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External validation of the Predicting Asthma Risk in Children tool in a clinical cohort

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Abstract

Introduction: The Predicting Asthma Risk in Children (PARC) tool uses questionnaire-based respiratory symptoms collected from preschool children to predict asthma risk 5 years later. The tool was developed and validated in population cohorts but not validated using a clinical cohort. We aimed to externally validate the PARC tool in a pediatric pulmonology clinic setting.

Methods: The Swiss Paediatric Airway Cohort (SPAC) is a prospective cohort of children seen in pediatric pulmonology clinics across Switzerland. We included children aged 1–6 years with cough or wheeze at baseline who completed the 2-year follow-up questionnaire. The outcome was defined as current wheeze plus use of asthma medication. We assessed performance using: sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV), area under the curve (AUC), scaled Brier's score, and Nagelkerke's R^2 scores. We compared performance in SPAC to that in the original population, the Leicester Respiratory Cohort (LRC).

Results: Among 346 children included, 125 (36%) reported the outcome after 2 years. At a PARC score of 4: sensitivity was higher (95% vs. 79%), specificity lower (14% vs. 57%), and NPV and PPV comparable (0.84 vs. 0.87 and 0.37 vs. 0.42) in SPAC versus LRC. AUC (0.71 vs. 0.78), R^2 (0.18 vs. 0.28) and Brier's scores (0.13 vs. 0.22) were lower in SPAC.

Conclusions: The PARC tool shows some clinical utility, particularly for ruling out the development of asthma in young children, but performance limitations highlight the need for new prediction tools to be developed specifically for the clinical setting.

KEYWORDS
asthma, children, external validation, PARC, prediction, preschool, risk, SPAC, wheeze

1 | INTRODUCTION

Symptoms such as cough and wheeze in preschool-aged children can be an early sign of asthma and cause a high burden of morbidity and health-care utilization.[1–4] Asthma also remains an important cause of morbidity later in childhood.[5,6] To reduce childhood asthma morbidity and overtreatment, it is important for clinicians to identify children with asthma early. For this, they require tools that help distinguish preschool children who are at risk of developing asthma from those who cough or wheeze for other reasons and will possibly outgrow their symptoms.

Several asthma prediction tools have been developed to help identify preschool children at risk of developing asthma. These prediction tools vary in their target population, geography, predictors used, and applicable settings. Most use validated questions on respiratory symptoms and some include invasively measured traits such as atopy, fractional exhaled nitric oxide (FeNO), lung function, and genetic markers.[7–15]

The Predicting Asthma Risk in Children (PARC) tool has the advantage that it predicts asthma risk in preschool children by using questions asked in routine clinical care and avoids the use of invasive measures that may not be available in primary care or resource-poor settings. The tool was developed by Pescatore et al.[16] using data of preschool children from the population-based Leicester Respiratory Cohort (LRC) who had seen their doctor at age 1–3 years with symptoms of cough or wheeze, and aimed to predict whether they would have asthma 5 years later (Supporting Information: Table S1). The outcome of asthma was defined as wheeze and asthma medication use in the preceding 12 months. In internal validation in the LRC, the PARC tool demonstrated good discriminatory performance (area under the curve [AUC] of 0.78).[16] In external validation in community-based settings, the PARC tool demonstrated a good discriminatory performance in the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort (AUC: 0.77)[17] and very good discriminatory performance in the multicenter allergy study (MAS) cohort (AUC: 0.83).[18] The PARC tool has yet to be externally validated in clinical settings where preschool children are seen for wheeze or cough. We, therefore, aimed to perform an external

validation of the PARC tool in a prospective cohort of children with respiratory symptoms presenting to pediatric pulmonology outpatient clinics and assess its performance in predicting asthma 2 years later.

