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Bronchial Asthma Control Among School Children in Abha City, Saudi Arabia

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Abstract

**Background:** Asthma is a chronic disease known to have an increasing incidence and severity among children. The parents of children with bronchial asthma have an essential role in managing the disease. Therefore, the burden of this disease needs to be explored.

**Objective:** To assess the control of bronchial asthma among secondary school students in Saudi Arabia.

**Methods:** A cross-sectional study of 487 secondary schools in Abha City was done during the 2017 academic year. The data collected using an interviewer-administered questionnaire included personal characteristics, identified precipitants of asthmatic attacks and the Asthma Control Test.

**Results:** The most frequent allergens included dust (95.6%), smoke (80%) and incense (65.9%). The disease was not controlled in 80% of the asthmatic respondents. The prevalence of the disease was significantly higher among cigarette smokers than non-smokers (20.7% vs 8.5%, p = 0.028). Students who were allergic to incense had a significantly higher prevalence of uncontrolled asthma than those who were not allergic to incense (p = 0.021).

**Conclusions:** Most cases of asthma are not controlled, and some cases have seasonality, mainly during winter and autumn. Allergy to Arabian incense is a risk factor for poor control of bronchial asthma in the population studied.

**Keywords:** Asthma control, Bronchial asthma, Children, Saudi Arabia.

Introduction

Bronchial asthma is one of the common chronic inflammatory diseases in children, and remodelling of the airways can cause its progression into adulthood. The disease affects up to 300 million people worldwide, and it is estimated that an additional 100 million people will have asthma by the year 2025. [1] Bronchial asthma is characterized by variable and recurrent symptoms associated with air flow obstruction, hyper-responsiveness, and lower airway
inflammation. [2] The respiratory tract is periodically constricted, oedematous, and overloaded with excess mucus. These episodes may be triggered by exposure to natural precipitants like cold air, exercise or strenuous activity, or emotional stress. [3]

Bronchial asthma has placed a substantial economic burden on the population. Patients with bronchial asthma have physical, emotional, and social consequences of the disease, leading to lower quality of life and family burden. [4] The condition could be the main reason for school absenteeism and reduced participation in school activities and games. [5] The prevalence of bronchial asthma increases in many countries, with global bronchial asthma incidence expected to rise to 400 million by 2025. [6] However, the disease's intensity and poor degree of control appear to increase. [1] The prevalence of bronchial asthma varies from country to country and ranges from 1.1 to 9.9%. [1] The increasing prevalence of childhood asthma in developing countries also poses a challenge to the health sector: in the age group 6 to 14 years, the prevalence rate has risen from 4 to 32%. [7] In Saudi Arabia, the prevalence rate of bronchial asthma has increased. [8]

The causes of the increase in the prevalence of bronchial asthma are not fully understood. Some of the suggestions are related to changes in lifestyle and environmental factors [9-11] that trigger the immune system in the early stages of life. [11] There is additional evidence of a link between the nature or characteristics of food and the onset of bronchial asthma. [12, 13] Acute exacerbations tend to be related to pregnancy and schooling. On average, a child with active bronchial asthma may miss 2.6 school days a year. [14] The objective of this study was to assess the control of bronchial asthma among secondary school students.

Methods

This study used a c cross-sectional design. The study was conducted among secondary schools in Abha City, Saudi Arabia. There were 7779 male students in 55 secondary schools and 7775 female students in 36 secondary schools. [16] The minimum sample size was calculated as follows: [17]

\[ n = \left( \frac{Z_{1-\alpha}^2 \times p \times q}{d^2} \right) \]

where:

- \( n \) = Calculated minimum sample size
- \( Z_{1-\alpha} = \) The z-value for the selected level of confidence \((1-\alpha) = 1.96.\)
- \( p \) = Proportion of students who may be asthmatic (estimated to be 0.1) [15]
- \( q = 1 - p \)
- \( d = \) The maximum acceptable error = 0.03.

The calculated minimum sample size was 384, but 487 students were studied. Using simple random sampling, the researcher selected two secondary schools for boys and another two secondary schools for girls. Using the average number of students in each class as a guide, the classes were randomly selected until each school's required sample size was covered. Prior to data collection, a pilot study was done using 20 students.

