ASTHMA ALLERGY IMMUNOLOGY
ASTIM ALLERJİ İMMÜNOLOJİ

doi: 10.21911/aai.2026.1291
Asthma Allergy Immunol 2026;24:200-207

RESEARCH ARTICLE

Received: 03.02.2026 • Accepted: 03.05.2026
Online Published: 08.07.2026

HLA Class II Alleles Associated with Bronchial Asthma in the Karakalpakstan Population: An Immunogenetic Case-Control Study

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ABSTRACT

Objective: Bronchial asthma is a complex inflammatory disorder shaped by genetic susceptibility and environmental exposures. This immunogenetic case-control study aimed to investigate the association between HLA class II genes and bronchial asthma in a Central Asian population chronically exposed to Aral Sea-related airborne pollutants.

Materials and Methods: High-resolution genotyping of the HLA-DQA1, HLA-DQB1, and HLA-DRB1 loci was performed in patients with bronchial asthma and age- and sex-matched conditionally healthy controls.

Results: Asthma patients exhibited markedly elevated total IgE levels and widespread allergen-specific sensitization, supporting the predominance of an IgE-driven allergic endotype. Significant associations with increased asthma risk were identified for the HLA-DQB103:03 and HLA-DRB107 alleles, whereas HLA-DRB110 and HLA-DRB111 demonstrated potential protective effects. No independent association was observed for HLA-DQA1 alleles.

Conclusion: This study provides the first immunogenetic evidence of HLA class II involvement in bronchial asthma within an environmentally stressed Central Asian population characterized by chronic exposure to Aral Sea-related airborne pollutants. These findings underscore the importance of gene-environment interactions and support the integration of immunogenetic markers into future risk stratification and personalized prevention strategies in high-exposure regions.

Keywords: Asthma, genetic susceptibility, HLA class II, IgE, Karakalpakstan

INTRODUCTION

Bronchial asthma is a chronic multifactorial disease characterized by airway inflammation, immune hyperreactivity, and variable airflow obstruction. It represents one of the most prevalent non-communicable diseases worldwide and remains a major public health burden, particularly in low- and middle-income regions. According to the World Health Organization, asthma affects hundreds of millions of individuals globally and contributes substantially to morbidity and preventable mortality, with a disproportionate impact in environmentally and socioeconomically stressed populations (1,2).

In recent decades, the rising prevalence of asthma has been closely linked to global climate change, rapid urbanization, and increasing air pollution. Central Asia represents a unique high-risk region where environmental and social determinants converge. In particular, the Aral Sea ecological disaster has led to chronic exposure to airborne dust, salt aerosols, and chemical pollutants originating from the dried seabed (3). Reports from IQAir and the

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World Health Organization consistently rank several Central Asian cities among the most polluted worldwide, underscoring the epidemiological relevance of asthma in this region (4,5).

The adverse effects of environmental exposure are further compounded by socioeconomic factors, including limited healthcare infrastructure, reduced access to early diagnosis, and low population-level health literacy. These conditions contribute to delayed detection of asthma and an increased frequency of severe clinical phenotypes. In the Karakalpakstan population, additional demographic features—such as partial historical isolation, restricted migration, and relatively high rates of consanguinity—may reduce genetic diversity and influence population-specific immune responses (6,7).

At the immunological level, bronchial asthma is predominantly driven by IgE-mediated mechanisms and Th2-skewed immune responses. Central to this process are human leukocyte antigen (HLA) class II molecules, which mediate antigen presentation to $CD4^+$ T lymphocytes and regulate downstream cytokine signaling. Polymorphisms within HLA-DQ and HLA-DR loci can alter antigen-binding properties, influence Th2 polarization, and modulate IgE production, thereby shaping individual susceptibility to allergic inflammation and asthma endotypes (8,9).

Previous studies across diverse populations have identified both risk and protective associations between specific HLA class II alleles and asthma. Notably, certain HLA-DRB1 and HLA-DQB1 variants have been linked to enhanced allergic sensitization and disease severity, whereas others appear to confer immunological tolerance. However, data from environmentally stressed Central Asian populations remain scarce, limiting the understanding of gene-environment interactions in this context (9).

