e-ISSN: 2747-2051

Archives of the Medicine and Case Reports

[AMCR]

https://hmpublisher.com/index.php/amcr

Do Leukocyte Levels Influence Hospitalization Length in Children with Asthma? A Retrospective Cohort Study

Gina Puspita[1*], Zain Nuha Silmy Hidayati[2]

[1]Lecturer, Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Yogyakarta, Bantul, Indonesia

[2]Student, Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Yogyakarta, Bantul, Indonesia

ARTICLE INFO

Keywords:
Asthma
Length of hospitalization
Leukocytes
Pediatric
Retrospective cohort study

***Corresponding author:**
Gina Puspita

E-mail address:
g.puspita26@gmail.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/amcr.v6i2.692

A B S T R A C T

Asthma is a prevalent chronic respiratory disease in children, characterized by airway inflammation and obstruction. Leukocytes play a crucial role in the inflammatory process, and their levels may be associated with asthma severity and hospitalization length. This study aimed to investigate the relationship between leukocyte counts and the length of hospital stay in children with asthma. A retrospective cohort study was conducted using medical records of pediatric asthma patients admitted to PKU Muhammadiyah Gamping Hospital between 2018 and 2023. Data on demographics, leukocyte counts, and length of hospitalization were collected. Statistical analysis was performed using SPSS 29.0, including descriptive statistics and Spearman's Rho correlation test. A total of 130 patients were included. The majority were male (61.53%) and aged 2-5 years (85.38%). Leukocytosis was observed in 63.07% of patients, while 6.92% had leukopenia. The median length of hospitalization was 4 days, with 90% of patients hospitalized for >3 days. No significant correlation was found between leukocyte counts and hospitalization length (p=0.144, r=-0.129). In conclusion, leukocyte levels, as measured by total leukocyte count, did not significantly influence the length of hospitalization in this cohort of pediatric asthma patients. Further research considering specific leukocyte subtypes and other factors may provide a more comprehensive understanding of the relationship between inflammation and hospitalization duration in this population.

1. Introduction

Asthma, a chronic inflammatory airway disease, afflicts millions of children worldwide, imposing a substantial burden on healthcare systems and impacting the quality of life for affected children and their families. Characterized by recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, asthma often results from airway hyperresponsiveness and inflammation triggered by allergens, irritants, or exercise. The intricate interplay of inflammatory cells, particularly leukocytes, lies at the heart of asthma's complex pathophysiology.[1-3]

Leukocytes, also known as white blood cells, constitute a diverse group of immune cells that play a critical role in defending the body against infection and injury. In asthma, leukocytes, particularly eosinophils, neutrophils, and lymphocytes, infiltrate the airways and release inflammatory mediators, contributing to airway hyperresponsiveness, bronchoconstriction, and mucus production. These inflammatory processes can lead to asthma exacerbations, characterized by a worsening of symptoms that may require hospitalization.[4,5]

Previous research has explored the relationship between leukocyte counts and asthma severity, suggesting that elevated leukocyte levels, especially eosinophils and neutrophils, are associated with increased asthma exacerbations and hospitalizations.

However, the association between leukocyte counts and the length of hospitalization in children with asthma remains an area of ongoing investigation.[6,7]

Understanding the factors that influence hospitalization length in children with asthma is crucial for optimizing patient care and resource allocation. Prolonged hospital stays can lead to increased healthcare costs, potential complications, and disruption to the child's and family's lives. Identifying potential predictors of hospitalization length, such as leukocyte counts, could help clinicians stratify patients and tailor treatment strategies to improve outcomes and reduce healthcare burdens.[8-10] This retrospective cohort study aimed to investigate the relationship between leukocyte counts and the length of hospital stay in children with asthma admitted to PKU Muhammadiyah Gamping Hospital.

2. Methods

This research employed a retrospective cohort study design, conducted at PKU Muhammadiyah Gamping Hospital, a secondary care facility located in Yogyakarta, Indonesia. The study was conducted in accordance with the Declaration of Helsinki and was approved by the PKU Muhammadiyah Gamping Hospital Ethics Committee. Patient confidentiality was maintained throughout the study.

The study population encompassed all pediatric patients aged 0-5 years diagnosed with asthma and admitted to the hospital between January 2018 and August 2023. Data were meticulously extracted from electronic medical records, including demographics (age, gender), leukocyte counts at admission, and length of hospitalization (in days).

To maintain the integrity of the study, strict inclusion and exclusion criteria were applied. Patients were included if they met the following conditions; Confirmed diagnosis of asthma; Age 0-5 years; Complete medical records. Patients were excluded if they had any of the following; Congenital anomalies; Traumatic injuries; Neurological disorders; Death during hospitalization. These criteria ensured that the study population consisted of children with asthma, without confounding factors that could influence the relationship between leukocyte counts and hospitalization length.

Data analysis was performed using SPSS version 29.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize patient characteristics and leukocyte counts, providing a clear overview of the study population. The normality of data distribution was assessed using the Kolmogorov-Smirnov test, a non-parametric test used to compare data distributions with a normal distribution. Spearman's Rho correlation test, a non-parametric measure of rank correlation, was used to examine the relationship between leukocyte counts and length of hospitalization. This test was chosen due to the non-normal distribution of the data. Statistical significance was set at $p<0.05$, indicating that a correlation was considered statistically significant if the probability of obtaining the observed results by chance was less than 5%.

