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USING DIFFERENT DATA SOURCES FOR THE IDENTIFICATION OF ASTHMA PATIENTS AND THOSE AT HIGH RISK OF ADVERSE OUTCOMES

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Using different data sources for the identification of asthma patients and those at high risk of adverse outcomes

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Paper I

Sá-Sousa A, Pereira AM, Almeida R, Araujo L, Couto M, Jacinto T, et al. **Adult Asthma Scores-Development and Validation of Multivariable Scores to Identify Asthma in Surveys.** J Allergy Clin Immunol Pract. 2019 Jan; 7(1):183–190.e6.

Paper II

Sá-Sousa A, Almeida R, Vicente R, Martins H, Freitas A, Fonseca JA. **High oral corticosteroid exposure and overuse of short-acting beta-2-agonists were associated with insufficient prescribing of controller medication: a nationwide electronic prescribing and dispensing database analysis** (Submitted)

Paper III

Sá Sousa A, Pereira AM, Fonseca JA, Azevedo LF, Abreu C, Arrobas A, et al. **Asthma control and exacerbations in patients with severe asthma treated with omalizumab in Portugal.** Rev Port Pneumol. 2015; 21(6):327–33.

Paper IV

Sá-Sousa A, Fonseca JA, Pereira AM, Ferreira A, Arrobas A, Mendes A, et al. **The Portuguese Severe Asthma Registry: Development, Features, and Data Sharing Policies.** Biomed Res Int. 2018; Article ID 1495039.

Book Chapter

Sá-Sousa A, Fonseca JA. **Chapter 1 - Concept and Epidemiology.** In: Severe Asthma, ed Drummond M, Cordeiro CR, Neuparth N. Permanyer Portugal, pages 1-16 ISBN: 978-84-17221-78-2

What is already known about this topic?

Estimates obtained in surveys are highly dependent on the set of questions used for the operational definition of asthma. The identification of asthma patients in epidemiological studies and screening settings is still an issue.

Asthma patients with the recurrent use of OCS and over-use of SABA and with severe asthma are at risk of adverse outcomes and asthma-related death. Patients at risk should be identified, and flagged for frequent clinical review.

Patients with severe asthma represent only a small proportion of those with asthma, however, they account for a large proportion of asthma-related morbidity and health care expenditures. Improve data on severe asthma identification and characterization may contribute to a better understanding of the etiology, burden and management patterns of severe asthma.

What does this research project adds to our knowledge?

Two short, easy, self-reported scores, with very good properties to rule in/rule out asthma were developed.

In Portugal, exposure to high-dose of OCS and SABA over-use were frequent, and were associated insufficient prescription of maintenance treatment.

A real-life prospective study on Portuguese patients with severe persistent allergic asthma showed that these patients had frequent exacerbations. From this initial study, the necessity for a tool to improve severe asthma data became apparent, leading to the successful development and implementation of the Portuguese Severe Asthma Registry.

How does this research project impact current asthma management?

The provided validated screening tools can be used to identify asthma patients in asthma surveys and clinical screening/triage settings.

The national prescribing database is useful for the identification of patients at risk and provides evidence to support initiatives to reduce OCS and SABA inappropriate prescribing.

The Portuguese Severe Asthma Registry is a national web-based disease registry of severe asthma patients, available at *asmagrave.pt*. It includes an automatic feature for identification of severe asthma, allows prospective clinical data collection, and collaborative clinical research.

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ABSTRACT

Background

The identification of asthma patients and of those at risk of adverse outcomes and asthma-related death is of utmost importance for defining evidence-based healthcare policies. However, the prevalence estimates obtained from self-reported questionnaires are highly dependent on the operational definition of asthma used and asthma screening questionnaires are still lacking. Also, there is a paucity of data from patients at risk of adverse outcomes and of asthma-related death. These include patients with severe asthma and those with mild/moderate asthma with recurrent use of oral corticosteroids (OCS) and over-use of short-acting beta-2-agonists (SABA). The use of different data sources such as national surveys, prescription data and disease registries can be efficient to provide the much-needed real-world evidence.

Objectives

The main objective of this thesis was to improve the identification of patients with asthma and of those at high-risk of adverse asthma outcomes, including patients with severe asthma, using different data sources. Specifically, we aim 1) to develop and validate multivariable scores for adult asthma identification; 2) to quantify respiratory patients with high OCS exposure or with SABA over-use in Portugal; and 3) to improve the identification and characterization of severe asthma patients with poor outcomes.

Methods

For this purpose, we used three different data sources.

1) Data from a nationwide population-based study, were used to develop adult asthma identification scores. The predictors were self- administered questions identified in a literature review (the Adult Asthma Epidemiological Score - A2 score) and from the Global Allergy and Asthma Network of Excellence (GA2LEN) questionnaire (the GA2LEN score). These were compared with asthma diagnosed by a physician after clinical examination and diagnostic tests.

2) Data from the national electronic prescription and dispensing database (BDNP) was retrieved. A one-year data from random sample of adult patients was analyzed and high OCS exposure (≥1600mg of prednisolone/year) in patients on persistent respiratory treatment (PRT) and SABA over-use (>1 canister of 200x100μg of salbutamol /month) were assessed.

3) Data of severe asthma patients under treatment with omalizumab was collected at routine care over a 12-month period in an observational, prospective, multicentre study. Asthma outcomes were assessed for these patients.

Finally, through a multistep consensus process supported by an open collaborative network of asthma specialists, the Portuguese Severe Asthma Registry (RAG) was developed and implemented.

Main findings

Two multivariate scores were developed for the identification of adult asthma. The A2 score and the GA2LEN score comprises 8 and 6 questions, respectively. The scoring is the sum of positive answers. The scores have high level of discrimination and asthma is present (ruled in) for scores of 4 or more and is excluded (ruled out) for A2 scores of 0 to 1 or a GA2LEN score of 0.

Secondary data analysis showed that 125 per 100,000 respiratory patients had dispensed asthma medication that indicated a high risk of adverse outcomes – 101 per 100,000 patients were exposed to a high-dose of OCS and 24 per 100,000 were SABA over-users – additionally, 144 per 100,000 were SABA excessive users. About 1/6 of SABA over-users were not prescribed any controller medication. High OCS exposure or SABA over-use were not associated with primary adherence to controller medication but high OCS exposure was associated with a maintenance-to-total medication ratio <70%, age >45 years old and male sex. Noteworthy, 44% of the patients exposed to a high dose of OCS were on a triple or quadruple combination of controller medication, associated with step 4/5 of treatment for asthma.

Severe asthma patients under treatment with omalizumab had their asthma controlled in 1/3 of the visits and the 12-month exacerbation rate was 1.7 per patient. One-third of the patients needed unscheduled medical care because of asthma and 29% had to start or increase OCS. The lack of data limited the proper assessment of the treatment efficacy, supporting the need for a severe asthma registry.

The RAG is a national web-based disease registry of severe asthma patients, available at *asmagrave.pt*. RAG collects data from adults and paediatric severe asthma patients. Features of RAG include automatic identification of severe asthma, easy data input, and exportable data that can be pasted directly in patients' electronic health record and security features to enable data sharing.

Discussion and conclusions

The developed scores are very simple, can be used to rule in/ rule out asthma and contribute to reducing the inconsistencies of definitions of asthma in epidemiological studies. They may also be proven useful in clinical screening/triage settings to identify patients with asthma and the best candidates for a diagnostic workup.

Electronic prescription records could be used to identify patients at risk. In the BDNP a high-dose of OCS and SABA over-use were identified in a considerable proportion of patients and were associated with insufficient prescribing of controller medication. These results suggest there is a need for initiatives to reduce OCS and SABA inappropriate prescribing.

Within the first national effort of standardizing outcome assessment, the Portuguese patients with severe asthma had frequent exacerbations and poor asthma control.

Patients with asthma may now be identified by validated scores and the identification of those at high-risk of adverse asthma outcomes may be achieved by the analysis of electronic prescription records. However, the need for a better identification and characterization of severe asthma patients in order to provide adequate care, became apparent and led to the successful development of the RAG. This includes an automatic feature for identification of severe asthma, enables prospective clinical data collection, and collaborative clinical research.

RESUMO

Introdução

A identificação de doentes com asma e doentes em risco de resultados adversos e morte relacionada com a asma é de extrema importância para a definição de políticas de saúde baseadas na evidência. No entanto, as estimativas de prevalência, obtidas a partir de questionários de autopreenchimento, variam dependendo da definição operacional de asma utilizada e ainda não existem questionários estandardizados de triagem para a asma. Por outro lado, há uma escassez de dados de doentes em risco de resultados adversos e de morte relacionada com a asma. Estes incluem doentes com asma grave e aqueles com asma ligeira/moderada com uso recorrente de corticosteroides orais (OCS) e sobre-utilização de beta-2-agonistas de curta duração (SABA). O uso de diferentes fontes de dados, como estudos nacionais, dados de prescrição e registos de doenças podem ser ferramentas eficientes para fornecer a tão necessária evidência baseada no mundo-real.

Objetivos

O objetivo principal desta tese foi melhorar a identificação de doentes com asma e nestes os em risco elevado de resultados clínicos adversos, incluindo doentes com asma grave, utilizando diferentes fontes de dados. Especificamente, pretendemos 1) desenvolver e validar escalas multivariadas para identificação de asma em adultos; 2) quantificar doentes respiratórios expostos a doses elevadas de OCS e com sobre-utilização de SABA em Portugal; e 3) melhorar a identificação e caracterização de doentes com asma grave com resultados desfavoráveis.

Métodos

Com este objetivo, foram usadas três fontes de dados diferentes.

1) Dados de um estudo nacional com base na população, foram usados para desenvolver escalas para identificação de asma em adultos. Os preditores foram questões de autopreenchimento identificadas numa revisão da literatura (a escala de asma em adultos - Escala A2) e do questionário da *Global Allergy and Asthma Network of Excellence* (GA2LEN) (a escala GA2LEN). Estes foram comparados com asma diagnosticada por um médico especialista após o exame clínico estruturado e testes de diagnóstico.

2) Dados provenientes da Base de Dados Nacional de Prescrição e dispensa (BDNP) foram obtidos. Numa análise retrospetiva de um ano de uma amostra aleatória de adultos, foi estudada a exposição a doses elevadas de OCS (≥1600mg de prednisolona / ano) em doentes em tratamento respiratório persistente (PRT) e a sobre-utilização de SABA (>1 embalagem de 200x100g de salbutamol / mês).

3) Dados de doentes com asma grave em tratamento com omalizumab foram colhidos em consulta de rotina durante um período de 12 meses, num estudo observacional, prospetivo, multicêntrico. Os resultados clínicos relacionados com asma foram analisados nestes doentes.

Finalmente, através de um processo de consenso em várias etapas, apoiado por uma rede colaborativa de especialistas em asma grave, o Registo Português de Asma Grave (RAG) foi desenvolvido e implementado.

Principais resultados

Foram desenvolvidas duas escalas multivariadas para identificação de asma em adultos. A escala A2 e a escala GA2LEN consistem em 8 e 6 questões, respetivamente. A pontuação é a soma das respostas positivas. Os modelos têm alto nível de discriminação e a asma está presente (*rule in*) para somas de 4 ou mais e é excluída (*rule out*) para somas A2 de 0 a 1 na escala A2 ou de 0 para a escala GA2LEN.

A análise de dados secundários mostrou que 125 por 100.000 doentes respiratórios dispensaram medicação para asma indicativa de risco elevado de resultados clínicos adversos - 101 por 100.000 doentes foram expostos a uma dose elevada de OCS e 24 por 100.000 eram sobre-utilizadores de SABA – adicionalmente, 144 por 100.000 usavam SABA excessivamente. Cerca de 1/6 dos sobre-utilizadores de SABA não receberam qualquer medicação de controlo. A exposição a doses elevadas de OCS ou a sobre-utilização SABA não estavam associados à adesão primária da medicação de controlo. No entanto, a exposição a doses elevadas de OCS foi associada com uma proporção de medicação de manutenção-para-total <70%, idade > 45 anos e sexo masculino. Digno de nota, 44% dos doentes expostos a uma dose elevada de OCS estavam medicados para combinações triplas ou quadruplas de medicação de controlo, associada a degrau 4/5 de tratamento para a asma.

Doentes com asma grave em tratamento com omalizumab, tinham a sua asma controlada em 1/3 das visitas e a taxa de exacerbação aos 12 meses foi de 1,7 por doente. Um terço dos doentes necessitou de assistência médica não programada por causa da asma e 29% tiveram que iniciar ou aumentar o OCS. A falta de dados limitou a avaliçaõ de eficácia do tratamento, suportando a necessidade de um registo de asma grave.

O RAG é um registo nacional de doentes com asma grave, disponível em *asmagrave.pt*. RAG recolhe dados de doentes adultos e em idade pediátrica com asma grave. Os recursos do RAG incluem classificação

automática da gravidade da asma, introdução facilitada de dados, exportação de dados que podem ser copiados diretamente nos registros eletrónicos de saúde e recursos de segurança dos doentes para permitir a partilha de dados.

Discussão e Conclusões

As escalas desenvolvidas são simples, podem ser usadas para identificar ou excluir a presença de asma e contribuem para reduzir as inconsistências nas definições de asma em estudos epidemiológicos. As escalas poderão vir a ser úteis em contexto de triagem clínica para identificar doentes com asma e os melhores candidatos para um estudo diagnóstico.

Os registos eletrónicos de prescrições puderam ser usados para a identificação de doentes em risco. Na BDNP a frequente exposição a doses elevadas de OCS e a sobre-utilização de SABA foram identificadas numa proporção considerável de doentes e foi observada a sua associação com a prescrição insuficiente de medicação de manutenção. Estes resultados sugerem que há necessidade de iniciativas para reduzir a prescrição inadequada de OCS e SABA.

No primeiro esforço nacional de padronização da avaliação de resultados, os doentes portugueses com asma grave tiveram exacerbações frequentes e mau controlo da asma.

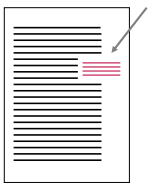
Os doentes com asma podem agora ser identificados através de escalas validadas e a identificação de doentes em risco elevado de resultados clínicos adversos pode ser feita pela análise de registos eletrónicos de prescrição. No entanto, a necessidade de melhor identificar e caracterizar doentes com asma grave de forma a fornecer cuidados de saúde adequados, tornou-se evidente e levou ao desenvolvimento com sucesso do RAG. Este inclui um recurso automático para identificação de asma grave, permite a colheita prospetiva de dados e a investigação clínica colaborativa.

ABBREVIATIONS

A2 Score	Adult Asthma Epidemiological Score
BDNP	Portuguese electronic prescription and dispensing database
BMI	Body Mass Index
CARAT	Control of Allergic Rhinitis and Asthma Test
COPD	Chronic Obstructive Pulmonary Disease
ECRHS	European Community Respiratory Health Survey
ENFUMOSA	European Network For Understanding Mechanisms Of Severe Asthma
ERS/ATS	European Respiratory Society and American Thoracic Society
GA2LEN	Global Allergy and Asthma European Network
GA2LEN Score	GA2LEN Asthma Epidemiological Score
GDPR	General Data Protection Regulation
GINA	Global Initiative for Asthma
ICAR	Control and Burden of Asthma and Rhinitis
ICS	Inhaled corticosteroids
IgE	Immunoglobulin E
IL	Interleukin
INAsma	Portuguese National Asthma Survey
ISAAC	International Study of Asthma and Allergies in Childhood
ISAAC	International Study of Asthma and Allergies in Childhood
LABA	Long-Acting Beta2-Agonists
LAMA	Long-Acting Muscarinic Antagonists
LTRA	Leukotriene Receptor Antagonists
mini-AQLQ	Mini Asthma Quality of Life Questionnaire
NRAD	United Kingdom National Review of Asthma Deaths
OCS	Oral corticosteroids
RAG	Registo de Asma Grave Portugal
REAG	Rede de Especialistas em Asma Grave
SABA	Short-Acting Beta2-Agonists
SAMA	Short-Acting Muscarinic Antagonists
SARP	Severe Asthma Research Program
SPMS	Shared Services of the Ministry of Health
TENOR	The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens
U-BIOPRED	Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes
WHOQOL-BREF	World Health Organization's Quality of Life
95% CI	95% Confidence Interval
AUC	Area Under the Curve
med	Median
OR	Odds Ratio
NPV	Negative Predictive Value
P25-P75	Percentiles 25- 75
PPV	Positive Predictive Value
ROC	Receiver-Operating Characteristic

INTRODUCTION

This chapter will introduce the topic of the thesis. An overview of chronic respiratory diseases will be presented with special focus on the impact of asthma definition on asthma estimates. The second part presents a framework of the impact of oral corticosteroids exposure, short-acting beta2-agonists over-use and severe asthma, as high-risk factors for asthma-related adverse clinical outcomes.



Text boxes in different color were placed throughout this section, summarizing the main points enclosed in the Introduction.

I1 Chronic respiratory diseases

Chronic respiratory diseases represent a wide variety of chronic diseases of the airways and other structures of the lungs (Bousquet et al., 2007) (**Figure 1**). These include obstructive lung diseases, such as asthma and chronic obstructive pulmonary disease (COPD), which represent high morbidity and mortality. The availability of inflammatory markers, including blood eosinophils and Fractional exhaled Nitric Oxide (FeNO), and of novel therapies targeting very specific immune pathways are seen as opportunities to gain knowledge on the pathophysiology of these diseases. Real-life studies provide evidence that asthma and COPD share clinical, physiological and immunological features (Porsbjerg et al., 2018). Supporting the concept of "one airway, one disease", an unsupervised approach to Portuguese data, shown the importance of nasal and ocular symptoms along with bronchial symptoms for the classification of phenotypes of allergic respiratory diseases (Amaral, Bousquet, et al., 2018). In face of the rapidly expanding insight of common features shared by chronic respiratory diseases, an approach to deconstruct airway disease into identifiable and treatable traits has been proposed (Pavord et al., 2017).

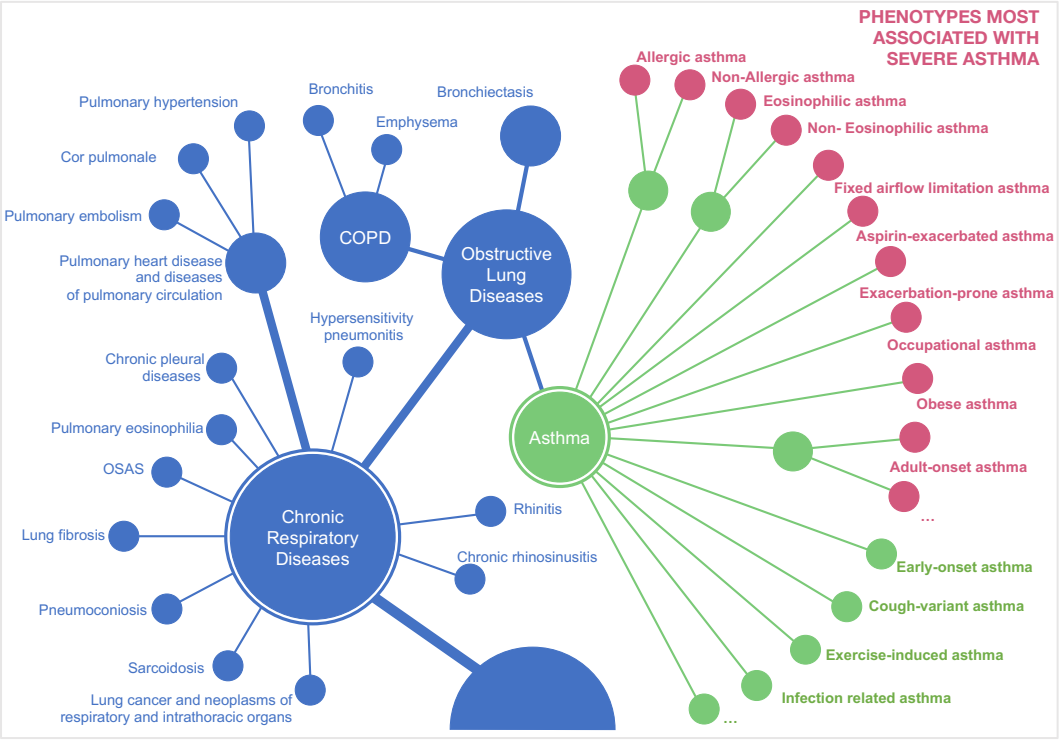


Figure 1: Heterogeneity among chronic respiratory diseases, asthma and severe asthma phenotypes.
COPD – chronic obstructive pulmonary disease; OSAS – obstructive sleep apnoea syndrome

Asthma concept evolution

The concept of asthma is moving from being an “umbrella” term to be considered a syndrome as a result of the discovery of new pathogenic pathways and of new treatments options (Pavord et al., 2017). The Global Initiative for Asthma (GINA), is a network aiming to gather scientific evidence, to achieve a worldwide consensus on asthma diagnosis and management and to disseminate it, with the goal of improving asthma care (GINA, 2018). According to GINA, asthma has consensually been defined as “a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation”. This definition has limitations considering that asthma-like symptoms may be induced by comorbid factors such as rhinitis, gastroesophageal reflux, obesity, anxiety and depression or by environmental behavioural factors such as smoking, occupational exposure, allergen exposure and treatment adherence. Moreover, the symptoms are common to other chronic diseases and asthma is not always associated with airway inflammation or even variable airflow limitation.

To rely only on measures of variable expiratory airflow limitation to diagnose asthma has disadvantages (Pavord et al., 2017). Importantly, fixed airflow limitation is also present in patients with asthma (asthma with persistent airflow limitation) possibly as result of structural changes of the airways wall, termed ‘airway remodelling’ (Barnig et al., 2018). Fixed airflow limitation has been associated with various risk factors such smoking and occupational exposure, bronchial eosinophilia (Hekking & Bel, 2014), or even due to early-life events in patients without asthma or COPD (Pavord et al., 2017). Fixed airflow limitation is associated with adult-onset, non-allergic, severe or difficult-to-control asthma (Hekking & Bel, 2014) and the rate of lung function decline is associated with frequent exacerbations either due to asthma or COPD (Contoli et al., 2010). Therefore, to use exclusively the criteria of variable airflow limitation to distinguish between asthma and COPD is not straightforward.

COPD - Chronic Obstructive Pulmonary Disease

The airway inflammation has different pathogenic pathways. Activated cells in airway epithelial and smooth muscle together with inflammatory cells perpetuate the chronic inflammation. The chronic inflammation present in most cases of asthma is mediated by type 2 responses, releasing pro-inflammatory mediators such as Interleukin (IL)-5 and IL-13 and causing eosinophilic presentation (Barnig et al., 2018). The so-called allergic asthma is triggered by environmental allergens, usually of early onset and inversely associated with persistent airflow obstruction and airway remodelling (Schatz & Rosenwasser, 2014). Nevertheless, clustering methods have shown that this is a heterogeneous phenotype, ranging in symptoms severity and pulmonary function. Non-allergic asthma has been associated with late-onset, at times more severe, and more difficult-to-treat asthma than allergic asthma (Peters, 2014). Airway inflammation may also be non-type 2. Neutrophilic asthma is associated with smoking, age, air pollution, occupation, body mass index (BMI), high-grade exercise, respiratory infection, sensitization to Aspergillus, gastroesophageal disease, and even corticosteroid use (Hekking & Bel, 2014). The activation of this inflammation pathway is notable in asthma exacerbations (Barnig et al., 2018). Another phenotype characterized by the lack of eosinophilic airway inflammation is obese asthma (Hekking & Bel, 2014). Thus, relying on the type of inflammatory response to distinguish between asthma and COPD is quite insufficient since asthma, COPD and Asthma-COPD-Overlap might be eosinophilic, neutrophilic or mixed (Gibson & McDonald, 2015).

COPD - Chronic Obstructive Pulmonary Disease

Asthma shares common features with other chronic respiratory diseases, and can be considered a syndrome of various overlapping phenotypes, due to its diversity of clinical characteristics, underlying inflammatory pathways, genetic background and risk factors.

Distinct asthma phenotypes are becoming more relevant for the optimisation of treatments and development of new drugs. However, asthma phenotypes overlap among patients are associated with poorer asthma outcomes, including reduced lung function (Amaral, Fonseca, et al., 2018). It remains a challenge to define asthma phenotypes in order to choose the most adequate treatment regimes.

Asthma prevalence

Epidemiological studies are essential to assess the population needs concerning chronic respiratory diseases. This is a pivotal process to better define adequate health policies, as recommended by the World Health Organization (Bousquet et al., 2007). Asthma is the most prevalent chronic respiratory disease worldwide, with twice the number of cases of COPD (GBD 2015 Chronic Respiratory Disease Collaborators, 2017). In 2015, asthma affected more than 350 million people. The main multinational studies on asthma prevalence are the European Community Respiratory Health Survey (ECRHS) in adults (Burney et al., 1996), and the International Study of Asthma and Allergies in Childhood (ISAAC) in children and adolescents (ISAAC et al., 1998). The European Union–funded Global Allergy and Asthma European Network (GA2LEN) conducted a large survey on the prevalence of airway and allergic diseases, built mainly on the questions and definitions used in the ECRHS (Bousquet et al., 2009). In 2010, we conducted the first Portuguese National Asthma Survey - *Inquérito Nacional sobre Asma* (INAsma), a cross-sectional, population-based, including a large sample size from all municipalities and all age groups, representative of the Portuguese population (Sa-Sousa et al., 2012). Results from this survey estimated that in the Portuguese population, the prevalence of 'current asthma' was 6.8% (95%CI 6.0-7.7) and of 'lifetime asthma' was 10.5% (95%CI 9.5-11.6). In children and adolescents, the prevalence of 'current asthma' as 8.4% (Ferreira-Magalhães et al., 2016).

COPD - Chronic Obstructive Pulmonary Disease

Asthma definition heterogeneity

Despite several studies on asthma prevalence, most of them use non-standardized methods, and prevalence estimates are difficult to compare. Estimates obtained in epidemiological studies are highly dependent on the set of questions used for the operational definition of asthma, on both adults and children (Sá-Sousa et al., 2014; Van Wonderen et al., 2010).

Self-reported questionnaires are simple and direct tools often used in epidemiological studies. In a clinical context, the initial diagnosis of asthma is based on identifying a pattern of respiratory symptoms, supported by pulmonary function tests, including the study of airflow obstruction reversibility and/or bronchial hyperresponsiveness (GINA, 2018). However, because these procedures are seldom feasible in population-based studies, efforts have been made to find accurate definitions of asthma on the basis of questionnaires.

The operational definitions of asthma vary extensively among prevalence studies and do not allow comparisons between studies, even if similar data collection methods were used (Sá-Sousa et al., 2014). In 2014 we conducted a review of the literature and by the application of the definitions of current asthma to two datasets from population studies, we have shown that depending on the definition used, the prevalence of asthma ranged from 5.3% to 39.5% in the Portuguese population (using INAsma dataset) and from 1.1% to 17.2% in the United States population (using National Health and Nutrition Examination Survey dataset). Definitions of asthma differ according to the certainty of a diagnosis ('diagnosed asthma'), to the time of occurrence of symptoms ('lifetime asthma' or 'current asthma') and to the type and number of symptoms included. In the 117 studies included in the review of the literature, several questionnaires were applied and 'lifetime asthma' was defined in 8 different ways, while 12 different ways were used to define 'diagnosed asthma', and 29 to define 'current asthma'. Elements used for the definition of 'current asthma' are represented in **Figure 2**. Having wheeze was the symptom most commonly used to define asthma, especially in children. However, it should be noted

INAsma – Portuguese National Asthma Survey

that wheezing-based asthma definitions are limited leading to estimates that may not be accurate (Ferreira-Magalhães et al., 2016; Skytt et al., 2012; Wright, 2002). The prior asthma diagnosis by a health professional was also commonly used to define asthma. However, in some countries and cultural contexts, the use of prior diagnosis may lead to an under- or overestimation of asthma prevalence (ECRHS, n.d.). The variety of definitions identified illustrates both the difficulty of identifying people with asthma by questionnaire and the difficulty of establishing an internationally accepted definition, even when the same questionnaire is used. Standardized definitions are necessary for prevalence comparisons worldwide.

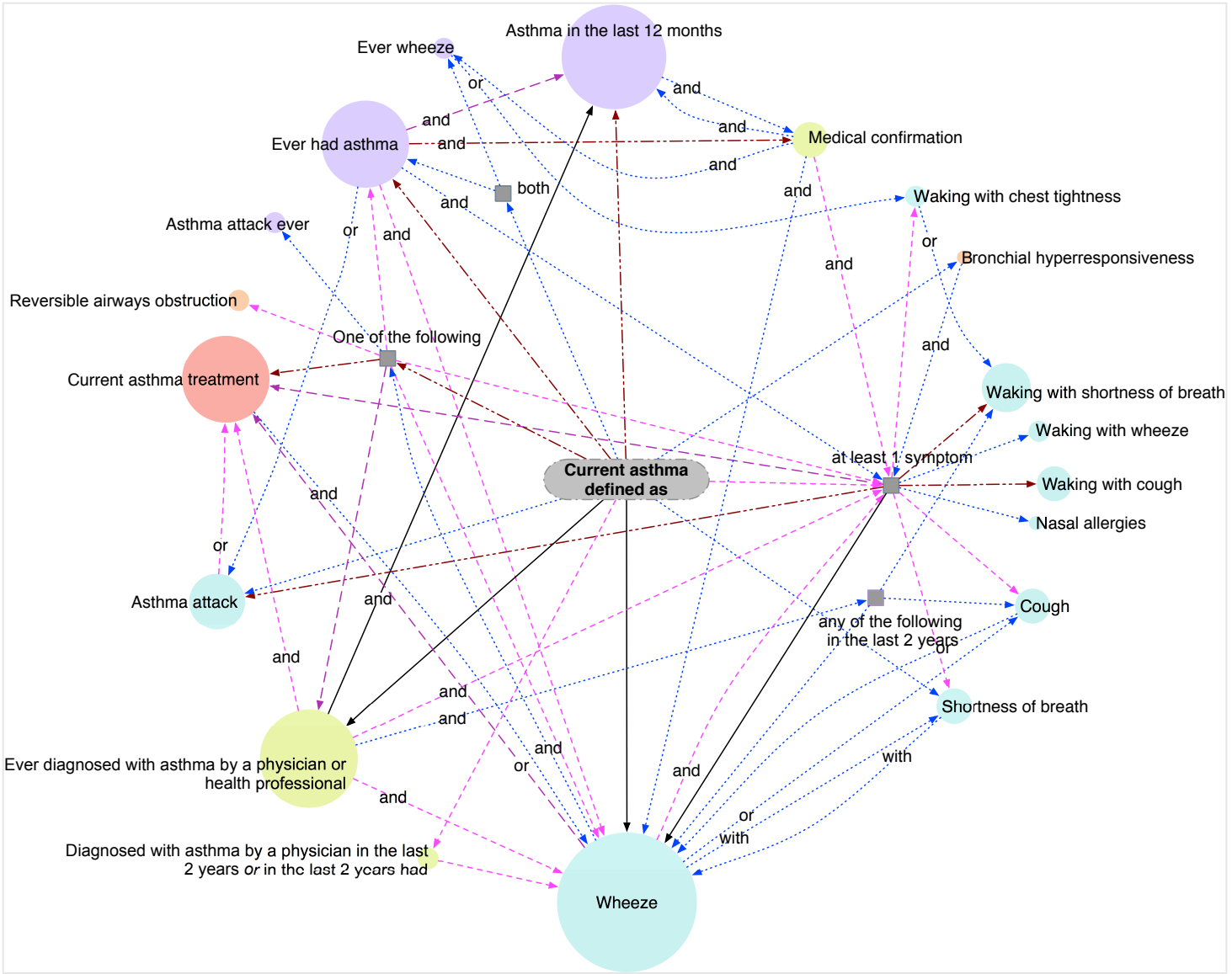


Figure 2: Elements of the definitions of 'Current asthma' connected in the order established by each study. *Symptoms in the last 12 months are represented in blue, lung function tests in orange and physician diagnosis in green. The size of each element is proportional to the number of definitions using the element. The colour of the lines indicates the number of times each connection was used: once (blue), twice (pink), three times (purple), four to eight times (red) and more than ten times (black). To simplify the diagram, breathlessness and dyspnoea were considered the same* (Sá-Sousa et al., 2014).

Several prediction models have been previously developed to identify children with asthma-like symptoms. A systematic review on prediction models for children reported extensive variability both on predictors and on outcome definitions, with none having the ability to rule in and rule out asthma simultaneously (Smit et al., 2015). In adults, Pekkanen et al. developed a continuous asthma score to define asthma on the basis of the ECRHS questionnaire and used bronchial hyperreactivity as the comparator (Pekkanen et al., 2005). This score showed good predictive capability in a prospective study when compared with self-reported use of asthma medication and asthma attacks and with bronchial hyperreactivity test at the end of follow-up (Sunyer et al., 2007). However, its validity was not supported by the results in another population setting (Vianna et al., 2007). The ECRHS score was also compared with the self-reported previous diagnosis of asthma (Vianna et al., 2007), but not against in-person physician diagnosis confirmed after clinical examination. Pekkanen et al. argued on the use of a continuous score over a dichotomous definition of asthma, since the choice of a cut-off depends mainly on the aims of the classification. In fact, self-reported questionnaires may be used 1) to identify asthma in prevalence studies assessing participants only once (e.g., the GA2LEN survey (Jarvis et al., 2012)) and 2) as initial screening questionnaires, being a feasible and effective way for preselecting patients for additional diagnostic workup, including pulmonary function tests (e.g., the ECRHS (Burney et al., 1994)).

ECRHS – European Community Respiratory Health Survey

GA2LEN – Global Allergy and Asthma European Network

Asthma prevalence varies widely in different regions, and a "precise and universally accepted definition of asthma" is still lacking. Furthermore, it is lacking a screening questionnaire to rule in and rule out asthma, enabling its use both in population-based studies and in screening/triage clinical settings. In 2014, based on the literature review findings, we proposed a set of questions to be reported in population-based studies on asthma prevalence, but these questions have not been evaluated (Sá-Sousa et al., 2014).

Asthma Burden

Chronic respiratory diseases, such as asthma and COPD, are a source of substantial burden of disease, including morbidity, mortality and reduced quality of life. The impact of such diseases is felt worldwide and in people of all ages (GBD 2015 Chronic Respiratory Disease Collaborators, 2017; Global Asthma Network, 2018). Globally, in 2016, asthma caused 420,000 deaths, 23.7 million disability-adjusted life years and was ranked 28th among the leading causes of burden of disease. In Portugal in 2016, respiratory diseases were the third cause of death in Portugal (12.1% of mortality in the country) and the death rate for asthma was 1.4 per 100,000 inhabitants (Instituto Nacional de Estatística, 2016). Asthma is also a major source of economic burden in terms of both direct and indirect costs. Based on INAsma survey, we conducted a detailed prevalence-based, cost-of-illness analysis of asthma in adults and children. In Portugal, adult asthma costs over €380 million per year, corresponding to an average of over €700 per patient, 93% of which corresponding to direct costs (Barbosa et al., 2017). The major costs were related to acute care usage (30.7%) and treatment (37.4%). Childhood asthma costs over €150 million per year, corresponding to more than €900 per child with current asthma, including state subsidies of €129.24 (Magalhães et al., 2017). Altogether, the total annual asthma costs in Portugal are about €550 million (over €760 per patient), 3% of the total healthcare expense in 2010 (Barbosa et al., 2017).

COPD – Chronic Obstructive Pulmonary Disease

INAsma – Portuguese National Asthma Survey

Adequate asthma management reduces the socioeconomic burden of asthma and improves patients' quality of life (Bateman et al., 2007). The proportion of patients achieving asthma control remains low worldwide (Demoly et al., 2012; Gold et al., 2013; Partridge et al., 2006; Rabe et al., 2000; Slejko et al., 2013). In Portugal, based on INAsma survey results, we provided the first nationwide results on asthma control (Sá-Sousa et al., 2015). Patients with controlled asthma had significant better asthma-related quality of life comparing to patients with non-controlled asthma, however almost half (43%) of the patients presented uncontrolled asthma, based on Control of Allergic Rhinitis and Asthma Test (CARAT).

Hospital admissions for asthma are an indirect indicator of the burden of more severe or uncontrolled asthma. Most of the asthma exacerbations are mild and self-limiting and the proportion of episodes resulting in hospital admission varies greatly, both within and between countries (Global Asthma Network, 2018). In Portugal, between 2000 and 2010, 5% of the total hospitalizations were due to obstructive lung diseases, 1% due to asthma (Vieira et al., 2016). In the same study period, 28.1 per 100,000 inhabitants per year were hospitalized because of asthma, and this rate was 66.6 per 100,000 in children (Santos et al., 2016). During this 11-year period, the hospital admissions decreased 18.6% for all patients, and 47.0% in those aged 0 to 2 years old. In-hospital mortality occurred in 8.0 per 1000 asthma hospitalizations, with an annual rate of was 2.4 per 1,000,000 inhabitants, which remained stable during the study period. Ventilation support was used in 5.1% of the hospitalizations of adults (Alves et al., 2014), indicating near-fatal asthma exacerbations.

Asthma is an important public health problem causing significant health resource utilization. The proportion of patients achieving asthma control remains low, hospitalizations and deaths because of asthma are still frequent. The identification of patients at risk is the first step to deliver adequate asthma care, reducing disease burden.

I2 High-risk asthma patients

Patients who are at increased risk of asthma-related death should be identified for more frequent review (GINA, 2018). The United Kingdom National Review of Asthma Deaths (NRAD), a large study on the analysis of asthma deaths aimed of the NRAD to identify avoidable factors surrounding asthma deaths (Royal College of Physicians, 2014). This study reported that only 39% of the patients who died had severe asthma classification, highlighting that asthma deaths may also occur in mild and moderate cases of the disease. In these cases, death was mainly due to inappropriate therapeutic prescription and medical care. Even in patients with few symptoms, short-acting beta2-agonists (SABA) over-use and recurrent use of oral corticosteroids (OCS) are important modifiable risk factors for future asthma exacerbations (GINA, 2018). Not clearly distinguishing between loss of symptom control and severe asthma attacks has often contributed to the assumption that these attacks are mildly inconvenient and readily reversible, rather than being a marker of a high risk of future attacks or even death (Pavord et al., 2017).

High-risk asthma patients include patients with severe asthma and those with mild or moderate asthma that have poor asthma control and frequent exacerbations, including patients with SABA over-use and high OCS exposure.

Asthma management evolution

Asthma concept evolution conveys the evolution of the disease management. Key features of asthma – airway responsiveness and inflammation – have been disclosed by therapeutic discoveries. More than 50 years ago the introduction of inhaled beta2-agonists was offered as the key for airway responsiveness. This enabled some degree of control of symptoms, but asthma deaths have been attributed to excessive use of SABA and also to the use of long-acting beta2-agonists (LABA) as single therapy (Royal College of Physicians, 2014). With the discovery of eosinophilic inflammatory mechanisms, new therapeutics emerged, namely the inhaled corticosteroids (ICS). The use of ICS in combination with LABA is encouraged by guidelines and resulted in substantial reduction of hospital admissions and mortality for asthma (GINA, 2018). However, the use of ICS

in high doses is inappropriate in non-eosinophilic asthma and has been associated with the increased airway neutrophilia observed in severe asthma patients (Hekking & Bel, 2014). Biological therapy is recommended for patients whose asthma is uncontrolled on treatment with corticosteroids (moderate/high dose ICS and/or OCS) (GINA, 2019). Therapies targeting anti-immunoglobulin E (IgE) and type 2 cytokines IL-5 and IL-4/IL-13 have shown consistent efficacy in severe asthma patients with evidence of type 2 inflammation. For patients without type 2 inflammation, new therapies have been less successful and await further investigation. Biologic approaches are promising, but much remains unclear related to their long-term efficacy and safety, comparative efficacy and cost-effectiveness (Fajt & Wenzel, 2015). In short, asthma can no longer be managed on an "one size fits all" basis, as exemplified by inappropriate escalating of ICS in patients with non-eosinophilic asthma or with fixed airflow obstruction, or by the inappropriate under-treatment with ICS in patients with uncontrolled eosinophilic asthma.

ICS – Inhaled corticosteroids

OCS – Oral corticosteroids

IL - Interleukin

The goals of asthma management are to achieve symptoms control and minimize the risk of future exacerbations, and side-effects of treatment (GINA, 2019). Current guidelines consider disease management as a continuous cycle of assessment, treatment, and review of the patient's response. Asthma-specific medication may be grouped in medication for maintenance treatment and reliever medication. Although the pharmacological treatment proposed by guidelines is adequate for most patients with asthma, it emphasises the treatment with ICS and beta-agonist therapy, not considering treatment according to specific pathways or phenotypic groups (GINA, 2019; Pavord et al., 2017).

GINA - Global Initiative for Asthma

ICS – Inhaled corticosteroids

SABA - Short-Acting Beta2-Agonists

LABA – Long-Acting Beta2- Agonists

LTRA - Leukotriene Receptor Antagonists

LAMA - Long-Acting Muscarinic Antagonists

IgE – anti-Immunoglobulin E

OCS – Oral corticosteroids

Ab –Antibodies

Until 2019, GINA guidelines recommended the use of SABA as the first-line of asthma treatment (GINA, 2018). In agreement with the evidence on the risk of the use of SABA without any controller medication, the recently published guide for asthma management by GINA network, recommends that ICS should be used whenever SABA is used, and ICS combined with formoterol may be used in low dose as a reliever option (**Figure 3**) (GINA, 2019). In a stepwise approach, if the response to the treatment is suboptimal, it is recommended to intensify the treatment, either by increasing the dose of currently used ICS and adding another controller medication, such as LABA, leukotriene receptor antagonists (LTRA), and xanthines. The higher level of care corresponds to the add-on long-acting muscarinic antagonists (LAMA), IgE, low dose of OCS or biological therapy.

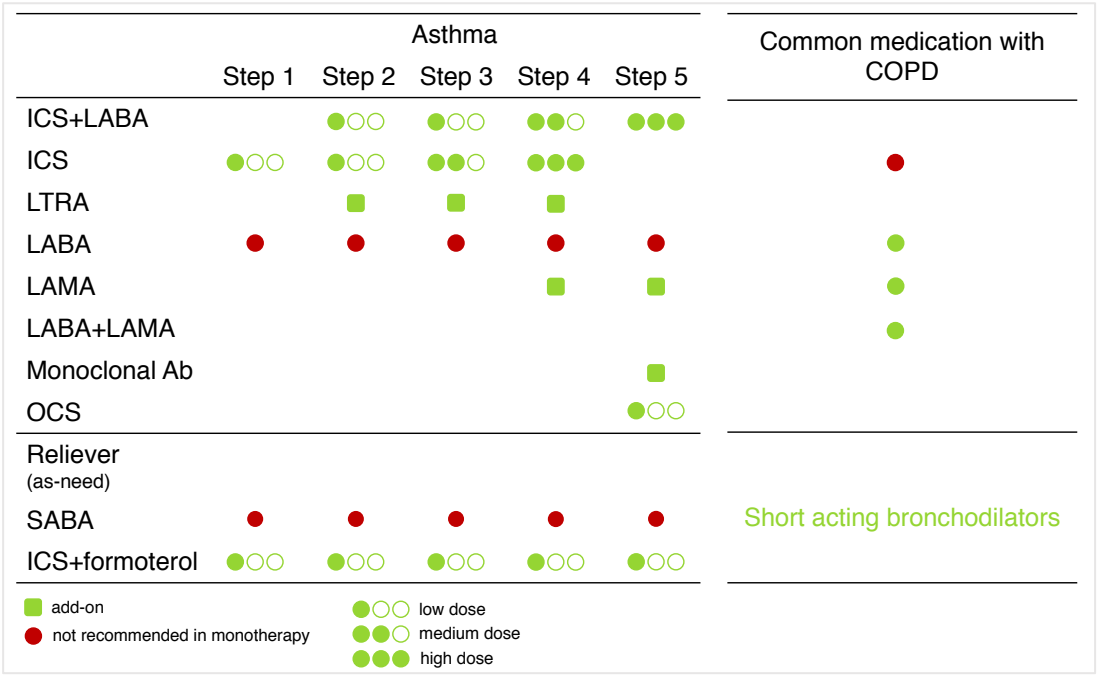


Figure 3: Medication used in asthma management and common medication with COPD.

COPD – Chronic Obstructive Pulmonary Disease

Asthma and COPD are heterogeneous diseases with similar symptoms and management options, moreover, some patients present an overlap of asthma and COPD features (**Figure 3**). The Global Initiative for Chronic Obstructive Lung Disease guidelines alert to the lack of sufficient evidence supporting the initial treatment in COPD patients (GOLD, 2019). Guidelines advise different COPD initial treatments depending on the severity symptoms, exacerbations and airflow limitation. For group A, it consists of a

bronchodilator, either short- or long-acting (SABA or short-acting muscarinic antagonists (SAMA) or LABA or LAMA). Patients in group B should be treated with LABA or LAMA, and both LABA+LAMA if the symptoms persist. Group C initial therapy should consist of LAMA, and, in patients with persistent exacerbation, LABA+LAMA or ICS+LABA is recommended. For more severe cases (group D) the recommended initial therapy is LAMA+LAMA or, in patients with a history suggestive of asthma-COPD overlap or based on eosinophilic counts, ICS+LABA. The higher level of pharmacological care corresponds to triple therapy with LAMA+LABA+ICS or add-on of phosphodiesterase-4 inhibitor or a macrolide.

ICS – Inhaled corticosteroids

LABA – Long-Acting Beta2- Agonists

LAMA - Long-Acting Muscarinic Antagonists

OCS exposure and excessive SABA use

The identification of patients at risk of asthma-related death encompasses the history of a previous exacerbation and medication-related factors such as 1) the over-use of inhaled SABA, defined as more than 1 canister (200 doses of 100μg) of salbutamol or equivalent monthly; 2) the current use of OCS; 3) the absence of ICS use and 4) poor adherence with asthma maintenance medication (GINA, 2019). These potential modifiable factors increase the risk of asthma-related death, even in patients with few asthma symptoms. Furthermore, exposure to OCS has been associated with pneumonia, osteoporosis, cataracts, and diabetes in a dose-responsive manner (Daugherty et al., 2018; Price et al., 2018; Sullivan et al., 2018). In severe exacerbations, when a response to SABA fails, short-treatment with OCS may be required. Adequate adherence to maintenance treatment is expected to improve asthma symptoms control, reducing the need for SABA or OCS (Engelkes et al., 2015); on the other hand, increases in SABA dosages and recurrent use of OCS indicate the need to reassess treatment. Inhaled SABA are the medication of choice for bronchodilation during acute exacerbation, as they are highly effective effect as quick relievers of bronchoconstriction symptoms. However, SABA only provides symptom relieve, while underlying inflammation of the airways remains untreated. Despite the evidence on the risks of the use of SABA without maintenance treatment, patients tend to rely on SABA when they have symptoms and

SABA - Short-Acting Beta2-Agonists

OCS – Oral corticosteroids

to disregard adherence to the controller medication (Martin & Harrison, 2019). Efforts are being made to reduce or even to dismiss SABA from the asthma treatment plan (IPCRG, 2018). A systematic review and meta-analysis showed that single maintenance and reliever therapy for the management of persistent asthma was associated with a lower risk of asthma exacerbations compared with ICS (combined or not with LABA) and SABA as the relief therapy (Sobieraj et al., 2018). As mentioned above, the most recent update of asthma guidelines recommends the use of ICS whenever SABA is taken – even the mildest cases of intermittent asthma – and as-needed combined use of ICS and formoterol as the controller and the quick relief therapy (step 1) (GINA, 2019).

SABA - Short-Acting Beta2-Agonists

ICS – Inhaled corticosteroids

LABA – Long-Acting Beta2- Agonists

Electronic medical records and administrative claims data, including prescription databases, have been used to assess exacerbation patterns and identify patients at risk of asthma exacerbations. A major independent risk-factor for an asthma exacerbation is having at least one previous exacerbation in the last 12 months (GINA, 2019). In fact, a long follow-up study in asthma patients based on electronic healthcare records, found that having one exacerbation, was the most important factor associated with an increased risk of a future exacerbation in the following 5 years (Bloom et al., 2019). A study aiming to identify patients at risk of recurrent exacerbations reported that a frequent use of SABA and >2 courses of OCS during one year were among the risk factors associated with future need of OCS or emergency visit due to asthma (Blakey et al., 2017). The NRAD study mentioned above, assessed the factors related to asthma deaths based on the analysis of data from multiple sources (primary, secondary and tertiary care, ambulance paramedic and out-of-hours care providers) (Royal College of Physicians, 2014). According to this report, in the last year of life, 39% of the patients had been prescribed more than 12 SABA inhalers, and 38% and 80% were prescribed fewer than 4 and 12 controller inhalers, respectively. Similar problems were found in other studies and countries. In 2013, inappropriate patterns of asthma therapy, including SABA over-use and LABA monotherapy, were found at least in 210,000 and 190,000 asthma patients from the United Kingdom and France, respectively. In

OCS – Oral corticosteroids

NRAD – UK National Review of Asthma Deaths

Canada, inappropriate use of SABA (2 or more puffs of SABA per week in the absence of any ICS, or use of more than 9 canisters of SABA during the year and no more than 100 μg/day of ICS) was associated with a 45% increase in the risk of asthma-related hospitalization in the following three-month period. In addition, such inappropriate use was associated with a 25% increase in the risk of asthma-related emergency department visits and with a 6% increase in total-asthma-related costs (FitzGerald et al., 2017).

ICS – Inhaled corticosteroids

SABA - Short-Acting Beta2-Agonists

OCS – Oral corticosteroids

In fact, the use of pharmacy records, namely the number of SABA canisters filled over a one-year period, has been validated as a proxy for predicting the risk of asthma-related hospitalization or emergency department visit and to OCS dispensing (Schatz et al., 2006). In Portugal, to our knowledge, research based on the national electronic prescription database is scarce (Bigotte Vieira et al., 2019; Sousa et al., 2017) and non-existent on OCS or SABA use.

