

Effectiveness of Zinc as an Adjuvant to Standard Therapy Versus Standard Therapy Alone in Children (5-10 Years) with Moderate Persistent Asthma

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EFFECTIVENESS OF ZINC AS AN ADJUVANT TO STANDARD THERAPY VERSUS STANDARD THERAPY ALONE IN CHILDREN (5-10 YEARS) WITH MODERATE PERSISTENT ASTHMA

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ABSTRACT

Background: Bronchial asthma, a hypersensitivity condition of the airway is increasing significantly in south asia due to rapid modernization and environmental pollution. Limited trial has been conducted on Zinc as adjuvant therapy for Asthma. This randomized controlled trial aimed to evaluate the effectiveness of Zinc in bronchial asthma.

Objective: To determine the effectiveness of zinc as an adjuvant to standard therapy compared to the standard therapy alone in children with moderate persistent asthma.

Methodology: This registered randomized controlled trial was done at Department of Pediatric Medicine unit-I, Mayo Hospital, KEMU, Lahore over 6months (1st April, 2022 to 31st September, 2022) after IRB approval.

A total of 84 patients were enrolled and divided randomly by lottery into two groups : Group A(Intervention) who received standard therapy alongwith oral elemental zinc ; Group B(Control) who received only standard therapy. Patients were followed up 4 weekly for 2 months and the results was assessed by Asthma Control Test and Emergency Visit.

Results:

Results of this study showed that addition of zinc in standard treatment had significantly better asthma control response at 1st follow up. i.e. Group-A: 90.48% vs. Group-B: 54.8%, p-value<0.001 However at 2nd follow up treatment response was significantly higher in Group-A patients as that of Group-B patients. i.e. Group-A: 100% vs. Group-B: 83.33%. p-value=0.009. Mean age of children in Group-A and Group-B was 7.60 ± 2.03 and 8.07 ± 1.95 years. In both treatment groups the age of children ranges between 5-10 years. In Group-A 23(54.76%) were male and 19(45.24%) female patients while in Group-B 27(64.29%) patients were male and 15(35.71%) were female. At 1st follow-up 4(9.52%) patients in Group-A and 5(11.9%) patients in Group-B had visited the emergency department with acute exacerbation of asthma. i.e. p-value 0.724. There were no emergency department visits made by any patients in Group-A while in Group-B 5(11.9%) patients had an emergency visit with acute exacerbation at the second follow-up visit. i.e. p-value 0.034. At baseline, children in both group had ACT score <16, indicating all children at this point had uncontrolled asthma. Data were collected and analyzed by SPSS .

Conclusion:

Based on the results of this study it can be concluded that addition of zinc with standard therapy was more effective than standard therapy alone with better asthma control , moderate persistent asthma among children.

Keywords:

Children, Moderate, Persistent asthma, Effectiveness, Zinc, Adjuvant, Standard therapy, Asthma control Test.

Trial Registration

Registry : Clinical trials.gov

NCT06869798 First Submitted Date : 06/22/2022 First Posted Date : 03/11/2025,

Retrospectively registered

Ethical approval and Patients consent

Ethical approval was taken from Institutional Review Board of King Edward Medical University/ Mayo Hospital Lahore prior to initiation of research work.(Ref No. 27/RC/KEMU Dated: 11/01/2022)

Informed consent were taken from the parents of all patients, to participate and to publish the data concerning their cases.

All experiments were performed in accordance with the principles outlined in the Declaration of Helsinki and relevant guidelines and regulations.

INTRODUCTION :

The chronic inflammatory disease asthma is characterized by intermittent obstruction of airflow and hyper responsiveness to bronchial airways. It commonly presents as wheeze, breathlessness, cough, and chest tightness¹. The prevalence of childhood asthma has increased up to 8.6% worldwide and 14% in Pakistan².

The pathophysiology of asthma is complex involving varying degrees of mononuclear cell and eosinophil infiltration, hyper secretion of mucus, desquamation of epithelium, smooth cell hyperplasia, and airway remodeling. Allergens, irritants, cold air, etc. are risk factors³.

The standard protocol of treatment include immediate relieving agents, which include short acting bronchodilators, ipratropium, and systemic corticosteroids, while controller agents mainly comprise long- acting bronchodilators, inhaled corticosteroids, theophylline, and antileukotrienes⁴. Inflammatory cytokines are produced and inflammatory cells are recruited to the airways, inducing swelling, mucus hyper secretion, and smooth muscle contraction, which narrow the airways⁵.

