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ORIGINAL ARTICLE

Study of Interleukin-18 Gene Polymorphism and Risk Factors in Preschool Asthmatic Children in Iraq

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ABSTRACT

Background: *Bronchial asthma is a chronic respiratory condition characterized by airway inflammation and episodes of wheezing and breathlessness. Respiratory Syncytial Virus (RSV) impacts pediatric asthma, with early infections linked to a higher asthma risk later. The polymorphism in single nucleotide of interleukin -18 may affect the production and function of this interleukin. Among these, interleukin -18 (IL18) . Single Nucleotide Polymorphism (SNP) 137 C>G is common studies because of its role involvement in the development of allergic disease.* ***Objectives:*** *The aim was to investigate the relationship between the IL-18-137 C/G polymorphism and the risk of pediatric asthma in Iraqi children, compares serum IgE levels between asthmatic and healthy controls, and assesses the role of RSV in asthma development and exacerbation.* ***Methodology:*** *Between December of 2023 and march of 2024, a case-control study was carried out in Dhi-Qar hospitals on children with asthma who were between the ages of six months and six years. There were 85 children with asthma and 85 healthy controls in the sample. Serological and molecular analyses utilized Touchdown PCR to identify IL-18 (137 C/G) gene polymorphism, followed by sequencing and ELISA for measuring serum IL-18 and IgE levels at the hospitals and Marsh Research Center, University of Dhi-Qar.* ***Results****. Children with asthma exhibited elevated IL-18 and IgE levels compared to healthy controls. The IL-18 137 C>G polymorphism showed a trend towards association with asthma, with the GG genotype being more frequent in cases (OR 1.44, 95% CI 0.62-3.36, p=0.514). However, this association did not reach statistical significance. Similarly, the CC genotype was less common in cases (OR 0.36, 95% CI 0.08-1.73, p=0.228), and the G allele frequency was slightly higher in the asthma group (OR 1.55, 95% CI 0.78-3.07, p=0.277), but these differences were not statistically significant.* ***Conclusion:*** *Children with asthma showed significantly higher levels of IL-18 and IgE compared to healthy controls, the association between the IL-18 137 C>G polymorphism and asthma risk in this study was not statistically significant.*

INTRODUCTION

Bronchial asthma is a common respiratory illness in children, marked by fluctuating airflow limitation that leads to coughing, wheezing, chest tightness, shortness of breath, and chronic inflammation[1]. Symptoms often worsen in the morning or at night due to airway hyper-responsiveness triggered by irritants such as gas or pollen[2]. In Iraq, 16.22% of children under five years age have been diagnosed with asthma[3]. As a chronic inflammatory condition, research suggests that an imbalance in T-helper cells, especially Th1 and Th2, may contribute to asthma development[4]. Th1 cells produce IFN-γ and IL-2, enhancing pro-inflammatory immune responses, while Th2 cells generate cytokines such as IL-4, IL-5, IL-6, IL-9, and IL-13, which foster allergic inflammation and antibody-dependent immunity[5].

Interleukin 18 (formerly IFN-γ inducing factor) is a member of the IL-1 family that regulates Th1/Th2 immune response balance[6]. It stimulates INF-γ production in conjunction with IL-12, promoting Th1 responses and it also induces IL-13, which can activate Th2 responses[7,8]. Immunoglobulin E (IgE) can contribute to allergic inflammation by indirectly linking B-cell isotypes to IgE and Th2 cytokines[9].

Together, IL-18 and IL-12 can suppress IgE production[10]. The IL-18 gene is located on human chromosome 11 (11q22.2-22.3), which has various functional promoter region variations[11]. Strong evidence suggests that these genetic variations can lead to abnormal IL-18 expression, impacting T-cell regulation and contributing to allergy disorder[12]. Research into specific IL-18 gene variants and their association with bronchial asthma is ongoing, with potential insights into individual asthma susceptibility and the development of targeted therapies to modify immune responses in asthmatic patients[13,14].