The questionnaire collected data across (a) personal sociodemographic and personal health profiles (age, gender, nationality, parents' educational levels, parents' employment status, family size, average number of occupants per bedroom, birth order, Body Mass Index, smoking status, smoking status of the family members, average monthly family income, practice of vigorous sports, presence of cockroaches and pets home), (b) precipitants of asthmatic attacks and type and quality of asthma treatment and care, and (c) Asthma Control Test, which is a five-item questionnaire developed as an easy method to assess asthma control using symptoms, use of rescue medications, and impact of disease on activities. Each question was graded
from one to five hence, the total score ranged from 5 to 25. Well-controlled asthma was defined as a score above 20 on the Asthma Control Test (ACT) scale. [18]

Data collection
Following official permissions, the researcher visited the two schools for boys. In contrast, a female nurse trained by the researcher visited the schools for girls for data collection under the tenets of human subject research guidelines. Written consent was obtained from the participants, and all the students were recruited into the study.

Data analysis
The Statistical Package for Social Sciences (SPSS version 23.0) was used for data entry and analysis. The crowding index was calculated as the number of persons per bedroom. [19] Descriptive statistics (i.e. frequency, percentage, mean and standard deviation) were calculated, and the Chi-Squared test was used to test hypotheses of proportions. Statistical significance was defined by p values less than 0.05.

Results
Table I shows that 49.9% of the participants were males, and more than two-thirds were aged 17 -18 years. Most of them (87.5%) were Saudis and of middle birth order (57.1%). Although only 6% were current cigarette smokers, 7.4% were overweight, while 0.6% were obese. Only 18.5% indulged in vigorous exercise. While 41.1% and 35.5% of the fathers had university and secondary education, 29.8% and 27.5% of the mothers had tertiary and secondary education. About one-third of fathers (38%) had a government job, while more than two-thirds of the mothers (69%) were unemployed. The family size of 59.3% of the students had 6-8 members, while almost half of the participants (46%) had a family monthly income of 5000-10000 SR, but 36.8% had a family monthly income greater than 10000 SR. Half of the students had a crowding index of fewer than two persons per bedroom. Less than one-fifth of the students (18.7%) had pets at home, while 6.2% had cockroaches. Overall, 9% (44/487) of the study participants had bronchial asthma.

Table II shows that in the preceding four weeks, bronchial asthma prevented 48.9% of asthmatic participants from getting as much done at school or home, while 8.9% had a similar experience most of the time. One-third of the asthmatic participants experienced shortness of breath more than once a day, while 24.4% had it once a day or once or twice a week. More than one-third of asthmatic participants (37.8%) experienced waking up at night or earlier than usual in the morning four or more nights a week. More than two-thirds did not use rescue inhalers or nebulizer medication during the preceding four weeks. However, more than one-third of the asthmatic participants (35.6%) rated their asthmatic attacks as "poorly controlled", whereas using the Asthma Control Test questionnaire, 36 out of 45 asthmatics (80.0%) had scores ≤ 20, implying that they had poorly controlled asthma while the remaining 9 (20.0%) had a well-controlled disease. In Table III, the disease was not controlled among all the students whose fathers had no formal education or intermediate education and those whose mothers had primary education and whose fathers were unemployed. Students whose mothers were employed had a higher prevalence of uncontrolled asthma than those whose mothers were unemployed (86.7% vs 76.7%, respectively) but without statistical significance. The prevalence rate of uncontrolled bronchial asthma was highest among participants whose family size was 6-8 members (89.7%), those with a family monthly income >10000 SR (84.6%), and those who had a smoker in the family (92.3%) those with high crowding index (84.8%), and those with cockroaches at home (83.3%).
Table Ia: Sociodemographic, lifestyle and environmental characteristics of respondents

| Parameters                  | Frequency (n = 487) | Percentage |
|-----------------------------|--------------------|------------|
| Gender                      |                    |            |
| Male                        | 243                | 49.9       |
| Female                      | 244                | 50.1       |
| Age (Years)                 |                    |            |
| <17                         | 121                | 24.8       |
| 17                          | 200                | 41.1       |
| 18                          | 134                | 27.5       |
| ≥19                         | 32                 | 6.6        |
| Nationality                 |                    |            |
| Saudi                       | 426                | 87.5       |
| Non-Saudi                   | 61                 | 12.5       |
| Body Mass Index             |                    |            |
| Normal (<25kg/m²)           | 76                 | 15.6       |
| Overweight (25-29.9(<25kg/m²)| 36                 | 7.4        |
| Obese (>30kg/m²)            | 5                  | 0.8        |
| Smoking Status              |                    |            |
| Smoker                      | 29                 | 6.0        |
| Non-smoker                  | 458                | 94.0       |
| Vigorous exercise (Sporting)|                    |            |
| Yes                         | 90                 | 18.5       |
| No                          | 397                | 81.5       |