The role of zinc supplementation in diarrhea and malnutrition is well known^{6,7}. Recently, it has been proposed that zinc has an immunomodulatory function by different mechanisms including improvement of Th1/ Th2 balance and suppression of the cell development⁸. It acts as an antioxidant which prevents damage to mitochondrial respiratory chain complexes and thus prevents airway inflammation, vascular permeability and mucus hyper secretion⁹. Zinc deficiency state is common worldwide, and especially more in low and middle-income countries¹⁰. A study published by G.khanbabaee, states that 42% of asthmatic patients had hypozincemia¹¹. Some studies suggest an association of zinc in patients with asthma that zinc protects respiratory tract epithelial integrity by both preventing caspase 3 activation and the lysis of proteins that provide intercellular connection, significantly decreased eosinophils and other inflammatory cells, resulting in a less severe inflammatory response¹².

The risk of developing bronchial asthma has been linked to a low level of zinc in the body¹³.

Research trials on zinc supplementation with standard treatment are going on. A study conducted by Setyoningrum RA, Endaryanto A et al showed the improvement in clinical manifestations of asthma. In the intervention group, the mean score at the end of the evaluation was 23.27 ($p = 0.003$), whereas in the control group, the mean score was 19.92 ($p = 0.004$)¹⁴. Another study conducted by Ghaffari J, Khalilian A, Salehifar E et al showed that there was improvement in cough and wheezing by 18%, and dyspnea by 15%¹⁵. Thus, with a background of a high prevalence of zinc deficiency, and its link to bronchial asthma, the present study had been aimed to determine the role of zinc in controlling the symptoms in children with moderate persistent asthma in the local pediatric population.

METHODOLOGY

Setting

Department of Pediatric Medicine, Asthma Clinic, Mayo Hospital, KEMU, Lahore, Pakistan

Duration of study

Since April 1st, 2022 till 31st September, 2022

Trial Design

Parallel group, superiority trial comparing zinc plus standard therapy versus standard therapy alone. Allocation ratio 1:1

Reporting Guidelines

The trial was reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Harms : Harms were defined according to the organ systems involved.

Sample size

The sample size is estimated to be 84 patients, 42 in each group; power of 90%; and expected percentage of patients in each group of partially controlled asthma zinc group as 51% and control group as 80%(52).

$$\left\{ \frac{Z1 - \alpha \sqrt{2\bar{P}(1 - \bar{P})} + Z1 - \beta \sqrt{P1(1 - P1) + P2(1 - P2)}}{(P1 - P2)^2} \right\}^2$$

$Z1-\alpha$ = Confidence level 95% = 1.96

$Z1-\beta$ = Power of test 90% =1.28

P1 = Population proportion I = 51%

P2 = Population proportion II = 80%

Sampling technique

Probability random sampling technique. Single Blinding done with lottery method.

Inclusion Criteria:

