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2023/2024

Catarina Leça Laranjeira

Validation of the Adult Asthma Epidemiological Score: a secondary analysis of EPI-ASTHMA

fevereiro, 2024

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Validation of the Adult Asthma Epidemiological Score: a secondary analysis of EPI-ASTHMA

Mestrado Integrado em Medicina

Área: Medicina Clínica

Tipologia: Dissertação

Trabalho efetuado sob a Orientação de:

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E sob a Coorientação de:

Doutora Rita da Silva Amaral

Trabalho organizado de acordo com as normas da revista: The Journal of Allergy and Clinical Immunology: In Practice

fevereiro, 2024

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Medicina clínica

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Validation of the Adult Asthma Epidemiological Score: a secondary analysis of EPI-ASTHMA

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UC Dissertação - DECLARAÇÃO DE TRANSPARÊNCIA RELATIVAMENTE À UTILIZAÇÃO DE FERRAMENTAS DE CHATBOT GENERATIVO BASEADAS EM LARGE LANGUAGE MODELS

Eu, Catarina Leça Laranjeira, abaixo assinado, nº mecanográfico 201807492, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro que:

☒ Não procedi à utilização de ferramentas de chatbox generativo baseadas em large language models para nenhuma das tarefas no contexto do meu trabalho de Dissertação ou Monografia

☐ Procedi à utilização de ferramentas de chatbox generativo baseadas em large language modelsno contexto do meu trabalho de Dissertação ou Monografia, encontrando -se todas as interacções (prompts e respostas) transcritas em anexo bem como a indicação das aplicações utilizadas.

Neste sentido, confirmo que a eventual utilização de ferramentas de chatbox generativo baseadas em large language modelsno contexto do meu trabalho de Dissertação ou Monografia foi exclusivamente descrita na sequência de prompts e respostas transcritos em anexo e nas aplicações indicadas.

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Catarina Leça Laranjeira

Dedicatória

Aos meus pais e irmã, que sempre me apoiam e suportam nas minhas escolhas

À Dra. Cristina Jácome e à Dra. Rita Amaral, que me guiaram neste caminho e que respondem aos meus emails desesperados ao fim de semana e nas épocas festivas

A Deus, que nunca desiste de mim

"De tudo sou capaz

naquele que me dá força"

Filipenses 4, 13

Validation of the Adult Asthma Epidemiological Score: a secondary analysis of EPI-ASTHMA

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Funding: This study was sponsored and funded by AstraZeneca, Portugal

Conflict of interest: none

Abstract word count: 244

Text word count: 2826

Abstract

Background: The A2 score is an 8-question patient-reported outcome measure that has been validated for ruling in (score ≥4) and ruling out (score 0-1) asthma. However, this screening tool has been validated in a cohort similar to the derivation cohort used.

Objective: This study aims to validate the predictive accuracy of the A2 score in a primary care population against general practitioner (GP) clinical assessment and to determine whether the proposed cut-offs are the most appropriate.

Methods: This accuracy study is a secondary analysis of the EPI-ASTHMA population-based study. Random adult participants recruited from primary healthcare centers in Portugal were analyzed. Participants answered the A2 score by telephone interview. Those with an A2 score ≥1 (plus 5% with an A2 score of 0) were invited to a diagnostic visit carried out by a GP to confirm or not a diagnosis of asthma. Diagnostic accuracy was assessed using receiver operating characteristic (ROC) curves.

Results: A total of 1283 participants (median 54[p25-p75 43-66] years; 60% female) were analyzed. The A2 score showed high discriminatory power in identifying asthma, with an area under the ROC curve of 82.9(95%CI 80.4-85.4)%. The proposed cut-off ≥4 was the most appropriate to rule in asthma (specificity 83.1%, positive predictive value 62.4%, accuracy 78%). Similarly, the proposed cut-off <2 was the most suitable for excluding asthma (sensitivity 92.7%, negative predictive value 93.7%, accuracy 60.5%).

Conclusion: The A2 score is a useful tool to identify patients with asthma in a primary care population.

Resumo

Enquadramento: O A2 score é uma medida de resultado auto-reportada, que foi validade para identificar (pontuação ≥4) e excluir (pontuação de 0-1) asma. No entanto, esta ferramenta de rastreio foi validada numa coorte semelhante à coorte de derivação utilizada para o seu desenvolvimento.

Objetivo: Este estudo pretende validar a capacidade preditiva do A2 score em comparação com a avaliação clínica realizada por um médico clínico geral (CG) numa população dos cuidados primários e determinar se os pontos de corte propostos são mais adequados.

Métodos: Este estudo é uma análise secundária do estudo populacional EPI-ASTHMA. Foram analisados participantes adultos recrutados aleatoriamente em centos de saúde de Portugal. Participantes com uma pontuação no A2 score ≥1 (mais 5% com pontuação de 0) foram convidados para uma consulta de diagnóstico efetuada por um CG para confirmação do diagnóstico de asma. A acuidade do diagnóstico foi avaliada utilizando curvas ROC (receiver operating characteristic).

Resultados: Um total de 1283 participantes (mediana 54[p25-p75 43-66] anos; 60% do sexo feminino) foram analisados. O A2 score demonstrou elevado poder discriminativo para identificação de asma, com uma área sob a curva ROC de 82,9(IC95% 80,4-85,4)%. O ponto de corte proposto ≥4 foi o mais adequado para identificar asma (especificidade 83,1%, valor preditivo positivo 62,4%, precisão 78%). O valor de corte proposto <2 foi o mais adequado para excluir asma (sensibilidade 92,7%, valor preditivo negativo 93,7%, precisão 60,5%).

