



Development and validation of a risk score to identify children at risk of life-threatening asthma

Menolly Lee , Yulia Bogdanova , Mei Chan , Louisa Owens , Sandy Wales ,
Melinda Gray , Christine Burns , Nancy Briggs , Adam Jaffe & Nusrat Homaira

To cite this article: Menolly Lee , Yulia Bogdanova , Mei Chan , Louisa Owens , Sandy Wales , Melinda Gray , Christine Burns , Nancy Briggs , Adam Jaffe & Nusrat Homaira (2020): Development and validation of a risk score to identify children at risk of life-threatening asthma, Journal of Asthma, DOI: [10.1080/02770903.2020.1841224](https://doi.org/10.1080/02770903.2020.1841224)

To link to this article: <https://doi.org/10.1080/02770903.2020.1841224>



Published online: 03 Nov 2020.



Submit your article to this journal [↗](#)



Article views: 39



View related articles [↗](#)



View Crossmark data [↗](#)



Development and validation of a risk score to identify children at risk of life-threatening asthma

Menolly Lee, BMed/BSc(Med)(Hons)/MD^a , Yulia Bogdanova, BMed/MD^a, Mei Chan, PhD^a, Louisa Owens, PhD^b, Sandy Wales, MSN^b, Melinda Gray, BScN^b, Christine Burns, BScN^b, Nancy Briggs, PhD^a, Adam Jaffe, MD^{a,b}, and Nusrat Homaira, PhD^{a,b}

^aDiscipline of Paediatrics, School of Women's and Children's Health, Faculty of Medicine, UNSW Sydney, Sydney, Australia;

^bRespiratory Department, Sydney Children's Hospital, Randwick, Australia

ABSTRACT

Objective: To develop and validate a prediction risk score for identification of children at risk of developing life-threatening asthma (LTA).

Methods: Our study utilized existing medical records and retrospective analysis to develop and validate a risk score. The study population included children aged 2-17 years, admitted with a primary diagnosis of asthma, to Sydney Children's Hospital between 2011-2016. Children admitted in the intensive care unit with asthma at risk of LTA (cases) and those admitted into general ward (comparison group), were randomly divided into a derivation and a validation cohort. Candidate predictors from derivation cohort were selected through multivariable regression, which were used to estimate each child's risk of developing LTA in the validation cohort. Predictive performance of the risk score was evaluated by the area under the receiver operating characteristic curve (AUROC) and Hosmer-Lemeshow goodness-of-fit test.

Results: The study population comprised of 1171 children; 586 in the derivation and 585 in the validation cohort. Four independent candidate variables from derivation cohort (age at admission, socioeconomic status, a family history of asthma/atopy and previous asthma hospitalizations) were retained in the predictive model (AUROC 0.759; 95% CI, 0.694-0.823), with a sensitivity of 78.5% and specificity of 46.6%.

Conclusions: Our risk algorithm based on routinely collected clinical data may be used to develop a user-friendly risk score for early identification and monitoring of children at risk of developing LTA.

ARTICLE HISTORY

Received 16 April 2020

Revised 13 August 2020

Accepted 18 October 2020

KEYWORDS

Asthma; paediatrics; fatal outcome; risk factors; risk management

Introduction

Asthma is the most common chronic childhood condition worldwide (1,2). Despite significant advances in management, asthma still remains life-threatening and a major cause of morbidity and distress to patients and their families (3). Although rare in children, asthma mortality remains a critical public health issue as the majority of deaths are preventable (1,2). The New South Wales (NSW) Child Death Review Team (CDRT) report highlighted 85% of childhood asthma deaths between 2004-2013 had modifiable factors that increased their mortality risk. Children at risk of dying from asthma attacks have now been identified as a priority group of the NSW Ministry of Health, with a subsequent recommendation to develop a risk

score for severe, potentially life-threatening asthma (LTA) (4).

LTA is usually defined as an asthma attack with risk of progression to respiratory failure, refractory to treatment with inhaled bronchodilators and systemic corticosteroids, and requiring intensive care unit (ICU) admission and care (5,6). ICU admission is a significant risk factor and potential precursor for asthma death (7,8) and has been associated with increased mortality even after the attack has resolved (9). Early and correct identification of children who are at risk of developing LTA, may prevent future mortality by close monitoring of these children and assisting in improved clinical decision-making. Despite numerous scores predicting risk of asthma attacks in children (10-14), there is no effective risk

score identifying children at risk of developing LTA to date. Therefore, the aim of this study was to develop and internally validate a convenient and inexpensive novel prediction risk score for identification of children at risk of developing LTA, to address the CDRT's recommendation.

Methods

Ethics

This study was approved by the Sydney Children's Hospital Network (SCHN) Human Research Ethics Committee.

Study design and site

We utilized existing medical records and conducted a retrospective analysis to develop and validate a risk score for predicting LTA in children. The study was conducted within Sydney Children's Hospital (SCH), Sydney, Australia. SCH is one of Australia's leading tertiary pediatric healthcare entities and a major teaching hospital, providing all levels of care to a diverse population of over 70 000 children. SCH also receives children with acute severe asthma attacks from other metropolitan and rural hospitals.

Study participants

The study participants included all children with a primary diagnosis of asthma aged 2–17 years who were admitted to SCH during 1 January 2011–31 December 2016. Children were identified from the patient record database at the SCH using ICD-10 diagnostic codes associated with asthma (J45), predominantly allergic asthma (J45.0), non-allergic asthma (J45.1), mixed asthma (J45.8), asthma unspecified (J45.9) and status asthmaticus (J46). Children were included if their presenting diagnoses were related to respiratory infection/symptoms or allergy, as these are common triggers for asthma attacks or can be difficult to distinguish from asthma. Children presenting for surgery, procedures and unrelated conditions such as skin infection, gastroenteritis etc. were excluded. Details of the study population selection is illustrated in Figure 1.