Therefore, the aim of this study was to investigate the distribution of HLA class II alleles (HLA-DQA1, HLA-DQB1, and HLA-DRB1) in patients with bronchial asthma and conditionally healthy controls from the Karakalpakstan population, and to evaluate their association with IgE-mediated allergic sensitization under conditions of chronic environmental exposure. The findings are expected to contribute to population-specific risk stratification and to support the development of personalized preventive strategies in high-exposure regions.

MATERIALS and METHODS

Participants

The study included patients with bronchial asthma and conditionally healthy controls recruited from the same regional population of Karakalpakstan. The asthma group comprised adults aged 18-45 years with a confirmed diagnosis established in accordance with the Global Initiative for Asthma (GINA) guidelines, based on characteristic respiratory symptoms and objective evidence of variable airflow limitation demonstrated by spirometry and bronchodilator reversibility testing (increase in FEV_1 ≥12% and ≥200 mL). The control group consisted of individuals aged 50-60 years with no history of asthma, chronic respiratory or allergic diseases, or other immunological conditions; all participants underwent clinical screening and medical record review to exclude respiratory and atopic pathology. Both groups were derived from the same geographic region and shared comparable environmental exposure conditions.

Statement of Ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki (2013). The study protocol was reviewed and approved by the Ethics Committee of the Republican Scientific and Specialized Allergological Center, Tashkent, Uzbekistan, in collaboration with the Tashkent Medical Academy (Ethics approval code: Uz.TMA.Allergological. №.1610.1987). Written informed consent was obtained from all participants prior to enrollment.

Determination of Allergen-Specific IgE (ALEX Panel)

To identify disease-causative allergens in patients with bronchial asthma, the ALEX panel was applied. This immunoblot-based assay enabled the simultaneous detection of allergen-specific immunoglobulin E (sIgE) against multiple allergens, allowing a comprehensive assessment of the allergen-dependent characteristics of bronchial asthma.

DNA Extraction

Genomic DNA was extracted using the QIAamp DNA Blood Kits 250 (QIAGEN Inc., Valencia, CA, USA). DNA concentration was quantified using a Qubit 2.0 Fluorometer (Thermo Fisher Scientific, USA). All samples were di-

luted to a working concentration of 25-45 ng/μL and subsequently used for sequencing-based genotyping of HLA class II genes.

HLA Genotyping

For the identification of HLA class II alleles—HLA-DQ (DQA1, DQB1) and HLA-DR (DRB1)—in patients with bronchial asthma and conditionally healthy control subjects, the SeCore™ DQA1 Locus Seq Kit, SeCore™ DQB1 Locus Seq Kit, and SeCore™ DRB1 Locus Exon 2, 3 Seq Kit amplification kits developed by Thermo Fisher Scientific (USA) were used.

Sanger sequencing was performed on an automated 3500 Genetic Analyzer platform (Applied Biosystems, USA). Allele identification and genotyping of HLA loci based on nucleotide sequence data were carried out using uTYPE™ HLA Sequence Analysis Software and HLA SBT uTYPE CE-IVD 7.3 software. All genotyping results were interpreted in accordance with international HLA nomenclature standards.

Statistical Analysis

Statistical analysis was performed using standard methods appropriate for categorical genetic data. Allele and genotype frequencies of HLA class II genes were compared between patients with bronchial asthma and the conditionally healthy control group using Pearson's χ^2 test. The suitability of the χ^2 approximation was assessed by examining expected cell counts, and Fisher's exact test was applied where appropriate (expected counts <5).

For contingency tables containing zero values, the Haldane-Anscombe correction was applied to enable stable estimation of odds ratios (ORs) and 95% confidence intervals (CIs), while Yates' continuity correction was used in analyses involving small sample sizes. The strength of association between specific alleles and disease susceptibility was expressed as ORs with corresponding 95% CIs. A p-value <0.05 was considered statistically significant.

Hardy-Weinberg equilibrium (HWE) was assessed in the conditionally healthy control group to evaluate genotype distribution consistency and genotyping quality. HWE testing for the HLA-DQA1, HLA-DQB1, and HLA-DRB1 loci was performed using the χ^2 goodness-of-fit test with Monte Carlo simulation (10,000 iterations), taking into account the high polymorphism and low-frequency alleles characteristic of HLA genes. All analyzed loci were consistent with Hardy-Weinberg equilibrium (p>0.05).