Conclusão: O A2 score é uma ferramenta útil para identificar doentes com asma numa população de cuidados primários.

Highlights box

What is already known about this topic? The A2 score is a self-reported asthma diagnosis questionnaire validated in a cohort extracted from the same population as the derivation one.

What does this article add to our knowledge? A2 score and its proposed cut-offs showed good discriminatory power for asthma diagnosis in a Portuguese primary care population.

How does this study impact current management guidelines? The A2 could be used in epidemiological studies as an asthma screening tool.

Key-words: asthma; epidemiology; diagnostic screening; patient-reported outcome measure

Abbreviations

ECRHS: European Community Respiratory Health Survey
GA2 LEN: Global Allergy and Asthma European Network
WHS: World Health Survey
COPD: chronic obstructive pulmonary disease
CDQ: COPD Diagnostic Questionnaire
SCSQ: COPD-screening questionnaire
PROM: patient-reported outcome measure
A2 score: Asthma Epidemiological Score
PPV: positive predictive value
NPV: negative predictive value
NHS: National Health Service
GP: general practitioner
ROC: receiver operating characteristic
AUC: area under the ROC curve
ASQ: Asthma Screening Questionnaire
CAPTURE: COPD Assessment in Primary Care to Identify Undiagnosed Respiratory Disease and Exacerbation Risk

Introduction

Asthma is a chronic disease characterized by a wide range of respiratory symptoms, such as wheezing, shortness of breath, coughing, and chest tightness, and by a variable expiratory airflow limitation, both of which vary in time and intensity.[1] This is a growing health problem that affects more than 262 million people worldwide, making it one of the most prevalent chronic diseases, which reflects a severe burden on the healthcare system.[2] The prevalence of asthma varies considerably across continents, ranging from 3.4% to 8.3%, with Europe having approximately 5.86% of the population suffering from this disease.[3]

Differences in asthma prevalence among regions are mainly due to real regional variations but may also result from using different definitions of asthma. Indeed, the definition of asthma has not been standardized for use in epidemiological studies, so each study uses a different questionnaire-based methodology, leading to varying asthma estimates and the inability to make comprehensive comparisons.[4, 5] Ideally, asthma diagnosis is based on the identification of typical symptoms and supported by the performance of lung function tests, such as spirometry with reversibility test.[1] However, this makes the diagnosis more expensive and less accessible, especially in resource-limited regions and in population-based studies.

The prevalence of asthma symptoms in epidemiological studies has been mainly measured through written questionnaires.[5] Commonly, literature reports the use of questionnaires in multinational epidemiological studies on asthma prevalence in adults, mainly the European Community Respiratory Health Survey (ECRHS).[6] The Global Allergy and Asthma European Network (GA2 LEN) also conducted a large multicenter European prevalence study using a questionnaire mostly based on the asthma definitions used in the ECRHS [7], and the World Health Survey (WHS) provides the most information on asthma prevalence in low-income countries [8]. In fact, the World Health Organization Global Alliance against Chronic Respiratory Diseases highlights the importance of the development of simple and affordable diagnostic tools for chronic respiratory diseases, which could be adapted for different realities.[9] A systematic review of the diagnostic accuracy of screening tests for chronic obstructive pulmonary disease (COPD)

129 compares the use of the COPD Diagnostic Questionnaire (CDQ) against handheld flow meters.[10]
130 Moreover, Martinez et al developed the CAPTURE (COPD Assessment in Primary Care to
131 Identify Undiagnosed Respiratory Disease and Exacerbation Risk) questionnaire to identify
132 subjects who would benefit from further diagnostic investigation.[11] In the specific context of
133 asthma, Sá Sousa et al designed and validated a patient-reported outcome measure (PROM) for
134 asthma screening, the Adult Asthma Epidemiological Score (A2 score), a short and easy-to-use
135 questionnaire.[12] This was the first self-reported questionnaire to be validated against a physician's
136 clinical assessment and diagnostic workup for identifying asthma in adults. Furthermore, it
137 showed the ability to rule in and rule out asthma, meaning that it can be applied in prevalence
138 studies as well as used as a screening tool. The cut-offs suggested – score ≥4 to rule in and scores
139 of 0-1 to rule out – were established based on positive and negative predictive values (PPV and
140 NPV, respectively), which are closely related measurements to the prevalence of asthma, so
141 further testing in epidemiological studies is needed. The A2 score showed high accuracy in a
142 validation cohort extracted from the same population of the derivation cohort.[12] However, until
143 now, no validation study applied the A2 score to another population, lacking external validation.

144 Therefore, this study aimed to validate the predictive accuracy of the A2 score against a general
145 practitioner clinical assessment and to determine whether the proposed cut-offs are the most
146 appropriate in this population.

Methods

Study design

This accuracy study is a secondary analysis of the EPI-ASTHMA population-based nationwide prevalence study (NCT05169619). Further details regarding this study can be found elsewhere.[13] We used data collected between May 2021 and September 2023 from 34 primary healthcare centers in the North, Center and Lisbon Metropolitan Area of Portugal. The study was approved by the ethics committees of the Regional Health Administration of North (CE/2022/117), Center (27/2021), and of Lisbon and Tagus Valley (2775/CES/2022) and of the Local Health Units of Matosinhos (38/CES/JAS) and Alto Minho (38/2021). All the participants provided oral informed consent during the telephone interview and latter a written informed consent during the clinical assessment visit. This study was reported according to STARD (The Standards for Reporting of Diagnostic Accuracy Studies) guidelines.

