pro-inflammatory cytokines, which disrupts the use of amino acid for protein synthesis leading to malnutrition.<sup>14, 15</sup> However, studies have shown that the administration of anti-tuberculosis treatment in the first two months improved the nutritional status and can be regarded as a valuable indicator of treatment success, as this phase coincides with the most significant reduction of bacillary load. A study conducted in Vietnam reported that the majority of the weight gain occurs within the first 2 months of treatment.<sup>16</sup> Similarly, our study revealed an improvement of nutritional status in pediatric TB patients after 2 months of intensive treatment. The improvement was also seen across all groups, regardless of the tuberculosis types and existence of comorbidities.

This study found a significant association between nutritional status and both the tuberculosis type and presence of comorbidities. For the type of tuberculosis, extrapulmonary tuberculosis was 0.6 times more likely to experience nutritional status improvement compared to the pulmonary tuberculosis group (RR = 0.621, 95% CI: 0.422 – 0.914),  $p = 0.014$ . This finding is consistent with %IBW calculations, which demonstrated a higher increase of nutritional status in the extrapulmonary tuberculosis group compared to the pulmonary tuberculosis group after two months of treatment. This result aligns with the study by Laghari et al., which reported a higher treatment success rate in patients with extrapulmonary tuberculosis compared to those with pulmonary tuberculosis.<sup>17</sup>

Greater improvement in nutritional status among extrapulmonary TB patients in this study may be attributed to the high proportion of extrapulmonary TB cases located in the lymph nodes. In children, many cases of lymph node tuberculosis were the extension of primary TB infections from the apex of the lung or abdomen, with smaller bacterial populations.<sup>18, 19</sup> Primary infection of TB differs from secondary infection, which is commonly found in adults, as secondary TB occurs due to the endogenous reactivation from pre-existing lesions.<sup>19</sup> Thus, in this case, secondary resistance events triggering tuberculosis reactivation in pediatric TB patients is less likely. It is also important to note that the higher success rate in the extrapulmonary tuberculosis group could be influenced by the smaller proportion of subjects in this group (23.1%) compared to the pulmonary tuberculosis group (76.9%). In contrast, the lower improvement in nutritional status among pulmonary TB patients was thought to be due to the persistent cough. A study by Devrim et al. reported a significantly higher incidence of cough symptoms in the pulmonary TB group compared to the extrapulmonary TB group (81.5% versus 36.0%;  $p < 0.05$ ).<sup>20</sup> This

persistent cough can interfere with food intake, making it one of the obstacles to improving nutritional status.

For the presence of comorbidities, children with tuberculosis without comorbidities have a 1,6 times greater chance of experiencing improvement of nutritional status during treatment compared to the group of children with tuberculosis and comorbidities (RR = 1,591; 95% CI = 1,063 – 2,382,  $p = 0.020$ ). Additionally, the most common comorbidities among the participants were HIV (21.9%), malignancies (13.5%), and congenital heart disease (13.5%). The lower improvement observed in patients with comorbidities is postulated to result from the independent effects of each condition on the patients' nutritional status and recovery. Additionally, the presence of these concurrent conditions likely elevates the body's overall energy requirements, thereby compromising the nutritional status of these patients further.<sup>8</sup>

The World Health Organization has reported that HIV prevalence among children with TB ranges between 10-60%.<sup>21</sup> Co-infection of TB with HIV has been reported to cause serious nutritional problems, such as poor eating habits, nutrient deficiencies, malnutrition, and weight loss.<sup>9</sup> Moreover, patients with HIV co-infection were at higher risk to develop disseminated *Mycobacterium tuberculosis* infection, which potentially further exacerbate the existing condition.<sup>18</sup> Study by Ali et al. revealed a significant correlation between stage 4 HIV and CD4 counts <40% with anti-tuberculosis drug induced hepatotoxicity.<sup>22</sup> This condition predominantly occurs during the intensive phase of treatment, making the effective administration of anti-tuberculosis drugs more challenging.<sup>22, 23</sup> Hence, the coexistence of HIV and tuberculosis may disrupt the treatment and recovery process, leading to the poorer improvements in the nutritional status of these patient.

The second leading comorbidities in this study is malignancy, with the majority being hematological malignancies, primarily acute lymphoblastic leukemia and lymphoma. Patient with hematological malignancies experience immune deficiency, which increases their susceptibility to infection and hinders the recovery of TB patients.<sup>24, 25</sup> This immune deficiency potentially caused by the pathogenesis of the disease or the side effect of the treatment such as chemotherapy or stem cell transplantation. Additionally, chemotherapy may trigger side effects such as nausea and vomiting, leading to decreased food intake and affecting the nutritional status.<sup>26</sup>

The third main comorbidities found in this study was heart disease. Among 13 children with heart disease as comorbidity, 10 were diagnosed acyanotic heart disease. In acyanotic heart disease, increased pulmonary blood flow enhances perfusion in the upper lung regions, creating a more aerobic environment that favors the growth of tuberculosis bacteria.<sup>27</sup> Furthermore, the weight of children with acyanotic heart

disease was initially lower compared to those with cyanotic heart disease due to several contributing factors. First, acyanotic heart disease is often accompanied by pulmonary hypertension, which, along with the increased metabolic demands seen in heart disease, especially in cases of heart failure, leads to higher caloric needs and reduced intake.<sup>28, 29</sup> Second, reduced caloric intake due to diminished appetite, malabsorption, eating difficulties caused by dyspnea, lack of energy to eat, and nausea further contribute to poor nutritional status.<sup>28-31</sup>

This study is the first to examine the relationship between nutritional status, tuberculosis type, and the presence of comorbidities in Indonesian children with tuberculosis. However, several limitations should be acknowledged. The research was conducted using a retrospective observational study design, which relied on anthropometric data extracted from medical records rather than direct measurements by the researchers. Consequently, measurement bias may have occurred. Despite this, efforts were made to ensure the anthropometric data used were obtained from the same pediatric pulmonology clinic for both the initial assessment and the follow-up after two months of treatment. Furthermore, due to the lack of height data in many records, the number of subjects meeting the inclusion criteria was limited. As a result, the subjects were selected using non-probability consecutive sampling rather than random sampling.

## Conclusion

In conclusion, patients with tuberculosis showed notable improvements in nutritional status after two months of treatment, with a decrease in malnutrition and an increase in good nutritional status. Furthermore, extrapulmonary TB and the absence of comorbidities are associated with greater improvement in nutritional status post-tuberculosis treatment for 2 months. These results highlight the importance of integrating nutritional management with anti-tuberculosis treatment, particularly during the initial two months of therapy, and addressing comorbidities comprehensively.

## Acknowledgements

The authors extend their sincere gratitude to the Faculty of Medicine, Universitas Indonesia and Cipto Mangunkusumo Hospital for their invaluable support in conducting this research.

## Funding

This research was a self-funded study.

## Conflict of Interest

None declared.

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Original Article

# Prevalence of Soil-Transmitted Helminthiasis and Its Association with Pediatric Diarrhea in Perobatang Village, Southwest Sumba

Saleha Sungkar<sup>1</sup>, Imam Rahadian Soleman<sup>2</sup>

<sup>1</sup>Department of Parasitology, Faculty of Medicine, Universitas Indonesia, dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia

<sup>2</sup>Faculty of Medicine, Universitas Indonesia, dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia



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e-ISSN: 2830-5442

**Corresponding author:**

Imam Rahadian Soleman  
imamsoleman@live.com

**Published:**

31<sup>st</sup> August 2024

**DOI:**

<https://doi.org/10.58427/apghn.3.3.2024.12-9>

**Citation:**

Sungkar S, Soleman IR. Prevalence of Soil-Transmitted Helminthiasis and Its Association with Pediatric Diarrhea in Perobatang Village, Southwest Sumba. *Arch Pediatr Gastr Hepatol Nutr.* 2024;3(3):12-9.

**Abstract:**

**Background:** Diarrhea is a prevalent health issues in developing countries and often linked to soil-transmitted helminthiasis (STH). This study aims to investigate the association between STH and diarrhea in Perobatang, Southwest Sumba.

**Method:** A cross-sectional study was conducted in Perobatang, January 2017. Participants were children aged 1–15 years. Stool samples were collected from each child and examined macroscopically for signs of diarrhea and microscopically for STH eggs. Positive cases were treated with albendazole 400 mg.

**Result:** A total of 333 samples were analyzed and 257 children were infected with STH (77%). The prevalence of *A. lumbricoides* was 56%, *T. trichiura* was 55%, and hookworm was 5%. Mixed infections were more common in children 6–15 years. 92 children (28%) had diarrhea. There is an association between the STH infection (combination of all three worm species) and diarrhea incidence (chi-square test,  $p=0.041$ ). However, there is no association between the prevalence of single infections or the combination of two worm species and diarrhea incidence.

**Conclusion:** STH infections are associated with incidence of diarrhea in Perobatang, Sumba Barat Daya. This finding highlights the necessity for targeted, community-based interventions by local stakeholders to effectively address and mitigate this public health challenge.

**Keywords:** diarrhea, perobatang village, soil-transmitted helminthiasis, prevalence

## Introduction

Diarrhea is a significant health problem in developing countries, including Indonesia. This disease can affect all age groups, with children as the most vulnerable population.<sup>1</sup> The incidence of diarrhea in eastern Indonesia is 9%.<sup>2</sup> The high incidence of diarrhea was due to the lack of knowledge about diarrhea, poverty, and low hygiene in the area.<sup>1</sup>

Soil-transmitted helminthiasis (STH) is a common parasitic infection associated with chronic diarrhea. In Indonesia, *Ascaris lumbricoides* and *Trichuris trichiura* are the most prevalent STH infections among children. In severe infections of both species may lead to malnutrition and chronic diarrhea, often misdiagnosed as simple diarrhea. Despite the potential for STH-related complications and chronic diarrhea, many parents delayed seeking medical attention, contributing to the persistence of infection and environmental contamination.<sup>1</sup>

Southwest Sumba, a district in East Nusa Tenggara, has limited water resources, poor sanitation, and a contaminated environment, with a high prevalence of STH. In Perobatang Village, the prevalence of *T. trichiura*, *A. lumbricoides*, and hookworm were 68.2%, 77.3%, and 3%, respectively. Despite the high prevalence in the region, the association between STH and diarrhea in Southwest Sumba, East Nusa Tenggara, Indonesia remained unclear.<sup>1</sup> Therefore, this study aims to investigate the association between STH and diarrhea in Perobatang Village, Southwest Sumba.