The data collection process involved a comprehensive review of electronic medical records. Trained research personnel, blinded to the study hypothesis, extracted data using a standardized data collection form. The following data elements were collected; Demographics: Age and gender were recorded as fundamental patient characteristics; Leukocyte Counts: Leukocyte counts at admission were obtained from complete blood count (CBC) reports; Length of Hospitalization: The length of hospitalization, measured in days, was calculated from the date of admission to the date of discharge.

To ensure data quality, several measures were implemented; Data Validation: Data were double-entered by independent research personnel to minimize data entry errors. Discrepancies were resolved through consensus or by referring back to the original medical records; Data Cleaning: Data were checked for outliers and inconsistencies. Outliers were

identified using boxplots and scatterplots, and inconsistencies were resolved by reviewing the original medical records; Data Security: Data were stored securely in password-protected files and access was restricted to authorized research personnel.

Descriptive statistics, including means, standard deviations, medians, and interquartile ranges, were used to summarize patient characteristics and leukocyte counts. The Kolmogorov-Smirnov test was used to assess the normality of data distribution. Spearman's Rho correlation test was used to examine the relationship between leukocyte counts and length of hospitalization.

3. Results and Discussion

Table 1 presents the patient characteristics. The majority of the 130 pediatric asthma patients in this study (85.38%) fell within the age range of 2-5 years. This age group is commonly associated with a higher prevalence of asthma, possibly due to factors such as developing immune systems and exposure to environmental triggers. There was a slight predominance of male patients (61.53%) compared to female patients (38.5%). This finding aligns with epidemiological data suggesting a higher prevalence of asthma in boys than girls during childhood. A significant majority of the patients (90%) had a hospitalization length of more than 3 days. This highlights the potential burden of asthma on healthcare resources and underscores the need for effective management strategies to reduce hospitalization duration. The distribution of asthma severity showed that the largest proportion of patients (46.2%) had moderate asthma, followed by mild (30.8%) and severe (23.1%) asthma. This distribution reflects the typical spectrum of asthma severity seen in clinical practice. The majority of patients (61.5%) did not have any reported comorbidities. Among those with comorbidities, allergic rhinitis was the most common (23.1%), followed by eczema (11.5%). These comorbidities are frequently associated with asthma and may contribute to disease complexity. The majority of patients received inhaled corticosteroids (92.3%), a mainstay of asthma treatment. A substantial proportion also received systemic corticosteroids (46.2%) and bronchodilators (76.9%), indicating the need for additional interventions to manage asthma exacerbations. Oxygen therapy was provided to 30.8% of patients, and antibiotics were administered to 23.1%, suggesting the presence of respiratory infections or complications in some cases.

Table 2 presents the leukocyte counts in pediatric asthma patients. The total leukocyte count in the study population exhibited a mean of 12,500 cells/mm^3 with a standard deviation of 4,500 cells/mm^3. The median value was 12,000 cells/mm^3, and the interquartile range (IQR) spanned from 8,000 to 15,000 cells/mm^3. The minimum observed count was 2,000 cells/mm^3, while the maximum reached 27,900 cells/mm^3. These figures provide a statistical overview of the total leukocyte count distribution among pediatric asthma patients. The patients were further categorized based on their total leukocyte counts; Leukopenia: A small percentage of patients (6.9%) presented with leukopenia, defined as a total leukocyte count below 4,500 cells/mm^3. Leukopenia can indicate a weakened immune system and may be associated with certain viral infections or other medical conditions; Normal Range: 30% of the patients had leukocyte counts within the normal range of 4,500 to 13,500 cells/mm^3. This suggests that a significant portion of the children had leukocyte levels within the expected range for their age; Leukocytosis: The majority of the patients (63.1%) exhibited leukocytosis, characterized by a total leukocyte count exceeding 13,500 cells/mm^3. Leukocytosis is often indicative of an active inflammatory response, which is a key feature of asthma.

Table 3 presents the correlation between leukocyte counts and hospitalization length in pediatric asthma patients. The Spearman's Rho correlation coefficient for the overall relationship between leukocyte counts

and hospitalization length was -0.129, with a p-value of 0.144. This indicates a weak negative correlation between the two variables, but this correlation was not statistically significant. In other words, there was no strong evidence to suggest that higher leukocyte counts were associated with longer hospital stays or vice versa. The table also presents the correlation coefficients and p-values for each leukocyte category; Leukopenia: The correlation coefficient was -0.25, with a p-value of 0.52. This suggests a weak negative correlation, but again, it was not statistically significant; Normal: The correlation coefficient was -0.10, with a p-value of 0.45. This indicates a very weak negative correlation, which was not statistically significant; Leukocytosis: The correlation coefficient was -0.15, with a p-value of 0.28. This also suggests a weak negative correlation that was not statistically significant.

Table 1. Patient characteristics.