Participants

This secondary analysis included part of the patients included in the EPI-ASTHMA study. The EPI-ASTHMA study included a random sample of subjects aged ≥ 18 years who were registered in the primary care National Health Service (NHS) database and provided voluntary consent during an invitation phone call. Those with any specific physical and/or cognitive disabilities that prevented them from cooperating with the study procedures (including lung function tests) and/or understanding/answering the self-reported questionnaires were excluded.

Data collection

Participants who fulfilled the eligibility criteria were invited for a telephone screening interview performed by a centralized team of experienced interviewers. During the interview, they answered the A2 score[12]. This score includes 8 questions: about previous physician diagnosis ("Did a physician confirm you had asthma?" and "Do you still have asthma (previously diagnosed by a physician)?"; about asthma medication intake and asthma symptoms. The resulting score for each patient is the direct sum of all positive answers, ranging from 0 to 8. The original authors suggested that asthma presence could be ruled in for scores of 4 or more (PPV of 93.3%, with

99.2% specificity and 89.4% accuracy) and ruled out for scores of 0 to 1 (NPV of 98.2%, with 93.1% specificity and 89.4% accuracy).[12] Participants with an A2 score ≥1 were invited to a diagnostic visit undertaken in a mobile outpatient clinic. For quality control, ~5% of those with an A2 score of 0 were also invited. The confirmation of an asthma diagnosis was carried out by a general practitioner (GP) and was based on clinical history, physical examination, lung function tests (spirometry pre- and post-bronchodilator; fractional exhaled nitric oxide measurement), peripheral blood counts (eosinophil), and electronic PROMs (e.g., Control of Allergic Rhinitis and Asthma test).[14, 13] Subjects diagnosed with asthma were included and those without asthma were randomly selected, resulting in a final sample of ~30% with asthma and ~70% without, in each region.

Analysis

To describe the characteristics of the participants, mean and standard deviation were used for normally distributed variables, while median and interquartile range (p25-p75) were used for skewed distributions. As for categorical variables, absolute frequencies, proportions, and 95% confidence intervals (95% CI) were performed. To compare continuous variables between patients with and without asthma, t-tests for independent samples or Mann-Whitney tests were used depending on the normality of variables. To assess associations between two categorical variables, a chi-square (X^2) test was performed. Internal consistency of the A2 score was assessed by Cronbach α, which was considered adequate if ≥ 0.70 [15]. To evaluate the discriminative power of the A2 score in comparison to the physician's final diagnosis, receiver operating characteristic (ROC) curve analysis was carried out. Sensitivity, specificity, PPV, NPV, and accuracy were used as diagnostic accuracy measures. The two cut-off points were validated by analyzing the ROC curve performance, which included calculating the Youden index (sensitivity + specificity - 1)[16,17]. Additionally, we considered the combination of PPV, NPV, sensitivity, and specificity that best suited the purpose of this score for each case. Statistical analysis was performed using IBM SPSS Statistics, version 29 (IBM Corp, Armonk, NY, USA). A p-value of less than 0.05 was considered statistically significant.

Results

Participants

This secondary analysis included 1283 participants (Figure 1), with a median age (p25-p75) of 54 (43-66) years old, of which 60% were females (Table I). There were no statistically significant differences between participants with and without asthma regarding age, gender, body mass index, smoking status, or geographic region of residence ($p>0.005$) (Table I). Sample characteristics are shown in Table I.

Diagnostic accuracy of the A2 score

Participants with asthma had a A2 score median (p25-p75) significantly higher than those without asthma (5(3-6) vs 2(1-3), $p<0.001$) (Table I). Internal consistency of the A2 score was adequate (Cronbach's α 0.746). The graphic representation of the ability of the A2 score to discriminate between participants with and without asthma is shown in Figure 2. As the cut-off point increases, the A2 score becomes more sensitive and less specific, the PPV increases and the NPV decreases (Table II). Thus, the higher the score, the more likely it is to predict the asthma diagnosis, however, the higher the false positive rate.

The discriminatory capacity of the A2 score, summarized by the area under the ROC curve (AUC), was 82.9% (95% CI 80.4-85.4). The predictive power of each cut-off point is shown in Table II. The Youden index is at its highest value when the cut point is set at 3 (sensitivity 82%, specificity 69,3%, NPV 89.9%, and PPV 53.3%). This corresponds to the optimal trade-off between sensitivity and specificity. To meet the purpose of our study, a cut-off point of less than 2 positive answers (scores of 0 or 1) was chosen to exclude the presence of asthma. This cut-off point showed a high ability to select individuals who should undergo further diagnostic evaluation, and NPV of 93.7% was obtained, with high sensitivity (92.7%) and an accuracy of 60.5% (Table II). A cut-off of 4 or higher was selected as the most appropriate to rule in asthma. This cut-off had a reasonable accuracy in identifying asthma cases (78%), a PPV of 62.4%, and a specificity of 83.1% (Table II).

Discussion

This secondary analysis was the first external validation of the accuracy of the A2 score self-reported questionnaire. The A2 score showed good discriminatory power for asthma diagnosis in a Portuguese primary care population. The proposed cut-offs (scores ≥4 to rule in and scores 0-1 to rule out) were validated in this study population.

