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Early View

Original research article

Development and validation of a predictive model combining patient-reported outcome measures (PROMs), spirometry and FeNO for asthma diagnosis

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Development and validation of a predictive model combining patient-reported outcome measures (PROMs), spirometry and FeNO for asthma diagnosis

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Take home message

Misdiagnosis of asthma is common in clinical practice. Here, we developed and validated a predictive model, combining symptom intensity scales, spirometry and FeNO, that offers a new simple and minimally invasive way to aid in diagnosing asthma.

INTRODUCTION: Although asthma is a common disease, its diagnosis remains a challenge in clinical practice with both over/under-diagnosis. Here, we performed a prospective observational study investigating the value of symptom intensity scales alone or combined with spirometry and FeNO to aid in asthma diagnosis.

METHODS: We recruited, over a 38-month period, 303 untreated patients complaining with symptoms suggestive of asthma (cough, chest tightness, dyspnea, airway secretion and wheezing). The whole cohort was split in a training cohort (n=166) for patients recruited in odd months and a validation cohort (n=137) for the patients recruited in even months. Asthma was diagnosed either by a positive reversibility test (≥12% and 200ml) and/or a positive bronchial challenge test (PC20M≤8mg/ml). In order to assess the diagnostic performance of symptoms, spirometric indices and FeNO, we performed ROC curve analysis and multivariable logistic regression to identify the independent factors associated with asthma in the training cohort. Then, the derived predictive models were applied to the validation cohort.

RESULTS: 63% of patients in the derivation cohort and 58% in the validation cohort were diagnosed as being asthmatics. After logistic regression wheezing was the only symptom to be significantly associated with asthma. Similarly, FEV_1% predicted, FEV_1/FVC% and FeNO were significantly associated with asthma. A predictive model combining these four parameters yielded an AUC of 0.76 (95%CI: 0.66-0.84) in the training cohort and 0.73 (95%CI: 0.65-0.82) when applied to the validation cohort.

CONCLUSION: Combining wheezing intensity scale with spirometry and FeNO may help in improving asthma diagnosis accuracy in clinical practice.

KEYWORDS: Asthma – Diagnosis – Symptoms perception – PROM – FeNO – Spirometry

Abbreviations used:

ATS: American Thoracic Society

AUC-ROC: Area under the receiver operating characteristic curve

BMI: Body mass index

ERS: European Respiratory Society

FeNO: Fraction of exhaled nitric oxide

FEV_1: Forced expiratory volume in 1 second

FVC: Forced vital capacity

GINA: Global initiative for asthma

PROM: Patient-reported outcome measure

ROC: Receiver operating characteristic curve

INTRODUCTION

Asthma is a common chronic respiratory disease defined by the conjunction of respiratory symptoms (breathlessness, wheezing, cough and chest tightness) and the demonstration of excessive airway caliber fluctuation that varies over time ([1]). This pathology is a major public health problem affecting approximately 334 millions of people worldwide ([2]). In addition to its important prevalence, asthma is responsible for considerable direct (such as hospital admission and the cost of pharmaceutical medicines) and indirect (such as school and work days lost and income lost because of premature death) economic costs ([3 4]). Next to these public health implications of asthma, recent surveys in primary care have indicated that many patients living with asthma are underdiagnosed, while several studies point out an overdiagnosis in as much as 30% of the patients who had received a diagnosis ([5 6]). Both under- and overdiagnosis produce adverse consequences to patient's health-related quality of life (such as exposing the patient to adverse effects of the therapies prescribed and generating patient anxiety) and to health care systems (such as the cost of inappropriate medicines prescription) ([7]).

European Respiratory Society (ERS) has recently published guidelines for the diagnosis of asthma for both children ([8]) and adults ([9]). These guidelines underline, for each patient complaining of recurrent asthma like symptoms, the importance of spirometry combined with a bronchodilator reversibility test for diagnosing asthma in primary care. In the absence of a significant bronchodilator reversibility in primary care, the guidelines recommend measuring fraction of exhaled nitric oxide (FeNO) level and highlights the value of bronchoprovocation test in secondary care setting if diagnosis has not been established in primary care.

Though being a common disease, the diagnostic of asthma may be all but trivial in clinical practice. In this respect, it is worth to note that, in the recently published Novelty study only a minority of patients labelled as being asthmatics satisfied the bronchodilating criteria for asthma ([10 11]). The reason is that lung function tests are often not performed and consequently diagnosis is reduced to the clinical history and signs at the physical examination ([12]). There has been much

emphasis on the utility of discovering and using biomarker to help in the diagnosis ([13] [14] [15]). In contrast, the respective value of symptoms as reported directly by the patients have been somewhat neglected ([5] [11]) and the recent ERS guidelines acknowledge the importance of new researches focusing on detailed symptoms history ([9]). Indeed, despite the increasing recognition of the need to include patient's perspective in routine practice as captured by patient-reported outcome measures (PROMs) ([16] [17]), few asthma studies have explored the contribution of patient-reported asthma symptoms in the diagnosis ([18] [19]). Therefore, in line with the growing importance given to the patient's perspective, we decided to explore the diagnostic performance of the intensity of each classical asthma symptom as reported directly by the patient and to investigate how their combination with spirometric indices and FeNO might improve diagnostic accuracy.

METHODS

Study design, setting and participants

We conducted a prospective observational study, between November 2018 and December 2021, on adult patients (≥ 18 years) investigated in a real clinical practice setting at the asthma clinic of CHU (secondary care centre) Liège (Belgium). We recruited 303 untreated patients who sought medical attention and in whom asthma was suspected based on clinical history. We split our global cohort (N=303) into a training cohort that comprised patients recruited during odd months (n=166) and a validation cohort of patients recruited during the even months (n=137). In accordance with the Global initiative for asthma (GINA) criteria, the asthma diagnosis was based on the presence of typical symptoms (wheezing, breathlessness, chest tightness, sputum secretion and cough) combined with a 12% and 200 ml forced expiratory volume in 1 second (FEV_1) reversibility after inhalation of 400 μg salbutamol and/or a provocative concentration of methacholine causing a 20% drop in FEV_1 ≤8mg/ml when FEV_1 ≥70% predicted. Patients attended the asthma clinic on two days at an interval of 1-2 weeks. On day one, each patients underwent FeNO measurement, spirometry with bronchodilation, sputum induction, gave a blood sample, and filled in asthma control and asthma quality of life questionnaire as well as symptom intensity scales. On day two, subjects underwent methacholine challenge if baseline FEV_1 was not less than 70% predicted.

Study parameters

Asthma symptoms intensity scales

The intensity level of the 5 classic asthma symptoms ([20]) including dyspnea (breathlessness), wheezing, chest tightness, cough, and sputum production were measured using Likert scales that extends over 5 levels (from 0 to 4), where the level 0 means that the symptom is not present, and level 4 expresses the greatest intensity of the symptom concerned.

Demographic and disease characteristics

Demographic characteristics were age, gender, atopy, smoking status and BMI. Atopy was defined by a positive IgE test (>0.35 kU/L) to one or more common aeroallergens from our area (grass pollen, tree pollen, cat, dog, molds and house dust mite). Smoking status was divided in three categories: never-smoker, ex-smoker (quit smoking at least 6 months previously) and current smokers.

Disease characteristics were lung function and systemic and airway inflammation. Lung function testing was performed by spirometry (PFT spirostick, Geratherm, Germany), according to the ERS/ATS standard ([21]). A post-bronchodilator (reversibility) test was done for each patient, irrespective of their baseline FEV_1 and FEV1/forced vital capacity (FVC) ratio, as a standard procedure. Patients were administrated 400 μg of inhaled salbutamol via a metered-dose inhaler (Ventolin), one puff at a time into the spacer, and spirometry was performed again 15 minutes later. Patients with baseline $FEV_1 \geq 70\%$ predicted underwent a methacholine challenge test, as previously described ([22] [23]). Using tidal breathing, the subjects inhaled successive quadrupling methacholine concentrations from 0.06 mg/ml to 16 mg/ml for 30 seconds each through a Hudson jet nebulizer (Hudson RCI; Micro Mist, Research Triangle Park, NC) ([22]); FEV_1 was measured 30 and 90 seconds after each concentration. The test was stopped if FEV_1 fell at least 20% from its baseline value. The PC20M was calculated by linear interpolation from the last two points of the curve. Inflammatory parameters included FeNO, sputum cell counts, blood cell counts, and systemic markers. FeNO was measured at a flow rate of 50ml/s (NIOX; Aerocrine, Solna, Sweden) before spirometry. Sputum induction and processing were performed as previously described ([24]). Blood eosinophils counts and total serum IgE were determined by routine laboratory analysis at Liège University Hospital.

