


RESEARCH ARTICLE

MALT1 in asthma children: A potential biomarker for monitoring exacerbation risk and Th1/Th2 imbalance-mediated inflammation

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Abstract

Background: Mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) participates in the immune-related allergic response and inflammation flare, while its clinical role in asthma children is still unknown. Herein, this study aimed to investigate MALT1 expression, and its correlation with exacerbation risk, T helper (Th)1, Th2 cells (and their secreted cytokines), as well as inflammatory cytokines in asthma children.

Methods: Sixty children with asthma exacerbation and 60 children with remission asthma were enrolled in this study; then their blood MALT1, Th1, Th2 cells, tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), interferon-gamma (IFN- γ), and interleukin-4 (IL-4) were detected. Besides, blood MALT1 in another 20 health controls was also determined.

Results: Mucosa-associated lymphoid tissue lymphoma translocation protein 1 was highest in children with asthma exacerbation, followed by children with remission asthma, and lowest in health controls ($p < 0.001$). MALT1 could distinguish children with asthma exacerbation from children with remission asthma (area under the curve (AUC): 0.757, 95% CI: 0.670–0.843). In children with asthma exacerbation, MALT1 was negatively linked with IFN- γ ($p = 0.002$) and Th1 cells ($p = 0.050$), but positively related to Th2 cells ($p = 0.027$) and exhibited a positive correlation trend (without statistical significance) with IL-4 ($p = 0.066$); meanwhile, MALT1 was positively correlated with exacerbation severity ($p = 0.010$) and TNF- α ($p = 0.003$), but not linked with IL-6 ($p = 0.096$). In children with remission asthma, MALT1 only was negatively associated with Th1 cells ($p = 0.023$), but positively linked with TNF- α ($p = 0.023$).

Conclusion: Mucosa-associated lymphoid tissue lymphoma translocation protein 1 serves as a potential biomarker for monitoring exacerbation risk and Th1/Th2 imbalance-mediated inflammation of asthma children.

Liying Liu and Yang Gao contributed equally to this work.

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KEYWORDS

asthma children, exacerbation risk, inflammatory cytokines, MALT1, Th1/2 cells

1 | INTRODUCTION

Asthma is one of the most common chronic airway diseases with nearly 37 million new cases worldwide in 2019 and it frequently occurs in children, whose symptoms usually include wheeze, cough, shortness of breath, chest tightness, exercise intolerance, etc.,¹⁻⁴ Besides, asthma children often suffer from sleeping disorders, affected academic performance, impaired growth, etc., which tend to impact both their physical and psychological health.^{5,6} Even though most children can achieve symptom control after treatment (including intermittent inhaled corticosteroids, leukotriene receptor antagonists, long-acting beta-agonist, etc.), some children still encounter life-threatening exacerbation risk and impaired quality of life.⁷⁻¹¹ Therefore, finding some biomarkers which can help clinicians to identify children with high exacerbation asthma risk is meaningful to realize individual management and improve their prognosis.

Mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1), a cysteine protease expressed in T cells, B cells, and innate immune cells, is known for its dual functions (scaffold function and proteolytic activity), which is reported as a crucial regulator in allergic response.¹²⁻¹⁶ A systematic review supports that MALT1 plays an essential role in T helper (Th)2-mediated allergy via disturbing the homeostasis of T cells and refining proinflammatory signaling.¹⁴ Also, one study reports that the protease activity of MALT1 regulates the attenuation of Th1 cells in human peripheral T cells.¹⁷ Besides, another study finds that MALT1 participates in allergic response through modulating mast cell cytokines and endothelial permeability.¹⁶ Consequently, we speculated that MALT1 might serve as a potential biomarker for asthma children management. However, the previous studies only focus on the underlying mechanism of MALT1 in the allergic response, which lacks further validation under real-clinical settings, and its clinical role in asthma children remains unanswered.^{14,18}

Herein, the current study detected blood MALT1 in 60 children with asthma exacerbation, 60 children with remission asthma, and 20 healthy controls, aiming to investigate its expression in different subjects and its correlation with exacerbation risk, Th1, Th2 cells (and their secreted cytokines), as well as inflammatory cytokines in asthma children.

2 | METHODS

2.1 | Subjects

This case-control study serially enrolled 60 children with asthma exacerbation as well as 60 children with remission asthma from

March 2020 to March 2021. All asthma children were diagnosed in accordance with the Global Initiative for Asthma Criteria.¹⁹ The asthma exacerbation was defined as an acute or subacute attack related to airflow obstruction.²⁰ The remission asthma was defined as the absence of reported asthma symptoms and no use of asthma medications.²¹ All asthma children were less than 16 years old. The asthma children who had a severe infection, autoimmune disease, other respiratory diseases, or a history of malignant disease were excluded from the study. Additionally, a total of 20 subjects without any abnormalities in health examinations were also enrolled in the study as healthy controls. The healthy controls who had a history of asthma or other respiratory diseases, severe infection, autoimmune disease or malignant disease were ineligible for the study. The study protocol was permitted by Ethics Committee. All subjects' statutory guardians signed the informed consents.

