

Characteristics of Asthma Patients and Risk Factors of Uncontrolled Asthma in Children

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Objective: To identify factors associated with baseline severity and control of asthma in pediatric patients.

Materials and Methods: The medical records of 279 newly diagnosed patients with asthma aged younger than 15 years and that visited Taksin Hospital in Bangkok were reviewed. Demographic and clinical characteristics at first diagnosis and three months after treatment were collected. Medication and treatment compliance were recorded. Asthma control status was classified according to the Global Initiative for Asthma (GINA) guideline. Factors associated with baseline severity and levels of control were determined.

Results: Among the 279 pediatric patients with asthma, 48 (17.6%) were severe asthma at time of diagnoses. Patient's comorbidities, including acute rhinosinusitis, a family history of atopy, and a history of preterm birth, were significantly associated with severe asthma at baseline. Asthma severity can be assessed retrospectively from the level of treatment required to control symptom and exacerbation according to the GINA. At the 3-month visit, 105 (37.6%) patients had uncontrolled asthma. Factors associated with uncontrolled asthma included severe asthma at baseline (RR 4.86, 95% CI 2.96 to 7.99), a family history of atopy (RR 1.54, 95% CI 1.12 to 2.12), acute rhinosinusitis and snoring (RR 1.54, 95% CI 1.09 to 2.17), severe allergic rhinitis (RR 2.32, 95% CI 1.78 to 3.04), poor compliance (RR 4.66, 95% CI 3.36 to 6.45), and aggravated factors (RR 3.88, 95% CI 3.05 to 4.92). Environmental factors, such as owning pets and environmental tobacco smoke, were not associated with asthma control.

Conclusion: Good treatment compliance for asthma and other comorbidities are important for well-controlled asthma.

Keywords: Uncontrolled asthma, Pediatric asthma, Asthma severity, Treatment compliance, Asthma control

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Asthma is characterized by chronic airway inflammation. The diagnosis of asthma generally relies on a history of respiratory symptoms, such as wheeze, shortening of breath, chest tightness, and cough, particularly at night or during exertion⁽¹⁾. Asthma affects 300 million people worldwide and is predicted to affect an additional 100 million people

by 2025⁽²⁾. Symptoms and variable airflow limitation are often triggered by some factors, such as exercise, allergen sensitization, stress, obesity, environmental tobacco smoke, a change in weather, and viral respiratory tract infection^(1,3). Host and environmental factors may affect the severity of asthma. Allergen sensitization is positively associated with allergic inflammation, severity of allergic rhinitis, and severity of asthma⁽³⁾. Atopic characteristics and allergen sensitization can enhance an allergic inflammatory process because of inadequate control of asthma⁽¹⁾. Allergic rhinitis has a direct effect on controlling the symptoms of asthma⁽⁴⁾. Obesity is associated with uncontrolled asthma and this effect is stronger in females than in males⁽⁵⁾. Environmental tobacco smoke has direct and indirect effects on the severity of asthma and pulmonary function⁽⁶⁾. Generally, the severity of asthma can be assessed retrospectively from the level of treatment required to control the

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symptom and exacerbation, following the Global Initiative for Asthma (GINA) guideline. The severity of asthma is classified into mild, moderate, and severe asthma⁽¹⁾.

Control of asthma requires early diagnosis and regular follow-up visits for appropriate case management. Inhaled corticosteroid (ICS) can be used to control asthma symptoms, reduce exacerbation, and improve lung function⁽⁷⁾. Although receiving appropriate medication can help to control asthma, modification of the risk factors can play an important role in controlling asthma⁽²⁻⁴⁾. The level of asthma control can be classified into three levels according to the GINA guideline as controlled, partly controlled, and uncontrolled asthma. This approach assumes that patients have received appropriate treatment. Uncontrolled asthma is defined as poor asthma symptoms, acute asthma exacerbation, and an impaired pulmonary function test (forced expiratory volume in one second is less than 80% of the predicted or personal best)⁽¹⁾. Patients with well-controlled asthma can reduce the risk of exacerbation of asthma and comorbid diseases.