On the other hand, participants who had pets at home had a lower prevalence rate of uncontrolled disease (77.8% vs 80.6%). However, all the observed differences in the prevalence of uncontrolled bronchial asthma among groups of students, distributed according to family or environmental characteristics, were not statistically significant.

Table IV shows that all asthmatic students with summer/spring seasonality had an uncontrolled disease. However, differences in the prevalence of uncontrolled asthma according to seasonality were not statistically significant. Moreover, the students who were allergic to incense had a significantly higher prevalence of uncontrolled asthma than those not allergic to incense (p = 0.021). The prevalence rate of uncontrolled disease did not differ significantly according to the regularity of bronchial asthma treatment or regular clinic visits.

Discussion

Allergic diseases are common health problems during childhood, with asthma being the leading cause of morbidity and mortality. Therefore, it is very important to understand the pattern and factors associated with the control of bronchial asthma to avoid complications hence, the present study. The findings in this study revealed that 9% of secondary school students in Abha City had bronchial asthma. This is in accordance with the prevalence rates reported by several studies conducted in Saudi Arabia. In Abha City, Alshehri et al. [20] reported a prevalence rate of 9% among urban schoolboys. In contrast, in the rural Aseer Region, the prevalence of bronchial asthma was reported by Al-Ghamdi et al. [21] to be 14% among individuals aged 11 years or older.
Table Ib: Sociodemographic, lifestyle and environmental characteristics of respondents

| Parameters          | Frequency (n = 487) | Percentage |
|---------------------|---------------------|------------|
| Father’s Education  |                     |            |
| None formal         | 14                  | 2.9        |
| Primary             | 40                  | 8.2        |
| Intermediate        | 60                  | 12.3       |
| Secondary           | 173                 | 35.5       |
| Tertiary            | 200                 | 41.1       |
| Mother’s Education  |                     |            |
| None formal         | 60                  | 12.3       |
| Primary             | 71                  | 14.6       |
| Intermediate        | 77                  | 15.8       |
| Secondary           | 153                 | 31.0       |
| Tertiary            | 145                 | 29.8       |
| Father’s Occupation |                     |            |
| Government          | 185                 | 38.0       |
| Military            | 155                 | 31.8       |
| Private             | 75                  | 15.4       |
| Unemployed          | 72                  | 14.8       |
| Mother’s Employment Status |               |            |
| Employed            | 151                 | 31.0       |
| Unemployed          | 336                 | 69.0       |
| Family size         |                     |            |
| <6                  | 80                  | 16.4       |
| 6-8                 | 289                 | 59.3       |
| ≥9                  | 118                 | 24.2       |
| Family Income       |                     |            |
| <5000 SR            | 84                  | 17.2       |
| 5000-10000 SR       | 224                 | 46.0       |
| >10000SR            | 179                 | 36.8       |
| Smoking Family Member |                  |            |
| Yes                 | 111                 | 22.8       |
| No                  | 376                 | 77.2       |
| Crowding Index      |                     |            |
| <2 persons/bedroom  | 244                 | 50.1       |
| ≥2 persons/bedroom  | 243                 | 49.9       |
| Presence of pets at home |              |            |
| Yes                 | 91                  | 18.7       |
| No                  | 396                 | 81.3       |
| Presence of cockroaches at home |         |            |
| Yes                 | 30                  | 6.2        |
| No                  | 457                 | 93.8       |

In Iran, Boskabady and Simaei [22] reported that the prevalence of bronchial asthma among high school students aged 14-20 years was 15.9%. This wide variability in the reported prevalence rates is probably due to differences in study population characteristics, diagnostic criteria and data collection techniques. The differences in the prevalence of uncontrolled asthma according to seasonality were not statistically significant in the present study. Teague et al. [23] stated that air pollution and environmental smoke are well known to augment the severity and persistence of asthma symptoms. The incidence of acute exacerbations among school-age children has been shown to peak during fall and spring. [24-26] Moreover, in Ontario, Canada, Johnston et al. [27] reported a sharp annual rise in asthma exacerbations, known as the September
epidemic, when children return to school. Lemanske et al. [28] explained the seasonality of bronchial asthma among adolescents by the high positivity rate in the test for rhinovirus among children and young adults who experience acute exacerbations of bronchial asthma during falls.

