Original Article

# The Relationship Between Urinary Bromotyrosine Levels and Eosinophils in Asthma and Non-Asthma Patients at Harum Melati Clinic, Pringsewu, Lampung, Indonesia

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## Abstract

**Background:** In the era of personalized medicine, biomarkers have become an important tool for detecting and predicting asthma episodes over the last decade, one of them is urinary bromotyrosine. It has several advantages as a potential biomarker for asthma, including its stability and the practicality of noninvasive urine sampling. Therefore, this study aims to investigate further the role of urinary bromotyrosine levels and their correlation with eosinophil levels in asthma patients.

**Methods:** This is an analytical observational study with a cross-sectional design. From May to December 2023, the study involved 82 patients from the Harum Melati Clinic in Pringsewu, Lampung, Indonesia. The participants underwent spirometry, differential leukocyte count, urinalysis, and chest X-rays. The severity of asthma obstruction was classified into asthmatic (n=72) as the case group, with non-asthmatic patients (n=10) serving as the control group. Urinary bromotyrosine levels were tested using the 3-BrY ELISA Kit EU3112.

**Results:** Urinary bromotyrosine levels were significantly higher in asthma patients compared to the non-asthma group (154.11 ng/mL vs. 11.87 ng/mL; *P*=0.0001). Furthermore, elevated eosinophil levels in asthma patients showed a strong correlation coefficient (0.307) with higher urinary bromotyrosine levels, indicating statistical significance (*P*=0.005).

**Conclusion:** This study found a significant difference in urinary bromotyrosine levels between asthmatic and non-asthmatic participants. There was a strong correlation between elevated eosinophil counts in patients with asthma and increased urinary bromotyrosine levels.

**Keywords:** asthma, eosinophils, urinary bromotyrosine

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## INTRODUCTION

Asthma is a prevalent non-communicable disease that greatly affects quality of life. The high number of asthma-related medical visits indicates chronic inflammation in the lower airways, which predisposes individuals to airway hyperresponsiveness and obstruction. If not properly managed, this condition can trigger exacerbations.

Worldwide, as reported by the World Health Organization (WHO) in 2021, an estimated 262 million people are affected by asthma, with an estimated 461,000 deaths attributed to the disease.[1] In Indonesia, based on the 2018 Riskesdas, the prevalence of asthma was 2.4%, with a relapse proportion of 57.5%.[2] Furthermore, a study by Soemarwoto et al in 2019 found that the prevalence of asthma among elementary school children in urban areas of Bandar Lampung, aged 10–17 years, was 11.5%, with a history of allergic rhinitis reported in 41.1% of cases.[3]

In the era of personalized medicine, the use of biomarkers for diagnosing and predicting asthma attacks has become an essential approach over the past decade.[4] Recent evidence also emphasizes the importance of phenotype- and endotype-based approaches in asthma management and biomarkerguided therapy.[5] A valid biomarker should possess several key characteristics, such as the ability to distinguish between disease and health with high positive predictive value and negative predictive value, provide information about disease prognosis, monitor treatment outcomes, be reproducible, analytically measurable with good performance, and cost-effective.[6]

Biomarkers in asthma are useful for assessing and studying exacerbations, but their primary function is to identify patients at increased risk of exacerbations.[6] In children and the elderly, the primary challenge is identifying biomarkers in samples that are easier to collect. One of the most easily obtainable samples from patients is urine, which contains various metabolic byproducts, including bromotyrosine (Br-Tyr).[7]

Bromotyrosine serves as a promising biomarker due to its stability and the ease of non-invasive urine sample collection.[7] Research by Wedes et al has demonstrated that eosinophils produce strong brominated oxidants, such as hypobromous acid, in the airways of asthma patients, which are activated by pro-inflammatory mediators. During respiratory inflammation, eosinophil activation leads to the release of granule proteins, including eosinophil peroxidase. Studies have shown that eosinophil peroxidase utilizes hydrogen peroxide, generated by superoxide dismutase, as a response to protect cells from oxidative stress. With the assistance of bromide binding, it forms reactive brominators, such as hypobromous acid, a highly potent antimicrobial oxidant that can brominate tyrosine protein residues to form 3-bromotyrosine, which is subsequently excreted in the urine.[8]

Research on the correlation between Br-Tyr and asthma has been conducted previously, including a 2011 study by Wedes et al that focused specifically on a pediatric population.[8] Additionally, in 2015, Cowan et al also compared the roles of biomarkers, including exhaled nitric oxide fraction (FeNO), sputum eosinophils, and urinary Br-Tyr levels, in response to corticosteroid therapy in asthma patients.[9] Therefore, this study aims to investigate further the role of urinary Br-Tyr levels and their correlation with eosinophil levels in asthma patients, particularly in adults.