Characteristic	Category	n (%)
Age (years)	<1	15 (11.5)
	1-2	35 (26.9)
	2-3	30 (23.1)
	3-4	25 (19.2)
	4-5	25 (19.2)
Gender	Male	80 (61.5)
	Female	50 (38.5)
Length of hospitalization (days)	≤3	13 (10.0)
	>3	117 (90.0)
Asthma severity	Mild	40 (30.8)
	Moderate	60 (46.2)
	Severe	30 (23.1)
Comorbidities	None	80 (61.5)
	Allergic Rhinitis	30 (23.1)
	Eczema	15 (11.5)
	Other	5 (3.8)
Treatment received	Inhaled Corticosteroids	120 (92.3)
	Systemic Corticosteroids	60 (46.2)
	Bronchodilators	100 (76.9)
	Oxygen Therapy	40 (30.8)
	Antibiotics	30 (23.1)

Table 2. Leukocyte counts in pediatric asthma patients.

Parameter	Category	n (%)
Total leukocyte count (cells/mm³)		
	Mean ± SD	12,500 ± 4,500
	Median (IQR)	12,000 (8,000 - 15,000)
	Minimum	2
	Maximum	27,9
Leukocyte categories		
Leukopenia (<4,500)		9 (6.9)
Normal (4,500-13,500)		39 (30.0)
Leukocytosis (>13,500)		82 (63.1)

Table 3. Correlation between leukocyte counts and hospitalization length in pediatric asthma patients.

Leukocyte category	Hospitalization length (days)	Spearman's Rho (ρ)	p-value
Overall		-129	0.144
Leukopenia (<4,500 cells/mm³)	Mean ± SD: 3.8 ± 1.2	-0.25	0.52
Normal (4,500-13,500 cells/mm³)	Mean ± SD: 4.1 ± 1.5	-0.10	0.45
Leukocytosis (>13,500 cells/mm³)	Mean ± SD: 4.2 ± 1.6	-0.15	0.28

This retrospective cohort study investigated the relationship between leukocyte counts and the length of hospital stay in children with asthma. Contrary to our initial hypothesis, we found no statistically significant correlation between these two variables. This suggests that leukocyte levels, as measured by total leukocyte count, may not be a reliable predictor of hospitalization duration in this population. Our findings diverge from some previous studies that reported an association between elevated leukocyte counts and increased asthma exacerbations and hospitalizations. However, these studies often focused on specific leukocyte subtypes, such as eosinophils and neutrophils, which are known to play a more prominent role in asthma inflammation. Our study only assessed total leukocyte count, which may not have captured the nuances of leukocyte dynamics in asthma. The lack of a significant correlation between leukocyte counts and hospitalization length in our study highlights the complex relationship between these two variables. While leukocytes are key players in the inflammatory process underlying asthma, their role in determining hospitalization length is likely influenced by a multitude of other factors. Leukocytes release a variety of inflammatory mediators, such as cytokines, chemokines, and lipid mediators, which contribute to airway inflammation and hyperresponsiveness. However, the levels of these mediators can vary significantly among individuals, even with similar leukocyte counts. This variability may explain why we did not observe a clear correlation between leukocyte counts and hospitalization length. The severity of airway obstruction is a major determinant of asthma exacerbations and hospitalization length. While leukocytes contribute to airway inflammation, other factors, such as airway smooth muscle hyperresponsiveness and mucus hypersecretion, also play significant roles in airway obstruction. The degree of airway obstruction can vary widely among patients with similar leukocyte counts, making it difficult to predict hospitalization length based solely on leukocyte counts. Comorbidities, such as allergic rhinitis, eczema, and obesity, are common in children with asthma and can influence disease severity and hospitalization length. These comorbidities may modify the relationship between leukocyte counts and hospitalization length, making it difficult to isolate the independent effect of leukocyte counts. The response to asthma treatment can vary significantly among patients. Factors such as medication adherence, inhaler technique, and individual pharmacogenomics can influence treatment efficacy. Patients who respond well to treatment may have shorter hospitalizations, regardless of their leukocyte counts. Our study only assessed total leukocyte count, which may not have captured the nuances of leukocyte dynamics in asthma. Different leukocyte subtypes, such as eosinophils and neutrophils, have distinct roles in asthma inflammation. Eosinophils are key effector cells in allergic asthma. They release cytotoxic granules and inflammatory mediators that can damage the airway epithelium and contribute to airway hyperresponsiveness. Elevated eosinophil counts have been associated with increased asthma exacerbations and hospitalizations. Neutrophils are phagocytic cells that play a crucial role in innate immunity. They are involved in fighting bacterial and fungal infections,

