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Contents

Editorial

The present issue of Pediatric Respirology and Critical Care Medicine has three interesting articles from very different settings and on varied issues, namely, an epidemiological study on association between asthma and other allergic diseases and risk of Dengue virus infection from Taiwan,[1] a retrospective diagnostic study on role of fractional nitric oxide concentration in exhaled breath (FeNO) levels to identify patients with exercise induced bronchoconstriction (EIB) from Hong Kong SAR, and, a diagnostic study on simple laboratory parameters in neonatal sepsis from India.[3]

The epidemiological study from Taiwan,[1] reports an interesting association between Allergic disorders and risk for Dengue fever. The authors report that those suffering from allergic rhinitis and / or Asthma had a lower risk of Dengue fever while no such association was found among those with atopic dermatitis. The authors hypothesise that the alterations in skin dendritic cells-specific intercellular adhesion molecule 3-grabbing non-integrin (DC-SIGN) protein affects the entry of Dengue virus into the body thus offering a protective effect. However, the authors have not offered explanations for lack of the same association among children with atopic dermatitis. The study was conducted through retrospective search of National Health Insurance Research Database (NHIRD) of Taiwan which covers more than 99% of the population of the nation. Design of the study brings some limitations as it is unlikely to cover mild cases of dengue infection which may not necessarily be tested or treated at a health facility. Likewise, there can be some degree of over representation of allergic diseases among the control group as these diseases by themselves remain an important cause for seeking healthcare.

Au and colleagues[2] have tried to develop z-score of normative data for FeNO among their own population and to find cutoff that would be more accurate in predicting EIB. They argue that this approach is better than using a single internationally recommended cutoff level for children of all ages because not only the FeNO level varies with age but also the international data may not be suitable as Asian children have high FeNO level compared to the white children. Retrospective record analysis of the children with asthma and exercise related symptoms who underwent evaluation at a Hospital in Kowloon, Hong Kong SAR was used to identify best cutoffs of FENO levels to predict presence of EIB. The prevalence of EIB among children with asthma may be pretty high (40–90%) and there is an another group of elite athletes who tend to develop EIB only after significant level of physical training in cold dry weather. Nearly one in five adolescents (12–13 years of age) were estimated to have EIB on standardised exercise challenge test with dry air in a small population based study in Sweden. Interestingly in less than half of the adolescents reporting exercise-induced dyspnea, the occurrence of airway obstruction during exercise could be confirmed.[4] Difficulties in performing standardized exercise testing, especially in children, fuels the need to identify more easily accessible predictors of EIB. FeNO levels are increased in presence of eosinophilic inflammation of the airway and the same mechanism is also relevant in EIB. The study using retrospective evaluation of data from Lung function laboratory in the Department of Paediatrics at Kwong Wah Hospital, Hong Kong SAR has tried to identify the FeNO levels among the cases with EIB to identify cutoff levels at which a diagnosis of EIB could be made with certainty. This is likely to be useful as the current tests for EIB are time consuming as well as not available outside of bigger hospitals. However, the present study is limited in its use as the data originates from children with asthma reporting exercise induced symptoms which may be different from those with Exercise induced symptoms alone despite sharing the possible pathogenic mechanism.

The study from India[3] focusses on simple diagnostic tests like platelet count, serum ferritin and CRP levels to identify neonatal sepsis. The study includes neonates diagnosed to have clinical or culture proven sepsis and draws strength from a high proportion of culture positive cases. However, the authors have used multiple approaches to discuss their results often in an inconsistent and confusing manner.

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Conflicts of interest

There are no conflicts of interest.

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A Clinicopathological Study of Thrombocytopenia, Acute-Phase Reactants, and Blood Culture in Neonatal Sepsis

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Abstract

Introduction: Neonatal sepsis is a clinical syndrome described as any systemic bacterial infection in neonates documented by positive blood culture. However, blood culture is positive in only 5.0%–10.0% of suspected cases. Serum concentration of many acute-phase reactants rises in response to infection, which can be used as a non-specific indicator of bacterial sepsis. **Aim and Objectives:** The aim of this study was to correlate the levels of serum markers C-reactive protein (CRP), serum ferritin, and thrombocytopenia with neonatal sepsis. **Materials and Methods:** This was a prospective cross-sectional study conducted in the Neonatal Intensive Care Unit, Department of Paediatrics and Pathology, Jawaharlal Nehru Medical College (JNMC), Aligarh from 2019 to 2021 on 172 babies (cases =142; controls = 30). Neonates with sepsis who presented with clinical signs or symptoms of sepsis were taken as case group and healthy neonates served as control. **Result:** Blood culture was positive in 58 (40.8%) neonates in the case group and Klebsiella was present in maximum number of cases. Blood culture was positive in only 8 (13.8%) cases out of 31 cases of mild thrombocytopenia. The total culture-positive organism was 58 (40.8%), with 09 (15.5%) gram-positive, 46 (79.3%) gram-negative organisms, and 03(5.2%) fungus. Positive CRP was seen in 88 (61.9%) neonates in the case group, out of which, positive culture was noted in 38 (65.5%) neonates and negative in 50 (59.5%) neonates. Serum ferritin values >400 µgm/L was seen in 97 (68.3%) neonates in the case group and 6 (20.0%) neonates in control group. The mean serum ferritin in culture positive neonates was 1024 ± 309 µgm/L and in culture-negative neonates was 999 ± 301 µgm/L. **Conclusions:** The signs and symptoms of neonatal sepsis are non-specific, leading to difficulty in diagnosis and treatment. Biomarkers such as hematological indices, blood culture, and acute-phase reactants could be more reliable in rapid evaluation and early diagnosis of sepsis and may provide a new diagnostic strategy for the neonates with sepsis.

Keywords: C-reactive protein, ferritin, neonatal sepsis, serum, thrombocytopenia

Introduction

Neonatal sepsis can be defined as a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteraemia in the first month of life. It describes any systemic bacterial infection in neonates documented by positive blood culture.[1]

Despite advances in maternal and neonatal care, infections during early life remain a frequent and important cause of neonatal and infant morbidity and mortality.[2] According to the World Health Organization (WHO), 4 million newborn children die each year during the first 4 weeks of their lives. Of these, 75.0% die prematurely during the first week of life.[3]

Positive blood culture is considered the gold standard for the diagnosis of microbiological infection. However, blood culture is positive in only 5.0%–10.0% of suspected cases because of early exposure to antibiotics before samples are withdrawn. Hematological screen is done which includes absolute neutrophil count, immature/total leukocyte count, platelet count, C-reactive protein (CRP), and serum ferritin, which are useful markers for the early diagnosis of neonatal sepsis.[4]

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Serum concentration of many acute-phase reactants such as CRP, ferritin, interleukin 6, interleukin 8, tumor necrosis factor-alpha, and procalcitonin rise in response to infection, which can be used as a non-specific indicator of bacterial sepsis and lead to the diagnosis of neonatal sepsis.[5-7]

Early-onset sepsis (EOS) occurring within 72 h of birth due to organisms present in the surrounding delivery area and late-onset sepsis (LOS) occurring after 72 h of birth mainly due to microorganisms present in the surrounding external environment.[8,9] The aim of this study was to correlate the levels of serum markers CRP, serum ferritin, and thrombocytopenia with neonatal sepsis.

Materials and Methods

This was a hospital-based prospective cross-sectional study conducted in the Neonatal Intensive Care Unit, Department of Pediatrics in collaboration with the Department of Pathology Jawaharlal Nehru Medical College (JNMC), Aligarh from 2019 to 2021 on 172 babies (cases = 142; controls = 30). Neonates with sepsis who presented with clinical signs or symptoms of sepsis such as hypoglycemia, hyperthermia, poor feeding, lethargy, tachypnea, and grunting were taken as case group and healthy neonates served as control. All neonates with congenital malformations and neonatal hyperbilirubinemia due to causes other than sepsis were excluded from the study. The ethical clearance was obtained from the institutional ethics committee (D.No.165/FM/IEC) and proper consent was taken from the parents of neonates.

The study groups comprised cases and controls. The cases included 142 neonates, who were culture positive: neonates having positive blood culture along with clinical or laboratory evidence of sepsis and culture negative with neonates having clinical criteria of sepsis as per Integrated Management of Childhood Illness (IMNCI)/ WHO criteria or having positive sepsis screen but without positive blood culture. Thirty neonates were taken as Controls, who were without any clinical or laboratory evidence of sepsis

Thrombocytopenia was graded according to differing counts into mild degree with a platelet count of 100,000–1,49,000/µL, moderate degree: 50,000–99,000/µL, and severe degree: <50,000/µL.[2] The positive CRP was considered, if levels were above the normal range of 0.8–15.8 mg/L in males and 0.9–15.8 mg/L in females.[10]

Statistical analysis was done using the SPSS software program, version 25.0 software and Microsoft Excel and a value of $P < 0.05$ was considered significant. The results were analyzed using tables and the presentation of the categorical variables was done in the form of number and percentage; on the contrary, the quantitative data were presented as the mean ± standard deviation (SD). The association of qualitative variables was analyzed using Pearson's chi-square test and quantitative variables were analyzed using the Independent *t* test (for two groups) and ANOVA test (for more than two groups).

Observations

Blood culture was positive in 58 (40.8%) neonates in the case group, with no positive blood culture in control group ($P = 0.02$). In our study, *Klebsiella pneumoniae* (32.8%) was the most commonly isolated organism, followed by coagulase-negative *Staphylococcus* (18.9%) and *Pseudomonas* in 17.2% cases. Gram-negative bacteria was seen in 46 (79.3%) cases, followed by gram-positive bacteria in 9 (24.1%) cases and fungus constituted 3 (5.2%) cases. The results were correlated clinically and test sampling was repeated in case of disparity.