OCS exposure and SABA over-use are modifiable risk factors for having adverse clinical outcomes, and even death. Prescription data analysis may provide evidence on the identification of patients who are at risk for future acute asthma health care use. However, to our knowledge, research based on Portuguese electronic prescription database is scarce and none on respiratory medication, namely OCS or SABA.

Severe asthma

The use of secondary data to identify patients with severe asthma is challenging (Jacob et al., 2017) and as these patients represent a small and heterogeneous group among patients with asthma, the adequate approach to provide the evidence to their adequate identification, characterization and treatment would be by the creation of a disease registry. However, considerable gaps make the implementation of this type of initiative difficult. There is not even a consensus on the definition of severe asthma. Nevertheless, several efforts efforts have been made over the years to define severe asthma. A first consensual definition from the American Thoracic Society, in 2000, defined ‘refractory asthma’ (Fahy, 2000). In 2009, the World Health Organization proposed a uniform definition of severe asthma by which severe asthma was defined as ‘‘Uncontrolled asthma which can result in risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic

ICS – Inhaled corticosteroids

LABA – Long-Acting Beta2- Agonists

GINA – Global Initiative for Asthma

morbidity (including impaired lung function or reduced lung growth in children)'' (Bousquet et al., 2010). A task force, supported by the European Respiratory Society and the American Thoracic Society (ERS/ATS), reviewed this definition (Chung et al., 2014). According to ERS/ATS, when the diagnosis of asthma is confirmed and comorbidities addressed, severe asthma was defined as "asthma that requires treatment with high dose ICS plus a second controller (LABA or LTRA modifier/theophylline) and/or systemic corticosteroids (for 50% or more of the previous year) to prevent it from becoming 'uncontrolled' or that remains 'uncontrolled' despite this therapy". GINA guidelines defined severe asthma as "asthma that requires Step 4 or 5 treatment, e.g. high-dose ICS/LABA, to prevent it from becoming 'uncontrolled' or asthma that remains 'uncontrolled' despite this treatment" (GINA, 2018). The need to differentiate between difficult asthma, asthma with comorbidities and severe treatment-refractory asthma is a common problem in severe asthma research and management. According to GINA, 'difficult-to-treat' asthma is "used for patients in whom ongoing factors such as comorbidities, poor adherence, and allergen exposure interfere with achieving good asthma control"; 'refractory' asthma "refers to patients with a confirmed diagnosis of asthma, whose symptoms or exacerbations remain poorly controlled despite high-dose ICS plus a second controller", and 'severe asthma' "includes patients with refractory asthma, and those in whom response to treatment of comorbidities is incomplete". The guidelines also highlight that before establishing a diagnosis of severe asthma, some common problems need to be excluded, such as 1) poor inhaler technique, poor medication adherence, incorrect diagnosis of asthma, with symptoms due to alternative conditions (such as upper airway dysfunction, heart failure or lack of fitness); 2) untreated comorbidities such as rhinosinusitis, gastroesophageal reflux, obesity and obstructive sleep apnoea; and 3) ongoing exposure to sensitizing or irritant agents in the home or work environment. Overall, severe asthma definition is mainly based on the symptom control and continuous high-dose treatment, regardless of medication side-effects and high long-term risk.

The concept of high-dose ICS itself is not always clear (Zervas et al., 2018). The ERS/ATS and GINA 2018 propose different dose ranges for ' high-dose' ICS (**Table 1**). Zervas and coworkers recently suggested that the dose ranges proposed by GINA guidelines seem to be closer to real-life practice.

ICS – Inhaled corticosteroids

ERS/ATS – European Respiratory Society and American Thoracic Society

GINA – Global Initiative for Asthma

Table 1: High-dose inhaled corticosteroids proposed by the ERS/ATS and the GINA (Zervas et al., 2018).

	ERS/ATS 2014 High dose µg	GINA 2018 High dose µg
Beclomethasone dipropionate (chlorofluorocarbon)	⩾2000	>1000
Beclomethasone dipropionate (hydrofluoroalkane)	⩾1000	>400
Budesonide	⩾1600	>800
Ciclesonide	⩾320	>320
Fluticasone furoate	Not applicable	200
Fluticasone propionate	⩾1000	>500
Mometasone furoate	⩾800	⩾440
Triamcinolone acetonide	⩾1200	>2000

ERS/ATS, European Respiratory Society and American Thoracic Society (Chung et al., 2014); GINA, Global Initiative for Asthma (GINA, 2018).

As the concept of asthma is evolving from an "umbrella" term to a syndrome-like definition, so is that of severe asthma. It is often characterized by severe airway hyperresponsiveness and/or fixed airflow limitation, and complex interactions between inflammation, airway remodelling and altered lung mechanics (King et al., 2018). Type 2 inflammation in severe asthma may be triggered, among others, by allergens or by airway infections, via the innate system. The mechanisms for resolution of inflammation are impaired in severe asthma contributing to treatment resistance. The treatment with monoclonal antibodies targeting type 2 inflammation pathways is very effective for many patients but not for all. Although less understood, irreversible structural changes to the airway wall, independently from inflammation, are also important in severe

asthma. To improve care, a better understanding of the aetiology, burden and management patterns of severe asthma is needed.

The management of severe asthma is challenging and involves treatment of comorbidities, medication adherence, and allergens exposure avoidance, among others. One of the greatest difficulties is the choice of the optimal treatment for each given patient, although algorithms for treatment decisions have been suggested (GINA, 2019b; Zervas et al., 2018). Monoclonal antibodies targeting IgE, IL-5 and IL4/13 are currently available and new biologics are under development. Omalizumab is a humanized anti-IgE antibody recommended for treating severe allergic IgE-mediated persistent asthma as an add-on to optimize standard therapy in people aged 6 years or older who need continuous or frequent treatment with OCS (defined as 4 or more courses in the previous year) (NICE, 2013). Recently, it has been suggested that its action may not be limited to anti-IgE activity, affecting airway remodelling and having clinical efficacy also in non-allergic asthma (Loureiro et al., 2018). Previous studies in adults have shown that treatment with omalizumab is associated with an improvement in the control of asthma symptoms, with decreased frequency and use of rescue medication and OCS, and with an overall reduction in the asthma-related emergency visits (including hospital admissions, emergency department visits and unscheduled medical visits) (NICE, 2013). However, most of these data come from clinical trials, primarily designed to assess treatment efficacy in highly selected patients; this poses problems when generalizing to daily clinical practice. Real-life prospective studies, presented as a pragmatic approach to everyday clinical practice, are fundamental to assess the impact of omalizumab treatment in patients with severe asthma and should contribute to future informed decisions about this treatment. The international multicentric observational post-marketing registry eXpeRience assessed the efficacy and safety of omalizumab treatment and included Portuguese patients (Pereira Barbosa et al., 2015). In Portugal, four more studies described outcomes of omalizumab treatment in real-life settings (Alfarroba et al., 2014; Dias et al., 2012; Simões Saldanha Mendes et al., 2013; Vieira et al., 2012), but only one had a prospective design and it was

IgE - Immunoglobulin-E

IL - Interleukin

OCS – Oral corticosteroids

conducted in a single healthcare unit. New biologics include Mepolizumab, Reslizumab (both targeting IL-5), Benralizumab (targeting IL-5 Receptor), and Dupilumab (targeting alpha subunit of IL-4 Receptor). However, it is not easy to choose between the biologics to be the first-choice treatment, and head-to-head comparison studies between them do not exist (Drazen & Harrington, 2018). A trial involving the direct comparison of two or more treatments is a pressing need, but it may never be carried out (Drazen & Harrington, 2018). Hence, clinical observational studies of real-world large patient populations should contribute to the knowledge on how to select the best biologic treatment for an individual patient.

IL - Interleukin

Real-world studies on prevalence and burden of severe asthma

Over the past decade, our understanding of severe asthma has benefited from results of clinical observational studies of broad real-world patient populations providing evidence on asthma heterogeneity (Porsbjerg et al., 2018). Recent studies on large databases estimate that severe asthma prevalence ranges between 1.5% and 8.5% of the asthmatic populations (**Table 2**). Using the data from the INAsma, we estimated that 7.4% of patients were on step 4 or 5 treatment as defined by GINA (unpublished data).

INAsma – Portuguese National Asthma Survey

GINA – Global Initiative for Asthma

Table 2: Prevalence of severe asthma, based on different study designs.

Country	Data Source	Study period	Participants	Outcome Definitions	Prevalence	Reference
Spain	Patients from 164 pneumology and allergology hospital units	6 months (previous to 2006)	n= 36,649 (>12 y.o)	Uncontrolled severe persistent asthma. Asthma severity was determined by clinicians on the basis of their own criteria.	3.9% (95% CI, 3.7%-4.1%) of the asthma patients	(Quirce et al., 2011)
Denmark	Nationwide prescription database	1year (2010)	n=61,583 (18-44 y.o.)	Severe asthma if 1) Redeemed high ICS doses (>800 mg/daily budesonide or equivalent) and at least 1 dispensed prescription of a second controller; and/or 2) omalizumab therapy.	8.1% (0.26% of the entire population in Denmark)	(von Bülow et al., 2014)
Netherlands	Dispensing records from 65 community pharmacies (3% of the population) and self-administered questionnaires	1year (2011)	n=500,500 (≥18 y.o.)	Severe refractory asthma if all 4 features: 1) high dose ICS (>1000 mcg/daily of fluticasone or equivalent or 500-1000 mcg/daily of fluticasone plus ≥5mg/daily prednisone or equivalent) and LABA; 2) Uncontrolled or well-controlled with OCS; 3) good primary adherence and 4) correct inhalation technique	3.6% (95% CI, 3.0% to 4.1%) of the Dutch adult asthmatic population	(Hekking et al., 2015)
Israel	Insurance healthcare provider (55% of the population)	1year (2012)	n=351,799 (20-70 y.o.)	Severe asthma if medium/high-dose ICS and LABA (≥800 mcg/daily of budesonide or equivalent) Severe-uncontrolled asthma if 1) medium/high-dose ICS/LABA and 2) excessive SABA and/or OCS	4.6% of the asthmatic population insured 1.5% of the asthmatic population insured	(Varsano et al., 2017)

y.o., years old; ICS, Inhaled Corticosteroid; LABA, Long Acting Beta2-Agonist; OCS, Oral Corticosteroids; SABA, Short Acting Beta2-Agonist; FEV1, Forced Expiratory Volume in 1 second

Table 2(cont): Prevalence of severe asthma, based on different study designs.

Country	Data Source	Study period	Participants	Outcome Definitions	Prevalence	Reference
Sweden	Postal questionnaire	4 years (2008-2012)	n=18,087 (16-75 y.o.)	Asthma severity signs: 1) reporting ≥ 4 daytime asthma symptoms despite the ongoing use of medication; 2) impaired lung function corresponding to an FEV1 < 70% of predicted; 3) daily or almost daily use of rescue medications; 4) nocturnal symptoms occurring once or more per week; and 5) lung-related emergency department visits or use of OCS regularly or during exacerbations	3.1% with 1 sign and 1.3% with for at least 2 signs of severity	(Mincheva et al., 2018)
Sweden	Medical records from 36 primary care centres	6 years (2006-2013)	n=18,724 (>18 y.o.)	Severe asthma if prescription of high dose ICS (> 800 budesonide mcg/daily or equivalent) and leukotriene receptor antagonist and/or LABA	4.2% of asthma patients	(Larsson et al., 2018)

y.o., years old; ICS, Inhaled Corticosteroid; LABA, Long Acting Beta2-Agonist; OCS, Oral Corticosteroids; SABA, Short Acting Beta2-Agonist; FEV1, Forced Expiratory Volume in 1 second

Severe asthma patients have more symptoms and exacerbations compared to patients with the mild/moderate disease (Moore et al., 2007). Results from the European U-BIOPRED (Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes) adult severe asthma cohort have shown that patients with severe asthma experienced 2.5 exacerbations in the preceding 12 months, compared to 0.4 in the mild/moderate asthma cohort ($p<0.001$) (Shaw et al., 2015). Moreover, the number of severe asthma exacerbations are important and independent predictors of future severe exacerbations (Chipps et al., 2012) and were positively associated with lung function deterioration and higher sputum eosinophil count (Denlinger et al., 2017; Shaw et al., 2015).

Severe asthma patients have worse asthma-related quality of life and higher level of anxiety and depression compared to mild/moderate asthma patients. For example, in U-BIOPRED study, patients with severe asthma had an average Asthma Quality of Life Questionnaire scores of 4.4 and an Hospital Anxiety and Depression Score of 12.3, compared to 5.8 and 7.9, respectively) (Shaw et al., 2015). Hiles et al. observed that severe asthma patients were 3.2 times more likely to report work impairment and 2.3 times more likely to report impairment in daily activity compared to participants with non-severe asthma (Hiles et al., 2018). Lower likelihood of being employed was associated with more exacerbations, defined by OCS courses and emergency department visits in the year before (Odds Ratios, 95% Confidence Intervals: 0.93, 0.87-0.99 and 0.57,0.34-0.97, respectively).

Even though they represent a small proportion, severe asthma patients have higher morbidity, mortality, and costs than patients with non-severe asthma. The higher burden attributed to severe asthma patients is associated with more exacerbations, worse quality of life and coexistence of more comorbidities.

OCS – Oral corticosteroids

The presence of comorbidities, often reported in severe asthma patients, influences the outcomes in asthma and have an adverse impact on disease control and exacerbation rates (Pavord et al., 2017). The most common comorbidities are rhinitis, sinusitis, nasal polyposis, allergic conjunctivitis, gastroesophageal reflux, pneumonia, obstructive sleep apnea, obesity, and psychological/psychiatric disorders (Chipps et al., 2012; Moore et al., 2007;

Shaw et al., 2015). Steroid-induced morbidity has a high impact on the overall severe asthma burden. Systemic corticosteroids, especially OCS, are used in the treatment of severe asthma exacerbations and their anti-inflammatory effects are helpful to improve asthma control and often reduce exacerbation rates in the long-term. However, systemic corticosteroid exposure is associated with the substantial excess morbidity from multiple disease and adverse effects (Price et al., 2018) and this association is dose-responsive (Daugherty et al., 2018). Asthma-related direct costs among patients with severe asthma are three times those of patients with persistent asthma, particularly due to greater utilization of asthma medication and healthcare resources (Chastek et al., 2016). Steroid-induced morbidity represents additional costs of healthcare utilization and drugs prescriptions in severe asthma patients (Barry et al., 2017).

OCS – Oral corticosteroids

Severe asthma management represents an unmet clinical need. The NRAD concluded that among the patients who died, 39% had severe asthma classification, 10% died within 28 days of discharge from hospital after treatment for asthma, and 21% had attended a hospital emergency department with asthma at least once in the previous year (Royal College of Physicians, 2014). This indicates that strategies to identify high-risk asthma patients are needed.

NRAD – UK National Review of Asthma Deaths

Severe asthma research networks and disease registries

Research networks are playing a critical role in the advances in severe asthma. They can run both multicentre severe asthma studies and real-life severe asthma patient registers.

The main international severe asthma studies on severe asthma, described in **Table 3** are: 1) ENFUMOSA (European Network For Understanding Mechanisms Of Severe Asthma), which was an important kick-off study to understand severe asthma as a different phenotype of asthma, rather than an increase in asthma symptoms; 2) TENOR (The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens), a multicentre observational study conducted in the United States of America; 3) U-BIOPRED (Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes), an European Union consortium of academic institutions, pharmaceutical companies and patient organisations; and 4) SARP (Severe Asthma Research Program), which is described as the world's most comprehensive study of adults and children with severe asthma.

Disease registries are recognized as powerful tools to improve disease-related knowledge and improvement of care. They consist of organized systems that use observational study methods to collect uniform data aiming at evaluating specific outcomes for a heterogeneous population defined by a particular disease (Gliklich, 2014). This type of study design enables the assessment of the effect of different therapies in the context of a single disease and the enrolment of severe asthma patients in a disease registry is recommended by GINA guidelines (GINA, 2019b). Severe asthma registries are being created throughout Europe, including in the United Kingdom, Belgium, Germany, Austria, Netherlands, Italy, and Spain (**Table 3**). However, for prospective long-lasting studies with the coordination of a wide range of expertise, an international or even global level may be required when aiming at reducing the severe asthma-related burden (Soriano et al., 2016). With the goal of establishing a global collaborative initiative, the International Severe Asthma Registry was created, and

GINA – Global Initiative for Asthma

29 national registries are currently engaged in the project (ISAR, n.d.). The European Respiratory Society Research Agency also promotes collaborative Europe-wide research based on data collected from disease registries (Belvisi et al., 2015). Its actions include the development of Standard Operational Procedures and guidelines, consent forms to collect and handle data in compliance with the European Union legal and regulatory framework, and establishment of a central point to access datasets from multiple projects. In 2016, the Severe Heterogeneous Asthma Research collaboration, Patient-centred (SHARP) was accepted as a European Respiratory Society Clinical Research Collaborations (European Respiratory Society, n.d.). Taking this into consideration, new registries should be designed to enable sharing information and coordination among databases (e.g., federated databases).

The management of severe asthma is puzzling and the choice of the best treatment for each patient remains a challenge. Although randomized clinical trials are the basis for treatment efficacy assessment, with the lack of evidence on the severe asthma pathophysiologic mechanisms and the upcoming of new therapies, there is a need for organized systems based on observational study design, such as disease registries.

Table 3: Real-world severe asthma studies, including European registries of severe asthma – a non-comprehensive review.

Project / Registry	Countries	Study period / Year of release	Study design and supporting network (if applicable)	Website	Patients	No.of Centres	Sources / published studies
Severe asthma studies							
ENFUMOSA	9 European countries		Cross-sectional, observational, multicentre	-	n=321 (51% severe asthma and 49% mild-to-moderate asthma patients)	12	(ENFUMOSA, 2003)
TENOR I	USA	3 years (2001-2004)	Prospective, observational, multicentre	-	n= 4 756 (48% severe, 48% have moderate, 3% have mild and 96% have difficult-to-treat asthma patients)	283	(Dolan et al., 2004)
TENOR II	USA	2013/2014	Cross-sectional, observational, multicentre, follow-up study of TENOR I patients	-	n=341 (severe or difficult-to-treat asthma patients)	59	(Chipps et al., 2018)
U-BIOPRED	11 European countries	5 years (2010-2014)	Prospective, observational, multicentre, supported by the European Lung Foundation	http://www.europeanlung.org/en/projects-and-research/projects/u-biopred/home	n=610 (69% severe asthma, 14% mild/moderate asthma patients, 17% healthy participants)	16	(Shaw et al., 2015)
SARP I	USA	2003-2005	Cross-sectional, observational, multicentre, supported by National Institutes of Health/ National Heart, Lung & Blood Institute	http://www.severeasthma.org/home.html	n=438 (47% severe, 16% moderate and 37% mild asthma patients)		(Moore et al., 2007)
SARP II	USA	2009-2011	Cross-sectional, observational, multicentre, supported by National Institutes of Health/ National Heart, Lung & Blood Institute	http://www.severeasthma.org/home.html	n=155 (33% severe asthma patients and 17% healthy participants)		(Modena et al., 2014)
SARP III	USA	Started in 2012	Prospective, observational, multicentre	http://www.severeasthma.org/home.html	n=714 severe asthma patients	7	(Denlinger et al., 2017)

ENFUMOSA, European Network For Understanding Mechanisms Of Severe Asthma; TENOR, The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens; U-BIOPRED, Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes; SARP, Severe Asthma Research Program; USA,United States of America

Table 3(cont): *Real-world severe asthma studies, including European registries of severe asthma – a non-comprehensive review.*

Project / Registry	Countries	Study period / Year of release	Study design and supporting network (if applicable)	Website	Patients	No.of Centres	Sources / published studies
Severe asthma patient registries							
United Kingdom Severe Asthma Registry	United Kingdom	Released in 2006	British Thoracic Society	http://rs2.e-dendrite.com/csp/asthma/frontpages/index.html	>500	8	[1]
Belgian Severe Asthma Registry	Belgium	Released in 2008	Belgische Vereniging voor Pneumologie / Société Belge de Pneumologie	http://www1.citobi.be/SAR/Welcome_en.act	>350	9	[2]
Register Schweres Asthma	Germany	Released in 2011	German Asthma Net e.V.	http://www.german-asthma-net.de	>100	12	[3]
Banco de Datos de Asma	Spain	Released prior to 2012	Sociedad Española de Neumologia y CirurgiaToracica	https://www.separ.es/?q=node/71	>290	30	[4]
Austrian Severe Asthma Net	Austria	Released in 2012	Austrian Severe Asthma Net	http://www.asa-net.at/register/	<80	16	[5]
Severe/ Uncontrolled Asthma Registry	Italy	Released in 2014	Italian Severe Asthma Network	http://www.sani-asma.org	>400	63	[6]
Registry of Adult Patients with Severe asthma for Optimal Disease management	Netherlands	Released in 2016	Academisch Medisch Centrum	https://www.zonmw.nl/nl/over-zonmw/innovatie-in-de-zorg/programmas/project-detail/goed-gebruik-geneesmiddelen/registry-of-adult-patients-with-severe-asthma-for-optimal-disease-managementrapsodi/verslagen/	>20	3	[7]

[1] (Burn et al., 2017; Chaudhuri et al., 2016; Gibeon et al., 2013; Heaney et al., 2010; Newby et al., 2014; O'Neill et al., 2015; Sferrazza Papa et al., 2017; Sweeney et al., 2012; Sweeney et al., 2016; Thomson et al., 2013); [2] (Schleich et al., 2014; Schleich et al., 2017); [3] (Korn, Hübner, Hamelmann, et al., 2012; Korn, Hübner, Bergmann et al., 2012); [4] (De Llano et al., 2013; Vennera et al., 2012); [5] (Doberer et al., 2015); [6] (Casella, 2017; Senna et al., 2017); [7] (Schippers et al., 2016)

The REAG - *Rede de Especialistas em Asma Grave* is an open collaborative network of asthma specialists (allergists, paediatricians, and pulmonologists) who manage severe asthma patients in Portuguese hospitals. The foundational principle of REAG is the informal peer collaboration among colleagues with different medical specialties and backgrounds, maintaining an un-hierarchical organization and consensual decision processes to improve sharing of medical experience, data, and knowledge. Since 2011, this network of experts has been working towards a better care of severe asthma patients by (1) promoting a better coordination between medical specialties for early diagnosis and referral of severe asthma patients; (2) describing and implementing harmonized procedures to adopt in severe asthma healthcare; and (3) improving scientific knowledge on severe asthma in Portugal. In 2015, REAG conducted a real-life prospective study on Portuguese patients with severe persistent allergic asthma, treated with omalizumab, described in Study III. This was the first-time specialists from different Portuguese centres made an effort to harmonize the registration procedures for severe asthma and assess treatment efficacy in these patients. From this initial study, the necessity for a computerized disease registry became even more evident and the Portuguese Severe Asthma Registry (*Registo de Asma Grave Portugal*-RAG) was developed and implemented, as described in Study IV.

OBJECTIVES

The main objective of this thesis was to improve the identification of patients with asthma and those at high-risk of adverse asthma outcomes, including patients with severe asthma, using different data sources.

As specific aims, we intended to:

1. Develop and validate scores to identify asthma patients in epidemiological studies and clinical screening/triage settings. (Study I)
2. Quantify respiratory patients with high-risk of having adverse clinical outcomes in the Portuguese electronic prescription and dispensing database. (Study II)
3. Improve the identification of severe asthma patients with poor outcomes, namely
   - assess uncontrolled disease and exacerbations in patients with severe asthma treated with omalizumab (Study III)
   - develop and implement the Portuguese Severe Asthma Registry to gather of evidence on severe asthma care (Study IV)

DATA SOURCES

Three data sources were used to pursue the aims of this thesis:

- Study I was based on data from the Control and Burden of Asthma and Rhinitis study - ICAR (*Impacto e Controlo da Asma e Rinite*)
- Study II was based on data from the Portuguese electronic prescription and dispensing database – BDNP (*Base de Dados Nacional de Prescrições)*
- Study III was based on the omalizumab administration database.

An overview of the data sources will be presented in this section.

Control and Burden of Asthma and Rhinitis - ICAR

ICAR was a nationwide population-based observational cross-sectional study. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, consistent with good clinical practice and the applicable regulatory requirements, and was approved by a hospital ethics committee (*Comissão de Ética do Hospital São João EPE*, on October 17, 2011) and by the national data protection committee (no. 12372/2011). The study protocol containing standard operational procedures was registered in ClinicalTrials.gov (NCT01771120). All participants signed the consent form.

Participants and data collection

INAsma – Portuguese National Asthma Survey

In the ICAR study, all subjects who have been included in the INAsma study (Sa-Sousa et al., 2012; Sá-Sousa, Amaral et al., 2015) and who have expressed their willingness to participate in a clinical assessment were eligible along with their family members. Furthermore, local media and posters were used to disseminate the study and invite participants. Persons who did not understand Portuguese and who had cognitive or physical conditions that could hamper their participation in the study were excluded.

Data were collected between October 30, 2012, and July 12, 2014, in two allergy clinics (Lisbon and Porto) or by using a mobile diagnostic unit, on the basis of the participants' geographical proximity.

Participants were screened by telephonic interview and divided into four groups: 1) patients with a self-reported diagnosis of asthma alone; 2) patients with a self-reported diagnosis of rhinitis alone; 3) patients with a self-reported diagnosis of asthma and rhinitis; and 4) patients with no history of respiratory symptoms or diseases. A total of 858 participants living at 90 Portuguese cities and aged between 3 and 89 years, either with asthma and/ or rhinitis or with no previous history of respiratory symptoms or diseases, were included. Data collection comprised anthropometric measurements, lung function and exhaled nitric oxide tests, skin prick

tests, a structured clinical assessment, and standardized questionnaires. Anthropometric measurements of height, weight, and waist/hip circumference followed the procedures manual of the National Health and Nutrition Examination Survey (NHANES, 2009). Lung function tests included spirometry with postbronchodilator reversibility (EasyOne Pro, ndd, Zurich, Switzerland, and Jaeger IOS, CareFusion, San Diego, Calif), carbon monoxide in exhaled air (SmokeCheck, Micro Medical, Kent, UK), and exhaled nitric oxide (NIOX Mino, Aerocrine AB, Solna, Sweden), and were done according to standardized methods (MacIntyre et al., 2005; Miller, Crapo, et al., 2005; Miller, Hankinson, et al., 2005). Atopy was determined with skin prick tests. Blood sampling allowed for the determination of total IgE, eosinophilic cationic protein, and C-reactive protein. The structured clinical assessment performed by a trained physician included physical examination, comorbidities screening, use of health resources and medications because of asthma/rhinitis, assessment of the degree of control of allergic diseases, family history, environmental exposures (at home and workplace), and social habits. In the ICAR study, self-administered questionnaires included the assessment of the following:

IgE – Immunogloblulin E

- disease symptoms and control, using the Portuguese versions of the GA2LEN survey questionnaire (Bousquet et al., 2009), the allergy airway diseases screening questionnaire (Fischer et al., 2006), visual analogue scales, the CARAT (Fonseca et al., 2010), the CARAT for kids (Linhares et al., 2014) and the Allergic Rhinitis Control Test (Demoly et al., 2011);
- quality of life, using the Portuguese versions of the EuroQol 5-dimensional questionnaire (EuroQol, n.d.) the WHOQOL-BREF (Skevington et al., 2004), the Mini Asthma Quality of Life Questionnaire (mini-AQLQ) (Juniper et al., 1999), the Mini Rhinoconjunctivitis Quality of Life Questionnaire (Juniper et al., 2000) and the Paediatric Asthma Caregiver's Quality of Life Questionnaire (Juniper et al., 1996);
- work/school absenteeism and impairment, using the Work Productivity and Activity Impairment questionnaire (Ciconelli et al., 2006);

GA2LEN – Global Allergy and Asthma European Network

CARAT – Control of Allergic Rhinitis and Asthma Test

WHOQOL-BREF – World Health Organization's Quality of Life

- adherence to prescribed treatment, using the Medication Adherence Report Scale (Vanelli, Chendo, Gois, Santos, & Levy, 2011); and
- physical activity, using the International Physical Activity Questionnaire (Fogelholm et al., 2006).

Portuguese electronic prescription and dispensing database – BDNP

In 2011, the Portuguese Ministry of Health started promoting the electronic prescription of medications (Ministério da Saúde, 2010). The use of electronic prescriptions is compulsory in mainland Portugal since 2012. The Decree-Law no. 11/2012 of March 8th and Ordinance no. 137-A / 2012 of May 11th defines a new approach to electronic prescription of medication and the dematerialization of the procedures associated with the prescription-dispensing-billing-conference circuit, in order to achieve efficiency, accuracy and safety in the prescribing process.

The BDNP is the central system, responsible for the validation of all steps of the prescriptions and dispensing cycle in Portugal, and for the recording of all prescription and dispensing data. The electronic prescriptions system is used by physicians in private and public healthcare units. In 2012, the Ministry of Health developed an application for the electronic medical prescription, meant to be the standardized tool to be used by healthcare institutions of the National Health System for the prescription of medication (Ministério da Saúde, 2015a), but other applications are also used. Nevertheless, all the software for electronic prescription must be interoperable with BDNP (Ministério da Saúde, 2018).

Each prescribed medication consists of a 'prescription line' and includes:

- International Common Denomination of the active substance,
- pharmaceutical form
- dosage
- number of packages (Assembleia da República, 2012) (Ministério da Saúde, 2015b). In general, in each 'prescription line', up to 4 packages may be prescribed.

Information regarding the prescriber speciality and the healthcare unit where the of prescription was issued are also recorded.

The system of electronic prescriptions completed its implementation process in 2014, whereas the implementation of the electronic dispensing system in each community pharmacy was concluded by the end of 2015.

Data availability

This database collects information continuously and its management is under the responsibility of Shared Services of the Ministry of Health *(SPMS - Serviços Partilhados do Ministério da Saúde*. Restrictions apply to the availability of these data, which are only available upon reasonable request and permission of *SPMS*.

A formal agreement was celebrated between SPMS and CINTESIS in 2014, for data analysis aiming to detect data quality problems and to develop algorithms to identify individuals at risk of adverse events. Based on this agreement, regarding the current thesis, six formal meetings were held with SPMS, between December 2014 and May 2016, via Skype or in-person at the institution's headquarters in Lisbon. Between these meetings, several working contacts were made, in an attempt to solve technical problems, which resulted in the submission of three collaboration forms and data extraction requests, that had no practical results. On April 2017 the SPMS appointed a task force to respond to all data requests under Research & Development projects. After a meeting with members of this task force, the criteria for data extraction from BDNP were consensually established. On August 2017, the data were obtained. After the pre-processing and analysis of inconsistencies in the database, a document was sent to SPMS. On 5 January 2018, doubts and inconsistencies regarding the previous analysis were clarified and it was confirmed data extraction did not completely meet the initially agreed criteria. After this date, SPMS did not respond to any contact attempt and, therefore, to guarantee the project delivery deadlines, the protocol was redefined according to the available data.

Omalizumab administration database

This database includes all the patients under treatment with omalizumab from seven Pulmonology and Allergology departments from six hospitals in north and centre regions of mainland Portugal, between 2011 and 2013 (**Table 4**).

Table 4: Data collection description by study site

Hospital units	Patients (n, %)		Follow-up period (median, min-max)		Data collection		Visits per patient (median, min-max)	
					Start	End		
Hospital São João, EPE – Pulmonology	8	16.6	12.2	12-12	May 2012	Aug 2013	26	18-23
Hospital São João, EPE – Allergology	12	25.0	12.2	9-12	Feb 2012	Dec 2013	18	10-27
Centro Hospitalar e Universitário de Coimbra, EPE – Pulmonology	15	31.3	11.2	7-12	Jan 2011	Nov 2012	12	7-25
Centro Hospitalar do Porto – Allergology	6	12.5	12.0	12-12	Feb 2012	Feb 2013	21	13-16
Centro Hospitalar de Trás-os-Montes e Alto Douro	4	8.3	11.2	8-12	May 2011	Sep 2012	24	8-26
Hospital Pedro Hispano – Allergology	2	4.2	4.2	3-5	Nov 2011	Nov 2012	9	7-10
Centro Hospitalar do Alto Ave – Pulmonology	1	2.1	12.0	-	Dec 2011	Dec 2012	9	-

Data were collected at each routine visit for omalizumab administration, during 12 consecutive months. A structured form, to be filled by both the patient and the nurse responsible for omalizumab administration, was developed in order to standardize data collection at the different study sites. Omalizumab was administered at 2- or 4-week intervals; in each administration, data was collected on:

CARAT – Control of Allergic Rhinitis and Asthma Test

- omalizumab dosage;
- asthma control (based on CARAT questionnaire (Fonseca et al., 2010);
- absenteeism because of asthma;
- unscheduled medical care because of asthma.

After 12 months under omalizumab treatment, data was collected on:

- omalizumab dosage;
- inhaled medication;
- absenteeism because of asthma;
- oral corticosteroid intake
- unscheduled medical care because of asthma;
- hospitalizations because of asthma and need of ventilation support;
- adverse effects related to omalizumab
- anthropometric measures
- pulmonary function tests results
- asthma control (based on CARAT questionnaire (Fonseca et al., 2010, 2012))

Mini-AQLQ – Mini Asthma Quality of Life Questionnaire

- quality of life (EuroQol-5 dimensional questionnaire (EuroQol, n.d.), Asthma Life Quality (Fonseca et al., 2004), mini-AQLQ (Juniper et al., 1999))
- blood sample analysis
- global omalizumab efficacy assessment

STUDY I

Sá-Sousa A, Pereira AM, Almeida R, Araujo L, Couto M, Jacinto T, et al. **Adult Asthma Scores-Development and Validation of Multivariable Scores to Identify Asthma in Surveys.**

J Allergy Clin Immunol Pract. 2019 Jan;7(1):183–190.e6. (Sá-Sousa et al., 2019)

Aims

We aimed to (1) develop and validate multivariable scores for adult asthma identification in epidemiological studies on the basis of answers to questions commonly used in these studies and (2) to explore the best cut-off to rule in and to rule out asthma.

Methods

Source of data

ICAR - Control and Burden of Asthma and Rhinitis

We used data from the ICAR study (PTDC/SAU-SAP/119192/2010), a nationwide population-based observational cross-sectional study conducted in Portugal (ClinicalTrials.gov: NCT01771120). The study was approved by a hospital ethics committee (*Comissão de Ética do Hospital São João EPE, on October 17, 2011*) and by the national data protection committee (no. 12372/2011). All participants signed the consent form. Methods regarding sample size calculations, participants, and data collection in the ICAR study are described in the Data source section. Data collection included lung function and exhaled nitric oxide, skin prick tests, a structured clinical assessment, and standardized questionnaires. The structured clinical assessment was performed by a trained physician and included physical examination, use of health resources and medications because of asthma/rhinitis, and detailed personal and family medical history. In the ICAR study, self-administered questionnaires assessed disease symptoms and control, including the Portuguese version of the GA2LEN survey questionnaire (Bousquet et al., 2009) among other questionnaires.

GA2LEN – Global Allergy and Asthma European Network

Participants

ICAR - Control and Burden of Asthma and Rhinitis

We included participants from the general population aged 18 years and older from the ICAR study (n = 728). Considering an asthma prevalence of 23% (in the study sample), a specificity of 90%, and a maximum marginal error of estimate not exceeding 3% with a 95% CI, the required sample size was 498 participants (Hajian-tilaki, 2014). Approximately 80% (n = 560) of the participants were randomly selected into a derivation cohort and 20% (n = 151) into a validation cohort.

Outcome and predictors

GINA – Global Initiative for Asthma

GA2LEN – Global Allergy and Asthma European Network

Asthma diagnosis (criterion standard) was defined by a physician on the basis of a structured clinical assessment of symptoms and detailed medical history, and supported by objective measurements (details in 'ICAR' in Data source section), according to the GINA guidelines. The physician had no previous access to the results of the self-administered questionnaires. The predictors were asthma-related questions from the self-administered questionnaires. Sixteen questions were selected as initial predictors (**Table 5**), namely, (1) questions previously suggested in a literature review (Sá-Sousa et al., 2014) and (2) questions on asthma from the GA2LEN questionnaire. On the basis of these predictors, 2 separate scores were built: the Adult Asthma Epidemiological Score (A2 score), based on the literature, and the GA2LEN Asthma Epidemiological Score (GA2LEN score), based on the GA2LEN questionnaire. Subjects with missing data in any of the predictors were excluded from the analysis (n = 17 [2.3%])

Table 5: Initial predictors (Portuguese and English versions) used to develop the multivariable prediction models and predictors included in the ECRHS asthma score previously developed

Portuguese version of the predictors	Predictors	From literature, as suggested by Sá-Sousa et al. (A2-score)	From GA2LEN questionnaire (GA2LEN-score)	Asthma score based on ECRHS
1. Já alguma vez teve asma?	1. Have you ever had asthma?	•	•	•
2. Alguma vez um médico lhe disse que tem asma?	2. Did a physician confirmed you had asthma?	•		
3. Ainda tem asma?	3. Do you still have asthma?	•		
4. Alguma vez esteve hospitalizado por asma?	4. Have you ever been hospitalized because of asthma?		•	
5. Teve um ataque de asma nos últimos 12 meses?	5. Have you had any asthma attack in the last 12 months?	•	•	•
6. Presentemente está a tomar remédios (inaladores, aerossóis ou comprimidos) para a asma?	6. Are you currently taking any medicines including inhalers, aerosols or tablets for asthma?	•	•	•
7. Alguma vez teve chiadeira ou pieira no peito nos últimos 12 meses?	7. Have you ever had wheezing or whistling in the chest at any time in the last 12 months?	•	•	
8. Teve a chiadeira ou a pieira sem estar constipado?	8. Have you had this wheezing or whistling when you did not have a cold?	•	•	
9. Teve falta de ar quando a chiadeira estava presente?	9. Have you been at all breathless when the wheezing noise was present?	•	•	•
10. Alguma vez teve uma crise de falta de ar, depois de atividade física moderada ou intensa, nos últimos 12 meses?	10. Have you had an attack of shortness of breath after exercise in the last 12 months?	•		•
11. Alguma vez teve uma crise de falta de ar, que surgiu durante o dia, quando estava em repouso, nos últimos 12 meses?	11. Have you had an attack of shortness of breath that came on during the day when you were at rest at any time in the last 12 months?	•		•
12. Acordou com a sensação de aperto no peito nos últimos 12 meses?	12. Have you woken up with the feeling of tightness in your chest at any time in the last 12 months?	•	•	•
13. Alguma vez foi acordado devido a um ataque de falta de ar nos últimos 12 meses?	13. Have you been woken up by an attack of shortness of breath at any time in the last 12 months?	•	•	•
14. Alguma vez foi acordado devido a um ataque de tosse nos últimos 12 meses?	14. Have you been woken up by an attack of coughing at any time in the last 12 months?	•	•	
15. Alguma vez teve tosse seca durante a noite nos últimos 12 meses, não contando com a tosse associada a constipação ou infeção?	15. In the last 12 months, have you had a dry cough during the night, apart from a cough associated with a cold or a chest infection?	•		
16. Na maioria dos dias produz muco do seu peito durante um período de três meses por ano?	16. Did you have phlegm when coughing for at least 3 months in the last year?		•	

A2 score, Adult Asthma Epidemiological Score; GA2LEN score, Global Allergy and Asthma European Network Asthma Epidemiological Score; ECRHS, European Community Respiratory Health Survey

Statistical analysis

Categorical variables are presented as absolute frequencies and proportions. Comparisons of proportions and associations were tested. A *p-value* of less than 0.05 was considered as statistically significant. Statistical analysis was performed using IBM SPSS Statistics, version 24.0 (IBM Corp, Armonk, NY).

An exploratory factor analysis was performed to construct a score reducing the number of predictors while retaining, as much as possible, the information contained in the initial combination of predictors, identifying the possible statistical redundancy of the predictors (Field, 2009). A factor analysis was run for the initial predictors (**Table 5**). Principal-component analysis and oblimin rotation were used. Predictors with more than 95% responses in a single category were excluded. An item was considered redundant and was excluded if any one of the following occurred: highly intercorrelated (>0.900), considerable cross-loading (>0.300 in more than 1 factor), low item-total correlation (<0.400), or increased Cronbach α if the predictor was deleted.

Discriminative/predictive power of the scores was evaluated by Receiver-Operating Characteristic (ROC) curve analysis. Internal consistency was assessed by Cronbach α. The diagnostic accuracy measures used were sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV), and accuracy.

The scores' performance was tested in the derivation and validation cohorts, and compared with the ECRHS asthma score. The cut-off to rule in asthma was defined as the minimum number of positive answers to obtain a PPV of 85% or more simultaneously in both cohorts. The cut-off to rule out asthma was defined as the maximum number of positive answers to obtain an NPV of 95% or more simultaneously in both cohorts.

ECRHS – European Community Respiratory Health Survey

For each of the 2 scores, 2 scoring methods were tested: the weighted sum, obtained by multivariable logistic regression of the included predictors, and the direct sum of the included predictors. The scores obtained by both the scoring methods were compared by the Spearman correlation factor. The values for the Area Under the Curve (AUC) for the scores obtained by both the methods were also compared.

Results

This study included 711 participants (**Figure 4**), with a median age (percentile 25 to percentile 75) of 42 (32-55) years, and 447 (63%) were females. The number of participants with asthma was 162 (23%). No statistically significant differences were observed between the derivation and the validation cohorts regarding sex, age, geographic region of residence, and presence of asthma ($p > 0.1$). Specifically, no differences between the cohorts were observed in the proportion of participants with asthma (23.8% vs 19.2%; $p = 0.24$).

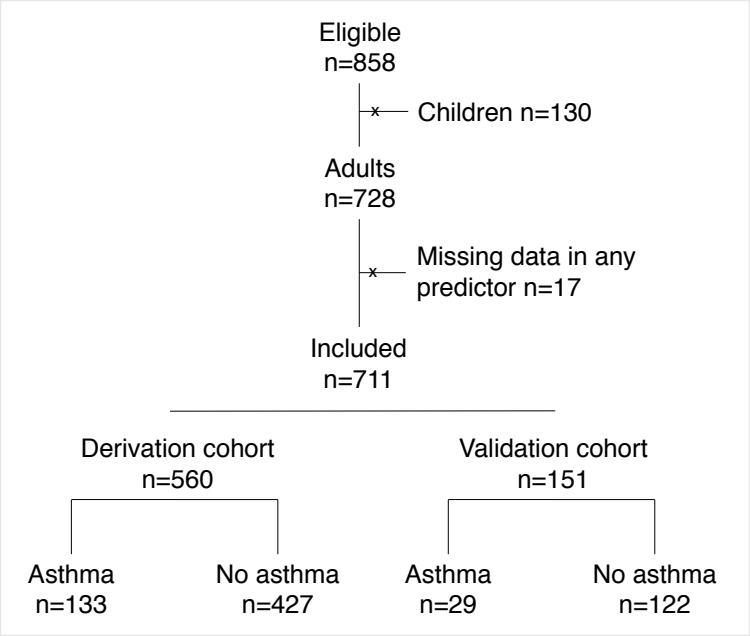


Figure 4: Participants' flowchart.

In the derivation cohort, having asthma was highly associated with all the initial predictors but not with the demographic variables (**Table 6**). In general, the ability to identify patients with asthma using any asthma predictor alone was low (PPV < 70%; **Table 7**).

PPV – Positive Predictive Value

Table 6: Characterization of the cohorts.

	Derivation cohort				Validation cohort			
		Asthma presence				Asthma presence		
	Total (n=560)	No (427, 76.3%)	Yes (133, 23.8%)	*p-value*	Total (n=151)	No (122, 80.8%)	Yes (29, 19.2%)	*p-value*
Demographics								
Age, median P25-P75	41.5 32-55	43 32-56	37 31-55	0.119*	42 33-52	43 32-54	40 33-48	0.501*
Sex, n %				0.302†				0.903‡
Female	360 64.6	279 65.8	81 60.9		87 57.6	70 57.4	17 58.6	
Male	197 35.4	145 34.2	52 39.1		64 42.4	52 42.6	12 41.4	
Region, n %				0.561§				0.701§
North	285 50.9	216 50.6	69 51.9		80 53.0	66 54.1	14 48.3	
Centre	35 6.3	27 6.3	8 6.0		11 7.3	10 8.2	1 3.4	
Lisbon	183 32.7	139 32.6	44 33.1		36 23.8	27 22.1	9 31.0	
Alentejo	26 4.6	18 4.2	8 6.0		10 6.6	6 4.9	4 13.8	
Algarve	31 5.5	27 6.3	4 3.0		14 9.3	13 10.7	1 3.4	
Predictors, n %								
1. Have you ever had asthma?‖ ¶	138 24.6	36 8.4	102 76.7	<0.001†	30 19.9	10 8.2	20 69.0	<0.001†
2. Did a physician confirm you had asthma?‖	132 23.6	30 7.0	102 76.7	<0.001†	29 19.2	10 8.2	19 65.5	<0.001†
3. Do you still have asthma (previously diagnosed by a physician)?‖	104 18.6	14 3.3	90 67.7	<0.001†	24 15.9	6 4.9	18 62.1	<0.001‡
4. Have you ever been hospitalized because of asthma? ¶	40 7.1	10 2.3	30 22.6	<0.001†	8 5.3	2 1.6	6 20.7	0.001‡
5. Have you had any asthma attack in the last 12 mo?‖ ¶	51 9.1	7 1.6	44 33.1	<0.001†	7 4.6	1 0.8	6 20.7	<0.001‡

P25-P75, Percentile 25-Percentile 75; * Mann-Whiney U test; † Chi-square test; ‡ Fisher's exact test; § Linear-by-linear test; || Initial predictors used to develop A2-score; ¶ Initial predictors used to develop GA2LEN-score

Table 6 (cont): Characterization of the cohorts.

	Derivation cohort				Validation cohort			
		Asthma presence				Asthma presence		
	Total (n=560)	No (427, 76.3%)	Yes (133, 23.8%)	*p-value*	Total (n=151)	No (122, 80.8%)	Yes (29, 19.2%)	*p-value*
6. Are you currently taking any medicines including inhalers, aerosols or tablets for asthma?|| ¶	66 11.8	5 1.2	61 45.9	<0.001†	11 7.3	1 0.8	10 34.5	<0.001‡
7. Have you ever had wheezing or whistling in the chest at any time in the last 12 mo?|| ¶	178 31.8	85 19.9	93 69.9	<0.001†	38 25.2	17 13.9	21 72.4	<0.001†
8. Have you had this wheezing or whistling when you did not have a cold?|| ¶	104 18.6	41 9.6	63 47.4	<0.001†	18 11.9	4 3.3	14 48.3	<0.001‡
9. Have you been at all breathless when the wheezing noise was present?|| ¶	118 21.1	41 9.6	77 57.9	<0.001†	24 15.9	7 5.7	17 58.6	<0.001‡
10. Have you had an attack of shortness of breath after exercise in the last 12 mo?||	45 8.0	16 3.7	29 21.8	<0.001†	9 6.0	1 0.8	8 27.6	<0.001‡
11. Have you had an attack of shortness of breath that came on during the day when you were at rest at any time in the last 12 mo?||	78 13.9	26 6.1	52 39.1	<0.001†	13 8.6	2 1.6	11 37.9	<0.001‡
12. Have you woken up with the feeling of tightness in your chest at any time in the last 12 mo?|| ¶	98 17.5	59 13.8	39 29.3	<0.001†	25 16.6	15 12.3	10 34.5	0.010‡
13. Have you been woken up by an attack of shortness of breath at any time in the last 12 mo?|| ¶	57 10.2	23 5.4	34 25.6	<0.001†	14 9.3	8 6.6	6 20.7	0.029‡
14. Have you been woken up by an attack of coughing at any time in the last 12 mo?|| ¶	226 40.4	156 36.5	70 52.6	0.001†	54 35.8	37 30.3	17 58.6	0.004†
15. In the last 12 mo, have you had a dry cough during the night, apart from a cough associated with a cold or a chest infection?||	222 39.6	144 33.7	78 58.6	<0.001†	59 39.1	40 32.8	19 65.5	0.001†
16. Did you have phlegm when coughing for at least 3 months in the last year? ¶	19 3.4	8 1.9	11 8.3	0.001†	4 2.6	2 1.6	2 6.9	0.167‡

P25-P75, Percentile 25-Percentile 75; * Mann-Whiney U test; † Chi-square test; ‡ Fisher's exact test; § Linear-by-linear test; || Initial predictors used to develop A2-score; ¶ Initial predictors used to develop GA2LEN-score

Table 7: Diagnostic accuracy measures for each predictor, in the derivation and validation cohorts.