As the objective of the study was to develop and validate a risk score to identify children at risk of developing LTA, we considered all children who were admitted to the pediatric intensive care unit (PICU) with an asthma attack as “cases”. These children were admitted via the emergency department and the

general ward due to worsening respiratory status, or transferred from other metropolitan or rural hospitals. The admission criteria for PICU were based on the SCHN guidelines (i.e. patients with severe or life-threatening conditions which may progress rapidly to respiratory failure and/or require endotracheal intubation and mechanical ventilation, or require more frequent or continuous inhaled nebulized medications e.g. salbutamol infusion, that cannot be administered safely on the general pediatric patient care unit) and there were no changes during the study period. Children admitted to the general ward with asthma diagnostic codes and had no previous PICU admissions were considered as the “comparison group”. Only the most recent index admission was included for children with multiple admissions during the study period.

Data collection

Risk factors for developing LTA, including advancing age, previous asthma hospitalization, family history of asthma/atopy, lower socioeconomic status (SES), comorbidities, immunization status, ethnicity background and obesity were identified from published studies (6,7,15–28) and based on clinical expertise of the investigators. Two investigators (ML and YB) extracted the data from the patient records and entered into a pre-defined template. Data collected included socio-demographic and clinical factors such as age, sex, Indigenous status, postcode of area of residence, exposure to environmental tobacco smoke (ETS); asthma history, and admission data including relevant investigations and potential biomarkers. Area-level socioeconomic status (SES) was assessed using the Australian Bureau of Statistics Socio-Economic Indexes for Areas (SEIFA), Index of Relative Socioeconomic Advantage and Disadvantage (IRSAD), based on the child's postcode of residence. IRSAD was stratified into five categories from least to most disadvantaged according to the postcode's NSW percentiles (29).

Statistical analysis

Data were analyzed using statistical software SPSS version 25.0 (30). To be able to develop and validate a risk score for LTA within a single data set all children (including cases and comparison group) were randomly allocated into two equal groups: a derivation cohort to develop the risk score, and a validation cohort to determine its predictive value, using computer-generated random numbers.

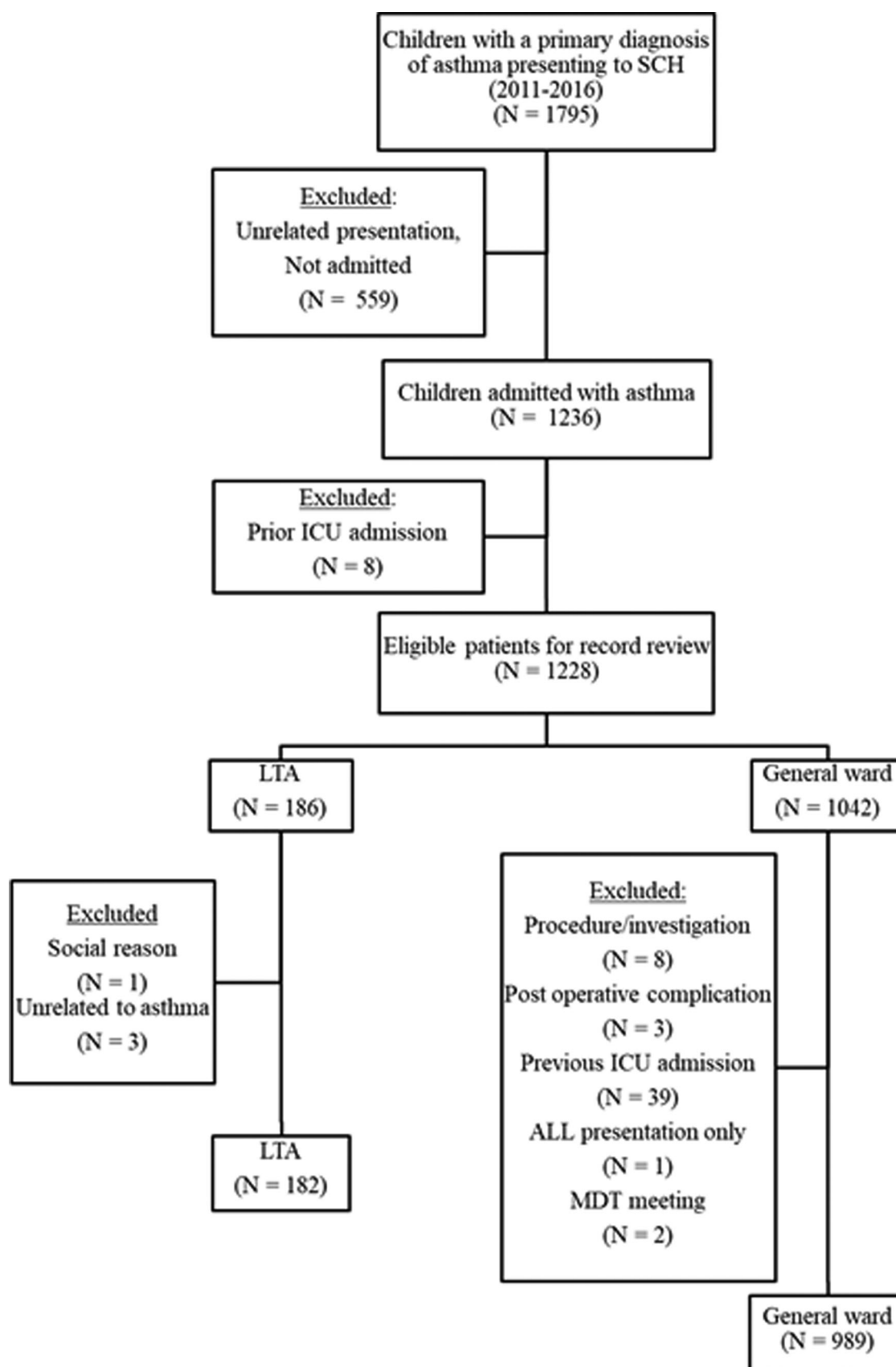


Figure 1. Flow diagram showing the process of cohort selection. The exclusion of children is explained in the text. MDT, multidisciplinary team. ALL, Acute lymphoblastic leukemia.

To reduce the amount of missing data, we reclassified variables into broader categories, for example, atopic conditions (hay fever, eczema, food allergy and sensitization to any other allergens); and family history (both asthma and atopy) and dichotomized the variable into “yes” vs negative or non-reported. However, variables with >15% missing data that could not be reclassified were excluded from analysis.