On correlating culture positive and culture negative neonates with degree of thrombocytopenia; it was found that blood culture was positive in only 8 (13.8%) cases out of 31 cases of mild thrombocytopenia. Blood culture was positive in 22 (37.9%) cases out of 47 cases of moderate thrombocytopenia, whereas positive blood culture was seen in 17 cases (29.3%) out of 24 cases of severe thrombocytopenia [Table 1].

The total culture-positive organisms were 58 (40.8%), with 09 (15.5%) gram-positive, 46(79.3%) gram-negative organisms, and 03(5.2%) fungus. Moderate thrombocytopenia was seen in 05 (8.6%) gram-positive organisms and 17 (29.3%) gram-negative organisms. Severe thrombocytopenia was found in 3 (5.2%) gram-positive organisms, 12 (20.7%) gram-negative organisms, and 02 (3.4%) in fungus [Table 2].

Positive CRP was seen in 88 (61.9%) neonates in the case group and 1 (3.3%) in control group. Of the CRP-positive neonates with sepsis, culture positive was noted in 38

Table 1: Correlation of blood culture with thrombocytopenia in cases with sepsis

Thrombocytopenia	Culture positive cases	Culture negative cases	*P* Value	χ^2
Mild thrombocytopenia	08 (13.8%)	23 (27.4%)	0.001	15.5
Moderate thrombocytopenia	22 (37.9%)	25 (29.8%)		
Severe thrombocytopenia	17 (29.3%)	07 (8.3%)		
No thrombocytopenia	11 (18.9%)	29 (34.5%)		
Total	58 (40.8%)	84 (59.2%)		

Table 2: Microbiological spectrum of sepsis cases with degree of thrombocytopenia

Thrombocytopenia	Gram-positive bacteria	Gram-negative bacteria	Fungus	*P* Value	χ^2
Mild thrombocytopenia	0 (0%)	07 (12.1%)	01(1.7%)	0.007	22.5
Moderate thrombocytopenia	05 (8.6%)	17 (29.3%)	00 (0%)		
Severe thrombocytopenia	03 (5.2%)	12 (20.7%)	02 (3.4%)		
No thrombocytopenia	01 (1.7%)	10 (17.2%)	00 (0%)		
Total	09 (15.5)	46 (79.3%)	03 (5.2%)		

Table 3: Correlation of blood culture with C-reactive protein (CRP) in neonates with sepsis

CRP	Culture positive	Culture negative	*P* Value	χ^2
Positive	38 (65.5%)	50 (59.5%)	0.50	0.523
Negative	20 (34.5%)	34 (40.5%)		
Total	58 (40.8%)	84 (59.2%)		

Table 4: Distribution of cases according to C-reactive protein and serum ferritin values

		Cases	Control	*P* Value	χ^2
CRP	Positive	88 (61.9%)	01 (3.3%)	<0.001	34.1
	Negative	54 (38.1%)	29 (96.7%)		
Ferritin values (µg/L)	0–400	45 (31.7%)	24 (80.0%)	<0.001	24.1
	>400	97 (68.3%)	6 (20.0%)		

Table 5: Correlation of blood culture with serum ferritin in neonates with sepsis

Culture status	Serum ferritin 1–400 µgm/L (mean ± SD)	Serum ferritin >400 µgm/L (mean ± SD)	*P* Value
Culture negative	149 ± 108	999 ± 301	0.90
Culture positive	174 ± 130	1024 ± 309	

(65.5%) neonates and culture was negative in 50 (59.5%) neonates [Table 3].

Serum ferritin values >400 µgm/L were seen in 97 (68.3%) neonates in the case group and 6 (20.0%) neonates in control group [Table 4]. On correlating, mean serum ferritin with culture positive and culture negative neonates, raised mean ferritin in culture positive neonates was 1024 ± 309 µgm/L and in culture-negative neonates was 999 ± 301 µgm/L [Table 5].

Discussion

A positive microbial culture from a normally sterile site (blood) is frequently used as the gold standard to define neonatal sepsis. In our study, it was seen that blood culture was positive in 58 (40.8%) neonates in the study group, with *Klebsiella* the most common organism isolated. Shoukry *et al.*[11] and Samreen *et al.*[12] showed *Klebsiella pneumoni*a as the most frequent bacteria in neonatal sepsis.

In our study, out of total culture-positive organisms, mild thrombocytopenia was seen in 7 (12.1%), moderate thrombocytopenia in 17 (29.3%), and severe thrombocytopenia in 12 (20.7%) cases of neonatal sepsis. Hassan *et al.*[13] stated gram-negative organisms were a predominant causative agent for sepsis in 84.1% cases. Arif *et al.*[14] on correlating thrombocytopenia with blood culture showed thrombocytopenia in 71 (83.5%) cases, although blood culture was positive in only 24 (33.8%) cases. Ree *et al.*[15] found that thrombocytopenia was present in 226 (49.0%) cases of gram-positive sepsis, and 33 (69.0%) of gram-negative sepsis.

CRP is a good but late marker of infection. It has been used as an acute-phase reactant to diagnose and follow the course of neonatal sepsis. On correlating CRP with blood culture, out of 88 neonates with positive CRP, culture was positive in 38 (65.5%) neonates and negative in 50 (59.5%). Hisamuddin *et al.*[16] have reported a positive correlation of CRP with blood culture. Simonsen *et al.*[17] have stated that CRP levels rise within 6–8 h of infection and peak at 24 h. Monga *et al.*[18] reported 47% blood culture positive cases, of which 40%also showed positive CRP.

Ferritin biology focuses on its role in iron storage and homeostasis. However, iron redox biology and inflammation are linked and serum ferritin has been established as an acute-phase reactant. High value of this marker represents an intense inflammatory response scenario that seems to be an indicator of unfavorable outcomes. In this study, serum ferritin more than 400 µgm/L was seen in 97 (68.3%) in the case group and 6 (20.0%) cases in control group. However, on correlating mean serum ferritin with culture, raised mean ferritin in culture positive neonates was 1024 ± 309 µgm/L and culture

negative neonates was 999 ± 301 µgm/L. Mithal *et al.*[19] reported that the acute-phase reactant such as ferritin levels were elevated in the confirmed EOS. Horvat *et al.*[20] have stated that the combined use of maximum ferritin with CRP during hospitalization was able to predict death in 21.7% of the patients. Kulkarni *et al.*,[21] Nandy *et al.*,[22] and Sarkar *et al.*[23] have reported that serum ferritin level was significantly high in nonsurvivors, with 42 patients of the study group had serum ferritin level >2375 ng/mL; out which 29 (69.0%) succumbed to infection.

Conclusions

Though positive blood culture and thrombocytopenia are poor screening tools for neonatal sepsis, they are strong pointers to the presence of sepsis. CRP and serum ferritin are significantly raised in sepsis and their high values represent an intense inflammatory response scenario and may provide a new diagnostic strategy for the patients of neonatal sepsis.

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Conflicts of interest

There are no conflicts of interest.

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The Relationship of Fractional Exhaled Nitric Oxide Level with Exercise-Induced Bronchoconstriction in Asian Asthmatic Children: A Local Single-Centre Retrospective Diagnostic Study

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Abstract

Background and Aims: Exercise-induced bronchoconstriction (EIB) is associated with eosinophilic inflammation of the airway in asthmatic children and studies showed fractional exhaled nitric oxide (FeNO) is associated with it. The aim of this study was to explore the relationship between FeNO and EIB and find a cutoff reference of FeNO for EIB based on existing normative data from healthy Asian children by Yao *et al.* in 2012. **Materials and Methods:** Asian asthmatic children who had undergone FeNO and exercise challenge test from January 1, 2016 to December 31, 2019 in a local respiratory centre were reviewed retrospectively. The FeNO values of the individuals were converted to *z*-score with reference to the predicted value of FeNO in Asian children by Yao *et al.* in 2012. A receiver-operating characteristic (ROC) curve is plotted to identify a cutoff representing EIB. **Results:** Data of 88 Asian asthmatic children aged 5–18 were retrieved. There is a significant overlapping of the FeNO *z*-scores of normal and mild EIB groups. The cutoff value determined by the Youden index (0.724) to predict moderate or severe EIB in asthmatic patients is 3.276 with sensitivity of 88.9% and specificity of 83.5% **Conclusion:** High FeNO value of *z*-score 3.276 has high sensitivity and specificity to moderate to severe EIB in Asian asthmatic children. FeNO could be used as a simple test in clinic setting before exercise challenge test is available.

Keywords: Asthma, fractional exhaled nitric oxide, exercise-induced bronchoconstriction

Introduction

Exercise-induced bronchoconstriction (EIB) occurs in a substantial proportion of patients with asthma. It could also occur in patients without known asthma.[1-3] The diagnosis of EIB is based on a change in lung function in an exercise challenge test. However, the test is time- and cost-consuming and requires complex equipment. On the other hand, assessing EIB by symptoms induced by vigorous exercise is often neither sensitive nor specific.[4-6] Several surrogates for exercise to identify EIB were studied, such as dry air with inhalation of hyperosmolar aerosols of 4.5% saline or dry powder mannitol yet none of them had near 100% sensitivity/specificity for EIB.[7-12]

It is clear that eosinophils and mast cells in the airway play a role in releasing inflammatory mediators in EIB.[13] Measurement of fractional nitric oxide concentration in exhaled breath (FeNO) is a quantitative, non-invasive, simple, and safe method that has been used as a complementary tool to other ways of assessing airways eosinophilic inflammation.[14] Although it has been already reported that FeNO is associated with EIB,[2,15-18] no studies were done to identify the clinical use of FeNO in predicting EIB. Using *z*-score of normative data as cutoff would be more reasonable than using a single cutoff recommended by international guidelines as FeNO level varies with age.[19] It is also known that Asian children have high FeNO level compared to the white children.[19] In this study, we would like to assess the association between FeNO level with EIB; and identify the

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cutoff values of FeNO across age representing EIB, using *z*-score from normative data from a Taiwan study: Reference values of exhaled nitric oxide in healthy Asian children aged 5–18 years by *Yao et al.* in 2012.[20]

Materials and Methods

This is a single-centre retrospective study approved by the research ethics committee of the Kowloon Central/ Kowloon East Clusters of the Hospital Authority in Hong Kong. Ref. no: KC/KE-20-0017/ER-2

Patients

Asian children aged 5–18 years old with doctor-diagnosed asthma who had exercise challenge tests done in the lung function laboratory in the Department of Paediatrics at Kwong Wah Hospital from January 1, 2016 to December 31, 2019 were included. All of them had FeNO done successfully in the same session as per our department protocol. Children with chronic lung diseases apart from asthma were excluded. The demographics, lung function test parameters, and FeNO values were reviewed retrospectively from the laboratory computer database.