## METHODS

This study is an observational analytic study with a cross-sectional design, which was conducted from May 2023 to December 2023 at Harum Melati Clinic, Pringsewu, Lampung, Indonesia. The study involved 82 patients, with 72 patients having asthma and 10 patients without asthma. This study used a consecutive sampling method. All asthma patients who attended Harum Melati Clinic, Pringsewu, Lampung, during the study period and fulfilled the inclusion criteria were recruited consecutively until the target sample size was reached. While the control group consisted of non-asthmatic subjects recruited from the same clinical setting during the same study period, a smaller number was intentional as a baseline comparator, so can evaluate urinary Br-Tyr levels among asthma patients receiving montelukast therapy and combination therapy.

The study subjects included patients with intermittent, mild persistent, or moderate persistent asthma who were not experiencing exacerbations during outpatient visits. Eligible participants of the inclusion criteria were newly diagnosed asthma patients or those with a prior physician diagnosis of asthma or those with a history of controlled asthma with spirometry findings showing a reduced $FEV_1/FVC$ ratio (<0.75) and/or significant bronchodilator reversibility (increase in $FEV_1$ ≥12% and ≥200 mL) based on the Global Initiative for Asthma (GINA) criteria.

Participants were excluded if they had acute respiratory infections at the time of sampling, chronic pulmonary diseases other than asthma (such as chronic obstructive pulmonary disease or bronchiectasis), systemic inflammatory or autoimmune diseases, renal or hepatic impairment, pregnancy, or incomplete clinical and laboratory data. In addition, participants who had received medications that could influence inflammatory or oxidative stress markers within the past three months were excluded. These medications included antihistamines, systemic corticosteroids, inhaled corticosteroids, and other immunomodulatory or anti-allergic drugs. Meanwhile, asthma control status was assessed clinically by the treating physician based on symptom evaluation, as no standardized asthma control questionnaire (e.g., ACT) was used.

The samples collected were urine spot samples obtained after a two-hour accumulation in the bladder to minimize variations in urinary creatinine levels. The collected urine had to be centrifuged at 2000 rpm for 10 minutes before analysis. The centrifuged urine samples were then analyzed by Enzyme-Linked Immunosorbent Assay (ELISA) to measure the absorbance of urinary Br-Tyr metabolites. In addition, study subjects also underwent chest X-rays, complete blood count tests, and spirometry.

The data were subsequently analyzed using SPSS (Statistical Product and Service Solution) version 26.0. Continuous variables were presented as mean±SD and median (minimum–maximum), while categorical variables were presented as frequencies and percentages. Clarified the statistical tests also used for continuous and categorical variables, including the use of the independent t-test, Mann–Whitney U test, chi-square test, and Fisher's exact test where appropriate.

## RESULTS

This study included 82 patients who met the inclusion and exclusion criteria, with 10 in the non-asthma group and 72 in the asthma group. The mean age of asthma patients was 39.67±18.10 years, while the mean age of the non-asthma group was 35.20±4.18 years, with a narrower age range (31–44 years), indicating that the non-asthma group was more homogeneous in age. The majority of asthma patients were female (66.7%), whereas the majority of the non-asthma group were male (70%).

The distribution of educational levels showed that most asthma patients had completed high school or vocational education (38.9%). Meanwhile, all non-asthmatic participants had a diploma degree (D3). Lower levels of education may affect patients' understanding of therapy and adherence to treatment. The average body mass index (BMI) of asthma patients was within the normal range (22.05±4.80 kg/m²), as was that of the non-asthma group (21.89±2.34 kg/m²). The greater variation in BMI values within the asthma group may indicate differences in lifestyle patterns and levels of physical activity.