There is sparse literature on the performance of predictive scores for adult asthma. In a pilot study, the Asthma Screening Questionnaire (ASQ), an asthma screening tool, showed high sensitivity (96%) and specificity (100%) to discriminate between asthma cases and control subjects.[18] Accuracy of the A2 score could be interpreted as lower than this ASQ. However, it is important to note that the study conducted by Shin et al was based on a small sample size of 50 participants.[18] Additionally, the high accuracy reported may be attributed to the methodology used: the cases were recruited from a clinical setting so they may report more symptoms, while the controls were healthy and asymptomatic subjects, and all confounding comorbid conditions were excluded.[18] In contrast, all participants in our study were randomly recruited from primary care centers, better mimicking the performance of a screening tool in clinical practice.

Pekkanen et al used the ECRHS definitions to develop a continuous asthma score that can identify individuals for further investigation.[19] This method uses the same number of questions as the A2 score questionnaire, mainly based on symptom evaluation. However, the main difference lies in the comparator used: the ECRHS score only compares its results with bronchial hyperreactivity; while the A2 score incorporates a physician's clinical assessment that includes clinical history, physical examination, pulmonary function tests, peripheral blood counts, and PROMs. The ECRHS questionnaire was applied to the original A2 score study's data. The study reported an AUC of 86.8% (95%CI: 82.8-90.8%), a sensitivity of 87.2% (95%CI: 80.3-92.4%), and a specificity of 98.4% (95%CI: 96.7-99.3%).[12] Compared to the ECRHS questionnaire, the A2 score showed, in our sample, overlapping discrimination power (AUC 82.9%, 95%CI: 80.4-85.4%), higher sensitivity to exclude the presence of asthma (92.7%, 95%CI: 89.7%-95.1%) and low specificity to identify asthma (83.1%, 95%CI: 80.5%-85.5%).

The accuracy of A2 score is also high when compared with the accuracy of other known COPD screening tools. A systematic review found a pooled sensitivity of 64.5% (95%CI: 59.9-68.8%) and specificity of 65.2% (95%CI: 52.9-75.8%) for the CDQ.[10] In our sample, the cut-off selected to rule out asthma (scores of 0 or 1) had higher sensitivity than that reported for the CDQ (92.7% vs. 64.5% respectively), and the cut-off to rule in asthma (scores ≥4) had higher specificity (83.1% vs. 65.2% respectively).[10] The CAPTURE questionnaire had lower discrimination power than the A2 score (AUC of 79.5% vs. 82.9% respectively).[11] This case-finding questionnaire showed a sensitivity of 95.7% and a specificity of 67.8% in differentiating cases from the control subjects with no COPD.[11] Compared to the CAPTURE questionnaire's diagnostic accuracy, our validation study had slightly lower sensitivity to exclude the presence of the disease (92.7% vs. 95.7% respectively) and higher specificity to identify the presence of the disease (83.1% vs. 67.8% respectively).[11]

To select the optimal cut-off points a balance between sensitivity and specificity is necessary and should be adapted to meet the specific purposes of the score.[20] When conducting prevalence studies, it is more crucial to have a cut point with high specificity rather than sensitivity, as the focus is to rule in asthma with few false positives. However, high sensitivity is preferable when the focus is on identifying patients who are candidates for further diagnostic investigation. Therefore, we believe that a cut point with few missed cases is better suited for use as a screening tool or, in this case, to rule out asthma. For this reason, even though the cut point of 3 corresponds to the highest Youden index, we considered that a cut point of 4 or higher to rule in asthma and a cut point of less than 2 to rule out asthma as the most appropriate in our sample, validating the cut-offs proposed by the authors of this score. Moreover, they reported a specificity of 96.7% (95%CI: 94.6-98.2%) and PPV of 85% (95%CI: 76.8-90.6%) for the rule in cut-off [12], while in our sample, this cut-off showed lower specificity (83.1%, 95%CI: 80.5-85.5%) and PPV (62.4%, 95%CI: 58.5-66.1%).

According to Price et al, a PPV of at least 50% is reasonable,[21] so although the PPV found in our study is lower than that reported by Sá-Sousa et al, it is still very reasonable. For the rule out cut-

off, the authors reported a sensitivity of 85.7% (95%CI: 78.6-91.2%) and a NPV of 95% (95%CI: 92.5-96.6%).[12] In our sample, this cut-off point had overlapping sensitivity (92.7%, 95%CI: 89.7-95.1%) and NPV (93.7%, 95%CI: 91.2-95.6%). The discriminative power (AUC; 95%CI) found is slightly lower than that reported by the authors (82.9%; 80.4-85.4% and 90.4%; 87.0-93.9%, respectively). These differences in the measures of diagnostic accuracy and discriminative power may be attributed to variations in symptom prevalence and asthma severity in the specific settings, as well as differences in sample sizes. In fact, our study has a considerably larger sample size compared to the original A2 score study.

This study has strengths and limitations that should be acknowledged. The large sample size recruited from the three most populated regions of the country is an important strength. However, we did not include any participants from the primary healthcare centers of southern Portugal. This study used a sample taken only from primary care, which may limit the extrapolation of results to other settings. In future studies, researchers should validate this score in other settings.

Another strength is the fact that we excluded patients with any cognitive disability that would prevent them from understanding or answering the A2 score autonomously. However, as this eligibility screening was made during a phone call invitation, we cannot guarantee that all the participants fully understood the questions of the score, and this may have influenced the results. In addition, A2 score was applied by different healthcare professionals which may also have led to small differences in the administration of the A2 score. To overcome this limitation, an interview guide was used to standardize the procedures among the interviewers. Future studies could compare the reliability of A2 score applied as an electronic PROM and as a telephone interview.