Exercise challenge test

Exercise challenge test was performed using MGC diagnostics Ultima PFX pulmonary function/stress testing system with adherence to American Thoracic Society (ATS) guidelines.[21] Forced vital capacity (FVC) and forced expiratory volume at 1 second (FEV1) were collected as the baseline. Patients were asked to run on a treadmill with the aim to reach the 80% of the predicted maximum heart rate (as defined by 220 – age in years) for 6 min. Post-exercise FEV1 were measured at 5-, 10-, 15- and 30-min intervals based on the percentage drop of FEV1 from the baseline. The test was completed if post-exercise FEV1 decreased by more than 30% from baseline at any test interval. If post-exercise FEV1 decreased between 15% and 30% from baseline at any test interval, an additional spirometry would be performed at the next test interval.

Definition of EIB is a decrease in FEV1 by 10% at any stage. The level of EIB is then classified according to the percentage drop of FEV1 from the baseline. The severity of EIB can be graded as mild, moderate, or severe if the percentage fall in FEV1 from the pre-exercise level is >= 10% but <25%, >=25% but <50%, and >= 50%, respectively.[21]

FeNO measurement

FeNO measurements were performed online before exercise challenge test using a nitric oxide analyser following its instructions and American Thoracic Society (ATS) recommendations.[22] Aerocrine NIOX MINO nitric oxide analyser (Aerocrine AB, Solna, Sweden) was used from January 1 till August 15, 2018. From August 15, 2018 onwards, the department has changed the FeNO analyser to HypAir FeNO (Medisoft, Sorinnes Belgium). FeNO results were expressed in parts per billion (ppb). Single-breath, online measurement of FeNO was performed at an exhalation pressure of 10–20 cmH2O to maintain a fixed flow rate of 50 ml/s. Patients were tested at a resting state. After inhalation of ambient air through a nitric oxide scrubber to total lung capacity, patients were asked to exhale into the mouthpiece with a steady flow. The first trial would be measured in 10-s mode. The 6-s mode would be used if the patient fails the first trial or in younger patients if indicated. The machine would fail the test if the duration of exhalation is not adequate.[23,24]

The measurements were performed once by Aerocrine NIOX MINO due to the cost of the consumables while they were repeated at least twice by Hypair FeNO to achieve results within 10% of each other as per current guidelines and the mean value was recorded for analysis. The clinical use of both analysers was well documented, and the results are comparable.[25]

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM, Armonk, New York). The FeNO levels of our individuals are converted into *z*-scores of the reference values of FeNO of Yao *et al.*[20]

The normality of data was assessed by Shapiro–Wilk test. Continuous variables were presented depending on their distribution as means and standard deviation (SD) for normally distributed data or median and interquartile range (IQR) for non-normally distributed data. Categorical variables were presented as numbers and percentages.

The relationship between FeNO values collected by NIOX MINO and the Medisoft HypAir machine was assessed using the Pearson correlation coefficient. The chi-square statistic was used for testing relationships between categorical variables. Student's t-test and ANOVA test were used to compare the means of two groups or more, respectively, for normally distributed data. The Mann-Whitney U test and the Kruskal–Wallis test were used to compare the median of two groups or more, respectively, for non-normally distributed data. If a comparison of multiple groups provides a significant difference, the post hoc analysis then was used for pair-wise comparison of post hoc ANOVA with the Dunnett T3 test for the parametric test and the Dunn–Bonferroni test for the non-parametric test.

The receiver-operating characteristic (ROC) curve analysis is used to determine the *z*-score of FeNO level that best identifies EIB. The cutoff level with the optimal combination of sensitivity and specificity was calculated using the Youden index (sensitivity + specificity-1).

The optimal cutoff value in *z*-scores of FeNO represented EIB were converted into actual FeNO values across ages and were plotted on the graph of predicted FeNO values with different ages and the upper limit of normal (ULN) by Yao *et al.* [Figure 1].

All *P*-values were calculated by two-sided tests and were considered statistically significant if $P < 0.05$.

Results

Demographic data of the patients

There were a total number of 88 patients aged 5–18 year old who had successfully undergone exercise challenge tests from January 1, 2016 to December 31, 2019. All of them had FeNO measurement successfully done by NIOX MINO or Medisoft HypAir in the same session. The numbers of patients with FeNO measured by NIOX MINO and Medisoft HypAir were 48 and 40, respectively.

Among 88 individuals, 46 (52.3%) of them had FeNO *z*-score >1.96 (>97.5th percentiles); 30 (34%) were positive for exercise challenge test. Their demographics are presented in Table 1. No significant difference was evident in terms of mean age, sex distribution, or prior

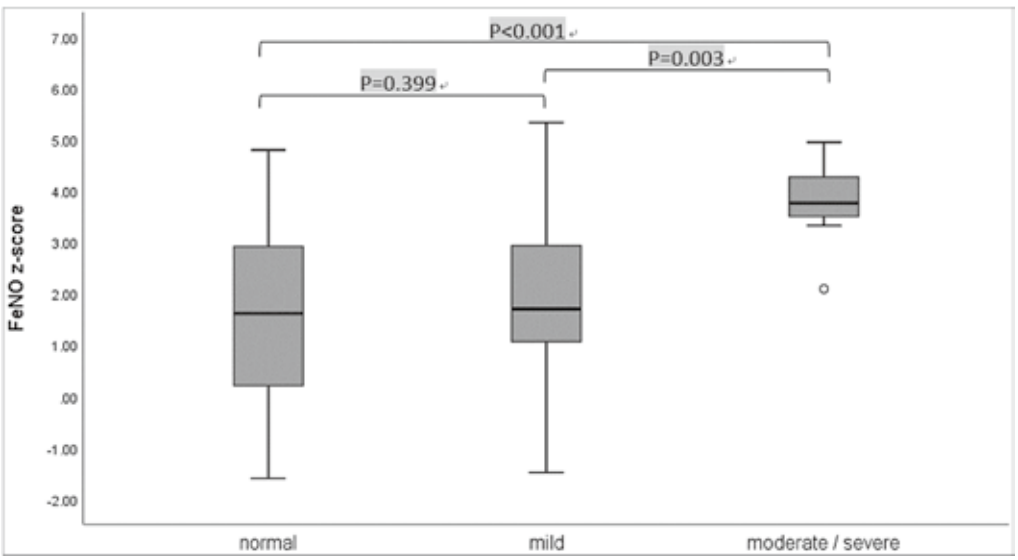

Figure 1: Reference FeNO values with age from Yao *et al.* group and from this study. The quotation and modification of the figure is acknowledged and permit by Yao *et al.* (2012).[20] FENO_UL = upper limit of normal (97.5 percentiles) from healthy individuals from Yao *et al.* study. FENO_predicted = predicted FeNO values from healthy individuals from Yao *et al.* study. Dotted line = FeNO level of *z*-score 3.276 from predicted FeNO value. Thick line = FeNO level of *z*-score 1.4 from predicted FeNO value

Table 1: Demographic data of the participants

	All (n = 88)	Severity of EIB			*P* Value
		Normal (n = 58)	Mild (n = 21)	Moderate/ Severe (n = 9)	
Male gender, *n*(%)	60 (68.2%)	39 (67.2%)	13 (61.9%)	8 (88.9%)	0.336
Age, year, median (IQR)	10.4 (8.4–12.2)	10.1 (8.1–11.7)	11.4 (8.4–13.8)	10.9 (9.7–12.4)	0.280
Height, cm, median (IQR)	135.9 (126.1–151.8)	134.8 (125.7–149.1)	141.0 (124.3–156.2)	146.0 (131.0–150.9)	0.561
Weight, kg, median (IQR)	35.3 (26.2–46.4)	33.6 (24.6–42.0)	41.0 (27.9–49.4)	36.1 (33.0–50.3)	0.136
BMI, kg/m^2, median (IQR)	17.7 (15.4–21.1)	16.4 (15.0–20.0)	18.6 (17.0–21.8)	19.5 (18.2–22.5)	0.016[ab]
BMI *z*-score, median (IQR)	0.5 (–0.3–1.3)	0.1 (–0.4–1.2)	0.7 (–0.1–1.5)	1.0 (0.4–1.6)	0.097
FeNO, ppb, median (IQR)	29.0 (15.0–53.8)	27.8 (12.0–43.0)	25.5 (20.0–42.3)	68.0 (54.5–89.0)	0.001[bc]
FeNO *z*-score, median (IQR)	2.1 (0.5–3.2)	1.6 (0.2–2.9)	1.7 (1.0–3.0)	3.8 (3.4–4.4)	0.001[bc]
FeNO *z*-score >1.645 (>95th), *n* (%)	50 (56.8%)	29 (50.0%)	12 (57.1%)	9 (100.0%)	0.019
FeNO *z*-score >1.96 (>97.5th), *n* (%)	46 (52.3%)	27 (46.6%)	10 (47.6%)	9 (100.0%)	0.010
Exercise challenge test positive, *n* (%)	30 (34%)	0 (0%)	21 (100.0%)	9 (100.0%)	<0.001
Prior ICS use within 14 days, *n* (%)	26 (29.5%)	18 (31%)	4 (19.0%)	4 (44%)	0.344
FeNO by NIOX MINO (%)	47 (53.4%)	33 (56.9%)	9 (42.9%)	5 (55.6%)	0.538
FeNO by Medisoft HypAir (%)	41 (46.6%)	25 (43.1%)	12 (57.14%)	4 (44.4%)	0.538

EIB = exercise-induced bronchoconstriction, BMI = body mass index, FeNO = fractional exhaled nitric oxide, ICS = inhaled corticosteroid

Kruskal–Wallis test with the Dunn–Bonferroni *post hoc* test

[a]*Post hoc* test, $P < 0.05$, normal group vs mild group

[b]*Post hoc* test, $P < 0.05$, normal group vs moderate/severe group

[c]*Post hoc* test, $P < 0.05$, mild group vs moderate/severe group

use of inhaled corticosteroid (ICS) in different severity of EIB groups.