## Method

A cross-sectional study was conducted among children aged 1–15 years in Perobatang Village, Southwest Sumba, East Nusa Tenggara, Indonesia, from January 2017 to August 2018. Children who had received anthelmintic medication within the previous three months or were acutely ill were excluded.

To encourage community participation, village heads and officials disseminated information about the study, informing village residents regarding the upcoming stool examinations for worms on children. Children and their parents were gathered and informed on how to collect stool samples. Stool samples were collected using 10 mL plastic containers, labeled with the name of participants and a code number. Collected samples were assessed macroscopically for color and consistency to identify diarrhea and microscopically (with 40x magnification) using the Kato-Katz technique to detect STH eggs and determine the infection intensity. Positive cases were treated with three-days course of albendazole 400 mg.

Data analysis was performed using SPSS ver. 20.0. Univariate analysis was used to describe the demographic characteristics of the study population and the prevalence

of diarrhea and STH. Bivariate analysis, using the chi-square test, was used to examine the association between STH and diarrhea, and between STH prevalence and age.

Ethical approval for this study was obtained from the Faculty of Medicine Universitas Indonesia-Cipto Mangunkusumo Hospital's ethics committee (No. 876/UN2.F1/etik/2016). Additionally, permission was obtained from District Health Office Head, and the village head of Perobatang. Informed consent was obtained from participants' legal guardians prior to their inclusion in the study. The consent process ensured that the guardians understood the study's objectives and the voluntary nature of their participation.

## Results

A total of 333 children participated in this study, of which 58% were female. Participants aged 6–15 years (69%) were more prevalent than those aged 1–5 years. A number of 77% subjects were diagnosed with STH infections. However, only 28% of the children had diarrhea (**Table 1**).

**Table 1.** Characteristics of study participants

| Characteristics | Frequency<br>n (%) |
|-----------------|--------------------|
| Age (years)     |                    |
| 1–5 years old   | 103 (31)           |
| 6–15 years old  | 230 (69)           |
| Gender          |                    |
| Male            | 141 (42)           |
| Female          | 192 (58)           |
| STH Infection   |                    |
| Yes             | 257 (77)           |
| No              | 76 (23)            |
| Diarrhea        |                    |
| Yes             | 92 (28)            |
| No              | 241 (72)           |

In children aged 1–5 years, single STH infections were more prevalent than mixed infections. In contrast, mixed infections were more common in the 6–15 age group. Among the total of 257 children diagnosed with STH infections, a higher proportion of single infections were observed compared to mixed infections (**Table 2**).

**Table 2.** Prevalence of Single and Mixed Infection

| Age (years) | Single Infection n (%) | Mixed Infection n (%) |
|-------------|------------------------|-----------------------|
| 1–5         | 49 (60)                | 32 (40)               |
| 6–15        | 83 (47)                | 93 (53)               |
| Total       | 132 (51)               | 125 (49)              |

**Table 3** presents the prevalence of each type of STH. *A. lumbricoides* was the most prevalent STH infection among the children (n=187) and *A. lumbricoides* and *T. trichiura* was the most common mixed infection (n=118).

**Table 3.** Prevalence of STH Types

| Age (years) | STH n (%) | Al n (%) | Tt n (%) | Hw n (%) | Al+Tt n (%) | Al+Hw n (%) | Tt+Hw n (%) | Al+Tt+Hw n (%) |
|-------------|-----------|----------|----------|----------|-------------|-------------|-------------|----------------|
| 1–5         | 82 (25)   | 62 (19)  | 50 (15)  | 1(1)     | 32 (10)     | 0(0)        | 0(0)        | 0(0)           |
| 6–15        | 175 (52)  | 125 (37) | 134 (40) | 18(5)    | 86(25)      | 9(3)        | 14(4)       | 8(2)           |
| Total       | 257 (77)  | 187 (56) | 184 (55) | 19(6)    | 118 (35)    | 9(3)        | 14(4)       | 8(2)           |

Al=*A. lumbricoides*; Tt=*T. trichiura*; Hw=hookworm

**Table 4** presents the intensity of infection. The majority of the cases were classified as mild, with only four cases exhibiting severe intensity. All hookworm infections were classified as mild. There is an association between STH infection and diarrhea (p-value=0.041), however, there is no association between STH infection and diarrhea incidence (**Table 5**).

**Table 4.** Infection Intensity

| Infection Intensity | Al n (%)  | Tt n (%)  | Hw n (%) |
|---------------------|-----------|-----------|----------|
| Severe              | 2 (1)     | 2 (1)     | -        |
| Moderate            | 89 (48)   | 37 (20)   | -        |
| Mild                | 96 (51)   | 145 (79)  | 19 (100) |
| Total               | 187 (100) | 184 (100) | 19 (100) |

Al=*A. lumbricoides*; Tt=*T. trichiura*; Hw=hookworm

**Table 5.** The Association between STH Infection and Diarrhea

| Type of Infection                          | Diarrhea          |                   | Total | p-value |
|--|-------------------|-------------------|-------|---------|
|  | Positive<br>n (%) | Negative<br>n (%) |       |         |
| STH  |                   |                   |       |         |
| Positive                                   | 64 (25)           | 193 (75)          | 257   | 0.041   |
| Negative                                   | 28 (37)           | 48 (63)           | 76    |         |
| <i>A.lumbricoides</i> + <i>T.trichiura</i> |                   |                   |       |         |
| Positive                                   | 29 (25)           | 89 (75)           | 118   | 0.356   |
| Negative                                   | 63 (30)           | 152 (70)          | 215   |         |
| <i>A. lumbricoides</i>                     |                   |                   |       |         |
| Positive                                   | 48 (26)           | 139 (74)          | 187   | 0.366   |
| Negative                                   | 44 (30)           | 102 (70)          | 146   |         |
| <i>T. trichiura</i>                        |                   |                   |       |         |
| Positive                                   | 43 (23)           | 141 (77)          | 184   | 0.053   |
| Negative                                   | 49 (33)           | 100 (67)          | 149   |         |

## Discussion

This study reported a high prevalence (77%) of STH infections in Perobatang Village, Southwest Sumba. The result is consistent with a previous study in Central Sumba which shows a prevalence of 83.3%.<sup>3</sup> The same study identified an association between STH infection and defecating outside the latrine, poor hand hygiene, nail-biting, finger-sucking, and barefoot walking. Several factors likely contribute to the high prevalence, including limited access to clean water, open defecation due to a lack of toilets, poor hygiene practices, poverty, and low levels of education. A meta-analysis is in line these findings, demonstrating an association between the availability of sanitation facilities and reduced STH infection risk (OR=0.46–0.58).<sup>4</sup>

Our study find that STH infection was most commonly found in children aged 6–15 years old (68%). This is potentially due to the higher engagement of children from this age group in outdoor activities compared to those aged 1–5 years old. This also explains why children aged 6–15 years old were more prone to combined infection, while those aged 1–5 years old were more likely to have single infection. A study in Ethiopia by Alelign et al.<sup>5</sup> reported similar findings, showing that older children more likely to be infected compared to younger children.

The most prevalent type of STH infection in this study was *A. lumbricoides* (56%), followed by *T. trichiura* (55%), and hookworm infection (6%). The higher prevalence of *A. lumbricoides* and *T. trichiura* infections compared to hookworm infection in Perobatang Village is likely attributed to the clay soil, which provides a more favorable environment for the development of *A. lumbricoides* and *T. trichiura* eggs than hookworm eggs. Hookworm eggs thrive in more porous soil, typically found in

agricultural areas. Thus, as children in this region may have limited exposure to farms, their risk of hookworm infection is smaller.<sup>6</sup>

A study conducted in Central Sumba reported a different distribution of STH infections, with mixed infections of *A. lumbricoides* and *T. trichiura* being the most common (35.6%) while *A. lumbricoides* infection was the least common (14.9%).<sup>3</sup> *A. lumbricoides* is a prevalent and widely distributed parasite due to its ability to produce large quantities of eggs which can survive in harsh environments. Each adult female produces approximately 200,000 eggs per day in the small intestine. These eggs remain viable in warm, shaded, and moist soil for up to 10 years and become infectious within 10 to 15 days.

Chronic diarrhea is a common symptom of STH infection that should be suspected in individuals from endemic regions.<sup>7</sup> Of the 92 children who experienced diarrhea in this study, 64 (69%) were positive with STH infection. Furthermore, this study also revealed an association between diarrhea incidence and STH infection. In ascariasis infection, diarrhea may occur due to the mechanical effects of the large *A. lumbricoides* worms, as well as the toxic and inflammatory responses triggered by the worms, increased the intestinal peristalsis.<sup>8</sup> Meanwhile, in trichuriasis infection, diarrhea was resulted from adult worms embedding their heads into the intestinal mucosa, causing damage, stimulating intestinal peristalsis, and potentially leading to bloody diarrhea.<sup>9</sup>

In single infections case with *A. lumbricoides*, *T. trichiura*, or hookworms, diarrhea typically occurs high infection intensity, whereas mild infections often do not cause symptoms. Diarrhea is more likely to manifest in severe infections, such as infection with high *T. trichiura* egg counts exceeding 10,000 eggs per gram of stool, presence of adult *A. lumbricoides* in the stool, or mixed infections which involve more than two species of worms.<sup>6,8,10</sup> In this study, mild infections were more prevalent, with only 64 out of 257 children with STH infections experiencing diarrhea. This explains why there is no association between diarrhea and helminth infections.

STH infections can have significant health consequences beyond diarrhea, including intestinal obstruction and hepatobiliary or pancreatic involvement in ascariasis.<sup>11</sup> A meta-analysis showed an association between STH infections and an increased risk of stunting, which is one of the most concerning effects of the infection.<sup>12</sup>

The limitation of this study is the absence of patient anamnesis, which are important for determining the underlying causes of diarrhea. However, this limitation does not diminish the significance of the study's findings. The results highlight the high prevalence of STH infections and association between STH and diarrhea, emphasizing the urgent need for interventions to mitigate these health risks.