Risk score development

Patient or clinical factors that can be associated with risk of LTA were selected and ordered based on literature review. Among the children in derivation cohort only (which had both cases and comparison children) a multivariable logistic regression model was used to determine which of the patient characteristics had independent predictive value for developing LTA. Significant predictors were selected by backwards elimination (with a $p > 0.05$ for removal of variables). Only seven variables were entered at a time to avoid overfitting. Only predictor variables at $p \leq 0.05$ were retained in the final model.

Risk score validation

The β -coefficients associated with each independent predictor from final model derived in the developmental phase were then used to calculate a risk score between 0–1 for each child in the validation cohort (including both cases and comparison group). Score performance was evaluated using discrimination, by determining area under the receiver-operating characteristic curve (AUROC), and calibration, using the Hosmer-Lemeshow goodness-of-fit test. A score threshold to define ‘high risk’ was selected by optimizing the balance between sensitivity and positive predictive value (PPV).

Sample size and calculation

Sample size in prediction model development is usually determined by the event per variable (EPV) ratio: the number of events (children with LTA in our study) divided by the number of regression coefficients in the model. An EPV of ≥ 10 is usually required to avoid overfitting (31). We anticipated 4–5 independent predictors of LTA (18), therefore we required a minimum 50 children with LTA in each of derivation and validation cohort. Annually there are around 300 pediatric admissions in the general ward and 30 admissions in the PICU with an asthma associated diagnosis code. A retrospective record review of data for 2010–2016 would provide us with a sample of ~ 90 children who were admitted in PICU for asthma in the derivative and validation cohort.

Results

Background characteristics

This study included 1171 children, of which 989 (84.46%) were admitted to the general ward and 182 (15.54%) were admitted to PICU (Figure 1). The mean age of children admitted to the general ward (comparison group) (4.56 years, $SD \pm 2.90$) was younger than those admitted to PICU (cases) (6.83 ± 3.78 years). Males were predominant in both groups (60.0% in comparison group vs 57.1% in case group), and almost all children were recorded as non-Indigenous (98.2% in comparison group and 98.4% in case group).

For 19.3% ($n = 226$) of the children in this study, this was their first hospital admission with asthma i.e. 201 in comparison group and 25 in case group. The average length of stay (LOS) was shorter among children in the comparison group (1.59 ± 0.98 days) than those in case group (3.41 ± 2.37 days). There was only one death recorded in case group. The background characteristics of the derivation cohort and the validation cohort are presented in Table 1.

Model development

The results of univariate and multivariable logistic regression are presented in Table 2. Only four variables remained significant with $p < 0.05$ and thus the final model (Table 3) retained these four independent variables: age at admission, history of asthma/atopy in the immediate family, SES of the child and number of previous asthma hospitalizations.

The discriminative ability of this model in the derivative cohort was good (AUROC = 0.796; 95% CI, 0.740–0.851) (Figure 2A). Predicted and actual risks were in fairly close agreement (Figure 3A), with the Hosmer-Lemeshow test showing no indication of a poor fit ($X^2 = 7.28$, $p = 0.106$).

Model validation

In the validation cohort, although the discriminative properties of the model were expectedly lower than those in the derivative cohort (AUROC = 0.759; 95% CI, 0.694–0.823) (Figure 2B), the risk score was still significantly predictive of LTA ($p < 0.001$). The calibration bar graphs of our model (Figure 3B) showed there was a trend in under-diagnosis in lower deciles and over-diagnosis in the upper deciles on internal validation. The Hosmer-Lemeshow test showed acceptable calibration ($X^2 = 10.13$, $p = 0.068$). Crude

Table 1. Baseline characteristics of the derivation and validation cohort.

	Derivative cohort N = 586 n/N (%)	Validation cohort N = 585 n/N (%)	Total n (%)
Demographic features			
Mean age (years $\pm$ SD)	4.89 $\pm$ 3.15	4.93 $\pm$ 3.18	1171 (100)
Male	365/586 (62.3)	332/585 (56.8)	1171 (100)
Indigenous	10/586 (1.7)	11/585 (1.9)	1171 (100)
No private insurance	270/586 (46.1)	290/584 (49.7)	1170 (99.9)
Area-level SES			
SES5 (highest)	252/570 (44.2)	241/578 (41.7)	1148 (98)
SES4	181/570 (31.8)	201/578 (34.8)	
SES3	74/570 (13.0)	86/578 (14.9)	
SES2	41/570 (7.2)	22/578 (3.8)	
SES1 (lowest)	22/570 (3.9)	28/578 (4.8)	
Preferred language: not English	57/586 (9.7)	66/585 (11.3)	1171 (100)
Obesity	68/500 (13.6)	68/502 (13.5)	1002 (85.6)
Atopy and exposures			
Food allergy	93/582 (16.0)	115/583 (19.7)	1165 (99.5)
Anaphylaxis	30/582 (5.2)	50/583 (8.5)	1171 (100)
Drug allergy	34/557 (5.9)	35/579 (6.0)	1136 (97.0)
Atopic condition	333/586 (56.8)	333/585 (56.9)	1171 (100)
Atopic condition excluding food	314/586 (53.6)	312/585 (53.3)	1171 (100)
Family history of asthma/atopy	361/586 (61.6)	360/585 (61.5)	1171 (100)
Index asthma attack			
URTI symptoms	437/581 (24.8)	466/584 (79.8)	1165 (99.5)
Current antibiotics	53/586 (9.8)	44/585 (8.1)	1171 (100)
Illness duration (hours $\pm$ SD)	39.93 $\pm$ 37.51	44.43 $\pm$ 43.55	1171 (100)
Oxygen requirement	114/582 (19.6)	120/584 (20.5)	1166 (99.6)
Heart rate (bpm $\pm$ SD)	138.33 $\pm$ 22.49	140.59 $\pm$ 22.68	984 (84.0)
Respiratory rate (bpm $\pm$ SD)	42.87 $\pm$ 12.90	43.45 $\pm$ 12.40	1032 (88.1)
Accessory muscle use			
None	29/586 (5.1)	32/585 (5.5)	1171 (100)
Mild-moderate	504/586 (88.1)	511/585 (88.1)	
Severe	38/586 (6.6)	36/585 (6.2)	
Intubated	1/586 (0.2)	1/585 (0.2)	
Fever	291/583 (49.9)	283/584 (48.5)	1167 (99.7)
Length of stay (days $\pm$ SD)	1.84 $\pm$ 1.47	1.90 $\pm$ 1.46	1171 (100)
Season			
Summer	140/586 (23.9)	143/585 (24.4)	1171 (100)
Autumn	190/586 (32.4)	209/585 (35.7)	
Winter	128/586 (21.8)	133/585 (22.7)	
Spring	128/586 (21.8)	100/585 (17.1)	
Asthma history			
Current use: any preventers	213/583 (36.3)	207/583 (35.4)	1166 (99.6)
Current ICS use	133/583 (22.8)	141/583 (24.2)	1166 (99.6)
Cromones/ leukotriene antagonist	53/583 (6.0)	32/583 (5.5)	1166 (99.6)
ICS/LABA Combination therapy	67/583 (11.5)	50/583 (8.6)	1166 (99.6)
≥ 3 asthma medication classes	24/583 (4.1)	20/583 (3.4)	1166 (99.6)
Healthcare Utilization			
Previous asthma hospitalization ever			1141 (97.4)
0	335/571 (58.7)	316/570 (55.4)	
1-3	192/571 (33.6)	209/570 (36.7)	
≥ 4	44/571 (7.7)	45/570 (7.9)	
≥ 1 asthma hospitalizations in the last 12 months	125/553 (22.6)	131/565 (23.2)	1078 (92.1)
≥ 3 ED visits in the last 12 months	24/523 (4.6)	29/525 (5.5)	1052 (89.8)
ED visits ever			1059 (90.4)
0	291/530 (54.9)	279/529 (52.7)	
1	119/530 (22.5)	108/529 (20.4)	
≥ 2	120/530 (22.6)	142/529 (26.8)	
Treated with intravenous salbutamol/ aminophylline ever	44/485 (9.1)	52/481 (10.8)	966 (82.4)