Statistical analysis

Quantitative variables were summarized as mean (±SD) or median (IQR) while count and percentage were given for qualitative variables. Linear regression models were applied to analyze the comparison of the two cohorts, training and validation, as well as the comparison of asthmatic and non-asthmatic groups within both cohorts.

The objective of our study was to identify the parameters that could predict accurate asthma diagnosis. This analysis included symptoms VAS (cough, secretion, chest tightness, dyspnea, and wheezing), FEV_1 (%), FEV1/FVC (%) and FeNO. In order to assess the diagnostic performance of these different parameters, ROC curves were drawn in the training cohort. Afterwards, multivariable logistic regression analysis was applied in the training cohort considering significant parameters found in the univariate logistic regression analysis to derive different predictive models. Odds ratio (OR) with corresponding 95% confidence intervals (95% CI) were provided to assess the strength of association between asthma diagnosis and parameters. Finally, the validity of the predictive models were evaluated by analyzing the validation dataset. In order to achieve these objectives, the corresponding response operating characteristics (ROC) curve was depicted and sensitivities, specificities, negative predictive value (NPV), and positive predictive value (PPV) were also calculated. In order to compare the discriminant capacity of the different predictive models, the areas under curves (AUCs) and the corresponding 95% confidence interval (CI) were calculated. All analyses were performed using the R software at a significance level of 0.05.

Ethics

This study was approved by the Liège University Hospital ethics committee. Signed informed consent was obtained from patients as soon as they entered the asthma clinic. They agreed to allow their clinical data and the health outcomes they reported in the routine setting to be used for research purpose.

RESULTS

Characteristics of the study population

Demographic, functional, and inflammatory features of the training and the validation cohorts are given in Table 1. The training and the validation cohorts were similar regarding demographics, functional and inflammatory features. The majority of the patients had preserved baseline spirometric values and FeNO and blood eosinophils counts within the normal range.

Comparison between asthmatics and non-asthmatics in the training cohort

One hundred and five patients out of the 166 patients (63%) were found to be asthmatics in the training cohort. Asthmatics displayed lower FEV_1 % predicted ($p<0.0001$) and FEV_1/FVC % ($p<0.0001$) values and a higher FeNO ($p<0.05$) value as compared to non-asthmatics, while there was no significant difference for blood eosinophils and serum IgE (Table 2). With respect to symptoms, wheezing was the only symptom showing difference between asthmatics and non-asthmatics ($p<0.001$). Detailed analysis of asthmatics and non-asthmatics in the validation cohort are given in supplementary Table 1.

Diagnostic power of symptoms, spirometric indices and FeNO in the training cohort

The performance of each symptom, spirometric indices and FeNO in the training cohort was assessed by constructing ROC curve and is presented in Table 3. Among symptoms only wheezing provided a significant AUC=0.67 (95% CI: 0.59-0.76; $p<0.001$). While wheezing was the most discriminant symptom, 22% of the patients with an asthma diagnosis did not report any wheezing (Fig 1 & supplementary Fig.1). By comparison only 9% of patients did not report dyspnea and the corresponding values for chest tightness, cough and airway secretion were 25% ,12% and 25% respectively (Fig.1 & Fig.S1). Both FEV_1 % predicted and FEV_1/FVC % ratio also provided significant AUC equal to 0.68 (95% CI: 0.60-0.77; $p<0.0001$) and 0.69 (95% CI: 0.61-0.77; $p<0.0001$) respectively, whereas FeNO failed in providing a significant AUC equal to 0.56 (95% CI: 0.47-0.66; $p=0.184$).

Building predictive models from the training cohort

We performed univariate logistic regression for each parameter (Table 4). Only wheezing, FEV_1 %, FEV_1/FVC ratio and FeNO were found to be significant. Then, we constructed eight different predictive models using a multivariable logistic regression based on the significant parameters of the univariate logistic regression (Table 5). In each model, the probability of asthma diagnosis increased with wheezing intensity and FeNO levels. Likewise, the probability of asthma increased when FEV_1 % predicted and FEV_1/FVC ratio decreased. Only wheezing and FEV_1% were significant in any models where they were tested. The best model included wheezing, FEV_1 % predicted, FEV_1/FVC ratio and FeNO and provided an AUC of 0.76 (95% CI: 0.66-0.84) with a sensitivity and a specificity of 0.77 (95% CI: 0.54-0.85) and 0.69 (95% CI: 0.44-0.81) respectively (Fig.2, upper panel). The negative predictive value (NPV) and the positive predictive value (PPV) were 0.66 and 0.80 respectively (Table 6.a.).

Application of the predictive models to the validation cohort

Eighty patients out of the 137 patients (58%) in the validation cohort proved to be asthmatics. The application of the eight predictive models to the validation cohort is shown in Table 6.b. and in Figure 2, lower panel. The most performing model was the one that included all the parameters with an AUC=0.73 (95% CI: 0.65-0.82) with a sensitivity and a specificity of 0.52(95% CI: 0.21-0.64) and 0.91(95% CI: 0.63-0.96) respectively. The negative predictive value and the positive predictive value were 0.60 and 0.88 respectively.

Finally, including all the symptoms in the constructed models did not provide better diagnosis accuracy (supplementary tables 2-3).

DISCUSSION

Here we provide a predictive model based on non invasive measures that might improve the accuracy of asthma diagnosis in clinical practice. Our study shows that combining a wheezing intensity scale together with spirometric indices and FeNO provide a fair model to predict asthma defined by excessive fluctuation of airway calibre that is demonstrated either by a positive reversibility test or by a positive bronchial challenge to methacholine.

Wheezing came out as the best symptom to predict asthma. Wheezing is the resultant of turbulent airflow passing through the airways as a consequence of reduction in airway caliber. This obviously fits with asthma pathophysiology, which features episodes of airway caliber constriction ([25]). Interestingly, as the best threshold of the wheezing AUC is in the lower part of the scale it would suggest that the symptom is already discriminant even if relatively mild. However, it should be remembered that 22% of the patient with a proven asthma diagnosis denied any wheezing. Our findings are in line with a study conducted by Sistek et al. ([26]), where the authors demonstrated that, among chronic respiratory symptoms, wheezing was the best single predictor of confirmed asthma. However, the authors considered wheezing symptom in a dichotomous way (yes or no) and did not use a validation cohort to confirm their results. On the opposite, Shin et al. ([27]) developed a self-symptoms reported questionnaire to aid asthma diagnosis where they demonstrated that cough was the best symptom to discriminate in a trial conducted in secondary care. However, an important limit to their results was the size of their sample that only included 50 patients. Regarding the values of symptoms for diagnosing asthma, Schneider et al. ([18]) demonstrated that the diagnostic performance of each symptom was dependent of the health care sector. In this respect, they showed that dyspnea and chest tightness were better to discriminate in primary care, while wheezing and expectorations were better in secondary care.