We recommend that the study findings to be disseminated to the District Health Office of Southwest Sumba to inform local health policies and programs. In cases of diarrhea, fecal examination for STH should be considered, and appropriate preventive measures, such as periodic deworming programs, be implemented to control STH.

## Conclusion

The prevalence of STH infections is high in Perobatang Village, with *A. lumbricoides* being the most common type. While the overall intensity of infections is mild and diarrhea is uncommon, an association between STH infections and diarrhea persists.

## Acknowledgement

The authors would like to thank the Head of Perobatang Village and all of the residents for their contribution and support to this study.

## Funding Statement

This study was funded by Directorate of Research and Community Service Universitas Indonesia.

## Conflict of Interest

None declared.

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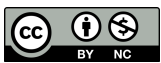
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Evidence-Based Case Report

# The Predictive Value of Gamma-Glutamyl Transferase on Jaundice Clearance in Biliary Atresia: An Evidence-Based Case Report and Meta-Analysis

Megan Quinka D. Toding<sup>1</sup>, Awliya Syamsul Munir<sup>1</sup>, Mutiara Ramadhanty<sup>1</sup>, Lowilius Wiyono<sup>1</sup>

<sup>1</sup>Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia



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e-ISSN: 2830-5442

## Corresponding author:

Megan Quinka D. Toding  
meganquinka@gmail.com

## Published:

31<sup>st</sup> August 2024

## DOI:

<https://doi.org/10.58427/apghn.3.3.2024.20-31>

## Citation:

Toding MQD, Munir AS, Ramadhanty M, Wiyono L. The Predictive Value of Gamma-Glutamyl Transferase on Jaundice Clearance in Biliary Atresia: An Evidence-Based Report and Meta-Analysis. *Arch Pediatr Gastr Hepatol Nutr*. 2024;3(3):20-31.

## Abstract:

**Background:** Biliary atresia (BA) is a neonatal condition characterized by the obstruction of extrahepatic bile ducts.

**Case:** A 2-year-old female with BA underwent a Kasai procedure at 3 months of age. Despite the surgery, she developed persistent jaundice and abdominal enlargement. Preoperative laboratory findings revealed elevated liver enzymes, GGT, and bilirubin levels. This case raises the clinical question of whether preoperative GGT levels can predict JC after the Kasai procedure, in addition to its role in diagnosis.

**Methods:** A systematic literature search was performed on 4 databases (PubMed, Scopus, Cochrane, and Proquest) by using relevant keywords and identified seven high quality studies.

**Results:** Five studies found higher GGT levels in patients who achieved JC following Kasai surgery, compared to those with unsuccessful jaundice clearance (JUC). However, two studies reported conflicting findings. A pooled analysis indicated a non-significant trend toward higher GGT levels in the JC group compared to the JUC group (WMD: 65.6, 95% CI: -58.6; 189.8).

**Conclusion:** Elevated preoperative GGT levels may be associated with improved JC in BA patients. However, further investigation to validate these findings, determine the optimal role of GGT in assessing prognosis, and later, guiding treatment decisions in BA patients.

**Keywords:** biliary atresia, gamma-glutamyl transferase, jaundice clearance, kasai surgery, prognosis

## Introduction

Biliary atresia (BA) is a neonatal disease characterized by the obstruction of extrahepatic bile ducts.<sup>1</sup> Most infants with BA present with pale stool and elevated levels of Gamma-Glutamyl Transferase (GGT), AST, ALT, and direct bilirubin. Abdominal ultrasound and liver histopathology can support the diagnosis.<sup>2</sup> The Kasai procedure is the primary treatment for BA. Successful Kasai surgery can improve bilirubin drainage and enable long-term native liver survival.<sup>3</sup> Most infants undergoing the Kasai procedure before 60 days of age will achieve jaundice clearance (JC).<sup>2</sup> Infants who experience JC after surgery are expected to have long-term survival with their native liver. Numerous studies have analyzed the prognostic factors for infants with BA who underwent the Kasai procedure and achieved JC, focusing on both preoperative and postoperative variables.<sup>1,4</sup>

This study aims to investigate the prognostic significance of preoperative GGT levels in infants undergoing the Kasai procedure, in addition to its role as a diagnostic marker.

## Case Illustrations

A 2-year-and-4-month-old female toddler was referred to Cipto Mangunkusumo Hospital from a private hospital after a one-month hospitalization. The initial reason for admission to the first hospital was a four-day history of vomiting (eight episodes). The patient also experienced fever (38°C) and black, bloody stools during this hospitalization. The patient's mother reported several infections, including gastric, intestinal, and respiratory infections.

The patient had been diagnosed with biliary atresia 1.5 months after birth and underwent the Kasai procedure at 3 months of age. The initial complaint was jaundice, noticeable in bright light, at 30 days of age. The patient had acholic stools from birth, and ultrasound findings were suggestive of biliary atresia. Following the Kasai procedure, the patient's jaundice was persistent, and her abdomen gradually enlarged. There was no history of meconium stools before or after the surgery. The patient was underweight, severely stunted, and severely wasted with hepatomegaly, splenomegaly, and a yellowish-green skin hue with decreased subcutaneous fat. The patient was diagnosed with cholangitis, post-Kasai procedure biliary atresia, and malnutrition.

Preoperative laboratory investigations revealed elevated liver enzymes (AST 226 U/L, ALT 111 U/L), increased gamma-glutamyl transferase (GGT) level (257 U/L), increased alkaline phosphatase (692 U/L), and hyperbilirubinemia (total 20.54 mg/dL, direct 14.15 mg/dL, indirect 6.39 mg/dL).

The diagnosis of biliary atresia was based on three findings: acholic stools, significantly elevated GGT levels (above 250 U/L), and ultrasound findings suggestive of biliary atresia. Subsequently, clinicians inquired whether the elevated preoperative GGT levels in this patient could potentially predict jaundice clearance after the Kasai procedure, in addition to its diagnostic role. Motivated by this clinician query, this case report contributes to the exploration of GGT as a potential prognostic factor in this patient population.

### Clinical Question

Therefore, an evidence-based case report was conducted with the clinical question: "Can preoperative GGT levels predict jaundice clearance following Kasai surgery in infants with biliary atresia?". This clinical question was broken down into the PICO format:

- Patient: Infants with biliary atresia who underwent Kasai surgery
- Intervention: Preoperative GGT levels
- Comparison: -
- Outcome: Jaundice clearance

### Methods

#### Data Sources and Search Strategy

A comprehensive literature search was conducted in four electronic databases: Scopus, PubMed, Cochrane Library, and ProQuest. The search strategy utilized a combination of keywords, including "jaundice clearance," "gamma-glutamyl transferase," and "biliary atresia." These terms were searched as both free text and, where applicable, Medical Subject Headings (MeSH) terms. Boolean operators (AND, OR) were used to refine the search results. The search queries for each database can be found in **Table 1**. Additionally, the references of included studies were screened manually to identify any further relevant studies through the hand-searching process. All studies were then compiled into a spreadsheet for further screening.

Table 1. Search queries and first-hit results of each electronic database.

| Database | Keyword   | First-hit articles |
|----------|---|--------------------|
| SCOPUS   | ( "jaundice-free" OR "jaundice clearance" OR outcome ) AND ( "gamma-glutamyl transpeptidase" OR "gamma glutamyl transpeptidase" OR "gamma-glutamyl transferase" OR "gamma glutamyl transferase" ) AND "biliary atresia" | 551                |

|          |   |    |
|----------|---|----|
| PUBMED   | (biliary atresia[MeSH Terms]) AND (gamma glutamyl transpeptidase[MeSH Terms]) AND ("jaundice-free" OR "jaundice clearance" OR "liver survival") | 4  |
| COCHRANE | ("jaundice-free" OR "jaundice clearance" OR outcome) AND Gamma-Glutamyltransferase  | 5  |
| PROQUEST | ("jaundice clearance" OR outcome) AND "gamma glutamyl transferase") AND "biliary atresia"   | 12 |

### Article Screening Process

All authors conducted the screening process independently to ensure objective assessment during the screening stage. Studies were included if they met the following criteria: (1) Original research articles assessing the role of GGT in predicting jaundice resolution in patients with biliary atresia; (2) Studies involving pediatric patients diagnosed with biliary atresia; (3) Studies that reported jaundice clearance as an outcome; (4) Articles published in English.

Meanwhile, we excluded case reports, review articles, conference abstracts, and articles that did not report specific data on GGT levels or jaundice resolution. Studies with a high risk of bias, as assessed by the Oxford Centre for Evidence-Based Medicine (CEBM) prognosis critical appraisal tool after the initial screening process, were also excluded. Articles with different screening outcomes by each author were discussed further within a group discussion.

### Data Extraction

Data extraction was conducted independently by four reviewers using a standardized data extraction form in a spreadsheet. The extracted data included study characteristics (authors, year of publication, country), patient demographics (age, gender), study design, sample size, GGT levels, jaundice clearance outcomes, and the duration of follow-up. We also extracted the results of bivariate analysis used in the articles to determine the effect of GGT level on jaundice clearance outcome, if available. Any discrepancies were resolved through discussion or by consulting with others if necessary.

### Data Synthesis

A meta-analysis was conducted to synthesize the results of the included studies with similar outcomes. This statistical technique will allow for a quantitative summary of the overall effect size and identify any heterogeneity among these studies. We conduct a random-effect continuous meta-analysis using mean difference as effect size. The results will be extrapolated into forest plots.

### Quality Assessment

The quality of the included studies was assessed using the Oxford Centre for Evidence-Based Medicine (CEBM) prognosis critical appraisal tool. This tool evaluates studies based on criteria such as patient selection, prognostic factor measurement, outcome measurement, and statistical analysis. Studies were classified as high, moderate, or low quality based on their scores. The quality assessment was conducted independently by all reviewers, with discrepancies resolved through group discussion.