2 | METHODS

We used the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis guidelines to report this external validation study.[19,20]

2.1 | The external validation cohort: Swiss Paediatric Airway Cohort

This external validation was performed using data from the Swiss Paediatric Airway Cohort (SPAC), a multicenter prospective cohort embedded in routine pediatric pulmonology care across Switzerland. SPAC includes children referred for respiratory symptoms such as wheeze, cough, and dyspnea.[21] As of February 28, 2022, SPAC includes 3547 children aged 0–16 years of whom 1079 have already completed 2 years of follow-up (Figure 1). The SPAC study was approved by the Bern Cantonal Ethics Committee (Kantonale Ethikkomission Bern 2016-02176).

2.2 | The PARC tool

The PARC tool includes 10 items in its prediction score. These include: age, sex, occurrence of wheeze episodes not associated with a cold, number of episodes of wheeze, impact of wheezing on daily activities, dyspnea, wheeze or cough triggered by exercise, laughing, crying or excitement, wheeze or cough triggered by dust, grass, pets or other animals, history of eczema in the child, and history of asthma, bronchitis or wheeze in the parents. Each item is assigned a score with the overall sum ranging from 0 to 15.
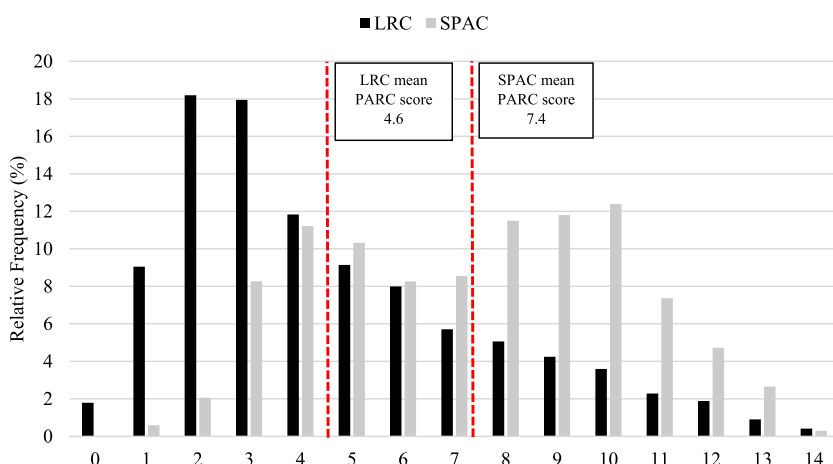
FIGURE 1 Distribution (relative frequency %) of PARC score in the external validation population (Swiss Paediatric Airway Cohort [SPAC], N = 346) versus original development population (Leicester Respiratory Cohort [LRC], N = 1226). Mean PARC scores of 7.4 for SPAC and 4.6 for LRC indicated by dashed vertical red lines. PARC, Predicting Asthma Risk in Children.

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2.3 | Inclusion criteria

Inclusion criteria for this external validation were selected to resemble original LRC inclusion criteria as closely as possible (Supporting Information: Table S1). To achieve a larger sample size the inclusion age range was expanded from 1–3 to 1–6 years. Children were included if at the baseline visit they responded "yes" to the question: "In the past 12 months, has your child ever had a dry cough at night, apart from a cough associated with a cold or chest infection?" or "Has your child had wheezing or whistling in the chest in the past 12 months?" and if they had responded to the 2-year follow-up questionnaire.

2.4 | Outcome criteria

Outcome criteria were selected to resemble original LRC outcome criteria (Supporting Information: Table S1). Time to the development of the outcome was shortened from 5 to 2 years due to current study limitations, as we do not yet have 5 years of follow-up. We defined the outcome as children who responded "yes" to the question: "Has your child reported wheeze in the past 12 months" at the 2-year follow-up questionnaire and who also reported having used an asthma medication in the previous 12 months.

2.5 | Sample size

As a rule of thumb, a sample used for external validation should include at least 100 outcome events and 100 nonoutcome events.[22] This external validation is based on 125 events and 221 nonevents.