Although asthma is a chronic disease, a previous study has indicated that proper diagnosis and treatment, good adherence to treatment, and risk factor modification improve the level of asthma control and enhance the quality of life⁽¹⁾. However, potential factors associated with the level of asthma control may vary across populations. Additionally, asthma control is a dynamic process, which can be affected by short- and long-term factors^(1,3). Therefore, a cross-sectional study may not be able to determine the temporal relationships between potential factors and the level of asthma control. The authors aimed to identify factors that were associated with uncontrolled asthma in pediatric patients using a cohort study. Findings from the study could be useful for planning proper management for pediatric patients with asthma.

Materials and Methods

Study population

The authors performed a retrospective cohort study. Medical records of patients with asthma at a pediatric allergy unit, Taksin Hospital in Bangkok, Thailand, between April 2012 and April 2016 were reviewed. Patients with newly diagnosed asthma that were younger than 15 years were included in the present study. Patients who had underlying diseases, such as other chronic lung diseases, cardiovascular diseases, and other chronic illnesses, were excluded. The diagnosis of asthma was based on clinical

symptoms and the current GINA guideline. According to the GINA guideline, the level of asthma control was classified into well-controlled, partly controlled, and uncontrolled asthma groups⁽¹⁾. The diagnosis of allergic rhinitis was based on the allergic rhinitis and its impact on asthma (ARIA) guideline⁽⁴⁾. Acute rhinosinusitis was defined when the symptoms lasted less than twelve weeks and completely subsided⁽⁸⁾.

Data collection

Medical records were reviewed at the patient's first diagnosis and then at the 3-month, 6-month, and 1-year visits. Baseline characteristics of the pediatric patients with asthma were recorded, including age of onset, age of diagnosis, sex, severity of asthma, allergic sensitization (pet owner, environmental tobacco smoke, aeroallergen sensitization, and family history of atopy), comorbid diseases (allergic rhinitis, atopic dermatitis, food allergy, acute rhinosinusitis, and snoring), and the severity of asthma assessment according to the GINA guideline⁽¹⁾.

According to the routine clinical practices, assessment of the severity of asthma according to the GINA guideline and a pulmonary function test were performed at each patient's visit. Asthma severity can be assessed retrospectively from the level of treatment required to control the symptom and exacerbation⁽¹⁾. Information regarding asthma medication, compliance of treatment, and aggravated factors affecting asthma symptoms were also reviewed and recorded in the study. All patients in the present study were treated by only one pediatrician following the standard GINA guideline. Treatment compliance was assessed by patients' self-reporting and monitoring of the medication by the checks and count procedures⁽⁹⁾.

Assessment of severity and asthma control

According to the GINA guideline, the severity of asthma can be assessed by using the frequency of daytime and night-time symptoms and the pulmonary function test. The severity of asthma was classified into mild, moderate, and severe asthma. The asthma severity could then be assessed retrospectively from prescribed treatment step. The treatment response was assessed by considering the level of asthma control three months after the treatment started. According to the GINA guideline, the level of asthma control was assessed by activity limitation, daytime and night-time symptoms, exacerbation, reliever use, and pulmonary function. The level of asthma control was classified into the categories of controlled, partly controlled, and uncontrolled asthma⁽¹⁾.

Statistical analysis

Demographic and clinical characteristics of the patients were described using descriptive statistics. Characteristics of patients with severe asthma at the initial diagnosis were described and compared with non-severe patients using the chi-square test or Student's t-test. To examine the potential factors associated with uncontrolled asthma, the level of asthma control three months after initial treatment was summarized into the two categories of uncontrolled asthma and others (controlled asthma and partly controlled). The relative risk (RR) and 95% confidence interval (CI) were calculated using log-binomial regression. Multiple regression was not performed due to strong correlation among the different clinical factors. Factors that were associated with uncontrolled asthma at 6-months and 1-year after initial treatment were not determined because of the small number of patients with uncontrolled asthma at the follow-up visits. A p-value of less than 0.05 was considered to be statistically significant. Analysis was performed in SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethical approval

The present study was approved by the Bangkok Metropolitan Administration Ethics Committee for Human Research (BMAEC-S010q/59_EXP), which is valid from 2016 to 2020.