This study explored the association between the IL-18-137 C/G polymorphism and the risk of pediatric

asthma in Iraqi children, evaluated serum IgE levels in asthmatic children compared to healthy controls, and investigated the impact of RSV infection on asthma development and exacerbation.

METHODOLOGY

Study Design and Participants

A case-control study examined children with asthma hospitalized at Muhammad Al-Moussawi Children's Hospital and Bint Al-Huda Teaching Medical Center for Women and Children in Dhi-Qar province from December of 2023 to March 2024. It included 85 children, aged six months to six years, with newly diagnosed asthma based on clinical symptoms, comprising 53 boys (62.3%) and 32 girls (37.7%). For comparison, 85 age- and sex-matched children were randomly selected from the hospital and surrounding community, consisting of 46 boys (54.1%) and 39 girls (45.9%). The Serological diagnosis was conducted in the laboratories of Muhammad Al-Moussawi and involved 85 asthma patients and 85 controls , while molecular analysis involved 100 samples (50 from asthma patients and 50 controls) were analyzed at the Biology Department of the Marsh Research Center, University of Dhi-Qar. The decision to conduct molecular analysis on a subset of 100 samples (50 cases and 50 controls) rather than the entire cohort (85 cases and 85 controls) was due to logistical constraints, including limited resources, funding, and availability of molecular analysis kits and equipment. This approach is commonly practiced in research where resource constraints limit comprehensive molecular testing for all enrolled participants. We ensured that the subset analyzed was representative, randomly selected, and appropriately matched to maintain the validity and reliability of our findings

Blood Samples Collection and Processing

Three milliliters (3 ml) of venous blood were withdrawn from each participant; samples were collected from asthmatic patients as well as healthy controls. As directed by the manufacturer, 2 ml was centrifuged for 15 minutes at 3000 rpm For serology testing and 1 ml was kept in EDTA tubes for molecular testing to find the IL18 SNP. After centrifuge, the serum was separated, transferred to Eppendorf tubes, and stored for use in immunological tests in a deep freezer (-20°c).

Serological Technique

Serum Interleukin-18 (IL18) levels were measured using an ELISA KITS (BT LAB/China) and an (AccuBind) for total IgE ELISA kit (LOT NO. 25K4H3). The operations were carried out in accordance with the kit manufacturer's instructions.

Detection of Respiratory Syncytial Virus (RSV) Antibodies (IgM and IgG)

Respiratory Syncytial Virus (RSV) antibodies (IgM and IgG) were detected using commercial enzyme-linked immunosorbent assay (ELISA) kits (BT Lab, China), following the manufacturer's instructions. Briefly, serum samples from all participants were collected, centrifuged at 1500 × g for 10 minutes, and stored at -20°C until analysis. Prior to testing, samples were brought to room temperature and diluted according to kit protocols. Optical density (OD) values were measured at a wavelength of 450 nm using an automated ELISA microplate reader (BioTek ELx800, BioTek Instruments Inc., USA).

Samples were considered positive or negative according to the manufacturer's recommended cutoff values provided with the kit. Positive results indicated recent (IgM) or past exposure (IgG) to RSV. Appropriate quality controls and standards provided in the kits were included in each assay run to ensure validity and reproducibility of results.

Molecular diagnosis

DNA Extraction

Genomic DNA was isolated from whole blood samples from 50 asthmatic patients and 50 healthy controls using a Geneaid DNA extraction kit manufactured in Taiwan. The concentration and purity of the DNA samples were assessed using a Nanodrop spectrophotometer. Pure DNA often has an optical density ratio lower than 260/280.