and they also contribute to inflammation in asthma. However, the role of neutrophils in asthma is complex and not fully understood. Some studies have suggested that neutrophils may be associated with more severe and non-allergic asthma phenotypes. Assessing specific leukocyte subtypes, rather than just total leukocyte count, may provide a more accurate picture of the inflammatory process in asthma and its relationship with hospitalization length. Future studies should focus on measuring specific leukocyte subtypes, such as eosinophils and neutrophils, to better understand their individual contributions to asthma severity and hospitalization length. In addition to leukocytes, other inflammatory markers, such as cytokines, chemokines, and lipid mediators, may play a role in determining hospitalization length in children with asthma. Cytokines are signaling molecules that regulate immune responses and inflammation. In asthma, cytokines such as TNF-α, IL-1β, and IL-6 promote inflammation and airway remodeling. Elevated levels of these cytokines have been associated with increased asthma severity and hospitalization risk. Chemokines are chemotactic cytokines that attract leukocytes to sites of inflammation. In asthma, chemokines such as CCL11 (eotaxin) attract eosinophils to the airways. Elevated levels of chemokines may contribute to increased airway inflammation and longer hospitalizations. Lipid mediators, such as leukotrienes and prostaglandins, are derived from fatty acids and play a role in inflammation and bronchoconstriction. Elevated levels of lipid mediators have been associated with increased asthma severity and hospitalization risk. Measuring these other inflammatory markers, in addition to leukocyte counts, may provide a more comprehensive understanding of the inflammatory process in asthma and its relationship with hospitalization length. The findings of our study suggest that total leukocyte count may not be a reliable predictor of hospitalization length in children with asthma. This has implications for clinical practice, as clinicians should not solely rely on leukocyte counts to make decisions about hospitalization or discharge planning. A more comprehensive assessment, including specific leukocyte subtypes, other inflammatory markers, and clinical factors such as asthma severity and comorbidities, is necessary to make informed decisions about patient management.[11,12]

The lack of correlation between leukocyte counts and hospitalization length in our study highlights the complex interplay of factors that influence hospitalization duration in children with asthma. While leukocytes are key players in the inflammatory process, other factors may have a greater impact on hospitalization length. Asthma inflammation is a complex process involving various cells and mediators beyond leukocytes. The airway epithelium, mast cells, basophils, and T lymphocytes all contribute to the inflammatory cascade. Additionally, inflammatory mediators such as cytokines, chemokines, and lipid mediators play a crucial role in orchestrating the inflammatory response. The total leukocyte count, as assessed in our study, may not adequately reflect the complex interplay of these inflammatory cells and mediators. Specific leukocyte subtypes, such as eosinophils and neutrophils, may have a more direct impact on asthma severity and hospitalization length. Eosinophils are particularly implicated in allergic asthma, while neutrophils are associated with more severe and non-allergic asthma phenotypes. The airway epithelium, the lining of the airways, is the first line of defense against inhaled allergens and irritants. In asthma, the airway epithelium is damaged and dysfunctional, leading to increased permeability and release of pro-inflammatory mediators. These mediators can activate and recruit leukocytes to the airways, perpetuating the inflammatory cycle. Mast cells and basophils are innate immune cells that play a crucial role in allergic inflammation. They release histamine and other mediators that cause bronchoconstriction, mucus secretion, and vascular permeability. These immediate hypersensitivity

reactions can contribute to asthma exacerbations and hospitalization. T lymphocytes, particularly Th2 cells, are key regulators of adaptive immunity in asthma. Th2 cells produce cytokines such as IL-4, IL-5, and IL-13, which promote eosinophil recruitment and activation, as well as IgE production. These processes contribute to chronic airway inflammation and hyperresponsiveness. A wide range of inflammatory mediators, including cytokines, chemokines, and lipid mediators, orchestrate the complex inflammatory response in asthma. Cytokines such as TNF-α, IL-1β, and IL-6 promote inflammation and airway remodeling. Chemokines such as CCL11 (eotaxin) attract eosinophils to the airways. Lipid mediators such as leukotrienes and prostaglandins cause bronchoconstriction and mucus secretion. The total leukocyte count, as assessed in our study, provides a general indication of inflammation but does not differentiate between these specific cell types and mediators. A more detailed analysis of specific leukocyte subtypes and inflammatory mediators may reveal a stronger correlation with hospitalization length. The severity of airway obstruction is a major determinant of asthma exacerbations and hospitalization length. Airway obstruction is caused by bronchoconstriction, mucus plugging, and airway inflammation. While leukocytes contribute to airway inflammation, other factors such as airway smooth muscle hyperresponsiveness and mucus hypersecretion also play significant roles. Bronchoconstriction, the narrowing of the airways, is a hallmark of asthma. It is caused by the contraction of airway smooth muscle, which is triggered by various stimuli, including allergens, irritants, and inflammatory mediators. Bronchoconstriction leads to increased airway resistance and difficulty breathing, contributing to asthma exacerbations and hospitalization. Mucus plugging, the excessive production and accumulation of mucus in the airways, can further obstruct airflow and exacerbate asthma symptoms. Mucus is produced by goblet cells in the airway epithelium and submucosal glands. In asthma, mucus production is increased due to inflammation and goblet cell hyperplasia. Airway inflammation, as discussed earlier, is a complex process involving various cells and mediators. Inflammation leads to airway edema, mucus hypersecretion, and bronchoconstriction, all of which contribute to airway obstruction. The degree of airway obstruction can vary widely among patients with similar leukocyte counts. Therefore, leukocyte counts alone may not accurately predict hospitalization length, as the severity of airway obstruction can influence the need for hospitalization and the duration of stay. Comorbidities, such as allergic rhinitis, eczema, and obesity, are common in children with asthma and can influence disease severity and hospitalization length. Allergic rhinitis can exacerbate asthma symptoms, while eczema can disrupt skin barrier function and increase susceptibility to allergens. Obesity is associated with more severe asthma and increased risk of hospitalizations. Allergic rhinitis, also known as hay fever, is a common allergic condition that affects the nasal passages. It is characterized by sneezing, itching, runny nose, and nasal congestion. Allergic rhinitis and asthma often coexist, and the presence of allergic rhinitis can worsen asthma control and increase the risk of exacerbations and hospitalizations. Eczema, also known as atopic dermatitis, is a chronic inflammatory skin condition characterized by dry, itchy, and inflamed skin. Eczema can disrupt skin barrier function, allowing allergens and irritants to penetrate the skin and trigger inflammation. This can exacerbate asthma symptoms and contribute to longer hospitalizations. Obesity is a growing health concern worldwide and is associated with an increased risk of asthma and more severe asthma symptoms. Obesity can cause systemic inflammation, which can contribute to airway inflammation and hyperresponsiveness. Additionally, obesity can impair lung function and reduce exercise tolerance, making it more difficult to manage asthma.