Results

Demographic and clinical characteristics of the patients

Two hundred seventy-nine pediatric patients with asthma were included in the study. The mean \pm standard deviation (SD) age of the patients was 6.87 ± 2.49 years (range 4 to 14.2), and 64.2% of the patients were boys. The mean age at first onset of asthma and at diagnosis was 3.31 ± 2.05 years and 4.88 ± 2.31 years, respectively. The mean disease duration before diagnosis was 1.57 ± 1.35 years (range 0 to 8). Approximately half (46.6%) of newly diagnosed patients were classified as having moderate severity asthma. Severe asthma was observed in 17.6% of newly diagnosed patients. The most common comorbid diseases were allergic rhinitis (40.5%), snoring (20.1%), and atopic dermatitis (14.7%). More than half of the patients had been exposed to known risk factors of asthma, including aeroallergen sensitization (76.9%), a family history of atopy (52.3%), and environment tobacco smoke (50.5%). The most common aeroallergen

sensitization was house dust mites (*Dermatophagoides pteronyssinus* 74.4%, *Dermatophagoides farina* 70.6%), cockroaches (40.7%), and cat pelt (20.6%). The proportions of patients who completed follow-up at 3-months, 6-months, and 1-year were 100%, 94.6%, and 81.7%, respectively.

Characteristics of patients with severe asthma

The severity of asthma was assessed retrospectively from prescribed treatment according to the GINA guideline. Among 279 patients, 48 (17.6%), 131 (46.6%), and 100 (35.8%) patients were defined as having severe, moderate, and mild asthma, respectively. The characteristics of patients with severe asthma were compared with those in the rest of the patients. There was no significant difference in sex, age, or age of onset of patients between those with and those without severe asthma. However, patients aged three to six years at diagnosis were more likely to have severe asthma at the first diagnosis compared with patients younger than three years ($p=0.012$). Being a pet owner or exposure to environmental tobacco smoke was not associated with asthma severity at diagnosis. With regard to the medical history, obesity ($p=0.039$), a family history of atopy ($p<0.001$), acute rhinosinusitis ($p=0.002$), and preterm birth ($p=0.013$) were more significantly likely to be observed in patients with severe asthma than in those with non-severe asthma (Table 1).

Management of asthma control

Most patients with asthma in the present study took an asthma controller. Asthma medication was considered on reducing asthma symptoms and reducing the risk of asthma-related exacerbation. Step treatment according to the GINA guideline was used. Most patients (188, 67.4%) received combination therapies. Monotherapy was administered to only 91 (32.6%) patients. ICS was the most common monotherapy, followed by a leukotriene receptor antagonist (LTRA) (28, 30.7%), a fixed-dose combination ICS plus long-acting β -agonist (FDC ICS/LABA) (24, 26.4%), and mast cell stabilizer (4, 4.4%). Combination therapies were usually used for difficult to treat asthma. The distribution of combination therapies was ICS plus LTRA (75, 39.9%), ICS/LABA plus LTRA (66, 35.1%), ICS/LABA plus LTRA plus xantine (45, 23.9%), and ICS/LABA plus xantine (2, 1.1%).