Of note, validation against a GP clinical assessment grounded in objective measures and diagnostic tests is also a major strength. This differs from other asthma screening questionnaires, which were only validated against a physician's diagnosis,[22] or based solely on lung functional tests such as spirometry and methacholine challenge test [18].

Moreover, the choice of cut-offs was not based solely on positive and negative predictive values, but also on the ROC curve performance and the Youden index, which is a strength of this study compared to other questionnaire validation studies, including the A2 score original study. The advantage of the ROC curve analysis is that since it is based on sensitivity and specificity, it is independent of disease prevalence.[17]

Conclusions

The A2 score is a simple and easily self-administered 8-question case-finding tool that has demonstrated good discriminatory power in a large primary care population of Portugal. In this validation study, the A2 score showed good diagnostic accuracy to be used in epidemiological studies, assessing the prevalence of asthma, as well as a screening tool in clinical settings, to identify individuals who would benefit from further investigation. Future studies are necessary to validate this score in different settings and countries, and to adapt the questionnaire for use in other languages and cultural contexts.

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Figures and tables

Figure legends

FIGURE 1 – Study flow diagram (n=1283)

FIGURE 2 – Receiver operating characteristics (ROC) curve for the A2 score

—— sum of all positive answers in the questionnaire (result score)

------- reference line

The solid line indicates the levels of sensitivity and false positive rate, for each cut-off point.

The area under the ROC curve is 0.829.

TABLE I - Characterization of the population

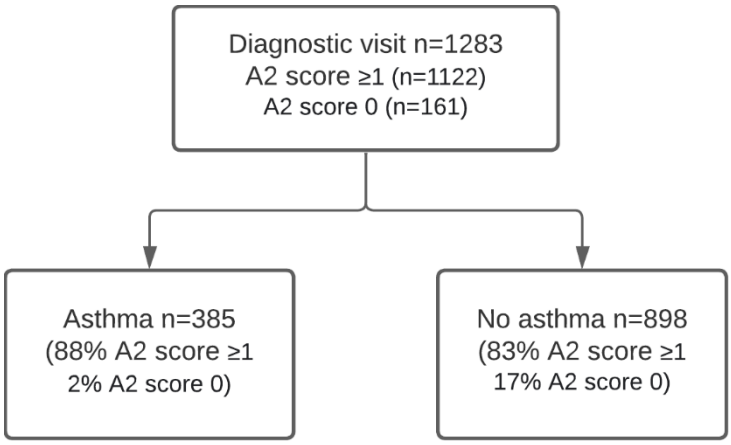
	Asthma (N=385)	No asthma (N=898)	Total (N=1283)	*p* value
Age (y), median (p25-p75)	52 (41-66)	54 (44-66)	54 (43-66)	0.074*
Female, n (%)	241 (62.6)	527 (58.7)	768 (60.0)	0.190+
BMI (kg/m^2), median (p25-p75)	27.1 (23.9-30.6)[a]	26.5 (23.9-30.1)[b]	26.7 (23.9-30.4)	0.212*
Smoking status, n (%)				0.196+
Never smoker	216 (56.1)[c]	456 (50.8)[d]	672 (52.4)	
Current smoker	72 (18.7)	198 (22.0)	270 (21.0)	
Ex smoker	96 (24.9)	241 (26.8)	337 (26.3)	
Region, n (%)				1+
North	148(38.4)	345 (38.4)	493 (38.4)	
Center	66 (17.1)	154 (17.1)	220 (17.1)	
Lisbon Metropolitan Area	171 (44.4)	399 (44.4)	570 (44.4)	
A2 score, median (p25-p75)	5 (3-6)	2 (1-3)	2 (1-4)	<0.001*

p25-p75, percentile 25 to percentile 75; BMI, body mass index; *Mann-Witney U test; +Chi-square test; [a]8 missing values; [b]17 missing values; [c]1 missing values; [d]3 missing values.

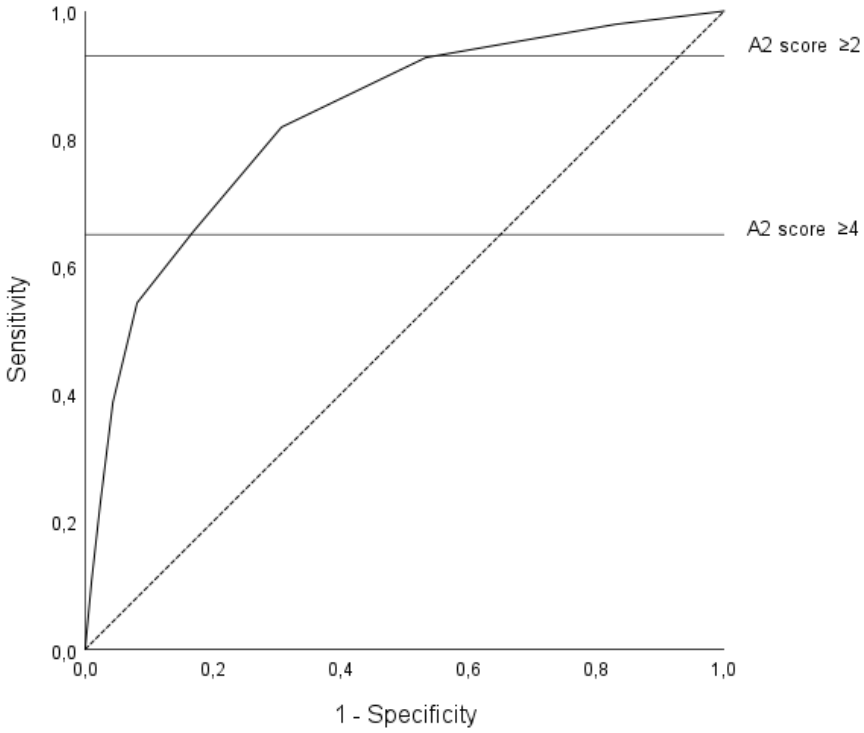
TABLE II – Diagnostic accuracy measures and predictive values