PCR and primer (Touchdown PCR)

In our investigation, we use the set of primers for IL-18 SNP 137G/C (rs187238) employed in table 1(26). The same primer combination, forward and reverse, was used to amplify the DNA template, using the Touchdown PCR protocol (2 step first 64 C^{o} at 5 cycles, followed by 62^{0}C for 30 cycles) in order to find the ideal primer annealing temperature. This helps to reduce non-specific amplification and improve the specificity of the PCR reactions by progressively lowering the annealing temperature. While the subsequent lower temperature (62°C) for effective amplification, the initial higher temperature (64°C) ensures specificity[15]. Thirteen microliters of Master Mix, one microliter each of forward and reverse primers, three microliters of DNA template, and seven microliters of nuclease-free water made up the 25 microliter PCR amplification volume. PCR Express (Thermal Cycler, Multigene Potimax, Germany) was used for PCR cycling.

Table 1: Specific Primers and Their Sequences

Product Name	Product size (bp)	Primer	Oligonucleotide sequence (5′-3′)
IL-18 -137	446 bp	IL-18F	CCAATAGGACTGATTATTCCGCA
		IL-18R	AGGAGGGCAAAATGCACTGG
	261 bp	G_ allele	CCCCAACTTTTACGGAAGAAAAG
		C_ allele	CCCCAACTTTTACGGAAGAAAAC

Sequencing and Alignment of Genes

The amplified PCR products were sequenced at Macrogen Company (South Korea) by sanger sequencing used " dideoxynucleosides method"Bioinformatics analysis software, such as Bio edit, was used to analyze the sequencing results after receiving them from the company, revealing the polymorphisms of the studied SNPs[16].

Statistical Analysis

GraphPad Prism 10 and R version 4.1.0, along with R packages for data administration and visualization, were used to conduct the statistical study. For normal data, the mean ± standard deviation was employed, and for non-normal data, the median with Interquartile Range (IQR). Using the Kolmogorov-Smirnov test and independent t-tests, normality was established. Relationships were analyzed using Pearson and Spearman correlations. While genetic investigations included genotype allele frequency comparisons and Hardy-Weinberg equilibrium tests, ROC curve analysis evaluated biomarkers, IL-18, and the accuracy of IgE diagnosis. was set with stronger limits for increasing significance at $p<0.05$[16].

RESULTS

In **Figure 1.** Asthma patients had higher IgE levels than the control group (185.0±49.00 pg/ml vs.165.0±26.33 pg/ml, p=0.001), according to the analysis of IgE levels. Additionally, with p-values (p <0.001), Asthmatic patients' levels of IL-18 were substantially greater than those of the control group (228.4±76.03 pg/ml vs. 156.4±44.00 pg/ml).