2.6 | Missing data

The data used to assess PARC score predictors was complete for the majority of predictors. For the remainder, the proportion of missing values was <2% for three predictors, 9% for two predictors, and 29% for one predictor. The predictor with the most missing values was derived from the question: "In the last 12 months, which of the following have caused the child to cough or wheeze: dust, grass, or animals?" We decided to recode these missing values to "no," assuming that if the parents had not decisively answered with "yes" the symptom was absent, borderline, or mild.

2.7 | Statistical analysis

We assessed the predictive performance of the PARC tool in SPAC using measures of discrimination and calibration. We assessed overall performance in terms of "goodness-of-fit" using maximum-scaled Brier's score and Nagelkerke's R^2 scores. For these scores 1 indicates perfect prediction and 0 noninformative prediction. The Brier Score evaluates mean square error of prediction while Nagelkerke's R^2 compares likelihoods between the prediction and a noninformative models. We assessed discrimination using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratios (LR+, LR−) and AUC. We used an AUC definition of good if >0.7, very good if >0.8, and excellent if >0.9.[23] We assessed calibration by assigning original probabilities derived from the developmental model by Pescatore et al.[16] of the outcome of asthma to each PARC score. We then recalibrated PARC scores in SPAC by fitting a logistic regression of the outcome on the calculated scores as a linear term and calculating predicted probabilities for each score from the fitted model. We then compared calibration performance of the recalibrated SPAC scores with the original scores. We examined calibration of the PARC tool graphically by plotting the predicted probability for each value of the score against the observed frequency of asthma among children in SPAC with that score value, using the function calibrate.plot and val.prob.ci.2 from the gbm package in R (R Foundation). We used STATA 17 for data preparation, descriptive analysis and logistic regression, and RStudio 2021.09.0 to assess model performance.

2.8 | Sensitivity analysis

To further examine the performance of the PARC tool in SPAC we undertook sensitivity analyses using alternative definitions for inclusion and outcome criteria. First, we modified inclusion criteria by age group. For outcome sensitivity analysis we modified the timing of the outcome to 1- and 3-year follow-up so that we could assess the role of different follow-up time frames on the performance of the model. As in the development cohort, LRC, and another external validation cohort, ALSPAC, we also did a sensitivity analysis assessing performance for a more severe definition of asthma.

3 | RESULTS

In the SPAC study, 346 of 1079 children (32%) satisfied the inclusion criteria (response yes to wheeze or cough in the past 12 months at baseline), were aged 1–6 years, and completed the 2-year follow-up (Supporting Information: Figure S1). A total of 125 (36% of the 346 children) had the defined outcome. In contrast, in LRC 1226 of 8700 children (14%) satisfied inclusion criteria and 345 (28%) had the outcome. Notable differences between the cohorts include: geographical area, study years (2017–2020 vs. 1998–1999), and study setting (clinical cohort vs. population-based cohort) (Supporting Information: Table S1). Follow-up time was 2 years in SPAC and 5 years in LRC.[24]

The median PARC score was higher in SPAC (median: 8, interquartile range [IQR]: 5–8) than in LRC (median: 4, IQR: 2–6; Figure 1). At a PARC score of 4, sensitivity was higher (95% vs. 79%) and specificity lower (14% vs. 57%) in SPAC compared to LRC. The PPVs and NPVs were comparable (37% vs. 42%) and (84% vs. 87%) in SPAC and LRC, respectively. The positive and negative LRs were also

comparable (1.1 vs. 1.83 and 0.38 vs. 0.38) in SPAC and LRC, respectively (Tables 1 and 2). The PARC tool's ability to discriminate between those children with and without the outcome was modest in SPAC (AUC: 0.71) and lower than in LRC (AUC: 0.78; Figure 3). The tool also showed poorer overall performance in SPAC than LRC with scaled Brier's score 0.13 versus 0.22 and Nagelkerke's R^2 0.18 versus 0.28 (Table 2).