	Derivation cohort (n=560)				Validation cohort (n=151)			
	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
1. Have you ever had asthma?	76.7 (69.0-83.8)	91.6 (88.7-94.0)	73.9 (66.2-80.8)	92.7 (89.9-94.9)	69 (51.0-91.8)	91.8 (86.1-95.8)	66.7 (48.9-81.7)	92.6 (87.0-96.4)
2. Did a physician confirm you had asthma?	76.7 (69.0-83.8)	93 (90.3-95.1)	77.3 (69.6-83.9)	92.8 (90.0-95.0)	65.5 (47.4-91.8)	91.8 (86.1-95.8)	65.5 (47.4-81.0)	91.8 (86.1-95.8)
3. Do you still have asthma (previously diagnosed by a physician)?	67.7 (59.4-75.2)	96.7 (94.7-98.1)	86.5 (79.1-92.2)	90.6 (87.7-93.0)	62.1 (43.9-78.2)	95.1 (90.3-98.0)	75 (55.7-89.2)	91.3 (85.6-95.4)
4. Have you ever been hospitalized because of asthma?	22.6 (16.0-30.1)	97.7 (95.9-98.8)	75.0 (60.3-86.6)	76.3 (72.6-79.6)	20.7 (8.8-37.5)	98.4 (95.0-99.7)	75 (40.9-95.3)	80.8 (74.0-86.5)
5. Have you had any asthma attack in the last 12 mo?	33.1 (25.5-41.3)	98.4 (96.9-99.3)	86.3 (75.1-93.9)	82.5 (79.1-85.6)	20.7 (8.8-37.5)	99.2 (96.4-100.0)	85.7 (50.6-99.1)	84.0 (77.5-89.4)
6. Are you currently taking any medicines including inhalers, aerosols or tablets for asthma?	45.9 (37.5-54.4)	98.8 (97.5-99.6)	92.4 (84.4-97.2)	85.4 (82.1-88.4)	34.5 (19.0-52.6)	99.2 (96.4-100.0)	90.9 (65.7-99.5)	86.4 (80.1-91.4)
7. Have you ever had wheezing or whistling in the chest at any time in the last 12 mo?	69.9 (61.8-77.3)	80.1 (76.1-83.7)	52.2 (44.9-59.5)	89.5 (86.2-92.3)	72.4 (54.7-86.3)	86.1 (79.2-91.4)	55.3 (39.5-70.3)	92.9 (87.2-96.7)
8. Have you had wheezing or whistling when you did not have a cold?	47.4 (39.0-55.8)	90.4 (87.4-93.0)	60.6 (51.0-69.6)	84.6 (81.2-87.8)	48.3 (30.8-66.0)	96.7 (92.5-99.0)	77.8 (55.7-92.5)	88.7 (82.6-93.3)
9. Have you been at all breathless when the wheezing noise was present?	57.9 (49.4-66.1)	90.4 (87.4-93.0)	65.3 (56.4-73.5)	87.3 (84.0-90.2)	58.6 (40.5-75.2)	94.3 (89.2-97.5)	70.8 (51.2-86.3)	90.6 (84.7-94.8)

PPV, Positive Predictive Value; NPV, Negative Predictive Value; 95%CI, 95% Confidence Interval

Table 7(cont): Diagnostic accuracy measures for each predictor, in the derivation and validation cohorts.

	Derivation cohort (n=560)				Validation cohort (n=151)			
	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
10. Have you had an attack of shortness of breath after exercise in the last 12 mo?	21.8 (15.4-29.3)	96.3 (94.2-97.8)	64.4 (49.9-77.3)	79.8 (76.2-83.1)	27.6 (13.7-45.3)	99.2 (96.4-100.0)	88.9 (59.5-99.3)	85.2 (78.8-90.4)
11. Have you had an attack of shortness of breath that came on during the day when you were at rest at any time in the last 12 mo?	39.1 (31.1-47.5)	93.9 (91.4-95.9)	66.7 (55.8-76.5)	83.2 (79.9-86.4)	37.9 (21.8-56.1)	98.4 (95.0-99.7)	84.6 (59.6-97.3)	87.0 (80.7-91.1)
12. Have you woken up with the feeling of tightness in your chest at any time in the last 12 mo?	29.3 (22.0-37.4)	86.2 (82.7-89.2)	39.8 (30.5-49.7)	79.7 (75.8-83.2)	34.5 (19.0-52.6)	87.7 (81.1-92.7)	40 (22.5-59.5)	84.9 (78.0-90.4)
13. Have you been woken up by an attack of shortness of breath at any time in the last 12 mo?	25.6 (18.7-33.4)	94.6 (92.2-96.5)	59.6 (46.7-71.8)	80.3 (76.7-83.6)	20.7 (8.8-37.5)	93.4 (88.1-96.9)	42.9 (19.8-68.3)	83.2 (76.4-88.8)
14. Have you been woken up by an attack of coughing at any time in the last 12 mo?	52.6 (44.2-61.0)	63.5 (58.8-67.9)	31 (25.2-37.2)	81.1 (76.7-85.1)	58.6 (40.5-75.2)	69.7 (61.2-77.4)	31.5 (20.2-44.5)	87.6 (80.1-93.2)
15. In the last 12 mo, have you had a dry cough during the night, apart from a cough associated with a cold or a chest infection?	58.6 (50.2-66.8)	66.3 (61.7-70.7)	35.1 (29.1-41.6)	83.7 (79.5-87.4)	65.5 (47.4-81.0)	67.2 (58.6-75.1)	32.2 (21.2-44.7)	89.1 (81.7-94.4)
16. Did you have phlegm when coughing for at least 3 mo in the last year?	8.3 (4.4-13.7)	98.1 (96.5-99.1)	57.9 (35.8-78.0)	76.3 (72.6-79.6)	6.9 (1.2-19.8)	98.4 (95.0-99.7)	50 (10.7-89.3)	80.8 (74.0-86.5)

PPV, Positive Predictive Value; NPV, Negative Predictive Value; 95%CI, 95% Confidence Interval

Exploratory factor analysis

On the basis of the initial set of questions (**Table 5**), 2 scores were developed to identify the presence of asthma (**Table 8**). The A2 score and the GA2LEN score derivations were obtained by exploratory factor analysis.

Table 8: Association of the variables included in the final multivariable scores with the presence of asthma as assessed by the physician

	A2-score		GA2LEN-score	
Predictors, n%	aOR	95%CI	aOR	95%CI
1. Have you ever had asthma?	*	*	13.36	6.79 -26.27
2. Did a physician confirm you had asthma?	7.91	3.17 -19.77	†	†
3. Do you still have asthma (previously diagnosed by a physician)?	4.28	1.33 -13.79	†	†
4. Have you had any asthma attack in the last 12 mo?	0.51	0.15 -1.78	1.07	0.36 -3.18
5. Are you currently taking any medicines including inhalers, aerosols or tablets for asthma?	4.07	1.23 -13.47	6.02	2.01 -18.00
6. Have you ever had wheezing or whistling in the chest at any time in the last 12 mo?	3.23	1.25 -8.36	3.35	1.32 -8.47
7. Have you had wheezing or whistling when you did not have a cold?	1.35	0.55 -3.30	1.36	0.58 -3.22
8. Have you been at all breathless when the wheezing noise was present?	1.13	0.42 -3.00	1.37	0.55 -3.42
9. Have you had an attack of shortness of breath after exercise in the last 12 mo?	*	*	†	†
10. Have you had an attack of shortness of breath that came on during the day when you were at rest at any time in the last 12 mo?	2.05	0.85 -4.98	†	†
Constant	0.05		0.05	

A2 Score, Adult Asthma Score; GA2LEN Score, GA2LEN Asthma Epidemiological Score

A2 Score - Adult Asthma Score

GA2LEN Score – GA2LEN Asthma Epidemiological Score

The A2 score derivation was obtained by exploratory factor analysis as follows. The predictors “asthma diagnosis by a physician” and “asthma self-report” were highly correlated and had similar loading factors; however, because “asthma diagnosis by a physician” improved the Cronbach α of the final score, it was included, whereas “asthma self-report” was excluded. “Waking up with chest tightness” and “dry cough during the night not associated with infection” were excluded because they had a low item-total correlation. The best Cronbach α was obtained when “waking up with an attack of cough,” “waking up with an attack of shortness of breath,” and “having an attack of shortness of breath after exercise” were excluded. The final A2 score included 8 predictors in 2 factors with eigenvalues of 3.997 (predictors 2-5 and 10; **Table 8**) and 3.535 (predictors 6-8; **Table 8**).

GA2LEN Score – GA2LEN Asthma Epidemiological Score

A2 Score - Adult Asthma Score

For the GA2LEN score, “phlegm when coughing” was excluded because it had more than 95% responses in a single category; “waking up with chest tightness” and “hospitalization because of asthma” were excluded because they had a low item total correlation. The best Cronbach α was obtained when “waking up with an attack of cough” and “waking up with an attack of shortness of breath” were excluded. The final GA2LEN score included 6 predictors in 2 factors with eigenvalues of 2.954 (predictors 6-8; **Table 8**) and 2.860 (predictors 1, 4, and 5; **Table 8**).

Scores specifications and performance

AUC – Area Under the Curve

The discriminative properties of the developed scores were similar, with an AUC of about 90% (**Figure 5**). The A2 score had higher Cronbach a than the GA2LEN score (0.887 vs 0.852, respectively; **Figure 5**).

A.

	AUC using direct sum, % (95%CI)	AUC using weighted score, % (95%CI)	Number of Items	Cronbach's Alpha (95%CI)
A2-score	90.4 (87.0-93.9)	91.3 (87.9-94.7)	8	0.887 (0.872-0.900)
GA2LEN-score	89.0 (85.4-92.5)	90.5 (87.0-94.0)	6	0.852 (0.832-0.870)

B.

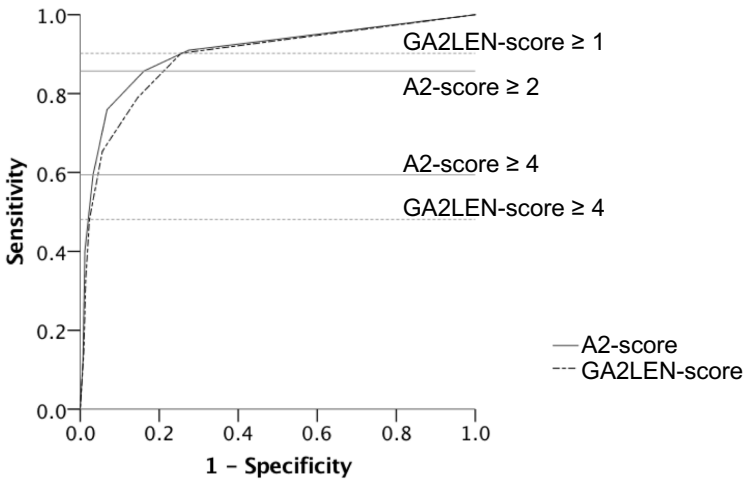


Figure 5: (A) Discriminative properties and internal consistency. (B) ROC curve of the scores, using participants from the derivation cohort (n = 560).

AUC: Area Under Curve; A2-score: Adult Asthma Epidemiological Score; GA2LEN-score: GA2LEN Asthma Epidemiological Score.

A2 Score - Adult Asthma Score

GA2LEN Score – GA2LEN Asthma Epidemiological Score

PPV – Positive Predictive Value

The scores obtained by the weighted sum (**Table 8**) were highly correlated with those obtained by the direct sum (Spearman correlation coefficient >0.98; P < 0.001). As so, the final result was the direct sum of the positive answers to the questions selected for each score, ranging from 0 to 8 for the A2 score and from 0 to 6 for the GA2LEN score.

Diagnostic accuracy measures were assessed for both scores and cohorts (**Table 9**). As expected, the definitions requiring more positive answers have higher specificity and PPV but lower sensitivity, indicating that the probability of having asthma increases with an increasing score.

On the basis of a PPV of 85% or more in both cohorts, we considered asthma to be present in patients with a sum of 4 or more positive answers (**Table 9**). Using this cut-off in the derivation cohort, the A2 score and the GA2LEN score had high accuracy (87.9% and 85.9%), high specificity (96.7% and 97.7%), and a sensitivity of 59.4% and 48.1%, respectively (**Table 9**). In the validation cohort, for the same cut-off based on PPV, the A2 score had a slightly higher accuracy compared with the GA2LEN score (89.4% vs 87.4%; **Figure 6**, C) and a higher sensitivity (48.3% vs 37.9%; **Figure 6**, A), but the same specificity (99.2%; **Figure 6**, A and **Table 9**) and false-positive rate (1%; **Figure 6**, E). The cut-off to rule out asthma was based on an NPV of 95% or more in both cohorts, which corresponds to a sum of less than 2 positive answers for the A2 score and 0 for the GA2LEN score (**Table 9**). Using this cut-off in the derivation cohort, the A2 score had a higher accuracy compared with the GA2LEN score (84.3% vs 78.2%) and a higher specificity (83.8% vs 74.5%; **Figure 6**, A), but both scores had high sensitivity (85.7% and 90.2%, respectively; **Figure 6**, A and **Table 9**). For this cut-off in the validation cohort, the A2 score had a higher accuracy compared with the GA2LEN score (89.4% vs 82.8%; **Figure 6**, B), but both scores had the same sensitivity (93.1%; **Figure 6**, A and **Table 9**); the scores also had similar NPVs (98.2% vs 98.0%, respectively, for the A2 score and the GA2LEN score; **Table 9**) and the same false-negative rate (7%; **Figure 6**, D).

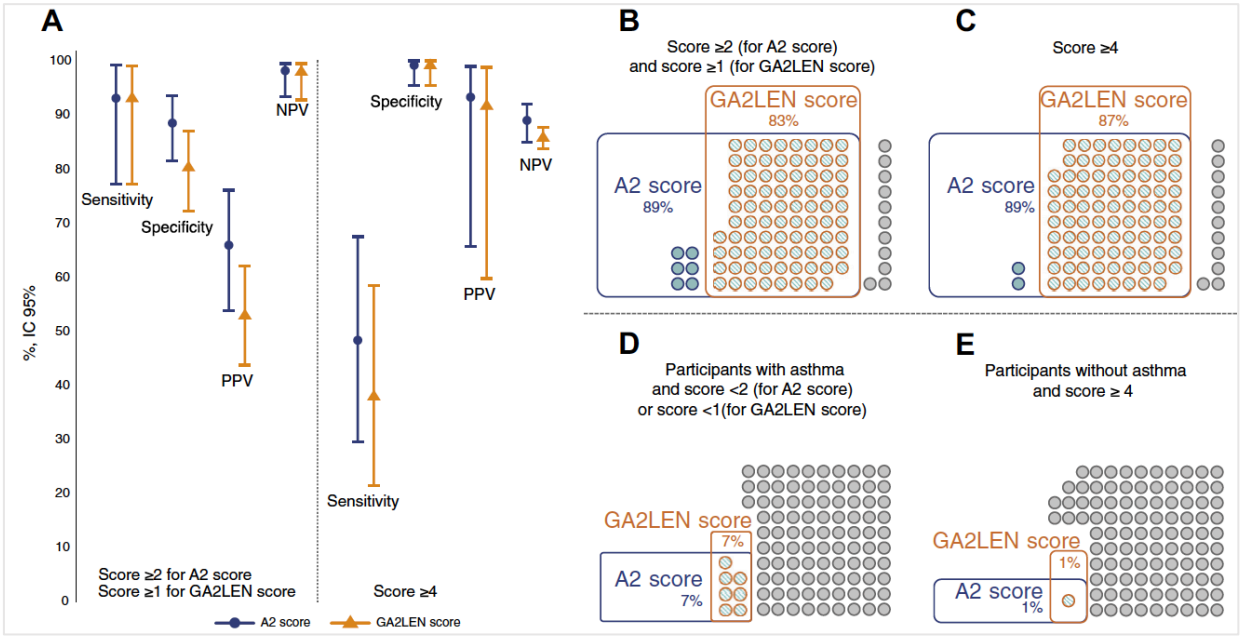


Figure 6: Diagnostic accuracy measures (A) and accuracy (B and C) of the 2 scores in patients from the validation cohort for considering possible asthma *(values ≥2 in the A2 score or values ≥1 in the GA2LEN score)* ***and probable asthma*** *(values ≥4);* ***false-negative rate (D) and false-positive rate (E).***

Table 9: Predictive values in derivation and validation cohorts

Score (no. of positive answers)	Derivation cohort (n=560) n (%)	Sensitivity % (95%CI)	Specificity % (95%CI)	PPV % (95%CI)	NPV % (95%CI)	Accuracy %	Validation cohort (n=151) n (%)	Sensitivity % (95%CI)	Specificity % (95%CI)	PPV % (95%CI)	NPV % (95%CI)	Accuracy %
A2-score												
Possible Asthma												
≥2*	183 (32.7)	85.7 (78.6-91.2)	83.8 (80.0-87.2)	62.3 (56.8-67.5)	95 (92.5-96.6)	84.3	41 (27.2)	93.1 (77.2-99.2)	88.5 (81.5-93.6)	65.9 (53.8-76.1)	98.2 (93.4-99.5)	89.4
≥3	130 (23.2)	75.9 (67.8-82.9)	93.2 (90.4-95.4)	77.7 (70.8-83.4)	92.6 (90.2-94.4)	89.1	24 (15.9)	65.5 (45.7-82.1)	95.9 (90.7-98.7)	79.2 (60.8-90.3)	92.1 (87.6-95.1)	90
Probable Asthma												
≥4†	93 (16.6)	59.4 (50.5-67.8)	96.7 (94.6-98.2)	85.0 (76.8-90.6)	88.4 (86.2-90.4)	87.9	15 (9.9)	48.3 (29.5-67.5)	99.2 (95.5-100.0)	93.3 (65.7-99.0)	89.0 (85.0-92.0)	89.4
≥5	70 (12.5)	46.6 (37.9-55.5)	98.1 (96.3-99.2)	88.6 (79.2-94.0)	85.5 (83.4-87.4)	85.9	12 (7.9)	37.9 (20.7-57.7)	99.2 (95.5-100.0)	91.7 (59.7-98.8)	87.1 (83.5-89.4)	87.4
≥6	58 (10.4)	39.9 (31.5-48.7)	98.8 (97.3-99.6)	91.4 (81.2-96.3)	84.1 (82.1-85.8)	84.8	10 (6.6)	31.0 (15.3-50.8)	99.2 (95.5-100.0)	90.0 (54.3-98.6)	85.8 (82.6-88.5)	86.1
≥7	39 (7.0)	26.3 (19.1-34.7)	99.1 (97.6-99.7)	89.7 (76.0-96.0)	81.2 (79.6-82.7)	81.8	7 (4.6)	20.7 (7.99-39.7)	99.2 (95.5-100.0)	85.7 (42.9-98.0)	84 (81.4-86.4)	84.1
8	20 (3.6)	12.8 (7.6-19.7)	99.3 (98.0-99.9)	85.0 (62.8-95.0)	78.5 (77.4-79.6)	78.8	2 (1.3)	6.9 (0.9-22.8)	100.0 (97.0-100.0)	100.0	81.9 (80.4-83.3)	82.1

A2 score, Adult Asthma Epidemiological Score; GA2LEN score, Global Allergy and Asthma Network of Excellence Asthma Epidemiological Score; PPV, Positive predictive value; NPV, negative predictive value. *Cut-off of ≥2 (for the A2 score) and of ≥1 (for the GA2LEN score) for considering possible asthma (NPV of 95% or more, simultaneously in derivation and validation cohorts). †Cut-off of ≥4 for considering probable asthma (PPV 85% or more, simultaneously in derivation and validation cohorts)

Table 9(cont): Predictive values in derivation and validation cohorts

Score (no. of positive answers)	Derivation cohort (n=560) n (%)	Sensitivity % (95%CI)	Specificity % (95%CI)	PPV % (95%CI)	NPV % (95%CI)	Accuracy %	Validation cohort (n=151) n (%)	Sensitivity % (95%CI)	Specificity % (95%CI)	PPV % (95%CI)	NPV % (95%CI)	Accuracy %
GA2LEN-score												
Possible Asthma												
≥1*	229 (40.9)	90.2 (83.8-94.7)	74.5 (70.1-78.5)	52.4 (48.1-56.7)	96.1 (93.6-97.6)	78.2	51 (33.8)	93.1 (77.2-99.1)	80.3 (72.2-87.0)	52.9 (43.7-62.0)	98.0 (92.8-99.5)	82.8
≥2	167 (29.8)	79.0 (71.0-85.5)	85.5 (81.8-88.7)	62.9 (57.0-68.4)	92.9 (90.4-94.8)	83.9	31 (20.5)	75.9 (56.5-89.7)	92.6 (86.5-96.6)	71.0 (55.8-82.6)	94.2 (89.4-96.9)	89.4
≥3	111 (19.8)	65.4 (56.7-73.4)	94.4 (91.8-96.4)	78.4 (70.7-84.5)	89.8 (87.4-91.7)	87.5	21 (13.9)	58.6 (38.9-76.5)	96.7 (91.8-99.1)	81.0 (60.7-92.1)	90.8 (86.4-93.8)	89.4
Probable Asthma												
≥4†	74 (13.2)	48.1 (39.4-57.0)	97.7 (95.7-98.9)	86.5 (77.2-92.4)	85.8 (83.7- 87.7)	85.9	12 (7.9)	37.9 (20.7-57.7)	99.2 (95.5-100.0)	91.7 (59.7-98.8)	85.8 83.7-87.7	87.4
≥5	50 (8.9)	33.1 (25.2-41.8)	98.6 (97.0-99.5)	88.0 (76.2-94.4)	82.6 (80.8- 84.2)	83.0	10 (6.6)	31.0 (15.3-50.8)	99.2 (95.5-100.0)	90.0 (54.3-98.6)	85.8 (82.6-88.5)	86.1
6	24 (4.3)	15.0 (9.4-22.3)	99.1 (97.6-99.7)	83.3 (63.5-93.5)	78.9 (77.7-80.1)	79.1	3 (2-0)	6.9 (0.9-22.8)	99.2 (95.5-100.0)	66.7 (15.8-95.5)	81.8 (80.2-83.2)	81.5

A2 score, Adult Asthma Epidemiological Score; GA2LEN score, Global Allergy and Asthma Network of Excellence Asthma Epidemiological Score; PPV, Positive predictive value; NPV, negative predictive value. *Cut-off of ≥2 (for the A2 score) and of ≥1 (for the GA2LEN score) for considering possible asthma (NPV of 95% or more, simultaneously in derivation and validation cohorts). †Cut-off of ≥4 for considering probable asthma (PPV 85% or more, simultaneously in derivation and validation cohorts)

.

The ECRHS score

ECRHS – European Community Health Survey

The previously developed ECRHS asthma score (Pekkanen et al., 2005) has 8 questions:

1. Have you been at all breathless when the wheezing noise was present?
2. Have you woken up with the feeling of tightness in your chest at any time in the last 12 months?
3. Have you had an attack of shortness of breath that came on during the day when you were at rest at any time in the last 12 months?
4. Have you had an attack of shortness of breath after exercise in the last 12 months?
5. Have you been woken up by an attack of shortness of breath at any time in the last 12 months?
6. Have you ever had asthma?
7. Have you had any asthma attack in the last 12 months?
8. Are you currently taking any medicines including inhalers, aerosols, or tablets for asthma?

We applied the ECRHS asthma score to our data, and its performance was tested in the derivation and validation cohorts. The AUC obtained by applying the previously developed ECRHS asthma score to our data was 86.8% (95% CI, 82.8%- 90.8%) and the Cronbach α was 0.826 (95% CI, 0.804-0.847).

The diagnostic accuracy measures are described in **Table 10**.

Table 10: Diagnostic accuracy measures of the ECRHS asthma score previously developed, using participants from the derivation and validation cohorts

Score (no. of positive answers)	Derivation cohort (n=560)						Validation cohort (n=151)					
	n (%)	Sensitivity % (95%CI)	Specificity % (95%CI)	PPV % (95%CI)	NPV % (95%CI)	Accuracy %	n (%)	Sensitivity % (95%CI)	Specificity % (95%CI)	PPV % (95%CI)	NPV % (95%CI)	Accuracy %
ECRHS-score												
Possible Asthma												
≥1*	244 (43.6)	87.2 (80.3-92.4)	70.0 (65.4-74.3)	47.5 (43.6-51.5)	94.6 (91.8-96.5)	74.1	60 (39.7)	93.1 (77.2-99.2)	73 (64.2-80.6)	45 (37.6-52.7)	97.8 (92.1-99.4)	76.8
≥2	147 (26.3)	74.4 (66.2-81.6)	88.8 (85.4-91.6)	67.4 (60.8-73.3)	91.8 (89.8-93.7)	85.4	29 (19.2)	72.4 (52.8-87.3)	93.4 (87.5-97.1)	72.41 (56.4-84.2)	93.4 (88.8-96.3)	89.4
≥3	89 (15.9)	54.1 (45.3-62.8)	96.0 (93.7-97.7)	80.9 (72.2-87.4)	87.1 (84.8-89.0)	86.1	16 (10.6)	51.7 (32.5-70.6)	99.2 (95.5-100.0)	93.8 (67.4-99.1)	89.6 (85.6-92.7)	90.1
Probable Asthma												
≥4†	68 (12.1)	45.9 (37.2-54.7)	98.4 (96.7-99.3)	89.7 (80.3-94.9)	85.4 (83.3-87.2)	85.9	12 (7.9)	37.9 (20.7-57.7)	99.2 (95.5-100.0)	91.7 (59.7-98.8)	87.1 (83.5-89.9)	87.4
≥5	44 (7.9)	28.6 (21.1-37.1)	98.6 (97.0-99.5)	86.4 (73.3-93.6)	81.6 (79.9-83.2)	82.0	6 (4.0)	17.2 (5.9-35.8)	99.2 (95.5-100.0)	83.3 (37.8-97.6)	83.5 (81.0-85.6)	83.4
≥6	34 (6.1)	22.6 (15.8-30.6)	99.1 (97.6-99.7)	88.2 (72.9-95.4)	80.42 (78.9-81.8)	80.9	5 (3.3)	13.8 (3.9-31.7)	99.2 (95.5-100.0)	80 (31.7-97.2)	82.9 (80.7-84.9)	82.8
≥7	18 (3.2)	12.0 (7.0-18.8)	99.5 (98.3-99.9)	88.9 (65.1-97.2)	78.4 (77.3-79.5)	78.8	3 (2.0)	10.3 (2.2-27.4)	100 (97.0-100.0)	100	82.4 (80.6-84.2)	82.8
8	7 (1.3)	4.5 (1.7-9.6)	99.8 (98.7-100.0)	85.7 (42.2-98.0)	77 (76.4-77.7)	77.1	2 (1.3)	6.9 (0.9-22.8)	100 (97.0-100.0)	100	81.9 (80.4-83.3)	82.1

ECRHS score, European Community Respiratory Health Survey Score; PPV, Positive Predictive Value; NPV, Negative Predictive Value. *Cut-off of of ≥1 for considering possible asthma (NPV of 95% or more, simultaneously in derivation and validation cohorts). †Cut-off of ≥4 for considering probable asthma (PPV 85% or more, simultaneously in derivation and validation cohorts)

STUDY II

Sá-Sousa A, Almeida R, Vicente R, Martins H, Freitas A, Fonseca JA.

High oral corticosteroid exposure and overuse of short-acting beta-2-agonists were associated with insufficient prescribing of controller medication: a nationwide electronic prescribing and dispensing database analysis (Submitted) (Sá-Sousa et al., sub)

Aims

We aim to quantify patients in high-risk of having adverse clinical outcomes, among patients with at least 1 prescription for respiratory disease or exacerbations medications, retrieved from the Portuguese electronic medical prescription and dispensing database. Specifically, we aim to describe the association of the exposure to high-dose of OCS and the SABA over-use with prescription and primary adherence to maintenance treatment for respiratory disease.

OCS – Oral corticosteroids

SABA – Short-Acting Beta2-Agonist

Methods

Study design

This was a one-year (2016) retrospective population-based analysis of a random sample of patients from the BDNP.

BDNP – Portuguese electronic prescription and dispensing database

Setting

The BDNP is the central system, responsible for the validation of all steps of the prescription-and-dispensing cycle in Portugal, and for the recording of all the prescription and dispensing data. The use of electronic prescriptions is compulsory in mainland Portugal, and the system of electronic prescriptions is implemented since 2014. The prescriptions must be filled at a community pharmacy by the patient. The implementation of the electronic medication dispensing system in each community pharmacy was concluded at the end of 2015. Details of BDNP are described in the 'Data source' section.

The population of interest in this study consists of patients to whom medication for respiratory and allergic diseases and/or exacerbations was prescribed at least once, between January 2016 and December 2016. The number of the prescriptions meeting these criteria was higher than to 250 million prescriptions, corresponding to 4 639 308 patients (45% of the Portuguese population). We retrieved 2% (n=103 647) of these patients, randomly selected from the BDNP database corresponding to 1 129 512 prescriptions (**Figure 7**). We assessed all the prescriptions of those aged

15 years old or above living in mainland Portugal (n= 82 714 patients). The number of patients in the sample per 100,000 Portuguese patients was calculated by multiplying the number of patients by the factor (45%/ 82 714).

Data were provided in an encrypted form by the government entity responsible for the electronic prescription and dispensing system, *SPMS-Serviços Partilhados do Ministério da Saúde* (Shared Services of the Ministry of Health). Data of the patients and of the prescribing physician had previously been anonymized by SPMS.

Participants

In this study we analysed the prescriptions (n=248 045, corresponding to 61 835 patients) between January 2016 and December 2016 for medication for respiratory disease and/or exacerbations (**Table 11**), from a sample of patients from the mainland Portugal, aged 15 years and above (**Figure 7**).

Table 11: Frequency of prescribed packages of medication for respiratory diseases and/or exacerbations.

	Packages (n=312 527)	
Medication for respiratory diseases, n %		
Maintenance		
ICS + LABA	37 007	11.8
LTRA	21 085	6.7
LAMA	15 897	5.1
LABA	10 738	3.4
ICS	10 368	3.3
LABA + LAMA	8 051	2.6
Relievers		
SABA	8 730	2.8
SAMA	5 639	1.8
SABA + SAMA	303	0.1
Other		
Expectorant (systemic)	24 857	8.0
Xanthine	8 475	2.7
Cough suppressant (systemic)	4 691	1.5
Cough suppressant with expectorant (systemic)	81	0.0
Anti Immunoglobulin E	5	0.0
Medication for exacerbation		
Exacerbation/infection markers		
Antibiotics	55 810	17.9
OCS	27 399	8.8
Other		
H1-antihistamines (systemic)	73 391	23.5

ICS, Inhaled Corticosteroids; LABA, Long-Acting Beta2 Agonists; LTRA, Leukotriene Receptors Antagonists; LAMA, Long-Acting Muscarinic Antagonist; SABA, Short-Acting Beta2 Agonist; SAMA, Short-Acting Muscarinic-Antagonist; OCS, Oral corticosteroids.

Variables

Persistent respiratory treatment (PRT) was defined as prescription for more than 2 packages of any of the six classes of respiratory maintenance medications: ICS alone or in fixed-dose combination with LABA; LTRA; LAMA alone or in a fixed-dose combination with LABA or LABA alone.

We analysed SABA usage in the sample of patients with at least one prescription for medication for respiratory disease and exacerbations whereas OCs usage was assessed only among patients on PRT, to reduce the confounding of its use for other conditions (**Figure 7**).

OCS users and SABA users were defined as patients that filled, respectively, at least 1 package of OCS or SABA at a community pharmacy.

ICS - Inhaled Corticosteroids

LABA - Long-Acting Beta2 Agonists

LTRA - Leukotriene Receptors Antagonists

OCS - Oral corticosteroids

SABA - Short-Acting Beta2 Agonist

OCS dosage was estimated for OCS users, considering that 1 dose of OCS contains 5mg of prednisolone or equivalent. SABA dosage was estimated for SABA users, considering that 1 dose contains 100µg of salbutamol or equivalent. The total annual amount of prednisolone-equivalent and salbutamol-equivalent was estimated.

Considering that 1 package of prednisolone contains 400mg of prednisolone (20 doses of 20mg each), OCS annual amount of prednisolone-equivalent was grouped in low-dose (>0: 400mg), medium dose (>400: <1600mg) and high dose (≥1600 mg); corresponding to up to 1; >1 to 3 and 4 or more packages of prednisolone (Sullivan et al., 2018).

ICS - Inhaled Corticosteroids

PRT - Persistent Respiratory Treatment

The one-year combinations of classes of respiratory maintenance treatment prescribed were assessed for each patient on PRT.

LABA - Long-Acting Beta2 Agonists

Outcomes

OCS high-dose exposure: ≥4 packages (20 doses of 20mg each) of prednisolone-equivalent, corresponding to ≥1600 mg of prednisolone-equivalent a year.

LTRA - Leukotriene Receptors Antagonists

SABA over-use: >1 canister (200 doses of 100 µg) of salbutamol-equivalent per month (GINA, 2018), corresponding to >240 000 µg of salbutamol-equivalent a year.

OCS - Oral corticosteroids

Ratio SABA-to-maintenance: ratio of the packages of SABA filled over packages of maintenance treatment filled.

SABA - Short-Acting Beta2 Agonist

SABA excessive use was defined as having at least one: 1) SABA over-use or 2) ratio SABA-to-maintenance above 1:1.

Maintenance-to-total: percentage of packages of maintenance treatment prescribed over the total (maintenance, relievers, and OCS) packages. This was dichotomized in <70% and ≥ 70%, based on previous research (Stanford et al., 2013). Insufficient prescription of maintenance treatment was considered for maintenance-to-total <70%.

Primary adherence to controller medication: percentage of packages redeemed by the patient at a community pharmacy over the packages

prescribed. This was dichotomized in ≤50% and >50% (medium adherence) and also in ≤70% and >70% (high adherence), to explore its association with high OCS exposure and with SABA over-use.

Statistical analysis

Descriptive statistics were used to characterize the population and the maintenance treatment prescribed.

OCS - Oral corticosteroids

The association of OCS high-dose exposure was explored using multinomial logistic regression for age, sex, maintenance-to-total, excessive SABA use and primary adherence to controller medication. The predictors included in the final model were: age (grouped into 15-44; 45-64 and >64 years old), sex and maintenance-to-total (dichotomized in <70% and ≥ 70%). All analyses were performed using RStudio (Version 1.1.456 – © 2009-2018 RStudio, Inc.). Adjusted odds ratios (OR) and 95%CI were reported for logistic regression results.

SABA - Short-Acting Beta2 Agonist

Results

Participants

In 2016, 33 640.9 per 100 000 patients were prescribed with at least 1 medication for respiratory diseases or exacerbations (**Figure 7**), 17 450.2 per 100 000 with at least 1 medication for respiratory diseases and 16 90.7 per 100 000 with prescriptions for antibiotics, OCS or H1-antihistamines only.

OCS - Oral corticosteroids

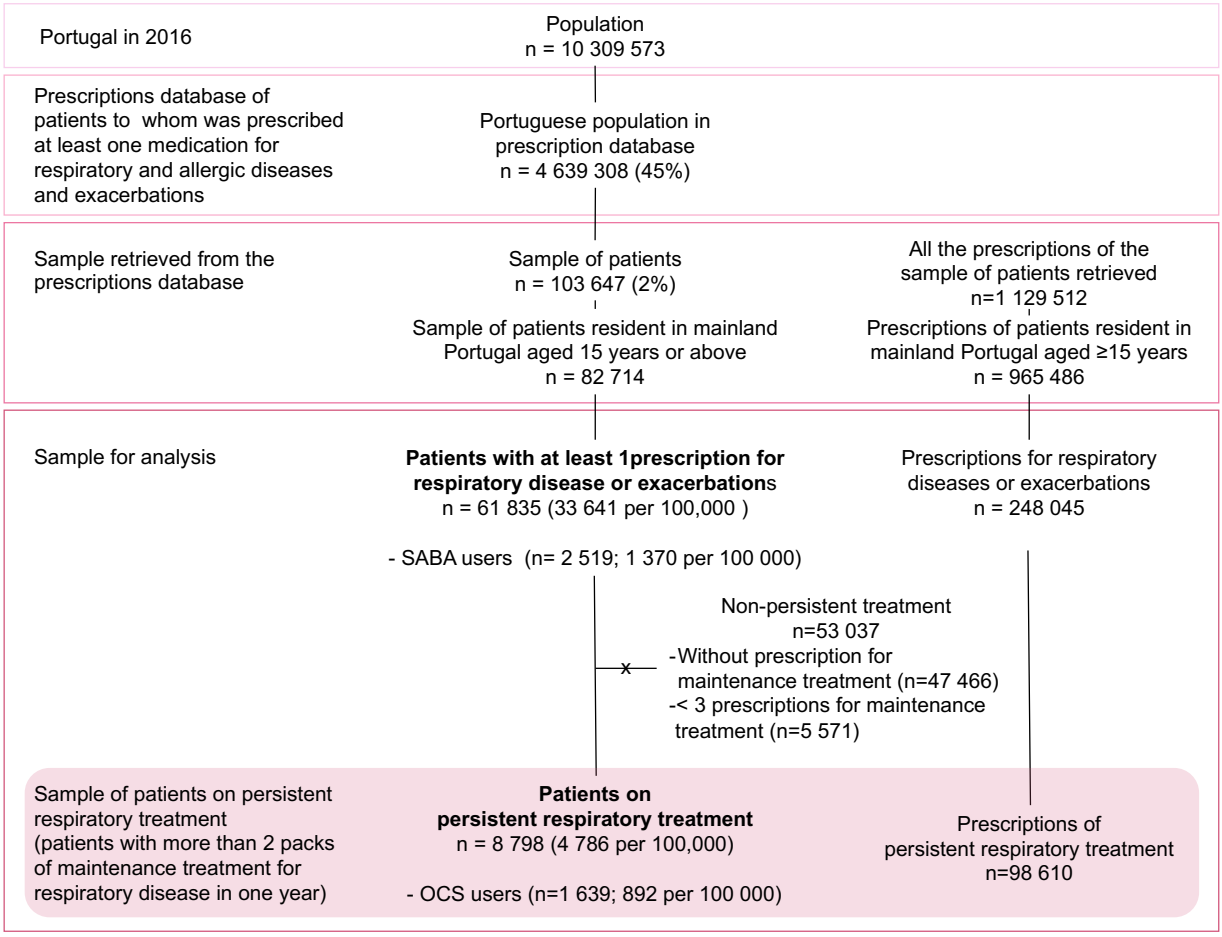


Figure 7: Flowchart of patients for analysis.

Persistent respiratory treatment (PRT), defined as prescriptions for more than 2 packages of respiratory maintenance medications, was found in 4 786.5 per 100 000 patients (**Figure 7**). Patients' characteristics are summarized in **Table 12**.

Table 12: Characteristics of patients on SABA over-use, on PRT with high OCS exposure, and on PRT.

	SABA over-use (23.9 per 100,000)		PRT with high OCS exposure (101.2 per 100,000)		PRT (4,786.5 per 100,000)		Total (33,640.9 per 100,000)	
Sex, % 95%CI								
Female	29.5	18.2-44.2	50.0	42.9-57.1	55.9	54.9-56.9	60.7	60.3-61.1
Male	70.5	55.8-81.8	50.0	42.9-57.1	44.1	43.1-45.1	39.3	38.9-39.7
Age, med P25-P75	61.0	50.8-73.5	69.0	57.3-78.8	64.0	47.0-76.0	53.0	37.0-69.0
Age, % 95%CI								
15:44	11.4	5.0-24.0	8.1	4.9-12.9	28.8	27.9-29.8	45.4	45.0-45.8
45:64	45.5	31.7-59.9	30.1	24.0-37.0	21.8	20.9-22.6	22.5	22.1-22.8
>64	43.2	29.7-57.8	61.8	54.7-68.5	49.4	48.3-50.4	32.1	31.7-32.4
Maintenance-to-total prescribed, % 95%CI								
No controller prescribed	15.9	7.9-29.4	-		-		76.8	76.4-77.0
>0%-20%	25.0	14.6-39.4	2.7	1.2-6.1	0.3	0.2-0.4	0.2	0.2-0.2
≥20%-<50%	31.8	20.0-46.6	35.5	29.0-42.6	3.3	2.9-3.7	1.0	1.0-1.1
≥50%-<70%	20.5	11.1-34.5	28.5	22.5-35.4	8.2	7.6-8.8	2.9	2.8-3.0
≥70%-<90%	6.8	2.3-18.2	28.0	22.0-34.8	16.3	15.5-17.1	2.3	2.2-2.4
≥90%-100%	0.0	0.0-8.0	5.4	2.9-9.6	72.0	71.0-72.9	16.8	16.5-17.0
Primary adherence to controller medication, % 95%CI								
0%	10.8	4.3-24.7	3.8	1.8-7.6	6.9	6.4-7.4	13.9	13.3-14.4
>0%-20%	5.4	1.5-1.8	5.4	2.9-9.6	5.2	4.8-5.7	3.2	2.9-3.5
>20%-50%	13.5	5.9-27.9	31.7	25.4-38.7	28.2	27.3-29.1	19.8	19.1-20.5
>50%-70%	13.5	5.9-27.9	23.1	17.6-29.7	18.1	17.2-18.9	25.7	24.5-27.0
>70%-90%	35.1	21.8-51.2	21.0	15.7-27.4	19.4	18.6-20.2	27.6	26.3-28.9
>90%-100%	21.6	11.4-37.2	15.1	10.6-20.9	22.3	21.4-23.1	40.2	39.4-41.0

SABA, short-acting beta 2 agonist; PRT, persistent respiratory treatment; OCS, oral corticosteroids; med, median; P25-P75, Percentiles 25-75; CI, Confidence Interval.

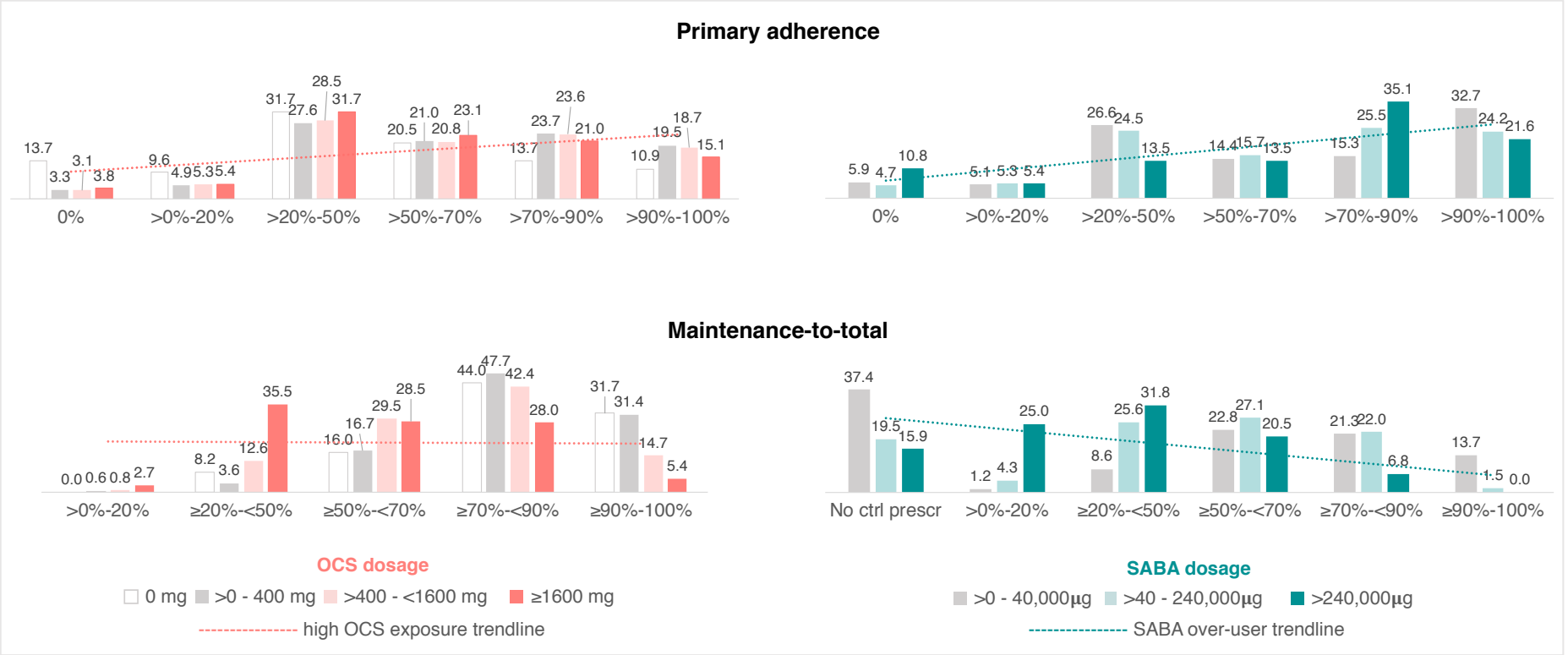


Figure 8: Frequency (%) of SABA users and OCS users on persistent respiratory treatment, by primary adherence to controller medication and ratio maintenance-to-total.

OCS usage

OCS - Oral corticosteroids

PRT – Persistent Respiratory Treatment

OCS was prescribed to 22.0% (95%CI 21.1-22.8) of the patients on PRT (1 051.1 per 100 000) and dispensed to 18.6% (95%CI 17.8-19.5). Maintenance-to-total ratio of 70% or more was associated with a lower likelihood of having at least one dispensing of OCS (crude OR, 95%CI; 0.2, 0.1-0.2) in patients on PRT.

Most of the OCS users were exposed to a low dose (>0: 400mg) of prednisolone-equivalent (57.6%, 95%CI 55.2-60.6), still, 101.2 per 100 000 (11.3%, 95%CI 9.9-13.0) were exposed to a high-dose (≥1600 mg). Two-thirds of the patients exposed to high-dose of OCS had a ratio maintenance-to-total below 70% and 38.2% below 50% (**Table 12** and **Figure 8).**

SABA usage

SABA - Short-Acting Beta2 Agonist

SABA was prescribed and dispensed to 1 370.4 per 100 000 patients; 82.6% (95%CI 81.0-84.0) filled 2 or fewer canisters of salbutamol-equivalent, 15.7% (95%CI 14.3-17.1) filled 2 to 12 canisters and 1.7% (95%CI 1.3-2.3) were SABA over-users corresponding to 23.9 per 100 000 patients (**Table 13**). Excessive use of SABA (defined as SABA over-use or ratio SABA-to-maintenance above 1:1) was found in 10.5% of the SABA users, corresponding to 144.2 per 100 000 patients.

Table 13: Frequency of patients by SABA canisters dispensed in one-year period.

	Patients	
SABA canisters*, n %		
≤ 2	2080	82.6
>2 - 4	213	8.5
>4 - 8	126	5.0
>8 - 12	56	2.2
>12	44	1.7

*1 canister contains 200 doses of 100 µg of salbutamol-equivalent.

SABA over-users filled between 260 000 µg and 1 540 000 µg of salbutamol-equivalent, corresponding to a mean of 12 SABA inhalations per day per patient.

About 1/6 of the over-users were not prescribed any controller medication (**Table 12**). Among those with a prescription for maintenance treatment, 77% had maintenance-to-total below 70%, and 57% below 50% (**Table 12** and **Figure 8**).

Primary adherence

In patients to whom maintenance treatment was prescribed, primary adherence to controller medication (median %, Percentile 25 - Percentile 75) for the SABA over-users was 75.0% (47.6-88.9); for all PRT patients was 66.7% (33.3-87.5) and for the patients on PRT exposed to high-dose of OCS was 59.6% (37.5-82.9) (**Table 12** and **Figure 8**). Primary adherence to controller medication >50% was not associated with reduced risk of high OCS exposure nor with SABA over-use (OR, 95%CI; 0.9, 0.7-1.2 and 1.4, 0.7-2.9, respectively). Similar results were observed for primary adherence to controller medication >70% (OR, 95%; 1.4, 0.7-2.7 and 0.9, 0.7-1.2, respectively for SABA over-use and high OCS exposure).

SABA - Short-Acting Beta2 Agonist

PRT – Persistent Respiratory Treatment

One-year maintenance treatment combinations

PRT – Persistent Respiratory Treatment

SABA - Short-Acting Beta2 Agonist

OCS - Oral corticosteroids

ICS - Inhaled Corticosteroids

LABA - Long-Acting Beta2 Agonist

LAMA – Long-Acting Muscarinic Antagonist

LTRA - Leukotriene Receptors Antagonists

Among patients on PRT exposed to a high-dose (≥1600 mg) of OCS, the most frequent combinations of maintenance treatment were ICS+LABA or ICS+LABA+LAMA. The combinations ICS+LABA+LAMA; ICS+LTRA+LABA+LAMA or ICS+LTRA+LABA were found in 44% of these patients and monotherapy of either ICS or LTRA in 8% (**Table 14**).

Most patients on PRT (61%) were prescribed for combinations of ICS+LABA, ICS+LABA+LTRA or ICS+LABA+LAMA (**Table 14**). Prescription of LTRA+LABA or/and LAMA, not recommended in the guidelines (GINA, 2018; GOLD, 2019), was prescribed to 2% of the patients.

Table 14: The one-year combinations of classes of medication prescribed to the 8 798 patients on PRT

	PRT with high OCS exposure (n=186)		PRT	
Maintenance treatment prescribed	n	%	n	%
ICS+LABA	61	32.8	3113	35.4
ICS+LABA+LAMA	46	24.7	1008	11.5
ICS+LTRA+LABA+LAMA	21	11.3	355	4.0
ICS+LABA+LTRA	15	8.1	1204	13.7
LABA+LAMA	13	7.0	635	7.2
ICS monotherapy	8	4.3	310	3.5
LTRA monotherapy	6	3.2	916	10.4
LABA monotherapy	5	2.7	340	3.9
ICS+LAMA	3	1.6	143	1.6
LAMA monotherapy	3	1.6	476	5.4
ICS+LTRA	2	1.1	126	1.4
LTRA+LABA	1	0.5	50	0.6
LTRA+LAMA	1	0.5	41	0.5
ICS+LTRA+LAMA	1	0.5	22	0.3
LTRA+LABA+LAMA	0	0.0	59	0.7

PRT, Persistent Respiratory Treatment; SABA, Short-Acting Beta2 Agonist; OCS, Oral corticosteroids; ICS, Inhaled corticosteroids; LABA, Long-Acting Beta2 Agonists; LTRA, Leukotriene Receptors Antagonists; LAMA, Long-Acting Muscarinic Antagonist.

Factors associated with high OCS exposure

High OCS exposure was independently associated with male sex, increased age and lower ratio maintenance-to-total prescribed medication, but not with excessive SABA use nor with primary adherence to controllers (**Table 15).** Results from the multinomial logistic regression showed that OCS high dose exposure was positively associated with maintenance-to-total <70%, age above 45 years old and male sex (**Figure 9**).