Table II: Indicators of bronchial asthma control within the preceding four weeks among 45 asthmatic respondents

| Indicators                                                                 | Frequency (n = 45) | Percentage |
|---------------------------------------------------------------------------|--------------------|------------|
| How much of the time did asthma keep you from getting as much done at home or in school? | All of the time     | 0          |
|                                                                           | Most of the time   | 4          |
|                                                                           | Some of the time   | 22         |
|                                                                           | A little of the time | 11   |
|                                                                           | None               | 8          |
| How often have you had shortness of breath?                               | More than once a day | 15  |
|                                                                           | Once a day         | 11         |
|                                                                           | 3-6 times a week   | 0          |
|                                                                           | Once or twice a week | 11  |
|                                                                           | Not at all         | 8          |
| How often did your asthma symptoms wake you up at night or earlier than usual? | 4 or more nights a week | 17  |
|                                                                           | 2 or 3 nights a week | 7   |
|                                                                           | Once a week        | 8          |
|                                                                           | Once or twice a month | 8   |
|                                                                           | Not at all         | 5          |
| How often have you used your rescue inhaler or nebulizer medication?      | 3 or more times per day | 3   |
|                                                                           | 1 or 2 times per day | 2   |
|                                                                           | 2 or 3 times per week | 7   |
|                                                                           | Once a week or less | 4   |
|                                                                           | Not at all         | 29         |
| How would you rate your asthma control during the past four weeks         | Not controlled at all | 2   |
|                                                                           | Poorly controlled  | 16         |
|                                                                           | Somewhat controlled | 13  |
|                                                                           | Well controlled    | 7          |
|                                                                           | Completely controlled | 7   |

This virus plays a significant role in precipitating attacks of wheezing throughout the year. Soto-Quiros [29] added that allergic inflammation, including high titres of allergen-specific immunoglobulin E antibody, significantly increases the odds that rhinovirus will provoke an attack of bronchial asthma that requires hospital care. Wisniewski et al. [26] stated that since allergen exposures that are likely to influence seasonal peaks differ in the regions studied, a better understanding of seasonal allergen exposures at the local level can provide an opportunity to enhance preventive measures and seasonal compliance with asthma medications. The impact of several factors such as personal, family, socioeconomic, and environmental variables on bronchial asthma control among school children has also been explored. Regarding environmental asthma triggers, the most frequent allergens in the present study included dust, smoke, incense, perfumes, food items, and certain drugs.
Students who were allergic to incense had a significantly higher prevalence of uncontrolled asthma than those who were not allergic to incense. Moreover, cigarette smoking, pet-keeping and cockroach-infested homes were associated with a higher prevalence of uncontrolled bronchial asthma.

Table IIIa: Relationship between asthma control and sociodemographic, lifestyle and environmental characteristics

| Parameters               | Not Controlled | Controlled | P value |
|--------------------------|----------------|------------|---------|
|                          | Frequency | Percentage | Frequency | Percentage |         |
| Gender                   | Male (n = 25) | 19 | 76.0 | 6 | 24.0 | 0.453 |
|                          | Female (n = 20) | 17 | 85.0 | 3 | 15.0 |         |
| Age (Years)              | <17 (n = 12) | 9 | 75.0 | 3 | 25.0 | 0.661 |
|                          | 17 (n = 17) | 13 | 76.5 | 4 | 23.5 |         |
|                          | 18 (n = 11) | 9 | 81.8 | 2 | 18.2 |         |
|                          | ≥19 (n = 5) | 5 | 100.0 | 0 | 0.0 |         |
| Nationality              | Saudi (n = 42) | 33 | 78.6 | 9 | 21.4 | 0.37 |
|                          | Non-Saudi (n = 3) | 3 | 100.0 | 0 | 0.0 |         |
| Body Mass Index          | Normal (<25 kg/m²) (n = 31) | 24 | 77.4 | 7 | 22.6 | 0.495 |
|                          | Overweight (25-29.9 kg/m²) (n = 9) | 7 | 77.8 | 2 | 22.2 |         |
|                          | Obese (>30 kg/m²) (n = 5) | 5 | 100.0 | 0 | 0.0 |         |
| Smoking Status           | Smoker (n = 6) | 6 | 100.0 | 0 | 0.0 | 0.188 |
|                          | Non-smoker (n = 39) | 30 | 76.9 | 9 | 23.1 |         |
| Vigorous exercise (Sporting) | Yes (n = 5) | 3 | 60.0 | 2 | 40.0 | 0.236 |
|                          | No (n = 40) | 33 | 82.5 | 7 | 17.5 |         |