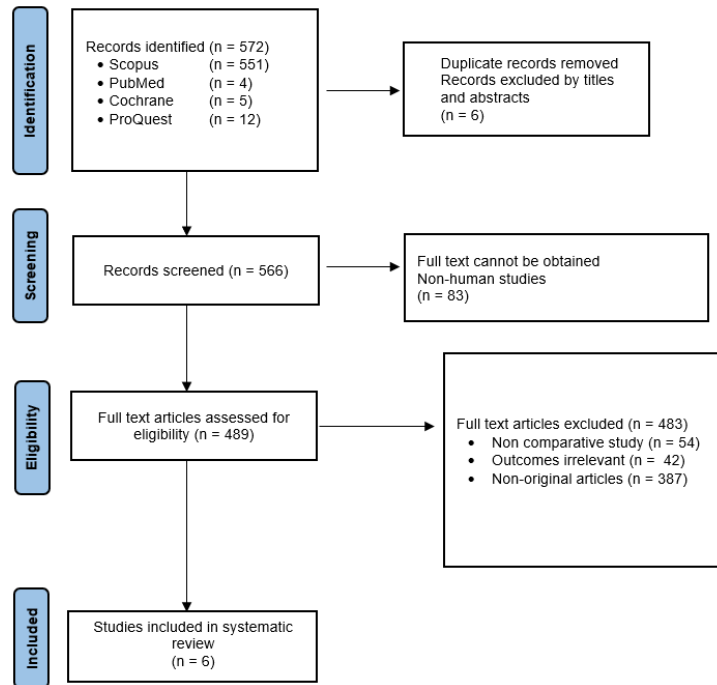


Figure 1. PRISMA flowchart on study screening and selection process.

### Ethical Considerations

As this study involved a systematic literature review, ethical approval was not required. All data used in this review were derived from publicly available sources.

### Results

Seven retrospective cohort studies were included in this analysis, with a summary of the included studies presented in **Table 2**. The critical appraisal result of each study is presented in **Table 3**. The studies by Sun et al.<sup>5</sup> and Shankar et al.<sup>6</sup> were the only ones that used a cut-off value for GGT levels. Sun et al. used 300 IU/L as the GGT cut-off value to divide the participants into low and high-level groups. The high-level group had a higher rate of jaundice clearance (JC) compared to the low-level group.<sup>5</sup> Meanwhile, Shankar et al. divided patients into two groups: <200 IU/L (normal) and

≥200 IU/L (high). Half of the patients (51%) in the high-level group achieved JC, compared to only 36% in the low-level group, although this difference was not statistically significant (P = 0.39).<sup>6</sup>

Zhang et al.<sup>4</sup> divided their cohort into training and testing groups, which were further divided into jaundice clearance (CJ) and unsuccessful jaundice clearance (UJC) groups. Zhang et al.<sup>4</sup> divided their cohort into training and testing groups, which were further divided into jaundice clearance (CJ) and unsuccessful jaundice clearance (UJC) groups. This study transformed the GGT value into logarithm. Both groups showed that patients who achieved CJ had higher GGT levels (6.3±0.8, 6.2±0.6) than those in the UJC group (5.7±0.8, 5.8±0.6), with these differences being statistically significant (P < 0.001).<sup>4</sup> A two-year follow-up study by Yassin et al.<sup>1</sup> showed that preoperative GGT levels in patients with JC 6 months postoperatively had a higher median value (846.5 vs. 802), although the difference was not statistically significant (P = 0.45).<sup>1</sup>

Qi et al.<sup>3</sup> analyzed 151 biliary atresia patients who underwent the Kasai procedure. One hundred and one patients achieved JC, with 67 achieving JC within three months and 34 achieving JC between three and six months. The mean GGT level in the JC group was 675 ± 473, while in the JUC group, it was 606 ± 443.<sup>3</sup>

Abdel-Aziz et al.<sup>7</sup> and Ihn et al.<sup>8</sup> reported results that contradicted other studies. In both studies, lower preoperative GGT levels were good predictors of surgical outcome, which was the clearance of jaundice. In Abdel-Aziz et al., a GGT level of 491 U/L or less was predictive of a successful outcome, and higher GGT levels were significantly associated with unsuccessful jaundice clearance (UJC) (P = 0.041).<sup>7</sup> In the study by Ihn et al., the GGT level in JC patients was 451.3, while in the JUC group, it was 499.9 (P = 0.429).<sup>8</sup>

Outcome assessment was conducted on three studies with similar outcome types, consisting of a statistical meta-analysis. The pooled analysis indicated a non-significant trend towards higher GGT levels in the JC group compared to the JUC group (WMD: 65.6, 95% CI: -58.6; 189.8) (Figure 2).

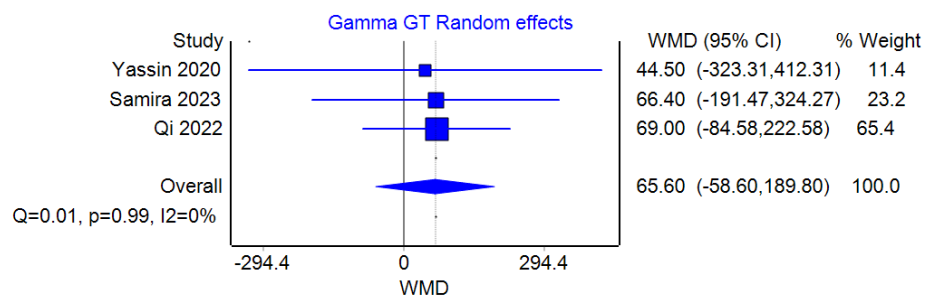


Figure 2. Pooled analysis of mean GGT level.

Table 2. Characteristics of included studies.

| Author, year                        | Study Design          | Study Location      | Sample number | Age at Procedure  | Pre-operative GGT Values                              | Number JC and JUC patients                      | LoE* |
|-------------------------------------|-----------------------|---------------------|---------------|---|---|---|------|
| Ihn K et al., 2018 <sup>8</sup>     | Restrospective cohort | Seoul, Korea        | 169           | 63.7 ± 31.8 days  | JC: 451.3 ± 341.1 IU/L<br>JUC: 499.9 ± 373.2 IU/L     | JC: 125<br>JUC: 44                              | 2b   |
| Shankar S et al., 2020 <sup>6</sup> | Restrospective cohort | Victoria, Australia | 113           | 61 days (30 – 149 days)   | Low GGT: <200 IU/L<br>High GGT: ≥200 IU/L             | JC Low: 5<br>High: 50<br>JUC Low: 9<br>High: 44 | 2b   |
| Yassin A et al., 2020 <sup>1</sup>  | Restrospective cohort | Cairo, Egypt        | 75            | 82 ± 23 days  | JC group: 419 (503) IU/L<br>JUC group: 414 (646) IU/L | JC: 28<br>JUC: 47                               | 2b   |
| Sun S et al., 2022 <sup>5</sup>     | Restrospective cohort | Shanghai, China     | 1998          | Low GGT group: 64.71 ± 21.35 days<br>High GGT group: 68.64 ± 22.42 days | Low GGT group: ≤300 IU/L<br>High GGT group: >300 IU/L | Low GGT: 167<br>High GGT: 730                   | 2b   |

|   |                        |                 |     |  |  |   |    |
|---|------------------------|-----------------|-----|--|--|---|----|
| Qi Q et al., 2022 <sup>3</sup>          | Restro-spective cohort | Shenyang, China | 151 | JC group: 58 (18 days)                                       | JC group: 675 (473 IU/L)                                       | JC: 101<br>JUC: 50  | 2b |
| Zhang Y et al., 2022 <sup>4</sup>       | Restro-spective cohort | Chengdu, China  | 175 | Training group: CJ: 61.2 ± 20.0 days<br>UJ: 68.2 ± 19.3 days | Training group: CJ: ln 6.3 ± 0.8 IU/L<br>UJ: ln 5.7 ± 0.8 IU/L | Training group: JC: 83<br>JUC: 37<br>Testing group: JC: 37<br>JUC: 18 | 2b |
| Abdel-Aziz SA et al., 2023 <sup>7</sup> | Restrospective cohort  | Menoufia, Egypt | 100 | JC group: 68.8 ± 14.8 days<br>JUC group: 80.9 ± 184.7 days   | JC: 965.1 ± 666.8 IU/L<br>JUC: 898.7 ± 507 IU/L                | JC: 33<br>JUC: 67   | 2b |

Data presented as mean ± standard deviation or median (interquartile range).  
\*LoE: Level of evidence, for prognostic studies were determined using the Cochrane classification.

Table 3. Critical appraisal of included studies.

| Author, year  | Ihn K et al., 2018 <sup>8</sup>       | Shan Kar S et al., 2020 <sup>9</sup> | Yassin A et al., 2020 <sup>1</sup> | Sun S et al., 2022 <sup>5</sup> | Qi Q et al., 2022 <sup>3</sup> | Zhan g Y et al., 2022 <sup>4</sup> | Abde l- Aziz et al., 2023 <sup>7</sup> |             |
|---------------|---------------------------------------|--------------------------------------|------------------------------------|---------------------------------|--------------------------------|------------------------------------|--|-------------|
| Validity      | Representative sample of patients     | +                                    | +                                  | +                               | +                              | +                                  | +                                      | +           |
|               | Follow-up sufficient                  | +                                    | +                                  | +                               | +                              | +                                  | +                                      | +           |
|               | Objective/blind outcome               | +                                    | +                                  | +                               | +                              | +                                  | +                                      | +           |
|               | Adjustment for prognostic factors     | +                                    | +                                  | +                               | +                              | +                                  | +                                      | +           |
| Importance    | Odds ratio                            | N/A                                  | 0.54                               | N/A                             | 0.52                           | N/A                                | 0.41                                   | N/A         |
|               | Prognostic estimates (95% CI)         | N/A                                  | 0.17 – 1.74                        | N/A                             | 0.41 – 0.65                    | N/A                                | 0.22 – 0.80                            | 0.51 – 0.74 |
| Applicability | Similarity to the patient on the case | +                                    | +                                  | +                               | +                              | +                                  | +                                      | +           |
|               | Clinically importance on conclusion   | +                                    | +                                  | -                               | +                              | -                                  | +                                      | +           |

N/A: Not available

## Discussion

Studies have shown that rapid and complete jaundice clearance (JC) following the Kasai procedure (KP) is a crucial indicator of long-term native liver survival.<sup>4,8</sup> While previous research has identified certain clinical factors associated with unsuccessful JC, accurately predicting JC at early stage remains challenging in clinical practice.<sup>8</sup> A timely and precise prediction of JC is essential for clinicians to assess risk stratification, estimate prognosis, develop individualized treatment plans, and prepare for potential liver transplantation.<sup>4</sup>