OCS – Oral corticosteroids

SABA - Short-Acting Beta2 Agonist

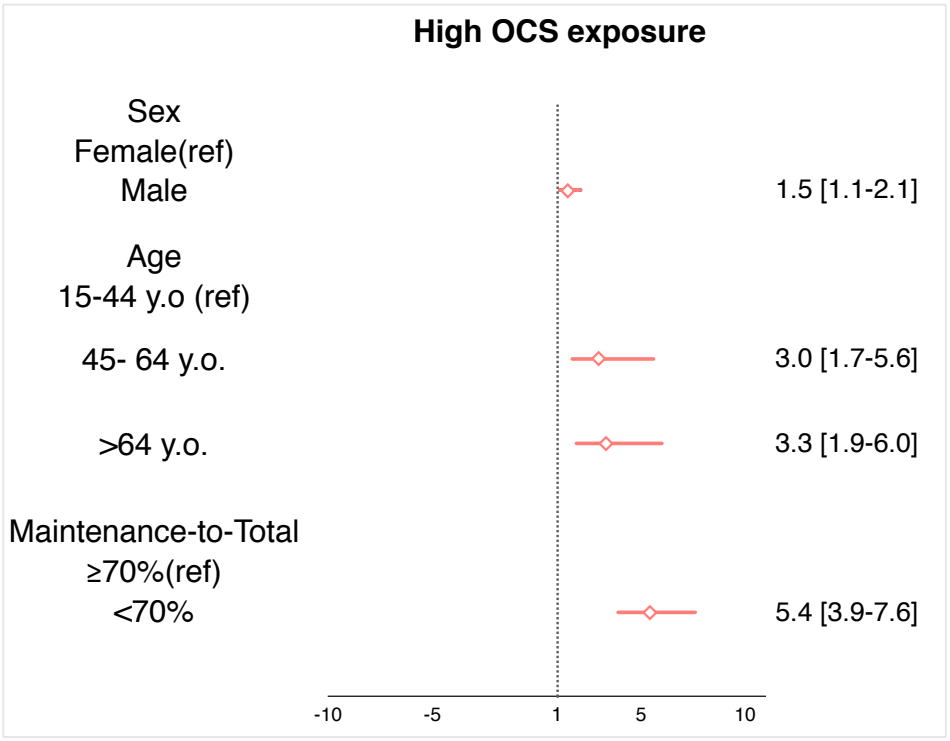


Figure 9: Factors associated to high OCS (adjusted OR [95%CI]) exposure.

Table 15: Unadjusted association of sex, age, maintenance-to-total prescribed medication and primary adherence to high OCS exposure.

	Total OCS		Low/medium dose OCS		High dose OCS		p-value	Crude OR	
								OR	95%CI
Sex, n %							0.03		
Female	1119	57.9	1026	58.8	93	50.0		1	
Male	813	42.1	720	41.2	93	50.0		1.4	1.1-1.9
Age, n %							<0.001		
15:44	384	19.9	369	21.1	15	8.1		1	
45:64	559	28.9	503	28.8	56	30.1		2.7	1.6-5.1
>64	989	51.2	874	50.1	115	61.8		3.2	1.9-5.8
Maintenance-to-total (a) n %							<0.001		
>0%-20%	15	0.8	10	0.6	5	2.7		1	
≥20%-<50%	188	9.7	122	7.0	66	35.5		1.1	0.4-3.6
≥50%-<70%	408	21.1	355	20.3	53	28.5		0.3	0.1-1.0
≥70%-<90%	847	43.8	795	45.5	52	28.0		0.1	0.0-0.4
≥90%-100%	474	24.5	464	26.6	10	5.3		0.0	0.0-0.2
Maintenance-to-total (b), n %							<0.001		
<70%	611	31.6	487	27.9	124	66.7		5.2	3.8-7.2
≥70%	1321	68.4	1259	72.1	62	33.3		1	
Excessive SABA use, n %							0.3		
No	1890	97.8	1710	97.9	180	96.8		1	
Yes	42	2.2	36	2.1	6	3.2		1.6	0.6-3.4
Primary adherence to controller medication(a), n %							0.8		
0%	94	4.9	87	5.0	7	3.8		1	
>0%-20%	111	5.7	101	5.8	10	5.4		1.2	0.5-3.5
>20%-50%	558	28.9	499	28.6	59	31.7		1.5	0.7-3.6
>50%-70%	407	21.1	364	20.8	43	23.1		1.5	0.7-3.7
>70%-90%	423	21.9	384	22.0	39	21.0		1.3	0.6-3.2
>90%-100%	339	17.5	311	17.8	28	15.1		1.1	0.5-2.9
Primary adherence to controller medication (b), n %							0.7		
≤50%	763	39.5	687	39.3	76	40.9		1	
>50%	1169	60.5	1059	60.7	110	59.1		0.9	0.7-1.3

OCS, Oral corticosteroids; SABA, Short-Acting Beta2 Agonist; OR, Odds Ratio.

STUDY III

Sá Sousa A, Pereira AM, Fonseca JA, Azevedo LF, Abreu C, Arrobas A, et al.

Asthma control and exacerbations in patients with severe asthma treated with omalizumab in Portugal.

Rev Port Pneumol. 2015;21(6):327–33. (Sá Sousa, Pereira et al., 2015)

Aims

The aim of this prospective multicentre study was to assess the clinical effect of omalizumab in Portuguese patients with severe persistent allergic asthma, specifically concerning asthma control and exacerbations.

Methods

Design

This was a multicentre, descriptive, observational, prospective study, conducted during routine asthma care. The target population consisted of individuals treated with omalizumab for severe persistent asthma.

Setting and participants

The study was conducted in seven Pulmonology and Allergology departments from six hospitals in the north and centre regions of mainland Portugal. In each unit, all asthma patients under treatment with omalizumab were included, regardless of their age, length of previous therapy with omalizumab or actual treatment schedule. All patients had omalizumab treatment approved by the therapeutic commission and hospital administration, as required in Portuguese hospitals. Minimal criteria for approval of omalizumab treatment for asthma are uncontrolled, severe persistent, allergic asthma, with frequent exacerbations.

Data collection

Data were collected at each routine visit for omalizumab administration, during 12 consecutive months. In the participating centres, omalizumab was administered at 2- or 4-week intervals with doses based on IgE serum levels and body weight, as recommended by European Medicines Agency (EMEA, 2014). A structured form, to be filled by both the patient and the nurse responsible for omalizumab administration, was developed in order to standardize data collection at the different study sites. This form included questions on asthma worsening, medication intake, healthcare resources utilization and work/school absenteeism; information on side effects was possibly related with the previous treatment administration.

IgE – Immunogloblulin E

CARAT - Control of Allergic Rhinitis and Asthma Test

The CARAT questionnaire (Fonseca et al., 2010, 2012) was also part of the form.

Data collection spanned from January 2011 to December 2013 in the different departments. More details on data source is described in the 'Data source' section.

Outcomes

Asthma and rhinitis control were defined by a CARAT global score >24. CARAT lower airways score ≥16 and an upper airways score >8 were the cut-off values for control of, respectively, the lower and upper airways only.

OCS – Oral corticosteroids

Asthma exacerbation was defined as having an unscheduled medical care or increases in OCS intake because of asthma. *Asthma worsening, unscheduled medical care and increases in OCS intake* were based on a positive answer to the questions: ''In the last 3 days, have you felt your asthma getting worse?''; ''Since the last administration, have you had any unscheduled healthcare visit or emergency room visit because of your asthma?'' and ''In the last 3 days, did you need to start or increase oral corticosteroid intake?'', respectively.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 21 (2012 SPSS Inc., IBM Company, Chicago, US). Categorical and continuous variables were analysed using descriptive statistics as appropriate. Survival analysis was used to assess the time until the first exacerbation. Generalized Estimating Equations, considering the multiple measurements in this longitudinal design, were used to assess variations in control scores over time; a Wald Chi-square test with a *p-value* of <0.05 was considered statistically significant. As CARAT evaluates a 4-week period, control scores were analysed for visits with at least a 4-week interval.

Results

A total of 48 adults with severe persistent allergic asthma were included (**Table 16**).

Table 16: Characteristics of the study population (n=48).

Female (n, %)	36	75
Age (mean, SD)	52	10
Hospital units (n %)		
Centro Hospitalar e Universitário de Coimbra, EPE – Pulmonology	15	31
Centro Hospitalar São João, EPE – Allergology	12	25
Centro Hospitalar São João, EPE – Pulmonology	8	17
Centro Hospitalar do Porto – Allergology	6	13
Centro Hospitalar de Trás-os-Montes e Alto Douro – Pulmonology	4	8
Hospital Pedro Hispano – Allergology	2	4
Centro Hospitalar do Alto Ave – Allergology	1	2
Follow-up period, months (median, min-max)	12	3-12
Visits with reported OCS intake (mean % per patient, SD)	15	32

SD – standard deviation; OCS – oral corticosteroids

Patients were under treatment with omalizumab for between 0 and 67 months, most for more than 3 years (median, 45 months). Most patients (n = 31, 65%) were prospectively followed for 12 months and five were followed for less than 9 months (**Table 4** in the 'Data source' section). During the study, the median (min-max) number of medical visits for each patient was 14 (7-28).

Asthma control

CARAT scores were analysed for visits with at least a 4-week interval in a total of 414 visits. During the study period, asthma was controlled in 34% of the visits; the mean (SD) CARAT score was 20.4 (7.5). There was no statistically significant variation in any of the CARAT mean scores during the 12-month follow-up period ($p > 0.05$).

CARAT - Control of Allergic Rhinitis and Asthma Test

Asthma exacerbations

During follow-up, 26 patients (54%) had at least one asthma exacerbation (**Figure 10**); the 12-month rate of asthma exacerbations per patient was 1.7 (1.3 increases with OCS intake and 0.6 unscheduled medical care). The first exacerbation occurred on average (mean, 95% CI) 7.2 (5.9-8.6) months after entering the study. There was no clear pattern of distribution of asthma exacerbations and control throughout the year (**Figure 11**). Thirty-three (69%) participants reported at least one period of worsening of asthma symptoms without needing unscheduled medical care or OCS intake. Eight (17%) had more than four periods of worsening of asthma.

OCS – Oral corticosteroids

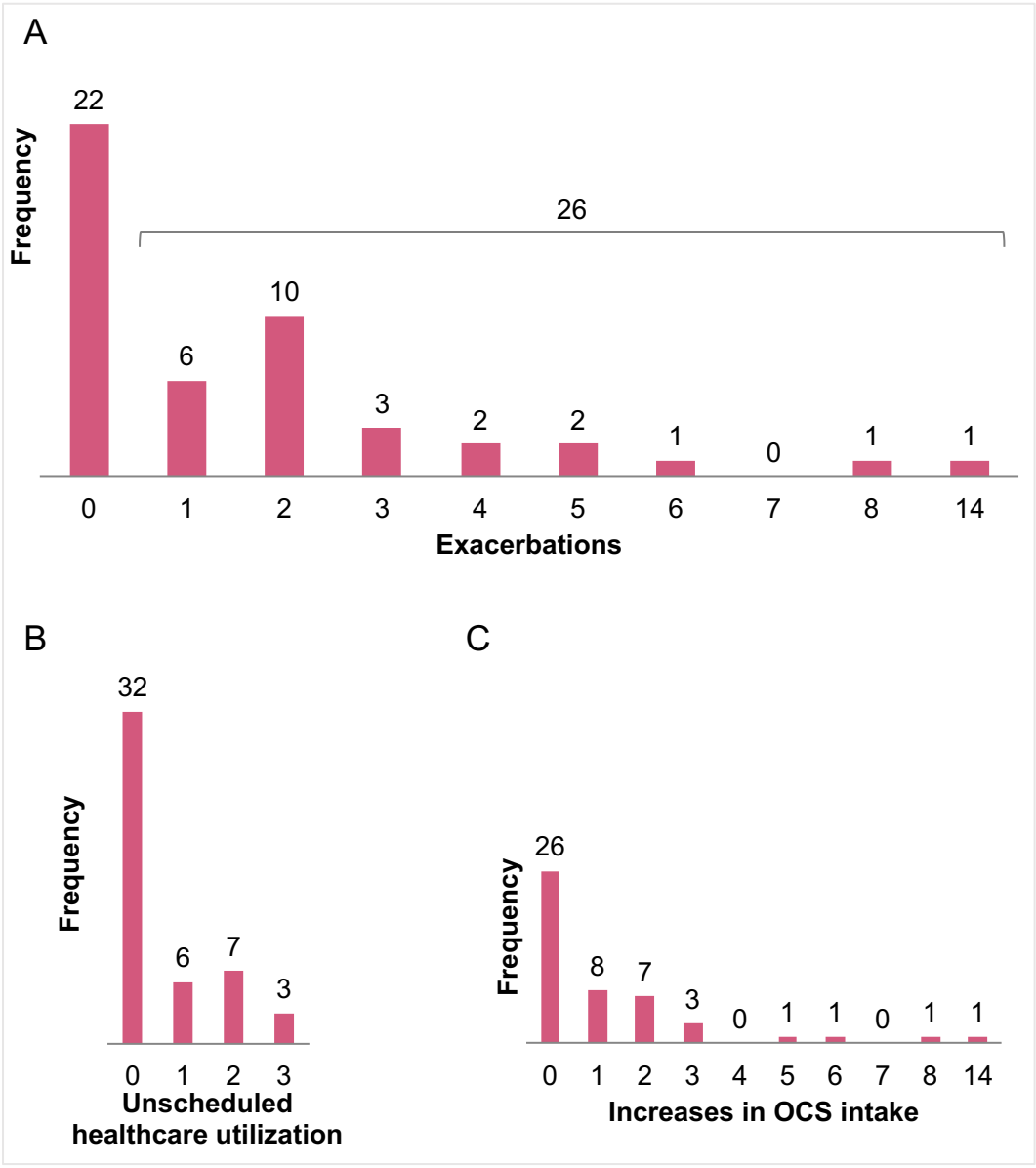


Figure 10: Distribution of the number of exacerbations (A) unscheduled medical care (B) and increases in OCS intake (C) in the 12-month follow-up period. *OCS, Oral corticosteroids*

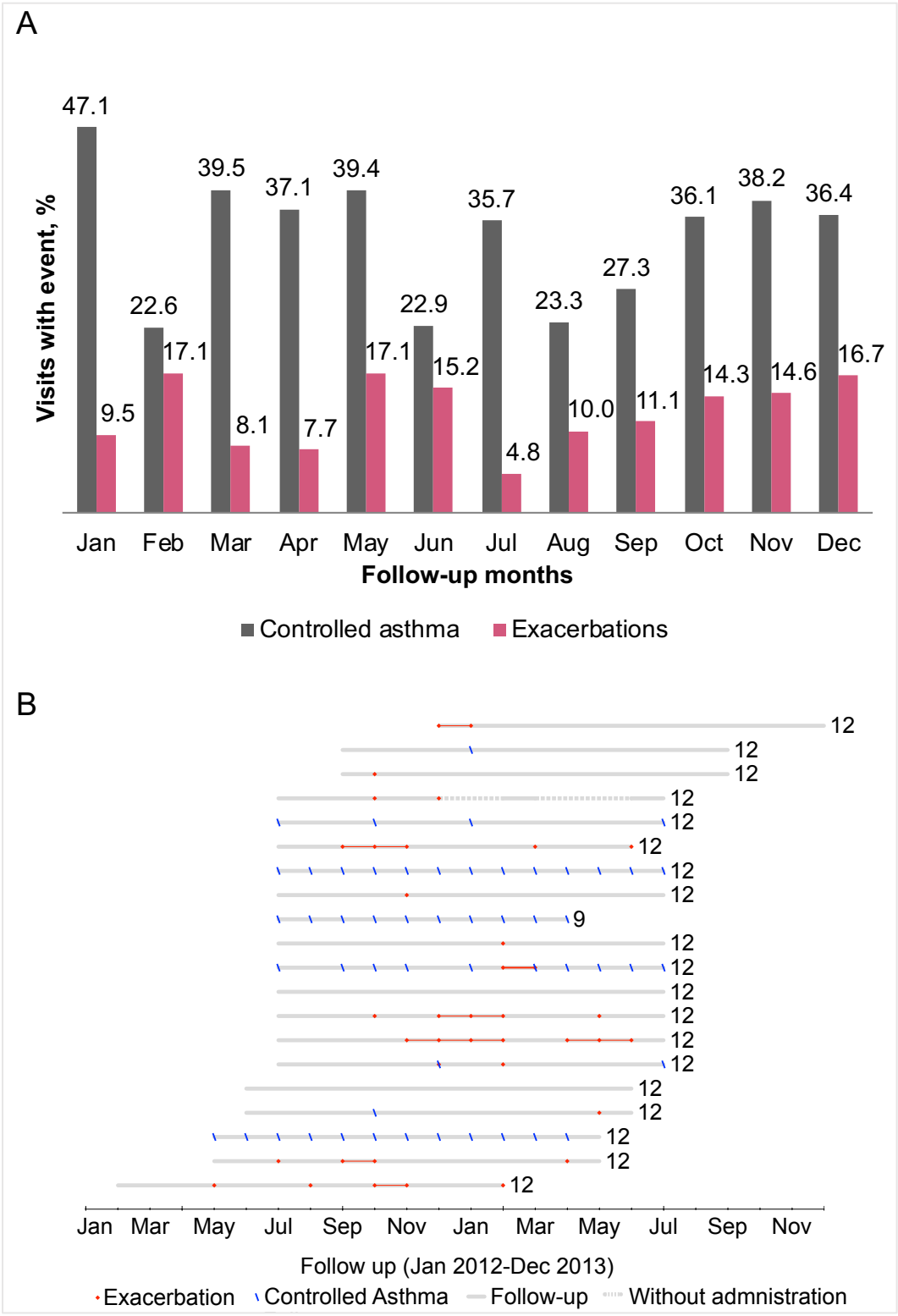


Figure 11: (A) Percentage of visits reporting controlled asthma and exacerbations according to the month of the year (all patients included). (B) Reports of controlled asthma and exacerbations during follow-up, per patient. *In (B) numbers on the right indicate total months of follow-up; continuous grey lines represent the follow-up period and dashed grey lines interruptions in omalizumab treatment; red dots represent visits with report of exacerbation and blue dashes visits with CARAT global score >24---data from the 20 patients treated with omalizumab in Centro Hospitalar São João, EPE.*

Oral corticosteroids intake

OCS – Oral corticosteroids

Fourteen patients (29%) took OCS because of asthma at least once during the follow-up. Seven patients were taking daily OCS in the first visit and five of them took OCS during the full length of the study, in a mean (SD) dosage of 18.9 (4.4) mg prednisolone/day. Comparing the first and the last trimesters of the study, seven patients reduced the daily dosage of OCS, four patients reported a dosage increase, and two had no variation. Overall, the daily dosage of OCS had a non-significant reduction of 41.6% (**Figure 12**). One patient had a follow-up inferior to two trimesters and was not considered for comparison purposes.

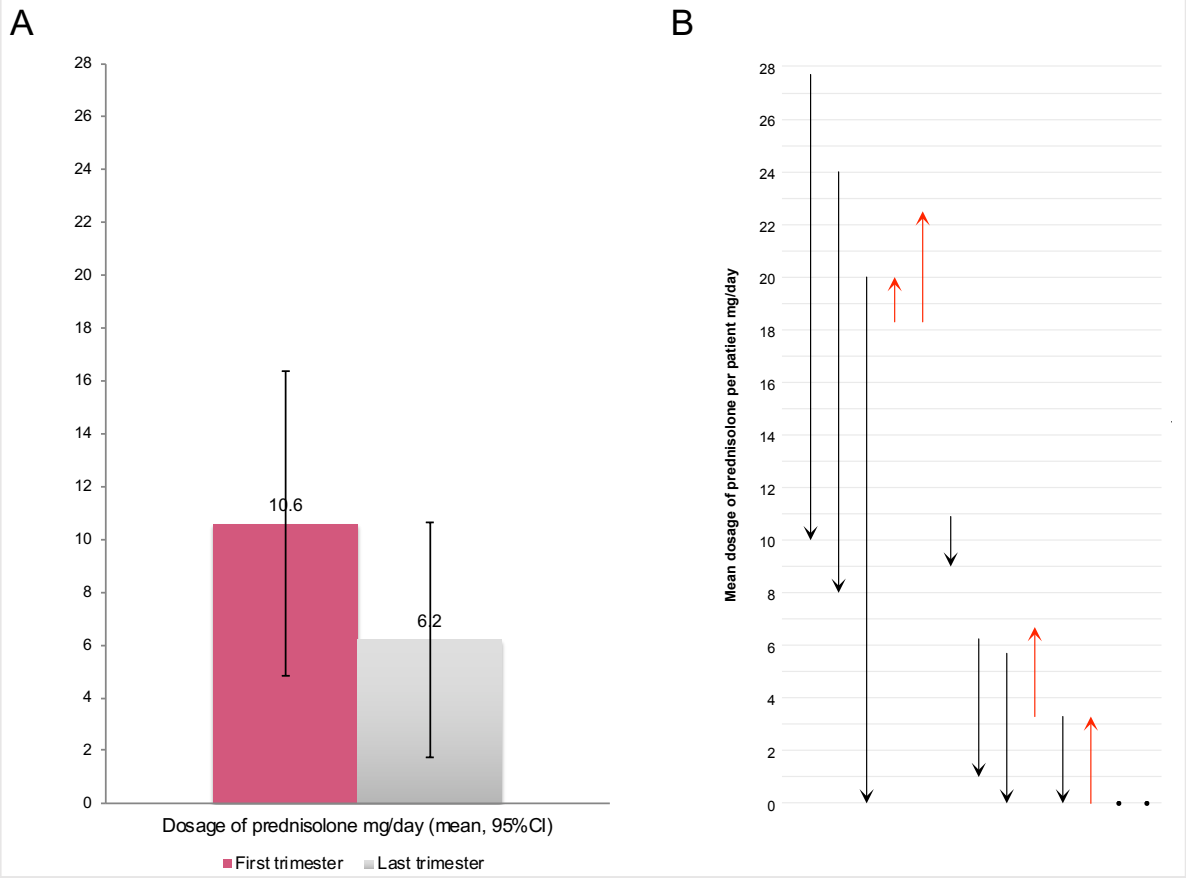


Figure 12: Mean dosage of oral corticosteroids intake in the first and last trimester of the follow-up year (considering the 13 patients with OCS intake), (A) Overall reduction (B) Per patient. *In (B) arrows represent the dose variation from the first to the last trimester; red lines represent increases and blue lines decrease in the dosage of oral corticosteroid intake; and dots represent no variation in the dosage.*

STUDY IV

Sá-Sousa A, Fonseca JA, Pereira AM, Ferreira A, Arrobas A, Mendes A, et al.

The Portuguese Severe Asthma Registry: Development, Features, and Data Sharing Policies.

Biomed Res Int. 2018;2018. (Sá-Sousa et al., 2018)

Aims

In this study, we describe the development and implementation of the Portuguese Severe Asthma Registry (*Registo de Asma Grave Portugal* - RAG), its features, and data sharing policies.

Methods

The purpose of the Portuguese Severe Asthma Registry (*Registo de Asma Grave Portugal*-RAG) is to gather evidence on severe asthma in Portugal contributing to eliminate information gaps and support the adoption of evidence-based health care policies. Specifically, the registry aims at 1) improving the healthcare delivery of severe asthma by identifying the best diagnosis and treatment practices and by standardizing disease management processes and clinical records; and 2) supporting collaborative research projects by promoting the cooperation between centres and assist with the implementation of research projects. For this, a collaboration between different stakeholders was established: the medical experts from REAG, the investigators from CINTESIS (Center for Health Technology and Services Research), and the software development company VirtualCare.

The development and implementation processes of RAG are summarized in **Figure 13**.

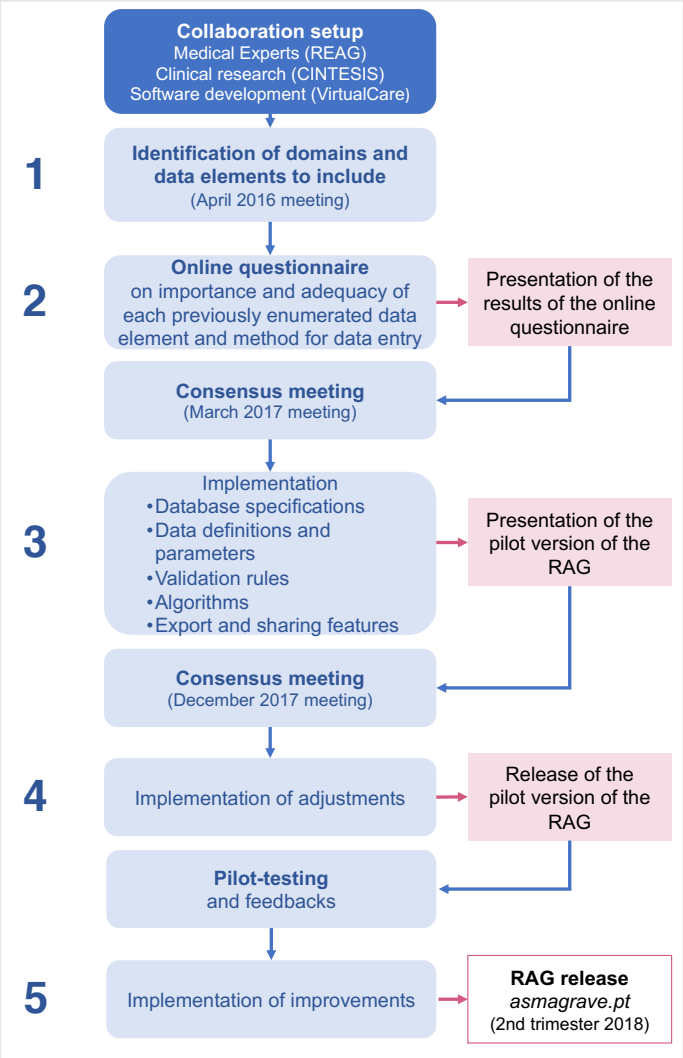


Figure 13: Development and implementation process of RAG. *RAG, Registo de Asma Grave Portugal*

Definition of Contents

RAG – Registo de Asma Grave Portugal

GINA – Global Initiative for Asthma

The criteria for patient inclusion in RAG, the domains, and data elements to be registered were defined by a multistep consensus method. The patients' inclusion criteria were based on the definition of Severe Asthma by GINA (GINA, 2018): (1) patient with treatment on step 4 or 5 according to GINA recommendations; and (2) verified optimization of treatment adherence and comorbidities management. An additional inclusion criterion was (3) the patient's signed consent to have his/her data included in the registry. During a meeting (April 2016), the domains and data elements were enumerated, based on the medical expertise of the network and taking into consideration the variables existing in three existing European Registries: the Belgian, the German, and the United Kingdom Severe Asthma Registries. Both data elements to be included in the initial patient registry and relevant follow-up information were identified. Different data entry methods were considered, so as to reduce the burden of response.

REAG – Rede de Especialistas em Asma Grave

An online questionnaire sent to 79 medical specialists from REAG was used to explore the importance of each data element and adequacy of data entry method. A total of 34 participants (43%) completed the questionnaire. For each domain, data elements and methods for data entry were chosen when gathering at least 80% of the votes. Comments and suggestions regarding additional variables or different data entry methods were also considered. The results of the questionnaire were presented in a meeting (March 2017) and disagreements were solved by consensus.

Features

Database specifications concerning data definitions and parameters and data validation rules were determined. To assist confirmation of the first criterion and support decision-making, an algorithm to automatically determine the step of treatment based on currently used asthma medication was created. The following additional features were implemented:

(i) Support on data entry by automatic validation of the inserted data and error messages
(ii) Creation of automatic reports, based on the information stored, to be integrated into the institutional electronic health record (the data recorded are exportable in natural language by generating a text that mimics clinical notes)
(iii) Graphic display of aggregated data on patients' inclusion by healthcare centre
(iv) Display for each physician a list of their patients and date of the last medical appointment
(v) At follow-up visit, automatic display of the information inserted in the last appointment for specified measurements
(vi) Export features for potential data exchange with international severe asthma databases and the pharmacovigilance authorities
(vii) Automatic emails with status report of each registration

Security and Data Sharing Policies.

Security features compliant with the new European General Data Protection Regulation (GDPR) (Council of the European Union & European Parliament, 2016) and required procedures according to this legislation are being incorporated into the platform.

The registry was built on a framework residing in a server hosted by VirtualCare. This server was configured with a Secure Sockets Layer (SSL) certificate from Comodo Security Solutions, Inc., ensuring that all data transferred between the web server and browsers remain private and

integral. The access to the database is restricted, requiring authentication (using health professional number and password) and all accesses to the database are stored and traceable. All changes to the database are also stored; each change generates a new document; the old document becomes out of date allowing the tracking of changes (when, where, and by whom changes were made to the documents).

RAG – Registo de Asma Grave Portugal

RAG does not record any identifiable personal data from patients (e.g., date of birth is replaced by the year of birth, no Identification numbers are registered, and patients' names are pseudo-anonymized so replaced with a code number) (Article 29 Data protection working party, 2014). The patients' participation on RAG is free and voluntary, and patients may, in any moment and without penalty, withdraw the registry or verify and/or delete their data, by contacting the technical support. Patients are informed on the purposes of RAG, the data collected, and the implications of participating in this registry. The informed consent form is automatically generated at the time of inclusion. Only patients that agree, by a clear affirmative consent given by a written statement, to the storage, processing, and sharing of data belonging to him/her are included in RAG. The signed consent forms are uploaded into the application server file system, encrypted using phpseclib's library of PHP, which allows the usage of one of its encryption algorithms combined with a private key. When encrypted, the consent file cannot be read unless the file decryption is activated with the correct combination of algorithm and private key. The algorithm and private key are known only to VirtualCare.

REAG – Rede de Especialistas em Asma Grave

An informed consent is also required by physicians who are registered in RAG since they provide identifiable personal data for that registration, namely, their name, health professional number, and email address. At the time of registration, physicians must indicate their acceptance by ticking a box with a clear statement on the storage and processing of their personal data. The registration of each physician in RAG must be validated by at least one of five members of REAG, designated coordinators of RAG.

RAG – Registo de Asma Grave Portugal

Data within RAG belongs primarily to each patient and then to the physician that inserted patients' data into the registry. Each physician is responsible for the management of the data that he/she inputted, belonging to his/her patients. Access to patients' data by their physicians is based on the Role Based Access Control model that associates privileges and permissions to the roles (e.g., professional categories). This model allows for an easier administration and independence in relation to the system users and permissions associated with its resources.

After authentication, each physician can access all the registrations inserted by himself/herself, both for clinical and research purposes. One local coordinator will be designated in each centre. Each centre coordinator has access, for pressing clinical purposes only, to all data inserted by the physicians at that centre. If a patient changes the attending physician, the new physician, if interested in having access to the previously inserted data, must request authorization to the former physician, with patient's consent. Local and national coordinators and RAG technical support may assist this contact.

REAG – Rede de Especialistas em Asma Grave

Data inserted by other physicians may be shared within REAG for research purposes, after authorization. For this, the physician proposing the data analysis must fill-in a form containing the aim and a brief description of the research project and of the principal investigator or research group. When a request for abstracting data is filled, each physician with data matching the request is notified by email and has a period of 5 days to refuse the sharing of the data. In the case of shared information, the privacy of the individual is assured, as registry data cannot be individually identifiable.

Pilot-Test

After the implementation of the selected data elements, the supporting features, and validation rules, a beta version of RAG was presented during a REAG meeting (December 2017) and, after adjustments, it was pilot-tested for a month. The pilot version was tested by 22 REAG members and 85 specific feedback comments were provided by 8 testers. The first version of RAG became ready after improvements were made based on the pilot-test feedback.

Results

REAG – Rede de Especialistas em Asma Grave

RAG – Registo de Asma Grave Portugal

GINA – Global Initiative

The Portuguese Severe Asthma Registry is a national web-based disease registry. The access is made from the website of REAG, *asmagrave.pt*, after authentication. RAG gathers data of adults and children with severe asthma followed at specialized care centres which, after treatment optimization and adequate management of comorbidities, require step 4 or 5 of treatment according to GINA recommendations (GINA, 2018). The implemented automatic algorithm determines the step of treatment for patients aged under 6, between 6 and 12 and over 12 years, based on asthma medication prescribed to the patient according to GINA recommendations (**Figure 14**, A). In any case, the physician makes the decision about the inclusion in the registry indicating the reason for inclusion (**Figure 14**, B). In fact, even if rarely used, some therapeutic combinations are not explicitly considered in any of the GINA 2018 treatment steps and, in these cases, the algorithm cannot present a result. The algorithm will be updated in the future when these recommendations change. The final data items of RAG are summarized in **Table 17**.

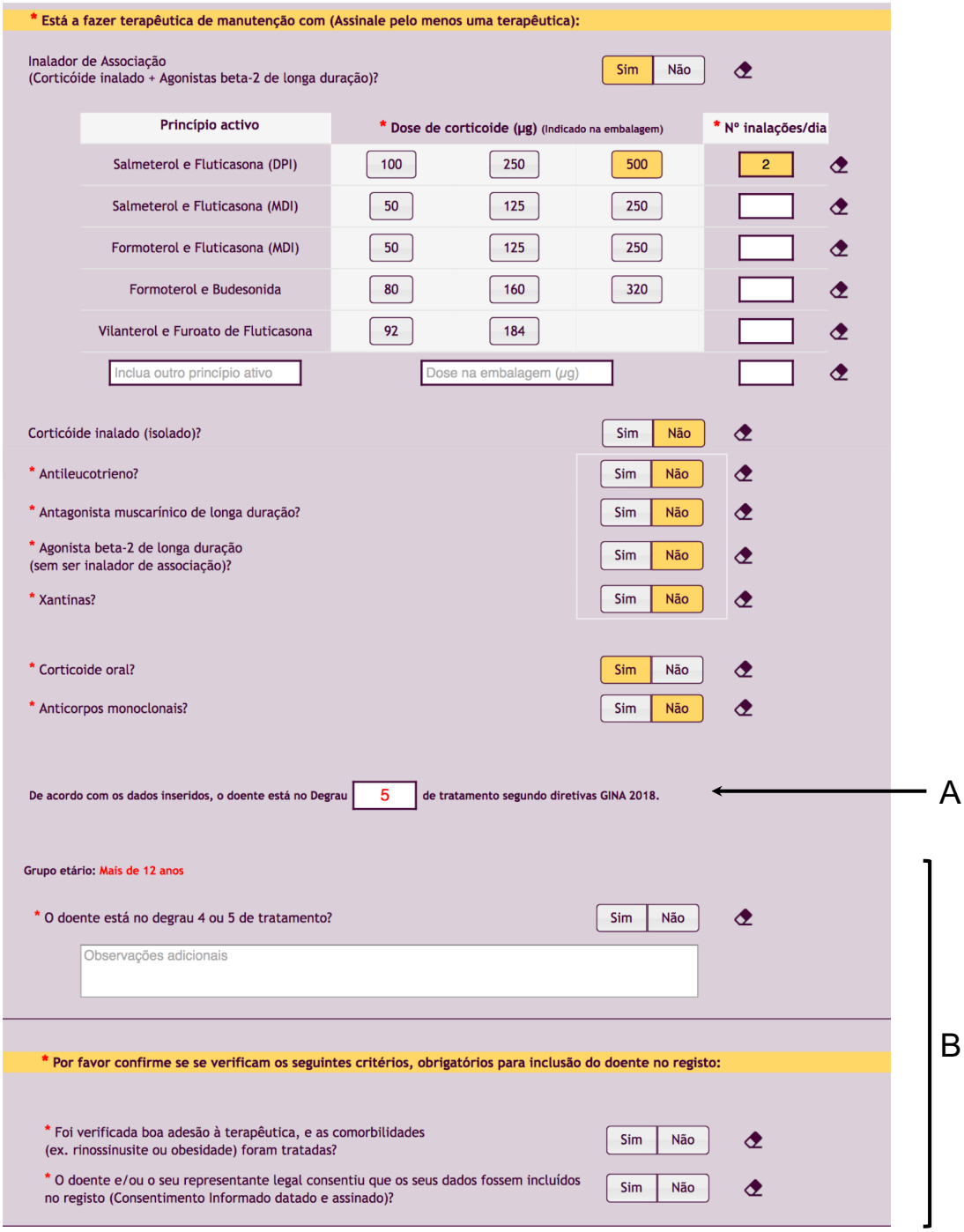


Figure 14: Screenshot of the implemented automatic algorithm to determine the step of treatment, based on asthma medication according to GINA recommendations. *A) treatment step calculated by the algorithm; B) the 3 criteria for patients' inclusion.*

Table 17: Domains and data elements recorded in the Portuguese Severe Asthma Registry.

Patient data
Demographic data *(gender*, birth of month* and year*, birthplace, place of residence*, body mass index calculation*, education years*, smoking habits*, occupation*, family history of asthma* and of asthma-related death*, personal history of respiratory infections during early childhood*, environmental exposures)*
Asthma care information *(age at asthma diagnosis*, age at severe asthma classification*, first year of specialized asthma follow-up, medical specialty of the attending physician*)*
Comorbidities*§
Atopy and Inflammation biomarkers
Atopy *(total serum IgE*, allergic sensitization*, type(s) of diagnostic test used to confirm allergic sensitization*)*
Inflammation biomarkers *(FeNO, blood eosinophils, sputum eosinophils, sputum neutrophils)*
Diagnostic tests
Lung function tests *(FEV1*, FVC*, MEF, residual volume, specific airway resistance, carbon monoxide diffusion capacity, bronchial challenge test)*
Imaging *(thorax X-ray*, thorax CT scan*, sinus CT scan, bronchial endoscopy, bone densitometry)*
Arterial blood gases
Control and Quality of Life
Asthma-related healthcare utilization due to asthma in previous 12 months (or since the last appointment, when at follow-up visit) *(number of routine primary care medical appointments, routine hospital care medical appointments, non-scheduled medical appointments*§, emergency service admissions*§, hospitalizations*§, intensive care unit admissions, need for mechanical ventilation, school or labor absenteeism)*
Asthma control assessment according to GINA recommendations[1] *(frequency of daytime symptoms*§, activity limitations due to asthma*§, any night awakening due to asthma*§, frequency of use of reliever medications for asthma*§, respiratory function, number of exacerbations in last year/week*§)*
Asthma control self-questionnaires *(CARAT*§ and external link to ACT)*
Quality of life self-assessment questionnaires *(external link to quality of life self-assessment questionnaires)*
Therapy
Asthma medication*§ *(OCs, ICs, LTRAs, LABAs, SABAs, LAMAs, SAMAs, xanthines, immunosuppressors, immunotherapy, monoclonal antibodies, antibiotics, therapy adherence, inhalation technique)*
Other medication *(proton pump inhibitor, anti-depressive/anxiolytics, intranasal steroids, antihistamines, long-term oxygen therapy, non-invasive ventilation)*

* Compulsory data elements at initial visit; § Compulsory data elements at follow-up.
IgE, Immunoglobulin E; FeNO, Fractional exhaled Nitric Oxide; FEV1, Forced Expiratory Volume in the first second; FVC, Forced vital capacity; MEF, Mid-Expiratory Flow; CT, Computed Tomography scan; CARAT, Control of Allergic Rhinitis and Asthma Test (Fonseca et al., 2012; Linhares et al., 2014) and ACT, Asthma Control Test (ACT, n.d.);OCS, Oral Corticosteroids; ICS, Inhaled Corticosteroids, LTRA, Leukotriene Receptor Antagonist; LABA, Long-Acting Beta2 Agonist; SABA, Short-Acting Beta Agonist; LAMA, Long-Acting Muscarinic Antagonist; SAMA, Short-Acting Muscarinic Antagonist

RAG – Registo de Asma Grave Portugal

OCS – Oral corticosteroids

RAG allows collecting data on different asthma medication, including OCS, monoclonal antibodies, and even new therapies that may become available (**Figure 15**). Data considered as essential are compulsory, whereas desirable but not essential data may be skipped. The elements to be collected in the follow-up appointments were also defined as RAG was designed to collect data prospectively.

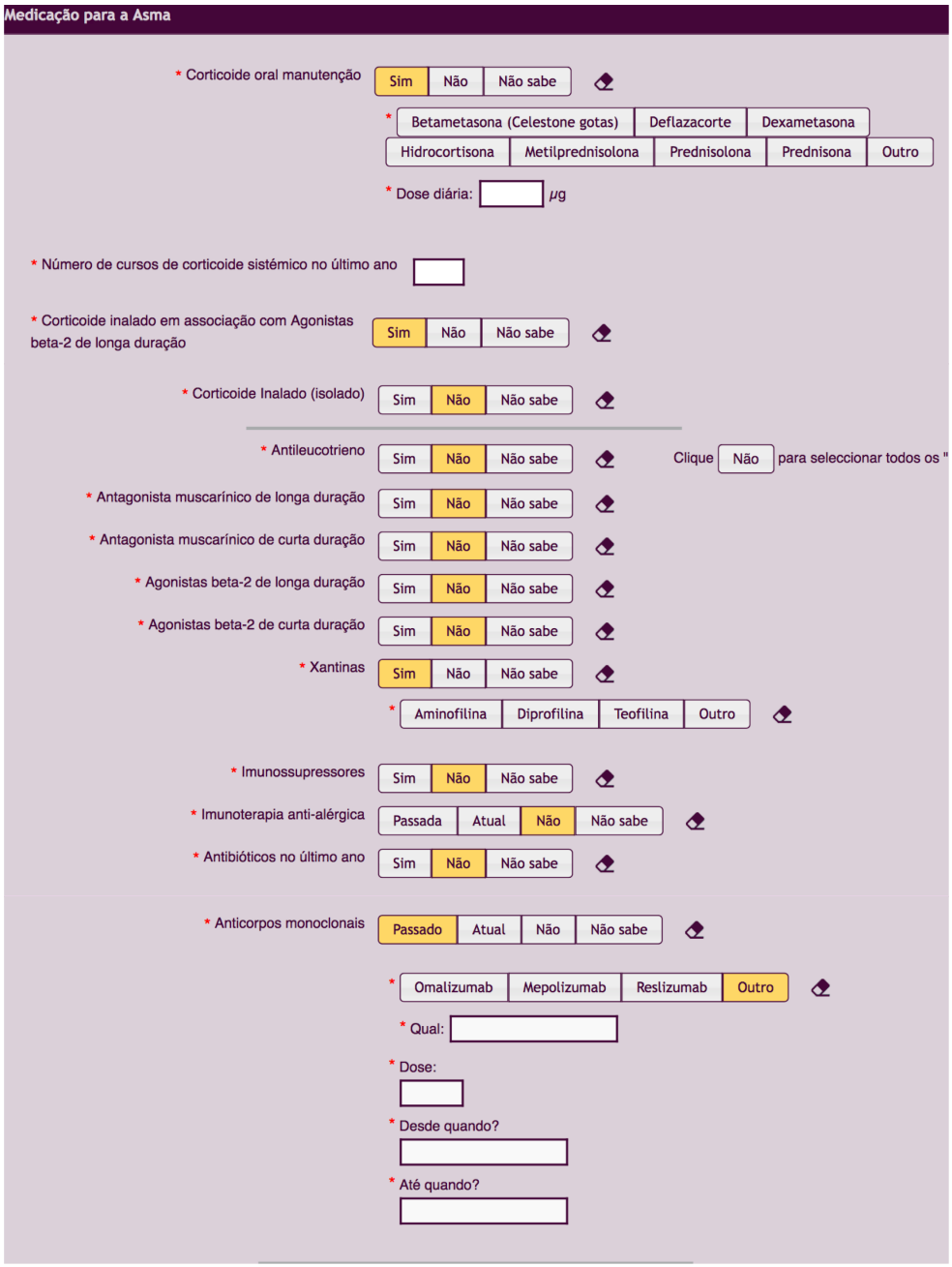


Figure 15: Screenshot of RAG, picturing asthma medication being collected by RAG.

DISCUSSION

This chapter consists of the discussion of the findings from the 4 studies included in this thesis. Main findings, strengths and limitations, discussion and comparison of the results of each study with the literature and future research are presented.

D1 Main findings

To overcome the inconsistencies in the asthma presence and prevalence estimations two multivariable scores, based on of self-administered questions, were developed and validated for the identification of asthma cases in epidemiological studies. The obtained scores have very good properties to rule in/rule out asthma, providing, for the first time, validated screening tools to be used in adult asthma epidemiological studies and clinical screening/triage settings.

The identification patients at risk of adverse outcomes, including asthma-related death, is need to deliver better care for these patients. Secondary data analysis, specifically the Portuguese electronic prescription and dispensing database, was proven useful for the identification of patients exposed to a high dose of OCS exposure or SABA over-use, known modifiable risk factors. OCS use was assessed in the patients on persistent respiratory treatment (PRT) and high OCS exposure (≥1600 mg of prednisolone-equivalent) was found in 11.3% of the OCS users. Among SABA users, 10.5% were excessive users and 1.7% were SABA over-users. Patients on PRT with high OCS exposure and SABA over-users have primary adherence to controller medication above 50%. However, most of them have an insufficient prescription of maintenance treatment. Exposure to high-dose of OCS was associated with a ratio maintenance-to-total under 70%, male sex and age above 45 years old. Of note, in our sample, 44% of patients exposed to a high dose of OCS in our data were on a triple or quadruple combination of controller medication associated with step 4/5 of treatment for asthma. According to the guidelines these severe patients are possible candidates for treatment with monoclonal antibodies.

OCS – Oral corticosteroids

SABA- Short-Acting Beta2 Agonist

PRT – Persistent Respiratory Treatment

Severe asthma patients are also patients at high-risk of adverse outcomes however, population surveys and secondary data analysis may be insufficient to identify, especially to characterize these patients. The observational study done at routine treatment sessions with omalizumab, during 12-months, showed that despite innovative treatment, some asthma patients are still at high-risk of adverse clinical outcomes.

Portuguese patients with severe persistent allergic asthma had their asthma controlled in only 34% of the visits; 1/3 had the need for unscheduled medical care due to asthma and 54% had at least one exacerbation in the 12-month follow-up. We observed an asthma exacerbation rate of 1.7 event per patient per year. Treatment effectiveness could not be properly assessed due to inconsistences in data collection, mostly by the lack of data prior to omalizumab treatment initiation. A systematic data collection, such as in disease registries, is important to the comparison of effectiveness of therapies and better understanding of severe asthma in order to achieve better care.

The Portuguese Severe Asthma Registry (RAG) was developed and implemented. RAG is a national web-based disease registry of adult and paediatric severe asthma patients. It includes a comprehensive list of data elements defined by a multistep consensus process and supported by international definitions of severe asthma. The registry offers features to identify severe asthma cases (patients at the higher steps of treatment, according to GINA guidelines), to facilitate data entry and to support decision-making. The collected data belongs primarily to each patient and then to the physician who inserted patients' data into the registry; such data can be shared for research purposes after authorization. This tool was consensually defined to be prospectively applied by specialists from Portuguese hospitals, aiming the identification and thorough characterization of severe asthma patients. This is ambitious but can improve the information on the disease and contribute to the adoption of evidence-based policies for severe asthma care. The RAG was designed to enable future linkage with other databases, including registries from other countries, as well as the Portuguese Pharmacovigilance Authority. This harmonized approach is essential to improve the management of the different phenotypes of this pathology.

D2 Strengths and limitations

The present thesis involved three data sources, including a population survey and clinical assessment, a prescription and dispensing database, and a prospective multicentre observational study. Secondary data analysis prove to be useful for the identification of high-risk patients, based on prescriptions and additionally three easy-to-use tools were developed: a) two short scores to identify asthma in adults in population surveys or even in screening settings to selected the best candidates for a diagnostic workup; b) and a web-based severe asthma registry to be systematically used by severe asthma experts aiming to the identification and characterization of patients with severe asthma. However, the external validity of the scores, the lack of information regarding the clinical condition underlying the prescriptions indication, and the involvement of few severe asthma specialists in the pilot-testing of the registry, are some of the limitations of this thesis that may be overcome in future studies.

Strengths

One of the strengths of this thesis was the use of three different data sources and a broad set of methods to achieve important advances in the identification of asthma patients and those at high risk of adverse asthma outcomes. Other, specific of each study, will be discussed in the following paragraphs.

The study focusing on improving identification of asthma patients (Study I) proposes scores that were developed on the basis of real-life data from the general population, and that can be used for either asthma identification or asthma screening/triage. These scores were validated against asthma diagnosis by a trained specialist based on the recommendations from GINA guidelines (GINA, 2018), supported by objective measurements, and blinded to the results of previous self-administered questionnaires. The obtained scores have very good discriminative power and high diagnostic accuracy measures.

GINA – Global Initiative for Asthma

For the first time, prescriptions for OCS and SABA medication from the official Portuguese prescription database were analysed (Study II). Noteworthy, the findings reported in this study are based not only on the prescription but also on the dispensing data. This study brings novel information on the Portuguese respiratory prescriptions.

OCS – Oral corticosteroids

SABA- Short-Acting Beta2 Agonist

Study III was the first multicentre real-life prospective study on asthma outcomes in patients with severe persistent allergic asthma in Portugal. This was the first-time specialists from different Portuguese centres came together to harmonize the registration of severe asthma management and care. From this initial study, the necessity for a computerized disease registry became even more evident.

The Portuguese Severe Asthma Registry was consensually developed and implemented (Study IV). The registry has the potential to identify the best diagnosis and treatment practices, and to support collaborative research projects, contributing to reduce the information gaps and support the definition and adoption of evidence-based health care policies related to severe asthma care in Portugal.

Limitations

Each study has specific limitations that need to be considered for an adequate interpretation of its results.

A limitation of the study on the development of asthma prediction scores (Study I) is that we did not validate the scores in other populations and settings, limiting its generalization. New studies using these scores are being designed, and their application to other datasets is warranted for external validation. Nevertheless, to improve the robustness of the validation results, we used bootstrap resampling techniques, obtaining very similar results to those reported for the validation cohort. Another limitation is the use of PPV-/NPV-based cut-offs, which are measurements highly dependable on asthma prevalence, and therefore these cut-off values may not be transferable to other settings. As so, presenting the results as continuous, before its dichotomization, is advisable when applying the scores.