The correlation of FeNO and EIB

Figure 2 shows the box plot of *z*-scores of FeNO of normal exercise challenged test, mild EIB, and moderate to severe EIB. There is a significant overlapping of FeNO *z*-score between normal and mild EIB, and there are statistical significant differences of FeNO *z*-score between normal and moderate or severe EIB (median (IQR) 1.6 (0.2–2.9) vs 3.8 (3.4–4.4); $P < 0.001$) and between mild and moderate or severe EIB (1.7 (1.0–3.0) vs 3.8 (3.4–4.4); $P = 0.003$). There is an outlier in moderate/severe EIB group with FeNO *z*-score of 2.1 which is represented by the small circle in Figure 2.

ROC curve for prediction of EIB

The area under the ROC curve (AUC) in prediction of EIB in asthmatic patients is 0.655 (95% CI: 0.534–0.776; $P = 0.018$ [Figure 3]). The best cutoff value determined by the Youden index (0.28) is *z*-score of 1.4 (91.9 percentiles) with a sensitivity of 80.0% and specificity of 48.3%, a positive predictive value of 0.44 and negative predictive value of 0.823. However, a *z*-score of 1.4 is even lower than the ULN of FeNO level (97.5 percentiles).

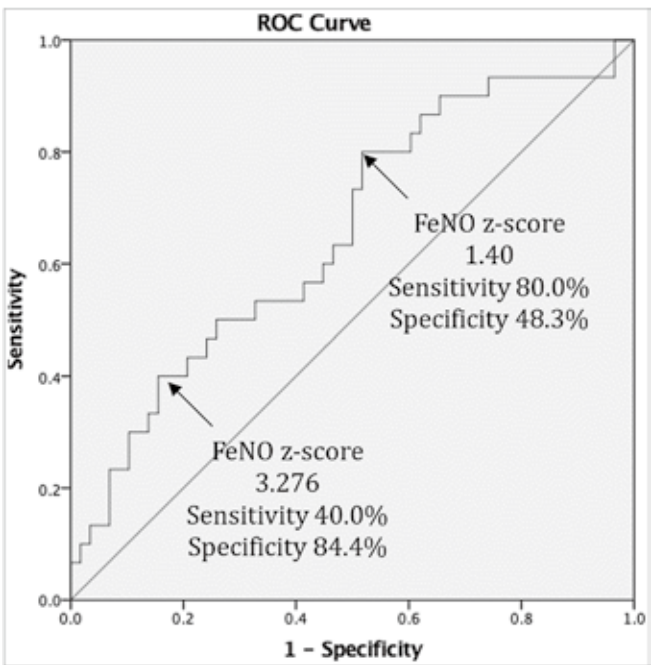

Figure 2: Box plot of *z*-scores of FeNO values of normal exercise challenge test, mild EIB and moderate or severe EIB. The mean FeNO *z*-score in normal group is 1.6 with IQR 0.2–2.9. The mean FeNO *z*-score in mild EIB group is 1.7 with IQR 1.0–3.0. The mean FeNO *z*-score in moderate / severe EIB group is 3.8 with IQR 3.4–4.4. There is a low potential outlier in moderate / severe EIB group with *z*-score of 2.1 (FeNO = fractional exhaled nitric oxide, EIB = exercise-induced bronchoconstriction, IQR = interquartile range)

ROC curve for prediction of moderate/severe EIB

Because of the significant overlapping of the FeNO *z*-scores of normal and mild EIB groups, another ROC curve of the performance of FeNO in predicting moderate or severe EIB in asthmatic patients AUC is 0.861 (95% CI: 0.764–0.957; $P < 0.001$ [Figure 4]). The best cutoff value determined by the Youden index (0.724) is still FeNO *z*-score of 3.276 with better sensitivity of 88.9% and specificity of 83.5%

Both *z*-scores (1.4 and 3.276) of FeNO were converted into actual FeNO values and were plotted in Figure 1.

Discussion

Current international guidelines of asthma are primarily derived based on data from Caucasian populations. They recommend the use of a single cutoff value of FeNO which is dependent on age.[26-29] The American Thoracic Society (ATS) guideline recommends a cutoff of FeNO <20 ppb representing non-eosinophilic or no airway inflammation in children; and another cutoff of FeNO >35 ppb representing airway inflammation. The National Institute for Health and Care Excellence (NICE) guideline, the British Thoracic Society, and the Scottish Intercollegiate Guidelines Network (BTS/SIGN) guidelines use a single cutoff of FeNO >35ppb for airway inflammation whilst the Global Initiative for Asthma (GINA) guideline recommends a value of 50ppb for children for airway inflammation.

However, ethnicity and genetic variations of nitric oxide synthase (the enzyme for NO production) are shown to be an important factor affecting FeNO level and non-white children and adults are shown to have higher FeNO levels.[20,30-34] *Yao et al.* study[20] in 2012 showed the rise in FeNO levels with age in normal Asian children which also made respirologists question the use of a single cutoff value of FeNO in children.

Yao *et al.*'s[20] study defines normal reference by the ULN of normal population. The ULN curve ranges from 20 to 40 ppb across different age groups, which echoes with ATS guideline that a cutoff value of FeNO <20 ppb is meaningful for non-eosinophilic or no airway inflammation. However, the clinical significance remains uncertain for people with higher values of FeNO.

From our study, all patients with moderate or severe EIB have high FeNO *z*-score greater than 2 as shown in Figure 2 (i.e., 2 standard deviations above the mean), even with one outlier whose FeNO *z*-score was 2.1. The moderate or severe EIB group has a significant difference in FeNO *z*-score compared to normal and mild EIB group and the two groups have considerably overlapping in FeNO *z*-score. A low FeNO *z*-score can confidently exclude moderate or severe EIB.

However, there are individuals who had high FeNO *z*-scores despite they had no EIB or mild EIB. Many confounding

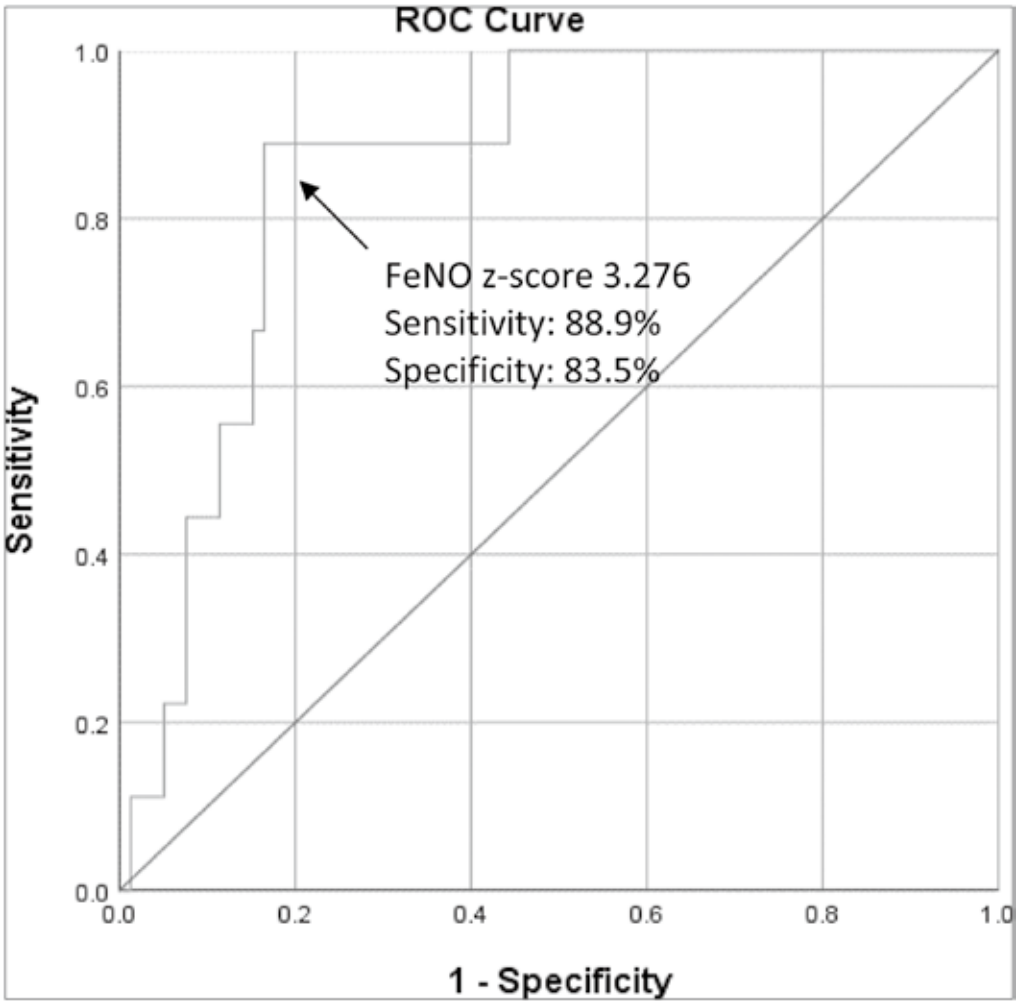

Figure 3: ROC curve of FeNO *z*-score for predicting exercise-induced bronchoconstriction in exercise test ($n = 88$). Area under ROC curve = 0.655 (95% CI: 0.534–0.776; $P = 0.018$) (FeNO = fractional exhaled nitric oxide, ROC = receiver-operating characteristic)

factors could influence FeNO level like genetics, atopy, body size, age, diet, exercise and environment, for example, exposure to second-hand smoke.[35-38] Individuals can have high FeNO values despite there is no asthma nor atopy.[37,39,40] Nine individuals from our study had negative exercise challenge test despite high FeNO which might be accounted by these confounding factors. Seven out of the nine individuals had skin prick test done before and all of them were positive to aeroallergens.