Gamma-glutamyl transferase (GGT) is primarily found in the hepatobiliary system, kidneys, spleen, seminal vesicles, and brain. However, the main sources of GGT are hepatocytes and biliary epithelial cells.<sup>10</sup> Elevated GGT levels (>300 IU/L) have been shown to accurately differentiate biliary atresia (BA) from neonatal hepatitis (NH) with 85% accuracy.<sup>11</sup> The study by Shen et al.<sup>12</sup> also found that infants with cholestasis and higher GGT levels were more likely to be diagnosed with BA. While GGT activity is often overlooked as a routine laboratory test in BA patients, its prognostic role remains relatively unexplored. Unlike its diagnostic utility, the longitudinal trends of serum GGT levels following the Kasai procedure (KP) have not been extensively studied.<sup>8</sup>

Our analysis of existing studies reveals that in five out of seven studies, patients with higher preoperative GGT levels were more likely to achieve jaundice clearance within six months than those with lower levels. This finding aligns with the known role of GGT in humans. GGT facilitates the transfer of the glutamyl group from glutathione, which helps replenish intracellular glutathione levels and supports bile-acid independent bile flow. A GGT deficiency could potentially exacerbate oxidative stress damage in the liver.<sup>13</sup>

However, the studies by Abdel-Aziz et al.<sup>7</sup> and Ihn et al.<sup>8</sup> found that lower preoperative GGT levels were more beneficial than higher levels for postoperative outcomes in BA patients. In BA patients, liver pathology worsens with age, accompanied by an increase in proliferation and a corresponding rise in GGT levels.<sup>11</sup> This may explain the results of both studies, as the patients who failed to achieve JC underwent the procedure at an older age (JC:  $68.8 \pm 14.8$  vs UJC:  $80.9 \pm 184.7$ ), while the other studies had similar procedure times for both patients who achieved JC and those who did not. Furthermore, our meta-analysis did not provide sufficient evidence to conclude that GGT levels were significantly higher in the JC group compared to the JUC group (WMD: 65.6, 95% CI: -58.6; 189.8) (**Figure 2**). Given the wide confidence interval and non-significant p-value, the clinical implications of this finding are uncertain.

Even though the available evidence is not entirely consistent, our findings suggest that GGT levels may have some prognostic value in predicting jaundice clearance (JC) in biliary atresia (BA) patients undergoing the Kasai procedure. Therefore, GGT could be incorporated into patient management and counseling by providing valuable information for risk stratification, prognosis estimation, and treatment planning.<sup>14</sup>

We acknowledge that our study has limitations, including its retrospective nature, single-center design, and small sample size, which may introduce bias. Therefore, further research is needed to establish definitive guidelines for the use of GGT in BA patients. By conducting larger studies and validating the findings, GGT could become

a valuable tool for clinicians in assessing the prognosis of BA patients and guiding their treatment decisions.

## Conclusion

Our findings suggest that elevated preoperative GGT levels may be associated with improved JC in BA patients. However, further investigation to validate these findings, determine the optimal role of GGT in assessing prognosis, and later, guiding treatment decisions in BA patients.

## Acknowledgment

The authors would like to thank the patient and their parents for consenting to the inclusion of her medical data in this report and Nielda Kezia Sumbung, M.D. for the contribution in preparing this manuscript.

## Funding Statement

This study was not supported by any external funding.

## Conflict of Interest

None declared.

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## Case Report

# Diagnostic Approach of Mesenteric Cyst in Children: A Case Report

Asep Aziz Purnama<sup>1</sup>, Hanifah Oswari<sup>2</sup><sup>1</sup>Department of Child Health, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia<sup>2</sup>Gastroenterology Division, Department of Child Health, Universitas Indonesia, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia

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e-ISSN: 2830-5442

**Corresponding author:**Asep Aziz Purnama  
asep559@gmail.com**Published:**31<sup>st</sup> August 2024**DOI:**<https://doi.org/10.58427/apghn.3.3.2024.32-7>**Citation:**Purnama AA, Oswari H. Diagnostic Approach of Mesenteric Cyst in Children: A Case Report. *Arch Pediatr Gastr Hepatol Nutr.* 2024;3(3):32-7.**Abstract:**

**Background:** Mesenteric cysts are intra-abdominal masses that arise from obstructed lymphatic drainage within the mesentery. Early diagnosis can be challenging, as it is often difficult to recognize based solely on clinical findings. The diagnosis is frequently made following imaging studies or during surgery. Despite their generally benign nature, delayed diagnosis can lead to serious complications. This case report aims to share our experience on the diagnostic approach for mesenteric cysts in children.

**Case:** A 2-year-old boy presented with a 14-month history of slowly progressive abdominal distension and signs of bowel obstruction, including weight loss. Abdominal ultrasound revealed thin-walled, well-demarcated, septated fluid sacs consistent with a cyst. Abdominal CT-Scan showed massive ascites filling the intraperitoneal cavity and pushing the intestine upward along the thickened mesentery, causing bowel obstruction. Histopathological examination confirmed the diagnosis of cyst lymphangioma derived from mesentery. The cyst was successfully excised via laparotomy, and histological examination confirmed it as a cystic lymphangioma.

**Discussion:** Our diagnostic approach focused on exclusion of differential diagnosis for abdominal distention in children, including ascites, abdominal tuberculosis, mesenteric cysts, and intra-abdominal masses. The absence of constitutional symptoms and lack of response to anti-tuberculosis therapy made it an unlikely diagnosis. While the CT-scan suggested ascites, the ultrasound results suggested a mesenteric cyst. Despite its large size, a complete excision of the cyst was successfully performed via laparotomy.

**Conclusion:** The nonspecific nature of mesenteric cysts often delays diagnosis, making abdominal ultrasound an essential initial imaging modality for patients suspected of having this condition.

**Keywords:** abdominal distension, bowel obstruction, diagnostic approach, mesenteric cysts, ultrasound

## Introduction

In 1907, Benevieni, an anatomy expert in Italy, first discovered a mesenteric cyst during an autopsy of an 8-year-old girl.<sup>1</sup> Mesenteric cysts are benign intra-abdominal masses that arise from obstructed lymphatic drainage within the mesentery, leading to cystic accumulation of lymph fluid.<sup>2</sup> While these cysts are generally benign, delayed diagnosis and treatment can increase the risk of rupture, leading to peritonitis, sepsis, and potentially death.<sup>3</sup>

The most common locations for mesenteric cysts are the small intestine (60%), colon (24%), and retroperitoneum (14.5%), with the ileal mesentery being the most frequent site. The mean age of incidence for mesenteric cysts is 4.9 years, and they are more prevalent in males (60%) than females (40%).<sup>3</sup>

Mesenteric cysts do not have specific (pathognomonic) signs or symptoms. The most common manifestation is a slowly developing, ascites-like abdominal enlargement, which may or may not be accompanied by signs of obstruction. Early diagnosis can be challenging, as it is often difficult to recognize based solely on history and physical examination. In most cases, the diagnosis of a mesenteric cyst is established after imaging studies or during laparotomy.<sup>4</sup>

Mesenteric cysts are relatively rare in children, occurring in approximately 1 per 250,000 cases compared to 1 per 105,000 in adults. One-third of mesenteric cyst cases occurred in children under 15 years old, and one-quarter occurred in children under 10 years old.<sup>5</sup>

Prompt and accurate diagnosis of mesenteric cysts is crucial for optimal treatment and prognosis. This case report aims to share our experience on the diagnostic approach for mesenteric cysts in children.

## Case Illustrations

A 2-year-old boy with a mesenteric cyst was admitted with abdominal distension-like ascites that had been present for 14 months before admission. On examination, the abdomen was distended, and a palpable soft mass with fluid consistency was observed. In the preceding month, the patient exhibited signs of bowel obstruction, such as vomiting 3 – 4 times a week, constipation, and difficulty passing gas. These symptoms were not accompanied by abdominal pain. The cyst caused mechanical obstruction, leading to weight loss and decreased appetite.

Abdominal examination revealed marked ascites with visible dilated veins (venodilation). An abdominal ultrasound revealed thin-walled, well-demarcated, septated fluid sacs consistent with a cyst. A contrast-enhanced abdominal CT-scan

showed massive ascites filling the intraperitoneal cavity and pushing the intestine upward along the thickened mesentery. An attempt at ascites puncture yielded no fluid production.

The patient underwent an excisional laparotomy, revealing a 46 cm x 26 cm x 5.9 cm cyst originating from the mesentery. Histological examination confirmed the presence of cystic lymphangiomas, consisting of endothelial cells, foam cells, and a thin wall containing lymphatic spaces, lymphoid tissue, and smooth muscle. This type of cyst is commonly found in children and is classified as mesenteric cysts.

## Discussion

In this case, a mesenteric cyst was diagnosed in a 2-year-and-10-month-old boy. Mesenteric cysts are relatively uncommon in pediatric populations. Tripathy et al. reported that majority of the pediatric mesenteric cysts occurred in children under 5 years of age, with a median age of 27 months. The condition in children is more prevalent in boys (60%) compared to girls.<sup>6</sup>

The clinical presentation of mesenteric cysts is markedly diverse. Common presentations include incidental findings on physical examinations or imaging studies (40%), nonspecific abdominal symptoms, such as distension, or complications of the cyst (33%). Typically, the signs and symptoms of mesenteric cysts are abdominal enlargement and rarely manifest acutely.<sup>6</sup>

The absence of pathognomonic symptoms in this disease complicates the initial diagnosis. Our patient presented with a chronic, slowly progressive abdominal distention over 14 months, without preceding associated pain or other bowel obstructive symptoms.

Loomba et al. reported abdominal distension in 50% of mesenteric cyst cases, abdominal pain in 58%, and bowel obstruction symptoms (nausea, vomiting, constipation) in 27 – 45%. Mesenteric cysts can range in size from 2 – 25 cm. However, cysts larger than 8 cm carried a significant risk of causing a mechanical bowel obstruction.<sup>7</sup> In this case, the large size of his cyst, measuring 46 cm x 26 cm x 5.9 cm, likely contributed to the mechanical bowel obstruction symptoms, and later, weight loss. Additionally, weight loss occurs in approximately 37% of mesenteric cyst cases and is more common in cysts with an enteric origin.