Risk factors of uncontrolled asthma

In the present study, partly controlled and

Table 1. Characteristics of patients with asthma and those with severe asthma

	Severe asthma at first diagnosis; n (%)		Total n (%)	p-value
	Yes	No		
Total	48	231	279	
Sex				0.21
Male	27 (56.3)	152 (65.8)	179 (64.2)	
Female	21 (43.7)	79 (34.2)	100 (35.8)	
Age group (years)				0.68
<5	14 (29.2)	61 (26.4)	75 (26.9)	
5 to 9	29 (60.4)	135 (58.4)	164 (58.8)	
≥10	5 (10.4)	35 (15.2)	40 (14.3)	
Age of onset (years)				0.41
<3	28 (15.8)	104 (54.2)	132 (55.5)	
3 to 6	18 (39.2)	88 (45.8)	106 (44.5)	
Age at diagnosis (years)				0.012
<3	15 (42.9)	34 (22.2)	49 (26.1)	
3 to 6	20 (57.1)	119 (77.8)	139 (73.9)	
Pet owner				0.74
Yes	14 (29.2)	62 (26.8)	76 (27.2)	
No	34 (70.8)	169 (73.2)	203 (72.8)	
Environmental tobacco smoke				0.58
Yes	26 (54.2)	115 (49.8)	141 (50.5)	
No	22 (45.8)	116 (50.2)	138 (49.5)	
Obesity				0.039
Yes	14 (29.2)	38 (16.5)	52 (18.6)	
No	34 (70.2)	193 (83.5)	227 (81.4)	
Family history of atopy				<0.001
Yes	36 (75.0)	110 (47.6)	146 (52.3)	
No	12 (25.0)	121 (52.4)	133 (47.7)	
Allergic rhinitis				0.14
Yes	24 (50.0)	89 (38.5)	113 (40.5)	
No	24 (50.0)	142 (61.5)	166 (59.5)	
Atopic dermatitis				0.67
Yes	8 (16.7)	33 (14.3)	41 (14.7)	
No	40 (83.7)	198 (85.7)	238 (85.3)	
Food allergy				0.42
Yes	2 (4.2)	17 (7.4)	19 (5.4)	
No	46 (95.8)	214 (92.6)	260 (94.6)	
Acute rhinosinusitis				0.002
Yes	13 (27.1)	24 (10.4)	37 (13.3)	
No	35 (72.9)	207 (89.6)	242 (86.7)	
Snoring				0.083
Yes	14 (29.2)	42 (18.2)	56 (20.1)	
No	34 (70.8)	189 (81.8)	223 (79.9)	
Aeroallergen sensitization				0.28
Yes	39 (83.0)	155 (75.6)	194 (77.0)	
No	8 (17.0)	50 (24.4)	58 (23.0)	
Preterm				0.013
Yes	8 (16.7)	12 (5.3)	20 (7.3)	
No	40 (83.3)	214 (94.7)	254 (92.7)	
Mode of delivery				0.38
Normal labor	38 (79.2)	162 (71.1)	200 (71.7)	
Cesarean section	10 (20.8)	66 (28.9)	76 (27.3)	

Table 2. Factors associated with uncontrolled asthma at 3 months after initial treatment

	Uncontrolled asthma group; n (%)		RR (95% CI)
	Yes	No	
Total	105	174	
Sex			
Male	65 (36.3)	114 (63.7)	1
Female	40 (40.0)	60 (60.0)	1.10 (0.81 to 1.50)
Age (years)			
<3	54 (40.9)	78 (59.1)	
3 to 6	41 (38.7)	65 (61.3)	0.95 (0.69 to 1.30)
Severity			
Mild	15(15.0)	85(85.0)	1
Moderate	55 (42.0)	76 (58.0)	2.80 (1.68 to 4.65)
Severe	35 (72.9)	13 (27.1)	4.86 (2.96 to 7.99)
Family history of atopy			
No	39 (29.3)	94 (70.7)	1
Yes	66 (45.2)	80 (54.8)	1.54 (1.12 to 2.12)
Acute rhinosinusitis			
No	85 (35.1)	157 (64.9)	1
Yes	20 (54.1)	17 (45.9)	1.54 (1.09 to 2.17)
Snoring			
No	76 (34.1)	147 (65.9)	1
Yes	29 (51.8)	27 (48.2)	1.52 (1.11 to 2.08)
Severe persistent allergic rhinitis			
No	66(29.7)	156 (70.3)	1
Yes	38 (69.1)	17 (30.9)	2.32 (1.78 to 3.04)
Compliance in the previous 3 months			
Good	33 (17.4)	157 (82.6)	1
Poor	72 (80.9)	17 (19.1)	4.66 (3.36 to 6.45)
Had aggravated factors in the previous 3 months			
No	55 (24.3)	171 (65.7)	1
Yes	50 (94.3)	3 (5.7)	3.88 (3.05 to 4.92)
Acute asthmatic attack in the previous 3 months			
No	85 (32.8)	174 (67.18)	1
Yes	20 (100)	0 (0.0)	2.03 (2.03 to 2.03)

RR=relative risk; CI=confidence interval

uncontrolled asthma based on the GINA guideline were categorized as the uncontrolled asthma group. One hundred five (33%), 79 (20%), and 53 (5%) patients had uncontrolled asthma at 3-month, 6-month, and 1-year visits, respectively. Only the factors associated with uncontrolled asthma at the 3-month visit were determined. Age and sex of the patients were not associated with uncontrolled asthma. Baseline severity was a strong predictor for

uncontrolled asthma three months after treatment. Patients with a baseline severity of moderate and severe asthma were 2.80 and 4.86 times more likely to have uncontrolled asthma, respectively (Table 2). A family history of atopy increased the risk of having uncontrolled asthma three months after treatment (RR 1.54, 95% CI 1.12 to 2.12). Comorbid diseases that were significantly associated with uncontrolled asthma included severe persistent allergic rhinitis (RR