SD, standard deviation. URTI, upper respiratory tract infection. ICS, inhaled corticosteroids. ICS/LABA, inhaled corticosteroid/long acting beta agonist. GP, general practitioner. bpm, beat per minute. ED, emergency department. SES, socioeconomic status.

calibration showed there was only a slight negative bias of -0.0126 observed.

A threshold to identify children at risk of developing LTA was chosen aiming for approximately 80% sensitivity and 50% specificity, which gave a score threshold of 0.0718 (sensitivity: 78.5%, specificity: 46.6%). The false positive rate was 53.4%.

Discussion

To our knowledge this is the first study that has developed and validated a risk score system for identification of children at risk of LTA. Our final prediction model contained four significant variables that are easily obtained from either history or administrative data: age, family history of asthma/atopy, SES and

Table 2. Predictor variables associated with risk of developing life-threatening asthma (LTA) in children.

	Children with LTA (case group) N = 91 n/N (%)	Children without LTA (comparison group) N = 495 n/N (%)	Univariate Analysis		Multivariable analysis	
			Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Sociodemographic						
Age at admission (per year)	91/91 (100)	495/495 (100)	1.18 (1.11 – 1.26)	<0.001	1.12 (1.03 – 1.21)	0.007
Female Sex	35/91 (38)	186/495 (37.6)	1.04 (0.66 – 1.64)	0.873	–	–
Indigenous	1/91 (1)	9/495 (1.8)	0.60 (0.08 – 4.79)	0.630	–	–
Preferred language: not English	7/91 (7.7)	50/495 (10.1)	0.74 (0.33 – 1.69)	0.477	–	–
No private insurance	57/91 (62.6)	213/495 (57.0)	2.22 (1.40 – 3.52)	0.001	–	–
Area-level SES						
SES 5 (highest, reference)	23/84 (27.4)	229/486 (47.1)	–	<0.001	–	0.004
SES4	22/84 (26.2)	159/486 (32.7)	1.38 (0.74 – 2.56)	0.310	1.56 (0.79 – 3.07)	0.201
SES3	17/84 (20.2)	57/486 (11.7)	2.97 (1.49 – 5.93)	0.002	2.54 (1.12 – 5.79)	0.026
SES2	13/84 (15.5)	28/486 (5.8)	4.62 (2.11 – 10.14)	<0.001	3.80 (1.50 – 9.62)	0.005
SES1 (lowest)	9/84 (10.7)	13/486 (2.7)	6.89 (2.66 – 17.86)	<0.001	6.42 (1.90 – 21.74)	0.003
Atopy						
Drug allergy	6/91 (6.1)	29/495 (5.9)	1.04 (0.39 – 2.78)	0.932	–	–
Anaphylaxis	5/91 (5.7)	28/495 (5.7)	1.13 (0.42 – 3.04)	0.808	–	–
Food allergy	11/88 (12.5)	82/494 (16.6)	0.72 (0.37 – 1.41)	0.335	–	–
Atopic condition excluding food	47/91 (51.6)	267/495 (53.9)	0.91 (0.58 – 1.43)	0.912	–	–
Atopic condition	48/91 (52.7)	285/495 (57.6)	0.82 (0.53 – 1.29)	0.393	–	–
Family history of asthma/atopy	65/91 (71.4)	296/495 (59.8)	1.68 (1.03 – 2.74)	0.037	2.34 (1.25 – 4.36)	0.008
Asthma history						
Previous asthma hospitalizations ever						
0	24/82 (29.3)	311/489 (63.6)	–	–	–	<0.001
1-3	32/82 (39.0)	160/489 (32.7)	2.59 (1.48 – 4.55)	0.001	2.09 (1.14 – 3.85)	0.017
≥4	26/82 (31.7)	18/489 (3.7)	18.72 (9.02 – 38.86)	<0.001	16.12 (7.22- 36.09)	<0.001
≥1 asthma hospitalizations in the last 12 months	24/67 (35.8)	101/486 (20.8)	2.13 (1.23 – 3.67)	0.007	–	–
≥3 ED visits for asthma in the last 12 months	1/46 (2.2)	23/477 (4.8)	0.439 (0.06 – 3.33)	0.425	–	–
ED visits ever						
0	21/55 (38.2)	270/475 (56.8)	–	0.005	–	–
1	12/55 (21.8)	107/475 (22.5)	1.44 (0.69 – 3.03)	0.335	–	–
≥2	22/55 (40.0)	98/475 (20.6)	2.89 (1.52 – 5.48)	0.001	–	–
Current ICS						
Current ICS/LABA combination therapy	33/89 (37.1)	100/494 (20.2)	2.32 (1.43 – 3.76)	0.001	–	–
≥3 asthma medication classes	19/89 (21.3)	48/494 (9.7)	2.52 (1.40 – 4.54)	0.002	–	–
Any preventer	9/89 (10.1)	15/495 (3.0)	3.60 (1.52 – 8.50)	0.003	–	–
Any preventer	52/89 (58.4)	161/494 (32.5)	2.77 (1.75 – 4.36)	<0.001	–	–
Obesity	14/88 (15.9)	54/412 (13.1)	1.25 (0.66 – 2.38)	0.487	–	–