2.2 | Collection of data and samples

After enrollment, clinical characteristics of all subjects were obtained, and exacerbation severity of children with asthma exacerbation was assessed according to international consensus on (ICON) pediatric asthma.²² Peripheral blood (PB) was sampled from all subjects, then peripheral blood mononuclear cells (PBMCs) and serum were separated for detection.

2.3 | Detection of samples

All separated PBMC samples were applied to evaluate MALT1 expression by reverse transcription-quantitative polymerase chain reaction (RT-qPCR). Total RNA was extracted by RNeasy Protect Mini Kit (Qiagen), then reverse transcription was finished using PrimeScript™ RT reagent Kit (Takara). After that, qPCR was achieved by SYBR® Premix DimerEraser™ (Takara). The expression of MALT1 was calculated by the $2^{-\Delta\Delta C_t}$ method, using GAPDH as the internal reference. Furthermore, qPCR primers were designed referring to the previous study.²³ Besides, among all collected PB samples, a total of 81 fresh PB samples (36 from children with asthma exacerbation, 34 from children with remission asthma, and 11 from health controls) were used to detect the percentages of Th1 cells and Th2 cells by flow cytometry (FCM) using Human Th1/Th2 Phenotyping Kit (BD). In addition, the isolated serum samples were used to assess the levels of tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), Interferon-gamma (IFN- γ), and interleukin-4 (IL-4) by enzyme-linked immunosorbent assay (ELISA) using Human Quantikine ELISA Kits (R&D Systems China Co., Ltd.).

2.4 | Statistics

All statistical analyses and graph plotting were carried out using SPSS V.24.0 (IBM Corp.) and GraphPad Prism V.6.01 (GraphPad Software Inc.), respectively. Comparison of clinical characteristics among three groups was analyzed using one-way analysis of variance (ANOVA) test, Chi-square test or Kruskal–Wallis H rank-sum test. Comparison of MALT1 expression, Th1 cell percentage, Th2 cell percentage, and cytokine levels among three groups was determined by Kruskal–Wallis H rank-sum test, followed by post hoc comparisons with Bonferroni test. The ability of MALT1 expression in distinguishing different subjects was evaluated using receiver-operating characteristic (ROC) curves. The correlation of two variables was assessed using Spearman's rank correlation test. A *p* value < 0.05 was supposed as statistically significant.

3 | RESULTS

3.1 | Clinical characteristics of all subjects

The mean ages of children with asthma exacerbation, children with remission asthma, and healthy controls were 6.2 ± 2.6 years, 6.3 ± 2.6 years, and 6.4 ± 2.8 years, respectively (Table 1). Besides, there were 32 (53.3%) females and 28 (46.7%) males in the children with asthma exacerbation, 26 (43.3%) females and 34 (56.7%) males

in the children with remission asthma, seven (35.0%) females and 13 (65.0%) males in health controls. Notably, most clinical characteristics were of no difference among these three groups, including age (*p* = 0.917), gender (*p* = 0.296), height (*p* = 0.535), weight (*p* = 0.856), and family history of asthma (*p* = 0.123). However, eosinophil count, immunoglobulin E (IgE), forced expiratory volume in 1 s (FEV₁)/forced vital capacity (FVC), and FEV₁ (% predicted) were varied among the three groups (all *p* < 0.001). In detail, eosinophil count and IgE were highest in children with asthma exacerbation, followed by children with remission asthma, and lowest in healthy controls; differently, FEV₁/FVC and FEV₁ (% predicted) were highest in healthy controls, followed by children with remission asthma, and lowest in children with asthma exacerbation. The specific clinical characteristics of all subjects are displayed in Table 1.

3.2 | Comparison of MALT1, Th1, Th2 cells, and inflammatory cytokines among three groups

In general, MALT1 (*p* < 0.001), IFN- γ (*p* < 0.001), Th1 cells (*p* < 0.001), IL-4 (*p* < 0.001), Th2 cells (*p* = 0.002), TNF- α (*p* < 0.001), and IL-6 (*p* < 0.001) were all varied among children with asthma exacerbation, children with remission asthma, and healthy controls (Figure 1A–F). In detail, MALT1 was highest in children with asthma exacerbation (median: 3.2 (interquartile range (IQR): 1.7–4.4)), followed by children with remission asthma (median: 1.6 (IQR: 1.1–2.4)), and lowest