PPV – Positive Predictive Value

NPV – Negative Predictive Value

An important limitation of the study on high-risk prescriptions patterns (Study II) is related to the risk of overestimation of drug use, since filling prescriptions does not mean actual medication intake. Nevertheless, the concept of primary adherence used in the present study – based on the proportion of prescriptions filled by patients – is frequently used in studies on prescriptions and adherence patterns (Blais et al., 2017; M. A. Fischer et al., 2010; Pottegård et al., 2014; Williams et al., 2007; Wu et al., 2015). Another limitation of this study is the lack of information regarding the underlying clinical condition that accounted for the treatment indication, as well as important demographic variables (such as smoking habits, BMI, education, race). Moreover, OCS are prescribed for several conditions non-related to respiratory disease. In fact, some authors state OCS may not be a reliable marker of respiratory exacerbation (Allen-Ramey et al., 2013). To minimize this error, we analysed OCS usage only among patients on PRT (prescription for > 2 packages of any respiratory maintenance medications). In addition, we assessed OCS usage when ordered by prescribers with specialties related to respiratory disease and we obtained identical results.

BMI – Body Mass Index

OCS – Oral corticosteroids

PRT – Persistent Respiratory Treatment

In the study on asthma outcomes in severe patients under omalizumab therapy (Study III), there were limitations related to data availability. Firstly, at enrolment, patients were already using omalizumab as add-on therapy and no comparable prior data were available. Additionally, in one-third of the patients, it was not possible to access the registries for the complete 12-month treatment period. Nevertheless, to mitigate the impact of different follow-up periods, a survival analysis was carried out.

Regarding the study on the development of the RAG (Study IV), few specialists tested the pilot-version of the registry. Nevertheless, after the implementation of RAG, the feedback from the use of the tool in real setting was accounted for new version of the web-registry already launched. Another limitation is that during the development of the algorithm to assist the assessment of asthma severity and identification of severe asthma patients, it became clear that GINA 2018 recommendations on treatment steps do not account for all possible therapeutic combinations. In the future, it would be important to implement measures to encourage patient enrolment in the registry and to assess if clinically relevant combinations are not included in the GINA recommendations.

RAG – Registo de Asma Grave Portugal

GINA – Global Initiative for Asthma

D3 Asthma prediction scores

A2 Score - Adult Asthma Score

GA2LEN Score – GA2LEN Epidemiological Asthma Score

PPV – Positive Predictive Value

NPV – Negative Predictive Value

COPD – Chronic Obstructive Pulmonary Disease

ECRHS – European Community Respiratory Health Survey

In prevalence studies, a questionnaire with high specificity (few false positives) and PPV for asthma diagnosis is preferable. However, if our interest is to screen subjects to undergo a confirmatory clinical evaluation, a questionnaire with high sensitivity (few false negatives) and NPV is preferable in the first stage. In this case, we can also use these scores to rule out asthma with the NPV-based cut-off. The scores developed in our study – the A2 score and the GA2LEN score – had high specificity (96.7% and 97.7%) and a sensitivity of 59.4% and 48.1%, respectively. The previously developed ECRHS asthma score used the question "Have you ever had asthma?" and bronchial hyperreactivity was the comparator. Comparing it with the scores developed in our study, we found that the A2 score has the same number of questions as the ECRHS asthma score, but shows better discriminative properties, better internal consistency, and better diagnostic accuracy measures. We also developed the GA2LEN score that has the advantage of being shorter than the ECRHS asthma score, with comparable diagnostic accuracy measures and better discriminative properties and internal consistency. The performance of asthma prediction scores has been mostly studied for childhood asthma. Smit et al. assessed 12 prediction models for children and reported a sensitivity ranging from 15% to 75% and a specificity ranging from 35% to 100% (Smit et al., 2015). Both our scores had high specificity for asthma diagnosis, which is related to the choice of a PPV-based cut-off to rule in asthma. A meta-analysis on screening tests for COPD diagnostic accuracy determined a pooled sensitivity of 64.5% (95% CI, 59.9%-68.8%) and a specificity of 65.2% (95% CI, 52.9%- 75.8%) for the COPD Diagnostic Questionnaire (Haroon et al., 2015). More recently, the development and validation study of the Salzburg COPD screening questionnaire reported a sensitivity of 69.1% (95% CI, 56.6%-79.5%) and an NPV of 91.8% (95% CI, 87.5%-95.7%) (Weiss et al., 2017). The values of sensitivity and NPV obtained for our scores, considering the cut-off to rule out asthma, were superior to those for the screening tests for COPD. These findings indicate that the A2 score and the GA2LEN score may be used for asthma surveys and

also for asthma screening, for instance, in clinical screening/triage settings. Such tools may help physicians in primary care or other specialties to screen patients with asthma using a simple score with a high level of discrimination and to identify the best candidates to be referred for a diagnostic workup. Of note, to choose between A2 and GA2LEN scores, the cultural context must be taken into consideration.

The use of a prior medical diagnosis as a predictor depends on cultural contexts. Attention to this potential problem is especially important in multinational studies and, in fact, neither ISAAC (ISAAC et al., 1998) nor ECRHS (Burney et al., 1996) consider a prior diagnosis definitive for asthma. The A2 score includes questions on previous physician diagnosis ("Did a physician confirm you had asthma?" and "Do you still have asthma (previously diagnosed by a physician)?"), whereas the GA2LEN score asks "Have you ever had asthma?" which can be preferable in settings with significant under-diagnosis or difficult access to healthcare. The questions included in the A2 score that are not in the GA2LEN score are part of the ECRHS (Burney et al., 1996) and of the National Health and Nutrition Examination Survey (NHANES, 2016). The GA2LEN score may be considered to be more practical than the A2 score, because it is shorter and 1 positive answer is enough to consider possible asthma.

ECRHS – European Community Respiratory Health Survey

ISAAC - International Study of Asthma and Allergies in Childhood

A2 Score - Adult Asthma Score

GA2LEN Score – GA2LEN Epidemiological Asthma Score

D4 High OCS exposure and SABA over-use

Patients with respiratory diseases with high OCS exposure or SABA over-use, factors associated with high-risk of having adverse clinical outcomes, were quantified from the Portuguese prescription and dispensing database (**Figure 16**).

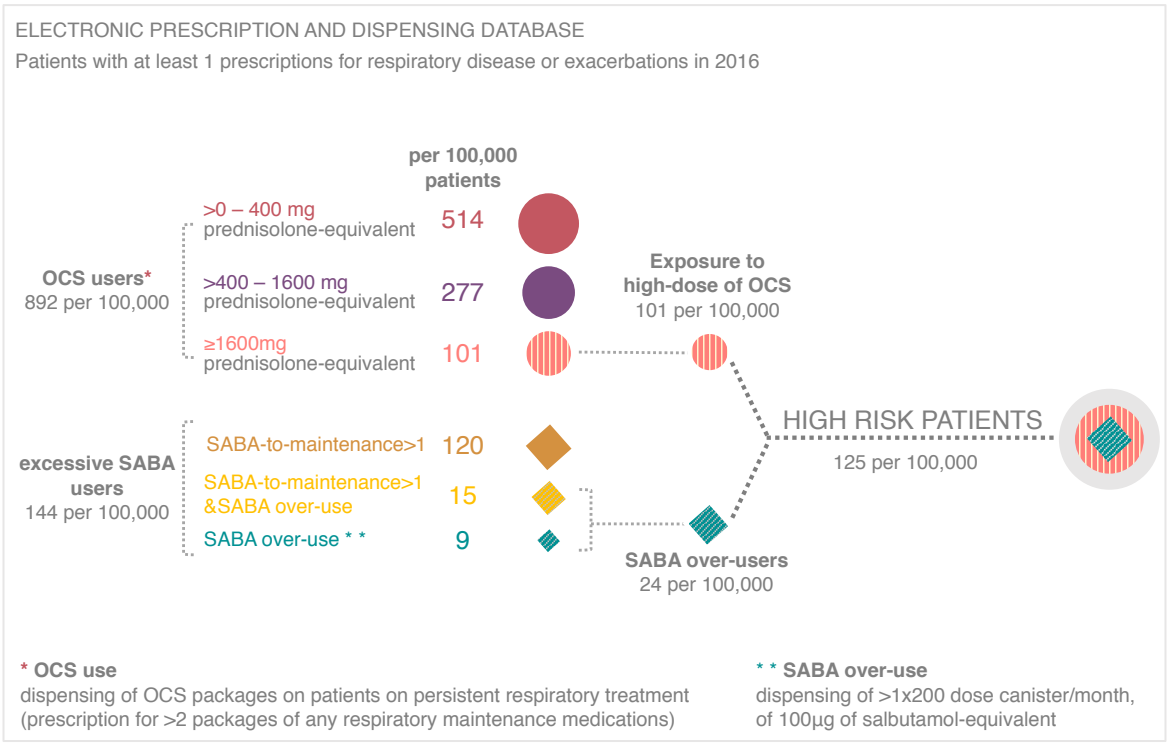


Figure 16: Patients with respiratory diseases with high-risk of having adverse clinical outcomes

The study II found that almost 19% of patients on PRT dispensed at least 1 package of OCS and 11% of the OCS users dispensed at least 4 packages. Fitzgerald et al. reported that 13% of asthma patients used OCS (FitzGerald et al., 2017). Cumulative exposure to systemic corticosteroid has long been associated with adverse effects and substantial excess morbidity from multiple diseases (Price et al., 2018; Sweeney et al., 2016), and having 4 or more prescriptions of OCS per year has been shown to i ncrease the incidence of adverse events in asthma patients (Sullivan et al., 2018). Specifically, high doses of OCS in asthma patients are associated with pneumonia (Price et al., 2018; Zazzali et al., 2015). Moreover, in older adults, the use of OCS and COPD are two of the main factors associated with increased risks of development of pneumonia (Jackson et al., 2016). This is particularly relevant in Portugal, where deaths related to respiratory

PRT – Persistent Respiratory Treatment

OCS – Oral corticosteroids

SABA – Short-Acting Beta2 Agonist

COPD – Chronic Obstructive Pulmonary Disease

diseases, especially pneumonia, remain a concern. In fact, in 2016, respiratory system diseases were the third cause of death in Portugal (12.1% of mortality in the country), with standardized deaths rates of 0.7 per 100,000 inhabitants for asthma, 12.3 per 100,000 for COPD and 25.7 per 100,000 for pneumonia (Instituto Nacional de Estatística, 2016). Although asthma deaths seem less important given its lower death rate, a Portuguese study on hospital admissions for obstructive lung disease occurring between 2000 and 2010 showed that having a principal diagnosis of pneumonia is often related with a secondary diagnosis of COPD or asthma, and vice-versa (Vieira et al., 2016).

The study II also showed that having a maintenance-to-total ratio below 70% was associated with the use of high-dose OCS. In our analysis we include prescriptions for respiratory patients as a whole and not only for asthma patients, therefore we used the ratio maintenance-to-total instead of the previously established ratios (Laforest et al., 2015; Stanford et al., 2013; Sullivan et al., 2019). Although similar in its construct, the association of the ratio assessed in the present study with adverse outcomes may be different. We also observed that having a ratio of maintenance-to-total of 70% or more was associated with a lower likelihood of being OCS user. Accordingly, Stanford et.al reported that controller-to-total asthma medication ratio of 70% or more, was associated with a reduction in OCS-dispensing events in 12-month follow-up (OR 0.81; 95% CI 0.76-0.88) (Stanford et al., 2013). In this study, the authors concluded that for adult Medicaid patients the optimal cut-off value was 70% and for the commercially insured patients was 50%. In Portugal in 2015, 65% of the health expenditures were supported by the government (OECD, 2017), as so we applied the cut-off of 70% to the ratio of maintenance-to-total, recommended for the Medicaid population. Nevertheless, since a ratio of less than 50% is known to be related to poor asthma control events, including the need for OCS (Laforest et al., 2015; Luskin et al., 2017), we also tested the cut-off of 50% and found the maintenance-to-total of < 50% was associated with a higher likelihood of high OCS exposure (adj OR, 95%CI; 7.6, 5.5-10.8).

OCS – Oral corticosteroids

SABA – Short-Acting Beta2 Agonist

COPD – Chronic Obstructive Pulmonary Disease

On the other hand, we found that over-prescription of SABA with insufficient controller medication prescription was frequent. Yang et al. showed that, in a one-year study on asthma patients from primary care healthcare records, 6.6% of the SABA over-users were not on ICS (Yang et al., 2018). We observed a higher rate (16%) of SABA over-users that did not receive a prescription for any controller medication in the 12-months period. A possible reason may be that we included all patients with respiratory treatment prescription and from all types of healthcare service, not only asthma patients from primary care. Moreover, in those with a prescription for controller medication, 77% had a ratio maintenance-to-total below 70%, and 57% below 50%. Overprescribing of SABA and insufficient provision of ICS was stated as a preventable cause of death for asthma (Royal College of Physicians, 2014). Other adverse outcomes associated with inappropriate use of SABA, specifically in absence of ICS or use of 9 canisters of SABA per year with no more than 100 mg/day of ICS (FitzGerald et al., 2017), were asthma-related hospitalizations, emergency department visits, and intense care unit admissions.

SABA – Short-Acting Beta2 Agonist

ICS – Inhaled corticosteroids

Our results suggest that high OCS exposure was associated with older age and male sex. Yang et al. reported similar results for age but not for sex. In a model adjusted for SABA over-use and COPD comorbidity, Yang et al. showed that older age and female sex increased the risk of taking ≥2 courses of OCS for asthma exacerbations (adj OR, 95%CI; 1.06, 1.01-1.12, for age and 0.64, 0.45-0.89, for male sex), (Yang et al., 2018). Age and sex play important roles in the progression of chronic respiratory diseases. Aging of the airways and parenchyma induces structural and immunological changes related to the increase of airflow limitations. Reasons for gender differences may be related to anatomical, hormonal or socio-environmental factors (Pignataro et al., 2017). Men seem to report fewer asthma symptoms, less impact on daily activities and less healthcare utilization (McCallister et al., 2013; Lee et al., 2006). Male sex has also been associated with a worse perception of airflow obstruction and airways deterioration (Cydulka et al., 2001; GINA, 2018) and tendency to delay seeking healthcare services when experiencing symptoms (Galdas et al., 2005).

OCS – Oral corticosteroids

COPD – Chronic Obstructive Pulmonary Disease

These may contribute to our observation of an association between male and the exposure to ≥1600mg of OCS, a known risk factor for serious health outcome.

Primary adherence was not associated with high-dose of OCS nor with SABA over-use. Previous studies have shown inconsistent results regarding the association between adherence to controller medication and SABA or OCS use. For example, a systematic review has found that non-adherence is a risk factor for severe exacerbations, defined mostly as events requiring for OCS, emergency department visit or hospitalization for asthma (Engelkes et al., 2015). Makhinova et al. showed that adherent patients were more prone to have more than 6 prescriptions for SABA (OR 1.967, 95%CI 1.8- 2.1), than non-adherent patients (Makhinova et al. , 2015). Murphy et al. reported that primary adherence to ICS below 80% was not associated with OCS courses or admissions to hospital, but was associated with the need for mechanical ventilation (Murphy et al., 2012). Interestingly, a recent study on patterns of patients who experienced near-fatal asthma exacerbations reported that adherence to controllers may be an important factor for some patients (namely those with rapid worsening of symptoms, young to middle-aged patients, smokers, with low BMI, t endency to depression and hypersensitive to environmental triggers), but not for other (Tanaka et al., 2018). In some severe phenotypes, asthma remains uncontrolled despite good adherence to step 4/5 of treatment controller medication (Papi et al., 2018). And in fact, in our study most of the patients exposed to high-dose of OCS were on a triple or quadruple combination of controller medication (ICS/LTRA+LABA+LAMA), suggesting that these severe patients are possible candidates for treatment with monoclonal antibodies (GINA, 2018). Overall, in our study, primary adherence was not a risk factor for high OCS exposure nor with SABA over-use but seem to be related to inappropriate prescription of maintenance treatment or to factors not available for analysis, including smoking habits or BMI. Prescriptions data may be used to identify patients in high risk of adverse outcomes, including patients with severe asthma that would benefit from an expert in severe asthma clinical assessment with access

OCS – Oral corticosteroids

SABA – Short-Acting Beta2 Agonist

ICS – Inhaled corticosteroids

LTRA – Leukotriene Receptor Antagonist

LABA – Long-Acting Beta2 Agonist

LAMA – Long-Acting Muscarinic Antagonist

BMI – Body Mass Index

to additional innovative treatment. However, due to their small proportion and high heterogeneity, the use of secondary data to identify patients with severe asthma is challenging and involves at least, the linkage to other databases for certainty in diagnosis and treatment indications of each patient.

D5 Severe asthma

Asthma outcomes in patients under biological treatment

Omalizumab has previously been reported as effective in the treatment of patients with severe persistent allergic asthma, based on observational studies performed in real-life settings (Brusselle et al., 2009; Cazzola et al., 2010; Costello et al., 2011; Korn et al., 2009; Molimard et al., 2008; Ohta et al., 2010; Simões Saldanha Mendes et al., 2013; Vennera et al., 2012). The mean CARAT score found in our study for patients with severe asthma (20.4) is similar to those found in patients with non-severe asthma. Previously published studies using CARAT questionnaire to assess the control of asthma and rhinitis found the following average (SD) CARAT scores: 17.8 (6.4) in a community of inner Portugal (Lourenco et al., 2014); 17.8 (0.2) in patients followed in the Allergology Department of a University Hospital (Pereira et al., 2013); and 17.2 (6.7) in patients referred to the Allergy outpatient clinic from a district hospital (Pereira & Lopes, 2013). Moreover, the proportion of patients with good asthma control in patients with severe persistent allergic asthma was stable, which is in accordance with several studies (Brusselle et al., 2009; Simões Saldanha Mendes et al., 2013) that reported improvements in asthma control in the first 16 weeks of omalizumab treatment and a tendency to stabilize the effect in the following months.

CARAT – Control of Allergic Rhinitis and Asthma Test

The rate of 0.6 emergency visits per patient-year observed in our study is inferior to the rates reported by Molimard and co-workers - 1.1 emergency visits per patient-year after a follow-up of more than 5 months (Molimard et al., 2008), and by Cazzola and co-workers - 1.2 visits per patient-year after a follow-up of 12 months (Cazzola et al., 2010).

The exacerbation rate observed in our study is lower than the rates reported in similar studies in France (Molimard et al., 2008) and in the PERSIST study (Brusselle et al., 2009) but greater than those of Germany (Korn et al., 2009), Italy (Cazzola et al., 2010), Ireland (Costello et al., 2011) and Spain (Vennera et al., 2012). In our study, the frequency of asthma exacerbations during one-year omalizumab treatment was lower than expected for these severe patients (Ayres et al., 2004). However, in spite of being treated with

OCS – Oral corticosteroids

omalizumab, five patients had ≥5 exacerbations. Moreover, although the reduction of OCS intake shown in our study is in accordance with previous reports (Alfarroba et al., 2014; Cazzola et al., 2010; Dias et al., 2012; Molimard et al., 2008), four patients increased OCS dosage during the study period and two had no variation. We could speculate whether before starting omalizumab the asthma control in these patients was even worse or if the treatment with omalizumab was ineffective and should be discontinued, but due to data constraints we could not confirm these hypotheses.

OCS – Oral corticosteroids

GINA – Global Initiative for Asthma

The national severe asthma registries have been pointed has the indispensable basis to gather systematic and harmonized data from a, as large and broad as possible, population of patients with severe asthma in order to promote optimal care for these patients, by the 1) identification and characterization of the clinical features and phenotypes of severe asthma, 2) assessment of the effectiveness, side effects and costs of novel treatments, 3) assessment of the burden of the disease 4) comorbidities management (Korn, Hübner, Hamelmann et al., 2012; Senna et al., 2017; Schippers et al., 2016; Schleich et al., 2014). Moreover, the enrolment of patients with severe asthma in a registry is recommended by GINA guidelines (GINA, 2019b).

The Portuguese Severe Asthma Registry

The RAG was developed to overcome the need for a tool to improve severe asthma data while harmonizing therapeutic management and overall care. A consensus method (Jones & Hunter, 1995) was used to summarize information from different sources, to gather insights from experts and to enable decision-making. Through a multistep consensus method, a balance was achieved between the data commonly used by clinicians, the data included in other severe asthma registries, the data needed for the RAG's reliability, and the expected overall burden for respondents.

RAG – Registo de Asma Grave Portugal

Disease registries are used to support healthcare providers on disease care and to gather evidence for scientific and policy purposes. Therefore, a disease registry should (1) facilitate the access to patient-specific information at the point of care for healthcare delivery and provide status reports of aggregated information to give feedback to physicians or to medical groups about the patient population (California Healthcare Foundation, 2004) and (2) provide real-world data on clinical practice, patient outcomes, safety, and/or comparative effectiveness for research purposes (Gliklich, 2014). RAG has several features to support healthcare providers on severe asthma care (**Table 18**). Although the data collected by RAG is common with other European registries in a more or less extensive manner – demographics, comorbidities, biomarkers, atopy, diagnostic tests, control assessment, quality of life, current medication – some of the RAG's features are unique. This is the case of the exportable data that can be pasted directly in patients' electronic health record, the security features compliant with the GDPR and the design to be linked with other databases and to enable data sharing. Another innovative feature is the automatic algorithm was implemented to assist on the assessment of asthma severity and patients' eligibility, based on GINA recommendations and according to the patients' inclusion criteria, defined by consensus. Clinical guidelines provide a link between the best available evidence and the clinical practice, having the potential to improve enormously patient care (Green & Piehl, 2003). However, these may have limitations especially for a particular disease where evidence is still insufficient as in severe asthma and cannot be used as a strict formula. Additionally, as suggested by the members of REAG, RAG includes the automatic generation of clinical notes based on the inputted data that can be pasted into the institutional electronic clinical record of the patient, avoiding duplication of effort.

RAG – Registo de Asma Grave Portugal

GDPR – General Data Protection Regulation

GINA – Global Initiative for Asthma

REAG – Rede de Especialista em Asma Grave

Table 18: RAG features useful to support severe asthma management

Elements of chronic care management [1]	RAG features	
	Current	Future
Ensure regular follow-up	Displays for each physician a list of their patients and date of the last medical appointment	Display a simple message with the counting the months since the last appointment and flag patients without medical review in more than 6 months
Facilitate individual patient care planning	For specified measurements, displays the information inserted in the last appointment and its progress over time	At the beginning of each follow-up appointments, a brief report of the previous appointment will be displayed
Embed evidence-based guidelines into clinical practice	Has a decision support tool to identify patients treated in step 4 or 5 according to GINA recommendations	
Monitor the performance of practice team	Displays aggregated data on the number of patients included by each center	Aggregated real-time data with different graphic displays of trends on specified management and clinical outcomes will be produced, to give a feedback to physicians about the status of the care of their patients and/or healthcare center, towards delivering the recommended care for severe asthma.

[1] (California Healthcare Foundation, 2004)

RAG – Registo de Asma Grave Portugal

The utility of a registry relies on the quality of data collection and storage (Gliklich, 2014). RAG's data are collected at the time of routine medical appointments in the same manner for every patient and with specific and consistent data definitions. To minimize errors related to data completeness and consistency, several logical and validation rules have been implemented and periodic data audits are being planned. An additional challenge is the recruitment and retention of participants that is critical to the generalizability of a registry (Gliklich, 2014). Potential RAG users were involved from the beginning in the development and implementation process, stating their motivation to include patients. Nevertheless, to retain users' interest, the burden of participation was kept as low as possible and

features wanted by the physicians were implemented. RAG was designed to comply with security and data protection standards, including key challenges of the new European GDPR. No individually identifiable information of the patient is recorded in the database. Only his/her physician can link the recorded data to the patient, who remains the owner of the data. RAG's data sharing policies allow the use of data for research, requiring the consent of the physician that recorded the data and a simple process to gather this consent was implemented. The effort to harmonize the variables collected in the RAG with other pre-existent registries, enables comparisons across populations and settings.

RAG – Registo de Asma Grave Portugal

GDPR – General Data Protection Regulation

D6 Future directions

The developed asthma scores for the identification of asthma in adults should be validated in other populations and settings. These scores are set to be used in a protocol for asthma screening in a community pharmacy context, and also in a prevalence study. For future work, it would be relevant to assess if adding predictors based on objective measures, such as exhaled Nitric Oxide, spirometry and/or bronchodilator reversibility testing, would improve the models.

Initiatives to reduce the number of high-risk patients with high OCS exposure and SABA over-use in Portugal are needed. The implementation of electronic alert in the electronic prescription system could reduce inappropriate SABA and OCS prescribing, as suggested in previous research (Mckibben et al., 2018) and could be also set to refer the patients with severe asthma for an assessment by an expert. Moreover, the linkage of the BDNP to electronic medical records from primary and secondary care could provide important information on treatment indication and demographic characteristic of the patients. Meanwhile, as high OCS exposure and SABA over-use seem more related to prescriptions than to adherence to medication, the further exploration of the prescription patterns of maintenance medication could provide important evidence to this concern.

OCS – Oral corticosteroids

SABA – Short-Acting Beta2 Agonist

BDNP – Portuguese electronic prescription and dispensing database

Real-world prospective observational research, including long-term follow-up data provided by registries, is increasingly considered important to generate evidence regarding effectiveness, safety, and quality of care (Dreyer & Garner, 2009). The RAG should contribute to gathering data with this purpose. Future versions of the RAG will include features highlighted in the Discussion section (**Table 18)**. Moreover, the RAG was design to be linked with other databases, including registries from other countries, as well as the Portuguese Pharmacovigilance Authority. Contacts for the inclusion of the Portuguese registry in the International Severe Asthma Registry are being made.

RAG – Registo de Asma Grave Portugal

CONCLUSIONS

This thesis contributes with three new tools for the identification of asthma patients and severe asthma patients and brings new evidence on the insufficient prescription of controller medication in patients in high-risk of adverse outcomes by the exposure to a high dose of OCS and by SABA overuse. Two scores for the identification of asthma cases in adults have been developed and validated (Study I); and, although secondary data analysis may be useful for the identification of patients with asthma at high risk of adverse outcomes (Study II), much remains unclear on the identification and characterization of patients with severe asthma, and on the effectiveness of severe asthma treatments (Study III). In order to promote optimal care to these patients and to fill the gap on the evidence related to severe asthma, a national severe asthma registry was developed and implemented (Study IV).

OCS – Oral corticosteroids

SABA – Short-Acting Beta2 Agonist

The two scores based on self-administered questions were developed and validated compared with physician-led asthma diagnostic workup. These scores are short, easy to use, and can be applied to identify the likely presence of asthma (prevalence) or absence (screening) of asthma in epidemiological studies and in clinical screening/triage settings. The A2 score may be preferred in studies aiming at maximum accuracy; however, the GA2LEN score is shorter and would be preferable for communities in which there may be difficulties related to physician diagnosis of asthma. Asthma presence can be considered for results of 4 or more affirmative responses in either the A2 score or the GA2LEN score and can be excluded for results of 0 in the GA2LEN score or of 0 to 1 in the A2 score. For in-between results, asthma is possible but requires a confirmatory clinical evaluation. Nevertheless, the presentation of the results as a continuum score before dichotomization using a cut-off is advisable. The use of the A2 score and the GA2LEN score may contribute to reducing the inconsistencies of asthma definitions across studies and surveys and have the potential to be used in clinical settings for screening/triage of asthma, where they may contribute toward identifying the best candidates to be referred for diagnostic workup.

A2 Score – Adult Asthma Score

GA2LEN Score – GA2LEN Epidemiological Asthma Score

The frequency of respiratory patients in high-risk of adverse clinical outcomes was assessed based on the BDNP. OCS was prescribed to more than 1/5 of the patients on persistent respiratory treatment, and 101 per 100,000 patients were exposed to doses of OCS ≥ 1600mg/year, associated with the risk of developing serious adverse outcomes. High OCS exposure and SABA over-uses were associated with insufficient prescription of maintenance treatment, but not with primary adherence to controller medication. These results suggest a need for initiatives to reduce the number of high-risk patients with high OCS exposure and SABA over-use in Portugal.

BDNP – Portuguese electronic prescription and dispensing database

OCS – Oral corticosteroids

SABA – Short-Acting Beta2 Agonist

The multicentre 12-months study showed that Portuguese adult patients with severe persistent allergic asthma on omalizumab treatment had poor asthma control and had frequent exacerbations requiring unscheduled or Emergency Room care. The limitations related to the data availability support the need to promote data registration on severe asthma, aiming to improve severe asthma care. The Portuguese Severe Asthma Registry is a national web-based disease registry of adult and paediatric severe asthma patients. The development and implementation of the RAG was a multistep consensus process. RAG includes automatic assessment of asthma severity enabling the identification of severe asthma patients and therefore eligibility for inclusion. Other features were integrated such as easy data input, and features for exporting and sharing data. RAG allows prospective clinical data collection, promotes standardized clinical records for asthma monitoring, and creates a secure virtual setting for collaborative clinical research. RAG database is prepared for future data exchange with international databases.

RAG – Registo de Asma Grave Portugal

Overall, using a broad set of methods and data sources, major advances on the identification of asthma patients and those at high risk of adverse asthma outcomes were possible. These may contribute to informing evidence-based healthcare policies for asthma.

VISUAL INDEX

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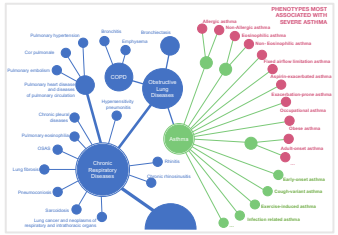

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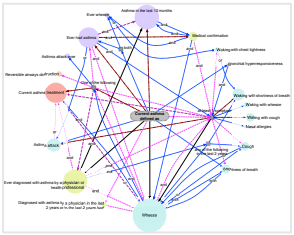

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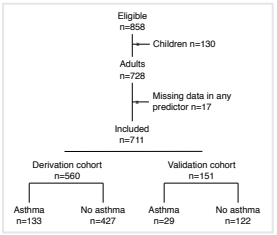

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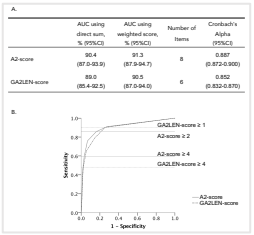

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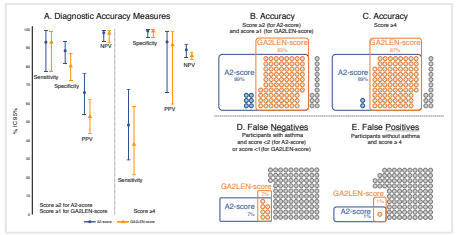

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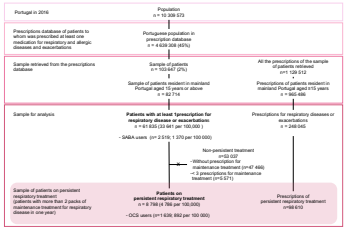

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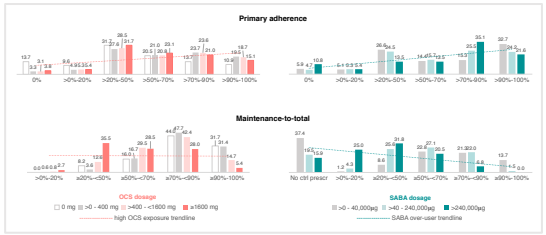

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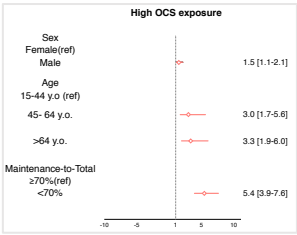
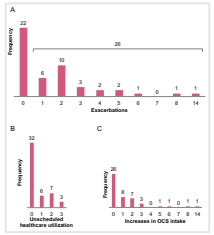
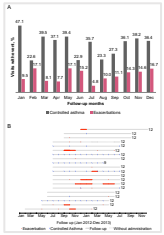
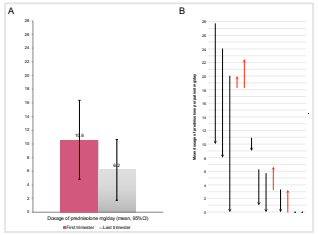
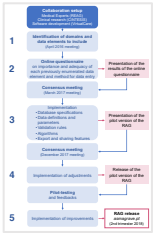
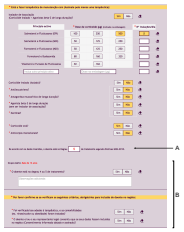


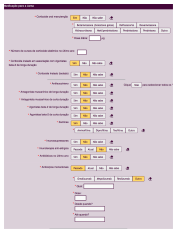
10. 

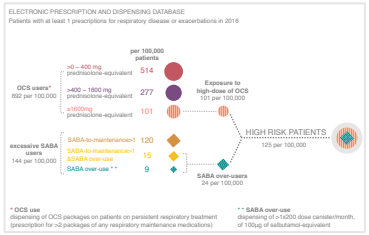
11. 

12. 

13. 

14. 

15. 

16. 

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APPENDICES

PhD Outputs

Original research articles

1 Full-paper published in *Journal of Allergy and Clinical Immunology: In Practice* [Impact factor JCR, ISI WoS 6.966, Q1 of Allergy category]

Sa-Sousa A, Pereira AM, Almeida R, Araujo L, Couto M, Jacinto T, et al. **Adult Asthma Scores-Development and Validation of Multivariable Scores to Identify Asthma in Surveys.** J Allergy Clin Immunol Pract. 2019 Jan; 7(1):183–190.e6.

2 Full-paper submitted to an international peer-review journal

Sa-Sousa A, Almeida R, Vicente R, Martins H, Freitas A, Fonseca JA. **High oral corticosteroid exposure and overuse of short-acting beta-2-agonists were associated with insufficient prescribing of controller medication: a nationwide electronic prescribing and dispensing database analysis.**

3 Full-paper published in *Revista Portuguesa de Pneumologia* [Impact factor JCR, ISI WoS 1.731, Q4 of Respiratory System category]

Sousa AS, Pereira AM, Fonseca JA, Azevedo LF, Abreu C, Arrobas A, et al. Asthma control and exacerbations in patients with severe asthma treated with omalizumab in Portugal. Rev Port Pneumol. 2015; 21(6):327–33.

4 Full-paper published in *Biomed Research International* [Impact factor JCR, ISI WoS 2.583 Q2 of Biotechnology & Applied Microbiology and Q3 of Medicine, Research & Experimental category]

Sá-Sousa A, Fonseca JA, Pereira AM, Ferreira A, Arrobas A, Mendes A, et al. **The Portuguese Severe Asthma Registry: Development, Features, and Data Sharing Policies.** Biomed Res Int. 2018; Article ID 1495039.

Book chapter

5 Chapter in: *Severe Asthma* [ISBN: 978-84-17221-7]

Sá-Sousa A, Fonseca JA. Chapter 1 **- Concept and Epidemiology**. In: Severe Asthma, ed Drummond M, Cordeiro CR, Neuparth N. Permanyer Portugal, pages 1-16 ISBN: 978-84-17221-78-2

Oral and Poster Communications in International Conferences

6 Poster Communications in European-Respiratory-Society International Congress 2018 and published in the *European Respiratory Journal [Impact factor 12.242]*

Sá-Sousa A, Almeida R, Freitas A, Fonseca JA. **SABA overuse in the Portuguese prescription database**. Eur Resp J; 52 (suppl 62) PA4002.

Conference: European-Respiratory-Society (ERS) International Congress, Paris, France, Sep 15-19, 2018.

7 Oral Communication in European-Academy-of-Allergy-and-Clinical-Immunology international conference 2018 and published in *Allergy* [Impact factor 6.048]

Sa-Sousa A, Pereira AM, Almeida R, Araujo L, Couto M, Jacinto T, et al. **The GA2LEN-Score: Development and validation of a new approach to identify adult asthma in epidemiological studies**. Allergy; 73 (SI Suppl 105): 83-84 Meeting Abstract: 0148.

Conference: Congress of the European-Academy-of-Allergy-and-Clinical-Immunology (EAACI), Munich, Germany, May 26-30, 2018.

8 Poster Communication in the World Conference of the International Primary Care Respiratory Group 2018

Sá-Sousa A, Almeida R, Freitas A, Fonseca JA. **LAMA and LABA prescriptions in Portuguese under 40 years old**.

Conference: 9th World Conference of the International Primary Care Respiratory Group (IPCRG), Porto, Portugal, 31 May- 2 Jun, 2018

9 Poster Communication in the International Severe Asthma Forum 2018

Sá-Sousa A, Almeida R, Freitas A, Fonseca JA. **OCS Use In Portuguese Respiratory Patients – Data From The National Prescription Database** .

Conference: International Severe Asthma Forum (ISAF) 2018, Madrid, Spain, 8 – 10 Nov, 2018

Oral and Poster Communications in National Conferences

10 Oral Communication in the national meeting of Sociedade Portuguesa Alergologia e Imunologia Clínica 2018 and published in *Revista Portuguesa de Imunoalergologia*

Sá-Sousa A, Fonseca JA, Pereira AM, Ferreira A, Arrobas A, Mendes A, et al. **O registo de asma grave Portugal – desenvolvimento, funcionalidades e partilha de dados**. Rev Port Imunoalergologia 2018; 26(S1).

Conference: XXXIX Annual Meeting of Sociedade Portuguesa Alergologia e Imunologia Clínica (SPAIC), Figueira da Foz, Portugal, 28-30 Sep, 2018

11 Oral Communication in the national meeting of Sociedade Portuguesa Alergologia e Imunologia Clínica 2017 and published in *Revista Portuguesa de Imunoalergologia*

Sá-Sousa A, Pereira AM, Araújo L, Couto M, Jacinto T, Freitas A, et al. **Identificar casos de asma em estudos epidemiológicos: desenvolvimento e validação de modelos multivariados de previsão.** Rev Port Imunoalergologia 2017; 25 (3).

Conference: XXXVIII Annual Meeting of Sociedade Portuguesa Alergologia e Imunologia Clínica, Figueira da Foz, Portugal, 6-8 Oct, 2017

Dissemination activities to the scientific community

12 Participation in the Clinical Village

Stand name: **Patient-reported technologies for asthma screening and monitoring**

Conference: Congress of the European-Academy-of-Allergy-and-Clinical-Immunology (EAACI), Munich, Germany, 1-5 Jun, 2018.

Dissemination activities to the community

13 Interview in the television program *Mentes que Brilham* in Porto Canal

Investigadores melhoram diagnóstico da Asma, 29 December 2018 20:00

Audience: 9684 people

Investigadores portugueses melhoram triagem da asma, was also disseminate

14 In Diário de Notícias Online | 04/12/2018

In Jornal de Notícias Online | 04/12/2018

In Correio da Manhã Online | 04/12/2018

In Atlas da Saúde Online | 04/12/2018

In Jornal Médico.pt Online | 04/12/2018

In Notícias ao Minuto Online | 04/12/2018

In Sábado Online | 04/12/2018

In Sapo Online - Sapo 24 Online | 04/12/2018

In Sapo Online - Sapo Lifestyle Online | 04/12/2018

Awards/Distinctions

1st Prize SPAIC for Oral Communication

Identificar casos de asma em estudos epidemiológicos: desenvolvimento e validação de modelos multivariados de previsão.

XXXVIII Annual Meeting of Sociedade Portuguesa Alergologia e Imunologia Clínica,

Figueira da Foz, Portugal, 6-8Oct, 2017

Prize SPAIC - AstraZeneca 2016

Identificação de utentes em risco utilizando dados existentes nos registos clínicos eletrónicos - Aplicação em Asma e Doença Pulmonar Obstrutiva Crónica

The Editors of the JACI: In Practice have selected ther article, **Adult asthma scores - development and validation of multivariable scores to identify asthma in surveys**, to be highlighted in the “LatestResearch” section of the American Academy of Allergy, Asthma & Immunology website.

Available from: https://www.aaaai.org/global/latest-research-summaries/New-Research-from-JACI-In-Practice/multivariable

Contributions of this thesis to other projects

NanoSTIMA: Macro-to-Nano Human Sensing: Towards Integrated Multimodal Health Monitoring and Analytics / NORTE-01-0145-FEDER-000016

financed by the North Portugal Regional Operational Programme (NORTE 2020), under the PORTUGAL 2020 Partnership Agreement, and through the European Regional Development Fund (ERDF).

AIRDOC: Aplicação móvel Inteligente para suporte individualizado e monitorização da função e sons Respiratórios de Doentes Obstrutivos Crónicos / NORTE-01-0247-FEDER-033275

financed by the North Portugal Regional Operational Programme (NORTE 2020), under the PORTUGAL 2020 Partnership Agreement, and through the European Regional Development Fund (ERDF).

PHE - Personal Health Empowerment / ITEA 3-16040,

as consortium integrating AIRDOC

Original papers

Original Article

Adult Asthma Scores—Development and Validation of Multivariable Scores to Identify Asthma in Surveys

Ana Sá-Sousa, MSc[a], Ana Margarida Pereira, MD[a,b,c], Rute Almeida, PhD[a], Luís Araújo, MD[b,c,d], Mariana Couto, MD, PhD[a,b,c], Tiago Jacinto, PhD[a,e], Alberto Freitas, PhD[a,b], Jean Bousquet, MD, PhD[f], and João A. Fonseca, MD, PhD[a,b,c] *Porto, Portugal; and Montpellier, France*

What is already known about this topic? Estimates obtained in surveys are highly dependent on the set of questions used for the operational definition of asthma. The identification of asthma in epidemiological studies is still an issue.

What does this article add to our knowledge? We developed 2 short, easy, self-reported scores, with very good properties to rule in/rule out asthma.

How does this study impact current management guidelines? This study provides validated screening tools to be used in adult asthma surveys and clinical screening/triage settings.

BACKGROUND: One of the questions in epidemiology is the identification of adult asthma in studies.
OBJECTIVE: To develop and validate multivariable scores for adult asthma identification in epidemiological studies and to explore cutoffs to rule in/rule out asthma, compared with asthma diagnosed by a physician after clinical examination and diagnostic tests, blinded to the self-administered questions.
METHODS: We analyzed data (n = 711 adults) from a nationwide population-based study. The predictors were self-administered questions identified in a literature review (the Adult Asthma Epidemiological Score [A2 score]) and from the Global Allergy and Asthma Network of Excellence (GA2LEN) questionnaire (the GA2LEN Asthma Epidemiological Score [GA2LEN score]). Scores were developed using exploratory factor analysis. Internal consistency, discriminative power, and diagnostic accuracy were assessed.
RESULTS: The A2 score comprises 8 questions (including "Did a physician confirm you had asthma?") and the GA2LEN score comprises 6 questions (including "Have you ever had asthma?"). Both had high Cronbach α (0.89 and 0.85, respectively, for the A2 score and the GA2LEN score) and good area under the receiver-operating characteristic curve (90.4% and 89.0%). The scoring is the sum of positive answers. Asthma is present (rule in) for scores of 4 or more (specificity, 99.2%; PPV, 93.3% and 91.7%; accuracy, 89.4% and 87.4%, respectively, for the A2 score and the GA2LEN score). Asthma is excluded (rule out) for A2 scores of 0 to 1 and a GA2LEN score of 0 (sensitivity, 93.1%; NPV, 98.2% and 98.0%; accuracy 89.4% and 82.8%, respectively, for the A2 score and the GA2LEN score).
CONCLUSIONS: These practical scores can be used to rule in/rule out asthma in epidemiological studies and clinical screening/triage settings. They may help physicians in primary care or other specialties to screen patients with asthma using a simple score with a high level of discrimination and to identify

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Conflicts of interest: J. Bousquet received personal fees outside the submitted work from Chiesi, Cipla, Hikma, Menarini, Mundipharma, Mylan, Novartis, Sanofi-Aventis, Takeda, Teva, Uriach, and Kyomed. J. A. Fonseca received fees outside the submitted work from ALK, AstraZeneca, Boehringer Ingelheim, Chiesi, Diater, GSK, HAL Allergy, Laboratórios Vitória, Leti, Menarini, Mundipharma, Novartis, and Teva. The rest of the authors declare that they have no relevant conflicts of interest.
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Abbreviations used
A2 score- Adult Asthma Epidemiological Score
AUC- area under the ROC curve
COPD- chronic obstructive pulmonary disease
ECRHS- European Community Respiratory Health Survey
GA2LEN- Global Allergy and Asthma Network of Excellence
GA2LEN score- GA2LEN Asthma Epidemiological Score
ICAR- Control and Burden of Asthma and Rhinitis
NPV- negative predictive value
PPV- positive predictive value
ROC- receiver-operating characteristic

the best candidates to be referred for a diagnostic workup. Moreover, their use may contribute to reducing the inconsistencies of operational definitions of asthma across studies and surveys. **(J Allergy Clin Immunol Pract 2019;7:183-90)**

Key words: *Asthma; Questionnaire survey; Factor analysis; statistical; Validation studies; Epidemiology*

INTRODUCTION

Asthma is an important public health problem that affects people of all ages and causes significant health resource utilization.[1] Its prevalence varies widely in different regions, and a "precise and universally accepted definition of asthma" is still lacking.[2] In fact, estimates obtained in epidemiological studies, on both adults[3] and children,[4] are highly dependent on the set of questions used for the operational definition of asthma.

In a clinical context, the initial diagnosis of asthma is based on identifying a pattern of respiratory symptoms, supported by pulmonary function tests, including the study of airflow obstruction reversibility and/or bronchial hyperresponsiveness.[1] However, because these procedures are seldom feasible in population-based studies, efforts have been made to find accurate definitions of asthma on the basis of questionnaires. In 2014, we proposed a set of questions to be reported in population-based studies on asthma prevalence on the basis of a literature review of the different asthma definitions used in epidemiological studies.[3]

Several prediction models have been previously developed to identify children with asthma-like symptoms. A systematic review[5] on prediction models for children reported extensive variability both on predictors and on outcome definitions and that none had the ability to rule in and rule out asthma simultaneously. In adults, Pekkanen et al[6] developed a continuous asthma score to define asthma on the basis of the European Community Respiratory Health Survey (ECRHS) questionnaire and used bronchial hyperreactivity as the comparator. This score showed good predictive capability in a prospective study when compared with self-reported use of asthma medication and asthma attacks and with bronchial hyperreactivity test at the end of follow-up.[7] However, its validity was not supported by the results in another population setting.[8] The ECRHS score was also compared with the self-reported previous diagnosis of asthma[8] but not against in-person physician diagnosis confirmed after clinical examination. This study argued on the use of a continuous score over a dichotomous definition of asthma, but in fact, the choice of a cutoff depends mainly on the aims of the classification. Self-reported questionnaires are tools used to identify asthma in prevalence studies assessing participants only once (eg, the Global Allergy and Asthma Network of Excellence [GA2LEN] survey[9]) and are also used as initial screening questionnaires, being a feasible and effective way for preselecting patients for additional diagnostic workup, including pulmonary function tests (eg, the ECRHS[10]). Screening questionnaires are often used in epidemiological studies on chronic obstructive pulmonary disease (COPD),[11,12] and their development was encouraged by the World Health Organization.[13]

To our knowledge, the existing score system for the identification of asthma in adults, based on self-administered questionnaires, has not been validated against actual diagnostic workup by a trained physician. Furthermore, it is lacking a screening questionnaire to rule in and rule out asthma, enabling its use both in population-based studies and in screening/triage clinical settings. We aimed to (1) develop and validate multivariable scores for adult asthma identification in epidemiological studies on the basis of answers to questions commonly used in these studies and (2) to explore the best cutoff to rule in asthma (preferable in prevalence studies) and to rule out asthma (preferable for screening/triage).

METHODS

Source of data

We used data from the Control and Burden of Asthma and Rhinitis (ICAR) study (PTDC/SAU-SAP/119192/2010), a nationwide population-based observational cross-sectional study conducted in Portugal (ClinicalTrials.gov: NCT01771120). The study was approved by a hospital ethics committee (*Comissão de Ética do Hospital São João EPE*, on October 17, 2011) and by the national data protection committee (no. 12372/2011). All participants signed the consent form.

Methods regarding sample size calculations, participants, and data collection in the ICAR study are described in the "Methods" section in this article's Online Repository at www.jaci-inpractice.org. Data collection included lung function and exhaled nitric oxide, skin prick tests, a structured clinical assessment, and standardized questionnaires. The structured clinical assessment was performed by a trained physician and included physical examination, use of health resources and medications because of asthma/rhinitis, and detailed personal and family medical history. In the ICAR study, self-administered questionnaires assessed disease symptoms and control, including the Portuguese version of the GA2LEN survey questionnaire[14] among other questionnaires.

Participants

We included participants from the general population aged 18 years and older from the ICAR study (n = 728). Considering an asthma prevalence of 23% (in the study sample), a specificity of 90%, and a maximum marginal error of estimate not exceeding 3% with a 95% CI, the required sample size was 498 participants.[15] Approximately 80% (n = 560) of the participants were randomly selected into a derivation cohort and 20% (n = 151) into a validation cohort.

Outcome and predictors

Asthma diagnosis (criterion standard) was defined by a physician on the basis of a structured clinical assessment of symptoms and detailed medical history, and supported by objective measurements (see the "Methods" section in this article's Online Repository), according to guidelines. The physician had no previous access to the results of the self-administered questionnaires.

The predictors were asthma-related questions from the self-administered questionnaires. Sixteen questions were selected as initial predictors, namely, (1) questions previously suggested in a literature review[2] and (2) questions on asthma from the GA2LEN questionnaire (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). On the basis of these predictors, 2 separate scores were built: the Adult Asthma Epidemiological Score (A2 score), based on the literature, and the GA2LEN Asthma Epidemiological Score (GA2LEN score), based on the GA2LEN questionnaire.

Subjects with missing data in any of the predictors were excluded from the analysis (n = 17 [2.3%]).