Sensitivity analysis with changes to inclusion and outcome criteria in SPAC resulted in modest adjustments to performance indicators (Table 2). Altering inclusion criteria to 1–3 year olds only as per LRC inclusion criteria resulted in AUC of 0.71. Altering the outcome criteria to a higher severity defined as >4 episodes of wheeze in the past 12 months plus asthma medication use improved the AUC to 0.74. This same sensitivity analysis resulted in an AUC of

TABLE 1 Questions used for each PARC score item at baseline in SPAC and LRC

Question in asthma prediction score		LRC (%)	Questionnaire item in SPAC		SPAC (%)	Comparability
1. What is the child's sex	Female = 0	(45)	Gender	Female = 0	(34)	Perfect
	Male = 1	(55)		Male = 1	(66)	
2. How old is the child? (in years)	1 year = 0	(27)	Age	0–1 year = 0	(11)	Very good
	2 = 1	(57)		2–6 years = 1	(89)	
	3 = 1	(15)				
3. In the last 12 months, has the child had wheezing or whistling in the chest even without having a cold or flu?	No = 0	(82)	In the last 12 months has the child had wheezing or whistling in the chest even without having a cold or flu?	No = 0	(25)	Perfect
	Yes = 1	(18)		Yes = 1	(75)	
4. How many attacks of wheeze has the child had during the last 12 months?	0–3 = 0	(77)	How many attacks of wheeze has the child had in the last 12 months?	0 or 1–3 = 0	(57)	Perfect
	>3 = 2	(23)		>3 = 2	(43)	
5. In the last 12 months, how much did wheezing interfere with the child's daily activities?	Never = 0	(64)	In the last 12 months, how much did wheezing or shortness of breath interfere with the child's daily activities?	Never = 0	(19)	Very good
	A little = 1	(26)		A little = 1 Moderately = 1	(53)	
	A lot = 2	(10)		A lot = 2	(28)	
6. Do these wheezing attacks cause the child to be short of breath?	Never = 0	(65)	Did the child have wheeze or shortness of breath during these episodes (i.e., wheezing attacks)?	Never = 0	(47)	Perfect
	Sometimes = 2	(29)		Sometimes = 2	(35)	
	Always = 3	(6)		Always = 3	(18)	
7. In the last 12 months, did exercise (playing, running) or laughing, crying or excitement cause wheezing or coughing in the child?	No = 0	(61)	In the last 12 months, which of the following have caused the child to cough or wheeze: exertion, laughing, crying loudly	Never = 0	(27)	Excellent
	Yes = 1	(39)		Sometimes = 1	(73)	
				Often = 1		
8. In the last 12 months, did contact with dust, grass, pets, or other animals cause wheezing or coughing in the child?	No = 0	(93)	In the last 12 months, which of the following have caused the child to cough or wheeze: dust, grass, or animals	Never = 0	(59)	Perfect
	Yes = 1	(7)		Sometimes = 1	(41)	
				Often = 1		
9. Has the child ever had eczema?	No = 0	(71)	Has your doctor ever told you that the child has eczema or dermatitis?	No = 0	(76)	Excellent
	Yes = 1	(29)		Yes = 1	(24)	
10. Have the child's parents ever suffered from wheezing, asthma, or bronchitis?	None = 0	(65)	Have the child's parents ever suffered from wheezing, asthma, or bronchitis?	None = 0	(59)	Excellent
	Mother = 1	(31)		Mother = 1	(35)	
	Father = 1			Father = 1		
	Both = 2	(4)		Both = 2	(6)	

Abbreviations: LRC, Leicester Respiratory Cohort; PARC, Predicting Asthma Risk in Children; SPAC, Swiss Paediatric Airway Cohort.