The US Environmental Protection Agency \[31\] reported that tobacco smoke contains more than 4000 chemical compounds, many of which are known poisons. The smell of tobacco smoke can trigger an allergic response that initiates the inflammatory process, leading to a runny nose, watery eyes, sinus congestion, lower peak flows, wheezing, and shortness of breath. Therefore, individuals who smoke should be advised to quit to minimize smoke's asthma-triggering effects. In addition, parents with asthma-prone children should keep smokes away from them. \[32\] Most animals shed dander which can trigger hypersensitivity reactions and provoke bronchial asthma attacks. Dust mites are tiny arachnids related to ticks and spiders found in most homes. Dust mite pieces and droppings are allergens that can travel by air to trigger the allergic cascade and worsen bronchial asthma. Moreover, cockroaches are usually difficult to avoid in crowded areas. For many individuals with bronchial asthma, the droppings and saliva of cockroaches trigger attacks.

Since cockroaches are ubiquitous, individuals with bronchial asthma should practice good house cleaning measures, especially cockroach-control techniques. \[32\] McGlaun \[33\] stated that, since dust mites, cockroaches, and household animals can trigger asthma attacks, it is helpful to clean and dust the home environment frequently.
Vacuum rather than sweep the floors since sweeping might stir specks of dust and other asthma triggers into the air. The findings in the present study are supportive of these theories. Moreover, Al-Rawas et al. [34] emphasized that it is crucial to raise public awareness about the potentially harmful effects of Arabian incense burning and to reduce exposure to this incense by keeping the room well-ventilated while burning incense. It is crucial to avoid such practice in the presence of asthmatic children and susceptible individuals. The findings in the present study

| Parameters                  | Uncontrolled | Controlled | P value |
|-----------------------------|--------------|------------|---------|
| **Father’s Education**      |              |            |         |
| None formal (n = 3)         | 3            | 0          | 0.267   |
| Primary (n = 2)             | 2            | 1          | 33.3    |
| Intermediate (n = 3)        | 3            | 0          | 0.0     |
| Secondary (n = 14)          | 13           | 1          | 7.1     |
| Tertiary (n = 22)           | 15           | 7          | 31.8    |
| **Mother’s Education**      |              |            |         |
| None formal (n = 8)         | 6            | 2          | 0.59    |
| Primary (n = 7)             | 7            | 0          | 0.0     |
| Intermediate (n = 6)        | 4            | 2          | 33.3    |
| Secondary (n = 12)          | 10           | 2          | 16.7    |
| Tertiary (n = 12)           | 9            | 3          | 25.0    |
| **Father’s Occupation**     |              |            |         |
| Government (n = 22)         | 15           | 7          | 0.155   |
| Military (n = 13)           | 12           | 1          | 7.7     |
| Private (n = 3)             | 2            | 1          | 33.3    |
| Unemployed (n = 7)          | 7            | 0          | 0.0     |
| **Mother’s Employment Status** |            |            |         |
| Employed (n = 15)           | 13           | 2          | 0.429   |
| Unemployed (n = 30)         | 23           | 7          | 23.3    |
| **Family size**             |              |            |         |
| <6 (n = 7)                  | 5            | 2          | 0.068   |
| 6-8 (n = 29)                | 26           | 3          | 10.3    |
| >9 (n = 9)                  | 5            | 4          | 44.4    |
| **Family Income**           |              |            |         |
| <5000 SR (n = 12)           | 9            | 3          | 0.83    |
| 5000-10000 SR (n = 20)      | 16           | 4          | 20.0    |
| >10000SR (n = 13)           | 11           | 2          | 15.4    |
| **Smoking Family Member**   |              |            |         |
| Yes (n = 13)                | 12           | 1          | 0.188   |
| No (n = 32)                 | 24           | 8          | 25.0    |
| **Crowding Index**          |              |            |         |
| <2 persons/bedroom (n = 12) | 8            | 4          | 0.178   |
| ≥2 persons/bedroom (n = 33) | 28           | 5          | 15.2    |
| **Presence of pets at home**|              |            |         |
| Yes (n = 9)                 | 7            | 2          | 0.852   |
| No (n = 36)                 | 29           | 7          | 19.4    |
| **Presence of cockroaches at home** |  |            |         |
| Yes (n = 6)                 | 5            | 1          | 0.826   |
| No (n = 39)                 | 31           | 8          | 20.5    |
showed that asthma was not controlled among 80% of asthmatic students. Moreover, only about one-third of asthmatic students received treatment for their asthma, while only one-fourth of them visited an asthma clinic. However, bronchial asthma control was not significantly different with respect to regularity of asthma treatment and attendance of asthma clinics.