Statistical analysis methods

Categorical variables are presented as absolute frequencies and proportions. Comparisons of proportions and associations were tested. A P value of less than .05 was considered as statistically significant. Statistical analysis was performed using IBM SPSS Statistics, version 24.0 (IBM Corp, Armonk, NY).

An exploratory factor analysis was performed to construct a score reducing the number of predictors while retaining, as much as possible, the information contained in the initial combination of predictors, identifying the possible statistical redundancy of the predictors.[16] A factor analysis was run for the initial predictors (see Table E1 in this article's Online Repository). Principal-component analysis and oblimin rotation were used. Predictors with more than 95% responses in a single category were excluded. An item was considered redundant and was excluded if any 1 of the following occurred: highly intercorrelated (>0.900), considerable cross-loading (>0.300 in more than 1 factor), low item-total correlation (<0.400), or increased Cronbach α if the predictor was deleted.

Discriminative/predictive power of the scores was evaluated by receiver-operating characteristic (ROC) curve analysis. Internal consistency was assessed by Cronbach α. The diagnostic accuracy measures used were sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy.

The scores' performance was tested in the derivation and validation cohorts and compared with the ECRHS asthma score. The cutoff to rule in asthma was defined as the minimum number of positive answers to obtain a PPV of 85% or more simultaneously in both cohorts. The cutoff to rule out asthma was defined as the maximum number of positive answers to obtain an NPV of 95% or more simultaneously in both cohorts.

For each of the 2 scores, 2 scoring methods were tested: the weighted sum, obtained by multivariable logistic regression of the included predictors, and the direct sum of the included predictors. The scores obtained by both the scoring methods were compared by the Spearman correlation factor. The values for the area under the ROC curve (AUC) for the scores obtained by both the methods were also compared.

RESULTS

This study included 711 participants (see Figure 1), with a median age (percentile 25 to percentile 75) of 42 (32-55) years,

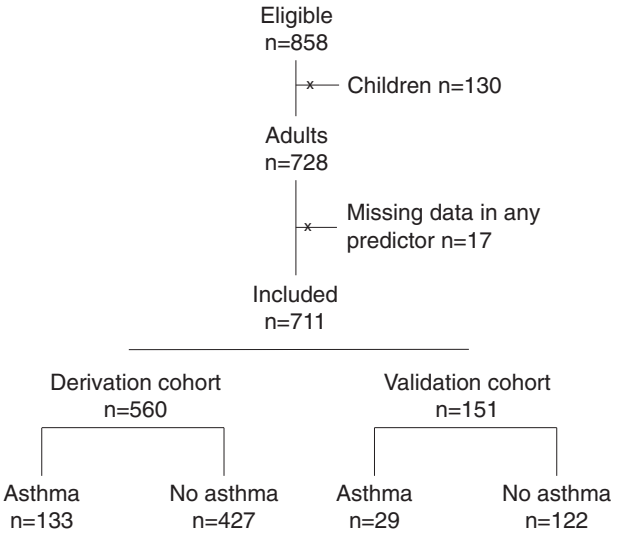

FIGURE 1. Participants' flowchart.

and 447 (63%) were females. The number of participants with asthma was 162 (23%). No statistically significant differences were observed between the derivation and the validation cohorts regarding sex, age, geographic region of residence, and presence of asthma ($P > .1$). Specifically, no differences between the cohorts were observed in the proportion of participants with asthma (23.8% vs 19.2%; $P = .24$).

In the derivation cohort, having asthma was highly associated with all the initial predictors but not with the demographic variables (Table I). In general, the ability to identify patients with asthma using any asthma predictor alone was low (PPV < 70%; see Table E2 in this article's Online Repository at www.jaci-inpractice.org).

Scores specifications and performance

On the basis of the initial set of questions (see Table E1 in this article's Online Repository), 2 scores were developed to identify the presence of asthma (Table II). The A2 score and the GA2LEN score derivations were obtained by exploratory factor analysis (see the "Exploratory factor analysis" section in this article's Online Repository at www.jaci-inpractice.org). The final A2 score included 8 predictors in 2 factors with eigenvalues of 3.997 (predictors 2-5 and 10; Table II) and 3.535 (predictors 6-8). The final GA2LEN score included 6 predictors in 2 factors with eigenvalues of 2.954 (predictors 6-8; Table II) and 2.860 (predictors 1, 4, and 5).

The discriminative properties of the developed scores were similar, with an AUC of about 90% (Figure 2). The A2 score had higher Cronbach α than the GA2LEN score (0.887 vs 0.852, respectively; Figure 2).

The scores obtained by the weighted sum (Table II) were highly correlated with those obtained by the direct sum (Spearman correlation coefficient >0.98; $P < .001$). As so, the final result was the direct sum of the positive answers to the questions selected for each score, ranging from 0 to 8 for the A2 score and from 0 to 6 for the GA2LEN score.

Diagnostic accuracy measures were assessed for both scores and cohorts (Table III; see also Table E3 in this article's Online Repository at www.jaci-inpractice.org). As expected, the

TABLE I. Characterization of the cohorts

Characteristic	Derivation cohort				Validation cohort			
		Asthma presence				Asthma presence		
	Total (n = 560)	No (427 [76.3%])	Yes (133 [23.8%])	*P* value	Total (n = 151)	No (122 [80.8%])	Yes (29 [19.2%])	*P* value
Demographic characteristics								
Age (y), median (P25-P75)	41.5 (32-55)	43 (32-56)	37 (31-55)	.119*	42 (33-52)	43 (32-54)	40 (33-48)	.501*
Sex, n (%)				.302†				.903‡
Female	360 (64.6)	279 (65.8)	81 (60.9)		87 (57.6)	70 (57.4)	17 (58.6)	
Male	197 (35.4)	145 (34.2)	52 (39.1)		64 (42.4)	52 (42.6)	12 (41.4)	
Region, n (%)				.561§				.701§
North	285 (50.9)	216 (50.6)	69 (51.9)		80 (53.0)	66 (54.1)	14 (48.3)	
Center	35 (6.3)	27 (6.3)	8 (6.0)		11 (7.3)	10 (8.2)	1 (3.4)	
Lisbon	183 (32.7)	139 (32.6)	44 (33.1)		36 (23.8)	27 (22.1)	9 (31.0)	
Alentejo	26 (4.6)	18 (4.2)	8 (6.0)		10 (6.6)	6 (4.9)	4 (13.8)	
Algarve	31 (5.5)	27 (6.3)	4 (3.0)		14 (9.3)	13 (10.7)	1 (3.4)	
Predictors, n (%)								
1. Have you ever had asthma?‖¶	138 (24.6)	36 (8.4)	102 (76.7)	<.001†	30 (19.9)	10 (8.2)	20 (69.0)	<.001†
2. Did a physician confirm you had asthma?‖	132 (23.6)	30 (7.0)	102 (76.7)	<.001†	29 (19.2)	10 (8.2)	19 (65.5)	<.001†
3. Do you still have asthma (previously diagnosed by a physician)?‖	104 (18.6)	14 (3.3)	90 (67.7)	<.001†	24 (15.9)	6 (4.9)	18 (62.1)	<.001‡
4. Have you ever been hospitalized because of asthma?¶	40 (7.1)	10 (2.3)	30 (22.6)	<.001†	8 (5.3)	2 (1.6)	6 (20.7)	.001‡
5. Have you had any asthma attack in the last 12 mo?‖¶	51 (9.1)	7 (1.6)	44 (33.1)	<.001†	7 (4.6)	1 (0.8)	6 (20.7)	<.001‡
6. Are you currently taking any medicines including inhalers, aerosols, or tablets for asthma?‖¶	66 (11.8)	5 (1.2)	61 (45.9)	<.001†	11 (7.3)	1 (0.8)	10 (34.5)	<.001‡
7. Have you ever had wheezing or whistling in the chest at any time in the last 12 mo?‖¶	178 (31.8)	85 (19.9)	93 (69.9)	<.001†	38 (25.2)	17 (13.9)	21 (72.4)	<.001†
8. Have you had this wheezing or whistling when you did not have a cold?‖¶	104 (18.6)	41 (9.6)	63 (47.4)	<.001†	18 (11.9)	4 (3.3)	14 (48.3)	<.001‡
9. Have you been at all breathless when the wheezing noise was present?‖¶	118 (21.1)	41 (9.6)	77 (57.9)	<.001†	24 (15.9)	7 (5.7)	17 (58.6)	<.001‡
10. Have you had an attack of shortness of breath after exercise in the last 12 mo?‖	45 (8.0)	16 (3.7)	29 (21.8)	<.001†	9 (6.0)	1 (0.8)	8 (27.6)	<.001‡
11. Have you had an attack of shortness of breath that came on during the day when you were at rest at any time in the last 12 mo?‖	78 (13.9)	26 (6.1)	52 (39.1)	<.001†	13 (8.6)	2 (1.6)	11 (37.9)	<.001‡
12. Have you woken up with the feeling of tightness in your chest at any time in the last 12 mo?‖¶	98 (17.5)	59 (13.8)	39 (29.3)	<.001†	25 (16.6)	15 (12.3)	10 (34.5)	.010‡
13. Have you been woken up by an attack of shortness of breath at any time in the last 12 mo?‖¶	57 (10.2)	23 (5.4)	34 (25.6)	<.001†	14 (9.3)	8 (6.6)	6 (20.7)	.029‡
14. Have you been woken up by an attack of coughing at any time in the last 12 mo?‖¶	226 (40.4)	156 (36.5)	70 (52.6)	.001†	54 (35.8)	37 (30.3)	17 (58.6)	.004†
15. In the last 12 mo, have you had a dry cough during the night, apart from a cough associated with a cold or a chest infection?‖	222 (39.6)	144 (33.7)	78 (58.6)	<.001†	59 (39.1)	40 (32.8)	19 (65.5)	.001†
16. Did you have phlegm when coughing for at least 3 mo in the last year?¶	19 (3.4)	8 (1.9)	11 (8.3)	.001†	4 (2.6)	2 (1.6)	2 (6.9)	.167‡

P25-P75, percentile 25 to percentile 75.
*Mann-Whitney *U* test.
†Chi-square test.
‡The Fisher exact test.
§Linear-by-linear test.
‖Initial predictors used to develop the A2 score.
¶Initial predictors used to develop the GA2LEN score.

TABLE II. Association of the variables included in the final multivariable scores with the presence of asthma as assessed by the physician

Predictors	A2 score		GA2LEN score	
	aOR	95% CI	aOR	95% CI
1. Have you ever had asthma?	*	*	13.36	6.79-26.27
2. Did a physician confirm you had asthma?	7.91	3.17-19.77	†	†
3. Do you still have asthma (previously diagnosed by a physician)?	4.28	1.33-13.79	†	†
4. Have you had any asthma attack in the last 12 mo?	0.51	0.15-1.78	1.07	0.36-3.18
5. Are you currently taking any medicines including inhalers, aerosols, or tablets for asthma?	4.07	1.23-13.47	6.02	2.01-18.00
6. Have you ever had wheezing or whistling in the chest at any time in the last 12 mo?	3.23	1.25-8.36	3.35	1.32-8.47
7. Have you had wheezing or whistling when you did not have a cold?	1.35	0.55-3.30	1.36	0.58-3.22
8. Have you been at all breathless when the wheezing noise was present?	1.13	0.42-3.00	1.37	0.55-3.42
9. Have you had an attack of shortness of breath after exercise in the last 12 mo?	*	*	†	†
10. Have you had an attack of shortness of breath that came on during the day when you were at rest at any time in the last 12 mo?	2.05	0.85-4.98	†	†
Constant	0.05		0.05	

aOR, Adjusted odds ratio.
*Question tested but not included in the final score.
†Question not included in GA2LEN questionnaire.

definitions requiring more positive answers have higher specificity and PPV but lower sensitivity, indicating that the probability of having asthma increases with an increasing score.

On the basis of a PPV of 85% or more in both cohorts, we considered asthma to be present in patients with a sum of 4 or more positive answers (Table III). Using this cutoff in the derivation cohort, the A2 score and the GA2LEN score had high accuracy (87.9% and 85.9%), high specificity (96.7% and 97.7%), and a sensitivity of 59.4% and 48.1%, respectively (see Table E3 in this article's Online Repository). In the validation cohort, for the same cutoff based on PPV, the A2 score had a slightly higher accuracy compared with the GA2LEN score (89.4% vs 87.4%; Figure 3, *C*) and a higher sensitivity (48.3% vs 37.9%; Figure 3, *A*), but the same specificity (99.2%; Figure 3, *A*) (see Table E3 in this article's Online Repository) and false-positive rate (1%; Figure 3, *E*).

The cutoff to rule out asthma was based on an NPV of 95% or more in both cohorts, which corresponds to a sum of less than 2 positive answers for the A2 score and 0 for the GA2LEN score (Table III). Using this cutoff in the derivation cohort, the A2 score had a higher accuracy compared with the GA2LEN score (84.3% vs 78.2%) and a higher specificity (83.8% vs 74.5%; Figure 3, *A*), but both scores had high sensitivity (85.7% and 90.2%, respectively; Figure 3, *A*) (see Table E3 in this article's Online Repository). For this cutoff in the validation cohort, the A2 score had a higher accuracy compared with the GA2LEN score (89.4% vs 82.8%; Figure 3, *B*), but both scores had the same sensitivity (93.1%; Figure 3, *A*) (see Table E3 in this article's Online Repository); the scores also had similar NPVs (98.2% vs 98.0%, respectively, for the A2 score and the GA2LEN score; Table III) and the same false-negative rate (7%; Figure 3, *D*).

DISCUSSION

We developed and validated 2 multivariable scores, on the basis of self-administered questions, for the identification of asthma cases in epidemiological studies. The scores obtained

A

	AUC using direct sum, % (95% CI)	AUC using weighted score, % (95% CI)	Number of items	Cronbach α (95% CI)
A2 score	90.4 (87.0-93.9)	91.3 (87.9-94.7)	8	0.887 (0.872-0.900)
GA2LEN score	89.0 (85.4-92.5)	90.5 (87.0-94.0)	6	0.852 (0.832-0.870)

B

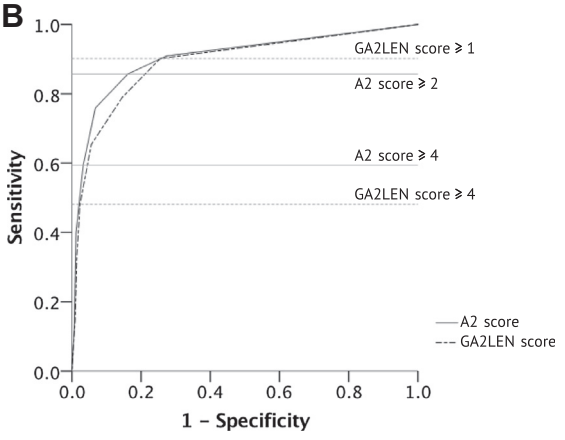

FIGURE 2. **(A)** Discriminative properties and internal consistency. **(B)** ROC curve of the scores, using participants from the derivation cohort (n = 560).

TABLE III. Predictive values in derivation and validation cohorts

Score (no. of positive answers)	Derivation cohort (n = 560)			Validation cohort (n = 151)		
	n (%)	PPV % (95% CI)	NPV % (95% CI)	n (%)	PPV % (95% CI)	NPV % (95% CI)
A2 score						
Possible Asthma						
≥2*	183 (32.7)	62.3 (56.8-67.5)	95.0 (92.5-96.6)	41 (27.2)	65.9 (53.8-76.1)	98.2 (93.4-99.5)
≥3	130 (23.2)	77.7 (70.8-83.4)	92.6 (90.2-94.4)	24 (15.9)	79.2 (60.8-90.3)	92.1 (87.6-95.1)
Probable Asthma						
≥4†	93 (16.6)	85.0 (76.8-90.6)	88.4 (86.2-90.4)	15 (9.9)	93.3 (65.7-99.0)	89.0 (85.0-92.0)
≥5	70 (12.5)	88.6 (79.2-94.0)	85.5 (83.4-87.4)	12 (7.9)	91.7 (59.7-98.8)	87.1 (83.5-89.4)
≥6	58 (10.4)	91.4 (81.2-96.3)	84.1 (82.1-85.8)	10 (6.6)	90.0 (54.3-98.6)	85.8 (82.6-88.5)
≥7	39 (7.0)	89.7 (76.0-96.0)	81.2 (79.6-82.7)	7 (4.6)	85.7 (42.9-98.0)	84.0 (81.4-86.4)
8	20 (3.6)	85.0 (62.8-95.0)	78.5 (77.4-79.6)	2 (1.3)	100.0	81.9 (80.4-83.3)
GA2LEN score						
Possible Asthma						
≥1*	229 (40.9)	52.4 (48.1-56.7)	96.1 (93.6-97.6)	51 (33.8)	52.9 (43.7-62.0)	98.0 (92.8-99.5)
≥2	167 (29.8)	62.9 (57.0-68.4)	92.9 (90.4-94.8)	31 (20.5)	71.0 (55.8-82.6)	94.2 (89.4-96.9)
≥3	111 (19.8)	78.4 (70.7-84.5)	89.8 (87.4-91.7)	21 (13.9)	81.0 (60.7-92.1)	90.8 (86.4-93.8)
Probable Asthma						
≥4†	74 (13.2)	86.5 (77.2-92.4)	85.8 (83.7-87.7)	12 (7.9)	91.7 (59.7-98.8)	85.8 (83.7-87.7)
≥5	50 (8.9)	88.0 (76.2-94.4)	82.6 (80.8-84.2)	10 (6.6)	90.0 (54.3-98.6)	85.8 (82.6-88.5)
6	24 (4.3)	83.3 (63.5-93.5)	78.9 (77.7-80.1)	3 (2-0)	66.7 (15.8-95.5)	81.8 (80.2-83.2)

A2 score, Adult Asthma Epidemiological Score; *GA2LEN score*, Global Allergy and Asthma Network of Excellence Asthma Epidemiological Score; *PPV*, Positive predictive value; *NPV*, negative predictive value.

*Cutoff of ≥2 (for the A2 score) and of ≥1 (for the GA2LEN score) for considering possible asthma (NPV of 95% or more, simultaneously in derivation and validation cohorts).

†Cutoff of ≥4 for considering probable asthma (PPV 85% or more, simultaneously in derivation and validation cohorts).

have very good properties to rule in/rule out asthma, providing, for the first time, validated screening tools to be used in adult asthma epidemiological studies and clinical screening/triage settings.

The performance of asthma prediction scores has been studied mostly for childhood asthma. Smit et al[5] assessed 12 prediction models for children and reported a sensitivity ranging from 15% to 75% and a specificity ranging from 35% to 100%. In

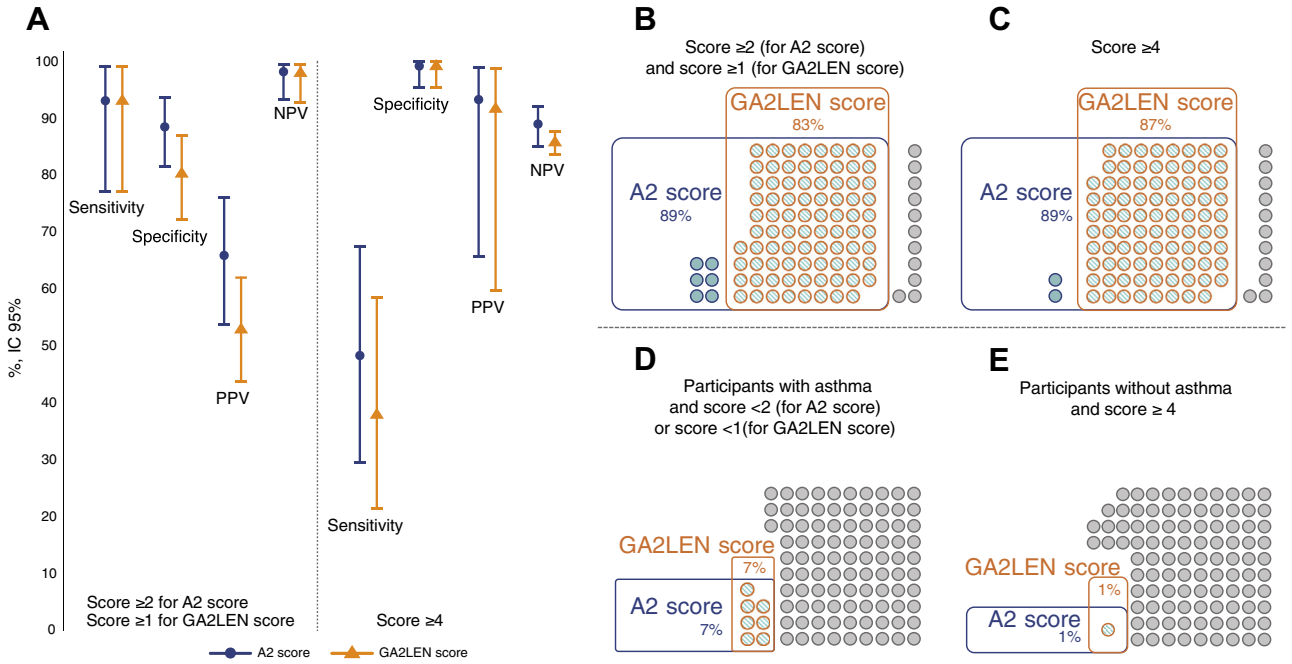

FIGURE 3. Diagnostic accuracy measures (**A**) and accuracy (**B** and **C**) of the 2 scores in patients from the validation cohort for considering possible asthma (values ≥2 in the A2 score or values ≥1 in the GA2LEN score) and probable asthma (values ≥4); false-negative rate (**D**) and false-positive rate (**E**).

prevalence studies, a questionnaire with high specificity (few false positives) and PPV for asthma diagnosis is preferable. Both our scores had high specificity for asthma diagnosis, which is related to the choice of a PPV-based cutoff to rule in asthma. However, if our interest is to screen subjects to undergo a confirmatory clinical evaluation, a questionnaire with high sensitivity (few false negatives) and NPV is preferable in the first stage. In this case, we can also use these scores to rule out asthma with the NPV-based cutoff. A meta-analysis on screening tests for COPD diagnostic accuracy determined a pooled sensitivity of 64.5% (95% CI, 59.9%-68.8%) and a specificity of 65.2% (52.9%-75.8%) for the COPD Diagnostic Questionnaire[12]; more recently, the development and validation study of the Salzburg COPD screening questionnaire reported a sensitivity of 69.1% (56.6%-79.5%) and an NPV of 91.8% (87.5%-95.7%).[11] The values of sensitivity and NPV obtained for our scores, considering the cutoff to rule out asthma, were superior to those for the screening tests for COPD. These findings indicate that the A2 score and the GA2LEN score may be used for asthma screening, for instance, in clinical screening/triage settings to identify the patients who could benefit from complete diagnostic workup. They may help physicians in primary care or other specialties to screen patients with asthma using a simple score with a high level of discrimination and to identify the best candidates to be referred for a diagnostic workup.

Pekkanen et al[6] developed the ECRHS asthma score using the question "Have you ever had asthma?" and with bronchial hyperreactivity as the comparator. It includes 8 questions (see the "ECRHS score" section and Table E1 in this article's Online Repository). Applying the ECRHS asthma score to our data and comparing it with the scores developed in the present study, we found that the A2 score has the same number of questions as the ECRHS asthma score, but shows better discriminative properties, better internal consistency, and better diagnostic accuracy measures. However, the GA2LEN score has the advantage of being shorter than the ECRHS asthma score, with comparable diagnostic accuracy measures and better discriminative properties and internal consistency (see the "ECRHS score" section and Table E4 in this article's Online Repository at www.jaci-inpractice.org).

The A2 score includes questions on previous physician diagnosis ("Did a physician confirm you had asthma?" and "Do you still have asthma (previously diagnosed by a physician)?"), whereas the GA2LEN score asks "Have you ever had asthma?" which can be preferable in settings with significant underdiagnoses or difficult access to health care. Moreover, the A2 score has 1 additional question: "Have you had an attack of shortness of breath that came on during the day when you were at rest at any time in the last 12 months?" The GA2LEN score may be considered to be more practical than the A2 score, because it is shorter and 1 positive answer is enough to consider possible asthma. The questions included in the A2 score that are not in the GA2LEN score are part of the ECRHS[10] and the National Health and Nutrition Examination Survey.[17]

This study has its strengths and limitations. In the present study, the Global Initiative for Asthma guidelines[1] for asthma diagnosis were followed by trained physicians, supported by objective measurements, and blinded to the results of previous self-administered questionnaires. A limitation of this study is that we did not validate the scores in other populations and settings, limiting its generalization. New studies using these scores are being designed, and their application to other data sets is warranted for external validation. To improve the robustness of the validation results, we used bootstrap resampling techniques, obtaining very similar results to those reported for the validation cohort (data not shown). Another limitation is the use of PPV-/NPV-based cutoffs, which are measurements highly dependable on asthma prevalence, and therefore these cutoff values may not be transferable to other settings. As so, presenting the results as continuous, before its dichotomization, is advisable when applying the scores. Despite these limitations, this study proposes scores developed on the basis of real-life data from the general population and on asthma diagnosis by a specialist that can be used for either asthma identification or asthma screening/triage.

CONCLUSIONS

Two scores based on self-administered questions were developed and validated compared with physician-led asthma diagnostic workup. These scores are short, easy to use, and can be applied to identify the likely presence of asthma (prevalence) or absence (screening) of asthma in epidemiological studies and clinical screening/triage settings. The A2 score may be preferred in studies aiming at maximum accuracy; however, the GA2LEN score is shorter and would be preferable for communities in which there may be difficulties related to physician diagnosis of asthma. Asthma presence can be considered for results of 4 or more in either the A2 score or the GA2LEN score and can be excluded for results of 0 in the GA2LEN score or of 0 to 1 in the A2 score. For results in between, asthma is possible but requires a confirmatory clinical evaluation. Nevertheless, the presentation of the results as a continuum score before dichotomization using a cutoff is advisable. The use of the A2 score and the GA2LEN score may contribute to reducing the inconsistencies of asthma definitions across studies and surveys and have the potential to be used in clinical settings for screening/triage of asthma, where they may contribute toward identifying the best candidates to be referred for diagnostic workup.

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ONLINE REPOSITORY

METHODS

This section describes in detail the methods of the ICAR study.

The ICAR was a nationwide population-based observational cross-sectional study. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, consistent with good clinical practice and the applicable regulatory requirements, and was approved by a hospital ethics committee (*Comissão de Ética do Hospital São João EPE*, on October 17, 2011) and by the national data protection committee (no. 12372/2011). The study protocol containing standard operational procedures was registered in ClinicalTrials.gov (NCT01771120). All participants signed the consent form.

Sample size

The ICAR sample size calculations were based on the comparison of quality of life measured by the World Health Organization's Quality of Life (WHOQOL-BREF)[E1] questionnaire. Considering previous participation and expressed willingness, we estimate a nonparticipation rate of 33%. We have assumed a WHOQOL-BREF SD of 3.0 units, on the basis of the previous reports for different domains and populations.[E1,E2] Consequently, to identify a change of 1 unit in the WHOQOL-BREF quality-of-life scores, in a 2-sided test, for a type I error probability of 0.05 and a statistical power of 80, 142 individuals in each group are required. We include individuals without respiratory symptoms at a 2:1 ratio to other groups. As so, we calculated a sample of 750 individuals divided into 4 patient groups: (1) patients with a self-reported diagnosis of asthma alone (n = 150), (2) patients with a self-reported diagnosis of rhinitis alone (n = 150), (3) patients with a self-reported diagnosis of asthma and rhinitis (n = 150), and (4) patients with no history of respiratory symptoms or diseases (n = 300).

Participants and data collection

In the ICAR study, all subjects who have been included in the INAsma (*Inquérito Nacional sobre Asma*) study[E3,E4] and who have expressed their willingness to participate in a clinical assessment were eligible along with their family members. Furthermore, local media and posters were used to disseminate the study and invite participants. Persons who did not understand spoken Portuguese and who had cognitive or physical conditions that could hamper their participation in the study were excluded.

Data were collected between October 30, 2012, and July 12, 2014, in 2 allergy clinics (Lisbon and Porto) or by using a mobile diagnostic unit, on the basis of the participants' geographical proximity.

Participants were screened by telephonic interview into 1 of the 4 groups. A total of 858 participants, either with asthma and/or rhinitis or with no previous history of respiratory symptoms or diseases (aged between 3 and 89 years), were included from 90 Portuguese cities.

Data collection comprised anthropometric measurements, lung function and exhaled nitric oxide tests, skin prick tests, a structured clinical assessment, and standardized questionnaires. Anthropometric measurements of height, weight, and waist/hip circumference followed the procedures manual of the National Health and Nutrition Examination Survey.[E5] Lung function tests included spirometry with postbronchodilator reversibility (EasyOne Pro, ndd, Zurich, Switzerland, and Jaeger IOS, CareFusion, San Diego, Calif), carbon monoxide in exhaled air (SmokeCheck, Micro Medical, Kent, UK), and exhaled nitric oxide (NIOX Mino, Aerocrine AB, Solna, Sweden), and were done according to standardized methods.[E6-E8] Atopy was determined with skin prick tests. Blood sampling allowed for the determination of total IgE, eosinophilic cationic protein, and C-reactive protein. The structured clinical assessment performed by a trained physician included physical examination, comorbidities screening (eg, gastroesophageal reflux and anxiety/depression), use of health resources and medications because of asthma/rhinitis, assessment of the degree of control of the allergic diseases, family history, environmental exposures (at home and workplace), and social habits. In the ICAR study, self-administered questionnaires included the assessment of the following:

1. disease symptoms and control, using the Portuguese versions of the GA2LEN survey questionnaire,[E9] the allergy airway diseases screening (ASF) questionnaire,[E10] visual analog scales, the Control of Allergic Rhinitis and Asthma Test,[E11] the Control of Allergic Rhinitis and Asthma Test for kids,[E12] and the Allergic Rhinitis Control Test[E13];
2. quality of life, using the Portuguese versions of the EuroQol 5-dimensional questionnaire,[E14] the WHOQOL-BREF,[E1] the Mini Asthma Quality of Life Questionnaire,[E15] the Mini Rhinoconjunctivitis Quality of Life Questionnaire,[E16] and the Paediatric Asthma Caregiver's Quality of Life Questionnaire[E17];
3. work/school absenteeism and impairment, using the Work Productivity and Activity Impairment questionnaire[E18];
4. adherence to prescribed treatment, using the Medication Adherence Report Scale[E19]; and
5. physical activity, using the International Physical Activity Questionnaire.[E20]

EXPLORATORY FACTOR ANALYSIS

This section contains complementary material on exploratory factor analysis results.

The A2 score derivation was obtained by exploratory factor analysis as follows. The predictors "asthma diagnosis by a physician" and "asthma self-report" were highly correlated and had similar loading factors; however, because "asthma diagnosis by a physician" improved the Cronbach α of the final score, it was included, whereas "asthma self-report" was excluded. "Waking up with chest tightness" and "dry cough during the night not associated with infection" were excluded because they had a low item-total correlation. The best Cronbach α was obtained when "waking up with an attack of cough," "waking up with an attack of shortness of breath," and "having an attack of shortness of breath after exercise" were excluded. The final A2 score included 8 predictors in 2 factors with eigenvalues of 3.997 (predictors 2-5 and 10; Table II) and 3.535 (predictors 6-8).

For the GA2LEN score, "phlegm when coughing" was excluded because it had more than 95% responses in a single category; "waking up with chest tightness" and "hospitalization because of asthma" were excluded because they had a low item-total correlation. The best Cronbach α was obtained when "waking up with an attack of cough" and "waking up with an attack of shortness of breath" were excluded. The final GA2LEN score included 6 predictors in 2 factors with eigenvalues of 2.954 (predictors 6-8; Table II) and 2.860 (predictors 1, 4, and 5).

TABLE E1. Initial predictors (Portuguese and English versions) used to develop the multivariable prediction models and predictors included in the ECRHS asthma score previously developed

Portuguese version of the predictors	Predictors	From literature, as suggested by Sá-Sousa et al (A2 score)	From GA2LEN questionnaire (GA2LEN score)	Asthma score based on ECRHS
1. *Já alguma vez teve asma?*	1. Have you ever had asthma?	×	×	×
2. *Alguma vez um médico lhe disse que tem asma?*	2. Did a physician confirm you had asthma?	×		
3. *Ainda tem asma?*	3. Do you still have asthma?	×		
4. *Alguma vez esteve hospitalizado por asma?*	4. Have you ever been hospitalized because of asthma?		×	
5. *Teve um ataque de asma nos últimos 12 meses?*	5. Have you had any asthma attack in the last 12 mo?	×	×	×
6. *Presentemente está a tomar remédios (inaladores, aerossóis ou comprimidos) para a asma?*	6. Are you currently taking any medicines including inhalers, aerosols, or tablets for asthma?	×	×	×
7. *Alguma vez teve chiadeira ou pieira no peito nos últimos 12 meses?*	7. Have you ever had wheezing or whistling in the chest at any time in the last 12 mo?	×	×	
8. *Teve a chiadeira ou a pieira sem estar constipado?*	8. Have you had this wheezing or whistling when you did not have a cold?	×	×	
9. *Teve falta de ar quando a chiadeira estava presente?*	9. Have you been at all breathless when the wheezing noise was present?	×	×	×
10. *Alguma vez foi acordado devido a um ataque de falta de ar, depois de atividade física moderada ou intensa, nos últimos 12 meses?*	10. Have you had an attack of shortness of breath after exercise in the last 12 mo?	×		×
11. *Alguma vez teve uma crise de falta de ar, que surgiu durante o dia, quando estava em repouso, nos últimos 12 meses?*	11. Have you had an attack of shortness of breath that came on during the day when you were at rest at any time in the last 12 mo?	×		×
12. *Acordou com a sensação de aperto no peito nos últimos 12 meses?*	12. Have you woken up with the feeling of tightness in your chest at any time in the last 12 mo?	×	×	×
13. *Alguma vez foi acordado devido a um ataque de falta de ar nos últimos 12 meses?*	13. Have you been woken up by an attack of shortness of breath at any time in the last 12 mo?	×	×	×
14. *Alguma vez foi acordado devido a um ataque de tosse nos últimos 12 meses?*	14. Have you been woken up by an attack of coughing at any time in the last 12 mo?	×	×	
15. *Alguma vez teve tosse seca durante a noite nos últimos 12 meses, não contando com a tosse associada a constipação ou infeção?*	15. In the last 12 mo, have you had a dry cough during the night, apart from a cough associated with a cold or a chest infection?	×		
16. *Na maioria dos dias produz muco do seu peito durante um período de três meses por ano?*	16. Did you have phlegm when coughing for at least 3 mo in the last year?		×	

TABLE E2. Diagnostic accuracy measures for each predictor in the derivation and validation cohorts

	Derivation cohort (n = 560)				Validation cohort (n = 151)			
Predictor	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**
1. Have you ever had asthma?	76.7 (69.0-83.8)	91.6 (88.7-94.0)	73.9 (66.2-80.8)	92.7 (89.9-94.9)	69.0 (51.0-91.8)	91.8 (86.1-95.8)	66.7 (48.9-81.7)	92.6 (87.0-96.4)
2. Did a physician confirm you had asthma?	76.7 (69.0-83.8)	93.0 (90.3-95.1)	77.3 (69.6-83.9)	92.8 (90.0-95.0)	65.5 (47.4-91.8)	91.8 (86.1-95.8)	65.5 (47.4-81.0)	91.8 (86.1-95.8)
3. Do you still have asthma (previously diagnosed by a physician)?	67.7 (59.4-75.2)	96.7 (94.7-98.1)	86.5 (79.1-92.2)	90.6 (87.7-93.0)	62.1 (43.9-78.2)	95.1 (90.3-98.0)	75.0 (55.7-89.2)	91.3 (85.6-95.4)
4. Have you ever been hospitalized because of asthma?	22.6 (16.0-30.1)	97.7 (95.9-98.8)	75.0 (60.3-86.6)	76.3 (72.6-79.6)	20.7 (8.8-37.5)	98.4 (95.0-99.7)	75.0 (40.9-95.3)	80.8 (74.0-86.5)
5. Have you had any asthma attack in the last 12 mo?	33.1 (25.5-41.3)	98.4 (96.9-99.3)	86.3 (75.1-93.9)	82.5 (79.1-85.6)	20.7 (8.8-37.5)	99.2 (96.4-100.0)	85.7 (50.6-99.1)	84.0 (77.5-89.4)
6. Are you currently taking any medicines including inhalers, aerosols, or tablets for asthma?	45.9 (37.5-54.4)	98.8 (97.5-99.6)	92.4 (84.4-97.2)	85.4 (82.1-88.4)	34.5 (19.0-52.6)	99.2 (96.4-100.0)	90.9 (65.7-99.5)	86.4 (80.1-91.4)
7. Have you ever had wheezing or whistling in the chest at any time in the last 12 mo?	69.9 (61.8-77.3)	80.1 (76.1-83.7)	52.2 (44.9-59.5)	89.5 (86.2-92.3)	72.4 (54.7-86.3)	86.1 (79.2-91.4)	55.3 (39.5-70.3)	92.9 (87.2-96.7)
8. Have you had wheezing or whistling when you did not have a cold?	47.4 (39.0-55.8)	90.4 (87.4-93.0)	60.6 (51.0-69.6)	84.6 (81.2-87.8)	48.3 (30.8-66.0)	96.7 (92.5-99.0)	77.8 (55.7-92.5)	88.7 (82.6-93.3)
9. Have you been at all breathless when the wheezing noise was present?	57.9 (49.4-66.1)	90.4 (87.4-93.0)	65.3 (56.4-73.5)	87.3 (84.0-90.2)	58.6 (40.5-75.2)	94.3 (89.2-97.5)	70.8 (51.2-86.3)	90.6 (84.7-94.8)
10. Have you had an attack of shortness of breath after exercise in the last 12 mo?	21.8 (15.4-29.3)	96.3 (94.2-97.8)	64.4 (49.9-77.3)	79.8 (76.2-83.1)	27.6 (13.7-45.3)	99.2 (96.4-100.0)	88.9 (59.5-99.3)	85.2 (78.8-90.4)
11. Have you had an attack of shortness of breath that came on during the day when you were at rest at any time in the last 12 mo?	39.1 (31.1-47.5)	93.9 (91.4-95.9)	66.7 (55.8-76.5)	83.2 (79.9-86.4)	37.9 (21.8-56.1)	98.4 (95.0-99.7)	84.6 (59.6-97.3)	87.0 (80.7-91.1)
12. Have you woken up with the feeling of tightness in your chest at any time in the last 12 mo?	29.3 (22.0-37.4)	86.2 (82.7-89.2)	39.8 (30.5-49.7)	79.7 (75.8-83.2)	34.5 (19.0-52.6)	87.7 (81.1-92.7)	40.0 (22.5-59.5)	84.9 (78.0-90.4)
13. Have you been woken up by an attack of shortness of breath at any time in the last 12 mo?	25.6 (18.7-33.4)	94.6 (92.2-96.5)	59.6 (46.7-71.8)	80.3 (76.7-83.6)	20.7 (8.8-37.5)	93.4 (88.1-96.9)	42.9 (19.8-68.3)	83.2 (76.4-88.8)
14. Have you been woken up by an attack of coughing at any time in the last 12 mo?	52.6 (44.2-61.0)	63.5 (58.8-67.9)	31.0 (25.2-37.2)	81.1 (76.7-85.1)	58.6 (40.5-75.2)	69.7 (61.2-77.4)	31.5 (20.2-44.5)	87.6 (80.1-93.2)
15. In the last 12 mo, have you had a dry cough during the night, apart from a cough associated with a cold or a chest infection?	58.6 (50.2-66.8)	66.3 (61.7-70.7)	35.1 (29.1-41.6)	83.7 (79.5-87.4)	65.5 (47.4-81.0)	67.2 (58.6-75.1)	32.2 (21.2-44.7)	89.1 (81.7-94.4)
16. Did you have phlegm when coughing for at least 3 mo in the last year?	8.3 (4.4-13.7)	98.1 (96.5-99.1)	57.9 (35.8-78.0)	76.3 (72.6-79.6)	6.9 (1.2-19.8)	98.4 (95.0-99.7)	50.0 (10.7-89.3)	80.8 (74.0-86.5)

TABLE E3. Diagnostic accuracy measures in derivation and validation cohorts

Score (no. of positive answers)	Derivation cohort (n = 560)						Validation cohort (n = 151)					
	n (%)	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Accuracy %	n (%)	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Accuracy %
A2 score												
Possible Asthma												
≥2*	183 (32.7)	85.7 (78.6-91.2)	83.8 (80.0-87.2)	62.3 (56.8-67.5)	95.0 (92.5-96.6)	84.3	41 (27.2)	93.1 (77.2-99.2)	88.5 (81.5-93.6)	65.9 (53.8-76.1)	98.2 (93.4-99.5)	89.4
≥3	130 (23.2)	75.9 (67.8-82.9)	93.2 (90.4-95.4)	77.7 (70.8-83.4)	92.6 (90.2-94.4)	89.1	24 (15.9)	65.5 (45.7-82.1)	95.9 (90.7-98.7)	79.2 (60.8-90.3)	92.1 (87.6-95.1)	90.0
Probable Asthma												
≥4†	93 (16.6)	59.4 (50.5-67.8)	96.7 (94.6-98.2)	85.0 (76.8-90.6)	88.4 (86.2-90.4)	87.9	15 (9.9)	48.3 (29.5-67.5)	99.2 (95.5-100.0)	93.3 (65.7-99.0)	89.0 (85.0-92.0)	89.4
≥5	70 (12.5)	46.6 (37.9-55.5)	98.1 (96.3-99.2)	88.6 (79.2-94.0)	85.5 (83.4-87.4)	85.9	12 (7.9)	37.9 (20.7-57.7)	99.2 (95.5-100.0)	91.7 (59.7-98.8)	87.1 (83.5-89.4)	87.4
≥6	58 (10.4)	39.9 (31.5-48.7)	98.8 (97.3-99.6)	91.4 (81.2-96.3)	84.1 (82.1-85.8)	84.8	10 (6.6)	31.0 (15.3-50.8)	99.2 (95.5-100.0)	90.0 (54.3-98.6)	85.8 (82.6-88.5)	86.1
≥7	39 (7.0)	26.3 (19.1-34.7)	99.1 (97.6-99.7)	89.7 (76.0-96.0)	81.2 (79.6-82.7)	81.8	7 (4.6)	20.7 (7.99-39.7)	99.2 (95.5-100.0)	85.7 (42.9-98.0)	84.0 (81.4-86.4)	84.1
8	20 (3.6)	12.8 (7.6-19.7)	99.3 (98.0-99.9)	85.0 (62.8-95.0)	78.5 (77.4-79.6)	78.8	2 (1.3)	6.9 (0.9-22.8)	100.0 (97.0-100.0)	100.0	81.9 (80.4-83.3)	82.1
GA2LEN score												
Possible Asthma												
≥1*	229 (40.9)	90.2 (83.8-94.7)	74.5 (70.1-78.5)	52.4 (48.1-56.7)	96.1 (93.6-97.6)	78.2	51 (33.8)	93.1 (77.2-99.1)	80.3 (72.2-87.0)	52.9 (43.7-62.0)	98.0 (92.8-99.5)	82.8
≥2	167 (29.8)	79.0 (71.0-85.5)	85.5 (81.8-88.7)	62.9 (57.0-68.4)	92.9 (90.4-94.8)	83.9	31 (20.5)	75.9 (56.5-89.7)	92.6 (86.5-96.6)	71.0 (55.8-82.6)	94.2 (89.4-96.9)	89.4
≥3	111 (19.8)	65.4 (56.7-73.4)	94.4 (91.8-96.4)	78.4 (70.7-84.5)	89.8 (87.4-91.7)	87.5	21 (13.9)	58.6 (38.9-76.5)	96.7 (91.8-99.1)	81.0 (60.7-92.1)	90.8 (86.4-93.8)	89.4
Probable Asthma												
≥4†	74 (13.2)	48.1 (39.4-57.0)	97.7 (95.7-98.9)	86.5 (77.2-92.4)	85.8 (83.7-87.7)	85.9	12 (7.9)	37.9 (20.7-57.7)	99.2 (95.5-100.0)	91.7 (59.7-98.8)	85.8 83.7-87.7	87.4
≥5	50 (8.9)	33.1 (25.2-41.8)	98.6 (97.0-99.5)	88.0 (76.2-94.4)	82.6 (80.8-84.2)	83.0	10 (6.6)	31.0 (15.3-50.8)	99.2 (95.5-100.0)	90.0 (54.3-98.6)	85.8 (82.6-88.5)	86.1
6	24 (4.3)	15.0 (9.4-22.3)	99.1 (97.6-99.7)	83.3 (63.5-93.5)	78.9 (77.7-80.1)	79.1	3 (2-0)	6.9 (0.9-22.8)	99.2 (95.5-100.0)	66.7 (15.8-95.5)	81.8 (80.2-83.2)	81.5

A2 score, Adult Asthma Epidemiological Score; *GA2LEN score*, Global Allergy and Asthma Network of Excellence Asthma Epidemiological Score; *PPV*, Positive predictive value; *NPV*, negative predictive value.
*Cutoff of ≥2 (for the A2 score) and of ≥1 (for the GA2LEN score) for considering possible asthma (NPV of 95% or more, simultaneously in derivation and validation cohorts).
†Cutoff of ≥4 for considering probable asthma (PPV 85% or more, simultaneously in derivation and validation cohorts.

TABLE E4. Diagnostic accuracy measures of the ECRHS asthma score previously developed, using participants from the derivation and validation cohorts

Score (no. of positive answers)	Derivation cohort (n = 560)						Validation cohort (n = 151)					
	n (%)	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Accuracy %	n (%)	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Accuracy %
Possible Asthma												
≥1*	244 (43.6)	87.2 (80.3-92.4)	70.0 (65.4-74.3)	47.5 (43.6-51.5)	94.6 (91.8-96.5)	74.1	60 (39.7)	93.1 (77.2-99.2)	73.0 (64.2-80.6)	45.0 (37.6-52.7)	97.8 (92.1-99.4)	76.8
≥2	147 (26.3)	74.4 (66.2-81.6)	88.8 (85.4-91.6)	67.4 (60.8-73.3)	91.8 (89.8-93.7)	85.4	29 (19.2)	72.4 (52.8-87.3)	93.4 (87.5-97.1)	72.41 (56.4-84.2)	93.4 (88.8-96.3)	89.4
≥3	89 (15.9)	54.1 (45.3-62.8)	96.0 (93.7-97.7)	80.9 (72.2-87.4)	87.1 (84.8-89.0)	86.1	16 (10.6)	51.7 (32.5-70.6)	99.2 (95.5-100.0)	93.8 (67.4-99.1)	89.6 (85.6-92.7)	90.1
Probable Asthma												
≥4†	68 (12.1)	45.9 (37.2-54.7)	98.4 (96.7-99.3)	89.7 (80.3-94.9)	85.4 (83.3-87.2)	85.9	12 (7.9)	37.9 (20.7-57.7)	99.2 (95.5-100.0)	91.7 (59.7-98.8)	87.1 (83.5-89.9)	87.4
≥5	44 (7.9)	28.6 (21.1-37.1)	98.6 (97.0-99.5)	86.4 (73.3-93.6)	81.6 (79.9-83.2)	82.0	6 (4)	17.2 (5.9-35.8)	99.2 (95.5-100.0)	83.3 (37.8-97.6)	83.5 (81.0-85.6)	83.4
≥6	34 (6.1)	22.6 (15.8-30.6)	99.1 (97.6-99.7)	88.2 (72.9-95.4)	80.4 (78.9-81.8)	80.9	5 (3.3)	13.8 (3.9-31.7)	99.2 (95.5-100.0)	80.0 (31.7-97.2)	82.9 (80.7-84.9)	82.8
≥7	18 (3.2)	12.0 (7.0-18.8)	99.5 (98.3-99.9)	88.9 (65.1-97.2)	78.4 (77.3-79.5)	78.8	3 (2.0)	10.3 (2.2-27.4)	100.0 (97.0-100.0)	100.0	82.4 (80.6-84.2)	82.8
8	7 (1.3)	4.5 (1.7-9.6)	99.8 (98.7-100)	85.7 (42.2-98.0)	77.0 (76.4-77.7)	77.1	2 (1.3)	6.9 (0.9-22.8)	100.0 (97.0-100.0)	100.0	81.9 (80.4-83.3)	82.1

ECRHS, European Community Health Survey; *PPV*, positive predictive value; *NPV*, negative predictive value.
*Cut-off of ≥1 for considering possible asthma (NPV of 95% or more, simultaneously in derivation and validation cohorts).
†Cutoff of ≥4 for considering probable asthma (PPV 85% or more, simultaneously in derivation and validation cohorts).

THE ECRHS SCORE

This section contains details on the previously developed ECRHS asthma score and the application of this score to our data. The previously developed ECRHS asthma score[E21] has 8 questions:

1. Have you been at all breathless when the wheezing noise was present?
2. Have you woken up with the feeling of tightness in your chest at any time in the last 12 months?
3. Have you had an attack of shortness of breath that came on during the day when you were at rest at any time in the last 12 months?
4. Have you had an attack of shortness of breath after exercise in the last 12 months?
5. Have you been woken up by an attack of shortness of breath at any time in the last 12 months?
6. Have you ever had asthma?
7. Have you had any asthma attack in the last 12 months?
8. Are you currently taking any medicines including inhalers, aerosols, or tablets for asthma?

We applied the ECRHS asthma score to our data, and its performance was tested in the derivation and validation cohorts. The AUC obtained by applying the previously developed ECRHS asthma score to our data was 86.8% (95% CI, 82.8%-90.8%) and the Cronbach α was 0.826 (95% CI, 0.804-0.847). The diagnostic accuracy measures are described in Table E4.