ICS, inhaled corticosteroids. ICS/LABA, inhaled corticosteroid/long acting beta agonist. ED, emergency department. SES, socioeconomic status.

Table 3. β coefficients of the independent predictor variables associated with risk of developing life-threatening asthma (LTA).

Intercept and predictors	β coefficient	Standard Error
Age (per year)	0.109	0.041
Family history: asthma/atopy	0.849	0.318
SES		
SES 5 (highest)	–	–
SES4	0.443	0.346
SES3	0.933	0.420
SES2	1.334	0.474
SES1 (lowest)	1.859	0.622
Previous asthma hospitalizations ever		
0	–	–
1–3	0.739	0.311
≥4	2.781	0.411
Intercept	–4.179	0.445

β coefficients are expressed per 1-year increase for age, for the condition present in dichotomous variables, and for the category of ordinal variables. SES, socioeconomic status.

number of previous asthma hospitalizations. This model performed well on validation with good discriminative ability (AUROC 0.759) and acceptable calibration despite showing a trend to becoming a poor fit ($X^2 = 10.13$, $p = 0.0684$). Our threshold of

0.0718 (sensitivity: 78.5%; specificity: 46.6%) is able to identify the majority of children at risk of developing LTA.

One major strength of this study was our large sample size (1171 children), constituting 6 years of asthma data from one of the largest pediatric facilities in NSW. It is the largest Australian study on this topic to date. Additionally, this score is clinically useful, incorporating easily obtainable clinical and socio-demographic data. The clinical application of this risk score model can be illustrated by the following example: a child aged 12 years with family history of asthma/atopy who lived in an area corresponding to SES1 and had experienced ≤ 4 asthma hospitalizations will have a risk score of 0.578, which is considered to be high risk of developing LTA.

Comparison with other studies

Our findings were consistent with other studies demonstrating increasing age (6,7,17), previous asthma

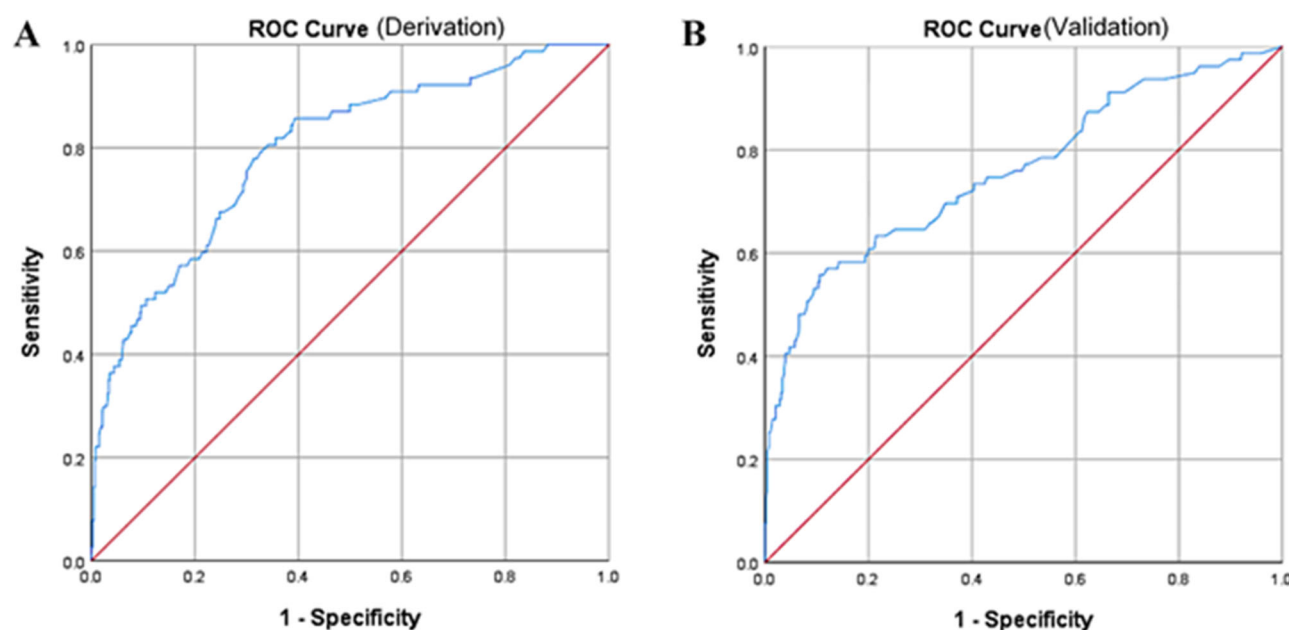


Figure 2. Receiver operating characteristic curve (ROC) for our model predicting development of LTA (shown in blue). The line of no difference (AUROC = 0.5) is also shown in red. Panel A is the ROC for the derivation cohort and Panel B, the validation cohort.

hospitalizations (18,20), family history of asthma/atopy (16) and lower SES (16) increase the risk of developing LTA. Notably, risk of LTA increased exponentially with each lower SES quintile in this study.

In this study, a history of ≥ 4 asthma hospitalizations were the strongest predictor of LTA (OR = 16.12; 95% CI, 7.22– 36.09, $p < 0.001$), similar to study done by Roberts et al. (20). This is a modifiable factor as each hospital visit provides an opportunity for follow-up and reassessment of severity, optimization of control, lung function, atopy education and referral to specialist care (18).