TABLE 1 Clinical characteristics

| Items | Children with asthma exacerbation (N = 60) | Children with remission asthma (N = 60) | Health controls (N = 20) | <i>p</i> Value |
|--|--|---|--------------------------|----------------|
| Age (years), mean \pm SD | 6.2 \pm 2.6 | 6.3 \pm 2.6 | 6.4 \pm 2.8 | 0.917 |
| Gender, <i>n</i> (%) | | | | 0.296 |
| Female | 32 (53.3) | 26 (43.3) | 7 (35.0) | |
| Male | 28 (46.7) | 34 (56.7) | 13 (65.0) | |
| Height (cm), mean \pm SD | 116.2 \pm 15.4 | 115.0 \pm 14.7 | 119.7 \pm 21.2 | 0.535 |
| Weight (kg), mean \pm SD | 22.9 \pm 7.2 | 22.5 \pm 7.9 | 23.6 \pm 10.6 | 0.856 |
| Family history of asthma, <i>n</i> (%) | | | | 0.123 |
| No | 44 (73.3) | 47 (78.3) | 19 (95.0) | |
| Yes | 16 (26.7) | 13 (21.7) | 1 (5.0) | |
| Eosinophil count ($\times 10^9/L$), median (IQR) | 0.452 (0.356–0.737) | 0.187 (0.128–0.293) | 0.093 (0.072–0.129) | <0.001 |
| IgE (IU/ml), median (IQR) | 241.5 (151.2–379.6) | 75.9 (51.3–113.8) | 32.5 (26.3–60.8) | <0.001 |
| FEV ₁ /FVC (%), mean \pm SD | 67.5 \pm 6.5 | 78.3 \pm 3.3 | 83.7 \pm 3.8 | <0.001 |
| FEV1 (% predicted), mean \pm SD | 77.4 \pm 6.7 | 88.4 \pm 4.6 | 99.7 \pm 7.5 | <0.001 |
| Exacerbation severity, <i>n</i> (%) | | | | - |
| Mild | 12 (20.0) | - | - | |
| Moderate | 34 (56.7) | - | - | |
| Severe | 14 (23.3) | - | - | |

Abbreviations: FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; IgE, immunoglobulin E; IQR, interquartile range; SD, standard deviation.