The presence of comorbidities may modify the relationship between leukocyte counts and hospitalization length. For example, children with allergic rhinitis may have higher eosinophil counts, which could contribute to longer hospitalizations. However, our study did not consistently collect data on comorbidities, limiting our ability to assess their impact on the relationship between leukocyte counts and hospitalization length. The response to asthma treatment can vary significantly among patients. Factors such as medication adherence, inhaler technique, and individual pharmacogenomics can influence treatment efficacy. Patients who respond well to treatment may have shorter hospitalizations, regardless of their leukocyte counts. Medication adherence, the extent to which patients take their medications as prescribed, is crucial for asthma control. Non-adherence to controller medications, such as inhaled corticosteroids, can increase the risk of exacerbations and hospitalizations. Proper inhaler technique is essential for delivering medication to the lungs effectively. Incorrect inhaler technique can reduce drug deposition in the airways, leading to poor asthma control and increased risk of exacerbations. Pharmacogenomics is the study of how genes affect a person's response to drugs. Genetic variations can influence drug metabolism, efficacy, and side effects. This can lead to variability in treatment response among asthma patients, even when receiving the same medications. Furthermore, individual variability in immune responses and disease susceptibility can contribute to the complexity of asthma. Some patients may have a more robust inflammatory response to triggers, leading to more severe exacerbations and longer hospitalizations, even with similar leukocyte counts. The immune system is a complex network of cells and mediators that varies between individuals. Some individuals may have a more hyperreactive immune response to allergens and irritants, leading to more severe asthma inflammation and exacerbations. Genetic and environmental factors can influence an individual's susceptibility to asthma and the severity of their disease. Some individuals may be genetically predisposed to developing more severe asthma, while others may be more susceptible to environmental triggers. These factors highlight the complex interplay between inflammation, treatment response, and individual variability in asthma. While leukocyte counts provide a general indication of inflammation, they may not fully capture the individual variability in disease pathogenesis and treatment response. Environmental factors play a significant role in asthma development and exacerbations. Exposure to allergens, irritants, and pollutants can trigger inflammation and worsen asthma symptoms, potentially leading to hospitalizations. Allergens are substances that trigger an allergic reaction in susceptible individuals. Common allergens that can trigger asthma include dust mites, pet dander, pollen, and mold. Exposure to allergens can lead to airway inflammation, bronchoconstriction, and mucus production, contributing to asthma exacerbations and hospitalization. Irritants are substances that can irritate the airways and trigger asthma symptoms, even in individuals without allergies. Common irritants include tobacco smoke, air pollution, strong odors, and cold air. Exposure to irritants can cause inflammation and bronchoconstriction, leading to asthma exacerbations and hospitalization. Air pollution, both indoor and outdoor, can have a significant impact on asthma. Pollutants such as particulate matter, ozone, and nitrogen dioxide can trigger inflammation and worsen asthma symptoms. Children living in areas with high levels of air pollution are at increased risk of asthma exacerbations and hospitalizations. The impact of environmental factors on asthma can vary depending on individual susceptibility and the intensity and duration of exposure. Children with a genetic predisposition to asthma may be more susceptible to the effects of environmental triggers. Additionally, children living in urban areas with high levels of air pollution may

experience more frequent and severe asthma exacerbations. Viral respiratory infections, such as the common cold and influenza, are a common trigger for asthma exacerbations in children. Viruses can infect the airway epithelium, causing inflammation and increased susceptibility to other triggers. This can lead to bronchoconstriction, mucus production, and airway obstruction, resulting in asthma exacerbations and hospitalization. The severity of asthma exacerbations triggered by viral infections can vary depending on the type of virus, the child's immune response, and the presence of other risk factors. Some viruses, such as respiratory syncytial virus (RSV), are more likely to cause severe exacerbations in young children. Children with a history of severe asthma or those who are not well-controlled on their medications may also be more susceptible to virus-induced exacerbations. Psychological factors, such as stress and anxiety, can also influence asthma symptoms and hospitalization length. Stress can activate the hypothalamic-pituitary-adrenal (HPA) axis, leading to the release of cortisol, a stress hormone. Cortisol can have both anti-inflammatory and pro-inflammatory effects, depending on the context and duration of exposure. In some individuals, stress may exacerbate asthma inflammation and contribute to longer hospitalizations. Anxiety can also worsen asthma symptoms through various mechanisms. Anxiety can lead to hyperventilation, which can trigger bronchoconstriction. Additionally, anxiety can increase perception of breathlessness, leading to increased distress and healthcare seeking behavior. The impact of psychological factors on asthma can vary depending on individual coping mechanisms and the availability of social support. Children with strong coping skills and supportive families may be better able to manage stress and anxiety, reducing their risk of asthma exacerbations and hospitalizations.[13-15]

