Are T² biomarkers of any help in asthma diagnosis?

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Introduction

Asthma is a common chronic airway disease, the diagnosis of which remains challenging, as recently highlighted by the great proportion of both under- and overdiagnosis. The current diagnosis is based on the conjunction of suggestive symptoms and the demonstration of an excessive airway calibre fluctuation either by a bronchodilation test or by a bronchial challenge. The majority of asthma patients encountered in daily practice are seen in primary care and are patients with mild disease. Therefore, it is of critical importance to help primary care physicians to improve diagnostic accuracy. Spirometry is essential in making the diagnosis but, unfortunately, it is not often performed in the primary care setting in most European countries. Therefore, finding a suitable biomarker to help clinicians to make a correct asthma diagnosis has been considered as a priority of future research (European Asthma Research and Innovation Partnership) in the asthma field.

Objective

Although finding a suitable biomarker to help clinicians to make a correct asthma diagnosis is of great interest, there are only a few studies that have carefully assessed the value of blood biomarkers in routine practice. However, the airway inflammatory component of asthma may be conveniently appreciated by measuring the level of nitric oxide in exhaled air (FENO). This test yields immediate results and is totally noninvasive, which makes it a perfect contender to become a key test in clinical practice. Therefore, in this study, the utility of type-2 (T²) biomarkers in diagnosing asthma along with spirometry is investigated.

Material

we conducted a retrospective study on our large database including untreated patients referred to our asthma clinic by two dedicated respiratory physicians for chronic or episodic respiratory symptoms that may suggest asthma. We identified 702 patients who were without any maintenance treatment before the investigations at our asthma clinic from October 2004 till December 2019.

Methods

The diagnosis of asthma was ascertained by lung function tests showing either significant reversibility to salbutamol (⩾12% from baseline and 200 mL) and/or bronchial hyperresponsiveness to methacholine (provocative concentration causing a 20% fall in forced expiratory volume in 1 s (FEV1) ⩽8 mg·mL−1) as recommended by the Global Initiative for Asthma. Therefore, asthma was excluded if the patient tested negative to both tests. The patients underwent a bronchodilating test, FENO measurement and blood sampling in the morning at visit 1, and a bronchial methacholine challenge 7–14 days later.

Comparison between the asthmatic and nonasthmatic groups was performed by Mann–Whitney test. Predicting values of biomarkers and spirometric indices were assessed by receiver operating characteristic (ROC) curves from which the cut-off providing the best combined sensitivity and specificity was derived, together with the 95% sensitivity and specificity thresholds. Furthermore, we performed univariate and multivariate binary logistic regression to compare the capacity of the biomarkers and the spirometric indices, alone or in combination, to predict asthma. For each considered model, the corresponding ROC curve was derived.

Results

The mean age of our patients was 51 years and 58% of our population were female. 57% were never-smokers, 24% were ex-smokers and 19% were current smokers. Median baseline FEV1 was 95% predicted. Out of the 702 patients, 349 (49.7%) were diagnosed as having asthma while 353 (50.3%) tested negative to both bronchodilating test and bronchial challenge.

Those diagnosed with asthma had a lower median (interquartile range) FEV1 (90% (79–100%) versus 100% (91–110%) predicted, p<0.001) and median FEV1/forced vital capacity (FVC) ratio (76% (70–82%) versus 81% (77–85%), p<0.001), and had a more frequent smoking history (27% and 22% ex-smokers and current smokers versus 20% and 15%, respectively).

When drawing ROC curves, blood eosinophils, IgE and FENO provided areas under the curve (AUCs) <0.6 (table 1).

The AUC for FEV1 and FEV1/FVC were slightly higher, reaching 0.67 for both the indices. None of the biomarkers nor the spirometric indices provided negative or positive predictive value >0.7 (table 1). In addition, the 95% sensitivity and specificity thresholds that can be used by the clinician to rule out or rule in an asthma diagnosis are provided in table 1. After binary logistic regression, both FENO and blood eosinophils were found to be significantly associated with asthma in all tested models (p<0.01 for both) while IgE was not. Our analysis also indicated that combining the three biomarkers did not increase the performance of the tests since the AUC remained at 0.6 (95 CI 0.56–0.64). However, when adding spirometric indices FEV1 and FEV1/FVC to T² biomarkers, the AUC of the model rose to 0.72 (95 CI 0.68–0.75) (Figure 1).

We further assessed the values of biomarkers to identify patients with eosinophilic asthma in the group of 561 patients with successful sputum induction. T² biomarkers were good at predicting eosinophilic asthma (n=104) (table 1) with an AUC rising to 0.82 (95 CI 0.78–0.86) when all three biomarkers were combined. By contrast, adding FEV1 and FEV1/FVC did not improve AUC, which remained at 0.82 (Figure 2).