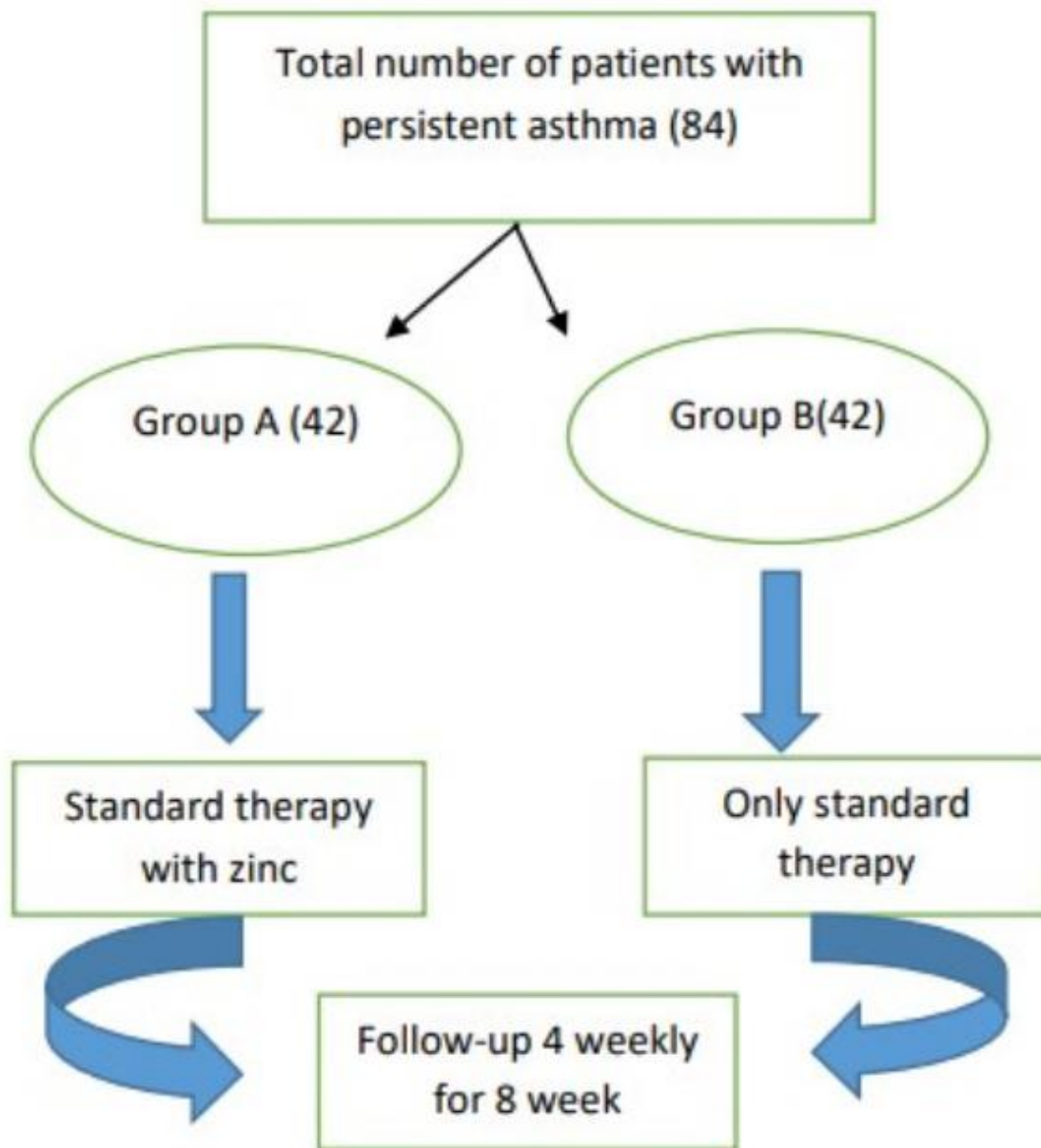
1. Children 5-10 years.
2. Either gender.
3. Patient label as moderate persistent asthma

Exclusion Criteria:

1. Child with diarrhoea and malnutrition (because of zinc deficient and replacement).

2. Child with other pulmonary disease (pneumonia, viral, infection cystic fibrosis) other than bronchial asthma (from history and examination).
3. Child taking zinc supplementation.
4. Cardiovascular disease.

In this study, children aged 5 to 10 years with asthma, either gender, presenting to Asthma Clinic of Pediatric Medicine, Mayo Hospital, who meet the inclusion criteria were enrolled after receiving approval from the Institutional Review Board of King Edward Medical University, Mayo Hospital, Lahore. Parental and guardian informed written consent was obtained. Demographic data was obtained and detailed history regarding symptoms, the onset of a duration of illness, progression, medication, level of control, and general physical along with systemic examination was carried out. Based on a classification of moderate persistent asthma patients (table 2), patients were divided by lottery method into two groups, Group A (intervention) and Group B (nonintervention). The patients in Group A received standard therapy along with oral elemental zinc 20mg/day OD for 2 months. While the patients in Group B received only Standard therapy. Then, all the patients of both groups were trained by physician in hospital to maintain daily regarding questionnaire asked in asthma control test, followed up 4 weekly for 2 months and all the findings were recorded in predesigned Performa. Asthma Control Test (attached) and emergency visits because of acute asthma exacerbations were used to assess the results regarding asthma control.



An analysis of the data was conducted using a statistical package for social sciences (SPSS) version 26. In a stratified study of moderate persistent asthma, continuous variables like age and duration of illness were expressed as mean $\pm$ SD deviation. The frequency and percentage of categorical variables like sex, control of symptoms were expressed. The chi-square test was applied to compare zinc with placebo in two groups. Statistics were considered significant when the P-value was less than 0.05.