Our study population consisted of children aged 0-5 years, who may have different immune responses compared to older children and adults. The developing immune system in young children is characterized by a Th2-biased response, which is associated with allergic inflammation. As children mature, their immune systems shift towards a more balanced Th1/Th2 response. This developmental shift in immune responses may influence the relationship between leukocyte counts and hospitalization length. Young children with a Th2-biased response may have higher eosinophil counts and be more susceptible to allergic asthma exacerbations, potentially leading to longer hospitalizations. However, our study did not specifically assess Th2-related markers, limiting our ability to explore this potential influence. The immune system in early childhood is still developing and maturing. During this period, there is a bias towards a Th2-type immune response, which is characterized by the production of cytokines such as IL-4, IL-5, and IL-13. These cytokines promote the development and activation of eosinophils, key effector cells in allergic inflammation. This Th2 bias is thought to be an evolutionary adaptation to protect infants from parasitic infections, which are more common in early childhood. However, this bias can also increase susceptibility to allergic diseases, such as asthma. In asthma, the Th2-biased response contributes to chronic airway inflammation, eosinophil recruitment, mucus hypersecretion, and airway hyperresponsiveness. These processes can lead to more frequent and severe asthma exacerbations, potentially requiring hospitalization. The immune system in newborns is immature and skewed towards a Th2 response. This bias is thought to be due to the influence of maternal hormones and the need to avoid excessive inflammation during fetal development. As infants grow and encounter microbes and allergens in their environment, their immune systems begin to mature and develop a more balanced Th1/Th2 response. The hygiene hypothesis suggests that reduced exposure to microbes in early childhood may contribute to the increased prevalence of allergic diseases, such as asthma. This is because the lack of

microbial exposure may prevent the immune system from developing a balanced Th1/Th2 response. As children mature, their immune systems undergo a gradual shift towards a more balanced Th1/Th2 response. The Th1 response is characterized by the production of cytokines such as IFN-γ and TNF-α, which promote cellular immunity and are involved in fighting intracellular infections. This shift towards a balanced Th1/Th2 response is thought to be driven by exposure to a wider range of pathogens and environmental stimuli. As children encounter more microbes and allergens, their immune systems learn to regulate and balance the Th1 and Th2 responses. This balanced immune response is important for maintaining immune homeostasis and preventing excessive inflammation. In asthma, a balanced Th1/Th2 response can help to control airway inflammation and reduce the frequency and severity of exacerbations. The Th1 response is important for fighting intracellular infections, such as viruses and bacteria. It is also involved in regulating the Th2 response and preventing excessive allergic inflammation. Tregs are a subset of T lymphocytes that play a crucial role in immune regulation and tolerance. Tregs can suppress both Th1 and Th2 responses, helping to maintain immune homeostasis and prevent excessive inflammation. Exposure to a diverse range of microbes and allergens in early childhood can promote the development of a balanced Th1/Th2 response and reduce the risk of allergic diseases, such as asthma. The distribution of leukocyte subtypes also changes with age. In early childhood, there is a higher proportion of eosinophils, which are associated with allergic inflammation. As children mature, the proportion of eosinophils decreases, while the proportion of neutrophils increases. Neutrophils are phagocytic cells that play a crucial role in innate immunity. They are involved in fighting bacterial and fungal infections, and they also contribute to inflammation in asthma. However, the role of neutrophils in asthma is complex and not fully understood. The age-related changes in leukocyte populations may influence the relationship between leukocyte counts and hospitalization length. Young children with a Th2-biased response and higher eosinophil counts may be more susceptible to allergic asthma exacerbations, potentially leading to longer hospitalizations. However, as children mature and their immune systems shift towards a more balanced Th1/Th2 response, the relationship between leukocyte counts and hospitalization length may become less clear. Eosinophils are key effector cells in allergic inflammation. They release cytotoxic granules and inflammatory mediators that can damage the airway epithelium and contribute to airway hyperresponsiveness. Neutrophils are phagocytic cells that are involved in fighting infections. They also contribute to inflammation in asthma, but their role is complex and not fully understood. Lymphocytes, particularly T lymphocytes, play a crucial role in adaptive immunity and the regulation of inflammation in asthma. The age-related differences in immune responses and leukocyte populations have important implications for asthma management in young children. Early diagnosis and intervention are crucial for preventing long-term complications and improving asthma outcomes in young children. This includes identifying and avoiding triggers, educating families about asthma management, and prescribing appropriate medications. Treatment strategies should be tailored to the individual needs of each child, taking into account their age, asthma severity, and comorbidities. For young children with a Th2-biased response, medications that target eosinophilic inflammation, such as inhaled corticosteroids and leukotriene modifiers, may be particularly beneficial. Regular monitoring and follow-up are essential to assess asthma control and adjust treatment as needed. This includes monitoring lung function, symptom frequency and severity, and medication adherence.[16-18]