There has been much emphasis on the need of clinical objectives parameters to help the clinician to make asthma diagnosis ([13] [14] [15]). Our data show that baseline spirometric indices

provided a moderate accuracy (FEV1 AUC=0.68; FEV1/FVC AUC=0.69) to make a correct asthma diagnosis in patients complaining with chronic respiratory symptoms. This is in line with the value of low FEV_1 % predicted and low FEV_1/FVC % as predictors of significant bronchodilating response ([22] [28]). Spirometric indices performed however better than measuring FeNO (AUC=0.56) in that regard, which is in keeping with previous studies conducted in other cohorts ([15] [29]). If FeNO was found to be a component of the predictive model that proved to be the best when applied on the validation cohort, its contribution in the predictive models was, however, clearly less than that of spirometric indices. Adding FeNO to the model that combined wheezing and spirometry results in a slight increment of the AUC from 0.74 to 0.76 and from 0.70 to 0.73 in the training and validation cohorts respectively. By contrast adding spirometrics indices to the model that combined wheezing and FeNO improved AUC from 0.67 to 0.76 and from 0.61 to 0.73 in the training and the validation cohorts respectively. The modest contribution of FeNO to asthma diagnosis does not discard its value as a predicting biomarker for good symptom response to ICS irrespective of the asthma label ([30]).

Overall, our data indicate that combining a subjective parameter (wheezing intensity score) with clinical objective parameters (spirometric indices and FeNO) provides a high positive predictive value (PPV=0.88) for asthma diagnosis. On the opposite, if the objective was to rule out asthma, the model with the highest negative predictive value should be chosen, that is the model 6 in our study. Whatever, our results support the idea recently recommended by Nawaz et al. ([31]) to combine subjective and objective parameters in order to improve the accuracy of asthma diagnosis. Using PROMs to help diagnosis has mainly been developed in detecting mental health conditions such as depression ([32]). Nevertheless, developing PROMs in order to aid the diagnosis of chronic disease such as asthma is equally relevant ([31]). In this regard, we believe that a systematic assessment by a symptom intensity scale contributes to improve asthma diagnosis by alerting clinicians about a symptom that the patient might not necessarily report spontaneously ([33]).

Given its high positive predictive value, our model should now be tested in primary care setting because it offers a simple and a quick way to make a first selection in patients with symptoms suggestive of asthma. Filling in a symptom questionnaire and performing a FeNO measurement followed by a spirometry will take only 10 min, which is less time consuming than the classic reversibility test, which requires 15-20 min and was, otherwise, found to be insensitive in capturing excess of airway variability in patient with preserved baseline airway calibre ([9 11]). Furthermore, developing a digital health tool that integrates an algorithm based on our results might be useful a useful diagnostic/screening tool to disseminate in primary care setting ([34 35]). Another algorithm for asthma diagnosis has recently been proposed by Drake et al.([36]) including wheeze on auscultation, blood eosinophils count and peak flow variability. Compared to the one proposed by Drake et al.([36]), our algorithm would have the advantage of providing the probability of being asthmatic in only one visit. It would be of great interest to compare the diagnostic performance of these two algorithms in a new prospective study.

Strengths and limitations of the study

A strength of our study is that we combined symptoms together with FeNO and spirometry where many previous studies investigated an index test alone ([13 29]). Furthermore, we derived in the training cohort a predictive model that we applied in a validation cohort. The way we selected the training and the validation cohorts with the odd months to set up the training cohort and the even months to build the validation cohort resulted in a validation cohort very similar to the training cohort. We believe this selection process may avoid bias linked to change in hospital organization and patient attendance due to the COVID19 pandemic, which strongly struk our region during early spring 2020 as well as during the fall of the same year. This mode of selection also allows to escape the bias that may result from recruiting patients during different seasons, which might influence allergen exposure known to impact FeNO values in sensitized patients. Our study has some limitations. First, it was performed in a secondary care center and the type of patients recruited might not be representative of patients seen in primary care where

most of asthma diagnosis are performed. However, health care organization in Belgium is so that mild asthmatics typically seen in primary care may have access to secondary care and seek a diagnosis for their complaint in an ambulatory care setting of a university hospital without GP's gatekeeping. The demographic and functional characteristics of our patient cohorts are in fact close to what is seen in a primary care setting ([37 38]) and in cohorts of adult incident asthma ([39 40]). Second, the symptom question only considered the intensity of the symptom but not the triggers. Third, the Likert scales extended over 5 levels, where patients had to choose one level (0,1,2,3 & 4), while having a scale that extends over 10 levels might have refined the results ([41]). Fourth, the criterion of significant reversibility after bronchodilation may be subject of discussion and has not been extensively validated to differentiate asthma from non-asthma patients in clinical studies ([42]). Fifth, some of the patients classified as non-asthmatics might have actually developed real asthma if followed over weeks or months illustrating the concept of fourth dimension in asthma diagnosis ([35]).

CONCLUSION

A wheezing intensity scale combined with spirometry and FeNO enables to build a predictive model which offers a new simple and minimally invasive way to aid in diagnosing asthma, yielding a high positive predictive value. Its value should now be externally validated in both another secondary care setting and, above all, in primary care setting.

DECLARATIONS

Ethics approval and consent to participate

Study was approved by the CHU Liège ethics committee. Signed informed consent was obtained from patients as soon as they entered the asthma clinic of the CHU Liège. They agreed that their clinical data and the health outcomes they reported in the routine setting would be used for the purposes of research.

Competing interests

Outside of this submitted work, RL received unrestricted research grants from GSK, AstraZeneca and Chiesi and lecture or adboard fees from GSK, AZ, Novartis and Sonafi. Outside of this submitted work, FS received lecture or adboard fees from Chiesi, AZ, GSK, and Novartis. The rest of the authors declare that they have no relevant conflicts of interest.

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The study also received support from a federal grant of Belgian Government (EOS 0013618F).

Authors' contributions

GL, BP, FS and RL contributed to the conception of the study. FS, FG, MH, VP and RL contributed to data acquisition. GL, HNZ, AFD performed statistical analysis. GL, BP, FS, RL, MG and DK drafted and critically revised the work. All authors gave final approval of the manuscript.

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APPENDIX

Table 1: **Patient demographic, functional and inflammatory characteristics in the training and validation cohort**

	Training cohort (n=166)	Validation cohort (n=137)
Asthmatic	63% (105)	58% (80)
Age (years)	51 (± 16)	51 (± 15)
Gender (male)	43% (71)	36% (50)
BMI (kg/m2)	27 (± 4.8)	26 (± 4.9)
Non-Smoker	52% (87)	51% (70)
Ex-Smoker	25% (42)	31% (42)
Smoker	23% (37)	18% (25)
Atopy	47% (78)	42% (58)
FEV1 % pred.	92 (± 17)	94 (± 17)
FEV1/FVC %	79 (± 8.3)	79 (± 7.9)
FeNO (ppb)	21 (14-34)	19 (13-29)
Sputum eosinophils % *	1 (0-3)	1 (0.2-2.5)
Blood eosinophils %	2.5 (1.3-4.2)	2.1 (1.2-3.1)
Blood eosinophils (1/μL)	170 (98-290)	160 (81-250)
Total serum IgE (KU/L)	60 (22-252)	78 (27-158)

Results are expressed as percentage (n), mean (±SD) or median (IQR)

*n=95 in the training cohort and n=94 in the validation cohort.

Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; FeNO, fraction of exhaled nitric oxide.