Our differential diagnoses were similar to those for abdominal distension in children, including mesenteric cysts, ascites, abdominal tuberculosis, abscess, and intra-abdominal masses.<sup>7</sup> While neuroblastoma and Wilms' tumor are common intra-abdominal masses in children under 5 years of age, our patient did not exhibit

associated symptoms such as abdominal pain, hypertension, asymmetric abdominal enlargement, or haematuria. Based on these findings, neuroblastoma and Wilms tumor seem less likely to be the diagnosis.

Weight loss, as observed in our patient, was more commonly observed in cases of abdominal tuberculosis compared to mesenteric cysts, occurring in approximately 61% of all abdominal tuberculosis cases.<sup>8</sup> On physical examination, abdominal percussion may confirm the presence of ascites, a finding commonly associated with mesenteric cysts. Approximately 60–70% of mesenteric cyst cases present as soft, fluid-filled intra-abdominal masses. To confirm ascites, a shifting dullness test should be performed. However, this was not conducted in the present case.

Furthermore, the previous hospital only conducted an abdominal CT-scan and did not conduct a tuberculin test to rule out abdominal tuberculosis. The CT scan revealed massive ascites and mesenteric thickening, raising the suspicion of tuberculosis.

To rule out the causes of ascites, routine laboratory tests, including complete blood count and blood chemistry, were performed and the results were within normal limits. There was no evidence of biliary obstruction, as indicated by normal GGT and bilirubin levels.

Considering that ascites was not definitively confirmed, along with normal laboratory results, the absence of constitutional symptoms (such as fever), and no response to anti-tuberculosis therapy after 12 months of treatment, abdominal tuberculosis was deemed unlikely in this case. However, abdominal tuberculosis should still be considered as a differential diagnosis in malnourished children with abdominal distension in endemic regions, particularly in Indonesia.

In our hospital, an abdominal ultrasound was performed. The ultrasound revealed septated ascites with thin intrinsic walls and no lymphadenopathy, suggestive of a mesenteric cyst. Ultrasound is an ideal initial diagnostic tool for mesenteric cysts, providing information about size, location, and the presence of internal septa. Its non-invasive nature and lower cost compared to CT scans make it preferably performed early in the diagnosis of mesenteric cysts.<sup>9</sup> Abdominal CT scans can offer more detailed anatomical information about the mass or cyst and its relationship with surrounding structures.<sup>10</sup> In some cases, CT scans still may be used to confirm ultrasound findings or guide surgical procedures.

In cases of ascites, ultrasonography typically demonstrates a homogenous and anechoic fluid collection within the peritoneal cavity and Morrison's pouch, without septations.<sup>11</sup> These findings are different with tuberculous peritonitis, which typically

presents with septated, thin ascites and associated lymphadenopathy.<sup>12</sup> In contrast, the ultrasound features in this case were more suggestive of a mesenteric cyst, characterized by thin-walled, septated ascites containing multiple anechoic structures.<sup>13</sup> The findings from the abdominal ultrasound strongly suggest the diagnosis of mesenteric cysts, which can be differentiated from ascites or abdominal tuberculosis.

Surgical enucleation is the treatment of choice for mesenteric cysts. In this patient, a complete excision of the cyst, or known as enucleation, was successfully performed via laparotomy, despite the large size of the cyst. Marsupialization, an alternative option for large or inaccessible cysts, was not necessary.<sup>14</sup>

Intraoperative macroscopic examination revealed a brown, firm, nodular cyst encapsulated by adipose tissue. The multilocular cyst contained a greenish-brown fluid. Cysts containing yellowish-brown or greenish-brown fluid are often associated with the posterior jejunum or ileum due to the abundant arterial vascularization of the mesentery in this region.<sup>15</sup> Given the cyst's location and the frequent occurrence of mesenteric cysts in the ileal mesentery, the origin of this cyst was likely from the ileal mesentery.

Histopathological examination confirmed the diagnosis of lymphangioma, characterized by the presence of lymphatic follicles in the cyst wall.<sup>16</sup> Lymphangiomas are congenital, benign neoplasms of the lymphatic system, resulting from malformations or disruptions of the lymphatic drainage system. Although acquired lymphangiomas may occur secondary to surgery, trauma, or radiation, the absence of such a history in this patient suggests a congenital origin.<sup>2</sup>

The prognosis for patients with lymphangioma is generally excellent, and the risk of recurrence after complete surgical excision is low, reported to be less than 3%.<sup>2</sup> In this case, the patient has had an uneventful postoperative course with no evidence of recurrence. This patient had good prognosis, as the condition is not life-threatening, does not require bowel resection, and has a low likelihood of recurrence.

## Conclusion

This case report highlights the diagnostic challenges associated with mesenteric cysts in children, as illustrated by a 2-year-old boy with a 14-month history of abdominal distension. Our differential diagnoses included mesenteric cysts, ascites, abdominal tuberculosis, abscess, and intra-abdominal masses. Given the nonspecific presentation of mesenteric cysts, relying solely on history and physical examination for diagnosis can be challenging. Therefore, abdominal ultrasound is necessary for initial imaging modality in the workup of patients suspected of having a mesenteric cyst.

## Acknowledgment

The authors would like to thank the patient and their parents for consenting to the inclusion of her medical data in this report.

## Funding Statement

This study was not supported by any external funding.

## Conflict of Interest

None declared.

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## Literature Review

# Inflammatory Bowel Disease in Children

Nabila Annisa Harum<sup>1</sup>, Primadita Syahbani<sup>1</sup>, Idznika Nurannisa Wibowo<sup>1</sup><sup>1</sup>Faculty of Medicine Universitas Airlangga – Dr. Soetomo General Hospital, Surabaya, Indonesia

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e-ISSN: 2830-5442

**Corresponding author:**

Nabila Annisa Harum  
ila.harumm@gmail.com

**Published:**31<sup>st</sup> August 2024**DOI:**

<https://doi.org/10.58427/apghn.3.3.2024.38-51>

**Citation:**

Harum NA, Syahbani P, Wibowo IN. Inflammatory Bowel Disease in Children. *Arch Pediatr Gastr Hepatol Nutr*. 2024;3(3):38-51.

**Abstract:**

**Background:** Pediatric inflammatory bowel disease (IBD) is an idiopathic inflammatory disease in the digestive system with chronic onset, which often presents with unique and atypical phenotypes. This study aimed to dissect the important features of inflammatory bowel disease in children

**Discussion:** The two types of inflammatory bowel disease (IBD) are ulcerative colitis (UC) and Crohn's disease (CD). In children, IBD may exhibit classic symptoms such as weight loss, abdominal pain, and bloody diarrhea. However, many patient present with atypical symptoms such as isolated poor growth, anemia, or other extraintestinal manifestations. Early diagnosis of IBD in children is crucial as delayed diagnosis may lead to serious complications like bowel narrowing or abnormal connections, and stunted growth. The recommended initial evaluations in a pediatric patient with suspected IBD are complete blood test, stool examination, endoscopy and imaging. Furthermore, the aims of IBD treatment in children are to improve quality of life, relieve symptoms, promote normal growth, and prevent complications, all while minimizing medication side effects.

**Conclusion:** Early diagnosis and treatment are essential in managing pediatric IBD. Additionally, addressing the disease's impact on bone health, growth, development, and psychosocial well-being is also crucial to achieve comprehensive management.

**Keywords:** children, crohn's disease, inflammatory bowel disease, ulcerative colitis

## Introduction

Inflammatory bowel disease (IBD) which includes Ulcerative colitis and Crohn's disease are long-term inflammatory conditions affecting the digestive system. These conditions commonly start in adolescence or early adulthood, with a growing number of cases occurring in children.<sup>1</sup> A pediatric onset of disease occurs in about 10% of all cases. Pediatric inflammatory bowel disease often presents with unique and atypical phenotypes compared to adult-onset IBD due to distinct genetic factors and age-related differences in inflammatory regulation. In ulcerative colitis (UC), unusual presentations may include rectal sparing in untreated cases, a short disease duration, involvement of the upper gastrointestinal (GI) tract, the presence of a cecal patch, and acute transmural disease. In Crohn's disease (CD), children tend to have more extensive and aggressive lesions in the left colon, while in adults, inflammation typically occurs in the terminal ileum.<sup>2,3</sup>

Children and adolescents with IBD face unique challenges including delayed growth, puberty, and body image issues. Even when the disease is in remission, many continue to experience ongoing problems like stomach pain and tiredness. Transitioning to adult care is often linked to disease flare-ups, highlighting the need for specialized support during this process.<sup>3</sup> In up to 10% of children with IBD, it's difficult to determine if they have Crohn's disease or ulcerative colitis. Over time, some of these unclear cases develop into one of these conditions.<sup>4</sup> Early diagnosis of IBD in children is crucial. Promptly identifying and examining patients with suspected IBD is important because delayed diagnosis can lead to serious complications like bowel narrowing or abnormal connections, and stunted growth.<sup>5</sup>

## Epidemiology

The global incidence and prevalence of IBD show an increasing trend in the last decade. In Asia, the incidence and prevalence per 100,000 people ranged from 0.5 to 21.6 and 5.0 to 52.2, respectively. Worldwide, the incidence and prevalence of IBD in children and adolescents remained steady from 1990 to 2019. Gender-wise the prevalence of IBD is similar in 2019 with 3.16 and 3.41 per 100,000 for boys and girls, respectively.<sup>6</sup> However, certain countries and regions, particularly in East Asia, have experienced a notable increase in the incidence of IBD among this age group. Around 25% of IBD patients are diagnosed before the age of 20. Among children with IBD, 4% are diagnosed before the age of 5, and 18% before the age of 10, with the highest incidence occurring during adolescence.<sup>7</sup>

## Pathogenesis

IBD is an idiopathic disorder caused by chronic and excessive inflammation of the gastrointestinal tract, leading to rectal bleeding, and weight loss.<sup>8</sup> The gastrointestinal

tract (GI) is chronically exposed to various antigens found in bacteria and food. GI tract also involves in a central role in maintaining homeostasis of our immune system such as, tolerance to non-pathogenic commensal bacteria, self-antigens, and food antigens. The GI tract defends the host by initiating an inflammatory response when it is attacked by pathogenic organisms.<sup>9</sup>

In the absence of intestinal inflammation, gut homeostasis is maintained by suppressing excessive immune responses to foreign antigens. When the homeostasis state is interrupted by some triggering factors, intestine barriers may be disrupted and chronic inflammation will occur resulting in disease such as IBD. IBD is classified into 2 archetypal phenotypes, ulcerative colitis (UC) and Crohn's disease (CD). Even though IBD is known as idiopathic and the mechanism of chronic gut inflammation is not fully understood, some triggering factors may make complex interactions related to pathogenesis of IBD. Genetic factors, changes in the gut microbiome, environmental changes, and immune response dysregulation including cytokines and immune cells are some factors that are frequently discussed along with IBD.<sup>10</sup>

a. Genetic factors

Predisposition of some genetics may play a role occurring IBD in some people and progressing to abnormalities of the immune system. More than 240 different genetic risk loci have been identified by genome-wide association studies (GWAS), next generation sequencing investigations, and other analyses. Out of these genetic locations, around 30 of them are shared by both CD and UC. Predisposition on those genes will interfere with the permeability of epithelial barrier and launch some immune responses that lead to chronic inflammatory responses<sup>11</sup>.