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Clinical and Translational Allergy

High oral corticosteroid exposure and overuse of short-acting beta-2-agonists were associated with insufficient prescribing of controller medication: a nationwide electronic prescribing and dispensing database analysis

--Manuscript Draft--

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Abstract:	Background:Recurrent use of oral corticosteroids(OCS) and over-use of short-acting beta-2-agonists (SABA) are factors associated with adverse side effects and asthma-related death. We aim to quantify high OCS exposure, SABA over-use and its association with prescription and adherence to maintenance treatment for respiratory disease, among patients with prescriptions for respiratory disease, from the Portuguese electronic prescription and dispensing database (BDNP). Methods:This was a one-year (2016) retrospective population-based analysis of a random sample of adult patients from the BDNP, the nationwide compulsory medication prescription system. We assessed high OCS exposure (dispensing ≥4 packages containing 20 doses of 20mg each of prednisolone-equivalent, ≥1600mg/year) on patients on persistent respiratory treatment (PRT-prescription for >2 packages of any respiratory maintenance medications). Excessive use of SABA was defined as having a ratio of SABA-to-maintenance treatment >1 or having SABA over-use (dispensing of >1x200 dose canister/month, of 100µg of salbutamol-equivalent). Factors associated with high OCS exposure were assessed by multinomial logistic regression. Results:The estimated number of patients on PRT was 4,786/100,000 patients. OCS was prescribed to more than 1/5 of the patients on PRT and 101/100,000 were exposed to a high-dose (≥1600mg/year). SABA excessive use was found in 144/100,000 patients and SABA over-use in 24/100,000. About 1/6 of SABA over-users were not prescribed any controller medication and 7% of them had a ratio maintenance-to-total ≥70% (high prescription of maintenance treatment). Primary adherence (median%) to controller medication was 66.7% for PRT patients, 59.6% for patients exposed to high OCS dose and 75.0% for SABA over-users. High OCS exposure or SABA over-use were not associated with primary adherence. High OCS exposure was associated with a maintenance-to-total medication ratio <70% (insufficient prescription of maintenance treatment), age >45 years old and male sex. Conclusions:Exposure to high-dose of OCS (101 per 100,000 patients) and SABA over-use (24 per 100,000) were frequent, and were associated with a low maintenance-to-total prescription ratio but not with primary non-adherence. These results suggest there is a need for initiatives to reduce OCS and SABA inappropriate prescribing.
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Response to Reviewers:	Authors' response to the decision letter for CTAL-D-19-00033 "High-risk patients in a nationwide prescribing and dispensing database analysis: Oral corticosteroids use in patients on respiratory treatment and SABA over-use" Dear Editor, We would like to thank the reviewers for their time and relevant comments. The response to reviewers includes the presentation of figures and tables, as so, the point-by-point response was submited in the file 'Response to reviewers with manuscript'. In this file, at the end of the resposnse, we also included a revised version of the manuscript according to editorial office requirements. We are sorry for the inconvenience this may cause. Sincerely yours, Ana Sá Sousa and João Almeida Fonseca on behalf of the authors

High oral corticosteroid exposure and overuse of short-acting beta-2-agonists were associated with insufficient prescribing of controller medication: a nationwide electronic prescribing and dispensing database analysis

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Abstract

Background: Recurrent use of oral corticosteroids (OCS) and over-use of short-acting beta-2-agonists (SABA) are factors associated with adverse side effects and asthma-related death. We aim to quantify high OCS exposure, SABA over-use and its association with prescription and adherence to maintenance treatment for respiratory disease, among patients with prescriptions for respiratory disease, from the Portuguese electronic prescription and dispensing database (BDNP).

Methods: This was a one-year (2016) retrospective population-based analysis of a random sample of adult patients from the BDNP, the nationwide compulsory medication prescription system. We assessed high OCS exposure (dispensing ≥4 packages containing 20 doses of 20mg each of prednisolone-equivalent, ≥1600mg/year) on patients on persistent respiratory treatment (PRT-prescription for >2 packages of any respiratory maintenance medications). Excessive use of SABA was defined as having a ratio of SABA-to-maintenance treatment >1 or having SABA over-use (dispensing of >1x200 dose canister/month, of 100µg of salbutamol-equivalent). Factors associated with high OCS exposure were assessed by multinomial logistic regression.

Results: The estimated number of patients on PRT was 4,786/100,000 patients. OCS was prescribed to more than 1/5 of the patients on PRT and 101/100,000 were exposed to a high-dose (≥1600mg/year). SABA excessive use was found in 144/100,000 patients and SABA over-use in 24/100,000. About 1/6 of SABA over-users were not prescribed any controller medication and 7% of them had a ratio maintenance-to-total ≥70% (high prescription of maintenance treatment). Primary adherence (median%) to controller medication was 66.7% for PRT patients, 59.6%

for patients exposed to high OCS dose and 75.0% for SABA over-users. High OCS exposure or SABA over-use were not associated with primary adherence. High OCS exposure was associated with a maintenance-to-total medication ratio <70% (insufficient prescription of maintenance treatment), age >45 years old and male sex.

Conclusions: Exposure to high-dose of OCS (101 per 100,000 patients) and SABA over-use (24 per 100,000) were frequent, and were associated with a low maintenance-to-total prescription ratio but not with primary non-adherence. These results suggest there is a need for initiatives to reduce OCS and SABA inappropriate prescribing.

Keywords

Asthma; Pulmonary Disease, Chronic Obstructive; Medication Adherence; Inappropriate Prescribing; Risk Factors; Retrospective studies; Multivariate Analysis.

Background

Chronic respiratory diseases, including obstructive lung diseases such as asthma and chronic obstructive pulmonary disease (COPD), are a source of significant morbidity and mortality worldwide (1). The prevalence of asthma in adults in Portugal, in 2010, was 6.8%(2), costing 2.0% of the total Portuguese healthcare expense that year(3).

A report on asthma deaths in the United Kingdom highlights that most asthma deaths occur in mild and moderate cases of the disease, mainly because of inappropriate prescription and medical care(4). According to Global Initiative for Asthma (GINA) guidelines, the factors that increase the risk of asthma-related death include 1) the over-use of inhaled short-acting beta 2 agonists (SABA), defined as more than 1 canister of salbutamol or equivalent monthly; 2) the current use of oral

corticosteroids (OCS); 3) the absence of inhaled corticosteroids (ICS) use and 4) the poor adherence with asthma maintenance medication(5). Furthermore, exposure to OCS has been associated with pneumonia, osteoporosis, cataracts, and diabetes in a dose-responsive manner(6–8).

Large databases, including prescription data, has been used to assess the risk of asthma exacerbations(9,10), describe patterns of frequent exacerbators(11) and inappropriate, high-risk prescriptions (12). The use of pharmacy records, namely the number of SABA canisters filled over a one-year period, has been validated as a proxy for future risk of 1) hospitalization or emergency department visit because of asthma and 2) OCS for exacerbations dispensing (13). Observational studies based on medical records including prescription data are important to provide real-world evidence on heterogeneous diseases such as chronic respiratory diseases. However, to our knowledge, research based on Portuguese electronic prescription database is scarce(14,15) and none on respiratory medication, namely OCS or SABA.

Aims

We aim to quantify patients in high-risk of having adverse clinical outcomes, among patients with at least 1 prescription for respiratory disease or exacerbations medications, retrieved from the Portuguese electronic medical prescription and dispensing database. Specifically, we aim to describe the association of the exposure to high-dose of OCS and the SABA over-use with prescription and primary adherence to maintenance treatment for respiratory disease.

Methods

Study design

This was a one-year (2016) retrospective population-based analysis of a random sample of patients from the BDNP – *Base de Dados Nacional de Prescrições* database.

Setting

The BDNP is the central system, responsible for the validation of all steps of the prescriptions and dispensing cycle in Portugal, and for the recording of all the prescription and dispensing data. All the software for electronic medical prescription must be interoperable with BDNP. The use of electronic prescriptions is compulsory in mainland Portugal(16), and the system of electronic prescriptions is implemented since 2013. The electronic prescriptions system is used by physicians in the private and public healthcare units; each prescription may contain several medication packages and different classes of medication. The prescriptions must be filled at a community pharmacy by the patient. The implementation of the electronic medication dispensing system in each community pharmacy was concluded at the end of 2015.

The population of interest in this study consists of patients to whom medication for respiratory and/or allergic diseases and exacerbations was prescribed at least once, between January 2016 and December 2016. The number of the prescriptions meeting these criteria was higher than to 250 million prescriptions, corresponding to 4 639 308 patients (45% of the Portuguese population). We retrieved 2% (n=103 647) of these patients, randomly selected from the BDNP database corresponding to 1 129 512 prescriptions (Figure 1). We assessed all the prescriptions of those aged 15 years old or above living in mainland Portugal (n= 82 714 patients). The number of patients in the sample per 100 000 Portuguese patients was calculated by multiplying the number of patients by the factor (45%/ 82 714).

Data were provided in an encrypted form by the government entity responsible for the electronic prescription and dispensing system*, SPMS- Serviços Partilhados do Ministério da Saúde* (Shared Services of the Ministry of Health). The data of the patients and the prescribing physician had previously been anonymised by SPMS.

Participants

In this study we analysed the prescriptions (n=248 045, corresponding to 61 835 patients) between January 2016 and December 2016 for medication for respiratory disease and/or exacerbations (see Additional file 1), from a sample of patients from the mainland Portugal, aged 15 years and above (Figure 1).

Variables

Persistent respiratory treatment (PRT) was defined as prescription for more than 2 packages of any of the five classes of respiratory maintenance medications: inhaled corticosteroids (ICS) alone or in fixed-dose combination with long-acting beta2 agonists (LABA); leukotriene receptors antagonists (LTRA); long-acting muscarinic antagonist (LAMA) alone or in a fixed-dose combination with LABA or LABA alone.

We analysed SABA usage in the sample of patients with at least one prescription for medication for respiratory disease and exacerbations whereas OCs usage was assessed only among patients on PRT, to reduce the confounding of its use for other conditions (Figure 1).

OCS users and SABA users were defined as patients that filled, respectively, at least 1 package of OCS or SABA at a community pharmacy.

OCS dosage was estimated for OCS users, considering that 1 dose of OCS contains 5mg of prednisolone or equivalent. SABA dosage was estimated for SABA users,

considering that 1 dose contains 100µg of salbutamol or equivalent. The total annual amount of prednisolone-equivalent and salbutamol-equivalent was estimated.

Considering that 1 package of prednisolone contains 400mg of prednisolone (20 doses of 20mg each), OCS annual amount of prednisolone-equivalent was grouped in low-dose (>0: 400mg), medium dose (>400:<1600mg) and high dose (≥1600 mg); corresponding to up to 1; >1 to 3 and 4 or more packages of prednisolone (7).

The one-year combinations of classes of respiratory maintenance treatment prescribed were assessed for each patient on PRT.

Outcomes

OCS high-dose exposure: ≥4 packages (20 doses of 20mg each) of prednisolone-equivalent, corresponding to ≥1600 mg of prednisolone-equivalent a year.

SABA over-use: >1 canister (200 doses of 100 µg) of salbutamol-equivalent per month(5), corresponding to > 240 000 µg of salbutamol-equivalent a year.

Ratio SABA-to-maintenance: ratio of the packages of SABA filled over packages of maintenance treatment filled.

SABA excessive use was defined as having at least one: 1) SABA over-use or 2) ratio SABA-to-maintenance above 1:1.

Maintenance-to-total: percentage of the packages of maintenance treatment prescribed over the total (maintenance, relievers, and OCS) packages. This was dichotomized in <70% and ≥ 70%, based on previous research (17). Insufficient prescription of maintenance treatment was considered for maintenance-to-total <70%.

Primary adherence to controller medication: percentage of packages of maintenance medication filled over the packages prescribed. This was dichotomized in ≤50% and

>50% (medium adherence) and also in ≤70% and >70% (high adherence), to explore its association with high OCS exposure and with SABA over-use.

Statistical methods

Descriptive statistics were used to characterize the population and the maintenance treatment prescribed.

The association of OCS high-dose exposure was explored using multinomial logistic regression for age, sex, maintenance-to-total, excessive SABA use and primary adherence to controller medication (Table S3). The predictors included in the final model were: age (grouped into 15-44; 45-64 and >64 years old), sex and maintenance-to-total (dichotomized in <70% and ≥70%). All analyses were performed using RStudio (Version 1.1.456 – © 2009-2018 RStudio, Inc.). Adjusted odds ratios (OR) and 95% confidence intervals (CI) were reported for logistic regression results.

Results

Participants

In 2016, 33 640.9 per 100 000 patients were prescribed with at least 1 medication for respiratory diseases or exacerbations (Figure 1), 17 450.2 per 100 000 with at least 1 medication for respiratory diseases and 16 190.7 per 100 000 with prescriptions for antibiotics, OCS or H1-antihistamines only.

Persistent respiratory treatment (PRT), defined as prescriptions for more than 2 packages of respiratory maintenance medications, was found in 4 786.5 per 100 000 patients (Figure1). Patients' characteristics are summarized in Table 1. Characteristics of the patients from the total sample are presented in Additional file 2.

205

206 *Table 1: Characteristics of patients on SABA over-use, on PRT with high OCS exposure, and on PRT.*

	SABA over-use (23.9 per 100,000)		PRT with high OCS exposure (101.2 per 100,000)		PRT (4 786.5 per 100,000)	
Sex, % 95%CI						
Female	29.5	18.2-44.2	50.0	42.9-57.1	55.9	54.9-56.9
Male	70.5	55.8-81.8	50.0	42.9-57.1	44.1	43.1-45.1
Age, med P25-P75	61.0	50.8-73.5	69.0	57.3-78.8	64.0	47.0-76.0
Age, % 95%CI						
15:44	11.4	5.0-24.0	8.1	4.9-12.9	28.8	27.9-29.8
45:64	45.5	31.7-59.9	30.1	24.0-37.0	21.8	20.9-22.6
>64	43.2	29.7-57.8	61.8	54.7-68.5	49.4	48.3-50.4
Maintenance-to-total prescribed, % 95%CI						
No controller prescribed	15.9	7.9-29.4	-		-	
>0%-20%	25.0	14.6-39.4	2.7	1.2-6.1	0.3	0.2-0.4
≥20%-<50%	31.8	20.0-46.6	35.5	29.0-42.6	3.3	2.9-3.7
≥50%-<70%	20.5	11.1-34.5	28.5	22.5-35.4	8.2	7.6-8.8
≥70%-<90%	6.8	2.3-18.2	28.0	22.0-34.8	16.3	15.5-17.1
≥90%-100%	0.0	0.0-8.0	5.4	2.9-9.6	72.0	71.0-72.9
Primary adherence to controller medication, % 95%CI						
0%	10.8	4.3-24.7	3.8	1.8-7.6	6.9	6.4-7.4
>0%-20%	5.4	1.5-1.8	5.4	2.9-9.6	5.2	4.8-5.7
>20%-50%	13.5	5.9-27.9	31.7	25.4-38.7	28.2	27.3-29.1
>50%-70%	13.5	5.9-27.9	23.1	17.6-29.7	18.1	17.2-18.9
>70%-90%	35.1	21.8-51.2	21.0	15.7-27.4	19.4	18.6-20.2
>90%-100%	21.6	11.4-37.2	15.1	10.6-20.9	22.3	21.4-23.1

207 *PRT: persistent respiratory treatment; SABA: short-acting beta 2 agonist; OCS: oral corticosteroids.*

208 ## OCS usage

209 OCS was prescribed to 22.0% (95%CI 21.1-22.8) of the patients on PRT (1 051.1

210 per 100 000) and dispensed to 18.6% (95%CI 17.8-19.5). Maintenance-to-total ratio

of 70% or more was associated with a lower likelihood of having at least one dispensing of OCS (crude OR, 95%CI; 0.2, 0.1-0.2) in patients on PRT.

Most of the OCS users were exposed to a low dose (>0: 400mg) of prednisolone-equivalent (57.6%, 95%CI 55.2-60.6), still, 101.2 per 100 000 (11.3%, 95%CI 9.9-13.0) were exposed to a high-dose (≥1600 mg). Two-thirds of the patients exposed to high-dose of OCS had a ratio maintenance-to-total below 70% and 38.2% below 50% (Table 1 and Figure 2).

SABA usage

SABA was prescribed and dispensed to 1 370.4 per 100 000 patients; 82.6% (95%CI 81.0-84.0) filled 2 or fewer canisters of salbutamol-equivalent, 15.7% (95%CI 14.3-17.1) filled 2 to 12 canisters and 1.7% (95%CI 1.3-2.3) were SABA over-users corresponding to 23.9 per 100 000 patients (Additional file 3). Excessive use of SABA (defined as SABA over-use or ratio SABA-to-maintenance above 1:1) was found in 10.5% of the SABA users, corresponding to 144.2 per 100 000 patients.

SABA over-users filled between 260 000 µg and 1 540 000 µg of salbutamol-equivalent, corresponding to a mean of 12 SABA inhalations per day per patient.

About 1/6 of the over-users were not prescribed any controller medication (Table 1). Among those with a prescription for maintenance treatment, 77% had maintenance-to-total below 70%, and 57% below 50% (Table 1 and Figure 2).

Primary adherence

In patients to whom maintenance treatment was prescribed, primary adherence to controller medication (median %, Percentile 25 - Percentile 75) for the SABA over-users was 75.0% (47.6-88.9); for all PRT patients was 66.7% (33.3-87.5) and for the patients on PRT exposed to high-dose of OCS was 59.6% (37.5-82.9) (Table 1 and

Figure 2). Primary adherence to controller medication >50% was not associated with reduced risk high OCS exposure nor with SABA over-use (OR, 95%CI; 0.9, 0.7-1.2 and 1.4, 0.7-2.9, respectively). Similar results were observed for primary adherence to controller medication >70% (OR, 95%; 1.4, 0.7-2.7 and 0.9, 0.7-1.2, respectively for SABA over-use and high OCS exposure).

One-year maintenance treatment combinations

Among patients on PRT exposed to a high-dose (≥1600 mg) of OCS, the most frequent combinations of maintenance treatment were ICS+LABA or ICS+LABA+LAMA. The combinations ICS+LABA+LAMA; ICS+LTRA+LABA+LAMA or ICS+LTRA+LABA were found in 44% of these patients and monotherapy of either ICS or LTRA in 8% (Table 2).

Most of the patients on PRT (61%) were prescribed for combinations of ICS+LABA, ICS+LABA+LTRA or ICS+LABA+LAMA (Table 2). Prescription of LTRA+LABA or/and LAMA, not recommended in the guidelines(5,18), was prescribed to 2% of the patients.

Table 2: The one-year combinations of classes of medication prescribed to the 8 798 patients on PRT

	PRT with high OCS exposure(n=186)		PRT	
Maintenance treatment prescribed	n	%	n	%
ICS+LABA	61	32.8	3113	35.4
ICS+LABA+LAMA	46	24.7	1008	11.5
ICS+LTRA+LABA+LAMA	21	11.3	355	4.0
ICS+LABA+LTRA	15	8.1	1204	13.7
LABA+LAMA	13	7.0	635	7.2
ICS monotherapy	8	4.3	310	3.5
LTRA monotherapy	6	3.2	916	10.4
LABA monotherapy	5	2.7	340	3.9
ICS+LAMA	3	1.6	143	1.6

LAMA monotherapy	3	1.6	476	5.4
ICS+LTRA	2	1.1	126	1.4
LTRA+LABA	1	0.5	50	0.6
LTRA+LAMA	1	0.5	41	0.5
ICS+LTRA+LAMA	1	0.5	22	0.3
LTRA+LABA+LAMA	0	0.0	59	0.7

PRT: persistent respiratory treatment; SABA: short-acting beta 2 agonist; OCS: oral corticosteroids; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonists; LTRA: leukotriene receptors antagonists; LAMA: long-acting muscarinic antagonist.

Factors associated with high OCS exposure

Results from the multinomial logistic regression, show that OCS high dose exposure was positively associated with maintenance-to-total <70%, age above 45 years old and male sex (Figure 3). The unadjusted independent associations of high OCS exposure are presented in Additional file 4.

Discussion

Limitations

This was the first analysis of prescriptions for SABA medication and OCS medication from the official Portuguese prescription database. Nevertheless, the present study has several limitations. An important limitation is related to the risk of overestimation of drug use since filling prescriptions does not mean actual medication intake. Another limitation is the lack of information regarding treatment indication. Moreover, OCS are prescribed for several conditions non-related to respiratory disease. In fact, some authors state OCS may not be a reliable marker of respiratory exacerbation (19). To minimize this error, we analysed OCs usage only among patients on PRT (prescription for > 2 packages of any respiratory maintenance medications). Alternatively, we assessed OCS usage when ordered by prescribers with specialties related to respiratory disease and we obtained identical results (data not shown). In

any case, SABA over-use and exposure to OCS are important risk-factors for serious adverse health outcomes, independently from the prescription indication.

The dataset has important limitations as it was not linked to non-prescription databases due to technical difficulties and privacy concerns, we could not assess the effect of important variables on the estimates, namely demographic variables (such as smoking habits, Body Mass Index (BMI), education, race).

We used the Portuguese prescription and dispensing database to quantify patients with respiratory diseases with high OCS exposure or SABA over-use, that are associated with high-risk of having adverse clinical outcomes (Figure 4). OCS use was assessed in the patients on persistent respiratory treatment (PRT) and high OCS exposure (≥1600 mg of prednisolone-equivalent) was found in 11.3% of the OCS users. Among SABA users, 10.5% were excessive users and 1.7% were SABA over-users. Patients on PRT with high OCS exposure and SABA over-users have primary adherence to controller medication above 50%. However, most of them have an insufficient prescription of maintenance treatment. Exposure to high-dose of OCS was associated with a ratio maintenance-to-total under 70%, male age above 45 years old and sex.

Almost 19% of patients on PRT dispensed at least 1 package of OCS and 11% of the OCS users dispensed at least 4 packages. Fitzgerald et al. reported that 13% of asthma patients used OCS (20). Cumulative exposure to systemic corticosteroid is associated with adverse effects and substantial excess morbidity from multiple diseases (8,21) and having 4 or more prescriptions of OCS per year has been shown to increase the incidence of adverse events in asthma patients(7).

In the present study, having a maintenance-to-total ratio below 70% was associated with the use of high-dose OCS. In our analysis we include prescriptions for respiratory patients and not only for asthma patients, therefore we used the ratio maintenance-to-total instead of the previously established ratios(17,22,23). Although similar in its construct, the association of the ratio assessed in the present study with adverse outcomes may be different. We also observed that having a ratio of maintenance-to-total of 70% or more was associated with a lower likelihood of being OCS user. Accordingly, Stanford et.al reported that controller-to-total asthma medication ratio of 70% or more, was associated with a reduction in OCS-dispensing events in 12-month follow-up (OR 0.81; 95% CI 0.76-0.88) (17). In this study, the authors concluded that for adult Medicaid patients the optimal cut-off value was 70% and for the commercially insured patients was 50%. In Portugal in 2015, 65% of the health expenditures were supported by the government (24), as so we applied the cut-off of 70% to the ratio of maintenance-to-total, recommended for the Medicaid population. Nevertheless, since a ratio of less than 50% is known to be related to poor asthma control events, including the need for OCS (22,25), we also tested the cut-off of 50% and found the maintenance-to-total of < 50% was associated with a higher likelihood of high OCS exposure (adj OR, 95%CI; 7.6, 5.5-10.8).

The over-prescription of SABA with insufficient controller medication prescription remains frequent. In a one-year study on asthma patients from primary care healthcare records, 6.6% of the SABA over-users were not on ICS(26). We observed a higher rate (16%) of SABA over-users that did not receive a prescription for any controller medication in the 12-months period, a possible reason may be the analysis of all patients with respiratory treatment prescription and from all types of healthcare service, not only asthma patients from primary care. Moreover, in those with a

prescription for controller medication, 77% had a ratio maintenance-to-total below 70%, and 57% below 50%. Overprescribing of SABA and insufficient provision of ICS was stated as a preventable cause of death for asthma (4) and other adverse outcomes, such as asthma-related hospitalizations, emergency department visits, and intense care unit admissions (20). In agreement with the evidence on the risk of the use of SABA without any controller medication, the recently published pocket guide for asthma management by GINA network, recommends that ICS should be used whenever SABA is used, and ICS combined with formoterol may be used in low dose as the preferred reliever (27).

Our results suggest that high OCS exposure was associated with older age and male sex. Yang et al. reported similar results for age but not for sex, as older age and female sex increased the risk of requirement for ≥2 courses of OCS for asthma exacerbations (adj OR, 95%CI; 1.06, 1.01-1.12, for age and 0.64 0.45-0,89, for male sex), in a model adjusted also for SABA over-use (2.35, 1.42-3.89) and COPD (2.01, 1.34-3.01)(26). Age and sex play important roles in the progression of chronic respiratory diseases. Aging of the airways and parenchyma induces structural and immunological changes related to the increase of airflow limitations. Reasons for gender differences may be related to anatomical, hormonal or socio-environmental factors (28).

Primary adherence was not associated with high-dose of OCS nor with SABA over-use. Previous studies show inconsistent results regarding the association between adherence to controller medication and SABA or OCS use. A systematic review indicated non-adherence as a risk factor for severe exacerbations, defined mostly as requiring for OCS, emergency department visit or hospitalization for asthma(29). Makhinova et.al shown that adherent patients, were more prone to have more than 6

prescriptions for SABA (OR 1.967, 95%CI 1.8- 2.1), than nonadherent patients (30). Murphy et al. reported that primary adherence to ICS below 80% was not associated with OCS courses, but was associated with the need for mechanical ventilation (31). A recent study on patterns of patients who experienced near-fatal asthma exacerbations reported that adherence to controllers may be an important factor for some patients (with rapid worsening of symptoms, young to middle-aged patients, smokers, with low BMI, tendency to depression and hypersensitive to environmental triggers), but not for other (32).

Of note, most of patients exposed to high-dose of OCS in our data were on a triple or quadruple combination of controller medication (ICS/LTRA+LABA+LAMA) associated with step 4/5 of treatment for asthma (5). According to the guidelines these severe patients are possible candidates for treatment with monoclonal antibodies as in some severe phenotypes asthma remains uncontrolled despite good adherence to step 4/5 of treatment controller medication (33).

Conclusion

OCS was prescribed to more than 1/5 of the patients on persistent respiratory treatment, and 101 per 100,000 patients were exposed to doses of OCS ≥1600mg/year, associated with the risk of developing serious adverse outcomes. High OCS exposure was associated with a low maintenance-to-total prescription ratio, older age and male sex, but not associated with primary adherence to controller medication. Most SABA over-users had an insufficient prescription of maintenance treatment and about 1/6 were not prescribed for any maintenance medication, a known risk for asthma-related death. These results suggest a need for

initiatives to reduce the number of high-risk patients with high OCS exposure and SABA over-use in Portugal.

List of abbreviations

BDNP - Portuguese electronic prescription and dispensing database

COPD - chronic obstructive pulmonary disease

GINA - Global Initiative for Asthma

ICS - inhaled corticosteroids

LABA - long-acting beta2 agonists

LAMA - long-acting muscarinic antagonist

LTRA - leukotriene receptors antagonists

OCS - oral corticosteroids

PRT - persistent respiratory treatment

RWD - real-world data

SABA - short-acting beta-2-agonists

SAMA - short-acting muscarinic-antagonist

Declarations

Ethics approval and consent to participate

Not applicable. Data had previously been anonymised.

Consent for publication

Not applicable.

Availability of data and material

The data that support the findings of this study are available from *Serviços Partilhados do Ministério da Saúde* (Shared Services of the Ministry of Health) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and permission of *Serviços Partilhados do Ministério da Saúde* (Shared Services of the Ministry of Health).

Competing interests

JAF received personal fees outside the submitted work from AstraZeneca, GSK, Mundipharma, Novartis, Teva. All other authors declare that they have no competing interests.

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Authors' contributions

AS-S participated in study design, data analysis and manuscript writing; RA participated in study design, data analysis and critical revision of the manuscript; RV

participated in data extraction and critical revision of the manuscript; NN participated in critical revision of the manuscript; HM and AF participated in study design and critical revision of the manuscript; JAF participated in study design, manuscript writing and critical revision of the manuscript. All authors read and approved the final manuscript.

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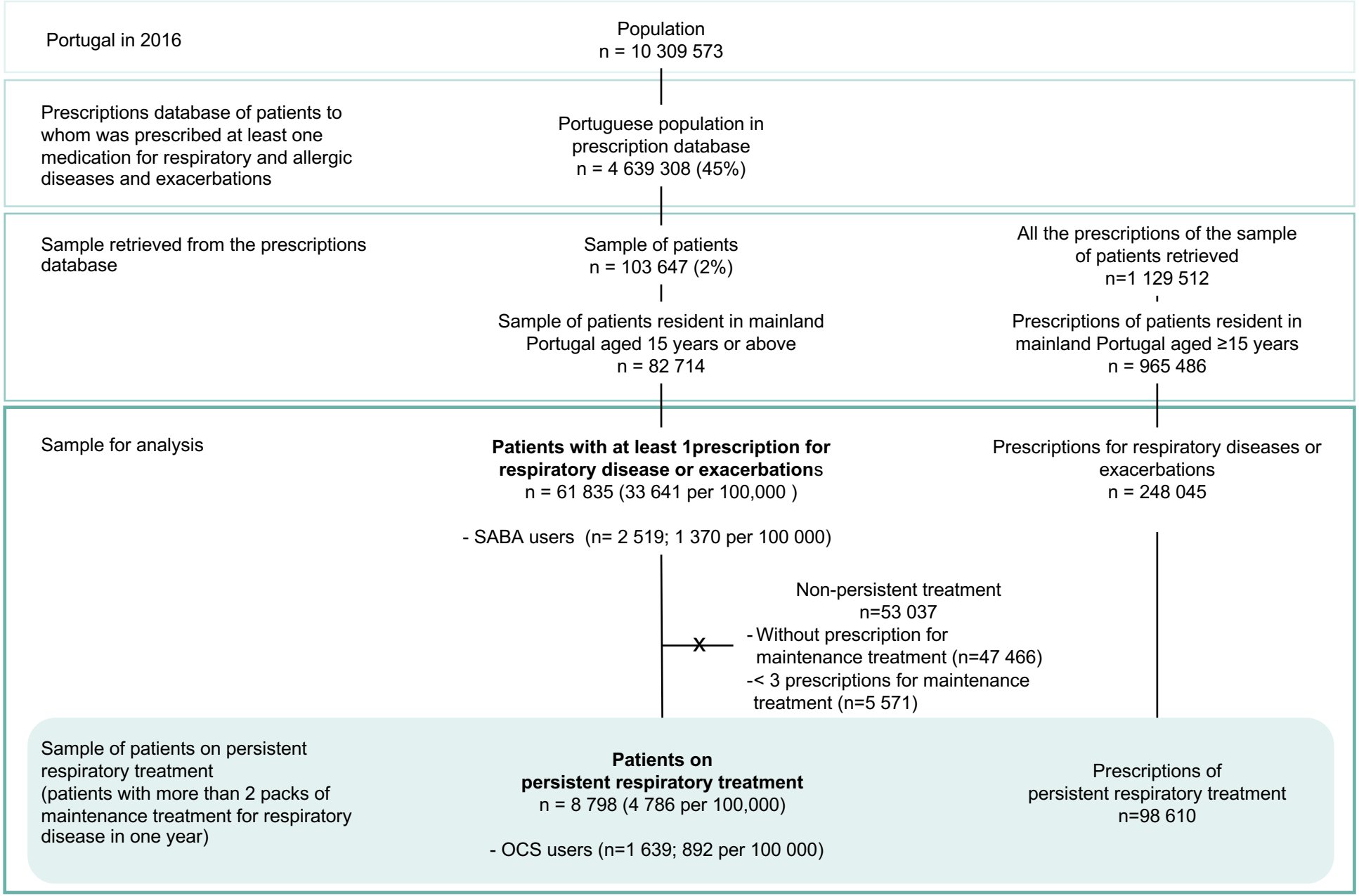
Figures titles

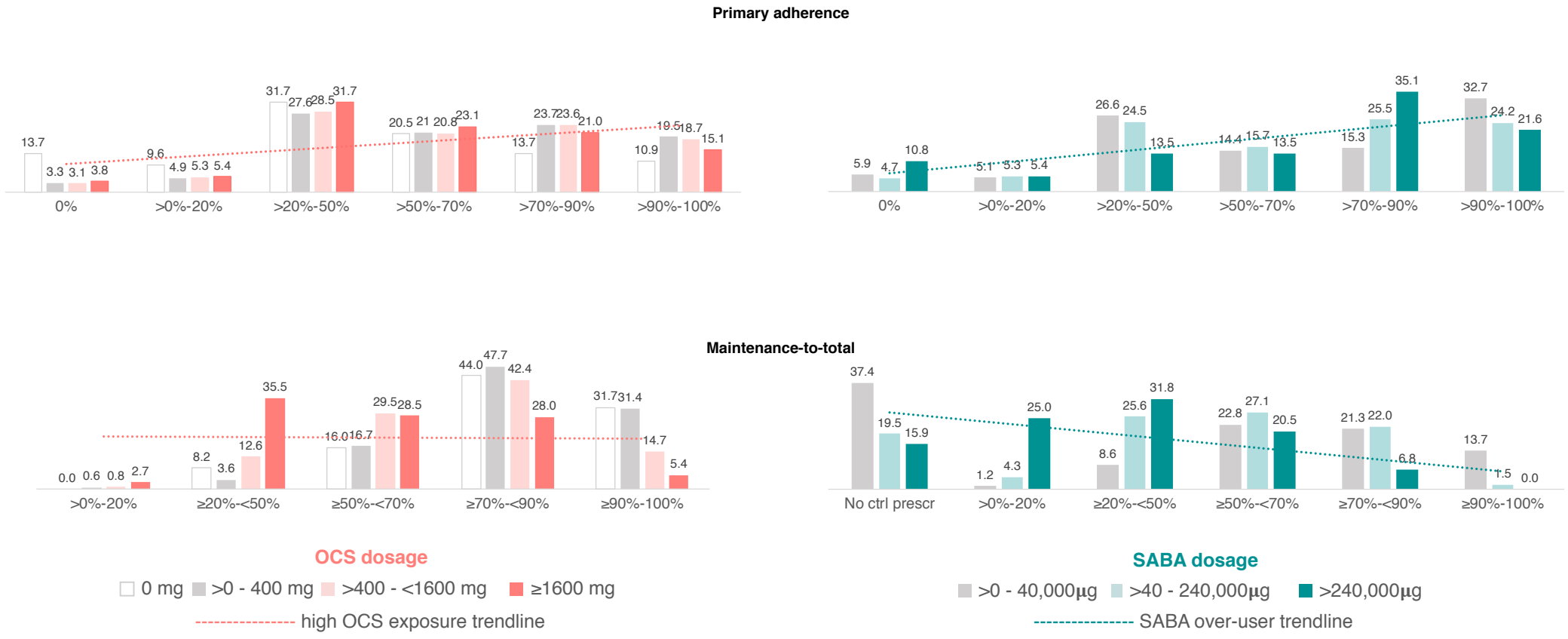
Figure 1: Flowchart of patients for analysis. SABA: short-acting beta 2 agonist; OCS: oral corticosteroids

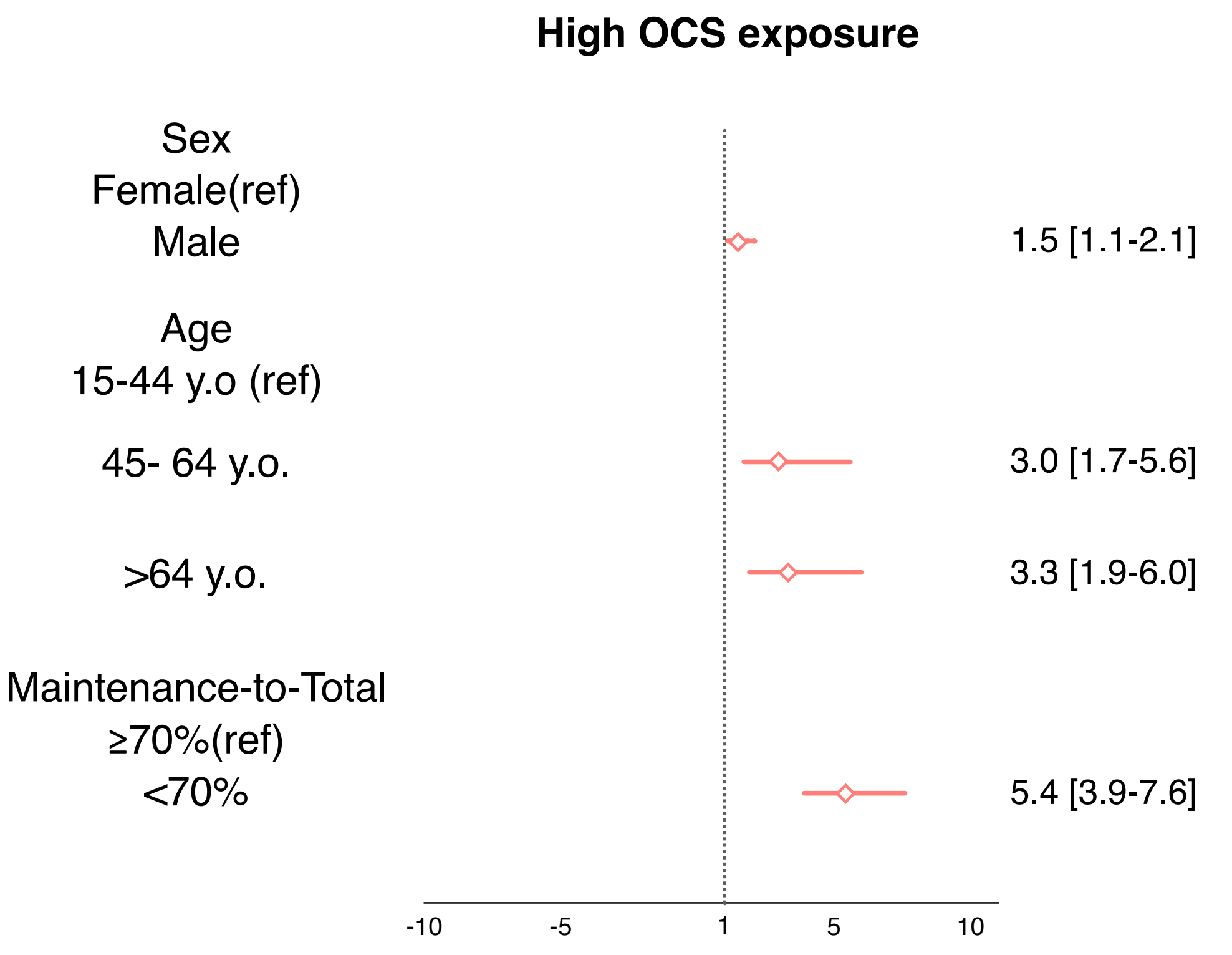
Figure 2: Frequency (%) of SABA users and OCS users on persistent respiratory treatment, by primary adherence to controller medication and ratio maintenance-to-total.

Figure 3: Factors associated (adjusted OR [95%CI]) to high OCS exposure.

Figure 4: Patients with respiratory diseases with high-risk of having adverse clinical outcomes. SABA: short-acting beta 2 agonist; OCS: oral corticosteroids

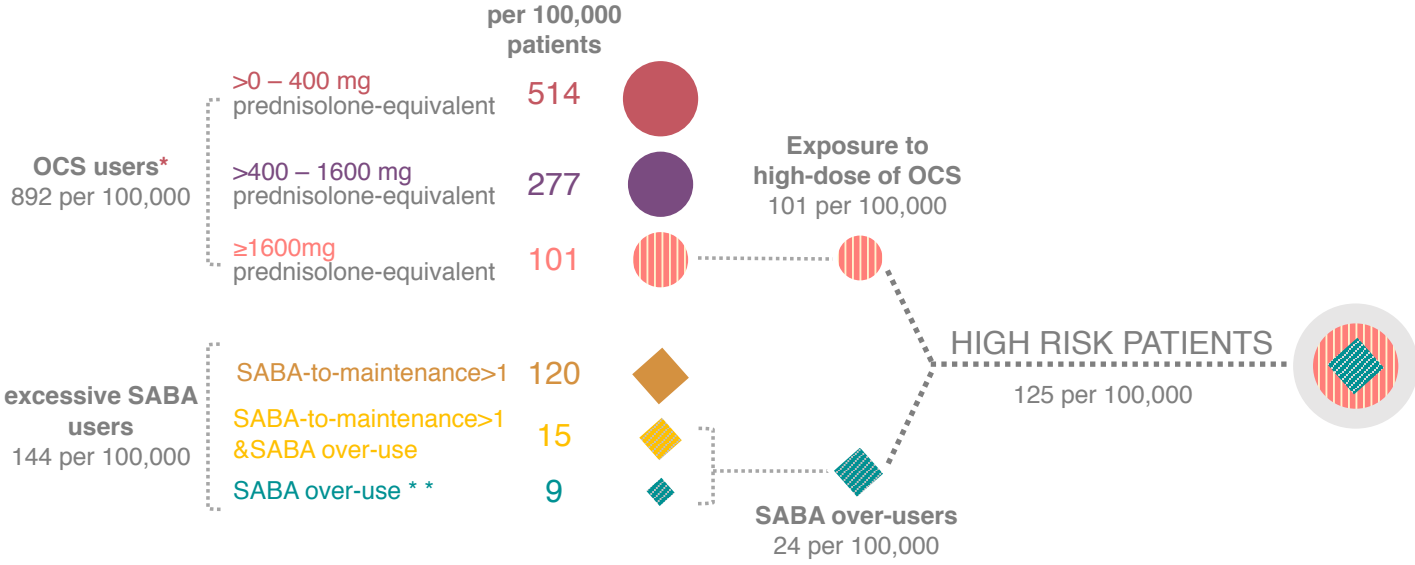

Portugal in 2016
Population
n = 10 309 573
Prescriptions database of patients to whom was prescribed at least one medication for respiratory and allergic diseases and exacerbations
Portuguese population in prescription database
n = 4 639 308 (45%)
Sample retrieved from the prescriptions database
Sample of patients
n = 103 647 (2%)
All the prescriptions of the sample of patients retrieved
n=1 129 512
Sample of patients resident in mainland Portugal aged 15 years or above
n = 82 714
Prescriptions of patients resident in mainland Portugal aged ≥15 years
n = 965 486
Sample for analysis
Patients with at least 1prescription for respiratory disease or exacerbations
n = 61 835 (33 641 per 100,000)
- SABA users (n= 2 519; 1 370 per 100 000)
Prescriptions for respiratory diseases or exacerbations
n = 248 045
Non-persistent treatment
n=53 037
- Without prescription for maintenance treatment (n=47 466)
-< 3 prescriptions for maintenance treatment (n=5 571)
Sample of patients on persistent respiratory treatment
(patients with more than 2 packs of maintenance treatment for respiratory disease in one year)
Patients on persistent respiratory treatment
n = 8 798 (4 786 per 100,000)
- OCS users (n=1 639; 892 per 100 000)
Prescriptions of persistent respiratory treatment
n=98 610


Primary adherence
13.7
3.3
3.1
3.8
9.6
4.9
5.3
5.4
31.7
27.6
28.5
31.7
20.5
21
20.8
23.1
13.7
23.7
23.6
21.0
10.9
19.5
18.7
15.1
0%
>0%-20%
>20%-50%
>50%-70%
>70%-90%
>90%-100%
5.9
4.7
10.8
5.1
5.3
5.4
26.6
24.5
13.5
14.4
15.7
13.5
15.3
25.5
35.1
32.7
24.2
21.6
0%
>0%-20%
>20%-50%
>50%-70%
>70%-90%
>90%-100%
Maintenance-to-total
0.0
0.6
0.8
2.7
8.2
3.6
12.6
35.5
16.0
16.7
29.5
28.5
44.0
47.7
42.4
28.0
31.7
31.4
14.7
5.4
>0%-20%
≥20%-<50%
≥50%-<70%
≥70%-<90%
≥90%-100%
37.4
19.5
15.9
1.2
4.3
25.0
8.6
25.6
31.8
22.8
27.1
20.5
21.3
22.0
6.8
13.7
1.5
0.0
No ctrl prescr
>0%-20%
≥20%-<50%
≥50%-<70%
≥70%-<90%
≥90%-100%
OCS dosage
0 mg
>0 - 400 mg
>400 - <1600 mg
≥1600 mg
high OCS exposure trendline
SABA dosage
>0 - 40,000µg
>40 - 240,000µg
>240,000µg
SABA over-user trendline


High OCS exposure
Sex
Female(ref)
Male
1.5 [1.1-2.1]
Age
15-44 y.o (ref)
45- 64 y.o.
3.0 [1.7-5.6]
>64 y.o.
3.3 [1.9-6.0]
Maintenance-to-Total
≥70%(ref)
<70%
5.4 [3.9-7.6]
-10
-5
1
5
10

ELECTRONIC PRESCRIPTION AND DISPENSING DATABASE

Patients with at least 1 prescriptions for respiratory disease or exacerbations in 2016



*** OCS use**

dispensing of OCS packages on patients on persistent respiratory treatment (prescription for >2 packages of any respiratory maintenance medications)

*** * SABA over-use**

dispensing of >1x200 dose canister/month, of 100µg of salbutamol-equivalent

Additional files

Rev Port Pneumol. 2015;21(6):327–333

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ORIGINAL ARTICLE

Asthma control and exacerbations in patients with severe asthma treated with omalizumab in Portugal

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KEYWORDS
Severe asthma;
Omalizumab;
Asthma control;
Exacerbations;
Observational study

Abstract The analysis of outcomes from patients with severe asthma treated with omalizumab, using real-life prospective data, should contribute to future informed decisions about this treatment in Portugal. 7 The aim of this study was to assess the clinical effect of omalizumab in Portuguese patients with severe persistent allergic asthma, considering specifically asthma control and exacerbations.

This was an observational, prospective, multicentre study. Data were collected at routine care over a 12-month period. Disease control was defined by Control of Allergic Rhinitis and Asthma Test (CARAT) global score >24.

All asthma patients already under treatment with omalizumab in 7 departments from 6 Portuguese hospitals were included ($n = 48$). Most (77%) patients were female and the mean (SD)

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age was 51.9 (10.2) years old. During the study period, asthma was controlled in 34% of the visits and the 12-month exacerbation rate was 1.7 per patient (0.6 with unscheduled medical care). One-third of the patients needed unscheduled medical care because of asthma and 29% had to start or increase oral corticosteroid. There was still a 41% reduction in the total sum of oral corticosteroids usage from the first to the last trimester of the study.

During routine treatment with omalizumab, Portuguese patients with severe asthma achieved asthma control in 1/3 of the visits and only 1/3 needed unscheduled or Emergency Room care because of asthma exacerbations. These outcomes support the maintenance of the clinical effect during treatment with omalizumab in routine care in Portugal.

Introduction

Severe asthma was recently defined by the European Respiratory Society/American Thoracic Society as ''asthma which requires treatment with high dose inhaled corticosteroids plus a second controller (and/or systemic corticosteroids) to prevent it from becoming 'uncontrolled' or asthma which remains 'uncontrolled' despite this therapy''.[1] It is estimated that up to 15% of asthma patients may have severe asthma.[2] These few patients account for a disproportionate part of the burden and healthcare costs associated with asthma.[3]

Omalizumab is a humanized anti-IgE antibody recommended for treating severe allergic IgE-mediated persistent asthma as an add-on to optimized standard therapy in people aged 6 years or older who need continuous or frequent treatment with oral corticosteroids (OCS) (defined as 4 or more courses in the previous year).[4] Previous studies in adults have shown that treatment with omalizumab is associated with an improvement in the control of asthma symptoms, with decreased frequency and use of rescue medication and OCS, and with a reduction in the total asthma-related emergency visits (including hospital admissions, emergency department visits and unscheduled visits to the doctor).[4] However, most of these data come from clinical trials, primarily designed to assess treatment efficacy in highly selected patients; this poses problems when generalizing to daily clinical practice. Real-life prospective studies, presented as a pragmatic approach to everyday clinical practice, are fundamental to assess the impact of omalizumab treatment in patients with severe asthma and should contribute to future informed decisions about this treatment. In Portugal, although four studies described outcomes of omalizumab treatment in real-life settings,[5–8] only one is prospective and it was conducted in a single healthcare unit.

The aim of this prospective multicentre study was to assess the clinical effect of omalizumab in Portuguese patients with severe persistent allergic asthma, specifically concerning asthma control and exacerbations.

Methods

Design

This was a multicentre, descriptive, observational, prospective study, conducted during routine asthma care. The target population was individuals treated with omalizumab for severe persistent asthma.

Setting and participants

The study was conducted in seven Pulmonology and Allergology departments from six hospitals in north and centre mainland Portugal. In each unit, all asthma patients under treatment with omalizumab were included, regardless of the age, length of previous therapy with omalizumab or actual treatment schedule. All patients had omalizumab treatment approved by the therapeutic commission and hospital administration, as required in Portuguese hospitals. Minimal criteria for approval of omalizumab treatment for asthma are uncontrolled, severe persistent, allergic asthma, with frequent exacerbations.

Data collection

Data were collected at each routine visit for omalizumab administration, during 12 consecutive months. In the participating centres, omalizumab was administered at 2- or 4-week intervals with doses based on IgE serum levels and body weight, as recommended by EMEA – European Medicines Agency.[9] A structured form, to be filled by both the patient and the nurse responsible for omalizumab administration, was developed in order to standardize data collection at the different study sites. This form included questions on asthma worsening, medication intake, healthcare resources utilization and work/school absenteeism; information on side effects was possibly related with the previous treatment administration. The Control of Allergic Rhinitis and Asthma Test (CARAT)[10,11] was also part of the form.

Data collection spanned from January 2011 to December 2013 in the different departments (Additional file 1).