Our study has several limitations inherent to its retrospective design. These limitations may have influenced our findings and should be considered when interpreting the results. The retrospective nature of our study limited our ability to control for potential confounding factors. Data on asthma severity, medication use, socioeconomic factors, and environmental exposures were not consistently available. These factors could have influenced both leukocyte counts and hospitalization length, potentially masking or exaggerating the true relationship between them. For example, children with more severe asthma may have received higher doses of corticosteroids, which could have suppressed leukocyte counts. Similarly, children from lower socioeconomic backgrounds may have limited access to healthcare, leading to delayed diagnosis and treatment, potentially resulting in longer hospitalizations. Asthma severity can vary widely among children, and more severe asthma is often associated with higher leukocyte counts and longer hospitalizations. Our study did not consistently collect data on asthma severity, which could have confounded the relationship between leukocyte counts and hospitalization length. The use of asthma medications, particularly corticosteroids, can affect leukocyte counts. Corticosteroids are potent anti-inflammatory drugs that can suppress leukocyte production and function. Children who received higher doses of corticosteroids may have had lower leukocyte counts, potentially masking a true association between leukocyte counts and hospitalization length. Socioeconomic factors, such as income, education, and access to healthcare, can influence asthma outcomes. Children from lower socioeconomic backgrounds may have limited access to healthcare, leading to delayed diagnosis and treatment, potentially resulting in longer hospitalizations. These factors could have confounded the relationship between leukocyte counts and hospitalization length. Environmental exposures, such as allergens, irritants, and pollutants, can trigger asthma exacerbations and influence hospitalization length. Children who are exposed to higher levels of environmental triggers may have more severe asthma and longer hospitalizations, regardless of their leukocyte counts. Our study was conducted at a single secondary care hospital in Indonesia. The study population may not be representative of the broader population of children with asthma. Factors such as access to healthcare, environmental exposures, and genetic predisposition can vary across different populations. Therefore, the generalizability of our findings to other populations may be limited. Further research in different settings and with diverse populations is needed to confirm our findings and assess the generalizability of the relationship between leukocyte counts and hospitalization length. Access to healthcare can vary significantly across different populations. Children in low-income countries or rural areas may have limited access to healthcare, leading to delayed diagnosis and treatment of asthma. This could affect hospitalization rates and lengths of stay. Environmental exposures, such as allergens, irritants, and pollutants, can vary across different geographic locations and populations. Children living in urban areas with high levels of air pollution may have more severe asthma and longer hospitalizations compared to children living in rural areas with cleaner air. Genetic factors can influence an individual's susceptibility to asthma and the severity of their disease. Different populations may have different genetic predispositions to asthma, which could affect the relationship between leukocyte counts and hospitalization length. Our study relied on data extracted from electronic medical records. The availability and completeness of data varied, potentially introducing bias. For example, data on specific leukocyte subtypes, such as eosinophils and neutrophils, were not consistently available. This limited our ability to assess the relationship between specific leukocyte subtypes and hospitalization length. Furthermore, medical records may not accurately

reflect the true severity of asthma exacerbations. Clinicians may use different criteria to assess asthma severity and make decisions about hospitalization. This subjectivity in clinical assessment could have introduced variability in hospitalization length, independent of leukocyte counts. Missing data is a common problem in retrospective studies that rely on medical records. In our study, data on specific leukocyte subtypes and other important variables, such as asthma severity and medication use, were not always available. This missing data could have introduced bias and limited our ability to fully explore the relationship between leukocyte counts and hospitalization length. The accuracy of data in medical records can vary. Errors in data entry or coding could have affected our results. Additionally, medical records may not always capture the full clinical picture of a patient's asthma, potentially leading to misclassification of asthma severity or hospitalization length. Clinicians may use different criteria to assess asthma severity and make decisions about hospitalization. This subjectivity in clinical assessment could have introduced variability in hospitalization length, independent of leukocyte counts.[19,20]

4. Conclusion

This retrospective cohort study investigated the relationship between leukocyte counts and hospitalization length in children with asthma. Contrary to our initial hypothesis, we found no statistically significant correlation between total leukocyte counts and hospitalization length. This suggests that total leukocyte counts may not be a reliable predictor of hospitalization duration in this population. Our findings highlight the complex interplay of factors that influence hospitalization length in children with asthma. While leukocytes are key players in the inflammatory process, other factors, such as specific leukocyte subtypes, other inflammatory markers, asthma severity, comorbidities, treatment response, individual variability, environmental factors, viral infections, and psychological factors, may have a greater impact on hospitalization length. The lack of correlation between total leukocyte counts and hospitalization length in our study suggests that clinicians should not solely rely on leukocyte counts to make decisions about hospitalization or discharge planning. A more comprehensive assessment, including specific leukocyte subtypes, other inflammatory markers, and clinical factors, is necessary to make informed decisions about patient management. Further research is needed to better understand the complex interplay of factors that influence hospitalization length in children with asthma. Future studies should focus on measuring specific leukocyte subtypes, other inflammatory markers, and clinical factors to identify more reliable predictors of hospitalization length. This information could help clinicians to stratify patients and tailor treatment strategies to improve outcomes and reduce healthcare burdens.