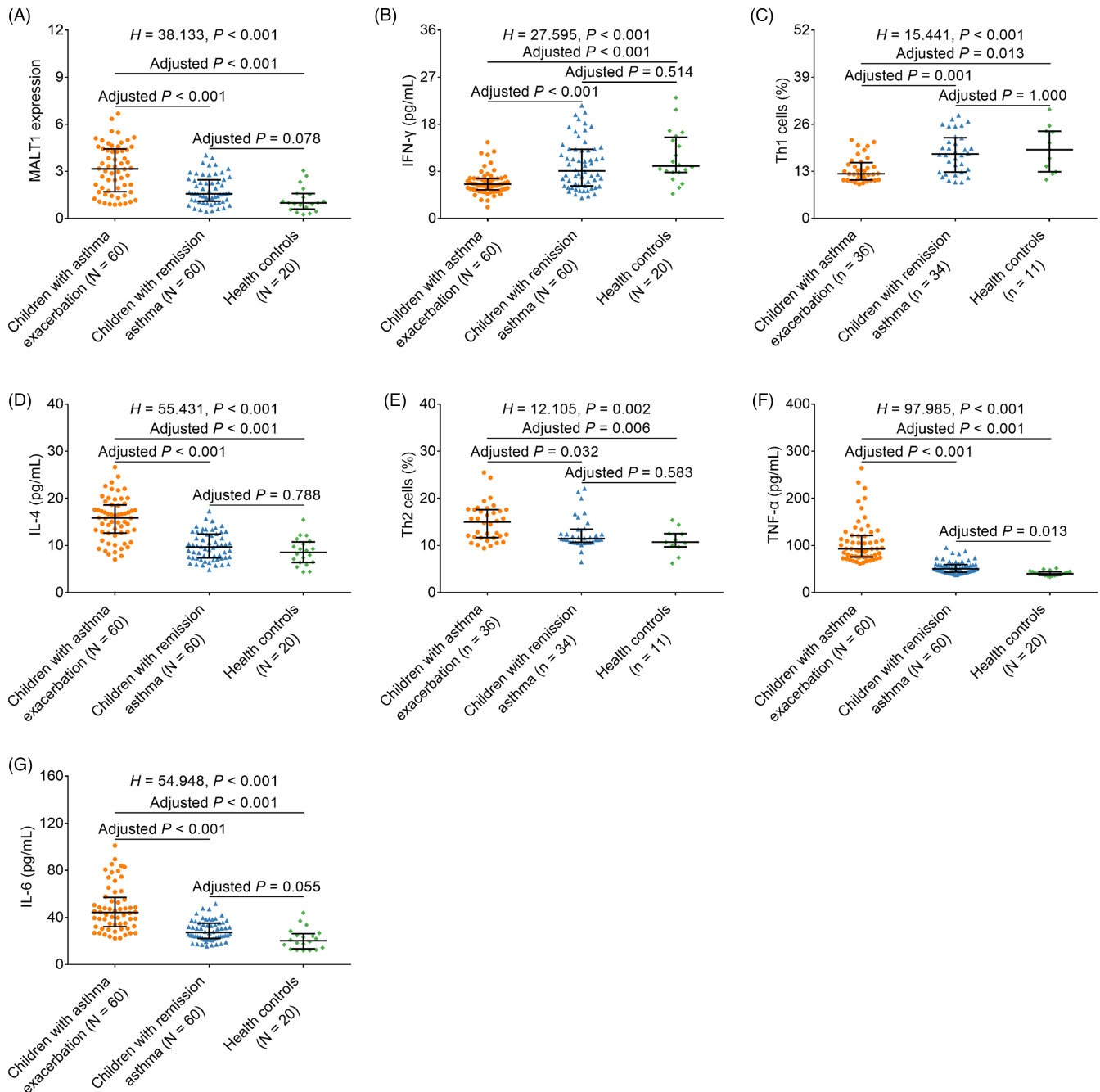


FIGURE 1 Mucosa-associated lymphoid tissue lymphoma translocation protein 1, Th1/2 cells, and inflammatory cytokines varied among the three groups. Comparison of MALT1 (A), IFN- γ (B), Th1 cells (C), IL-4 (D), Th2 cells (E), TNF- α (F), and IL-6 (G) among children with asthma exacerbation, children with remission asthma, and health controls was determined by Kruskal-Wallis H rank-sum test, followed by post hoc comparisons with Bonferroni test

in health controls (median: 1.0 (IQR: 0.7–1.5)). Moreover, IFN- γ , Th1 cells were both highest in health controls, followed by children with remission asthma, and lowest in children with asthma exacerbation; differently, IL-4, Th2 cells, TNF- α , and IL-6 were all highest in children with asthma exacerbation, followed by children with remission asthma, and lowest in health controls.

Moreover, MALT1 disclosed good value to distinguish children with asthma exacerbation from children with remission asthma (area under the curve (AUC): 0.757, 95% confidence interval (CI): 0.670–0.843, Figure 2A), children with asthma exacerbation from health

controls (AUC: 0.870, 95% CI: 0.790–0.951, Figure 2B), and children with remission asthma from health controls (AUC: 0.706, 95% CI: 0.570–0.842, Figure 2C).

3.3 | Correlation of MALT1 with Th1, Th2 cells, and their secreted cytokines in asthma children

In children with asthma exacerbation, MALT1 was negatively linked with Th1 cells ($r_s = -0.329, p = 0.050$) and IFN- γ ($r_s = -0.392,$

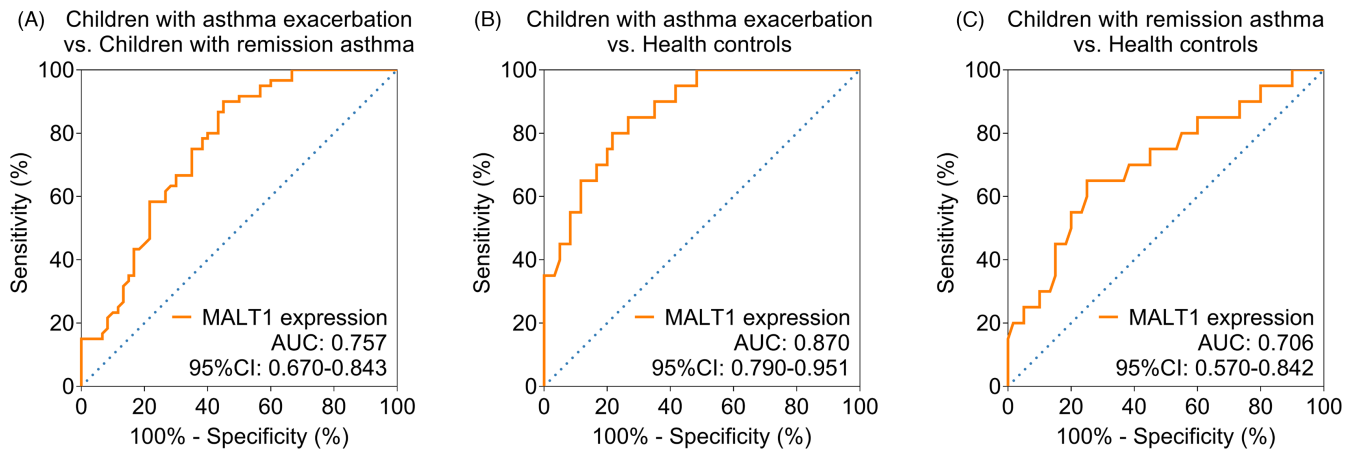


FIGURE 2 Mucosa-associated lymphoid tissue lymphoma translocation protein 1 could predict exacerbation risk of asthma children. The predictive value of MALT1 to distinguish children with asthma exacerbation from children with remission asthma (A), children with asthma exacerbation from health controls (B), and children with remission asthma from health controls (C) was evaluated using ROC curves