Table 2: Comparison between asthmatic and non-asthmatic demographic, functional and inflammatory characteristics in the training cohort

	Training cohort (N=166)	
	Asthmatic (n=105)	**Non-asthmatic (n=61)**
Age (years)	52 ± 16	48 ± 17
Gender (male)	40% (42)	47% (29)
BMI (kg/m2)	27 ± 4.3	27 ± 5.5
Non-Smoker	48% (51)	59% (36)
Ex-Smoker	28% (29)	21% (13)
Smoker	24% (25)	20% (12)
Atopy	48% (50)	44% (28)
FEV1 % pred. FEV1 < 80 % pred.	86 ± 18 27% (28)	98 ± 16 **** 11% (7)
FEV1/FVC % FEV1/FVC < 75 %	76 ± 9 43% (46)	82 ± 6.7 **** 16% (10)
FeNO (ppb) FeNO (ppb) > 25	22 (15-37) 40% (42)	19 (13-27.5) * 36% (22)
Sputum eosinophils % &	1 (0-5)	0.8 (0.05-2.65)
Blood eosinophils %	2.7 (1.45-4.5)	2.1 (1.3-3.2)
Blood eosinophils (1/μL) Blood eosinophils (1/μL) > 300	190 (110-320) 26% (27)	140 (98-260) 18% (11)
Total serum IgE (KU/L)	80 (27.5-272)	42 (17-148)
Wheezing intensity score	1.48 ± 1.1	0.84 ± 1.1 ***
Dyspnea intensity score	2.09 ± 1.1	1.87 ± 1.1
Chest tightness intensity score	1.57 ± 1.2	1.52 ± 1
Airway secretion intensity score	1.28 ± 1	1.08 ± 1.1
Cough intensity score	1.63 ± 1	1.52 ± 1.1

Results are expressed as percentage (n), mean (±SD) or median (IQR). *Significant at the $p < 0.05$ level; **Significant at the $p < 0.01$ level; ***Significant at the $p < 0.001$ level; ****Significant at the $p < 0.0001$ level.

& n=57 in asthmatics and n=38 in non-asthmatics

Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; FeNO, fraction of exhaled nitric oxide.

Table 3: **Performance of each symptom intensity scale, spirometric indices and FeNO to diagnose asthma in the training cohort (n=166)**

	Threshold	AUC (95% CI)	Sensitivity (%)	Specificity (%)	P value AUC
Cough intensity score	0.5	0.53 (0.44-0.62)	88 (80-93)	20 (11-32)	0.5410
Chest tightness intensity score	2.5	0.51 (0.42-0.6)	28 (19-37)	77 (65-87)	0.8762
Dyspnea intensity score	2.5	0.56 (0.46-0.64)	38 (29-48)	69 (56-80)	0.2485
Secretion intensity score	0.5	0.56 (0.47-0.65)	75 (66-83)	34 (23-48)	0.1847
Wheezing intensity score	0.5	0.67 (0.59-0.76)	78 (69-86)	54 (41-67)	**0.0002**
FEV1 (%)	96	0.68 (0.6-0.77)	71 (62-80)	59 (46-71)	**<0.0001**
FEV1/FVC (%)	78	0.69 (0.61-0.77)	54 (44-64)	79 (66-88)	**<0.0001**
FeNO (ppb)	33	0.56 (0.47-0.66)	32 (23-43)	83 (71 -92)	0.1839

Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; FeNO, fraction of exhaled nitric oxide.

Table 4. Univariate logistic regression on the training cohort (n=166)

	OR	**OR (95% CI)**
Cough intensity score	1.10	0.81-1.49
Chest tightness intensity score	1.03	0.79-1.35
Dyspnea intensity score	1.20	0.89-1.62
Secretion intensity score	1.21	0.89-1.66
Wheezing intensity score	1.72 ***	1.26-2.40
FEV1 (%)	0.95 ****	0.93-0.97
FEV1/FVC (%)	0.90 ****	0.86-0.95
FeNO (ppb)	1.02 *	1.002-1.04

*Significant at the p < 0.05 level; **Significant at the p <0.01 level; ***Significant at the p <0.001 level; ****Significant at the p <0.0001 level.

Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; FeNO, fraction of exhaled nitric oxide; VAS, visual analogue scale.

Table 5. Multivariate logistic regression on the training cohort (n=166)

		OR (95% CI)
Model 1	Wheezing	1.72**(1.26-2.40)
Model 2	Wheezing	1.59**(1.16-2.22)
	FEV1 (%)	0.96**(0.93-0.98)
Model 3	Wheezing	1.61**(1.17-2.27)
	FEV1/FVC (%)	0.91**(0.86-0.96)
Model 4	Wheezing	1.62**(1.19-2.25)
	FeNO	1.02(0.99-1.04)
Model 5	Wheezing	1.57**(1.14-2.19)
	FEV1(%)	0.97*(0.94-0.99)
	FEV1/FVC (%)	0.94*(0.88-0.99)
Model 6	Wheezing	1.53*(1.11-2.18)
	FEV1(%)	0.95***(0.93-0.98)
	FeNO	1.02*(1.00-1.05)
Model 7	Wheezing	1.50*(1.08-2.11)
	FEV1/FVC (%)	0.91***(0.86-0.96)
	FeNO	1.01(0.99-1.03)
Model 8	Wheezing	1.48*(1.07-2.11)
	FEV1(%)	0.96*(0.94-0.99)
	FEV1/FVC (%)	0.94(0.88-1.01)
	FeNO	1.02(0.99-1.04)

*** significant at 0.001 ** significant at 0.01 * significant at 0.05

Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; FeNO, fraction of exhaled nitric oxide.

Table 6.a. Diagnostic performance of the models derived from the training cohort and applied to the training cohort (n=166)

	AUC (95% CI)	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	NPV	PPV
Model 1	0.67(0.59-0.76)	0.20	0.78(0.62-0.86)	0.54(0.35-0.67)	0.59	0.74
Model 2	0.73(0.65-0.81)	0.22	0.80(0.58-0.89)	0.59(0.41-0.71)	0.63	0.77
Model 3	0.74(0.65-0.82)	0.33	0.75(0.57-0.87)	0.62(0.44-0.74)	0.59	0.77
Model 4	0.67(0.58-0.76)	0.24	0.74(0.53-0.85)	0.58(0.36-0.71)	0.59	0.73
Model 5	0.74(0.67-0.83)	0.12	0.85(0.62-0.93)	0.57(0.41-0.69)	0.69	0.77
Model 6	0.75(0.67-0.83)	0.14	0.83(0.64-0.91)	0.59(0.34-0.71)	0.69	0.76
Model 7	0.74(0.65-0.82)	0.34	0.73(0.53-0.83)	0.64(0.42-0.76)	0.60	0.76
Model 8	**0.76(0.68-0.84)**	**0.25**	**0.77(0.54-0.85)**	**0.69(0.44-0.81)**	**0.66**	**0.80**

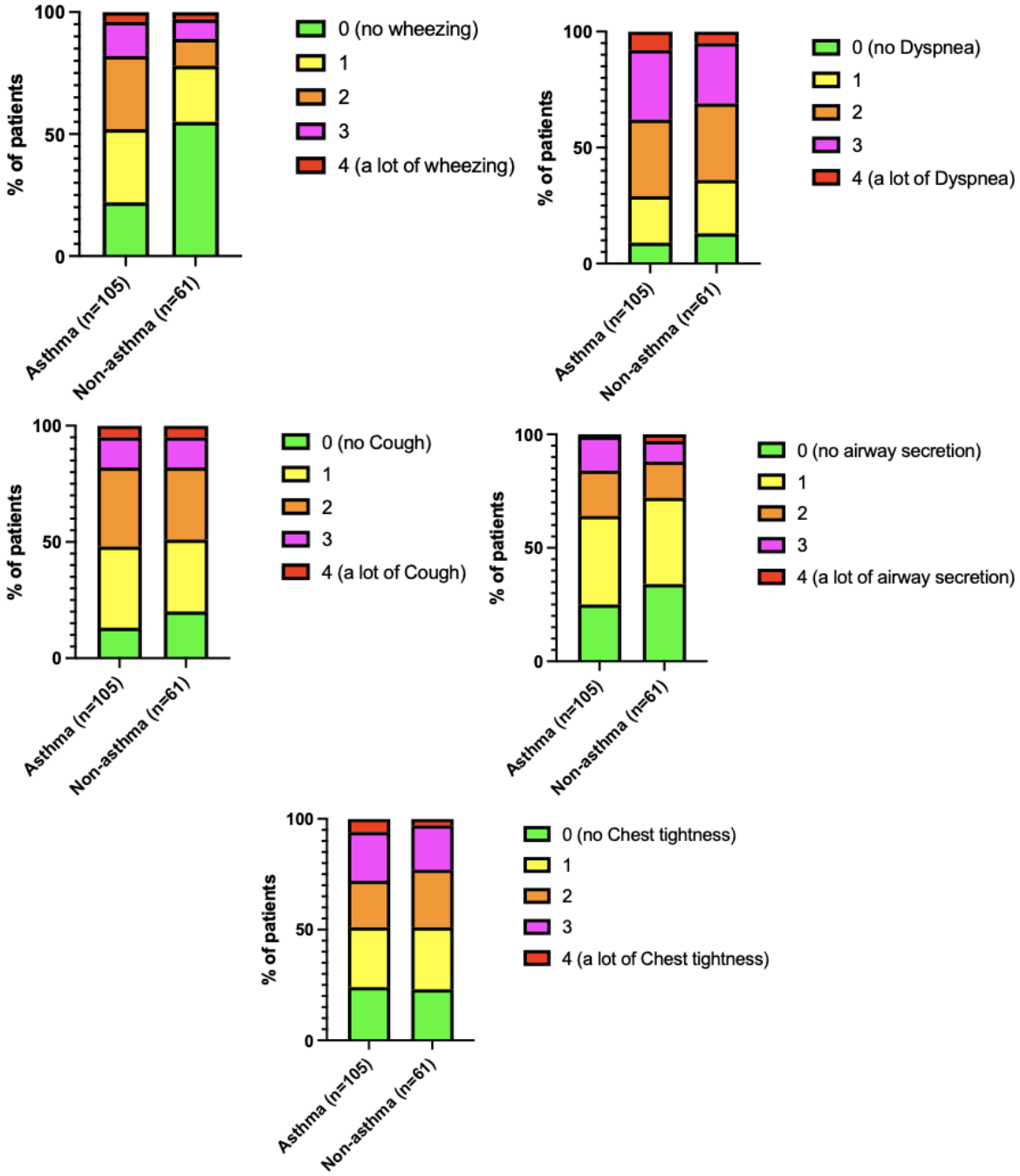
Table 6.b. Diagnostic performance of the models derived from the training cohort and applied to the validation cohort (n=137)