RESULTS

IgE profile and allergen-specific sensitization

In patients with bronchial asthma, allergen-related immune sensitization was evaluated using the ALEX panel, enabling simultaneous detection of allergen-specific IgE (sIgE) against a broad spectrum of inhalant and household allergens (Table I).

The asthma group demonstrated a clinically significant elevation of total IgE levels (n=100), with a mean concentration of 422.75 IU/mL and a median value of 165.00 IU/mL. The distribution showed wide variability (SD=562.93 IU/mL; range: 40-2500 IU/mL) and pronounced asymmetry, characterized by marked right skewness (skewness=2.65) and leptokurtic distribution (kurtosis=6.95). This pattern indicates a right-skewed distribution typical of severe IgE-driven allergic phenotypes.

When compared with established reference ranges, 71% of patients exhibited elevated total IgE levels. Total IgE levels above 100 IU/mL were considered elevated based on commonly accepted clinical laboratory reference ranges. In addition, the upper quartile (Q3=625 IU/mL) of the cohort-specific distribution was used to define markedly elevated IgE levels within the study population. These findings support the predominance of an IgE-mediated allergic endotype in the studied population. Positive sIgE responses were frequently polysensitized, reflecting broad immunological reactivity to multiple allergens and consistent with chronic immune hyperactivation (Table II).

Table I: Total IgE levels in patients with bronchial asthma

Parameter	Value
Number of patients (n)	100
Median (IQR), IU/mL	165.00 (65.00 - 625.00)
Mean ± SD, IU/mL	422.75 ± 562.93
Range, IU/mL	40 - 2500
Skewness	2.65
Kurtosis	6.95
Elevated IgE (>100 IU/mL), n (%)	71 (71)

Table II: Frequency of allergen-specific sensitization in patients with bronchial asthma stratified by age groups (sIgE>0.35 kUA/L)

Allergen	Overall (%)	≤18 years (n=65) (%)	19-40 years (n=28) (%)	>40 years (n=7) (%)
Cynodon dactylon (Bermuda grass)	35.0	27.27	42.86	100.0
Lolium perenne (Perennial ryegrass)	35.0	27.27	42.86	100.0
Paspalum notatum	25.0	18.18	28.57	100.0
Phleum pratense (Timothy grass)	35.0	27.27	42.86	100.0
Rye pollen	10.0	9.09	14.29	0.0
Alder pollen	5.0	0.0	14.29	0.0
Cryptomeria japonica	5.0	9.09	0.0	0.0
Cypress pollen	15.0	18.18	14.29	0.0
Walnut pollen	10.0	9.09	0.0	100.0
Date palm pollen	10.0	9.09	0.0	100.0
Platanus pollen	5.0	9.09	0.0	0.0
Artemisia (wormwood)	20.0	18.18	14.29	100.0
Mercurialis annua	10.0	9.09	0.0	100.0
Dermatophagoides farinae	5.0	9.09	0.0	0.0
Dermatophagoides pteronyssinus	10.0	18.18	0.0	0.0
Alternaria alternata	30.0	36.36	28.57	0.0
Oat	5.0	9.09	0.0	0.0
Rice	5.0	9.09	0.0	0.0
Corn	15.0	0.0	28.57	100.0
Mustard	10.0	18.18	0.0	0.0
Melon	10.0	9.09	0.0	100.0
Strawberry	10.0	9.09	0.0	100.0
Grapes	10.0	9.09	0.0	100.0
Celery	5.0	0.0	14.29	0.0
Sesame	15.0	18.18	14.29	0.0
Crab	10.0	9.09	14.29	0.0
Lobster	5.0	0.0	14.29	0.0
Oyster	5.0	0.0	14.29	0.0
Horse meat	10.0	9.09	14.29	0.0
Chicken meat	5.0	9.09	0.0	0.0
Migratory locust	10.0	9.09	14.29	0.0
Pork	5.0	9.09	0.0	0.0
Honey bee venom	5.0	9.09	0.0	0.0
Paper wasp venom	5.0	9.09	0.0	0.0
Common wasp venom	5.0	9.09	0.0	0.0
Dog epithelium	10.0	18.18	0.0	0.0
Dog urine (Can f 5)	5.0	9.09	0.0	0.0
Cat epithelium (Fel d 1)	35.0	54.55	14.29	0.0
Goat epithelium	5.0	9.09	0.0	0.0
Horse epithelium	5.0	9.09	0.0	0.0
Total IgE positivity	95.0	100.0	100.0	100.0

HLA class II allele distribution

A comparative analysis of HLA class II allele frequencies (%) was performed between patients with bronchial asthma and conditionally healthy controls for the HLA-DQA1, HLA-DQB1, and HLA-DRB1 loci (Tables III-V).