2.32, 95% CI 1.78 to 3.04), acute rhinosinusitis (RR 1.54, 95% CI 1.09 to 2.17), and snoring (RR 1.52, 95% CI 1.11 to 2.08). Compliance to treatment was associated with the asthma control level. Patients with poor compliance in the previous three months were 4.66 times more likely to have uncontrolled asthma. Additionally, having aggravated factors (respiratory tract infection or hospitalization) and an acute asthmatic attack in the previous three months significantly increased the risk of uncontrolled asthma by 3.88 and 2.03 times, respectively (Table 2). However, environmental factors, such as having pets, aeroallergen sensitization, and environmental tobacco smoke, were not significantly associated with uncontrolled asthma. Unfortunately, risk factors of uncontrolled asthma were not significant at the 6-month and 1-year visits.

Discussion

Patients with uncontrolled asthma generally have a worsening of symptoms or acute exacerbation and a decline in pulmonary function⁽¹⁾. Uncontrolled asthma can affect the patient's quality of life, school performance, and daily activities, which can lead to psychiatric comorbidities (anxiety or depression)⁽¹⁰⁾. Management of asthma, particularly among pediatric patients, is challenging. Control of asthma requires a combination of proper medication, patient's medical conditions and compliance, and environmental modification^(1,3). Identification of the potential factors that are associated with the control of asthma would be helpful for planning a proper management of the pediatric patients with asthma. In the present study, the baseline asthma severity of patients was a strong predictor of uncontrolled asthma three months after treatment. Characteristics of patients with severe asthma at baseline were also described.

Patients with severe asthma in the present study were likely to have the diagnoses of asthma at three to six years old. Persistent wheezing in children shows symptoms before the age of three years and continues beyond the age of six years⁽¹¹⁾. Approximate one third of the infants worldwide are estimated to have been infected with respiratory virus, including respiratory syncytial virus or rhinovirus, during their first year of life. Infection can result in acute bronchiolitis and an increase in the risk of developing recurrent wheezing and childhood asthma⁽¹²⁾. Obesity, a family history of atopy, acute rhinosinusitis, and preterm birth were associated with severe asthma. Obesity increases airway hyper-responsiveness. Restoring normal body weight is an appropriate strategy for reducing airway

hyper-responsiveness and controlling inflammation, which may help improve asthma control⁽¹³⁾. Therefore, lifestyle modifications for weight control, such as weight loss, dietary control, and exercise, should be considered in the management of asthma⁽¹⁴⁾.

The present study showed a significant relationship between the history of atopy in first-degree relatives and the patient's severity of asthma. A previous study also showed that a family history of asthma or allergy increases the probability of having respiratory symptoms due to asthma⁽¹⁾. Rhinosinusitis is the most common comorbidity of asthma, which can worsen symptoms of asthma⁽¹⁵⁾. Preterm infants are more susceptible to respiratory complications, which subsequently increase the risk of developing childhood asthma^(16,17). A large cohort study of Norwegian children also showed an association between preterm birth and severe asthma⁽¹⁷⁾.

The goal of managing asthma is to achieve control of symptoms and to minimize the future risk of exacerbation. Pharmacological and non-pharmacological strategies are important for managing asthma. An ICS is generally introduced to control symptoms, improve lung function, and reduce exacerbation and asthma-related morbidity. ICSs are safe and are used worldwide⁽¹⁾. In the present study, ICS was the most common drug for monotherapy. LTRAs are effectively used in young children with persistent asthma because they can modestly reduce symptoms, are easy to use (no need for appropriate devices), and have good adherence⁽¹⁸⁾. An LTRA was the second choice for treatment in young children with asthma in the present study. However, fixed-dose combination therapy (ICS/LABA) or other combination therapies (ICS plus LTRA, ICS/LABA plus LTRA, ICS/LABA plus LTRA plus xantine, and ICS/LABA plus xantine) were used in patients with moderate to severe asthma.