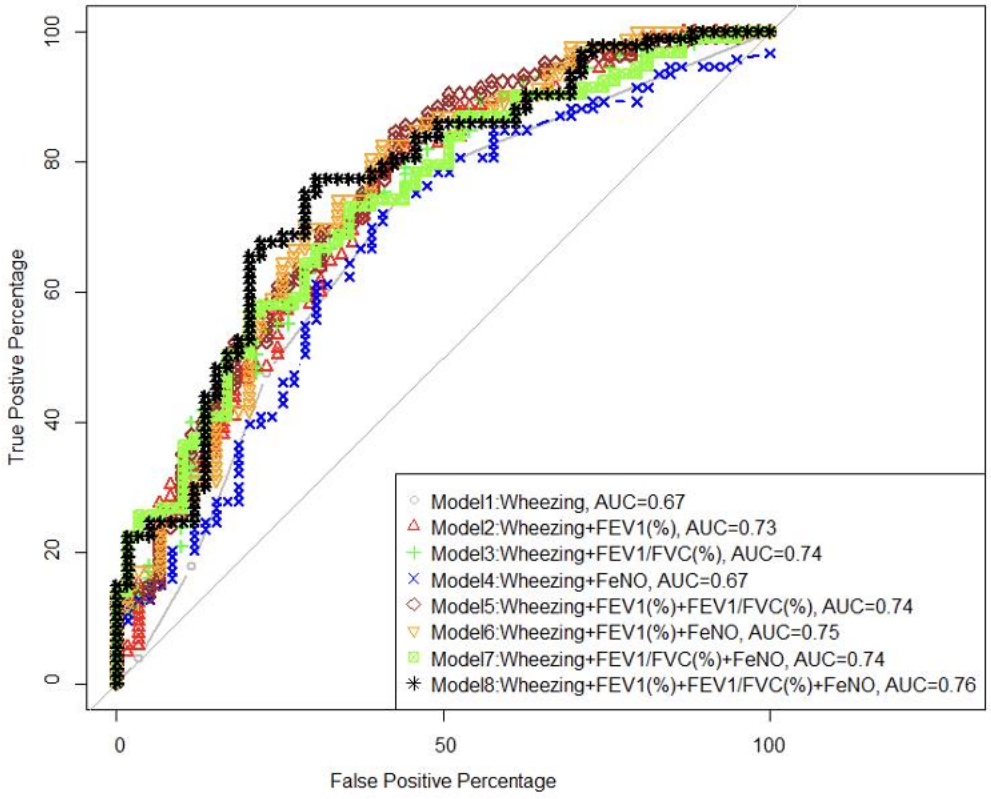
	AUC (95% CI)	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	NPV	PPV
Model 1	0.61(0.52-0.71)	0.55	0.69(0.5-0.8)	0.54(0.36-0.68)	0.55	0.67
Model 2	0.70(0.61-0.77)	0.46	0.86(0.57-0.95)	0.46(0.28-0.58)	0.70	0.69
Model 3	0.67(0.58-0.76)	0.71	0.45(0.22-0.59)	0.86(0.68-0.93)	0.53	0.82
Model 4	0.61(0.51-0.71)	0.57	0.64(0.35-0.76)	0.61(0.37-0.72)	0.57	0.68
Model 5	0.70(0.62-0.79)	0.71	0.42(0.22-0.54)	0.89(0.70-0.98)	0.52	0.85
Model 6	0.71(0.61-0.80)	0.37	0.88(0.65-0.97)	0.42(0.24-0.54)	0.74	0.66
Model 7	0.70(0.61-0.79)	0.64	0.55(0.33-0.68)	0.83(0.54-0.92)	0.59	0.81
Model 8	**0.73(0.65-0.82)**	**0.70**	**0.52(0.21-0.64)**	**0.91(0.63-0.96)**	**0.60**	**0.88**

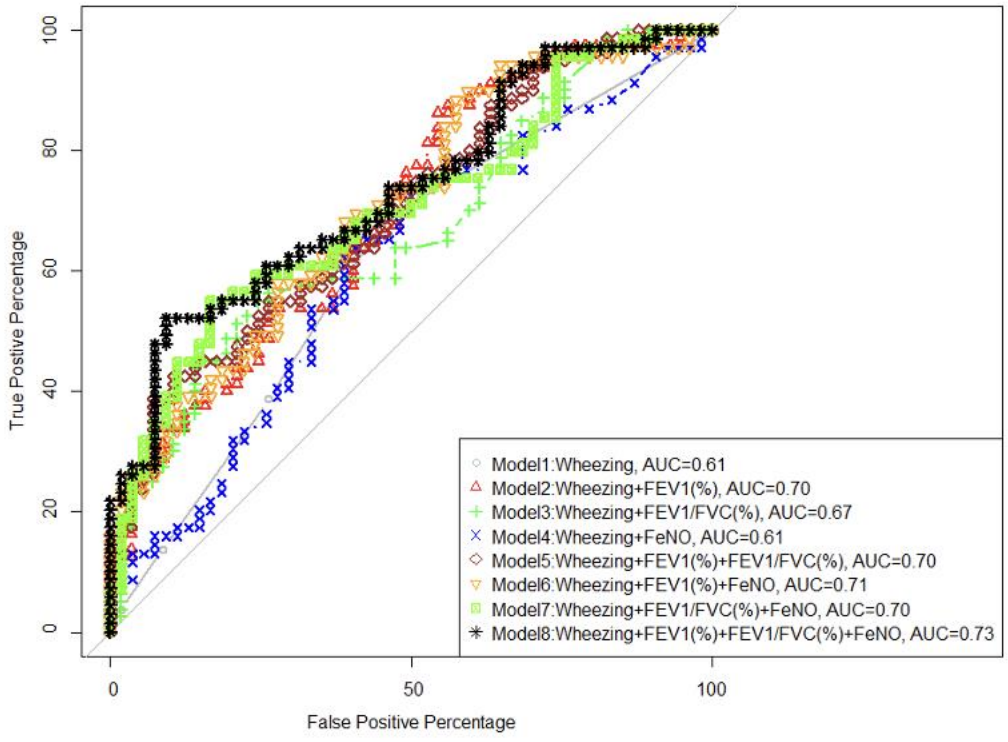
FIGURE LEGENDS

FIGURE 1: Asthma symptom intensity scales between asthmatics and non-asthmatics in the training cohort (n=166)

FIGURE 2: ROC curves showing the performance of the predictive models in the training cohort (upper panel) and in the validation cohort (lower panel). AUC-ROC, area under the receiver operating characteristics curve; FeNO: Fraction of exhaled nitric oxide; FEV1: Forced expiratory volume in 1 second; FVC: Forced vital capacity.