TABLE 2 Sensitivity analysis of SPAC versus LRC at a PARC Score of 4

	N	Cases N (%)	Sensitivity	Specificity	PPV	NPV	LR+	LR−	AUC	R^2	Brier
SPAC											
Main analysis	346	125 (36)	0.95	0.14	0.37	0.84	1.10	0.37	0.71	0.18	0.13
Altered inclusion criteria											
Only children aged 1–3 years	146	45 (36)	0.90	0.18	0.38	0.77	1.10	0.53	0.71	0.17	0.14
Altered outcome definition											
Follow-up 1 year later	509	233 (46)	0.93	0.25	0.51	0.80	1.23	0.30	0.72	0.19	0.14
Follow-up 3 years later	180	50 (28)	0.94	0.23	0.32	0.91	1.22	0.26	0.72	0.16	0.12
Severity: Wheeze in the past 12 months with more than 4 episodes and use of asthma medication	346	37 (11)	0.97	0.22	0.13	0.99	1.24	0.12	0.74	0.15	0.09
LRC											
Main analysis	1226	345 (28)	0.79	0.57	0.42	0.87	1.83	0.38	0.78	0.28	0.22
Altered outcome definition											
Severity: Wheeze in the past 12 months with more than 4 episodes and use of asthma medication	1030	86 (8)	0.86	0.61	0.17	0.98	2.19	0.23	0.84	0.32	−0.15

Abbreviations: AUC, area under the curve; LR, likelihood ratio; LRC Leicester Respiratory Cohort; NPV, negative predictive value; PARC, Predicting Asthma Risk in Children; PPV, positive predictive value; SPAC, Swiss Paediatric Airway Cohort.

0.84 when performed in the LRC.[17] Altering outcome criteria to follow-up 1 or 3 years later increased the AUC marginally to 0.72.

Assessment of performance at a PARC score of 7 showed higher sensitivity (79% vs. 46%), lower specificity (51% vs. 91%), comparable PPV and NPV (45% vs. 44% and 83% vs. 91%), lower positive LR (1.6 vs. 4.95) and comparable negative LR (0.42 vs. 0.59) in SPAC versus LRC (Figure 2). The maximum predicted probability of developing the outcome in SPAC was 76% compared to 95% in LRC (Figure 3). The Loess smoothed calibration plot demonstrated c statistic of 0.71 (confidence interval [CI]: 0.65–0.77), slope of 1 (CI: 0.69–1.31), and intercept of 0 (−0.24 to 0.24) (Figure 4).

4 | DISCUSSION

This is the first external validation of the PARC tool in a clinical cohort. The tool showed reduced predictive ability for asthma development in young children aged 1–6 years old in the clinical validation cohort (SPAC) than in the original population-based cohort (LRC). Discrimination, though modest in both cohorts, was somewhat reduced in SPAC (AUC: 0.71) compared to LRC (0.78). The PARC tool had a higher sensitivity (95% vs. 79%) at a score of 4 in the clinical setting of SPAC compared to the community-setting of LRC, and a similarly high negative predictive value (84% vs. 87%). However, all other indicators suggested reduced performance. The mean PARC score was higher in SPAC than LRC and AUC improved to 0.74 when the outcome was defined as moderately severe asthma (more than four attacks in the past year and use of asthma medication).

4.1 | Strengths and limitations

This study has several strengths. It is the first external validation of the tool in a clinical setting where children with respiratory problems are treated. In addition, SPAC is a longitudinal study embedded in routine pulmonology care across German-speaking parts of Switzerland, which represents a real-world setting. Questionnaire items used in SPAC are identical to those used in LRC. A strength of the PARC tool is, that it used state-of-the-art modeling strategies and selected predictors using a method (least absolute shrinkage and selection operator regression) that minimizes the risk of over-fitting the data. The main limitation of this external validation is the small sample size currently available in this clinical setting and the limited follow-up time. However, due to the longitudinal and ongoing nature of SPAC, there is scope to perform further external validations in the future when the participant number and follow-up time has increased.