Table 1. Participant Characteristics.

| Variable | Group | | *P* |
|---|---|---|---|
| | **Asthma (n= 72)** | **Non-asthma (n= 10)** | |
| Age (years) | | | |
| Mean±SD | 39.67±18.10 | 35.20±4.18 | 0.324 |
| Median (Min-Max) | 41.0 (6–69) | 33.50 (31-44) | |
| Sex | | | |
| Men | 24 (33.3%) | 7 (70.0% | 0.025 |
| Women | 48 (66.7%) | 3 (30.0%) | |
| Education | | | |
| Elementary School | 17 (23.6%) | 0 (0.0%) | 0.0001* |
| Junior High School | 8 (11.1%) | 0 (0.0%) | |
| High School | 28 (38.9%) | 0 (0.0%) | |
| Diploma | 4 (5.6%) | 10 (100%) | |
| Bachelor | 15 (20.8%) | 0 (0.0%) | |
| Body Mass Index (kg/m2) | | | |
| Mean±SD | 22.05±4.80 | 21.89±2.34 | 0.346 |
| Median (Min-Max) | 22.65 (10.10-35.40) | 22.7 (18.60-24.50) | |
| Allergen & environmental triggers | | | |
| Weather | 8 (11.1%) | 0 (0.0%) | 0.152 |
| Dust | 9 (12.5%) | 0 (0.0%) | |
| Smoke | 9 (12.5%) | 0 (0.0%) | |
| Unknown | 46 (63.9%) | 10 (100%) | |
| Brinkman Index | | | |
| Mild | 7 (9.7%) | 0 (0.0%) | 0.303 |
| Moderate | 0 (0.0%) | 0 (0.0%) | |
| Severe | 0 (0.0%) | 0 (0.0%) | |
| Non-smoker | 65 (90.3%) | 10 (100%) | |

Note: *significant $P<0.05$

The majority of participants in the asthma group were unaware of their allergy triggers (63.9%), while the rest reported triggers to weather conditions (11.1%), dust (12.5%), and smoke (12.5%). In contrast, all individuals in the non-asthma group had no history of allergies. This indicates that allergies and environmental triggers are a significant risk factor in the development of asthma, and awareness of allergy triggers is crucial for successful therapy. Most asthma patients (90.3%) and all individuals in the non-asthma group were non-smokers. The absence of heavy smokers in this study may reduce potential bias from exposure to cigarette smoke, which is known to increase oxidative stress and airway inflammation.

Table 2. Laboratory Examination Results.

| Variable | Asthma (n=72) | Non-Asthma (n=10) | P |
|---|---|---|---|
| Eosinophil (%) | | | |
| Mean±SD | 5.85±3.21 | 1.60±0.51 | 0.0001* |
| Median (Min-Max) | 5.00 (1-15) | 2.00 (1-2) | |
| Neutrophil (%) | | | |
| Mean±SD | 57.75±9.99 | 56.50±6.80 | 0.771 |
| Median (Min-Max) | 58.00 (39-79) | 57.50 (44-67) | |
| Bromotyrosine (ng/ml) | | | |
| Mean±SD | 154.11±136.09 | 11.87±11.07 | 0.0001* |
| Median (Min-Max) | 126.95 (0.30 – 548.70) | 10.81 (0.30-32.60) | |

Note: *significant *P*<0.05

Blood and urine test results showed that the asthma group had a mean eosinophil level of 5.85±3.21%, with a median of 5.00%. In contrast, the non-asthma group had a lower mean eosinophil level of 1.60±0.51%, with a median of 2.00%. This difference was statistically significant (*P*=0.0001).

The mean neutrophil level in the asthma group was 57.75±9.99%, with a median of 58.00%, whereas the non-asthma group had a mean of 56.50±6.80%, with a median of 57.50%. However, this difference was not statistically significant (*P*=0.771).

The mean urinary Br-Tyr level in the asthma group was 154.11±136.09 ng/mL. In contrast, the non-asthma group had a mean of 11.87±11.07 ng/mL (*P*=0.0001), indicating a significant difference between asthma patients and healthy individuals.

Table 3. Correlation Test Results of Urinary Br-Tyr Levels with Eosinophils and Neutrophils.

| Variable | Correlation coefficient | P |
|---|---|---|
| Br-Tyr Levels with Eosinophils | +0.307 | 0.005* |
| Br-Tyr Levels with Neutrophils | -0.020 | 0.860 |

Note: *significant *P*<0.05

Spearman's correlation analysis demonstrated a positive association between urinary Br-Tyr levels and eosinophil count (r=+0.307; *P*=0.005), indicating a weak-to-moderate association. This suggests that an increase in urinary Br-Tyr levels is associated with a higher eosinophil count. In contrast, the correlation coefficient for neutrophils was -0.020, indicating no significant relationship between urinary Br-Tyr levels and neutrophil count (*P*=0.860).