100
50
0
% of patients
Asthma (n=105)
Non-asthma (n=61)
0 (no wheezing)
1
2
3
4 (a lot of wheezing)
0 (no Dyspnea)
4 (a lot of Dyspnea)
0 (no Cough)
4 (a lot of Cough)
0 (no airway secretion)
4 (a lot of airway secretion)
0 (no Chest tightness)
4 (a lot of Chest tightness)


True Postive Percentage
False Positive Percentage
0
20
40
60
80
100
0
50
100
Model1:Wheezing, AUC=0.67
Model2:Wheezing+FEV1(%), AUC=0.73
Model3:Wheezing+FEV1/FVC(%), AUC=0.74
Model4:Wheezing+FeNO, AUC=0.67
Model5:Wheezing+FEV1(%)+FEV1/FVC(%), AUC=0.74
Model6:Wheezing+FEV1(%)+FeNO, AUC=0.75
Model7:Wheezing+FEV1/FVC(%)+FeNO, AUC=0.74
Model8:Wheezing+FEV1(%)+FEV1/FVC(%)+FeNO, AUC=0.76


True Postive Percentage
False Positive Percentage
0
20
40
60
80
100
0
50
100
Model1:Wheezing, AUC=0.61
Model2:Wheezing+FEV1(%), AUC=0.70
Model3:Wheezing+FEV1/FVC(%), AUC=0.67
Model4:Wheezing+FeNO, AUC=0.61
Model5:Wheezing+FEV1(%)+FEV1/FVC(%), AUC=0.70
Model6:Wheezing+FEV1(%)+FeNO, AUC=0.71
Model7:Wheezing+FEV1/FVC(%)+FeNO, AUC=0.70
Model8:Wheezing+FEV1(%)+FEV1/FVC(%)+FeNO, AUC=0.73

Supplementary Table 1: Comparison between asthmatic and non-asthmatic demographic, functional and inflammatory characteristics in the validation cohort

	Validation cohort (N=137)	
	Non-Asthmatic (n=57)	**Asthmatic (n=80)**
Age (years)	53 ± 14	50 ± 16
Gender (male)	39% (22)	35% (28)
BMI (kg/m2)	26 ± 4.5	26 ± 5.2
Non-Smoker	58% (33)	46% (37)
Ex-Smoker	31% (18)	30% (24)
Smoker	11% (6)	24% (19)
Atopy	39% (22)	48% (38)
FEV1 % pred.	101 ± 2.31	89.3 ± 1.62
FEV1 < 80 % pred.	11% (6)	20% (16)
FEV1/FVC %	81.3 ± 0.92	76.9 ± 0.09
FEV1/FVC < 75 %	17% (10)	34% (27)
FeNO (ppb)	19 (13.2-27.8)	19 (12-32)
FeNO (ppb) > 25	31% (18)	33% (26)
Sputum eosinophils % &	1.1 (0.4-2.1)	0.8 (0.2-4.4)
Blood eosinophils %	1.9 (1.02-3.2)	2.2 (1.3-2.9)
Blood eosinophils (1/μL)	160 (60-240)	160 (90-250)
Blood eosinophils (1/μL) > 300	12% (7)	18% (14)
Total serum IgE (KU/L)	75 (26.8-118)	89 (29.6-205)
Wheezing intensity score	0.82 ± 0.14	1.45 ± 0.12
Dyspnea intensity score	1.54 ± 0.15	2.24 ± 0.13
Chest tightness intensity score	1.4 ± 0.15	1.79 ± 0.12
Airway secretion intensity score	1.25 ± 0.14	1.42 ± 0.14
Cough intensity score	1.60 ± 0.15	2.04 ± 0.11

Results are expressed as percentage (n), mean (±SD) or median (IQR).

& n=57 in asthmatics and n=38 in non-asthmatics

Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; FeNO, fraction of exhaled nitric oxide.

Table S2. Multivariate logistic regression on Training data (n=166)

		OR (95% CI)
Model 1	Cough	0.747(0.49-1.13)
	Secretion	1.354(0.92-2.02)
	Oppression	0.76(0.52-1.10)
	Dyspnea	1.19(0.80-1.78)
	Wheezing	1.78**(1.23-2.63)
	FeNO	1.02(0.99-1.04)
Model 2	Cough	0.71(0.45-1.10)
	Secretion	1.36(0.91-2.06)
	Oppression	0.82(0.55-1.21)
	Dyspnea	0.99(0.64-1.52)
	Wheezing	1.77**(1.21-2.66)
	FEV1(%)	0.95***(0.93-0.98)
	FeNO	1.02*(1.00-1.04)
Model 3	Cough	0.78(0.50-1.19)
	Secretion	1.34(0.89-2.04)
	Oppression	0.82(0.55-1.19)
	Dyspnea	1.15(0.76-1.73)
	Wheezing	1.62*(1.11-2.43)
	FEV1/FVC (%)	0.91**(0.86-0.96)
	FeNO	1.01(0.99-1.04)
Model 4	Cough	0.74(0.47-1.15)
	Secretion	1.34(0.89-2.06)
	Oppression	0.85(0.57-1.24)
	Dyspnea	1.02(0.66-1.56)
	Wheezing	1.68*(1.14-2.53)
	FEV1(%)	0.96*(0.93-0.99)
	FEV1/FVC (%)	0.95(0.89-1.01)
	FeNO	1.02(0.99-1.04)

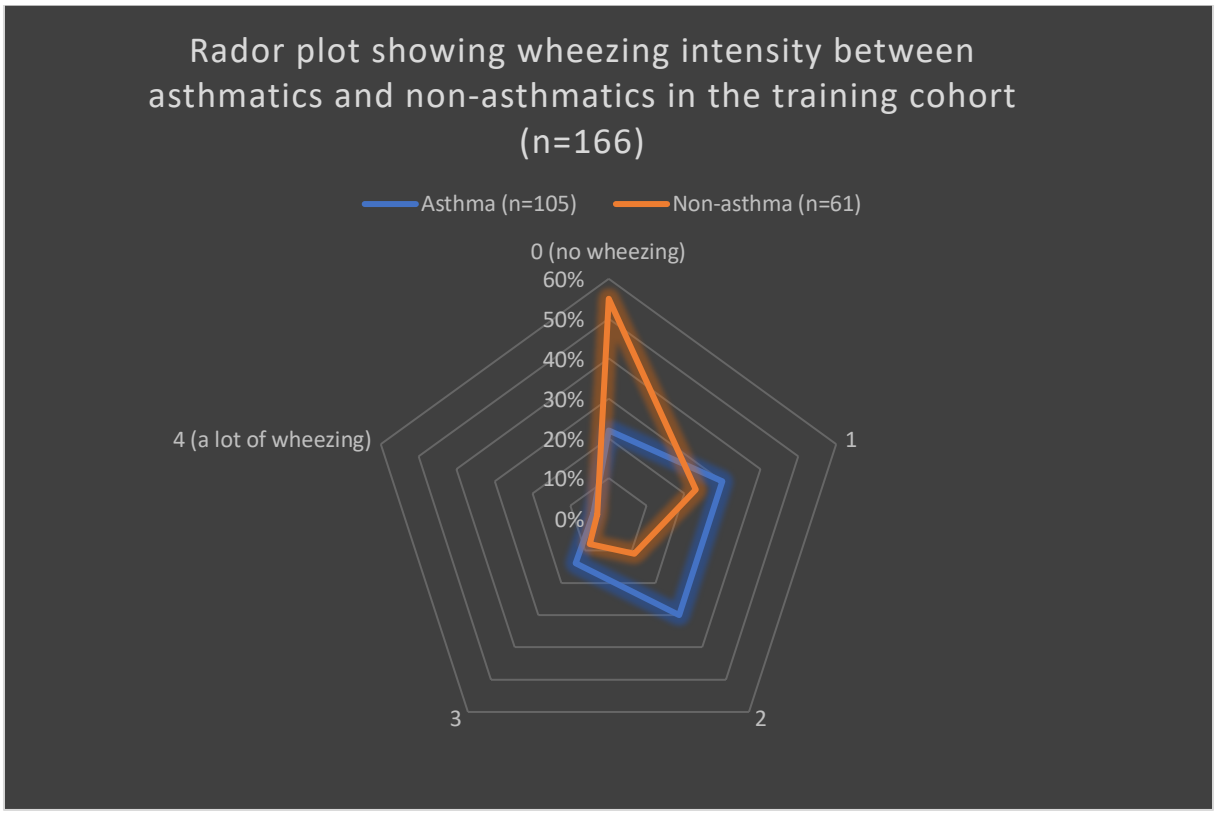
** significant at 0.01 * significant at 0.05