RESULTS:

1. Mean age of children in Group-A and Group-B was 7.60 ± 2.03 and 8.07 ± 1.95 years. In both treatment groups age of children ranges between 5-10 years. Table-1
2. In Group-A 23(54.76%) were male and 19(45.24%) female patients while in Group-B 27(64.29%) patients were male and 15(35.71%) were female. Table-2
3. At 1st follow up 4(9.52%) patients in Group-A and 5(11.9%) patients in Group-B had visited emergency department with acute exacerbation of asthma. i.e. p-value 0.724 Table-3
4. There were no emergency department visits with acute exacerbation, made by any patients in Group-A while in Group-B 5(11.9%) patients had emergency visit at the second follow-up visit. i.e. p-value 0.034 Table-4
5. Distribution of various ACT score among study group at presentation (base line). Children in both groups had ACT score <16 . Showing all children at this point have uncontrolled asthma. Table-5
6. Number of patients with ACT score at 1st follow up there were 38(90.48%) patients in Group-A and 22(52.4%) patients in Group-B had partially controlled asthma. i.e. ACT score: 16-19. On the other 4(9.52%) patients in Group-A and 20(47.6%) patients in Group-B had uncontrolled asthma. i.e. ACT score <16 . i.e. p-value 0.001 Table-6
7. Number of patients with ACT score at 2nd follow up 38(90.48%) patients in Group-A and 21(50%) patients in Group-B had controlled asthma. i.e. ACT score >20 . However, 4(9.52%) patients in Group-A and 21(50%) patients in Group-B had partially controlled asthma. i.e. p-value 0.001 Table-7

8. Patients in Group-A responded significantly better to treatment at 1st follow-up than those in Group-B. I.e. Group-A: 38(90.48%) vs. Group-B: 22(54.8%), p-value<0.001. Table-8
9. Treatment response was significantly high between groups at the 2nd follow-up. i.e. Group-A: 42(100%) vs. Group-B: 35(83.33%), p-value 0.009 Table-9
10. No significant harm was noted in the trial group in comparison to control group in any organ system.

Table 1: Age in Years, of children in study Groups (n=84)

	Group A n = 42	Group B n = 42
Mean	7.60	8.07
SD	2.03	1.95
Minimum Age	5	5
Maximum age	10	10

Group-A: Standard therapy+Oral Zinc

Group-B: Standard therapy

Table 2: Gender of children in Study Groups (n=84)

	Group A n(%age)	Group B n(%age)	Total
Male	23(54.76)	27(64.29)	50
Female	19(45.24)	15(35.71)	34
Total	42	42	84

Group-A: Standard therapy + Oral Zinc

Group-B: Standard therapy

Table 3: Any Emergency Visit (acute exacerbation of asthma) till 1st Follow-up in Study Group (n=84)

	Group A n(%age)	Group B n(%age)	Total
Yess	4(9.52)	5(11.9)	9
No	38(90.48)	37(88.1)	75
Total	42	42	84
P Value 0.724			

Group-A: Standard therapy+ Oral Zinc

Group-B: Standard therapy

Table 4: Any Emergency Visit (acute exacerbation of asthma) till 2nd Follow-up in Study Groups (n=84)

	Group A n(%age)	Group B n(%age)	Total
Yess	0(0)	5(11.9)	5
No	42(100)	37(88.1)	79
Total	42	42	84
P Value 0.034			

Group-A: Standard therapy+ Oral Zinc

Group-B: Standard therapy

Table-5: Distribution of various ACT Scores among study groups at Presentation (base line) (n=84)

	Group A n(%age)	Group B n(%age)	Total
Controlled(>20)	0(0)	0(0)	0
Partially Controlled (16-19)	0(0)	0(0)	0
Uncontrolled (<16)	42(100)	42(100)	84
Total	42	42	84

Group-A: Standard therapy+ Oral Zinc

Group-B: Standard therapy

Table 6: Distribution of various ACT Scores among Study groups at 1st follow up (n: 84)

	Group A n(%age)	Group B n(%age)	Total
Controlled (>20)	0(0)	0(0)	0
Partially Controlled (16-19)	38(90.48)	22(52.4)	60
Uncontrolled (<16)	4(9.52)	20(47.6)	24
Total	42	42	84
P Value < 0.001			

Group-A: Standard therapy+ Oral Zinc

Group-B: Standard therapy

Table 7: Distribution of various ACT Scores among Study groups at 2nd follow up (n=84)

	Group A n(%age)	Group B n(%age)	Total
Controlled (>20)	38(90.48)	21(50)	59
Partially Controlled (16-19)	4(9.52)	21(50)	25

Uncontrolled (<16)	0(0)	0(0)	0
Total	42	42	84
P Value < 0.001			

Group-A: Standard therapy+ Oral Zinc

Group-B: Standard therapy

Table 8: Treatment response (ACT) in study groups at 1st follow up (n=84)