The CDRT report also revealed psychosocial issues were a major factor, with 55% of children coming from vulnerable families (4). Although we attempted to examine this, it was largely missing. Assessing for psychosocial issues is usually challenging when using medical records.

Limitations

As this was a single center study, this may limit its generalisability. However, SCH has a broad catchment, providing care to a diverse population and readily receives children from wider Sydney and rural areas. Although we showed internal validity, external validity needs to be demonstrated in an alternative setting.

We also experienced limitations inherent to retrospective studies such as missing data, and documentation bias and errors. We could not include major factors such as asthma severity, medication adherence,

prior asthma education and a current asthma plan in our analysis due to missing data. Additionally, many investigations such as lung function and potential biomarkers also could not be included due to missing data. These factors have been shown to be important in the literature (15,17,18,20,32–35). Missing data could be the result of poor documentation, unawareness of LTA risk factors by the attending physician or non-response by the child/parent/carer.

Exposure to environmental tobacco smoke (ETS) was another potential predictor which was not included due to missingness. However, the association between ETS exposure and LTA has been inconsistent in the literature (6,7,15–17,22,23), and previous studies suggest self-reported ETS exposure was not a risk factor (18). However, self-reported smoking measures are generally under-reported (36), and thus an objective measure such as salivary or urinary cotinine may be useful in predicting risk associated with exposure to ETS.

Additionally, lack of objective measures was also an issue, as for almost all children serum IgE, skin prick testing (SPT) or food challenge results were unavailable, so self-reported atopy was used. Although food allergy and atopy were not significant in our analysis, using objective atopic markers may show different results. A small UK case-control study used SPT and serum-specific IgE to show food allergy was independent risk factor for LTA (20) and the previous study at SCH revealed higher IgE levels were also a risk factor (18). Using objective measures would have strengthen

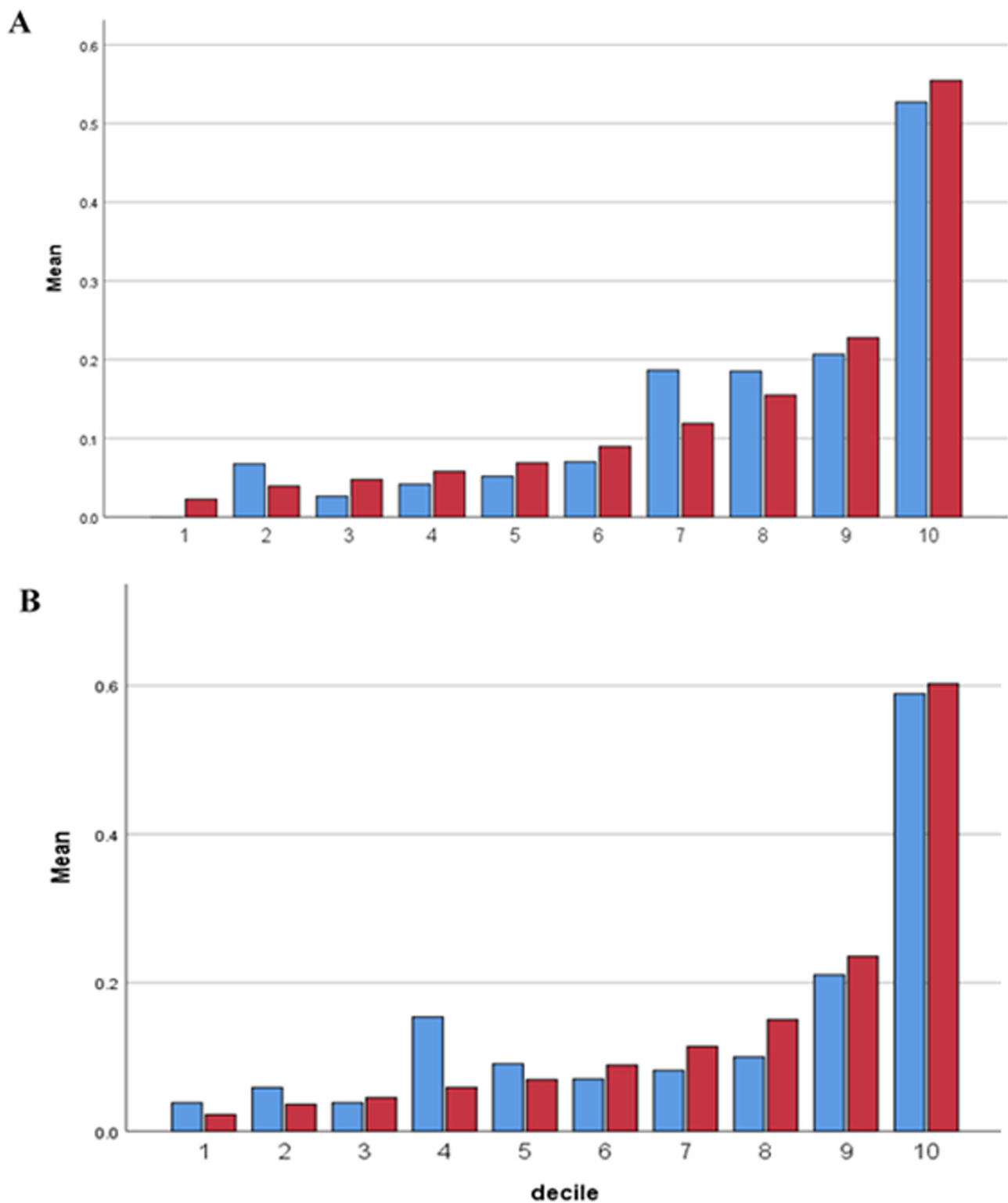


Figure 3. Calibration bar graph for our logistic prediction model showing the mean risk of each decile of predicted risks (red) and actual risks (blue). Panel A: Derivation cohort; Panel B: validation cohort.

this study's validity. Moreover, the recategorization and dichotomization of variables (atopy and family history of asthma/atopy) into broader categories, may have underestimated the true contribution of these variables to the risk of developing LTA.