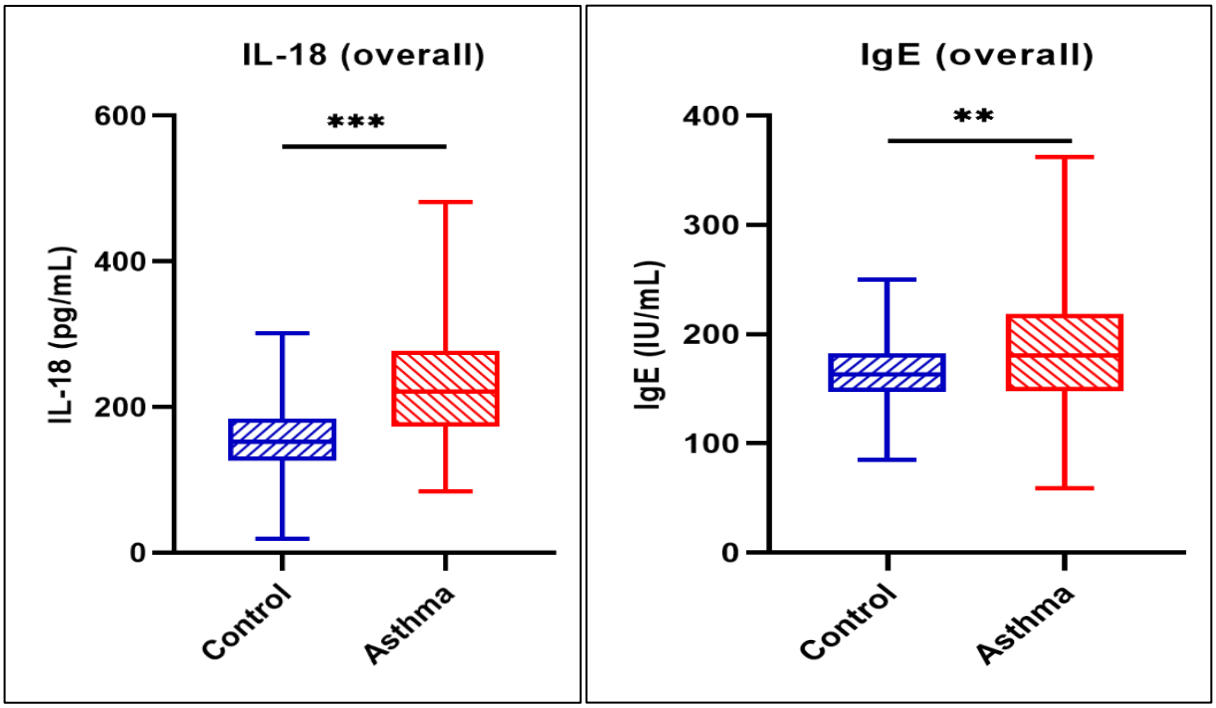

Fig. 1: Serum IgE concentrations in the control and asthmatic patient groups. The data is shown in the form of box plots, with the median indicated by the line within each box. Asterisks (**) for IgE and (***) for IL18 denote statistically significant differences ($p < 0.01$) between groups.

As shown in Figure 2. Within the asthma patient group, several comparisons were made to explore associations with IL-18 levels . Age-based analysis showed slightly higher IL-18 levels in patients >2.5 years compared to those ≤2.5 years (231.8±83.84 pg/ml vs. 226.3±71.41 pg/ml), though this difference was not statistically significant (p=0.748). Sex comparison revealed higher IL-18 levels in male patients compared to females (234.9±82.69 pg/ml vs. 217.7±63.28 pg/ml, p=0.316), but again, this difference did not reach statistical significance. Family history of asthma appeared to influence IL-18 levels, with mean values of 237.7±78.11 pg/ml for those with a family history versus 218.0±73.20 pg/ml for those without, although this difference was not statistically significant (p=0.156). The presence of cough as a symptom showed higher IL-18 levels (252.3±57.62 pg/ml without cough vs. 227.2±76.91 pg/ml with cough, p=0.392), but this difference also lacked statistical significance . As shown in Figure 2. allergies to dust and smoking sensitivity did not significantly affect IL-18 levels among asthma patients. Dust allergy showed minimal difference in IL-18 levels (229.3±88.32 pg/ml vs. 227.2±55.12 pg/ml, p=0.903), while smoking sensitivity had a slight, non-significant difference (232.3±89.43 pg/ml vs. 223.65±6.02 pg/ml, p=0.605). To end, RSV seropositivity, both for IgM and IgG, did not significantly correlate with IL-18 levels. RSV-IgM positive patients had slightly lower IL-18 levels compared to negatives (221.3±80.04 pg/ml vs. 229.7±75.80 pg/ml, p=0.842), while RSV-IgG positive patients showed marginally higher levels (234.4±70.43 pg/ml vs. 226.6±78.11 pg/ml, p=0.401).