	Group A n(%age)	Group B n(%age)	Total
Yess	38(90.48)	22(52.4)	60
No	4(9.52)	20(47.6)	24
Total	42	42	84
P Value < 0.001			

Table 9: Treatment response (ACT) in study groups at 2nd follow up (n=84)

	Group A n(%age)	Group B n(%age)	Total
Yess	42(100)	35(83.33)	77
No	0(0)	7(16.67)	7
Total	42	42	84
P Value : 0.009			

Group-A: Standard therapy+ Oral Zinc

Group-B: Standard therapy

DISCUSSION :

In this study, zinc adjuvant therapy was compared with standard therapy alone in children with moderate persistent asthma. Asthma is categorized as "Controlled" if ACT score is ≥ 20 , "Partially Controlled" if ACT score is 16-19, and "Uncontrolled" if ACT score is < 16 according to ACT score. All patients completed follow-up in both treatment groups. Study results showed significant treatment response at first follow-up when zinc was added to standard treatments. I.e. Group-A: 90.48% vs. Group-B: 52.4%, $p\text{-value} < 0.001$. On the other hand, at two months follow-up, treatment response was significantly higher in Group-A patients as that of Group-B patients. i.e. Group-A: 100% vs. Group-B: 83.33%, $p\text{-value} = 0.009$. Additionally, as the severity of asthma increases, the levels of zinc in children with asthma decrease sharply.¹⁷ Anti-inflammatory, anti-oxidant, and antiapoptotic properties of zinc are associated with asthma pathogenesis.¹⁸ Zinc supplementation for children with asthma improved clinical symptoms, according to a recently published study. The results of this study showed that 8 weeks of zinc supplementation significantly decreased attack frequency, nocturnal symptoms, clinical control of asthma symptoms, and, but there were no significant differences in daytime symptoms, limitation of activities or the need for reliever medications.¹⁹ Zinc supplementation was shown to be effective in treating asthma in Iranian children in a randomized controlled trial. A study found that 50 mg of zinc per day significantly improved both clinical symptoms and lung function in children with moderate asthma and a zinc deficiency.¹⁵

Children with asthma between the ages of 5 and 10 as subjects, Sajith Jayasree Sadanandan investigated the effects of zinc supplementation. The study findings indicated that zinc supplementation at 20 mg/day significantly reduced severe asthma attacks in children.²⁰ As an adjuvant therapy to the standard medical treatment, zinc supplementation (30 mg elemental

zinc/day) in Sanguansak Rerksuppaphol's study was found to result in rapid improvement of asthma exacerbations.²¹ Based on the results of this study, the above-mentioned studies have shown significant improvements in asthma symptoms among children.

In response to zinc supplementation, blood levels of FGF2 increased. As part of the formation of fibroblasts, zinc produces collagen and other extracellular proteins that maintain the integrity of the basement membrane of the respiratory tract. Consequently, zinc also prevents oxidative damage to cells and remodels respiratory tracts.

The age range for patients in this study was 5-10 years. The mean age of children in this study was 7.60 ± 2.03 (Group-A) and 8.07 ± 1.95 (Group-B) respectively. Gender distribution of children showed male dominance in both groups as compared to female children. i.e. 50 (59.52%) male and 34 (40.48%) female children. Iman Abdelaziz in his study reported the age range for children as 6-13 years with male children predominance as compared to female children.²⁹ Age range of children and gender distribution is in line with this study. J. Ghaffari in his study reported the mean age of children as 7.8 ± 1.2 years and male dominance in his study.¹⁵

Deficiencies in zinc disrupt collagen synthesis and fibroblast proliferation, which cause wound healing to slow down. As the damaged skin epithelializes and collagen accumulates in the thick layer, growth factor and zinc interact synergistically.^{15,22} Iman Abdelaziz¹⁹ in his study used zinc supplementation in children aged 6-13 years for treating bronchial asthma. As per his findings after zinc supplementation significant reduction was seen in frequency of asthma attacks per month, nocturnal symptoms and clinical control of asthma symptoms.¹⁹ A recently published systematic review and meta-analysis from Iran reported that zinc play a protective role against asthma²³ Retno Asih Setyoningrum in his study assessed the clinical improvement in children after zinc supplementation. As per his findings C-ACT score showed significant difference between zinc supplementation and placebo group post treatment. i.e. Zinc: 23.27 ± 2.88 vs. Placebo: 19.92 ± 2.72 , $p\text{-value} < 0.001$.²⁵ these results support the results of this study showing better treatment response for treating asthma among children. Very limited data is present in our local settings regarding zinc supplementation in standard treatment for asthma among children. However, keeping in mind the findings of above mentioned studies have shown the importance of zinc in respiratory diseases in children in our local settings