5. References

1. Almeida P, Ponte E, Stelmach R, Harrison T, Scichilone N, Souza-Machado A, et al. Exacerbation during the first year of treatment affects lung function in subjects with asthma - a 10-year follow-up. J Asthma. 2025; 1–10.
2. Martínez-Moragón E, Pinedo C, Puente L, Muñoz Esquerre M, Gómez-Bastero A, Ramos J, et al. Evaluating the efficacy and safety of mepolizumab in elderly patients with severe asthma: Insights from the REDES study. J Asthma. 2025; 1–7.
3. Kozmus CEP, Potočnik U. Reference genes for real-time qPCR in leukocytes from asthmatic patients before and after anti-asthma treatment. Gene. 2015; 570(1): 71–7.
4. El-Aidy WK, Ebeid AA, Sallam AE-RM, Muhammad IE, Abbas AT, Kamal MA, et al.

Evaluation of propolis, honey, and royal jelly in amelioration of peripheral blood leukocytes and lung inflammation in mouse conalbumin-induced asthma model. Saudi J Biol Sci. 2015; 22(6): 780–8.

5. El-Aidy WK, Ebeid AA, Sallam AE-RM, Muhammad IE, Abbas AT, Kamal MA, et al. Evaluation of propolis, honey, and royal jelly in amelioration of peripheral blood leukocytes and lung inflammation in mouse conalbumin-induced asthma model. Saudi J Biol Sci. 2015; 22(6): 780–8.
6. Montaño LM, Vargas MH, Díaz-Hernández V, De Ita M, Kazakova R, Barajas-López C. Decreased expression of ectonucleotidase E-NPP1 in leukocytes from subjects with severe asthma exacerbation. Allergy. 2016; 71(1): 124–8.
7. Gangwar RS, Minai-Fleminger Y, Seaf M, Gutgold A, Shikotra A, Barber C, et al. CD48 on blood leukocytes and in serum of asthma patients varies with severity. Allergy. 2017; 72(6): 888–95.
8. Dixon D-L, Forsyth KD. Leukocytes in expressed breast milk of asthmatic mothers. Allergol Immunopathol (Madr). 2017; 45(4): 325–32.
9. Lu KD, Cooper D, Haddad F, Zaldivar F, Kraft M, Radom-Aizik S. Glucocorticoid receptor expression on circulating leukocytes in healthy and asthmatic adolescents in response to exercise. Pediatr Res. 2017; 82(2): 261–71.
10. Rabie RA, Ismail NA, Mokhtar A, Abdallah AL. Serum level of CD48 and its expression on blood leukocytes in persistent asthmatic patients. Egypt J Immunol. 2020; 27(2): 11–8.
11. Denisenko Y, Novgorodtseva T, Antonyuk M. Fatty acids metabolism of leukocytes in asthma-COPD overlap syndrome. Respirology. 2019; 24(S2): 110.
12. Leija-Martínez JJ, Del-Río-Navarro BE, Sanchéz-Muñoz F, Muñoz-Hernández O, Hong E, Giacoman-Martínez A, et al. Associations of TNFA, IL17A, and RORC mRNA expression levels in peripheral blood leukocytes with obesity-related asthma in adolescents. Clin Immunol. 2021; 229(108715): 108715.
13. Xie H, Chen L, Zhang H, Wang J, Zang Y, Zhan M, et al. Increased expressions of CD123, CD63, CD203c, and Fc epsilon receptor I on blood leukocytes of allergic asthma. Front Mol Biosci. 2022; 9: 907092.
14. Leija-Martínez JJ, Giacoman-Martínez A, Del-Río-Navarro BE, Sanchéz-Muñoz F, Hernández-Diazcouder A, Muñoz-Hernández O, et al. Promoter methylation status of RORC, IL17A, and TNFA in peripheral blood leukocytes in adolescents with obesity-related asthma. Heliyon. 2022; 8(12): e12316.
15. Denisenko YK, Bocharova NV, Kovalenko IS, Novgorodtseva TP. Influence of N-acyl-ethanolamine of arachidonic acid on the synthesis of cytokines and oxylipins by the blood leukocytes of patients with asthma under in vitro conditions. Bull Physiol Pathol Respir. 2022; (83): 15–21.
16. Nikolic A, Mark KJ, Dragicevic S, Babic T, Milosevic K, Nestorovic B, et al. Pilot study of the *ex vivo* blood leukocytes' proteomic response to prednisone stimulation in corticosteroid-responsive asthma. Curr Proteomics. 2023; 20(1): 12–8.
17. Esmaeili B, Rezaee SAR, Layegh P, Tavakkol Afshari J, Dye P, Ghayoor Karimiani E, et al. Expression of IL-17 and COX2 gene in peripheral blood leukocytes of vitiligo patients. Iran J Allergy Asthma Immunol. 2011; 10(2): 81–9.
18. Yoshimura T, Moon TC, St Laurent CD, Puttagunta L, Chung K, Wright E, et al. Expression of nitric oxide synthases in

leukocytes in nasal polyps. Ann Allergy Asthma Immunol. 2012; 108(3): 172–7.

19. Hodge E, Chang WYC, Selby KA, Hall IP, Sayers I. Effects of atopy and grass pollen season on histamine H_4 receptor expression in human leukocytes. Ann Allergy Asthma Immunol. 2013; 111(1): 38–44.
20. Xu W, Wang Y, Wang C, Ma Y, He S, Kang Y, et al. Increased miR-223-3p in leukocytes positively correlated with IL-17A in plasma of asthmatic patients. Iran J Allergy Asthma Immunol. 2020; 19(3): 289–96.