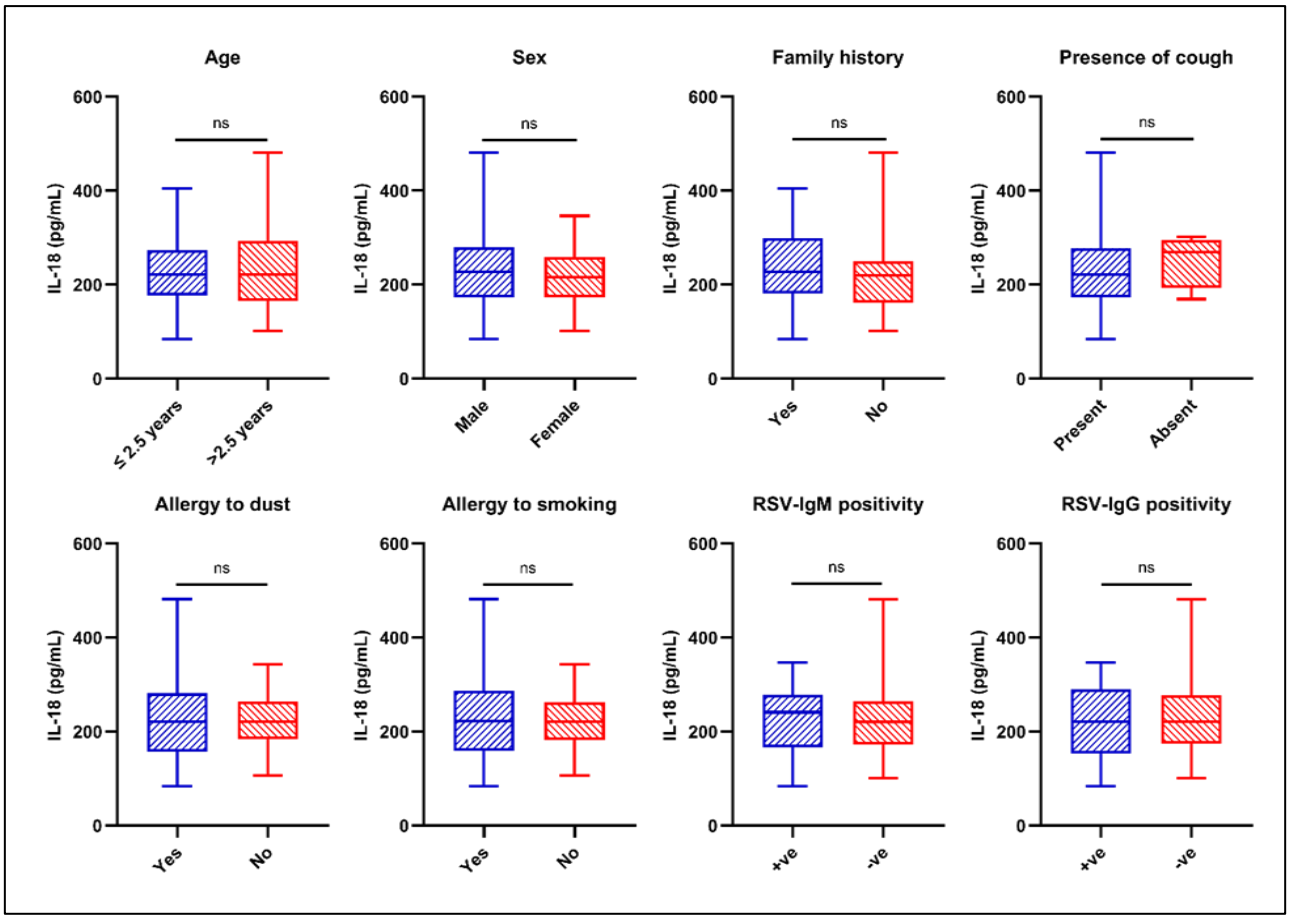

Fig. 2: Subgroup analyses of serum IL-18 levels within the asthma patient group. All plots are presented as box plots, with the line in each box representing the median.