HLA-DQA1

No statistically significant differences were observed in HLA-DQA1 allele frequencies between the asthma and control groups (all p>0.05). The DQA1*05:01 allele was detected at comparable frequencies in patients (30.0%, n=60) and controls (27.3%, n=120) (χ^2=0.38, p=0.538; OR=1.14; 95% CI: 0.79-1.65), indicating a limited independent contribution of this locus to asthma susceptibility in the studied population (Table III).

HLA-DQB1

Analysis of the HLA-DQB1 locus revealed a significant association for the DQB103:03 allele, which was more frequent in the asthma group than in controls (5.5% vs. 1.8%) (χ^2=5.26, p=0.022). This allele was associated with an increased risk of bronchial asthma (OR=3.14; 95% CI: 1.24-7.94). No other HLA-DQB1 alleles demonstrated statistically significant differences between groups. Although DQB105:01 was less frequent among asthma patients (6.0% vs. 10.9%), this difference did not reach statistical significance (p=0.067) (Table IV).

HLA-DRB1

The most pronounced genetic differences were observed at the HLA-DRB1 locus. The DRB1*07 allele occurred at a significantly higher frequency in asthma patients compared with controls (22.0% vs. 15.0%), conferring increased disease risk (χ^2=4.25, p=0.039; OR=1.60; 95% CI: 1.05-2.44).

Conversely, the DRB110 allele was detected less frequently in asthma patients (0.5% vs. 3.6%) and showed a strong protective trend (OR=0.13), although the confidence interval narrowly crossed unity (95% CI: 0.02-1.01), indicating borderline statistical significance. A similar protective association was observed for the DRB111 allele, which was significantly less frequent in the asthma group (6.5% vs. 12.3%) (χ^2=4.29, p=0.038; OR=0.50; 95% CI: 0.26-0.93). No other HLA-DRB1 alleles demonstrated significant intergroup differences (Table V).

Table III: HLA-DQA1 allele frequency (%) in patients with bronchial asthma and conditionally healthy controls.

Allele	Asthma, n (%)	Healthy, n (%)	χ^2	p-value	OR	95% CI
*01:01	26 (13.0)	66 (15.0)	0.30	0.584	0.85	0.52-1.38
*01:02	20 (10.0)	60 (13.6)	1.35	0.246	0.70	0.41-1.20
*01:03	28 (14.0)	44 (10.0)	1.82	0.177	1.47	0.88-2.43
*02:01	26 (13.0)	64 (14.5)	0.16	0.690	0.88	0.54-1.43
*03:01	34 (17.0)	74 (16.8)	0.00	1.000	1.01	0.65-1.58
*04:01	4 (2.0)	8 (1.8)	0.00	1.000	1.10	0.33-3.70
*05:01	60 (30.0)	120 (27.3)	0.38	0.538	1.14	0.79-1.65
*06:01	2 (1.0)	4 (0.9)	0.00	1.000	1.10	0.20-6.06

Table IV: HLA-DQB1 allele frequency (%) in patients with bronchial asthma and conditionally healthy controls.

Allele	Asthma, n (%)	Healthy, n (%)	χ^2	p-value	OR	95% CI
*02	53 (26.5)	110 (25.0)	0.09	0.760	1.08	0.74-1.58
*03:01	38 (19.0)	84 (19.1)	0.00	1.000	0.99	0.65-1.52
*03:02	22 (11.0)	58 (13.2)	0.42	0.519	0.81	0.48-1.37
*03:03	11 (5.5)	8 (1.8)	5.26	0.022*	3.14	1.24-7.94
*03:05	3 (1.5)	4 (0.9)	0.07	0.798	1.66	0.37-7.49
*04:01	2 (1.0)	6 (1.4)	0.00	1.000	0.73	0.15-3.65
*04:02	1 (0.5)	4 (0.9)	0.00	0.952	0.55	0.06-4.93
*05:01	12 (6.0)	48 (10.9)	3.34	0.067	0.52	0.27-1.00
*05:02	5 (2.5)	6 (1.4)	0.49	0.486	1.85	0.56-6.15
*05:03	4 (2.0)	20 (4.5)	1.81	0.178	0.43	0.14-1.27
*05:04	3 (1.5)	6 (1.4)	0.00	1.000	1.10	0.27-4.45
*06:01	15 (7.5)	30 (6.8)	0.02	0.884	1.11	0.58-2.11
*06:02	15 (7.5)	26 (5.9)	0.35	0.557	1.29	0.67-2.49
*06:08	16 (8.0)	28 (6.4)	0.35	0.555	1.28	0.68-2.42