The NOD2 gene, identified in 2001 as linked to Crohn's disease (CD), functions as an intracellular bacterial sensor that regulates immune responses against pathogens by recognizing muramyl dipeptide, a component of bacterial cell walls. Mutations in the NOD2 gene can impair the activation of the NF- $\kappa$ B pathway and reduce cytokine production, disrupting normal immune responses and contributing to inflammation in CD. Additionally, NOD2 plays a role in autophagy, a process that helps eliminate pathogens by degrading cellular components. Mutations in ATG16L1, another gene associated with CD, disrupt autophagy in intestinal cells, leading to increased bacterial invasion. Other genetic factors associated with CD and ulcerative colitis (UC) include mutations in the CARD9 and CLEC7A genes, as well as single-nucleotide polymorphisms (SNPs) in the IL-23R gene. Although many people carry these genetic markers, only a small percentage develop inflammatory bowel disease (IBD), indicating that environmental factors and changes in gut microbiota interactions with the mucosal immune system also play crucial roles in the disease's development.<sup>12,13</sup>

b. Gut microbiome

Gut microbiota play a vital role in maintaining intestinal homeostasis, health, and disease by acting as a key interface between the environment and the host. They contribute to immune system development, protect against enteric pathogens, and support overall gut function through mechanisms like colonization resistance and promoting mutualism. However, factors such as nutrition, probiotics, antibiotics, and environmental influences can alter gut microbiota composition. In genetically susceptible individuals, these changes can lead to dysbiosis, disrupting mucosal immune function and potentially contributing to the development of inflammatory bowel disease (IBD).<sup>14</sup>

Dysbiosis refers to an imbalance in gut bacteria, leading to a disruption in the balance between beneficial and harmful microbes, and a reduction in beneficial metabolites. This imbalance, combined with ongoing inflammation, creates a chronic inflammatory cycle that impairs immune function and delays healing of the gut lining. Although dysbiosis is linked to inflammatory bowel disease (IBD), the exact mechanisms remain unclear. Research has shown that individuals with IBD have a different gut microbiota composition compared to healthy individuals.<sup>15,16</sup>

c. Environmental changes

Environmental factors such as lifestyle, diet, psychological stress, medications, and exposure to pathogens are linked to the risk of developing inflammatory bowel disease (IBD). Specifically, factors like vaginal delivery, age above 10, low physical activity, deficient fruit intake, and exposure to antibiotics are associated with an increased risk of pediatric IBD. Prenatal exposures, including antibiotics, tobacco smoke, and early life otitis media, also contribute to IBD risk. Research has established a clear link between antibiotic use, particularly metronidazole and quinolones, and a higher likelihood of developing new-onset IBD in both adults and children, with risks heightened by antibiotic exposure during pregnancy.<sup>17,18,19</sup>

Diet and lifestyle factors, such as the adoption of Western diets high in saturated fats and simple carbohydrates, are contributing to the rising incidence of IBD, especially in newly industrialized countries. In pediatric cases, extended breastfeeding and safe water consumption may reduce the odds of developing IBD and ulcerative colitis. Stressful events have also been identified as novel risk factors for IBD, particularly in children. Stress can lead to the release of corticotrophin-releasing factor (CRF), which increases intestinal permeability and promotes inflammation, exacerbating existing IBD or triggering its onset.<sup>20,21</sup>

Childhood vaccines generally do not increase IBD risk, although studies on the rotavirus vaccine have shown mixed results, with some indicating a reduced risk of IBD in Asian children. Other factors, such as smoking, body mass index (BMI), and body fat percentage, have been associated with an increased risk of Crohn's disease. However, passive smoking has not been found to significantly increase IBD risk in pediatric cases in Saudi Arabia.<sup>22</sup>

d. Immune response

Inflammatory bowel disease (IBD) develops in genetically predisposed individuals due to an impaired immune response against intestinal pathogens. Both innate and adaptive immune systems are involved, with the innate system being activated by pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) from damaged cells. In IBD, innate immune functions are altered, leading to further inflammation. Neutrophils, a key component of the innate response, eliminate pathogens through processes like phagocytosis and degranulation, but also contribute to tissue damage and disruption of crypt architecture in IBD. Cytokines play a crucial role in the immunological development of IBD, with pro-inflammatory cytokines (IL-6, IL-12/IL-23, IL-17, IL-1 $\beta$ /IL-18, and TNF) promoting inflammation, while IL-10 acts as an anti-inflammatory cytokine, and IL-22 has a complex role in IBD's etiology.<sup>23,24</sup>

## Classifications

IBD is categorized into ulcerative colitis (UC) and Crohn's disease (CD). UC affects the colon continuously, while CD can occur anywhere in the digestive system. A key difference is the pattern of inflammation: UC involves continuous inflammation, while CD often has patchy inflammation. CD is more likely to cause complications around the anus. While both diseases show signs of inflammation and damage, UC is confined to the surface layer of the colon, while CD can affect the entire thickness of the bowel. Granulomas, small clumps of tissue, are often found in CD but rarely in UC.<sup>25</sup>

The Montreal Classification is the most common way to categorize IBD. This system divides CD based on Age (A), Location (L), behaviour (B), and if it affects the area of perianal (p). Based on the age it is classified into A1 category for individuals diagnosed at 16 years of age or younger, while A2 and A3 account for diagnoses made at 17–40 years of age and >40 years of age, respectively. The main types of locations are the small intestine, colon, or both. Based on the location of the disease and the 3 main phenotypes, location of IBD is classified into: involvement of the terminal ileum (L1), colon (L2), or both (L3), with an additional modifier if located in the upper

gastrointestinal location for denoting the presence proximal to the terminal ileum (+L4) (Table 1).<sup>26</sup>

**Table 1.** Montreal classification of Crohn's disease<sup>26</sup>

| Age at diagnosis       | Location                   | Behaviour                           |
|------------------------|----------------------------|-------------------------------------|
| A1 below 16 y          | L1 ileal                   | B1 non-stricturing, non-penetrating |
| A2 between 17 and 40 y | L2 colonic                 | B2 stricturing                      |
| A3 above 40 y          | L3 ileocolonic             | B3 penetrating                      |
|                        | L4 isolated upper disease* | P perianal disease**                |

\*L4 is a modifier that can be added to L1–L3 when concomitant upper gastrointestinal disease is present.

\*\*is added to B1–B3 when concomitant perianal disease is present.

In contrast with Crohn's disease, The Montreal classification of disease extent of ulcerative colitis allows extent to be defined into three subgroups (Table 2).<sup>26</sup>

**Table 2.** Montreal classification of extent of ulcerative colitis (UC)<sup>26</sup>

| Extent                          | Anatomy  |
|---------------------------------|--|
| E1<br>Ulcerative proctitis      | Involvement limited to the rectum (proximal extent of inflammation is distal to the rectosigmoid junction) |
| E2<br>Left sided UC (distal UC) | Involvement limited to a proportion of the colorectum distal to the splenic flexure                        |
| E3<br>Extensive UC (pancolitis) | Involvement extends proximal to the splenic flexure  |

### Diagnosis Criteria

IBD is diagnosed based on history and clinical findings, laboratory works, endoscopy, radiology and histopathology. In up to 10% of pediatric cases, it can be challenging to distinguish between CD and UC. As the disease advances, some of these IBD-unclassified cases eventually develop into either CD or UC. Additionally, a small

percentage of children, particularly those with UC, may also have primary sclerosing cholangitis.<sup>27</sup> Suspicions toward IBD are raised when patients present with persistent (-4 weeks) or recurrent (-2 if there are episodes in 6 weeks) symptoms such as abdominal pain, diarrhea, rectal bleeding and weight loss. It may also manifest as anemia, fever, growth retardation, and extraintestinal manifestations (such as episcleritis and erythema nodosum).<sup>28</sup> Patients who experience obvious rectal bleeding or perianal disease (such as abscesses, ulcers, or fistulae, but not skin tags or fissures) should undergo a colonoscopy, regardless of biomarker results. The likelihood of IBD is elevated in children with rectal bleeding or perianal disease. For those with nonspecific symptoms, using blood and stool markers is the best approach to determine which children should undergo endoscopy. However, in children with milder symptoms, distinguishing IBD from other organic or functional disorders can be more challenging. Laboratory results, such as reduced hemoglobin, increased ESR and CRP, thrombocytosis, hypoalbuminemia, suggest IBD. Infectious etiologies should be excluded by stool cultures. Colonoscopy and histology are conducted to confirm the diagnosis. In UC, there is continuous mucosal inflammation of the colon (without small bowel involvement) and granulomas are absent on biopsy. In CD, key features such as skip lesions, well-formed noncaseating granulomas, macroscopic lesions of the upper intestinal tract, stenosis or cobblestoning, and ulcers are usually identified. In addition, various Imaging modalities can be used to diagnose IBD, such as barium small bowel follow-through, computed tomography, magnetic resonance enterography, and bowel ultrasonography.<sup>29</sup>