PCR result

One hundred blood samples were isolated to amplify (446 bp), (261bp) annealing: 64-62c (IL18) gene area after gel electrophoresis on 1.5% Agarose Gel electrophoresis (Device & Power supply "Cleaver UK) at 70-voltage, 85 mA for 40 minutes stained with Green safr (abm Canada). M: Ladder 100 bp "Geneaid" was seen in the bands as shown in -**Figure 3.**

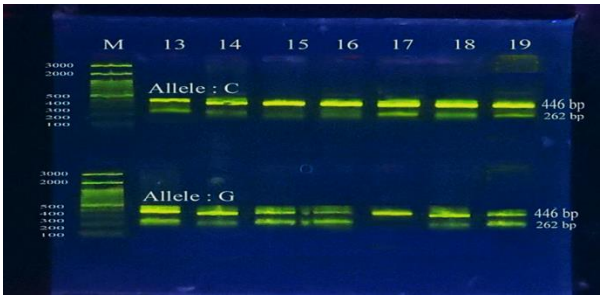

Figure 3. Agarose gel electrophoresis (1.5% agarose gel, run at 100 volts for 60 minutes) showing PCR products for IL-18 (−137 G/C) polymorphism. Lane M: 100 bp DNA ladder (Geneaid). Lanes 13–19 represent individual DNA samples analyzed from study participants;**Upper photo (Allele C):** Samples exhibiting the CC genotype, identified by a single PCR band at 446 bp; **Lower photo (Allele G):** Samples exhibiting the GG genotype, characterized by two distinct PCR bands at 446 bp and 262 bp due to allele-specific amplification; **PCR amplification conditions:** Initial denaturation at 95°C for 5 minutes, followed by 5 cycles at 64°C annealing temperature, then 30 cycles at 62°C annealing temperature, with extension at 72°C according to standard PCR protocols.

Relationship between asthma risk and IL-18 polymorphisms

The genotype distribution of the IL-18 137 C>G polymorphisms in asthma patients and controls was investigated, as shown in Table 2. For the IL-18 137 C>G polymorphism, the GG genotype was more prevalent in the asthma group (42 cases) than in the control group (19 cases), with an odds ratio (OR) of 1.44 (95% CI: 0.62-3.36). Nonetheless, this connection was not statistically significant (p = 0.514). Asthmatic patients (3 cases) had a lower prevalence of the CC genotype than controls (4 cases), with an odds ratio of 0.36 (95% CI: 0.08-1.73). However, the difference did not reach statistical significance (p = 0.228). All this finding were submitted to NCBI https://www.ncbi.nlm.nih.gov/nuccore/LC856639.1/.

In **Table 3**, the potential genetic connections, an allele-based analysis was performed, as shown in Table 3. The asthma group had a higher odds ratio of 1.55 (95% CI: 0.78-3.07) for the G allele of IL-18 137 C>G (0.800) than the control group (0.721). But the difference was not statistically significant (p = 0.277). Genotype determination for the IL-18 (−137 G/C) polymorphism was performed using allele-specific PCR followed by agarose gel electrophoresis. Allele frequencies were calculated based on the number of observed alleles in each genotype group. The association between allele frequency and asthma risk was statistically analyzed using odds ratios (OR) and 95% confidence intervals (CIs). The odds ratio (OR) provides an estimate of the risk conferred by the presence of the allele (G allele in this case) comparing asthma cases to controls.

As shown in **table 4.** Show the diagnostic utility of IgE and IL-18 as asthma biomarkers was assessed using the ROC analysis.

Table2: Relationship between asthma risk and IL-18 polymorphisms

Gene	Genotype	Type	No	OR (95% CI)	*P*-value
IL-18 137 C>G	GG	Control	19	1.44 (0.62-3.36)	0.5142
		Asthma	42		
Asthma and Control	GC	Control	11	0.93 (0.38-2.26)	1.0000
		Asthma	20		
	CC	Control	4	0.36 (0.08-1.73)	0.2279
		Asthma	3		

Table 3: Comprehensive genetic analysis of SNPs associated with asthma risk

SNP	Allele	Allele frequency		Association analysis	
		Control	Asthma	OR (95% CI)	*P*-value
IL-18 137 C>G	G	0.721	0.800	1.55 (0.78-3.07)	0.2768

Table 4: Receiver operating characteristic (ROC) analysis results of the studied biomarkers