4.2 | Interpretation and comparison with previous studies

There are several differences between SPAC and LRC which must be considered when interpreting the performance of the PARC tool in this external validation setting. First, the broader age range (1–6 vs. 1–3 years) and shorter follow-up time (2 vs. 5 years) in SPAC compared to LRC. Second, this analysis used information collected from parent-reported questionnaires written in German. The specific terms for "wheeze" are not easily interchangeable between the German and English languages. However, a previous external validation of the PARC tool in the German MAS population-based

Score Cut-Off	Sensitivity	Specificity	PPV	NPV	LR+	LR-
1	1	0	0.34	–	1.00	–
2	1	0	0.35	1	1.01	0.00
3	0.99	0.04	0.35	0.89	1.03	0.24
4	0.95	0.14	0.37	0.84	1.10	0.37
5	0.93	0.30	0.41	0.89	1.33	0.22
6	0.87	0.42	0.44	0.86	1.52	0.30
7	**0.79**	**0.50**	**0.46**	**0.83**	**1.59**	**0.42**
8	0.71	0.59	0.48	0.79	1.73	0.50
9	0.56	0.69	0.49	0.75	1.84	0.63
10	0.45	0.81	0.56	0.74	2.40	0.68
11	0.29	0.92	0.67	0.71	3.91	0.76
12	0.18	0.98	0.85	0.70	10.46	0.83
13	0.07	1	0.90	0.67	17.10	0.93
14	0.01	1	1	0.66	–	0.99

SPAC: Area under the curve 0.71

LRC: Area under the curve 0.78
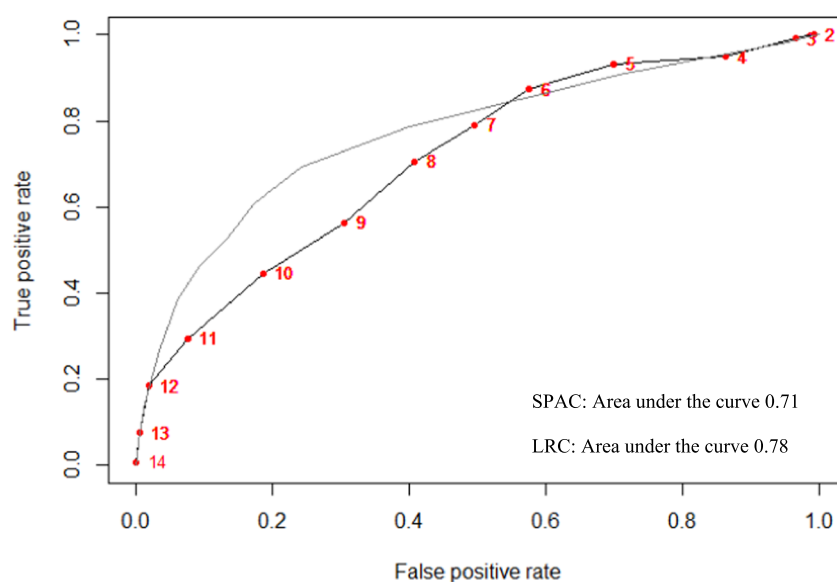
FIGURE 2 Receiver operating characteristic from external validation (SPAC in black with PARC scores marked in red) and development cohort (LRC in gray) including area under the curve. Table shows sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR), and negative LR for each score in SPAC. LRC, Leicester Respiratory Cohort; PARC, Predicting Asthma Risk in Children; SPAC, Swiss Paediatric Airway Cohort.

cohort showed very good discriminatory performance with an AUC of 0.83, suggesting that differences in language are not a likely explanation for the poorer performance of PARC in SPAC.[18] Third, SPAC represents a group of children with a high burden of respiratory disease in a clinical setting. A higher burden of respiratory disease results in a more homogenous case mix which has been shown in external validations to reduce the discriminative ability of prediction models[25] and the application of a prediction tool from a population or primary care setting to a tertiary setting has also been shown to demonstrate reduced spectrum transportability.[25]