## DISCUSSIONS

In asthma patients, airway inflammation is typically associated with increased activity of inflammatory cells and the release of inflammatory mediators, such as leukotrienes. This inflammatory process contributes to enhanced oxidative stress, which may lead to elevated urinary Br-Tyr levels. In contrast, non-asthmatic individuals generally exhibit lower levels of inflammation and oxidative stress, resulting in lower urinary Br-Tyr levels. The significant difference observed between the two groups in this study reflects disparities in inflammatory burden and oxidative stress.[10] Because Br-Tyr is a biomarker of oxidative stress generated through eosinophil activity, particularly via eosinophil peroxidase-mediated reactions.[8,10]

In asthma, chronic airway inflammation leads to eosinophil activation and increased production of reactive oxidant species, thereby elevating Br-Tyr levels. The findings of this study, demonstrating significantly higher urinary Br-Tyr levels in asthma patients compared to non-asthma patients, are consistent with previous studies reporting elevated oxidative stress markers in asthma. Prior research has shown that Br-Tyr levels are elevated in patients with eosinophilic airway inflammation and may serve as a non-invasive biomarker reflecting disease activity and oxidative imbalance.[10,11]

Several studies have also demonstrated that urinary Br-Tyr correlates with eosinophilic inflammation and asthma severity, supporting its role as a marker of type 2 airway inflammation. For instance, earlier investigations reported that higher Br-Tyr levels were associated with increased eosinophil counts and poorer asthma control, suggesting its potential utility in monitoring disease progression and inflammatory status.[12] These findings are in line with the present study, which identified a positive correlation between urinary Br-Tyr levels and eosinophil counts.

Need to know, environmental factors such as allergen exposure, air pollution, and smoking may also further exacerbate oxidative stress in asthma patients, contributing to increased Br-Tyr levels. But non-asthmatic individuals tend to maintain a more stable oxidative balance, so preventing significant increases in Br-Tyr. Variations in Br-Tyr levels may also be influenced by factors such as treatment status, degree of inflammation, and individual metabolic differences.[13]

The correlation between urinary Br-Tyr levels and eosinophil counts (r=+0.307) indicates a positive weak-to-moderate association, suggesting that increased eosinophilic activity is associated with greater oxidative stress. From a clinical perspective, this finding highlights the potential role of urinary Br-Tyr as a non-invasive biomarker for assessing eosinophilic inflammation in asthma patients.[14]

Measurement of urinary Br-Tyr may provide additional information beyond routine blood eosinophil counts, particularly in evaluating airway inflammation and monitoring response to therapy. Recent studies have highlighted the growing role of non-invasive biomarkers in guiding asthma treatment and precision medicine approaches.[14] Furthermore, it may help identify patients with eosinophilic phenotypes who are more likely to benefit from targeted anti-inflammatory treatments.[15]

In contrast, the absence of a significant correlation between Br-Tyr levels and neutrophil counts suggests that Br-Tyr is more specifically associated with eosinophil-driven inflammation rather than neutrophilic pathways. Neutrophils are typically involved in non-allergic inflammatory responses and infections, and their role in asthma is less prominent compared to eosinophils. Previous studies have similarly reported that neutrophilic inflammation represents a distinct asthma phenotype that may not be reflected in Br-Tyr levels.[16]

## LIMITATION

Urinary Br-Tyr biomarker levels are known to increase in asthma patients experiencing exacerbations during hospitalization, making the timing of sample collection a significant factor in variation in results. However, in this study, samples were collected from patients with outpatient asthma, and no interventions or treatments were administered to the subjects. Therefore, some other variables that are not researched may influence urinary Br-Tyr biomarker levels in this study.

## CONCLUSION

There was a significant difference in urinary Br-Tyr levels between asthma and non-asthma patients. In addition, eosinophil levels in asthma patients showed a statistically significant positive correlation with urinary Br-Tyr levels, indicating a weak-to-moderate association. These findings suggest that urinary Br-Tyr may serve as a non-invasive biomarker for assessing eosinophilic inflammation and oxidative stress in asthma patients. Clinically, measurement of urinary Br-Tyr has the potential to complement conventional markers such as blood eosinophil counts, aid in the evaluation of disease activity, and support monitoring of treatment response, particularly in patients with eosinophilic asthma phenotypes.

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## CONFLICT OF INTEREST

The authors declare no conflicts of interest that could influence the content of this manuscript.

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