$p = 0.002$) (Figure 3A,B); but positively related to Th2 cells ($r_s = 0.367$, $p = 0.027$) and exhibited a positive correlation trend (without statistical significance) with IL-4 ($r_s = 0.239$, $p = 0.066$) (Figure 3C,D). Besides, MALT1 was negatively correlated with Th1/Th2 ratio in children with asthma exacerbation ($r_s = -0.410$, $p = 0.013$, Figure 3E). Additionally, in children with remission asthma, MALT1 was negatively associated with Th1 cells ($r_s = -0.389$, $p = 0.023$), but not correlated with IFN- γ ($r_s = -0.250$, $p = 0.054$), Th2 cells ($r_s = 0.234$, $p = 0.184$), or IL-4 ($r_s = 0.209$, $p = 0.110$) (Figure 3F-I). Moreover, MALT1 was negatively correlated with Th1/Th2 ratio in children with remission asthma ($r_s = -0.457$, $p = 0.007$, Figure 3J).

3.4 | Correlation of MALT1 with TNF- α and IL-6 in asthma children

Mucosa-associated lymphoid tissue lymphoma translocation protein 1 was positively correlated with TNF- α in children with asthma exacerbation ($r_s = 0.382$, $p = 0.003$), but not related to IL-6 ($r_s = 0.217$, $p = 0.096$) (Figure 4A,B). Similarly, MALT1 was positively associated with TNF- α in children with remission asthma ($r_s = 0.294$, $p = 0.023$), but not linked with IL-6 ($r_s = 0.145$, $p = 0.270$) (Figure 4C,D).

3.5 | Correlation of MALT1 with exacerbation severity and disease features in asthma children

Elevated MALT1 was related to aggravated exacerbation severity in children with asthma exacerbation ($r_s = 0.329$, $p = 0.010$, Figure 5). It was also observed that MALT1 was positively linked with IgE ($r_s = 0.272$, $p = 0.036$), but negatively associated with FEV₁/FVC ($r_s = -0.255$, $p = 0.049$) in children with asthma exacerbation; besides, it was not related to eosinophil count ($r_s = 0.159$, $p = 0.224$) or FEV₁ (% predicted) ($r_s = -0.124$, $p = 0.343$) (Table 2). Additionally, MALT1 was not correlated with eosinophil count ($r_s = 0.123$, $p = 0.347$), IgE

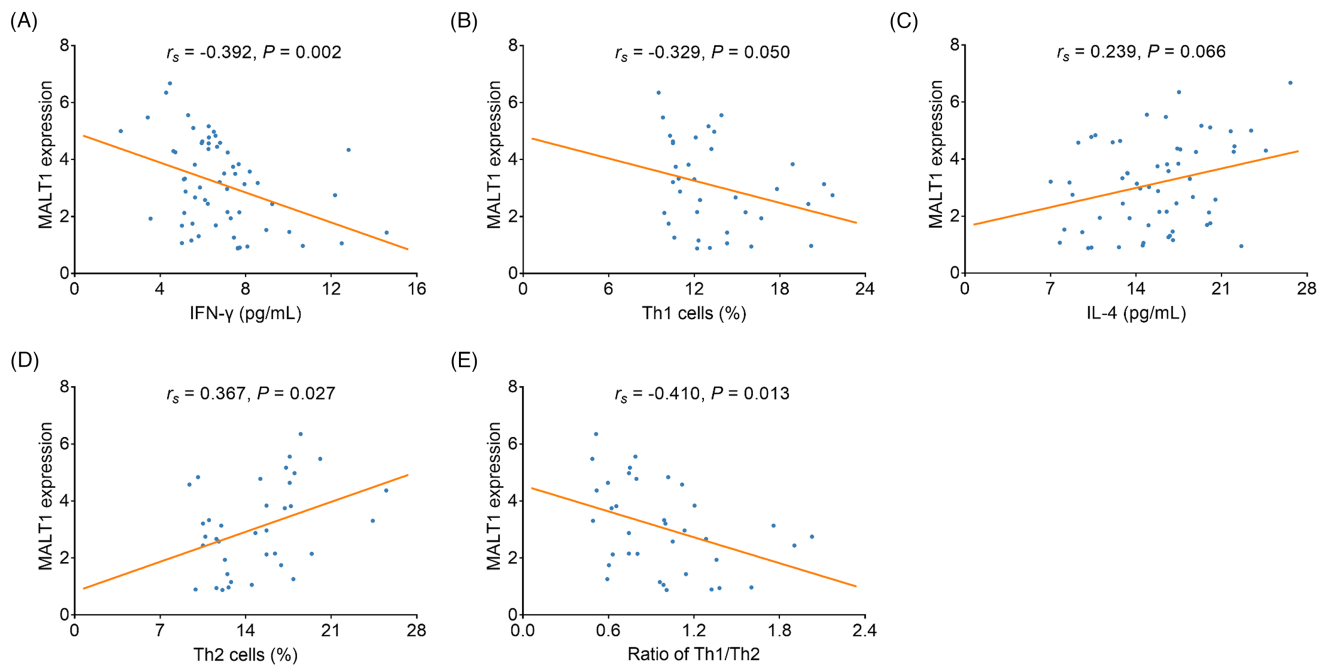
($r_s = 0.092$, $p = 0.484$), FEV₁/FVC ($r_s = -0.100$, $p = 0.446$), or FEV₁ (% predicted) ($r_s = -0.113$, $p = 0.391$) in children with remission asthma.