Non-pharmacological strategies are required for effective management of asthma. The present study showed that patient's factors, including asthma severity, compliance, and comorbidity, significantly affected asthma control. However, environmental factors, such as owning pets and environmental tobacco smoke, were not significantly associated with asthma control. Environmental modification is sometimes difficult to conduct. However, good treatment compliance for asthma and other comorbidities could result in well-controlled asthma. Good adherence to asthma treatment is associated with the level of asthma control. Patients with poor treatment adherence are likely have uncontrolled

asthma exacerbations more often than those with good treatment compliance⁽¹⁸⁾. The present study showed that patients with poor adherence to asthma treatment during the previous three months were 4.66 times more likely to have uncontrolled asthma.

Furthermore, having aggravating factors or events of acute asthmatic attack could affect the level of asthma control. Education on asthma should be performed to improve understanding of asthma control in patients and care givers and to emphasize the importance of good treatment adherence⁽¹⁹⁾. A survey in Thailand found that patients with asthma underestimated the burden of complications of asthma disease⁽²⁰⁾. Previous studies have shown that providing education to patients with asthma regarding self-management can reduce morbidity of asthma in adults and children^(21,22). A good healthcare provider partnership should enable patients with asthma to gain the knowledge and skill to assume a major role in managing their symptoms.

Several comorbidities are common in patients with asthma, such as allergic rhinitis, rhinosinusitis, and obesity. Active detection and management of comorbidities are recommended because they may contribute to the symptom burden, impaired quality of life, and poor asthma control⁽²³⁾. Most patients with asthma, either with the allergic or non-allergic type, have concurrent rhinitis, and 10% to 40% of patients with allergic rhinitis have asthma. The severity of allergic rhinitis has a direct effect on asthma severity and control⁽⁴⁾. This supports the relevance of the “one airway, one disease” concept of diseases (“from nostrils to alveoli”) for allergic rhinitis in asthma. Allergic rhinitis may contribute to other comorbidities, such as rhinosinusitis, obstructive sleep apnea, and snoring^(4,24). The present study also showed that severe persistent allergic rhinitis, acute rhinosinusitis, and snoring increased the risk of uncontrolled asthma. In addition, patients may have multiple comorbidities concurrently, indicated by a strong correlation among these variables. These findings support previous studies, which showed that early diagnosis and proper management of comorbid diseases can help to maintain a good level of asthma control and decrease asthma-related hospitalization and emergency department visits^(4,24).

The authors used a retrospective cohort study approach, which allowed determination of the temporal sequence of factors that were associated with the level of asthma control. Although results from the present study were based on only one hospital in Bangkok, the allergy clinic in this hospital

is considered as the largest pediatric allergy clinic in Bangkok. Patients visiting the allergy clinic in the present study represented those with a low to middle income living in a large city of a developing country. Additionally, all patients in the present study were assessed and treated by only one pediatrician. This could have reduced confounders and bias on the variability of asthma treatment to the level of asthma control. However, the present study only assessed the level of asthma control three months after initial treatment because most patients were controlled by six and twelve months. Although the first three months after treatment is a critical period for asthma treatment, further study is required to determine the factors that are associated with long-term asthma control.

Conclusion

The aim of pediatric asthma management is to achieve good control of symptoms, maintain the patient’s normal activity, and minimize the future risk of exacerbation or comorbidities. The present study suggested that patient’s factors, including baseline severity of asthma, treatment compliance, and asthma-related comorbidities, are important factors for controlling asthma. Appropriate pharmacological treatment and patient’s self-management are both required to achieve well-controlled asthma. Health care workers should encourage patients with asthma to gain knowledge, confidence, and skill of self-management to reduce morbidity of asthma. Good adherence of asthma treatment is the best benefit of well-controlled asthma and good quality of life of patients.

What is already known on this topic?

The authors aimed to identify the factors that are associated with uncontrolled asthma in pediatric patients based on a cohort study, whose result could be used to plan proper management for the patients.

What this study adds?

Good treatment compliance for asthma and other comorbidities are important for well-controlled asthma and can improve the quality of life.

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Conflicts of interest

The authors declare no conflict of interest.

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