Other asthma predictive tools have been developed for preschool children in clinical settings. A retrospective study by Boersma et al.[26] that aimed to examine how senitization to inhalant allergens among wheezing toddlers in secondary healthcare predicted asthma development, demonstrated an improvement in the AUC from 0.70 to 0.79 when it included invasive senitization measures compared to when they used only International Study of Asthma and Allergies in Childhood questions. Vial Dupuy et al.[14] developed and independently validated the Persistent Asthma Predicting Score in a clinical setting. They defined the outcome as

FIGURE 3 Predicted probability of developing asthma at follow-up in the LRC (gray line) and probability of developing asthma in recalibrated model in SPAC (black line). LRC, Leicester Respiratory Cohort; PARC, Predicting Asthma Risk in Children; SPAC, Swiss Paediatric Airway Cohort.
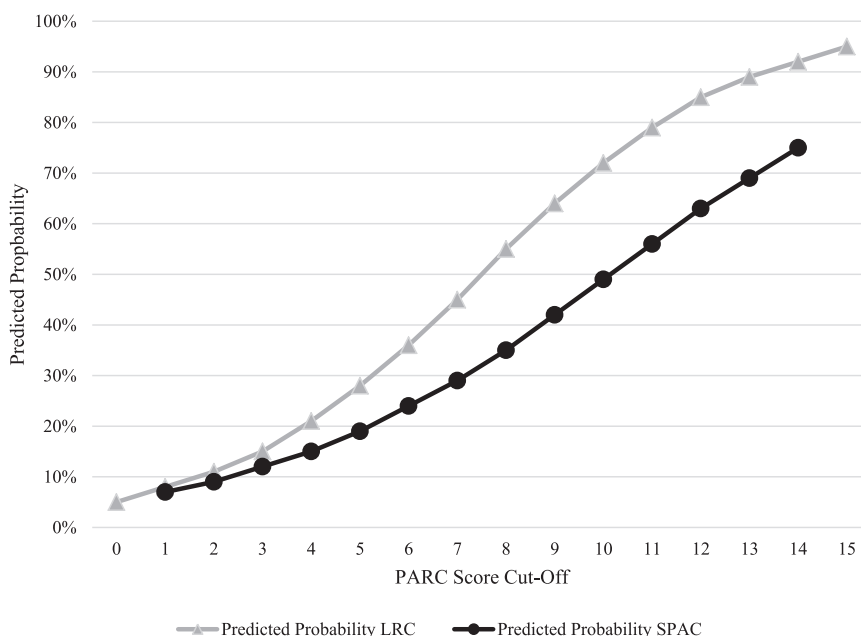
FIGURE 4 Calibration assessment of predicted probabilities in SPAC. LRC, Leicester Respiratory Cohort; SPAC, Swiss Paediatric Airway Cohort.
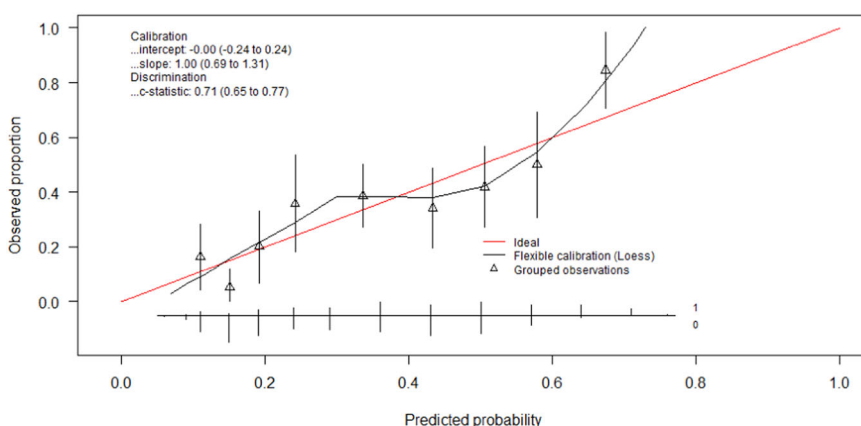
"persistent" asthma. Predictors included: family history of asthma, personal history of atopic dermatitis and immunoglobulin E (IgE) senitization. Their analysis demonstrated an AUC of 0.66 in the development population and 0.65 in the internal validation population demonstrating low overall discrimination of the tool. In a clinical setting including corticosteroid-naïve 3–47 month-old children in Zürich, Switzerland, Singer et al.[27] performed an external validation of a modified asthma predictive index (API) tool. They used an outcome of physician-diagnosed asthma and included FeNO as a predictor. Their analysis showed good discrimination with AUC of 0.76 when FeNO was used instead of blood eosinophilia, as per the original API tool.[27] Rodriguez-Martinez et al.[28] implemented the loose API and modified Prevalence and Incidence of Asthma and Mite Allergy (PIAMA) tools in a clinical setting in Bogota, Columbia. They reported a sensitivity and specificity for predicting asthma at age 5–6 years in preschoolers with recurrent wheeze of 71.4% and 33.3% (loose API) and 54.5% and 78.9% (modified PIAMA) for ideal receiver operator curves cut-off points. The authors suggested that these prediction tools could therefore be applicable in clinical practice. In