4 | DISCUSSION

Asthma is a chronic respiratory tract disease characterized by intermittent inflammation and bronchial hyperreactivity, which tends to occur in children.^{2,24} In terms of the complicated etiology of asthma, it has been noticed that the Th1/Th2 imbalance-mediated immune response plays a fundamental role in the pathogenesis of asthma.^{25,26} Additionally, MALT1 is observed to regulate the activation process of T cells; nevertheless, MALT1 expression in asthma children has not been analyzed yet.^{27,28} In this study, MALT1 was highest in children with asthma exacerbation, followed by children with remission asthma, and lowest in health controls; moreover, it had the potential to distinguish children with asthma exacerbation from children with remission asthma and health controls. The possible explanations could be that: (1) MALT1 enhanced the imbalance between Th1 and Th2 cells, which played important role in the pathogenesis of asthma.^{26,27,29} Thus, elevated MALT1 was correlated with increased disease susceptibility of asthma. (2) Asthma children with exacerbation risk were usually accompanied by high IgE level; meanwhile, MALT1 facilitated the production of IgE-driven cytokines through activating the nuclear-factor-kappa-B (NF- κ B) signaling pathway.^{16,30} Therefore, MALT1 could help to predict exacerbation risk in asthma children.

Some evidence exhibits that MALT1 regulates T-cell homeostasis and inflammation response in some immune-mediated diseases (including peanut allergy, inflammatory bowel disease, etc.).^{15,28,31,32} For instance, one study finds that MALT1 leads to T-cell activation and promotes it differentiating into Th2 cells via combining with B-cell lymphoma 10 (BCL-10), which further exacerbates the peanut allergy.³² Another study supports that MALT1 is positively associated with TNF- α , C-reactive protein in inflammatory bowel