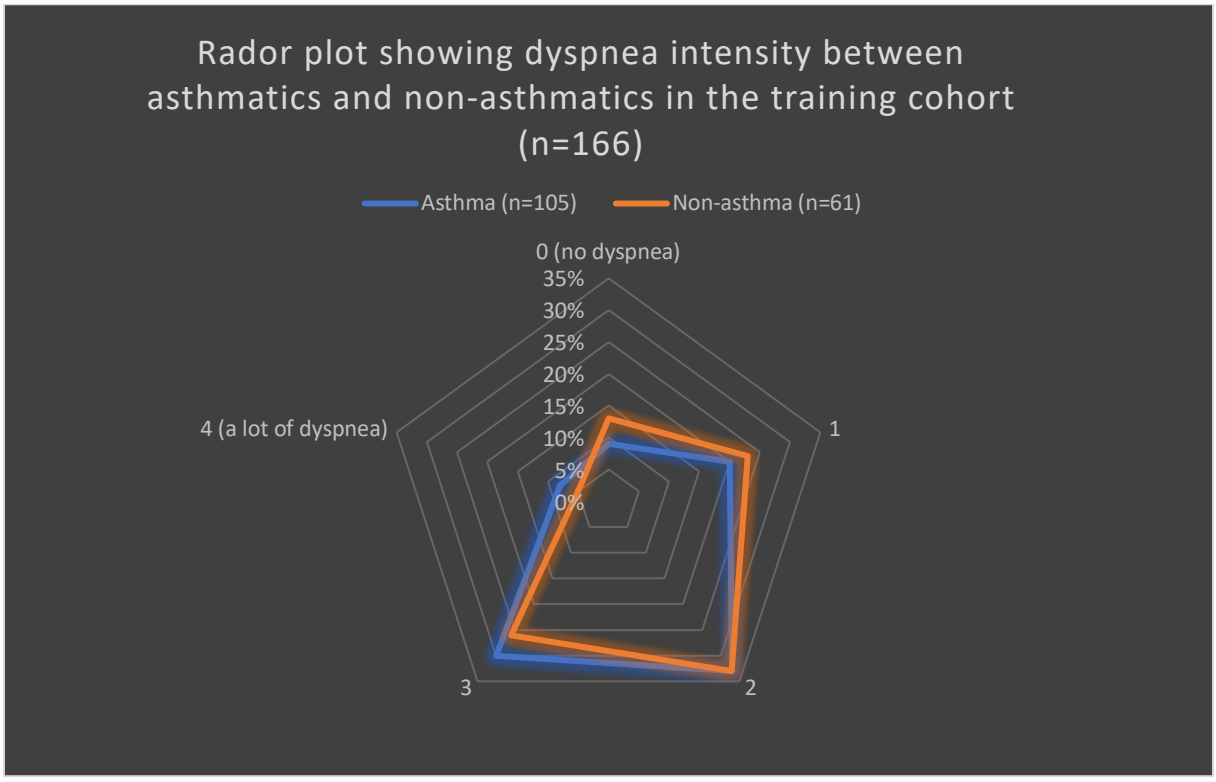
Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; FeNO, fraction of exhaled nitric oxide.

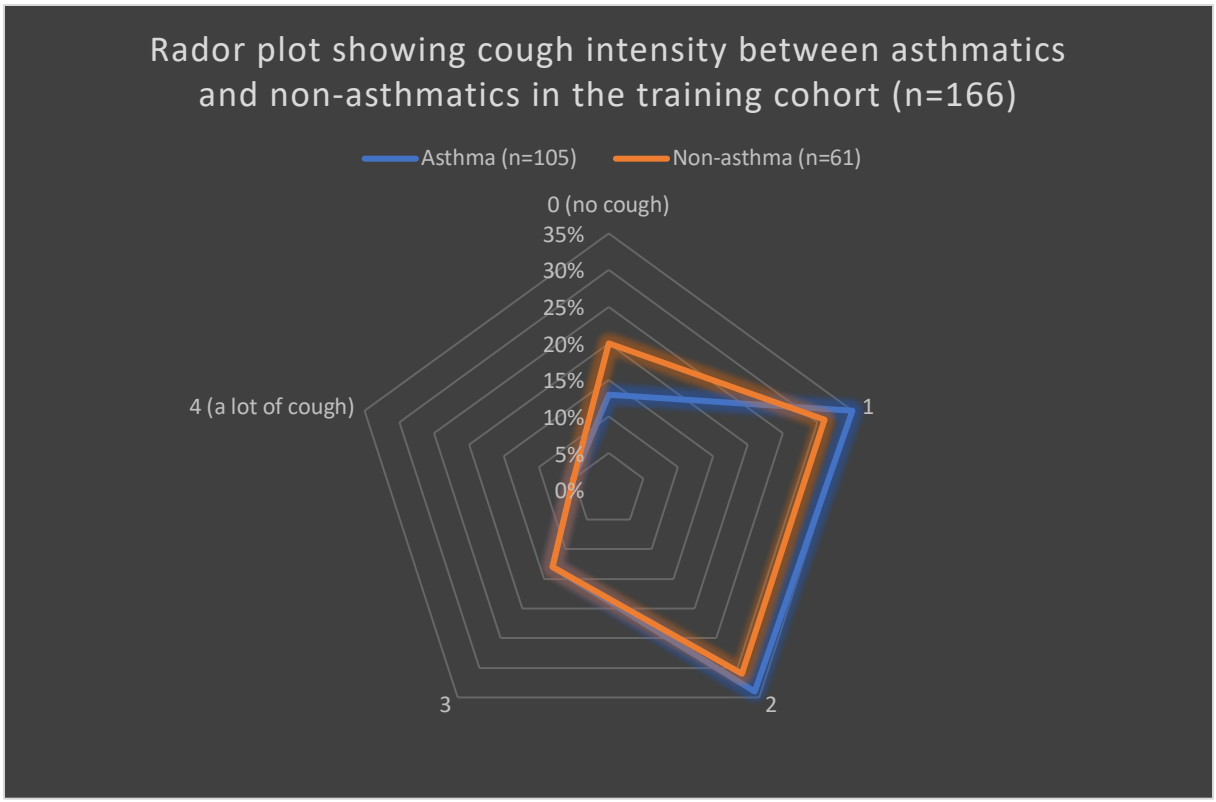
Table S3 Diagnostic performance of the models derived from the training cohort and applied to the validation cohort