We used the ROC curve to predict moderate or severe EIB instead of all EIB as it was shown that FeNO *z*-score of normal and mild EIB group are comparable by Figure 2. The ROC curve showed a FeNO *z*-score of 3.276 could predict moderate or severe EIB with a sensitivity of 88.9% and a specificity of 83.5%. The FeNO *z*-score of 3.276 is translated to actual FeNO values and plotted on the normative data of Yao *et al.*'s[20] study for easier reference.

We recommend considering the use of our new cutoff for patients with exercise induced symptoms as an office test to identify patient with moderate or severe EIB and consider treatment (e.g., earlier use of ICS) before the exercise challenge test is available.

Exercise challenge test remains the gold-standard for diagnosing EIB and we are unable to recommend a cutoff with good negative predictive value to avoid individuals undergoing an exercise challenge test.

Asthma patients have different phenotypes and patients without asthma could have a positive exercise challenge test. Further studies are still needed to have further subgrouping for different phenotypes and confounding factors to confirm a more robust value of FeNO in Asian children.

Limitation

One of the limitations is that we were unable to have all data concerning other markers of atopy for every individual including skin prick test, serum eosinophil counts, sputum eosinophil counts and serum IgE.

In our study, we did not do any subgroup analysis for inhaled steroid use. The asthma control should have been shown from the spirometry, regardless of the use of inhaled steroid.

We were also unable to account for other known factor which increases FeNO second-hand smoking, and we acknowledge that they could affect our results.

We have categorised normal and mild EIB as one group and moderate to severe EIB as another group to generate the ROC curve. The limitation is that there were only 9

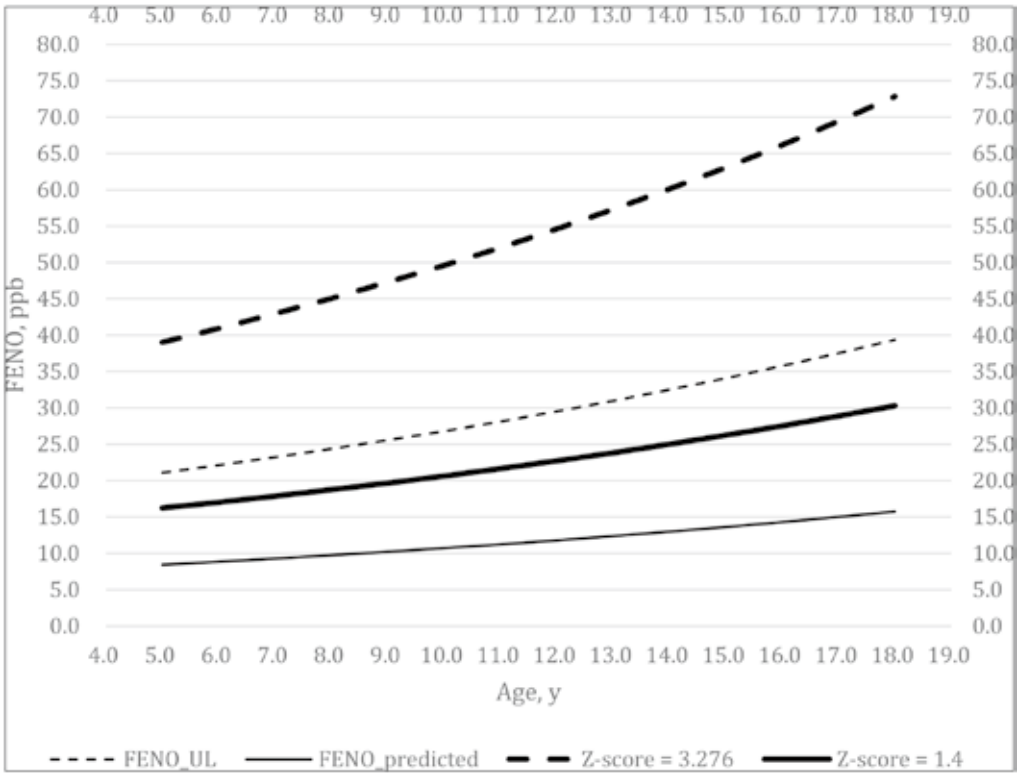

Figure 4: ROC curve of FeNO *z*-score for predicting moderate and severe exercise-induced bronchoconstriction in exercise test ($n = 88$). Area under ROC curve = 0.861 (95% CI: 0.764–0.957; $P < 0.001$) (FeNO = fractional exhaled nitric oxide, ROC = receiver-operating characteristic)

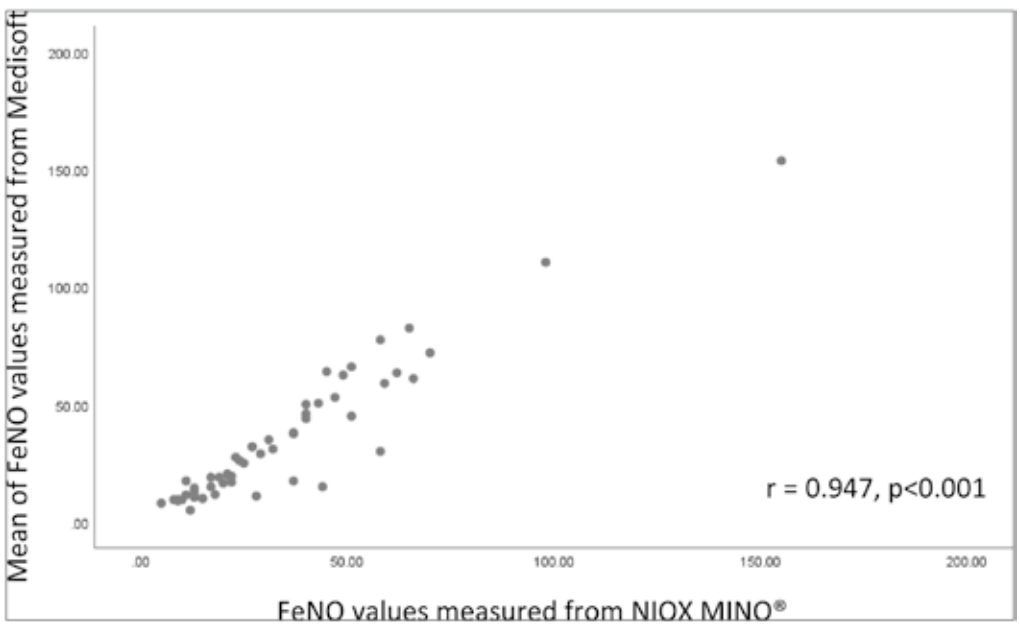

Figure 5: Correlation of the FeNO values collected by NIOX MINO and Medisoft HypAir machine in our lung function laboratory. *X*-axis shows the FeNO values from NIOX MINO and *y*-axis shows the FeNO values from Medisoft HypAir. $r = 0.947$, $P < 0.001$. FeNO values measured from NIOX MINO. Mean of FeNO values measured from Medisoft HypAir (FeNO = fractional exhaled nitric oxide)

patients with moderate or severe EIB during the study period.

Another drawback is that we have changed our model of FeNO machine during the study period. However, the agreement of both machines is good as shown by Brooks *et al.*[25]

Our lung function laboratory had also done an unpublished pilot study on comparison of the above two named FeNO analysers prior to the switching of machines in our department. The comparison was done by 53 individuals performing FeNO measurement by both machines in the same setting and it was analysed by Pearson correlation which showed strong correlation [Figure 5] ($r = 0.947$; $P < 0.001$)

Conclusion

High FeNO value of *z*-score 3.276 has high sensitivity and specificity to moderate or severe EIB in Asian asthmatic children. FeNO could be used as a simple test in clinic setting before exercise challenge test is available.

Acknowledgement

We would like to acknowledge Ms Chan Kwan Ting and Ms Ng Ching Man at lung function laboratory in the Department of Paediatrics at Kwong Wah Hospital for their assistance in conducting data collection.

Ethical policy and institutional review board statement

This was a single-centre retrospective study approved by the research ethics committee of the Kowloon Central/ Kowloon East Clusters of the Hospital Authority in Hong Kong. Ref. no: KC/KE-20-0017/ER-2.

Author contributions' statement

K-NA: conceptualisation, data curation, funding acquisition, investigation, methodology, project administration, writing – original draft preparation, reviewing and editing. EY-TC: conceptualisation, data curation, investigation, methodology, writing – reviewing and editing, supervision, resources, validation, and visualisation. LSY: formal analysis, visualisation, investigation, software, validation, and visualisation.

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Conflicts of interest

There are no conflicts of interest.