A2 score	N **(%)**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**	**PPV % (95% CI)**	**NPV % (95% CI)**
≥1	1122 (66.0)	97.9 (96.0-99.1)	17.0 (14.6-19.7)	33.6 (32.9-34.3)	95.0 (90.5-97.5)
≥2	836 (49.2)	92.7 (89.7-95.1)	46.7 (43.4-50.0)	42.7 (41.1-44.4)	93.7 (91.2-95.6)
≥3	591 (34.8)	82.0 (77.6-85.5)	69.3 (66.1-72.3)	53.3 (50.6-56.0)	89.9 (87.7-91.7)
≥4	404 (23.8)	65.5 (60.5-70.2)	83.1 (80.5-85.5)	62.4 (58.5-66.1)	84.9 (83.0-86.6)
≥5	282 (16.6)	54.3 (49.2-59.4)	91.9 (89.9-93.6)	74.1 (69.3-78.4)	82.4 (80.8-83.9)
≥6	188 (11.1)	38.7 (33.8-43.8)	95.7 (94.1-96.9)	79.3 (73.3-84.2)	78.5 (77.1-79.8)
≥7	108 (6.4)	22.6 (18.5-27.1)	97.7 (96.5-98.6)	80.6 (72.3-86.8)	74.6 (73.6-75.7)
8	50 (2.9)	10.7 (7.8-14.2)	99.0 (98.1-99.5)	82.0 (69.1-90.3)	72.1 (71.4-72.8)

Definition of abbreviations: A2 score, Adult Asthma Epidemiological Score; CI, confidence interval; PPV, predictive positive value; NPV, predictive negative value.


Diagnostic visit n=1283
A2 score ≥1 (n=1122)
A2 score 0 (n=161)
Asthma n=385
(88% A2 score ≥1
2% A2 score 0)
No asthma n=898
(83% A2 score ≥1
17% A2 score 0)

396


1,0
0,8
0,6
0,4
0,2
0,0
Sensitivity
0,0
0,2
0,4
0,6
0,8
1,0
1 - Specificity
A2 score ≥2
A2 score ≥4

397

Reporting guidelines STARD (The Standards for Reporting of Diagnostic Accuracy Studies)

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	p.2 "with an area under the ROC curve of 82.9"
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	p.2 "This accuracy study is a secondary analysis of the EPI-ASTHMA"; "methods"; "results"; "conclusions"
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	p.6 "Sá Sousa et al designed and validated a patient-reported outcome measure (PROM) for asthma screening, the Adult Asthma Epidemiological Score (A2 score) […] Furthermore, it showed the ability to rule in and rule out asthma, meaning that it can be applied in prevalence studies as well as used as a screening tool."
	4	Study objectives and hypotheses	p.6 "this study aimed to validate the predictive accuracy of the A2 score against a general practitioner clinical assessment and to determine whether the proposed cut-offs are the most appropriate in this population."
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	Not applicable. This study is a secondary analysis of the EPI-ASTHMA. p.7 "Further details regarding this study can be found elsewhere.[13]"
Participants	**6**	Eligibility criteria	p8 "Participants with an A2 score ≥1 were invited to a diagnostic visit undertaken in a mobile outpatient clinic. For quality control, ~5% of those with an A2 score of 0 were also invited."
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	p.7 "a random sample of subjects aged ≥ 18 years who were registered in the primary care National Health Service (NHS) database"
	8	Where and when potentially eligible participants were identified (setting, location and dates)	p.7 "data collected between May 2021 and September 2023 from 34 primary healthcare centers in the North, Center and Lisbon Metropolitan Area of Portugal" p.7 "during an invitation phone call."
	9	Whether participants formed a consecutive, random or convenience series	p.8 "Subjects diagnosed with asthma were included and those without