Children with asthma exacerbation



Children with remission asthma

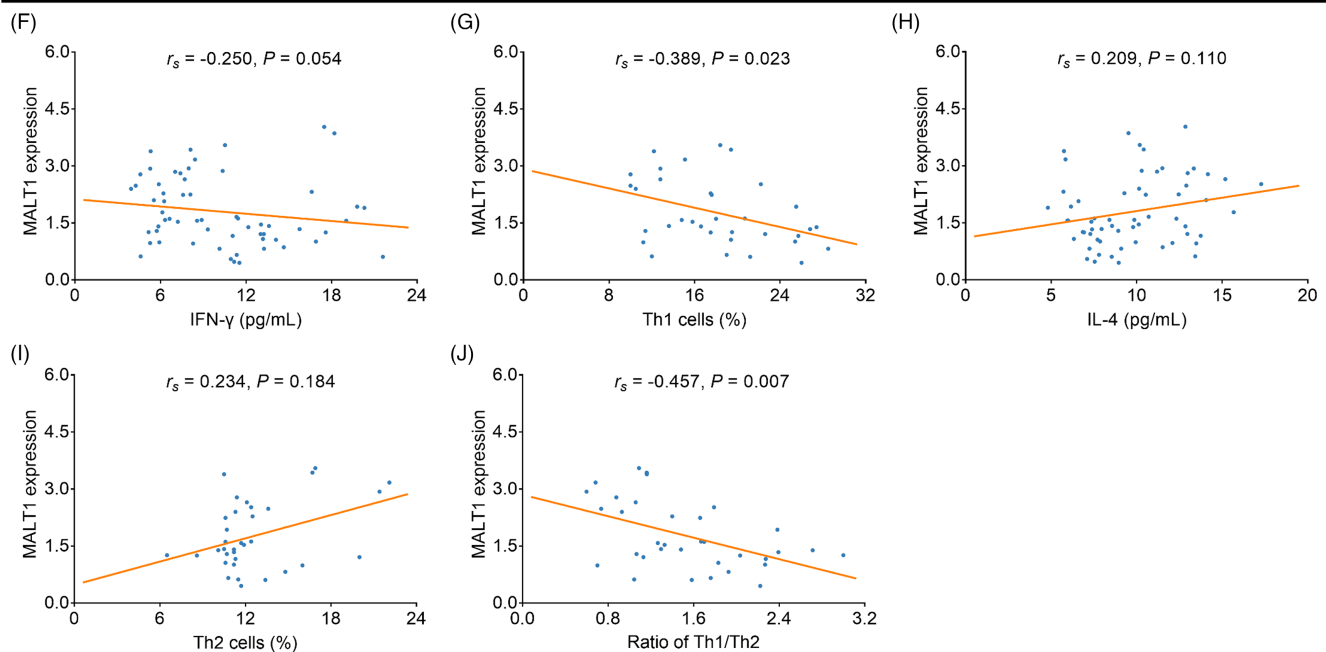


FIGURE 3 Mucosa-associated lymphoid tissue lymphoma translocation protein 1 is linked with Th1, Th2 cells, their secreted cytokines and Th1/Th2 ratio in children with asthma exacerbation. Correlation of MALT1 with IFN- γ (A), Th1 cells (B), IL-4 (C), Th2 cells (D), and Th1/Th2 ratio (E) in children with asthma exacerbation was assessed using Spearman's rank correlation test. Correlation of MALT1 with IFN- γ (F), Th1 cells (G), IL-4 (H), Th2 cells (I), and Th1/Th2 ratio (J) in children with remission asthma was assessed using Spearman's rank correlation test

disease patients.¹⁵ Nevertheless, it is rarely reported the correlation of MALT1 with Th1/Th2 imbalance and inflammatory cytokines in asthma children. Besides, the previous studies have observed that MALT1 correlates with TNF- α and IL-6 in other allergic diseases, while the latter two factors also modulate inflammation and involve in the development of asthma.^{33,34} Thus, this study detected TNF- α

and IL-6 to investigate the correlation of MALT1 with inflammation in asthma children. Subsequently, it was recognized that MALT1 was negatively linked with IFN- γ and Th1 cells in children with asthma exacerbation; while MALT1 was positively related to Th2 cells, TNF- α , and exhibited a positive correlation trend (but lacked statistical significance) with IL-4. The probable explanations might be as follows:

FIGURE 4 Mucosa-associated lymphoid tissue lymphoma translocation protein 1 is positively linked with TNF- α , but not related to IL-6 in asthma children. Correlation of MALT1 with TNF- α (A) and IL-6 (B) in children with asthma exacerbation was assessed using Spearman's rank correlation test. Correlation of MALT1 with TNF- α (C) and IL-6 (D) in children with remission asthma was assessed using Spearman's rank correlation test