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Allergic Rhinitis and Asthma Rather than Atopic Dermatitis Is a Protective Factor for Dengue Fever—A Nationwide Population: A Case-Control Study

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Abstract

Background/Purpose: Dengue fever (DF) may cause severe morbidity and mortality. Asthma has been proposed as a protective factor for DF. Asthma, allergic rhinitis, and atopic dermatitis are atopic diseases with a common background. Herein, we aimed to determine whether allergic rhinitis and atopic dermatitis are also protective factors for DF, as this aspect remained unknown. **Materials and Methods:** A resampled nationwide population-based retrospective case-control study was conducted. Multivariate logistic regression was used to identify independent protective factors of these atopic diseases for DF. The Kaplan–Meier method was used to compare dengue-free proportions between patients with or without atopic diseases. **Result:** This case-control cohort study included a total of 1119 patients with DF and 4476 age- and sex-matched patients without DF. At least one of these atopic diseases was observed in 1322 patients. Compared to patients with DF, the non-DF group had a high prevalence rate of atopic diseases (16.2% vs 25.5%, P <0.001). Both asthma and allergic rhinitis were protective factors for DF with an odds ratio (OR) of 0.40 (95% confidence interval (CI) 0.25–0.65, P<0.001) and 0.48 (95%CI, 0.38–0.61; P<0.001), respectively. Atopic dermatitis was not a protective factor for DF (OR, 0.96; 95%CI, 0.58–1.58; P=0.873). **Conclusion:** Asthma and allergic rhinitis, rather than atopic dermatitis, can be independent protective factors against DF. Our finding provides insights into the association between allergy and DF.

Keywords: Allergic rhinitis, asthma, atopic dermatitis, atopy, dengue fever

Introduction

Dengue fever (DF), prevalent in tropical and subtropical regions, is an arthropod-borne viral disease caused by one of four dengue viruses (DVs) transmitted by *Aedes aegypti* or *Aedes albopictus* mosquitoes.[1,2] DF is endemic in more than 100 countries and its incidence has increased 30-fold in the past half century.[3] DVs are introduced into the skin when an infected mosquito bite a susceptible host. When DVs enter the host through a DV-infected mosquito bite, the virus infects skin dendritic cells (DCs) via DC-specific intercellular adhesion molecule 3-grabbing non-integrin (DC-SIGN) and other mannose receptors. Infected DCs may then migrate to the lymph nodes, carrying viruses, and infect more cells, leading to viremia and ultimately DF.[4,5] The clinical manifestations of DF may be asymptomatic or present with a broad range of symptoms including mild fever, headache, retro-orbital pain, and myalgia, and life-threatening conditions, such as dengue hemorrhagic fever or dengue shock syndrome. The estimates of 390 million dengue infections per year worldwide and 2.5 billion individuals at risk for infection,[2] implies that DF remains an important issue from a public health perspective.

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The incidence of allergic diseases has continued to rise in recent decades, affecting approximately 20% of the global population, especially children.[6] Common atopic diseases, including asthma, allergic rhinitis (AR), and atopic dermatitis (AD), are regarded as an abnormal hyperreactive state of Th2 inflammation and the close association among asthma, AR and AD is well documented.[7,8] The atopic march is initially described as the development of AD in infancy and consecutive AR and asthma in later childhood and even into adulthood. Another concept of allergic march proposes that AD is associated with other atopic diseases, such as food allergies, asthma, and AR, which occur more frequently together than individually.[9] Several cross-sectional, longitudinal, and animal studies have supported the time-course sequence of the allergic march.[6,9,10]

House dust mites account for more than 90% of allergens for allergic asthma in Taiwan. We found asthma is a protective factor for DF based on a nationwide population-based cohort study.[11] This protective effect may be because of diminished cellular DC-SIGN expression and decreased cellular entry of DVs. Whether other common atopic diseases, in addition to asthma, can also be protective factors for DF is unknown. In this study, we conducted a nationwide study from a resampled database to validate the protective effect of asthma and evaluate the protective effect of AR and AD for DF.

Materials and Methods

Data sources

The study population and data were extracted from the National Health Insurance Research Database (NHIRD) of Taiwan. The Taiwan National Health Insurance program provides healthcare to more than 99% of the population in Taiwan (12). The database provides scrambled patient identification number, birth data, sex, diagnoses, medications, and date of visit to a medical institute. Claims data of one million subjects randomly selected from 23 million insured individuals registered from 1996 to 2013 were obtained from the NHIRD. Diagnoses were coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). For personal privacy protection, the electronic database was decoded with patient identifications scrambled for further public access for research. Informed consent was not required because of decoded and scrambled patient identification. To validate the protective effect of asthma for DF, a resampled database different from that used in the previous study (11) was utilized. This study was approved by the Institutional Review Board of Chang Gung Medical Foundation (IRB number: 201801109B0).

Study population and design

This was a case-control study. The cases were determined by claims for hospital admissions using dengue-related codes (ICD-9-CM codes 061, 065.4, and A90) between January 1, 1996 and December 31, 2013. The judgement of dengue fever in Taiwan much be reported to the Taiwan Centers for Disease Control and Prevention and met any of the following five conditions: 1. dengue virus was isolated and identified from the clinical specimens obtained within seven days of disease onset 2. The molecular biological test of the clinical specimen for dengue virus nucleic acid was positive 3. The serological test for "dengue virus NS1 antigen" was positive 4. The serum of acute phase or initial blood collection is positive for dengue virus-specific IgM or IgG antibody. 5. Between acute phase and recovery stage, there was a positive conversion for dengue virus-specific IgM or IgG antibody or IgG antibody had ≧4 times increase in serum. The comparisons without dengue were randomly selected as controls after they were frequency-matched at a ratio of 1:4 based on age, sex, and underlying diseases (hypertension (HTN), diabetes mellitus (DM), hyperlipidemia (HPL), and coronary artery disease (CAD)). Three common atopic diseases, including asthma, AR, and AD, were diagnosed based on the ICD-9-CM diagnostic criteria. The ICD-9-CM codes used for asthma was 493, for AR were 477.0, 477.1, 477.2, 477.8, and 477.9, and for AD were 691 and 691.8. To enhance diagnostic validity, we only selected patients who had inpatient diagnosis files with primary or secondary diagnosis of atopic diseases or outpatient diagnosis files with at least three consistent diagnoses of atopic diseases (13). Those who had already been diagnosed with DF before the atopic disease index date were excluded [Supplementary Figure 1].

Statistical analysis

All statistical analyses were performed using SAS statistical software (v. 9.3; SAS Institute, Cary, NC, USA). A two-tailed $P < 0.05$ was considered statistically significant. The demographic characteristics and prevalence of atopic diseases were compared between the dengue and non-dengue groups. Categorical data were analyzed using the $\chi 2$ test. A logistic regression model was used to identify the odds ratio (OR) with 95% confidence intervals (CI) of independent protective factors for dengue disease. The differences and the cumulative dengue-free rates among different cohorts were estimated by using the Kaplan–Meier method and log-rank test.

Results

Allergic rhinitis and asthma are protective factor for dengue fever, but atopic dermatitis is not protective factor for dengue fever

A total of 5595 patients were enrolled in this study, including 1119 patients with DF and 4-fold patients (n = 4476) without DF. Among the study population, 2665 patients (47.63%) were female (533 and 2132 in the DF and non-DF groups, respectively) and 2930 patients

(52.37%) were male (586 and 2344 in the DF and non-DF groups, respectively). For total covariate diseases (HTN, DM, HPL, and CAD), no matter the occur before or after DF, the DF group had higher prevalence of HTN and DM. However, when we selected the cases with covariate diseases from DF group before the occurrence of DF, the cases number for HTN, DM, HPL, and CAD were only 209, 101, 126, and 90, respectively [Supplementary Table 1]. This may due to most patients with DF were younger than 50 years old comorbidities had not yet occur. Therefore, we treated any comorbidity as a variable and adjusted it to be equal for DF and non-DF group for further analysis. As shown in [Table 1], the prevalence of having at least one atopic disease was significantly different between these two groups (16.18% vs 25.49% in the DF vs non-DF group, $P< 0.001$). The prevalence of solely asthma or AR was also lower in the DF group than that in the non-DF group (1.70% vs 3.75% for asthma, 7.60% vs 14.16% for AR, all $P< 0.001$), but the prevalence of solely AD was higher in the DF group than that in the non-DF group (1.79% vs 1.68%). Logistic regression analysis showed having atopic disease (asthma, AR, or AD) was a protective factor for DF with an OR of 0.57 (95%CI, 0.48–0.67; $P< 0.001$) [Table 2]. Further analysis was conducted to evaluate the protective effects of individual atopic diseases and a combination of different atopic diseases. "Asthma only" indicates patients have asthma but not AR or AD. In contrast, "having asthma" indicates patients with asthma who may have AR, AD, or both. "AR only" indicates patients have AR but not asthma or AD. "Having AR" indicates patients with AR who may have asthma, AD, or both. Similarly, "AD only" indicates patients have AD but not asthma or AR and "having AD" indicates patients with AD who may have asthma, AR, or both. We found either "asthma only" (OR, 0.40; 95%CI, 0.25–0.65; $P< 0.001$) or "AR only" (OR, 0.48; 95%CI: 0.38–0.61; $P< 0.001$) as a protective factor for DF. However, AD only was not a protective factor for DF (OR, 0.96; 95%CI, 0.58–1.58; $P = 0.873$) [Table 2]. Either "having asthma" or "having AR" was a protective factor for DF. Both "AD only" and "having AD" are not protective factors for DF.

allergic rhinitis and asthma are protective factors for dengue fever regardless of sex

In the subgroup analysis for sex, having atopic disease (asthma, AR, or AD) remained a protective factor for DF in both men (OR, 0.56; 95%CI, 0.44–0.72; $P < 0.001$) and women (OR, 0.57; 95%CI, 0.45–0.72; $P < 0.001$). Both asthma ("asthma only" and "having asthma") and AR ("AR only" and "having AR") were protective factors for DF regardless of sex [Table 3]. AD ("AD only" or "having

Table 1: The demographic characteristics and incidence of atopic disease among dengue fever and non-dengue fever group