Table V: HLA-DRB1 allele frequency (%) in patients with bronchial asthma and conditionally healthy controls.

Allele	Asthma, n (%)	Healthy, n (%)	χ^2	p-value	OR	95% CI
*01	11 (5.5)	34 (7.7)	0.73	0.393	0.69	0.34-1.40
*03	15 (7.5)	50 (11.4)	1.85	0.174	0.63	0.35-1.16
*04	34 (17.0)	56 (12.7)	1.74	0.187	1.40	0.88-2.23
*07	44 (22.0)	66 (15.0)	4.25	0.039*	1.60	1.05-2.44
*08	2 (1.0)	10 (2.3)	0.62	0.432	0.43	0.09-2.00
*09	8 (4.0)	18 (4.1)	0.00	1.000	0.98	0.42-2.29
*10	1 (0.5)	16 (3.6)	4.09	0.043*	0.13	0.02-1.01
*11	13 (6.5)	54 (12.3)	4.29	0.038*	0.50	0.26-0.93
*12	9 (4.5)	14 (3.2)	0.36	0.548	1.43	0.61-3.37
*13	20 (10.0)	46 (10.5)	0.00	0.972	0.95	0.55-1.66
*14	8 (4.0)	18 (4.1)	0.00	1.000	0.98	0.42-2.29
*15	33 (16.5)	52 (11.8)	2.23	0.136	1.47	0.92-2.36
*16	1 (0.5)	6 (1.4)	0.32	0.573	0.36	0.04-3.04

DISCUSSION

This immunogenetic case-control study suggests that bronchial asthma in the Karakalpakstan population predominantly manifests as an IgE-mediated allergic endotype and that specific HLA class II alleles may contribute to genetic susceptibility to the disease. The combined analysis of allergen-specific sensitization profiles and total IgE levels provides evidence of a persistently hyperreactive immune state in affected individuals (10).

Multicomponent allergen sensitization identified using the ALEX panel, together with a clinically significant elevation of total IgE concentrations (mean 422.75 IU/mL; values above the reference range in 71% of patients), indicates a clear predominance of the allergic asthma endotype in this population. The markedly right-skewed distribution of IgE values (skewness=2.65) and high kurtosis (kurtosis=6.95) reflect the predominance of extreme values, a pattern characteristic of severe allergic phenotypes and consistent with pronounced immunological heterogeneity (10).

Immunogenetic analyses revealed differential involvement of HLA class II loci in asthma pathogenesis. The absence of significant differences at the HLA-DQA1 locus suggests that this gene may not play a major independent role in asthma susceptibility in the studied population. This finding implies that potential effects of DQA1 alleles may be compensated by other HLA loci or modulated by environmental exposures (11).

In contrast, the HLA-DQB1*03:03 allele was significantly overrepresented in the asthma group (OR=3.14; p=0.022), indicating a positive association with disease susceptibility. This observation is concordant with previous studies highlighting the role of HLA-DQB1 molecules in efficient allergen presentation to $CD4^+$ T lymphocytes, thereby promoting Th2-driven inflammatory cascades (12). Similarly, the association of HLA-DRB1*07 with increased asthma risk (OR=1.60; p=0.039) underscores the importance of this locus as a potential immunogenetic determinant of disease development. Conversely, the reduced frequency of HLA-DRB1*11 suggests a possible protective effect (OR=0.50; p=0.038) (13).

Findings related to HLA-DRB1*10 warrant cautious interpretation. Although the p-value reached nominal statistical significance (p=0.043), the upper boundary of the 95% confidence interval encompassed unity (0.02-1.01), indicating a borderline association. This result highlights the need for validation in larger cohorts to clarify the role of this allele (14).