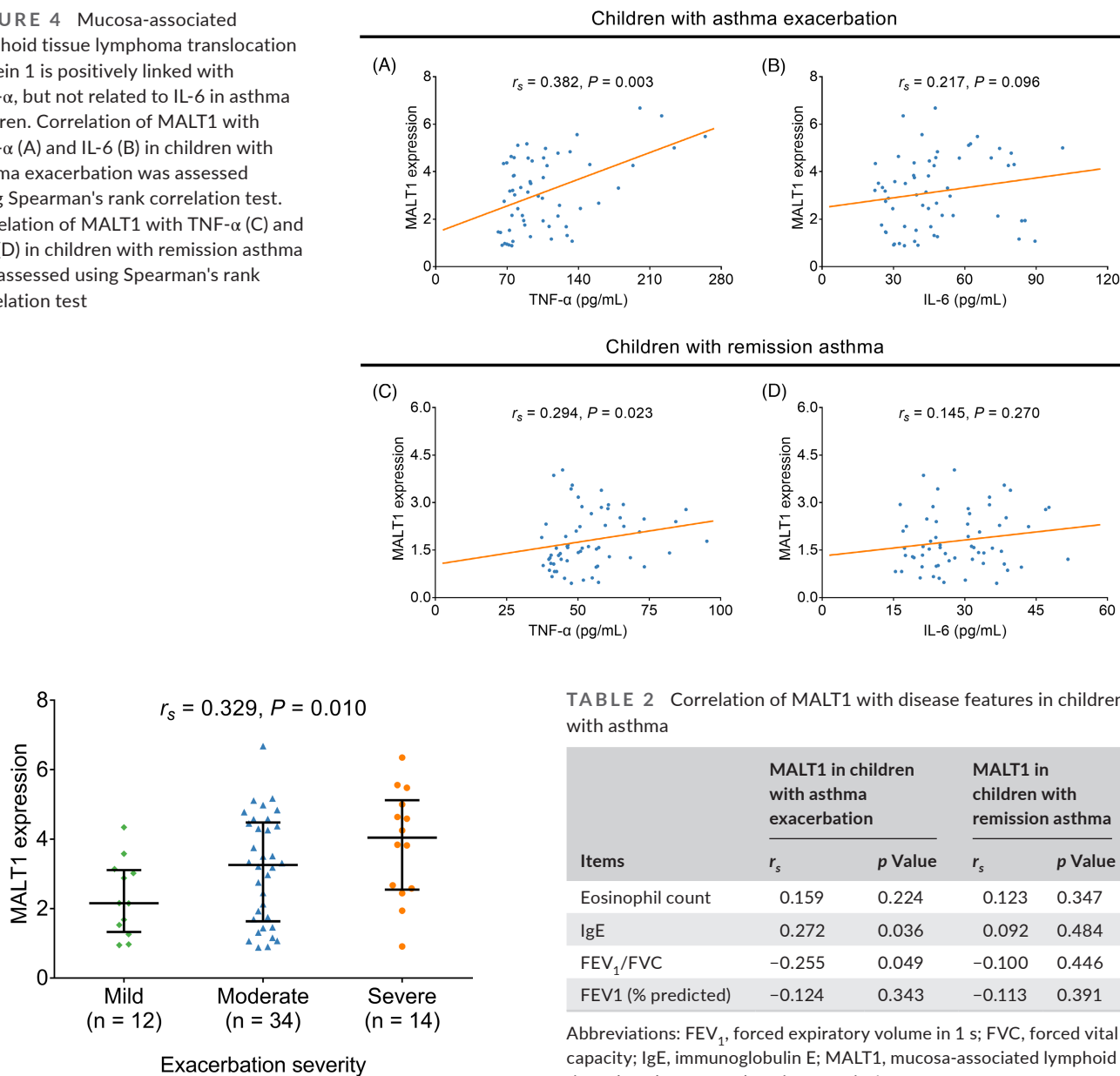


FIGURE 5 Spearman's rank correlation test showed that MALT1 is positively associated with exacerbation severity in asthma children

(1) MALT1, together with BCL-10 and CARD, formed CARD-BCL-10-MALT1 complex, which licensed the differentiation of CD4⁺ T cells into Th2 cells; while its regulating role on Th1 cells was relatively weak.³⁵ Thus, MALT1 was positively related to Th2 cells and disclosed a positive correlation trend with IL-4 (Th2 secreted cytokine). (2) MALT1 suppressed the recruitment of Th1 cells due to its protease activity.^{17,36,37} Hence, MALT1 was negatively correlated with Th1 cells and IFN- γ (Th1 secreted cytokine). (3) MALT1 promoted the activation of NF- κ B signaling pathway, which induced proinflammatory cytokine production (including TNF- α , etc.).³⁸ Therefore, MALT1 was positively related to TNF- α in asthma children. Another interesting finding was also disclosed in this study, in children with remission asthma, MALT1 was only negatively associated with Th1

TABLE 2 Correlation of MALT1 with disease features in children with asthma

| Items | MALT1 in children with asthma exacerbation | | MALT1 in children with remission asthma | |
|-----------------------|--|---------|---|---------|
| | r_s | p Value | r_s | p Value |
| Eosinophil count | 0.159 | 0.224 | 0.123 | 0.347 |
| IgE | 0.272 | 0.036 | 0.092 | 0.484 |
| FEV ₁ /FVC | -0.255 | 0.049 | -0.100 | 0.446 |
| FEV1 (% predicted) | -0.124 | 0.343 | -0.113 | 0.391 |

Abbreviations: FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; IgE, immunoglobulin E; MALT1, mucosa-associated lymphoid tissue lymphoma translocation protein 1.

cells, but not correlated with IFN- γ , IL-4, or Th2 cells. The possible reason might be that: The dysregulation of Th1, Th2, and inflammation was relatively weak in children with remission asthma, which consequently weakened the correlation of MALT1 with IFN- γ , Th2 cells, IL-4, and IL-6.³⁹

Apart from the correlation of MALT1 with Th1, Th2 cells, and inflammatory cytokines, the current study also showed that in children with asthma exacerbation, MALT1 was positively related to IgE and exacerbation severity, but negatively associated with FEV₁/FVC. The probable reasons might be as follows: (1) MALT1 upregulated IgE level via the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway.^{16,40} Hence, MALT1 was positively related to IgE in children with asthma exacerbation. (2) MALT1 was possibly associated with sustained inflammatory flare, which led to severe lung injury, then the exacerbation severity was correspondingly aggravated.^{15,41} Thus,

MALT1 was negatively correlated with FEV₁/FVC and positively associated with exacerbation severity in children with asthma exacerbation.

There were some limitations in this study. First, the sample size was relatively small, and a large-scale study was necessary to further verify the findings. Second, asthma was a recurrent disorder that needed long-time attention, thus, studies with a follow-up period were required. Third, the current study only enrolled asthma children, while the clinical role of MALT1 in adult asthma management was still unclear. Fourth, allergic rhinitis children could be enrolled as disease controls in further studies to explore the role of MALT1 as a biomarker in pediatric asthma. Fifth, the underlying mechanism of MALT1 in asthma children needed further in vivo and in vitro study to validate.

In conclusion, MALT1 serves as a potential biomarker for monitoring exacerbation risk and Th1/Th2 imbalance-mediated inflammation of asthma children.

ACKNOWLEDGEMENT

None.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article, as no datasets were generated or analyzed during the current study.

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