		Total	DF		Non-DF		*P*
		n=5595	n=1119 (20%)		n=4476 (80%)		
			n	%	n	%	
Gender	Female	2665	533	47.63%	2132	47.63%	1
	Male	2930	586	52.37%	2344	52.37%	
Age	<32 yr	1900	380	33.96%	1520	33.96%	1
	32 - 50 yr	1760	352	31.46%	1408	31.46%	
	>50 yr	1935	387	34.58%	1548	34.58%	
Total covariate disease							
HTN	None	3981	769	68.72	3212	71.76	0.0448
	Yes	1614	350	31.28	1264	28.24	
DM	None	4728	923	82.48	3805	85.01	0.0369
	Yes	867	196	17.52	671	14.99	
HPL	None	4416	866	77.39	3550	79.31	0.159
	Yes	1179	253	22.61	926	20.69	
CAD	None	4857	970	86.68	3887	86.84	0.892
	Yes	738	149	13.32	589	13.16	
Atopic disease	None	4273	938	83.82%	3335	74.51%	<0.001
	Yes	1322	181	16.18%	1141	25.49%	
	asthma only	187	19	1.70%	168	3.75%	<0.001
	AR only	719	85	7.60%	634	14.16%	<0.001
	AD only	95	20	1.79%	75	1.68%	<0.001
Having Asthma*	Yes	460	69	6.17%	391	8.74%	<0.001
Having AR*	Yes	1029	140	12.51%	889	19.86%	<0.001
Having AD*	Yes	181	35	3.13%	146	3.26%	<0.001

*Patients may also have the other two atopic diseases

HTN, hypertension; DM, diabetes mellitus, HPL, hyperlipidemia; CAD, coronary artery disease; DF, dengue fever; AR, allergic rhinitis; AD, atopic dermatitis

Table 2: Logistic regression to identify the risk factors for dengue fever

Non-atopic disease as reference (n=4273)		N	Number of Dengue	Univariate			Multivariate: overall (n=5595)		
				OR	95%CI	*P* value	OR	95%CI	*P* value
Atopic disease	Yes	1322	181	0.55	0.47-0.66	<0.001	0.57	0.48-0.67	<0.001
	Asthma only	187	19	0.4	0.24-0.64	<0.001	0.4	0.25-0.65	<0.001
	AR only	719	85	0.47	0.37-0.60	<0.001	0.48	0.38-0.61	<.0001
	AD only	95	20	0.93	0.57-1.54	0.790	0.96	0.58-1.58	0.873
Having Asthma*	Yes	460	69	0.61	0.47-0.80	<0.001	0.62	0.48-0.81	0.001
Having AR*	Yes	1029	140	0.55	0.45-0.67	<0.001	0.56	0.46-0.68	<0.001
Having AD*	Yes	181	35	0.84	0.57-1.22	0.351	0.85	0.58-1.24	0.395

* Patients may also have the other two atopic diseases

OR, odds ratio; CI, confidence intervals; AR, allergic rhinitis; AD, atopic dermatitis

Table 3: Subgroup analysis of the risk factors in different gender

Non-atopic disease as reference (n=4273)		Multivariate: Female (n=2665)			Multivariate: Male (n=2930)		
		OR	95%CI	*P* value	OR	95%CI	*P* value
Atopic disease	Yes	0.56	0.44-0.72	<0.001	0.57	0.45-0.72	<0.001
	Asthma only	0.23	0.09-0.56	0.001	0.55	0.31-0.98	0.042
	AR only	0.51	0.36-0.71	<0.001	0.45	0.32-0.64	<0.001
	AD only	0.79	0.34-1.80	0.569	1.07	0.57-2.01	0.838
Having Asthma*	Yes	0.57	0.38-0.85	0.005	0.67	0.46-0.96	0.029
Having AR*	Yes	0.59	0.45-0.78	0.002	0.53	0.40-0.70	<0.001
Having AD*	Yes	0.79	0.44-1.39	0.411	0.89	0.54-1.47	0.654

*Patients may also have the other two atopic diseases.

OR, odds ratio; CI, confidence intervals; AR, allergic rhinitis; AD, atopic dermatitis

Table 4: Subgroup analysis of the risk factors in different age group

Non-atopic disease as reference (n=4273)		Dengue age≦32 (n=1900)			Dengue Age 33 - 50 (n=1760)			Dengue age >50 (n=1935)		
		OR	95%CI	*P* value	OR	95%CI	*P* value	OR	95%CI	*P* value
Atopic disease	Yes	0.56	0.42-0.75	<0.001	0.57	0.40-0.79	<0.001	0.57	0.43-0.76	<0.001
	asthma only	0.09	0.01-0.59	0.02	0.37	0.11-1.23	0.105	0.52	0.30-0.91	0.023
	AR only	0.52	0.36-0.75	<0.001	0.48	0.31-0.75	0.001	0.43	0.27-0.67	<0.001
	AD only	0.41	0.12-1.38	0.150	1.06	0.45-2.50	0.894	1.41	0.67-2.97	0.367
Having asthma*	Yes	0.67	0.42-1.07	0.097	0.63	0.34-1.15	0.133	0.58	0.40-0.86	0.007
Having AR	Yes	0.63	0.47-0.85	0.002	0.53	0.36-0.77	<0.001	0.51	0.36-0.72	<0.001
Having AD	Yes	0.65	0.34-1.26	0.203	1.01	0.49-2.06	0.985	0.97	0.53-1.78	0.917

*Patients may also have the other two atopic diseases.

OR, odds ratio; CI, confidence intervals; AR, allergic rhinitis; AD, atopic dermatitis

AD") did not demonstrate a protective effect for DF in the male or female group.

Allergic rhinitis and asthma are protective factors for dengue fever in young and the elderly people

Further analysis was conducted for different age groups. The study population was divided into three groups of equal size. As illustrated in [Table 4], having an atopic disease (asthma, AR, or AD) was a protective factor for DF in all age groups. Both asthma ("asthma only" and "having asthma") and AR ("AR only" and "having AR") were protective factors for DF in young people and the elderly. However, "asthma only" or "having asthma" (may also have other atopic diseases simultaneously) was not a protective factor for DF in the middle-age group (OR, 0.37; 95% CI, 0.11–1.23; $P = 0.105$ and OR, 0.63; 95% CI, 0.34–1.15; $P = 0.133$, respectively). AD ("AD only" or "having AD") showed no protective effect for DF in any age group.

Discussion

In this study, we conducted another nationwide population-based retrospective cohort study based on the NHIRD database. Consistent with the result of the previous study, our current result validated asthma to be a protective factor for DF. In addition to asthma, AR, rather than AD, was also an independent protective factor against DF.

The atopic march consists of the development of AD in infancy and consecutive AR and asthma in later childhood

and even into adulthood. Some researchers suggest that the association among AD, AR, and asthma may be a cluster, rather than disease progression.[9] These diseases may involve shared genetic loci and environmental triggers, including microbiome dysbiosis. The time series reflects the tissue-specific peak timing of the occurrence of each disease.

AD is a chronic, pruritic, inflammatory skin disease that occurs most frequently in children but also affects adults. AD is often associated with an elevated serum level of immunoglobulin E (IgE) and a personal or family history of atopy, including asthma, AR, and AD.[12,13] Unlike asthma and AR that are mostly related to the exposure of the airway to inhaled allergens, food allergens sensitization may be found in more than 50% of patients with AD.[14,15] In addition to Th2 cell–skewed immune dysregulation, epidermal barrier dysfunction, genetic factors, altered skin microbiome, and environmental triggers of inflammation all contribute to the pathogenesis of AD.[16-18] Regarding genetic factors, the linkage of *FLG*, *SPINK5*, and *KLK7*, and gene mutations in tight junction protein claudin 1, IgE receptor NOD1, NOD2, TLRs, and several interleukins has been demonstrated.[19] In AD, the skin barrier is dysfunctional with abnormal expression of ceramides and other epidermal differentiation-related molecules, such as filaggrin, and impaired tight-junctions.[19,20] This multiplicity in pathogenesis may partially explain why AD is not a protective factor for DF. The prevalence of AD in adults and children is 3% and 30%, respectively.[21] For children with AD, epidemiological studies have revealed that near 50% of AD occurs before 6 months of age, 60% by 1 year of age, and 85% by 5 years of age.[22] Young children may receive improved care for DF exposure. This factor may also affect the occurrence of DF.

In contrast, the relationship between asthma and AR is much closer. A retrospective study reported a higher incidence of AR in patients with asthma than in those without asthma.[23] In a cohort study, AR was demonstrated in 74%–81% of patients with asthma. In contrast, asthma occurred in only 2% of patients without AR.[24] In AR, numerous inflammatory cells infiltrate the nasal lining upon exposure to an inciting allergen, including the most common airborne dust mite, cockroach residues, animal dander, molds, and pollens. Thereafter, these allergens trigger the inflammatory process and cause the symptoms of AR. Allergic rhinitis is not only a disease of the upper airway. It may also lead to inflammatory processes in the lower airways, which is supported by the fact that rhinitis and asthma frequently coexist.[25] In addition, house dust mites are the most common allergen that cause asthma and AR.[26,27] In our previous study,[11] we found that the expression of DC-SIGN was decreased in DCs of patients with allergic asthmatic. Moreover, the decreased DC-SIGN expression could thereafter limit the entrance of DVs into DCs. As a result, asthma becomes a protective factor against DF. In patients with AR, house dust mites are also important allergens that trigger atopy in atopic individuals. It may also explain why AR is also a protective factor of DF.

However, our study has several limitations. First, there may be bias in the definition of DF. Because DF was diagnosed by hospital admissions dengue-related codes, symptomatic patients were more likely to be screened. Second, DF always occurs in southern Taiwan where the weather is hotter than norther area and has a trend of paroxysmal outbreaks. Therefore, the era for sampling also affects the results.

In conclusion, this study validates asthma as a protective factor against DF as our previous finding. The results also show that AR but not AD is also a protective factor against DF. Our finding provides important implications for the association between allergy and DF. Our results require further validation across different geographies and ethnicities.

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Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author contributions

C-MT, C-KT, F-JC, Y-HY, C-NH, and H-RY contributed to study design; C-KT, F-JC, Y-HY, H-C C, and H-RY contributed to data acquisition; C-MT, F-JC, Y-HY, and H-RY performed data analysis and interpretation; C-MT, C-KT, F-JC, H-C C, C-NH and H-RY drafted the manuscript; C-MT, C-KT, Y-HY, C-NH and H-RY finalized the manuscript. All authors have read and approved the final manuscript and agreed to be accountable for all aspects of the work.