## Clinical Manifestation

IBD is a multifactorial immune disorder characterised by chronic relapsing inflammation of the intestine. Two types of IBD, whether UC and DC, have similar clinical manifestations such as diarrhea, hematochezia, and abdominal pain. However, some differences between UC and DC are found in some aspects like the location and depth of inflammation, complications, and prevalence.<sup>30</sup> Case of IBD in pediatric are found to be more severe than adults and childhood-onset IBD exhibits a higher level of aggressiveness and more rapid progression when compared to IBD that develops in adulthood.<sup>31</sup> Based on a cross sectional study, most common symptoms of CD in pediatric are weight loss (81.81%), diarrhea (72.72%) and abdominal pain (69.69%). Meanwhile in UC, most common symptoms in pediatric are bloody diarrhea (80%), abdominal pain (77.5%) and weight loss (57.5%).<sup>32</sup> Another study in IBD case of pediatric also stated that rectal bleeding is more prevalent in UC.<sup>33</sup> IBD may also affect other organs outside the intestine, called extraintestinal manifestations (EIMs). EIMs may be involved in many systems, such as musculoskeletal, dermatology, oral, and ophthalmological. The most common organs that are involved in EIMs in IBD are joints, skin, and eyes. Based on cross-sectional study, EIMs that commonly manifest in pediatric IBD are arthritis, oral plaque, and erythema nodosum.<sup>32</sup>

## Additional Examination

In any case of suspected IBD, a full blood count including ESR, liver function tests (including albumin), iron status, and CRP should be performed. In IBD patients, anemia, thrombocytosis, hypoalbuminemia, and elevated ESR and CRP levels are typical. On the other hand, in moderate UC (54%) or mild CD (21%), the readings could be deceptively normal.<sup>34</sup>

## Stool Examination

Stool tests should be analyzed for occult blood, bacterial pathogens (including *Clostridium difficile*), as well as ova and parasites. Fecal calprotectin, a protein produced by neutrophils that increases with intestinal inflammation, is becoming a valuable biomarker. It has shown 98% sensitivity and 68% specificity in children suspected of having IBD. In order to rule out infectious diarrhea, a stool culture is required. A recent stool sample should be examined for the presence of *Clostridium difficile* toxin, particularly if the children has taken many antibiotics. An established enteric infection does not rule out IBD.<sup>35</sup>

## Endoscopy and histopathology

Endoscopy is crucial for diagnosing, managing, and treating inflammatory bowel disease (IBD). It is vital for ruling out other causes, confirming diagnoses, distinguishing between Crohn's disease (CD) and ulcerative colitis (UC), tracking disease activity and treatment effectiveness, and identifying and addressing complications. In ulcerative colitis (UC), endoscopic observations often reveal signs such as swelling, diminished vascularity, redness, granular and fragile mucosa, erosions, ulcers, and pseudopolyps. In patients who have not yet received treatment, these symptoms usually start at the rectum and progress continuously in an upstream direction, eventually transitioning gradually to areas of normal mucosa. Several classic features of UC can also be observed in CD. However, three key endoscopic characteristics that help differentiate CD from UC include the presence of aphthous ulcers, cobblestoning, and discontinuous or "skip" lesions. While isolated involvement of the terminal ileum strongly suggests CD, "backwash ileitis" can occur in UC, especially with pancolitis. To resolve diagnostic uncertainties, mucosal biopsies with histological examination, upper gastrointestinal and small bowel endoscopy, small bowel imaging, and serologic markers can provide additional clarity.<sup>36</sup>

Histologically, ulcerative colitis (UC) is characterized by a widespread, continuous pattern of inflammation affecting the mucosa. This inflammation is marked by an elevated density of neutrophils, lymphocytes, and plasma cells in the lamina propria. Additionally, UC presents with epithelial architectural changes, including irregular mucosal surfaces that can resemble a "pseudovillous" appearance and distortion of

the glandular structure. Histological characteristics of Crohn's disease encompass localized active inflammation, marked by neutrophil-induced damage to epithelial glands, as well as nonactive inflammation, which includes transmucosal inflammation with the presence of plasma cells and eosinophils. Additionally, the disease often features granulomas and localized architectural distortion of the glandular structures. The histopathological report for Crohn's disease should thoroughly detail the various morphological aspects of the diagnosis, including: (a) a localized pattern of active inflammation accompanied by architectural distortion of crypts; (b) basal plasmacytosis with the presence of interspersed eosinophils; and (c) the presence of granulomas.<sup>37</sup>

### **Imaging studies**

Cross-sectional imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), are increasingly used for evaluating inflammatory bowel disease (IBD) because they can assess both mural and extramural manifestations of the disease simultaneously. CT findings in IBD can include thinning of the colonic wall, luminal distension, and pneumatosis. In severe cases, these issues can lead to perforation and free air. Common indicators of active Crohn's disease on CT enterography (CTE) include bowel wall thickening, increased mural enhancement with hyperenhancing mucosa, and haziness of the surrounding mesenteric fat.<sup>38</sup>

Magnetic resonance (MR) imaging findings indicative of the acute active inflammatory stage in Crohn's disease (CD) include bowel wall thickening (over 3 mm) with increased signal on T2-weighted fat-suppressed images, early and intense mucosal enhancement, and progressive transmural enhancement on post-gadolinium T1-weighted images. Ulcers and fistulas, best seen on fast imaging with steady-state precession, exhibit strong contrast enhancement. Enlarged adjacent mesenteric lymph nodes (>5 mm) often show contrast enhancement and high signal on diffusion-weighted imaging (DWI). DWI sequences, particularly with high b-values, are highly sensitive (95%) but less specific (82%) for detecting bowel wall inflammation.<sup>39</sup>

## **Management of Inflammatory Bowel Disease in Children**

The management of IBD, which consists of pharmacotherapy, surgery, nutrition, and psychosocial therapy, is individualized to each patient and clinical case. Changing the treatment regimens can be considered if clinical response is inadequate- a decrease of at least 20 points in PUCAI (Paediatric Ulcerative Colitis Activity Index) or a decrease of at least 12.5 in PCDAI (Paediatric Crohn's Disease Activity Index).<sup>40</sup>

### **5-aminosalicylates**

According to the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) recommended the use of oral 5-aminosalicylates (5-ASA) in first-line induction therapy for mild-to-moderate UC. 5-ASA inhibits multiple inflammatory pathways and possesses antioxidant properties.<sup>41</sup>

### **Immunomodulators**

Immunomodulators, which possess immunosuppressive properties, are recommended in maintaining remission. The Asian Pan-Pacific Society for Pediatric Gastroenterology, Hepatology, and Nutrition (APPSPGHAN) recommended azathioprine (AZA) as a first-line maintenance therapy for CD and UC.<sup>41</sup>

### **Oral Steroids**

According to the ESPGHAN and NASPGHAN guideline, oral steroids are effective in inducing but not maintaining remission. Oral steroids downregulate pro-inflammatory cytokines by the inhibition of protein synthesis and transcription.

In pediatric UC, remission is typically induced using corticosteroids, aminosalicylates, or a combination of both, with maintenance therapy primarily relying on aminosalicylate monotherapy.<sup>42</sup>

### **Antibiotics and Probiotics**

Antibiotics can be used to induce remission in perianal fistulizing disease. Further investigations are required to evaluate the efficacy of these agents in IBD.<sup>43</sup>

### **Biological agents**

Biologic therapy is recommended in induction and maintenance therapy (**Table 3**).<sup>3</sup>

### **Nutritional therapy**

Exclusive enteral nutrition (EEN) can be used to induce remission in CD while partial enteral nutrition (PEN) is used in maintaining remission.<sup>44</sup> Other dietary approaches that can be used as adjuvant maintenance therapy include PEN, specific carbohydrate diet, anti-inflammatory diet, low FODMAP (Fermentable Oligosaccharides, Disaccharides, Monosaccharides And Polyols) diet, and paleolithic diet.<sup>45</sup>

### **Surgery**

Surgery is indicated in emergency cases such as perforation and complete bowel obstruction. Aside from perforations, surgery is recommended in patients with medical treatment failure, bleeding, and toxic megacolon. Elective surgeries are indicated in patients with chronic disease, chronic steroid dependent and high level of dysplasia.<sup>46</sup>

**Table 3.** Pediatric IBD Biological Agents Treatments

| Mechanism of Action                       | Generic Name | Route of administration                           |   |
|---|--------------|---|---|
| Anti TNF                                  | Infliximab   | IV  | CD : Start with intensive treatment in patients who have predictors of poor outcomes and/or significant growth delays. For others, escalate treatment if there is no response to conventional induction therapies (such as EEN or steroids) or maintenance therapies (like methotrexate or thiopurines).<br>UC: Lack of response or loss of effectiveness to conventional induction or maintenance therapy (such as aminosalicylate monotherapy or combination therapy with a thiopurine), also indicated for steroid-dependent UC. |
|   | Adalimumab   | SC  | CD : Begin with aggressive treatment for patients who have predictors of poor outcomes and/or severe growth delays. For others, escalate treatment if there is no response to conventional induction or maintenance therapies.<br>UC : Loss of response to infliximab or intolerance to infliximab  |
|   | Golimumab    | SC  | UC : Loss of response to standard maintenance therapy   |
| Anti-integrin (α4β7 integrin heterodimer) | Vedolizumab  | IV  | UC and CD: Anti-TNF failure (nonresponse or loss of response)   |
| Anti-IL-12 and anti-IL-23                 | Ustekinumab  | Single IV-loading dose, then SC maintenance doses | CD: Anti-TNF failure (nonresponse or loss of response)  |

## Conclusion

Inflammatory bowel disease (IBD) presents unique challenges in pediatric patients, characterized by distinctive clinical manifestations and diagnostic complexities. Early and accurate diagnosis, combined with tailored management strategies, including pharmacotherapy and supportive care, is crucial for optimizing outcomes and improving quality of life.

## Acknowledgment

The authors would like to thank Airlangga University for the support and guidance during the process of writing this literature review.

## Funding

This study was not supported by any external funding.

## Conflict of Interest

None declared.

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Volume 3 / No. 3  
August 2024



Published by  
Indonesian Society of Pediatric Gastroenterology, Hepatology, and Nutrition