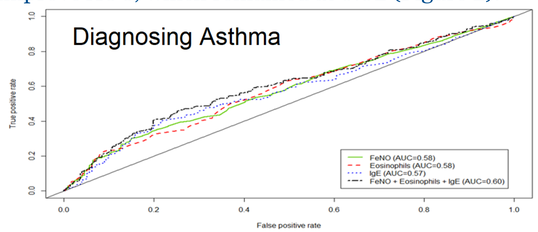

Figure 1: ROC curve for Global population (n=702)

TABLE 1 Performance of biomarkers and spirometry to diagnose asthma (upper part) and eosinophilic asthma (lower part)

	Cut-off	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	NPV	PPV	95% sensitivity	95% specificity
Global population (n=702)								
F_{ENO} ppb	36	0.58 (0.54–0.62)	0.30 (0.21–0.36)	0.85 (0.78–0.89)	0.55	0.66	6	72
IgE kU·L^{-1}	132	0.57 (0.53–0.61)	0.41 (0.32–0.46)	0.78 (0.67–0.83)	0.57	0.64	5	584
Eosinophils %	4.4	0.58 (0.54–0.62)	0.23 (0.15–0.27)	0.91 (0.83–0.94)	0.54	0.72	0.8	5.9
FEV_1 % predicted	96	0.67 (0.63–0.71)	0.66 (0.57–0.72)	0.62 (0.53–0.68)	0.65	0.63	117	67
FEV_1/FVC %	76	0.67 (0.63–0.71)	0.51(0.42–0.57)	0.76 (0.68–0.81)	0.61	0.68	88	68
Population with successful sputum induction (n=561)								
F_{ENO} ppb	31	0.76 (0.71–0.82)	0.64 (0.52–0.73)	0.80 (0.61–0.86)	0.91	0.42	10	81
IgE kU·L^{-1}	135	0.68 (0.63–0.74)	0.61 (0.47–0.68)	0.73 (0.58–0.82)	0.89	0.34	10	672
Eosinophils %	2.5	0.77 (0.72–0.81)	0.80 (0.66–0.86)	0.63 (0.52–0.69)	0.93	0.33	1.30	6
FEV_1 % predicted	90	0.60 (0.54–0.66)	0.51 (0.39–0.61)	0.66 (0.53–0.73)	0.85	0.25	120	64
FEV_1/FVC %	74	0.64 (0.58–0.70)	0.5 (0.39–0.60)	0.86 (0.62–0.82)	0.86	0.30	88	65

For the global population, 349 patients had asthma and for the population with successful sputum induction 104 had eosinophilic asthma (sputum ⩾3%). AUC: area under the curve; NPV: negative predictive value; PPV: positive predictive value; F_{ENO}: exhaled nitric oxide fraction; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

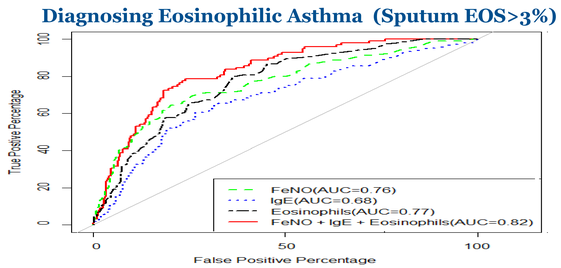

Figure 2: ROC curve for Population with successful sputum induction (n=561)

Discussion

To the best of our knowledge, our study including >700 untreated adult patients is the largest that has been reported so far. Another strength of our study is that asthma was carefully ascertained by lung function testing to confirm the diagnosis, so we are confident in our reference standard. The baseline demographics and baseline spirometric values of our population are representative of a mild asthma population, which is the most often encountered in daily practice.

Our data indicate that using T² biomarkers as index tests, either alone or in combination, fails to provide sufficient diagnostic accuracy in patients with suggestive symptoms of asthma. Overall, the T² biomarkers provided good specificity but poor sensitivity, which is in keeping with small-scale studies on IgE and blood eosinophils, and with a recent meta-analysis on FENO. This observation also supports the concept that asthma may also be a non-T² disease. Though all belonging to the so-called T² pathway, the three biomarkers we investigated have distinct regulation. It was important to investigate whether the combination of three biomarkers would improve accuracy, rather than each biomarker alone. In our study the performance of T² biomarkers, either alone or combined, was actually less than those of spirometric indices. This is not unexpected, as we can anticipate that excessive airway calibre fluctuation, which is the fundamental trait of asthma, may be more strongly related to other flow rate indices than to blood or airway inflammatory biomarkers.

Having said that, it does not deny the clinical value of measuring T² biomarkers in phenotyping asthma, once the diagnosis has been done. Indeed, there is accumulating evidence that the response to inhaled corticosteroids is dependent on the type of airway inflammation, with both sputum eosinophils and elevated FENO being predictive of good treatment responses. Here, we show that FENO and blood eosinophils both display an acceptable AUC (>0.75) with a very high negative predictive value (>0.9) to rule out eosinophilic asthma in untreated patients.

We conclude that relying on T² biomarkers to make an asthma diagnosis in patients with suggestive symptoms lacks accuracy. The demonstration of excessive airway fluctuation by using reversibility or bronchial challenge remains essential. Using T² biomarkers is an acceptable strategy to rule out eosinophilic asthma but not asthma by itself.