| Parameters                      | Uncontrolled | Controlled | P values |
|---------------------------------|--------------|------------|----------|
|                                | Frequency    | Percentage | Frequency | Percentage |          |
| Seasonality                     |              |            |          |            |          |
| No (n = 27)                     | 21           | 77.8       | 6         | 22.2       | 0.333    |
| Yes (n = 18)                    | 15           | 83.3       | 3         | 16.7       |          |
| Winter/Autumn (n = 11)          | 8            | 72.7       | 3         | 27.3       |          |
| Summer/Spring (n = 7)           | 7            | 100.0      | 0         | 0.0        |          |
| Identified allergens            |              |            |          |            |          |
| Dust (n = 43)                   | 35           | 81.4       | 8         | 18.6       | 0.278    |
| Smoke (n = 36)                  | 30           | 83.3       | 6         | 16.7       | 0.264    |
| Incense (n = 29)                | 26           | 89.7       | 3         | 10.3       | 0.021    |
| Perfumes (n = 13)               | 12           | 92.3       | 1         | 7.7        | 0.174    |
| Some food items (n = 5)         | 4            | 80.0       | 1         | 20.0       | 1.000    |
| Drugs (n = 9)                   | 7            | 77.8       | 2         | 22.2       | 0.852    |
| Regular treatment for asthma    |              |            |          |            |          |
| Yes (n = 17)                    | 15           | 88.2       | 2         | 11.8       | 0.282    |
| No (n = 28)                     | 21           | 75.0       | 7         | 25.0       |          |
| Regular asthma clinic attendance|              |            |          |            |          |
| Yes (n = 11)                    | 10           | 90.9       | 1         | 9.1        | 0.298    |
| No (n = 34)                     | 26           | 76.5       | 8         | 23.5       |          |

These findings reflect the lack of awareness among secondary school students and the urgent need to raise their knowledge regarding bronchial asthma management. Anwar et al. [14] stressed that health education about asthma is essential in schools, and this objective necessitates an interdisciplinary approach from various organizations, particularly schools. An important preliminary step is that the knowledge of schoolteachers should be improved and be continuously updated as this will be translated to knowledge, awareness and practices of students with bronchial asthma. The present study also revealed that the prevalence of bronchial asthma was higher among students with high crowding index. This finding agrees with the report of Mansour et al. [34] in Damietta Governorate, Egypt, that a significant association existed between bronchial asthma among school children and crowding index.

**Conclusion**

The prevalence of bronchial asthma among secondary school students in Abha City, Saudi Arabia, is about one-tenth, and most cases of bronchial asthma in this population are not controlled. Higher prevalence rates of bronchial asthma among secondary school students include smoking, high crowding index, and having cockroaches at home. On the other hand, exposure to Arabian incense was associated with uncontrolled bronchial asthma among secondary school students in Abha City, Saudi Arabia.

**Authors’ Contributions:** RKB conceived the study and designed it with AAA1. AAA1, AA and SHMA did the literature review. AAA2, AA, and SHMA did data acquisition. AAA2, SHMA, and AN did data analysis, while RKB, AAA1, SHMA, and AN did data interpretation. AAA2 and AN drafted the manuscript, while RKB and AA revised the manuscript for sound intellectual contents. All the authors approved the final version of the manuscript.
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