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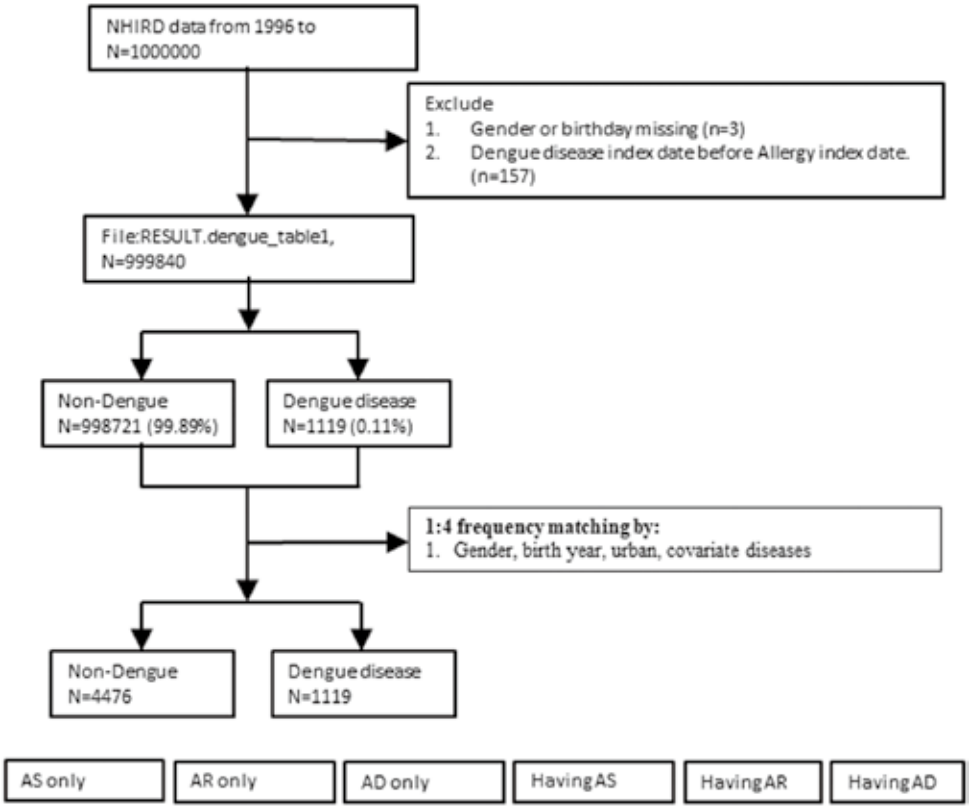
Supplementary Material



Supplementary Figure 1. Flowchart for study design

Covariate diseases including hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease

Abbreviation: NHIRD, National Health Insurance Research Database; AS, asthma; AR, allergic rhinitis; AD, atopic dermatitis.

*"Asthma only" indicates patients have asthma but not AR or AD. "Having asthma" indicates patients with asthma who may have AR, AD, or both. "AR only" indicates patients with AR but not asthma or AD. "Having AR" indicates patients with AR who may have asthma, AD, or both. "AD only" indicates patients have AD but not asthma or AR. "Having AD" indicates patients with AD who may have asthma, AR, or both.

Supplementary Table 1. Covariate disease before the diagnosis of Dengue fever

N=999840			Non-Allergy		Allergy		*P*
			n=733048 (73.32%)		n=266792 (26.68%)		
			n	%	n	%	
HTN	None	999631	732882	99.98	266749	99.98	0.0458
	Yes	209	166	0.02	43	0.02	
DM	None	999739	732972	99.99	266767	99.99	0.6608
	Yes	101	76	0.01	25	0.01	
HPL	None	999714	732950	99.99	266764	99.99	0.2575
	Yes	126	98	0.01	28	0.01	
CAD	None	999750	732981	99.99	266769	99.99	0.8088
	Yes	90	67	0.01	23	0.01	
N=999840			**Non Dengue**		**Dengue**		***P***
			n=998721 (99.89%)		**n=1119 (0.11%)**		
			n	**%**	**n**	**%**	
HTN	None	999631	998721	100	910	81.32	<0.0001
	Yes	209	0	0	209	18.68	
DM	None	999739	998721	100	1018	90.97	<0.0001
	Yes	101	0	0	101	9.03	
HPL	None	999714	998721	100	993	88.74	<0.0001
	Yes	126	0	0	126	11.26	
CAD	None	999750	998721	100	1029	91.96	<0.0001
	Yes	90	0	0	90	8.04	

Abbreviation: HTN, hypertension; DM, diabetes mellitus; HPL, hyperlipidemia; CAD, coronary artery disease

ACHIEVE LASTING CHANGE

DUPIXENT is the first-line systemic choice for achieving lasting change in patients as young as 6 years old with atopic dermatitis (AD)*

RAPID AND SUSTAINED CONTROL – CONSISTENT ACROSS ALL AGES

- Sustained improvement of itch, skin clearance, and QoL up to 52 weeks, with rapid control after first dose[1–16]

UNIQUE LONG-TERM SAFETY PROFILE

Only AD therapy:

- With 4-years long-term safety data in adults[17]
- Approved in patients as young as 6 years old[1]

START WITH EASE, STAY WITH CONFIDENCE

- DUPIXENT is not an immunosuppressant[1]
- 85% patient satisfaction with DUPIXENT treatment at 1 year[18**]

~340,000 AD PATIENTS TREATED WITH DUPIXENT WORLDWIDE[19]

*DUPIXENT is indicated to treat adults and adolescents ≥12 years with moderate-to-severe atopic dermatitis, and children aged 6 to 11 years with severe atopic dermatitis who are candidates for systemic therapy[1]

AD, atopic dermatitis; QoL, quality of life.

**adult population only

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Presentation: Dupilumab solution for injection in a pre-filled syringe with needle shield. **Indications:** *Atopic Dermatitis (AD):* Moderate-to-severe AD in adults and adolescents ≥12 years who are candidates for systemic therapy; severe atopic dermatitis in children 6 to 11 years old who are candidates for systemic therapy. *Asthma:* In adults and adolescents ≥12 years as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment. *Chronic rhinosinusitis with nasal polyposis (CRSwNP):* As an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control(for 300 mg) **Dosage & Administration:** Subcutaneous injection. *AD adults:* Initial dose of 600 mg (two 300 mg injections), followed by 300 mg every other week. *ADadolescents(12-17y/o):* Body weight <60 kg - initial dose of 400 mg (two 200 mg injections), followed by 200 mg every other week. Body weight ≥60 kg - same dosage as adults. Dupilumab can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for problem areas only, e.g. face, neck, intertriginous and genital areas. Consider discontinuing treatment in patients who have shown no response after 16 weeks. *AD Children(6-11y/o):* Body weight 15 kg ~ <60 kg - initial dose of 300 mg on Day 1 follow by 300 mg on Day 15, then 300 mg every 4 weeks. Bodyweight ≥60 kg - same dosage as adults. *The dose may be increased to 200 mg Q2W in patients with body weight of 15 kg ~ <60 kg based on physician's assessment. *Asthma:* Initial dose of 400 mg, followed by 200 mg every other week. For patients with severe asthma and on oral corticosteroids or with severe asthma and co-morbid moderate-to-severe AD or adults with co-morbid severe CRSwNP- initial dose of 600 mg, followed by 300 mg every other week. Patients receiving concomitant oral corticosteroids may reduce steroid dose gradually once clinical improvement with dupilumab has occurred. The need for continued dupilumab therapy should be considered at least annually as determined by a physician. If a dose is missed, administer it asap and thereafter, resume dosing at the regular scheduled time. **Contraindications:** Hypersensitivity to dupilumab or any of the excipients. **Precautions:** Safety and efficacy in children <6 years or <15 kg not been established. Not be used to treat acute asthma symptoms, acute exacerbations, acute bronchospasm or status asthmaticus. Do not discontinue corticosteroids abruptly upon start of dupilumab. Reduction should be gradual and performed under supervision of a physician; it may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy. Biomarkers of type 2 inflammation may be suppressed by systemic corticosteroid use. If systemic hypersensitivity reaction occurs, discontinue dupilumab and initiate appropriate therapy. Be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in patients with eosinophilia. Treat pre-existing helminth infections before initiating dupilumab. If patients become infected while receiving dupilumab and do not respond to anti-helminth treatment, discontinue dupilumab until infection resolves. Patients who develop conjunctivitis and keratitis that does not resolve following standard treatment should undergo ophthalmological examination. AD patients with comorbid asthma should not adjust or stop asthma treatments without consultation with physicians. Carefully monitor patients after discontinuation of dupilumab. Do not give live and live attenuated vaccines concurrently with dupilumab. Patients should be brought up to date with immunisations before starting dupilumab. **Drug Interactions:** Immune responses to TdaP vaccine and meningococcal polysaccharide vaccine were assessed. Patients receiving dupilumab may receive concurrent inactivated or non-live vaccinations. **Pregnancy and lactation:** Should be used during pregnancy only if potential benefit justifies potential risk to foetus. Unknown whether dupilumab is excreted in human milk or absorbed systemically after ingestion. Decision must be made whether to discontinue breast-feeding or dupilumab taking into account benefit of breast feeding for the child and benefit of therapy for the woman. **Undesirable effects:** Most common adverse reactions reported- injection site reactions, conjunctivitis, oral herpes and eosinophilia. Safety profile observed in adolescents consistent with that seen in adults. *For other undesirable effects, please refer to the full prescribing information.* **Preparation**: 2 x 300 mg/2 ml in pre-filled syringe with needle shield, 2 x 200 mg/1.14 ml in pre-filled syringe with needle shield. **Legal Classification:** Part 1, First & Third Schedules Poison ***Full prescribing information is available upon request.*** API-HK-DUP-22.06

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CONTINUOUS CONTROL