Implications and future directions

Identifying children at risk of developing LTA can help tailor more effective management strategies to prevent life-threatening asthma attacks and consequent mortality.

These children can be then referred to ongoing active follow-up through home visits, specialist care and continued asthma education. Enhanced coordination of primary, secondary and tertiary care schools and childcare services through integrated care to strategically target children for more assertive follow-up and improve engagement with health providers is vital to prevent children from falling through gaps in the healthcare system as elucidated in the CDRT report (35). Knowledge that their child is potentially at risk of LTA can also act as an incentive for parental/carer behavior changes, such as smoking cessation and medication adherence. It may also improve symptom recognition and allow earlier seeking of medical attention. Delays in seeking medical help is a modifiable factor in the final event for a substantial proportion of children and adults with a severe asthma attack (5,34,37–40). This accentuates the importance of educating patients, parents/carers, schools and childcare services in recognizing symptom severity and implementing asthma first-aid.

Conclusion

This study has demonstrated that children at risk of developing LTA can be identified using routinely collected data in the clinical setting. Incorporating the risk score into a computer-assisted tool may help clinicians to easily use this algorithm in the ambulatory setting and improve identification and monitoring of children at high-risk of developing fatal asthma.

Acknowledgements

Thank you to the Respiratory Department at the Sydney Children's Hospital for their timely and constructive feedback and the health data unit at the Sydney Children's Hospital for access to the medical records. I would also like to thank the Sydney Children's Hospital Foundation for their support in our research endeavour and the Rotary Club of Sydney Cove for their funding.

Declaration of interests

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Funding

This work was funded by Rotary Club of Sydney Cove.

ORCID

Menolly Lee  <http://orcid.org/0000-0003-0732-6268>

References

1. Deloitte Access Economics. The hidden cost of asthma. Sydney: Deloitte Access Economics; 2015.
2. Global Asthma Network (GAN). Global asthma report 2014. Auckland, New Zealand: Global Asthma Network; 2014.
3. Asher I, Pearce N. Global burden of asthma among children. *Int J Tuberc Lung Dis.* 2014;18(11):1269–1278. doi:10.5588/ijtld.14.0170.
4. NSW Child Death Review Team (CDRT). NSW child death review team annual report 2016–17. Sydney: NSW Ombudsman; 2017.
5. Serrano-Pariente J, Plaza V. Near-fatal asthma: a heterogeneous clinical entity. *Curr Opin Allergy Clin Immunol.* 2017;17(1):28–35. doi:10.1097/ACI.0000000000000333.
6. Vogel NM, Katz HT, Lopez R, Lang DM. Food allergy is associated with potentially fatal childhood asthma. *J Asthma.* 2008;45(10):862–866.
7. McDowell KM, Kercsmar CM, Huang B, Guilbert TW, Kahn RS. Medical and social determinants of health associated with intensive care admission for asthma in children. *Ann Am Thorac Soc.* 2016;13(7):1081–1088. doi:10.1513/AnnalsATS.201512-798OC.
8. Campbell DA, McLennan G, Coates JR, Frith PA, Gluyas PA, Latimer KM, Luke CG, Martin AJ, Roder DM, Ruffin RE, et al. A comparison of asthma deaths and near-fatal asthma attacks in South Australia. *Eur Respir J.* 1994;7(3):490–497. doi:10.1183/09031936.94.07030490.
9. Yilmaz O, Bakirtas A, Ertoyl Karagol HI, Topal E, Demirsoy MS. Allergic rhinitis may impact the recovery of pulmonary function tests after moderate/severe asthma exacerbation in children. *Allergy.* 2014;69(5):652–657. doi:10.1111/all.12391.
10. Sagara N, Suzuki R, Aota A, Akashi K, Kastunuma T. Modified pulmonary index score (MPIS) and indication of hospitalization for acute asthma exacerbation in children. *Eur Respir J.* 2016;48(suppl 60):PA4363.
11. Ahmaren O, Neill RS, Koe S, Elnazir B. Clinical asthma score as a predictor for hospital admissions and duration of stay in children presenting with acute asthma to a paediatric emergency department. *Eur Respir J.* 2013;42(Suppl 57):P1129.
12. Forno E, Fuhlbrigge A, Soto-Quirós ME, Avila L, Raby BA, Brehm J, Sylvia JM, Weiss ST, Celedón JC. Risk factors and predictive clinical scores for asthma exacerbations in childhood. *Chest.* 2010;138(5):1156–1165. doi:10.1378/chest.09-2426.
13. Maue DK, Krupp N, Rowan CM. Pediatric asthma severity score is associated with critical care interventions. *World J Clin Pediatr.* 2017;6(1):34–39. doi:10.5409/wjcp.v6.i1.34.
14. Leung TF, Ko FWS, Wong GWK, Li CY, Yung E, Hui DSC, Lai CKW. Predicting changes in clinical status of young asthmatics: clinical scores or objective parameters? *Pediatr Pulmonol.* 2009;44(5):442–449.
15. Keller K, Sran S, Laszlo D, Georgitis JW. Acute asthma management in children: factors identifying patients at risk for intensive care unit treatment. *J Asthma.* 1994;31(5):393–400. doi:10.3109/02770909409061319.