Comparative Context and Population Specificity

Studies conducted in diverse ethnic populations indicate that both the direction and magnitude of HLA-asthma associations vary across populations. In South Asian and Middle Eastern cohorts, alleles belonging to the HLA-DQB1*03 group have been consistently linked to allergic asthma and elevated IgE levels, supporting the relevance of our findings within a global context. However, reports of protective or neutral effects of HLA-DRB1*07 in certain populations suggest that ethnic composition, haplotype structure, and environmental exposure profiles critically shape immunogenetic risk. In this regard, the Karakalpakstan population exhibits a population-specific immunogenetic pattern that reflects both shared global trends and local genetic architecture (15).

Gene-Environment Interaction

The Karakalpakstan region is uniquely characterized by chronic exposure to Aral Sea-related dust-salt aerosols and long-term air pollution, creating sustained antigenic pressure on the respiratory tract. Under such conditions, variation within HLA class II molecules becomes clinically relevant, as individuals carrying risk alleles may present environmental allergens more efficiently. This enhanced antigen presentation can amplify Th2-polarized inflammation and IgE synthesis, thereby increasing both the likelihood and severity of bronchial asthma (16). Collectively, these findings support a gene-environment synergy model, in which genetic susceptibility and environmental stressors jointly shape disease burden and clinical heterogeneity (17).

Limitations and Future Directions

Several limitations should be acknowledged. First, the moderate sample size may have reduced statistical power for detecting associations involving low-frequency alleles. Second, the single-region study design limits direct extrapolation of results to other populations with distinct genetic or environmental backgrounds. Third, the absence of HLA-DQA1/DQB1/DRB1 haplotype analysis precluded assessment of synergistic allele combinations that may exert stronger effects than individual alleles. Future studies should incorporate larger, multicenter cohorts, haplo-

type-based analyses, and functional immunological assays to further elucidate underlying mechanisms (18-21).

In summary, this study provides compelling evidence that bronchial asthma in the Karakalpakstan population is strongly associated with an IgE-driven allergic endotype and identifies HLA-DQB103:03 and HLA-DRB107 as potential genetic risk markers. These findings offer a solid foundation for immunogenetic stratification, early risk identification, and the development of personalized prevention and disease-control strategies, particularly in regions characterized by high environmental exposure (22).

The observed age imbalance between the study groups may have influenced the estimation of odds ratios, as age-related alterations in immune function and HLA allele distribution can modulate the strength of the observed associations. Aging is known to be associated with changes in adaptive immune responses, cytokine profiles, and antigen presentation mechanisms, all of which may affect both the prevalence and functional impact of HLA class II variants.

Furthermore, the inclusion of an older control group may introduce potential selection or survival bias, as these individuals represent a subset of the population that has remained free of asthma and other allergic or immunological conditions over time. This may reflect a relatively more resilient genetic or immunological background, potentially leading to underestimation or, in certain cases, distortion of the observed associations.

Therefore, the findings of the present study should be interpreted with caution, taking into account the potential confounding effect of age and related biases. Future studies incorporating age-matched control groups and multivariable statistical adjustment are warranted to validate and refine the observed immunogenetic associations.

Acknowledgments

The authors express their sincere gratitude to all patients and control participants for their involvement in the study. We also thank the clinical and laboratory staff of the Republican Scientific and Specialized Allergological Center for their support in patient recruitment, sample collection, and diagnostic procedures.

Conflict of Interest

The authors declare that they have no competing interests.

Funding

This research received no external funding.

Disclosure

Generative AI (ChatGPT) was used during the preparation of this manuscript solely for English language editing, grammar correction, and improvement of text readability. The AI tool was not used for study design, data collection, data analysis, statistical evaluation, interpretation of results, or formulation of scientific conclusions. All scientific content was prepared, reviewed, and verified by the authors. The authors take full responsibility for the accuracy, integrity, and originality of the manuscript. ChatGPT does not meet the criteria for authorship and is therefore not listed as an author.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

Concept: **SK, IR, NA,** Design: **SK, IR, NA,** Data collection or processing: **NA, VB, GR,** Analysis or Interpretation: **SK, IR, NA, VB, GR,** Literature search: **SK, GR,** Writing: **SK, NA,** Approval: **SK, IR, NA, VB, GR.**

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