our external validation, the PARC tool had an NPV of 83%, PPV of 46%, and sensitivity and specificity of 79% and 50%, respectively at a PARC score of 7, which suggests that it also has scope for clinical application.

4.3 | Implications for clinical care and future research

The PARC tool has now undergone external validation in two population-based and one clinical cohort. The tool shows good to very-good discriminative ability in community settings and good discriminative ability in the clinical setting. However, it has a higher sensitivity of 95% and an NPV of 84% in SPAC, indicating a possible role for assisting clinicians to accurately identify children with a low risk of developing. For example, pediatric pulmonologists in Switzerland could use the PARC tool to reassure parents with children with a score of 4 or less that their child's risk of having asthma in 2 years' time is only 5%. The proportion of children in our analysis with a

PARC score 4 or less was 10%. The tool could also have potential applications for triaging patients for follow-up. Furthermore, by narrowing the definition of asthma to a more severe spectrum the tool performs better in SPAC. This suggests that, in a clinical context, the PARC tool may be able predict severe asthma better and that any adaptation of the PARC tool in the future should use different outcome definitions such as "severe asthma" or "asthma persistence." Previous applications of prediction tools to clinical settings have demonstrated a role for invasive measures such as blood eosinophils, IgE senitization, and FeNO with variable success.[14,25,26] Future prediction model development for asthma risk in preschool children attending respiratory clinics could include these invasive measures to improve their discriminatory performance.

5 | CONCLUSION

This external validation of the PARC tool in a clinical cohort embedded in routine pediatric pulmonology care suggested that the tool has a role for application in this setting. Currently, it can be used to help identify 1–6-year old children who are at low risk of having asthma at 2 years of follow-up, due to its negative predictive value and sensitivity at a cut-off of 4. Discrimination of the PARC tool between children who will and will not have asthma 2 years later was borderline good highlighting the need for new childhood asthma prediction tools in the clinical setting. We suggest that future efforts to improve asthma prediction in this setting should explore the added value of biomarkers of physiological asthma-related traits available in pulmonology clinics, such as FeNO, allergy tests, and lung function measurements.

AUTHOR CONTRIBUTIONS

Daria O. Berger, Eva S. L. Pedersen, Maria C. Mallet, Cristina Ardura-Garcia, and Claudia E. Kuehni made substantial contributions to the study concept and design. Daria O. Berger and Ben D. Spycher analyzed the data. Daria O. Berger drafted the manuscript. Daria O. Berger, Eva S. L. Pedersen, Maria C. Mallet, Carmen C. M. de Jong, Jakob Usemann, Nicolas Regamey, Ben D. Spycher, Cristina Ardura-Garcia, and Claudia E. Kuehni critically revised and approved the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Additional supporting information can be found online in the Supporting Information section at the end of this article.