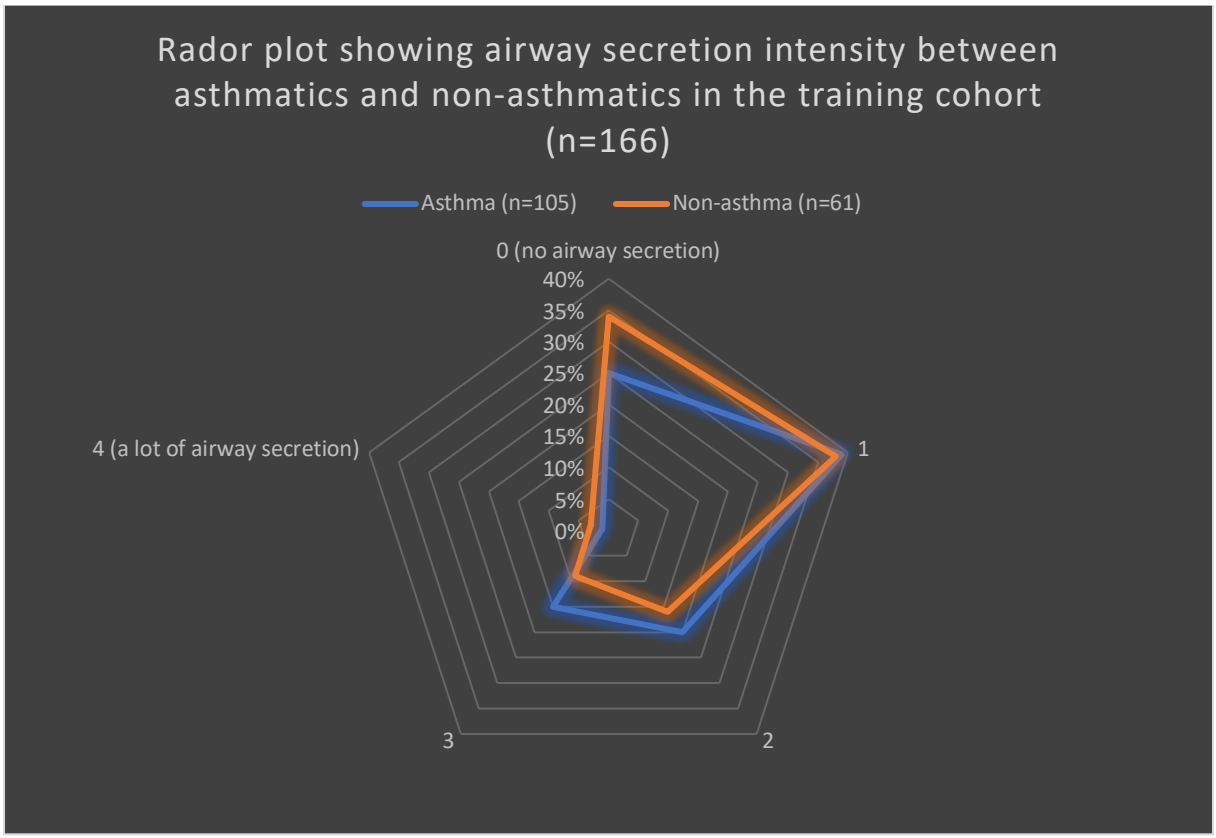
	AUC (95% CI)	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	NPV	PPV
Model 1	0.60(0.49-0.70)	0.48	0.72(0.50-0.85)	0.48(0.28-0.63)	0.56	0.65
Model 2	0.66(0.57-0.76)	0.51	0.69(0.40-0.82)	0.60(0.36-0.73)	0.59	0.69
Model 3	0.69(0.76-0.59)0.78	0.76	0.44(0.11-0.54)	0.92(0.63-0.98)	0.56	0.88
Model 4	0.69(0.60-0.79)	0.77	0.41(0.22-0.54)	0.92(0.71-0.98)	0.54	0.87

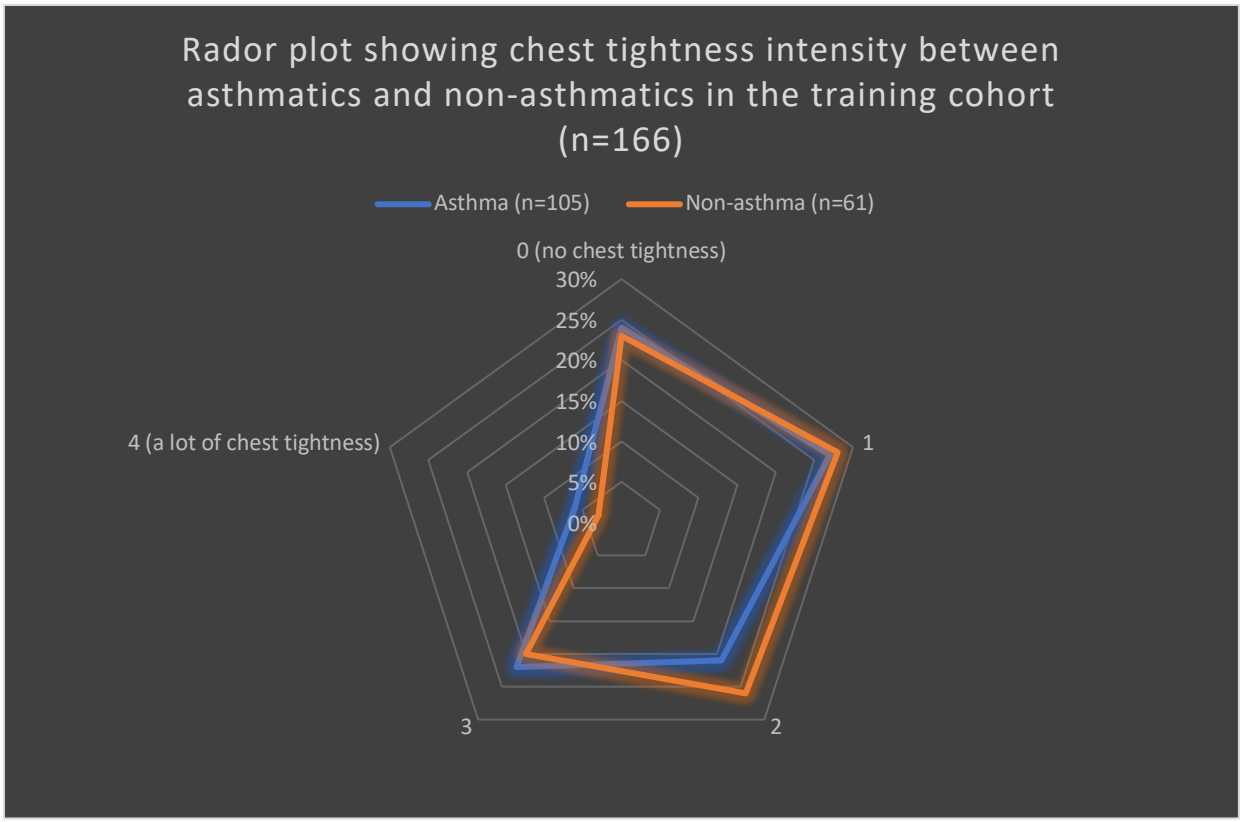
Supplementary Figure 1: Radar plots showing asthma symptom intensity scales between asthmatics and non-asthmatics in the training cohort (n=166)






Rador plot showing cough intensity between asthmatics and non-asthmatics in the training cohort (n=166)
Asthma (n=105)
Non-asthma (n=61)
0 (no cough)
1
2
3
4 (a lot of cough)
35%
30%
25%
20%
15%
10%
5%
0%


Rador plot showing airway secretion intensity between asthmatics and non-asthmatics in the training cohort (n=166)
Asthma (n=105)
Non-asthma (n=61)
0 (no airway secretion)
1
2
3
4 (a lot of airway secretion)
40%
35%
30%
25%
20%
15%
10%
5%
0%


Rador plot showing chest tightness intensity between asthmatics and non-asthmatics in the training cohort (n=166)
Asthma (n=105)
Non-asthma (n=61)
0 (no chest tightness)
30%
25%
20%
15%
10%
5%
0%
1
2
3
4 (a lot of chest tightness)