			asthma were randomly selected, resulting in a final sample of ~30% with asthma and ~70% without, in each region."
Test methods	**10a**	Index test, in sufficient detail to allow replication	Not applicable. Details about the index test can be found in the original A2 score study[12]
	10b	Reference standard, in sufficient detail to allow replication	Not applicable. This study is a secondary analysis of the EPI-ASTHMA. Details about the reference standard can be found in the study protocol.[13]
	11	Rationale for choosing the reference standard (if alternatives exist)	Not applicable. This study is a secondary analysis of the EPI-ASTHMA. Details about the reference standard can be found in the study protocol.[13]
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	p.8 "The two cut-off points were validated by analyzing the ROC curve performance, which included calculating the Youden index (sensitivity + specificity - 1)[16,17]. Additionally, we considered the combination of PPV, NPV, sensitivity, and specificity that best suited the purpose of this score for each case"
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	Not applicable. This study is a secondary analysis of the EPI-ASTHMA population-based nationwide prevalence study.
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	Not applicable. This study is a secondary analysis of the EPI-ASTHMA. Details about the reference standard can be found in the study protocol.[13]
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	Not applicable. This study is a secondary analysis of the EPI-ASTHMA. Details about the reference standard can be found in the study protocol.[13]
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	p.8 "To evaluate the discriminative power of the A2 score in comparison to the physician's final diagnosis, receiver operating characteristic (ROC) curve analysis was carried out. Sensitivity, specificity, PPV, NPV, and accuracy were used as diagnostic accuracy measures."
	15	How indeterminate index test or reference standard results were handled	Not applicable. This study is a secondary analysis of the EPI-ASTHMA population-based nationwide prevalence study.
	16	How missing data on the index test and reference standard were handled	Not applicable. This study is a secondary analysis of the EPI-ASTHMA population-based nationwide prevalence study.
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	Not applicable
	18	Intended sample size and how it was determined	Not applicable. This study is a secondary analysis of the EPI-ASTHMA. Details about the reference standard can be found in the study protocol.[13]
RESULTS			
Participants	**19**	Flow of participants, using a diagram	p.20 Figure 1

	20	Baseline demographic and clinical characteristics of participants	p.9 "This secondary analysis included 1283 participants (Figure 1), with a median age (p25-p75) of 54 (43-66) years old, of which 60% were females (Table I)." p.18 TABLE I
	21a	Distribution of severity of disease in those with the target condition	Not applicable. This study is a secondary analysis of the EPI-ASTHMA population-based nationwide prevalence study.
	21b	Distribution of alternative diagnoses in those without the target condition	Not applicable. This study is a secondary analysis of the EPI-ASTHMA population-based nationwide prevalence study.
	22	Time interval and any clinical interventions between index test and reference standard	Not applicable. This study is a secondary analysis of the EPI-ASTHMA population-based nationwide prevalence study.
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	p.19 Table II
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	p.9 "The discriminatory capacity of the A2 score, summarized by the area under the ROC curve (AUC), was 82.9% (95% CI 80.4-85.4)."
	25	Any adverse events from performing the index test or the reference standard	Not applicable. This study is a secondary analysis of the EPI-ASTHMA population-based nationwide prevalence study.
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	p.12 "This study used a sample taken only from primary care, which may limit the extrapolation of results to other settings."
	27	Implications for practice, including the intended use and clinical role of the index test	p.13 "In this validation study, the A2 score showed good diagnostic accuracy to be used in epidemiological studies, assessing the prevalence of asthma, as well as a screening tool in clinical settings, to identify individuals who would benefit from further investigation"
OTHER INFORMATION			
	28	Registration number and name of registry	p.6 "This accuracy study is a secondary analysis of the EPI-ASTHMA population-based nationwide prevalence study (NCT05169619)"
	29	Where the full study protocol can be accessed	p.6 "Further details regarding this study can be found elsewhere.[13]"
	30	Sources of funding and other support; role of funders	p.1 "This study was sponsored and funded by AstraZeneca, Portugal"

STARD 2015

AIM

STARD stands for “Standards for Reporting Diagnostic accuracy studies”. This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

Explanation

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or “2x2” table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.

Regras de formatação e normas da revista: The Journal of Allergy and Clinical Immunology: In Practice

Article types

The *Journal* will consider publication of several types of manuscripts:

A. Original articles. These articles should describe fully, but as concisely as feasible, the results of original clinical research. Original Articles should not exceed **3,500** words, not including the abstract, figure legends, and references. Each figure legend should be held to **60** words or less. Each Original Article may be accompanied by a total of no more than **8** graphic presentations (tables and/or figures).

Original Articles should include:
1. Title page. The first page of the manuscript should be a title page, containing the following items:

- A brief, clear title.
- The list of authors, including their full names, highest academic degrees, and institutional affiliations. **Please note:**
- The name, address, telephone number, and email address of the author who should be contacted regarding the manuscript *following its publication*. Note: A different author may be designated as the Corresponding Author in the submission system for the duration of the submission and review processes.
- Email addresses should be provided for all authors.
- A declaration of all sources of funding for the research reported in the manuscript. Note regarding National Institutes of Health (NIH)-sponsored research: JACI: *In Practice*'s publisher, Elsevier, facilitates author posting in connection with the posting request of the NIH (referred to as the NIH "Public Access Policy"). For more information about PubMed Central, please visit http://www.ncbi.nlm.nih.gov/pmc/about/faq/.
- Word count for the Abstract and word count for the text.

2. Abstract. The abstract should be no longer than **250** words. It should summarize the results and conclusions concisely. Tabular data should not be included and acronyms/abbreviations should be avoided or spelled out fully. Abstracts should be structured as follows:

- **Background:** What is the major problem that prompted the study?
- **Objective:** What is the purpose of the study?
- **Methods:** How was the study done?
- **Results:** What are the most important findings?
- **Conclusion:** What is the most important conclusion drawn?

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1. What is already known about this topic?
2. What does this article add to our knowledge?
3. How does this study impact current management guidelines
4. Key words. A list of up to 10 key words should follow the Highlights Box.

5. Abbreviations. Provide a list of any abbreviations/acronyms and their definitions following the key words. Only standard abbreviations are to be used. If you are uncertain whether an abbreviation is considered standard, consult *Scientific Style and Format* by the Council of Science Editors or the AMA's *Manual of Style*. A laboratory or chemical term or the name of a disease process that will be abbreviated must be spelled out at first mention, with the acronym or abbreviation following in parentheses. This policy should be followed for both the abstract and manuscript separately.