Several systematic reviews and meta-analyses concluded that the difference in mean serum zinc levels between children with asthma and healthy controls does not seem to be significant, and the level of zinc in children does not seem to be related to their asthma severity.²⁴ A recently published meta-analysis showed that circulating zinc was associated with a significant risk for childhood asthma and its related symptom wheezing.²⁶ The implication of zinc in the development of asthma is biologically plausible. First, zinc deficiency may disturb the balance between types 1 and type 2 T helpers, resulting in inflammation and eosinophilia.²⁷ Second, zinc deficiency may be associated with the production of IgE, which increases the risk of asthma.²⁸ Third, zinc is of powerful antioxidant activity in the lungs, which may be responsible for the imbalance between oxidation and antioxidant, ultimately reducing antioxidant function and increasing the risk of asthma.²⁹ Altogether, it is reasonable to speculate that circulating zinc is a promising marker in susceptibility to asthma. Previously, Ghaffari and colleagues pooled the results of 15 studies, and failed to support the association of serum zinc with asthma in children. With accumulating studies afterwards, there is a need to interrogate this association.¹⁶

In addition to assessing plasma zinc status and nutritional status in asthma management, studies discussed above indicate the importance of assessing plasma zinc. The management of asthma should be improved by supplementing zinc and nutritional counseling for those with deficiencies in these nutrients.

CONCLUSION

It is concluded that zinc therapy combined with standard therapy was more effective in controlling asthma because increase in ACT score and no emergency visit due to acute exacerbation of asthma in compare to standard therapy alone.

DECLARATIONS :

Abbreviations:

ACT	Asthma control test
CAMP	Childhood Asthma Management Program
COPD	Chronic obstructive pulmonary disease
DNA	Deoxyribonucleic acid
FEV1	Forced expiratory volume in 1 second
GINA	Global Initiative for Asthma
ICS	Inhaled corticosteroids
LABA	Long Acting Beta Agonist
LTRA	Leukotriene receptor antagonists
OCS	Oral corticosteroids
IL	Interleukin
ISAAC:	International Study of Asthma and allergies in Childhood
PEF	Peak expiratory flow
RNA	Ribonucleic acid
SARP	Severe Asthma Research Program
TGF-b	Transforming growth factor
TH1	Type 1 T helper

TH2	Type 2 T helper
WBC	White blood cells
DALY	Disability Adjusted Life Expectancy
RBM	Reticular Basement Membrane
Zn	Zinc
SARP	severe asthma research programme
ATS	American thoracic society
ERS	Eruopen respiratory society
FGF2	Fibroblast growth factor 2
IgE	Immunoglobulin E
GINA	Global Institute for Asthma
GERD	Gastro esophageal Reflux Disease
ATAQ	Asthma Therapy Assessment Questionnaire
ACQ	Asthma Control Questionnaire
FVC	Forced vital capacity
PRAM	Pediatric Respiratory Assessment Measure
SPSS	Statistical Package for the Social Sciences

Ethical approval and Consent to Participate

Ethical approval was taken from Institutional Review Board of King Edward Medical University/ Mayo Hospital Lahore prior to initiation of research work.(Ref No. 27/RC/KEMU Dated: 11/01/2022)

All experiments were performed in accordance with the principles outlined in the Declaration of Helsinki and relevant guidelines and regulations.

Consent for Publication

Informed consent were taken from the parents of all patients, to participate and to publish the data concerning their cases.

Availability of Data and materials

All datasets used and/or analysed during the current study are included in the published article and its supplementary files. Further data are available from the corresponding author on reasonable request.

Competing Interests

Authors declared no conflict of interest.

Funding:

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Authors contributions :

Kaushal Kumar shah: Writing, Data Collection, Original draft preparation, Editing, Study Concept

Sadia Shabir: Manuscript reviewer and supervisor.

Muhammad Haroon Hamid: Editing and Original draft preparation

Manish Kumar Sah: Writing original draft, Manuscript reviewer and supervisor

Rana Muhammad Sohail Akbar: Editing of original draft

Anish Sah : Manuscript reviewer and Supervisor

Pankaj Shah: Manuscript reviewer and supervisor.

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