	Cut-off	AUC	Sensitivity (95% CI)	Specificity (95% CI)	*P*-value
IgE	≤195.7	0.623	89.41 (80.8 – 95.0)	41.18 (30.6 – 52.4)	0.005
IL-18	≤203.1	0.795	87.06 (78.0 – 93.4)	64.71 (53.6 – 74.8)	<0.001

DISCUSSION

Our study offered information, that links an interleukin-18 gene promoter polymorphism -137G/C (IL-18) to asthma in Iraqi children under the age of six. Patients with bronchial asthma commonly develop this condition early in life, during infancy or childhood. Furthermore, the study showed that asthmatic children's IL18 and IgE serum levels were considerably greater than controls. The epidemiologic findings, revealing a positive correlation between total IgE andIL18 with asthma . Our findings are also comparable with those of Zeng, *et al.* [17]who discovered that asthmatic children have higher total IgE levels, with mean levels increasing significantly with asthma severity .

A study in 2022 had reported that children with asthma have much greater levels of IgE than children without the condition[18] . In addition to IgE, the findings of IL18 serum levels are supported by other studies showing higher levels of IL18 are significantly associated with asthma. One, a study highlighted those elevated levels of IL18 significantly contribute to the severity of asthma by worsening inflammation and immune responses[19]. Another study had reported that the higher levels of IL18 are associated with alternative inflammatory pathways in asthma patients leading to disease severity[20]. Furthermore, another study brought light to IL18 as a key role player leading to severity of asthma. It worsens inflammation which results in breathing difficulty and extra mucus build up[21]

Additionally, the ROC analysis shows that the biomarkers for IgE and IL18 have statistically significant potential for diagnosing asthma, as indicated by their p-values ($p<0.001$). The importance of genetic variations in interleukin genes as possible risk factors for asthma has been the subject of recent research. Among these, the IL-18 gene has three polymorphisms (GG, GC, and CC) that have been discovered through sequencing of SNP 137 (G>C). The mutation of this SNP took place in the 5'-nontranslated region and promoter (non-coding). The genotype distribution of the IL-18 137 polymorphism indicates that the GG genotype was more common in the asthma group (42 cases) than in the control group (19 cases), with an odds ratio (OR) of 1.44 (95% CI: 0.62-3.36). Nevertheless, statistical significance was not attained by this connection ($p=0.514$). In contrast, asthma patients had a lower prevalence of the CC genotype (3 instances) than controls (4 cases), with an OR of 0.36 (95% CI: 0.08-1.73). although this difference was also not statistically significant ($p=0.228$).

Many recent studies have suggested the same results of IL18 polymorphisms are not significantly linked to asthma risk (23) the allele-based analysis was conducted did not reach statistical significance ($p=0.277$). These results raise critical questions regarding the relevance of IL-18 polymorphisms in the pathogenesis of asthma. While the data suggest some potential associations, the lack of statistical significance points to the need for caution in interpreting these findings. One potential explanation for the lack of significant association between SNPs of IL18 and asthma could lie in the complex interplay of genetic factors influencing the disease. Asthma is known to be polygenic, with multiple SNPs contributing variably across different populations[22].

Moreover, there could be several factors at play, including sample size limitations, population heterogeneity, or the possibility that IL18 SNPs do not play a direct role in asthma pathogeneses, like many Interleukins with non significant association[13]. Future research should aim for a more understand the pathophysiology and comprehensive analysis of genetic variants to elucidate their collective impact on asthma development, thereby informing better therapeutic approaches for affected individuals.

CONCLUSION

Children with asthma showed significantly higher levels of IL-18 and IgE compared to healthy controls .This study highlights the genotype distribution and allelic frequencies of IL18 SNP 137 (G>C) among asthmatic children. In the current study, no statistically significant differences were seen between the asthmatic and control groups.

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Declaration

Conflict of Interest: We declare that there are no conflicts of interest associated with this manuscript.

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Authors contribution:

A.A.K: (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Writing – original draft; Writing – review & editing)

T.A.M: (Conceptualization; Formal analysis; Investigation; Methodology; Supervision; Writing – original draft; Writing – review & editing).

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