6. Text. The manuscript should be written in clear and concise English. The text should be organized into the following sections: **Introduction, Methods, Results,** and **Discussion**. Each section should begin on a new page. The generic terms for all drugs and chemicals should be used.

- In studies involving human subjects, a statement describing approval by the appropriate Institutional Review Board is required.

7. Acknowledgments. General acknowledgments for consultations, statistical analyses, and the like should be listed at the end of the text, including full names of the individuals involved. However, as noted above, acknowledgment of funding should be listed on the title page.

8. References. It is the Editors' expectation that authors will perform a comprehensive search of the literature to gather the most current articles relative to the subject matter. Guidelines for formatting references can be found below.

Basic formatting

The title page, abstract, key words, abbreviations, text, acknowledgments, references, and figure legends should be included in a single file (.doc or .docx format). Tables and their legends may be included at the end of the same file (after the reference list and figure legends, if applicable). Alternatively, tables and their legends can be loaded as a separate Tables file.

The generic terms for all drugs and chemicals should be used.

Figures should be uploaded each as separate Figure files, with the figure legends placed in the manuscript file, after the reference list. Tables can either be placed in the manuscript file, after the reference list and figure legends (if applicable), or uploaded as a separate Tables file. Please see the Artwork section for specific formatting information for Figures. Tables need to be created using Microsoft Word's Tables function, and uploaded a .doc file(s).

All sections should be double-spaced. On each page, the page number should appear in the upper right corner. Begin numbering with the title page as page 1. Be sure to display line numbers (1, 2, 3, and so forth) in the left margin of the manuscript. The line numbering should be continuous throughout the entire manuscript, from the title page through final page (i.e., do not begin numbering from 1 again at the top of each page).

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References

It is the Editors' expectation that authors will perform a comprehensive search of the literature to gather the most current articles relative to the subject matter.

References should follow "Vancouver style." See the examples below, or http://www.nlm.nih.gov/bsd/uniform_requirements.html for more information. Manuscripts in preparation, personal communications, and other unpublished information should not be cited in the reference list but may be mentioned in the text in parentheses. Citing abstracts as references is strongly discouraged. An abstract should only be included as a reference if the evidence it provides is important to the manuscript and exists nowhere else in citable form. Abstracts that are included in the reference list must be bolded so that reviewers can easily identify them and evaluate their appropriateness. The references must be identified in the text by superscript Arabic numerals and numbered in consecutive order as they are mentioned in the text. The list of references, in numeric sequence, should be typed at the end of the article. In the submitted version of the manuscript, references should not appear as footnotes or endnotes, and if you have used a program such as EndNote or Reference Manager to create them, the links between the reference numbers and the citations must be removed using the following steps:

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(3) Save. This will remove the links (permanently) without disturbing the reference numbers or the citations. It is recommended that you save one copy of your manuscript with the EndNote links in place (for your reference) and one copy of your manuscript without the EndNote links (for submission purposes).

Please note that inclusive page numbers are required. List **all** authors' names when there are six or fewer; when there are seven or more, list the first **six** before adding "et al."

When selecting a title for your paper

Please consider the following guidelines:
• Keep the title succinct: Limit it to 12 words or fewer.
• Communicate a single subject or idea in the title.
• Construct the title around the article's key words.
• Include the specific symptom, condition, intervention, mechanism, or function of the paper's central focus.
• Mention any defining population, age, or gender that distinguishes the work.
• Use terms that are specific rather than general (e.g., "penicillin" rather than "betalactam antibiotic") and include terms that clarify (e.g., "CXCR4" rather than "chemokine receptors").
• Avoid using strong words (such as "robust," "innovative," "significant," "vigorous," and "aggressive"), as they may suggest exaggerated or unwarranted claims.
• Use wit carefully and appropriately; be informative first and clever second. Although a universally understood pun can work well to attract interest, ensure that it will not confuse or mislead the reader.
• The titles of papers accepted for publication in the *Journal of Allergy and Clinical Immunology: In Practice* may be revised for improved clarity and appeal to the readership. Such revision will have final approval by the authors.

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The total number of graphic presentations (tables and/or figures) per manuscript should comply with the limits for the manuscript's Article Type; requests to include additional graphics must be approved by the Editors.

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General points
• Make sure you use uniform lettering and sizing of your original artwork.
• Preferred fonts: Arial (or Helvetica), Times New Roman (or Times), Symbol, Courier.
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• Use a logical naming convention for your artwork files.
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Figure legends should be listed in the manuscript file, on a separate page after the tables. They should not appear in the figure files. The figure legend will be included when sizing the figure and its length must therefore be taken into consideration. The figure title should appear at the beginning of each legend. The legends themselves should be succinct (no more than 60 words), identifying the data or subject being presented, but not explaining methods or results.

Tables

If tables appear in the manuscript, they must be included in the electronic submission. They may be placed within the manuscript file or loaded as separate files (in .doc or .docx format). Tables should supplement, not duplicate, the text; they should be on separate pages, one table per page, and should be numbered with Roman numerals in order of mention. A brief title should be provided directly above each table. Any abbreviations should be defined at the bottom of the table. When creating a table, use the wordprocessing program's table formatting feature; otherwise, use only tabs (not spaces) to align columns.