16. LeSon S, Gershwin ME. Risk factors for asthmatic patients requiring intubation. I. Observations in children. *J Asthma*. 1995;32(4):285–294. doi:[10.3109/02770909509044836](https://doi.org/10.3109/02770909509044836).
17. Lyell PJ, Villanueva E, Burton D, Freezer NJ, Bardin PG. Risk factors for intensive care in children with acute asthma. *Respirology*. 2005;10(4):436–441. doi:[10.1111/j.1440-1843.2005.00726.x](https://doi.org/10.1111/j.1440-1843.2005.00726.x).
18. Belessis Y, Dixon S, Thomsen A, Duffy B, Rawlinson W, Henry R, Morton J. Risk factors for an intensive care unit admission in children with asthma. *Pediatr Pulmonol*. 2004;37(3):201–209.
19. Davenport PW, Cruz M, Stecenko AA, Kifle Y. Respiratory-related evoked potentials in children with life-threatening asthma. *Am J Respir Crit Care Med*. 2000;161(6):1830–1835. doi:[10.1164/ajrccm.161.6.9903077](https://doi.org/10.1164/ajrccm.161.6.9903077).
20. Roberts G, Lack G. Food allergy and asthma - what is the link? *Paediatr Respir Rev*. 2003;4(3):205–212.
21. Sala KA, Carroll CL, Tang Y-S, Aglio T, Dressler AM, Schramm CM. Factors associated with the development of severe asthma exacerbations in children. *J Asthma*. 2011;48(6):558–564. doi:[10.3109/02770903.2011.585411](https://doi.org/10.3109/02770903.2011.585411).
22. van den Bosch GE, Merkus PJFM, Buysse CMP, Boehmer ALM, Vaessen-Verberne AAPH, van Veen LN, Hop WCJ, de Hoog M. Risk factors for pediatric intensive care admission in children with acute asthma. *Respir Care*. 2012;57(9):1391–1397. doi:[10.4187/respcare.01325](https://doi.org/10.4187/respcare.01325).
23. Hasegawa K, Ahn J, Brown MA, Press VG, Gabriel S, Herrera V, Bittner JC, Camargo CA. Underuse of guideline-recommended long-term asthma management in children hospitalized to the intensive care unit: a multicenter observational study. *Ann Allergy Asthma Immunol*. 2015;115(1):10–16.e1. doi:[10.1016/j.ana.2015.05.004](https://doi.org/10.1016/j.ana.2015.05.004).
24. Kifle Y, Seng V, Davenport PW. Magnitude estimation of inspiratory resistive loads in children with life-threatening asthma. *Am J Respir Crit Care Med*. 1997;156(5):1530–1535. doi:[10.1164/ajrccm.156.5.9703011](https://doi.org/10.1164/ajrccm.156.5.9703011).
25. Triasih R, Duke T, Robertson CF. Outcomes following admission to intensive care for asthma. *Arch Dis Child*. 2011;96(8):729–734. doi:[10.1136/adc.2010.205062](https://doi.org/10.1136/adc.2010.205062).
26. Yao T-C, Kuo M-L, See L-C, Chen L-C, Yan D-C, Ou L-S, Shaw C-K, Huang J-L. The RANTES promoter polymorphism: a genetic risk factor for near-fatal asthma in Chinese children. *J Allergy Clin Immunol*. 2003;111(6):1285–1292. doi:[10.1067/mai.2003.1506](https://doi.org/10.1067/mai.2003.1506).
27. Huang JL, Yao T, Kuoc ML. CRTH2 polymorphism: genetic risk factor for near-fatal asthma in the Chinese childhood population. *J Allergy Clin Immunol*. 2004;113(2):S340.
28. Chen L-C, Tseng H-M, Wu C-J, Kuo M-L, Wu C-J, Gao P-S, Yeh K-W, Yao T-C, Lee W-I, Ou L-S, et al. Evaluation of a common variant of the gene encoding clara cell 10 kd protein (CC10) as a candidate determinant for asthma severity and steroid responsiveness among Chinese children. *J Asthma*. 2012;49(7):665–672.
29. Australian Bureau of Statistics (ABS). Socio-Economic Indexes for Areas (SEIFA) 2016. 2018. Report No.: Cat. No. 2033.0.55.001.
30. IBM Corp. IBM SPSS statistics for windows, version 25.0. Armonk, NY: IBM Corp; 2017.
31. Pavlou M, Ambler G, Seaman SR, Guttman O, Elliott P, King M, Omar RZ. How to develop a more accurate risk prediction model when there are few events. *BMJ*. 2015;351:h3868. doi:[10.1136/bmj.h3868](https://doi.org/10.1136/bmj.h3868).
32. Bravo RC, Carroll CL, Schramm CM, Bhandari A. Reassessment of disease severity in patients following severe acute exacerbations of Asthma. *J Asthma Allergy Educ*. 2010;1(2):56–60.
33. Sheikh S, Khan N, Ryan-Wenger NA, McCoy KS. Demographics, clinical course, and outcomes of children with status asthmaticus treated in a pediatric intensive care unit: 8-year review. *J Asthma*. 2013;50(4):364–369. doi:[10.3109/02770903.2012.757781](https://doi.org/10.3109/02770903.2012.757781).
34. Stein R, Canny GJ, Bohn DJ, Reisman JJ, Levison H. Severe acute asthma in a pediatric intensive care unit: six years' experience. *Pediatrics*. 1989;83(6):1023–1028.
35. Fitzgerald DA, Gillis J. Asthma deaths in children in New South Wales 2004–2013: could we have done more? *J Paediatr Child Health*. 2015;51(11):1127–1133. doi:[10.1111/jpc.12947](https://doi.org/10.1111/jpc.12947).
36. Stelmach R, Fernandes FLA, Carvalho-Pinto RM, Athanazio RA, Rached SZ, Prado GF, Cukier A. Comparison between objective measures of smoking and self-reported smoking status in patients with asthma or COPD: are our patients telling us the truth? *J Bras Pneumol*. 2015;41(2):124–132.
37. Robertson CF, Rubinfeld AR, Bowes G. Pediatric asthma deaths in Victoria: the mild are at risk. *Pediatr Pulmonol*. 1992;13(2):95–100. doi:[10.1002/ppul.1950130207](https://doi.org/10.1002/ppul.1950130207).
38. Jørgensen IM, Jensen VB, Bülow S, Dahm TL, Prahl P, Juel K. Asthma mortality in the Danish child population: risk factors and causes of asthma death. *Pediatr Pulmonol*. 2003;36(2):142–147. doi:[10.1002/ppul.10305](https://doi.org/10.1002/ppul.10305).
39. Carter R, Klein R, Fritz GK, McQuaid EL, Kopel S. Asthma and perception in adolescents: a growing body of evidence demonstrates that adolescents with life-threatening asthma often underestimate the severity of their episodes. *J Respir Care Pract*. 2005;18(1):27–31.
40. Tough SC, Green FH, Paul JE, Wigle DT, Butt JC. Sudden death from asthma in 108 children and young adults. *J Asthma*. 1996;33(3):179–188. doi:[10.3109/02770909609054550](https://doi.org/10.3109/02770909609054550).