Outcomes

Asthma and rhinitis control was defined by CARAT global score >24. CARAT lower airways score $\geq$16 and upper airways score >8 were the cut-off values for control of, respectively, the lower and upper airways only.

Asthma exacerbation was defined as having unscheduled healthcare utilization or increases in OCS intake because of asthma. *Asthma worsening*, *unscheduled healthcare utilization* and *increases in oral corticosteroid intake* were based on a positive answer to the questions: ''In the last 3 days, have you felt your asthma getting worse?''; ''Since the last administration, have you had any unscheduled healthcare visit or emergency room visit because of your asthma?'' and ''In the last 3 days, did you need to start or increase oral corticosteroid intake?'', respectively.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 21 (2012 SPSS Inc., IBM Company, Chicago, US). Categorical and continuous variables were analyzed using descriptive statistics as appropriate. Survival analysis was used to assess the time until the first exacerbation. Generalized Estimating Equations, taking into account the multiple measurements in this longitudinal design, were used to assess variations in control scores over time; a Wald Chi-square test with a *p*-value of <0.05 was considered statistically significant. As CARAT evaluates a 4-week period, control scores were analyzed for visits with at least a 4-week interval.

Results

A total of 48 adults with severe persistent allergic asthma were included (Table 1). Patients were under treatment with omalizumab for between 0 and 67 months, most for more than 3 years (median, 45 months). Most patients ($n = 31$, 65%) were prospectively followed for 12 months and five were followed for less than 9 months (Additional file 1). During the study, the median (min–max) number of medical visits for each patient was 14 (7–28). Side effects were reported in 5% of the visits (Additional file 2); thirty-two (67%) patients did not report any side effect during the study.

Table 1 Characteristics of the study population ($n = 48$).

Female (n, %)	36	77
Age (mean, SD)	52	10
Hospital units (n, %)		
Centro Hospitalar e Universitário de Coimbra, EPE – Pulmonology	15	31
Centro Hospitalar São João, EPE – Allergology	12	39
Centro Hospitalar São João, EPE – Pulmonology	8	26
Centro Hospitalar do Porto – Allergology	6	13
Centro Hospitalar de Trás-os-Montes e Alto Douro – Pulmonology	4	8
Hospital Pedro Hispano – Allergology	2	4
Centro Hospitalar do Alto Ave – Allergology	1	2
Follow-up period, months (median, min–max)	12	3–12
Visits with reported OCS intake (mean% per patient, SD)	15	32

SD – standard deviation; OCS – oral corticosteroid.

Asthma control

CARAT scores were analyzed for visits with at least a 4-week interval in a total of 414 visits. During the study period, asthma was controlled in 34% of the visits; the mean (SD) CARAT score was 20.4 (7.5). There was no statistically significant variation in any of the CARAT mean scores during the 12-month follow-up period ($p > 0.05$).

Asthma exacerbations

During follow-up, 26 patients (54%) had at least one asthma exacerbation (Fig. 1); the 12-month rate of asthma exacerbations per patient was 1.7–1.3 increases with OCS intake and 0.6 unscheduled healthcare utilizations. The first exacerbation occurred on average (mean [95% CI]) 7.2 (5.9–8.6) months after entering the study. There was no clear pattern of distribution of asthma exacerbations and control throughout the year (Fig. 2).

Thirty-three (69%) participants reported at least one period of worsening of asthma symptoms without needing unscheduled medical care or OCS intake. Eight (17%) had more than four periods of worsening of asthma.

Oral corticosteroids intake

Fourteen patients (29%) took OCS because of asthma at least once during the follow-up. Seven patients were taking daily OCS in the first visit and five of them took OCS during the full length of the study, in a mean (SD) dosage of 18.9 (4.4) mg prednisolone/day. Comparing the first and the last trimesters of the study, seven patients reduced the daily dosage of OCS, four patients reported a dosage increase, and two had no variation. Overall, the daily dosage of OCS had a non-significant reduction of 41.6% (Fig. 3). One patient had a follow-up inferior to two trimesters and was not considered for comparison purposes.

Discussion

During the 12-month follow-up, patients with severe persistent allergic asthma treated with omalizumab had their asthma controlled in 34% of the visits; 2/3 had no need for unscheduled medical care due to asthma and 46% remained exacerbation free. The asthma exacerbation rate was 1.7 exacerbations per patient per year (the rate of treatment courses with OCS was 1.3 and of unscheduled healthcare utilizations was 0.6).

Previously published observational studies performed in real-life settings reported that omalizumab is effective in the treatment of patients with severe persistent allergic asthma.[5,12–18]

The present study showed that the proportion of patients with good asthma control in these patients with severe persistent allergic asthma was stable. The asthma control score did not change significantly during the follow-up period

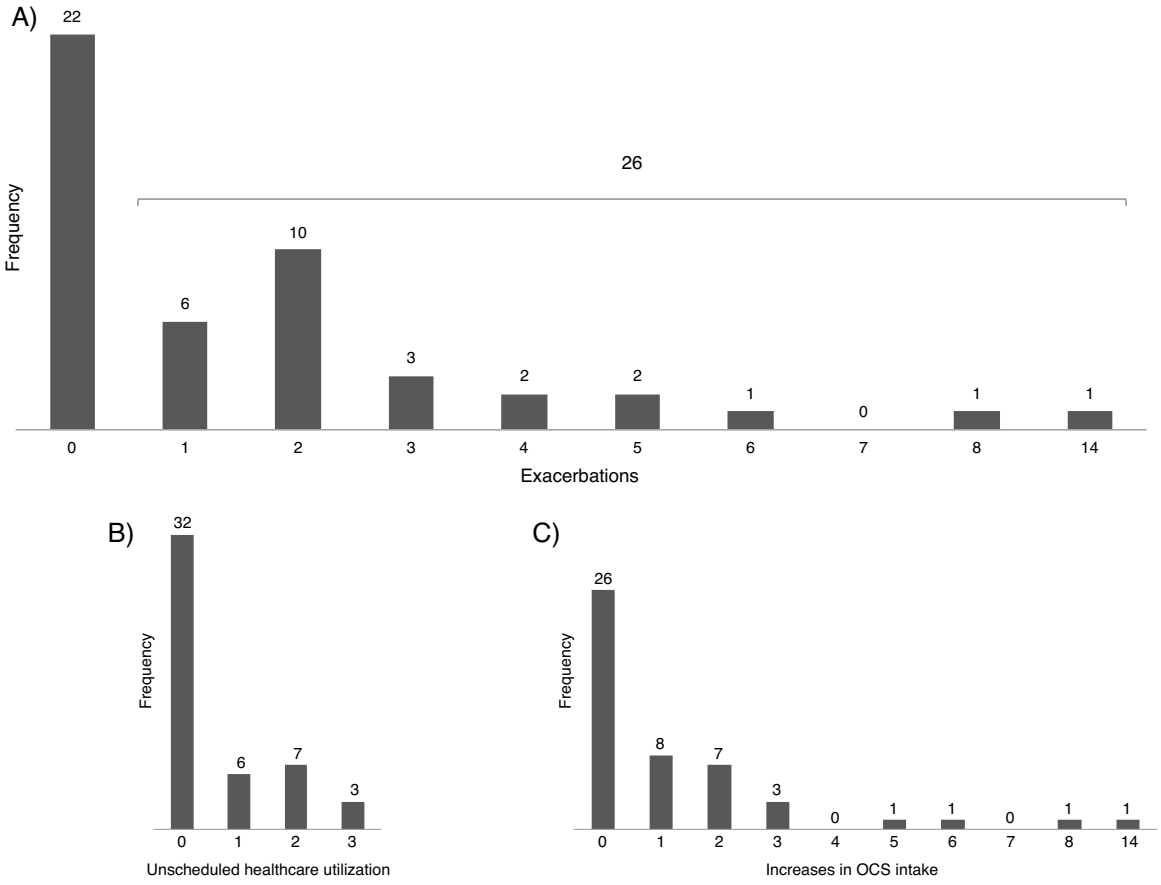

Figure 1 Distribution of the number of exacerbations (A) unscheduled healthcare utilization (B) and increases in OCS intake (C) in the 12-month follow-up period.

probably because patients were already under treatment with omalizumab at enrolment. This 'stability' concurs with several studies[5,16] that reported improvements in asthma control in the first 16 weeks of omalizumab treatment and a tendency to stabilize the effect in the following months. Previously published studies using CARAT questionnaire to assess the control of asthma and rhinitis in other settings found a mean (SD) CARAT score of 17.8 (6.4) in a community of inner Portugal,[19] 17.8 (0.2) in patients followed in the Allergology Department of a University Hospital[20] and 17.2 (6.7) in patients referred to the Allergy outpatient clinic from a district hospital.[21] The mean CARAT score found in the present study for patients with severe asthma is similar to those found in patients with non-severe asthma, suggesting a positive effect of omalizumab treatment.

The rate of 0.6 emergency visits per patient-year observed in the present study is inferior to the rates reported by Molimard and co-workers – 1.1 emergency visits per patient-year after a follow-up of more than 5 months,[18] and by Cazzola and co-workers – 1.2 visits per patient-year after a follow-up of 12 months.[12]

The exacerbation rate observed in the present study is lower than the rates reported in France[18] and in the PERSIST study[16] but greater than those of Germany,[17] Italy,[12] Ireland[14] and Spain,[15] in similar studies. Overall, in our study, the frequency of asthma exacerbations during one-year omalizumab treatment was lower than expected for these severe patients.[22] However, in spite of being treated with omalizumab, five patients had $\geq$5 exacerbations. We could speculate whether before starting omalizumab the asthma control in these patients was even worse or if the treatment with omalizumab was ineffective and should be discontinued.

Previous work found that omalizumab had a marked effect in the reduction of seasonal peaks of asthma exacerbations, with the monthly exacerbations rate remaining the same throughout the year.[23] Our study seems to support these results, as no pattern of seasonal asthma exacerbations was evident throughout the year in these patients treated with omalizumab.

The reduction of OCS intake shown in this study is in accordance with previous reports.[7,8,12,18]

Our study was the first multicentre real-life study on the effect of omalizumab in patients with severe persistent allergic asthma in Portugal. This study has several limitations. Firstly, at enrolment, patients were already using omalizumab as add-on therapy and no comparable prior data were available. Moreover, in one-third of the patients it was not possible to access the registries for the complete 12-month treatment period.

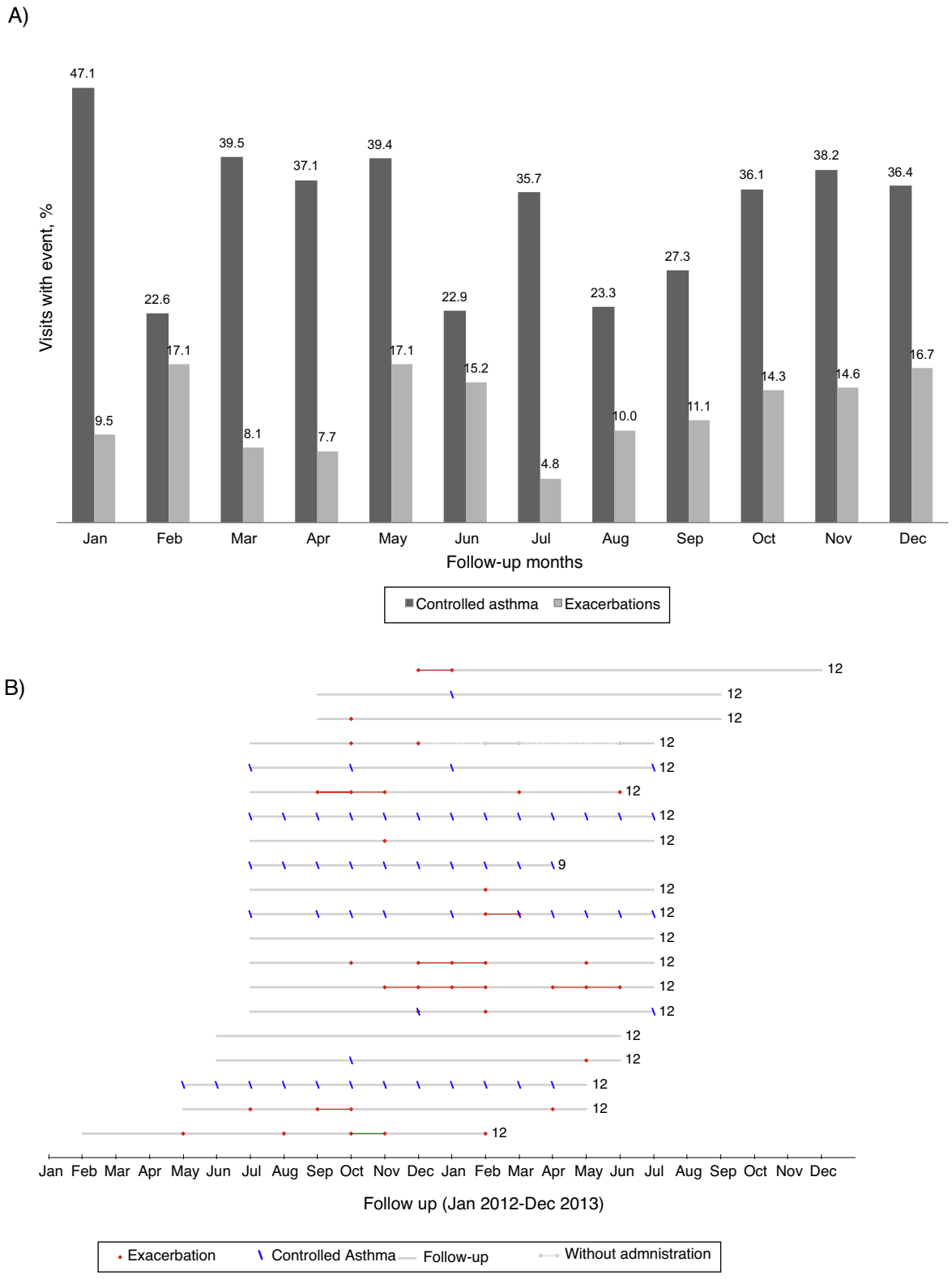

Figure 2 (A) Percentage of visits reporting controlled asthma and exacerbations according to the month of the year (all patients included). (B) Reports of controlled asthma and exacerbations during follow-up, per patient. In (B) numbers on the right indicate total months of follow-up; continuous grey lines represent the follow-up period and dashed grey lines interruptions in omalizumab treatment; red dots represent visits with report of exacerbation and blue dashes visits with CARAT global score >24–data from the 20 patients treated with omalizumab in Centro Hospitalar São João, EPE.

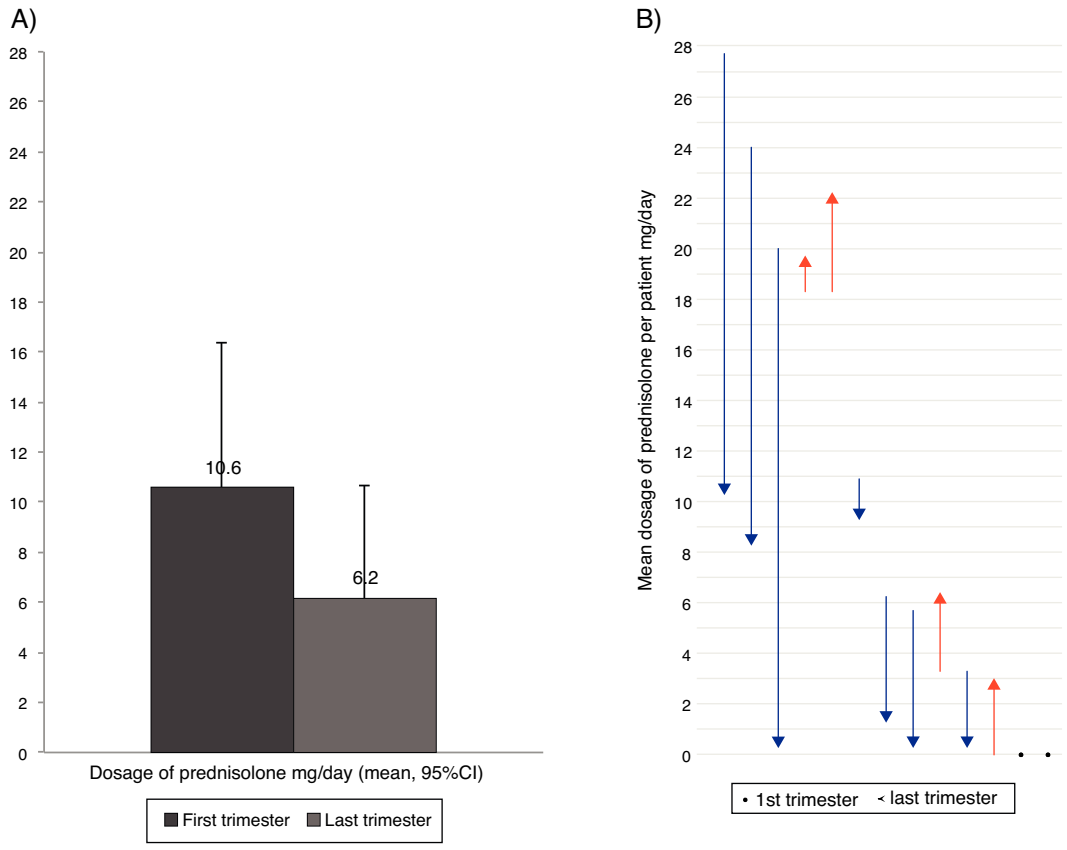

Figure 3 Mean dosage of oral corticosteroids intake in the first and last trimester of the follow-up year (considering the 13 patients with OCS intake), (A) Overall reduction (B) Per patient. In (B) arrows represent the dose variation from the first to the last trimester; red lines represent increases and blue lines decrease in the dosage of oral corticosteroid intake; and dots represent no variation in the dosage.

Conclusions

This multicentre study showed that Portuguese adult patients with severe persistent allergic asthma under treatment with omalizumab, achieved asthma control in 34% of the medical visits with only 1/3 requiring unscheduled or Emergency Room care because of asthma exacerbations, supporting the maintenance of the clinical effect during treatment with omalizumab in real life. Further prospective studies in real-life Portuguese settings are needed to assess the reduction in corticosteroids intake in patients starting omalizumab therapy. These studies should be useful for a grounded pharmacoeconomic evaluation of omalizumab treatment in Portugal.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work centre on the publication of patient data and that all the patients included in the study received sufficient information and gave their written informed consent to participate in the study.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Conflict of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary material

Supplementary material associated with this article can be found in the online version available at doi:10.1016/j.rppnen.2015.03.002.

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Research Article

The Portuguese Severe Asthma Registry: Development, Features, and Data Sharing Policies

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The Portuguese Severe Asthma Registry (*Registo de Asma Grave Portugal,* RAG) was developed by an open collaborative network of asthma specialists. RAG collects data from adults and pediatric severe asthma patients that despite treatment optimization and adequate management of comorbidities require step 4/5 treatment according to GINA recommendations. In this paper, we describe the development and implementation of RAG, its features, and data sharing policies. The contents and structure of RAG were defined in a multistep consensus process. A pilot version was pretested and iteratively improved. The selection of data elements for RAG considered other severe asthma registries, aiming at characterizing the patient's clinical status whilst avoiding overloading the standard workflow of the clinical appointment. Features of RAG include automatic assessment of eligibility, easy data input, and exportable data in natural language that can be pasted directly in patients' electronic health record and security features to enable data sharing (among researchers and with other international databases) without compromising patients' confidentiality. RAG is a national web-based disease registry of severe asthma patients, available at *asmagrave.pt*. It allows prospective clinical data collection, promotes standardized care and collaborative clinical research, and may contribute to inform evidence-based healthcare policies for severe asthma.

1. Introduction

Severe asthma has been defined as asthma which requires treatment with high dose inhaled corticosteroids plus a second controller (and/or systemic corticosteroids), to prevent it from becoming "uncontrolled" or asthma which remains "uncontrolled" despite this therapy [1].

To improve care, a better understanding of the etiology, burden and management patterns of severe asthma is needed. The management of severe asthma is challenging and involves treatment of comorbidities, medication adherence, allergens exposure avoidance, among others. One of the greatest difficulties is the choice of the optimal treatment for each given patient, although algorithms for treatment decisions have been suggested [2, 3]. Monoclonal antibodies targeting immunoglobulin-E (IgE) and interleukin-5 are currently available and new biologics are under development. However, it is not easy to choose between the biologics to be the first-choice treatment, and head-to-head comparison studies between them do not exist [4]. A trial involving the direct comparison of two or more treatments is a pressing needed, but it may never be carried out [4]. Hence, clinical observational studies of real-world large patient populations should contribute to the knowledge on how to select the best biologic treatment for an individual patient.

Disease registries are recognized as powerful tools to improve disease-related knowledge. They consist of organized systems that use observational study methods to collect uniform data aiming at evaluating specific outcomes for a heterogeneous population defined by a particular disease [5]. This type of study design enables the assessment of the effect of different therapies in the context of a single disease. Severe asthma registries are being created throughout Europe including in the United Kingdom (UK), Belgium, Germany, Austria, Netherlands, Italy, and Spain (Table 1). However, research aiming at reducing the disease-related burden requires prospective long-lasting studies and the coordination of a wide range of expertise, often only available

Table 1: European Registries of Severe Asthma, a noncomprehensive review.

Registry name	Country	Year of release	Promoting Society	Website	Patients included	No. of centers	Sources / published studies
United Kingdom Severe Asthma Registry	United Kingdom	2006	British Thoracic Society	https://www.brit-thoracic.org.uk/standards-of-care/lung-disease-registries/	>500	8	[13–22]
Belgian Severe Asthma Registry	Belgium	2008	Belgische Vereniging voor Pneumologie / Société Belge de Pneumologie	http://www1.citobi.be/SAR/Welcome_en.act	>350	9	[23, 24]
Register Schweres Asthma	Germany	2011	German Asthma Net e.V.	http://www.german-asthma-net.de	>100	17	[25, 26]
Banco de Datos de Asma	Spain	<2012	Sociedad Española de Neumologia y CirurgiaToracica	https://www.separ.es/?q=node/71	>290	30	[27, 28]
Austrian Severe Asthma Net	Austria	2012	Austrian Severe Asthma Net (ASA-Net)	http://www.asa-net.at/register/	>80	16	[29]
Severe/Uncontrolled Asthma Registry	Italy	2014	Italian Severe Asthma Network (SANI).	http://www.sani-asma.org	>400	63	[30, 31]
Registry of Adult Patients with Severe asthma for Optimal Disease management	Netherlands	2016	Academisch Medisch Centrum (Prof. dr. E.H.D. Bel)	https://www.zonmw.nl/nl/over-zonmw/innovatie-in-de-zorg/programmas/project-detail/goed-gebruik-geneesmiddelen/registry-of-adult-patients-with-severe-asthma-for-optimal-disease-managementrapsodi/verslagen/	>20	3	[32]
Registo de Asma Grave Portugal	Portugal	2018	Rede de Especialistas em Asma Grave	https://www.asmagrave.pt/	Release planned for 2nd trimester of 2018	31	-

at an international or even global level [6]. With the goal of establishing a global collaborative initiative, the International Severe Asthma Registry was created and the enrollment of 10 national registries is expected by December 2018[7]. The European Respiratory Society (ERS) Research Agency promotes collaborative Europe-wide research based on data collected from disease registries [8]. Its actions include the development of Standard Operational Procedures and guidelines, consent forms to collect and handle data in compliance with the EU legal and regulatory framework, and establishing a central point to access datasets from multiple projects. In 2016 the collaboration Severe Heterogeneous Asthma Research collaboration, Patient-centered (SHARP) was accepted as an ERS Clinical Research Collaborations [9]. Taking this into consideration, new registries should be designed to enable sharing information and coordination among databases (e.g., federated databases).

Asthma affects 6.8% of the Portuguese population [10]. Using the data from the Portuguese National Asthma Survey we estimate 7.4% of patients were on step 4 or 5 treatment as defined by Global Initiative for Asthma (unpublished data). Even though severe asthma patients represent only a small proportion of those with asthma, they account for a large proportion of asthma-related morbidity and health care expenditures [11].

REAG, *Rede de Especialistas em Asma Grave*, is an open collaborative network of asthma specialists (allergists, pediatricians, and pulmonologists) who manage severe asthma patients in Portuguese hospitals. The foundational principle of REAG is the informal peer collaboration among colleagues with different medical specialties and backgrounds, maintaining an unhierarchical organization and consensual decision processes to improve sharing of medical experience, data, and knowledge. Since 2011, this network of experts has been working towards a better care of severe asthma patients by (1) promoting a better coordination between medical specialties for early diagnosis and referral of severe asthma patients; (2) describing and implementing harmonized procedures to adopt in severe asthma healthcare; and (3) improving scientific knowledge on severe asthma in Portugal. In 2015, REAG published a real-life prospective study on Portuguese patients with severe persistent allergic asthma, treated with omalizumab [12]. This was the first-time specialists from different Portuguese centers who made an effort to harmonize the registration procedures for severe asthma. From this initial study, the necessity for a computerized disease registry became even more evident.

The purpose of the Portuguese Severe Asthma Registry (*Registo de Asma Grave Portugal (RAG)*) is to gather evidence on severe asthma in Portugal contributing to eliminate the information gaps and support the adoption of evidence-based health care policies. Specifically, the registry aims at

(1) improving the healthcare delivery of severe asthma by identifying the best diagnosis and treatment practices and by standardizing disease management processes and clinical records;

(2) supporting collaborative research projects by promoting the cooperation between centers and assist with the implementation of research projects.

In this paper, we describe the development and implementation of RAG, its features, and data sharing policies.

2. Material and Methods

RAG results from the collaboration between different stakeholders: the medical experts from REAG, the investigators from CINTESIS (Center for Health Technology and Services Research), and the software development company VirtualCare.

The development and implementation processes of RAG are summarized in Figure 1.

2.1. Definition of Contents. The criteria for patient inclusion in RAG, the domains, and data elements to be registered were defined by a multistep consensus method.

The patients' inclusion criteria were based on the definition of Severe Asthma by GINA [1]: (1) patient with treatment on step 4 or 5 according to GINA recommendations; and (2) verified optimization of treatment adherence and comorbidities management. An additional inclusion criterion was (3) the patient's signed consent to have his/her data included in the registry.

During a meeting (April 2016), the domains and data elements were enumerated, based on the medical expertise of the network and taking into consideration the variables existing in three existing European Registries: the Belgian, the German, and the UK Severe Asthma Registries. Both data elements to be included in the initial patient registry and relevant follow-up information were identified. Different data entry methods were considered to reduce the burden of response.

An online questionnaire sent to 79 medical specialists from REAG was used to explore the importance of each data element and adequacy of data entry method. A total of 34 participants (43%) completed the questionnaire. For each domain, data elements and methods for data entry were chosen when gathering at least 80% of the votes. Comments and suggestions regarding additional variables or different data entry methods were also considered. The results of the questionnaire were presented in a meeting (March 2017) and disagreements were solved by consensus.

2.2. Features. Database specifications concerning data definitions and parameters and data validation rules were determined. To assist confirmation of the first criterion and support decision-making, an algorithm to automatically determine the step of treatment based on currently used asthma medication was created.

The following additional features were implemented:

(i) Support on data entry by automatic validation of the inserted data and error messages

(ii) Creation of automatic reports, based on the information stored, to be integrated into the institutional electronic health record (the data recorded are exportable in natural language by generating a text that mimics clinical notes)

(iii) Graphic display of aggregated data on patients' inclusion by healthcare center

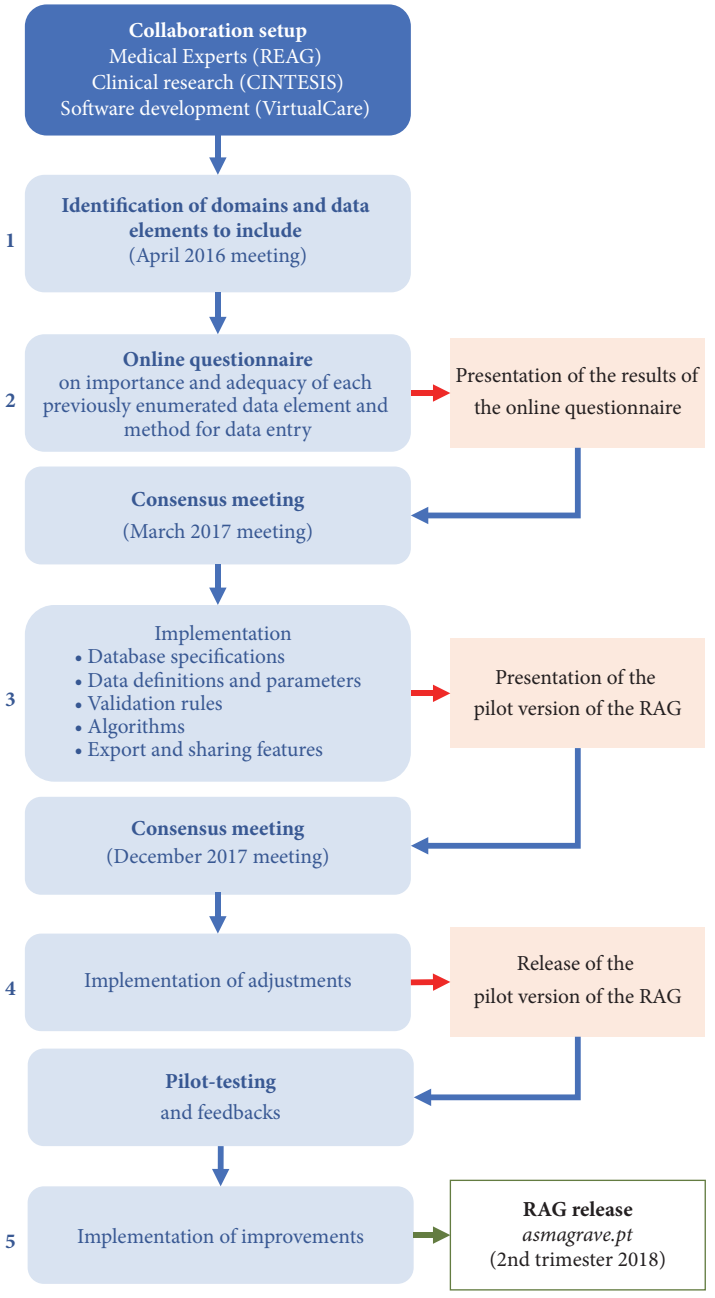

Figure 1: Development and implementation process of RAG.

(iv) Display for each physician a list of their patients and date of the last medical appointment

(v) At follow-up visit, automatic display of the information inserted in the last appointment for specified measurements

(vi) Export features for potential data exchange with international severe asthma databases and the pharmacovigilance authorities

(vii) Automatic emails with status report of each registration

2.3. Security and Data Sharing Policies. Security features compliant with the new European General Data Protection Regulation (GDPR) [37] and required procedures according to this legislation are being incorporated into the platform.

The registry was built on a framework residing in a server hosted by VirtualCare. This server was configured with a Secure Sockets Layer (SSL) certificate from Comodo Security Solutions, Inc., ensuring that all data transferred between the web server and browsers remain private and integral. The access to the database is restricted, requiring authentication (using health professional number and password) and all

accesses to the database are stored and traceable. All changes to the database are also stored; each change generates a new document; the old document becomes out of date allowing the tracking of changes (when, where, and by whom changes were made to the documents).

RAG does not record any identifiable personal data from patients (e.g., date of birth is replaced by the year of birth, no ID numbers are registered, and patients' names are pseudoanonymized so replaced with a code number) [38]. The patients' participation on RAG is free and voluntary, and patients may, in any moment and without penalty, withdraw the registry or verify and/or delete their data, by contacting the technical support. Patients are informed on the purposes of RAG, the data collected, and the implications of participating in this registry. The informed consent form is automatically generated at the time of inclusion. Only patients that agree, by a clear affirmative consent given by a written statement, to the storage, processing, and sharing of data belonging to him/her are included in RAG. The signed consent forms are upload into the application server file system, encrypted using phpseclib's library of PHP, which allows the usage of one of its encryption algorithms combined with a private key. When encrypted, the consent file cannot be read unless the file decryption is activated with the correct combination of algorithm and private key. The algorithm and private key are known only to VirtualCare.

An informed consent is also required by physicians who are registered in RAG since they provide identifiable personal data for that registration, namely, name, health professional number, and email address. At the time of registration, physicians must indicate their acceptance by ticking a box with a clear statement on the storage and processing of their personal data. The registration of each physician in RAG must be validated by at least one of five members of REAG, designated coordinators of RAG.

Data within RAG belongs primarily to each patient and then to the physician that inserted patients' data into the registry. Each physician is responsible for the management of the data that he/she inputted, belonging to his/her patients. Access to patients' data by their physicians is based on the Role Based Access Control (RBAC) model that associates privileges and permissions to the roles (e.g., professional categories). This model allows easier administration and independence in relation to the system users and permissions associated with its resources.

After authentication, each physician can access all the registrations inserted by himself/herself, both for clinical and research purposes. One local coordinator will be designated in each center. Each center coordinator has access, for pressing clinical purposes only, to all data inserted by the physicians in that center. If a patient changes the attending physician, the new physician, if interested in having access to the previously inserted data, must request authorization to the former physician, with patient's consent. Local and national coordinators and RAG technical support may assist this contact.

Data inserted by other physicians may be shared within REAG for research purposes, after authorization. For this, the physician proposing the data analysis must fill-in a form containing the aim and a brief description of the research project and the principal investigator or research group. When a request for abstracting data is filled, each physician with data matching the request is notified by email and has a period of 5 days to refuse the sharing of the data. In the case of shared information, the privacy of the individual is assured, as registry data cannot be individually identifiable.

2.4. Pilot-Test. After the implementation of the selected data elements, the supporting features, and validation rules, a beta version of RAG was presented during a REAG meeting (December 2017) and, after adjustments, it was pilot-tested for a month. The pilot version was tested by 22 REAG members and 85 specific feedback comments were provided by 8 testers. The first version of RAG became ready after improvements being made based on the pilot-test feedback.

3. Results

The Portuguese Severe Asthma Registry is a national web-based disease registry. The access is made from the website of REAG, *asmagrave.pt*, after authentication.

RAG gathers data of adults and children with severe asthma followed at specialized care centers which, after treatment optimization and adequate management of comorbidities, require step 4 or 5 of treatment according to GINA recommendations[1]. The implemented automatic algorithm determines the step of treatment for patients aged under 6, between 6 and 12 and over 12 years, based on asthma medication prescribed to the patient according to GINA recommendations (Figure 2.A). In any case, the physician makes the decision about the inclusion in the registry indicating the reason for inclusion (Figure 2.B). In fact, even if rarely used, some therapeutic combinations are not explicitly considered in any of the GINA 2018 treatment steps and in these cases, the algorithm cannot present a result. The algorithm will be updated in the future when these recommendations change.

The final data items of RAG are summarized in Table 2. RAG allows collecting data on different asthma medication, including Oral Corticosteroids (OCs), monoclonal antibodies, and even new therapies that may become available (Figure 3). Data considered as essential are compulsory, whereas desirable but not essential data may be skipped. The elements to be collected in the follow-up appointments were also defined as RAG was designed to collect data prospectively.

4. Discussion

The Portuguese Severe Asthma Registry is a national web-based disease registry of adult and pediatric severe asthma patients. It includes a comprehensive list of data elements defined by a multistep consensus process, supported by international definitions of severe asthma. The registry offers features to facilitate data entry and to support decision-making. The collected data belongs primarily to each patient and then to the physician who inserted patients' data into the registry and can be shared for research purposes after authorization. A thorough characterization of severe asthma

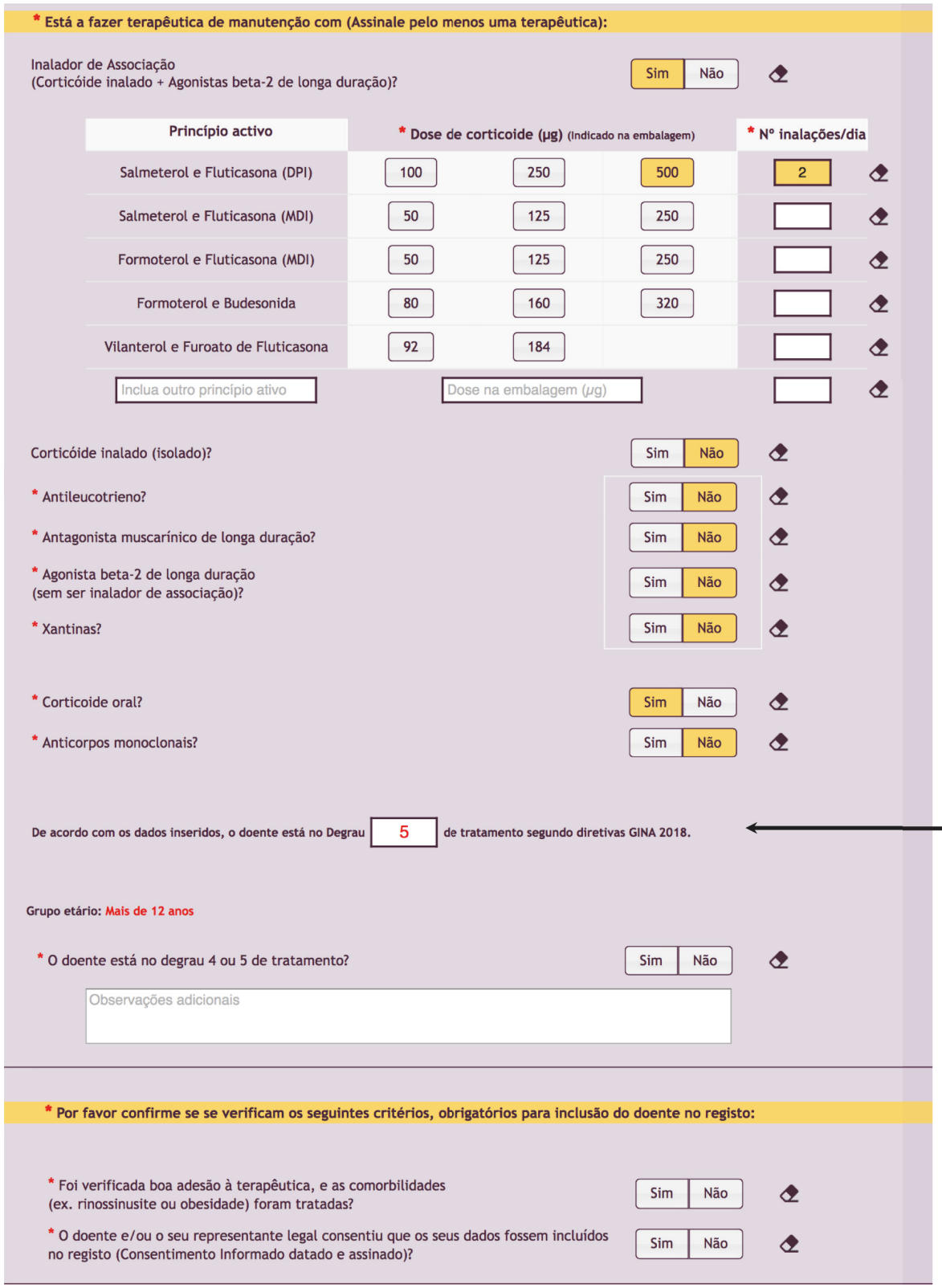

Figure 2: Screenshot of the implemented automatic algorithm to determine the step of treatment, based on asthma medication according to GINA recommendations. A: treatment step calculated by the algorithm; B: the 3 criteria for patients' inclusion.

Table 2: Domains and data elements recorded in the Portuguese Severe Asthma Registry.

Patient data
Demographic data *(gender∗, birth of month∗ and year∗, birthplace, place of residence∗, body mass index calculation∗, education years∗, smoking habits∗, occupation∗, family history of asthma∗ and of asthma-related death∗, personal history of respiratory infections during early childhood∗, environmental exposures)*
Asthma care information *(age at asthma diagnosis∗, age at severe asthma classification∗, first year of specialized asthma follow-up, medical specialty of the attending physician∗)*
Comorbidities∗§
Atopy and Inflammation biomarkers
Atopy *(total serum IgE∗, allergic sensitization∗, type(s) of diagnostic test used to confirm allergic sensitization∗)*
Inflammation biomarkers *(FeNO, blood eosinophils, sputum eosinophils, sputum neutrophils)*
Diagnostic tests
Lung function tests *(FEV1∗, FVC∗, MEF, residual volume, specific airway resistance, carbon monoxide diffusion capacity, bronchial challenge test)*
Imaging *(thorax X-ray∗, thorax CT scan∗, sinus CT scan, bronchial endoscopy, bone densitometry)*
Arterial blood gases
Control and Quality of Life
Asthma-related healthcare utilization due to asthma in previous 12 months (or since the last appointment, when at follow-up visit) *(number of routine primary care medical appointments, routine hospital care medical appointments, non-scheduled medical appointments∗§, emergency service admissions∗§, hospitalizations∗§, intensive care unit admissions, need for mechanical ventilation, school or labor absenteeism)*
Asthma control assessment according to GINA recommendations[1] *(frequency of daytime symptoms∗§, activity limitations due to asthma∗§, any night awakening due to asthma∗§, frequency of use of reliever medications for asthma∗§, respiratory function, number of exacerbations in last year/week∗§)*
Asthma control self-questionnaires *(CARAT∗§ and external link to ACT)*
Quality of life self-assessment questionnaires *(external link to quality of life self-assessment questionnaires)*
Therapy
Asthma medication∗§ *(OCs, ICs, LTRAs, LABAs, SABAs, LAMAs, SAMAs, xanthines, immunosuppressors, immunotherapy, monoclonal antibodies, antibiotics, therapy adherence, inhalation technique)*
Other medication *(proton pump inhibitor, anti-depressive/anxiolytics, intranasal steroids, antihistamines, long-term oxygen therapy, non-invasive ventilation)*

∗Compulsory data elements at initial visit; § compulsory data elements at follow-up.
IgE: immunoglobulin-E; FeNO: Fractional exhaled Nitric Oxide; FEV1: forced expiratory volume in the first second; FVC: forced vital capacity; MEF: midexpiratory flow; CT: computed tomography scan; CARAT: Control of Allergic Rhinitis and Asthma Test [33, 34] and ACT: Asthma Control Test [35]; OCs: Oral Corticosteroids; ICs: inhaled corticosteroids, LTRAs: Leukotriene Receptor Antagonist; LABA: Long-Acting Beta 2 Agonist; SABA: Short-Acting Beta Agonist; LAMA: Long-Acting Muscarinic Antagonist; SAMA: Short-Acting Muscarinic Antagonist.

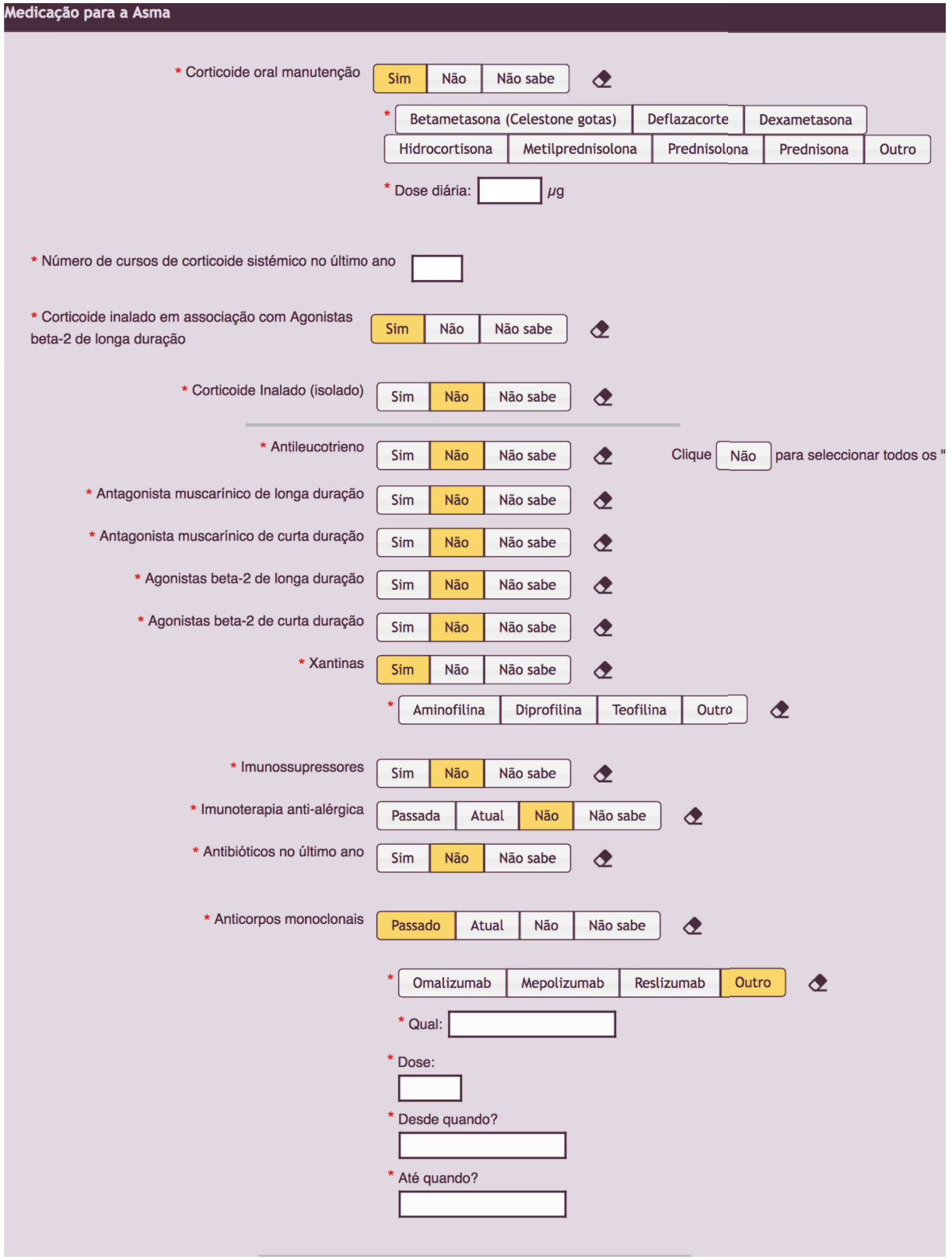

Figure 3: Screenshot of RAG, picturing asthma medication being collected by RAG.

Table 3: RAG features useful to support severe asthma management.

Elements of chronic care management [36]	**RAG features**	
	Current	Future
Ensure regular follow-up	Displays for each physician a list of their patients and date of the last medical appointment	Display a simple message with the counting the months since the last appointment and flag patients without medical review in more than 6 months
Facilitate individual patient care planning	For specified measurements, displays the information inserted in the last appointment and its progress over time	At the beginning of each follow-up appointments, a brief report of the previous appointment will be displayed
Embed evidence-based guidelines into clinical practice	has a decision support tool to identify patients treated in step 4 or 5 according to GINA recommendations	
Monitor the performance of practice team	Displays aggregated data on the number of patients included by each center	Aggregated real-time data with different graphic displays of trends on specified management and clinical outcomes will be produced, to give a feedback to physicians about the status of the care of their patients and/or healthcare center, towards delivering the recommended care for severe asthma.

patients, using a tool consensually defined to be applied prospectively by specialists from Portuguese hospitals, is ambitious but can improve the information on the disease and contribute to the adoption of evidence-based policies for severe asthma care. This harmonized approach is essential to improve the management of the different phenotypes this pathology. The Portuguese registry was designed to enable future linkage with other databases, as registries from other countries, as well as the Portuguese Pharmacovigilance Authority.

The data elements included in RAG were selected to reflect the current clinical status of the patient avoiding unnecessary burden within the clinical workflow. Through a multistep consensus method, a balance was achieved between the data commonly used by clinicians, the data included in other severe asthma registries, the data needed for the RAG's reliability, and the expected overall burden for respondents. Therefore, there was an effort to data collected by RAG which can be compared to data collected by other registries enabling comparisons across populations and settings. A consensus method was used to summarize information from different sources, to gather insights from experts and to enable decision-making [39]. After the selection and implementation of the data elements and validation rules, RAG was pilot-tested and iteratively improved before release.

The patients' inclusion criteria were also defined by consensus and an automatic algorithm was implemented to assist patients' eligibility assessment, based on GINA recommendations. Clinical guidelines provide a link between the best available evidence and the clinical practice, having the potential to improve enormously patient care [40]. However, these may have limitations especially for a particular disease where evidence is still insufficient as in severe asthma and cannot be used as a strict formula. During algorithm development became clear that GINA 2018 treatment steps do not account for all possible therapeutic combinations. In the future, it would be important to assess if clinically relevant combinations are not included in the GINA recommendations, to contribute to the improvement of the recommendations concerning severe asthma.

Disease registries are used to support healthcare providers on disease care and to gather evidence for scientific and policy purposes. Therefore, a disease registry should (1) facilitate the access to patient-specific information at the point of care for healthcare delivery and provide status reports of aggregated information to give feedback to physicians or to medical groups about the patient population [36] and (2) provide real-world data on clinical practice, patient outcomes, safety, and/or comparative effectiveness for research purposes[5]. RAG has several features to support healthcare providers on severe asthma care (Table 3). Additionally, as suggested by the members of REAG, RAG includes the automatic generation of clinical notes based on the inputted data that can be pasted into the institutional electronic clinical record of the patient, avoiding duplication of effort.

Real-world prospective observational research, including long-term follow-up data provided by registries, is increasingly considered important to generate evidence regarding effectiveness, safety, and quality of care [41]. The utility of a

registry relies on the quality of data collection and storage [5]. RAG's data are collected at the time of routine medical appointments, in the same manner for every patient, with specific and consistent data definitions. To minimize errors related to data completeness and consistency, several logical and validation rules have been implemented and periodic data audits are being planned. An additional challenge is the recruitment and retention of participants that is critical to the generalizability of a registry [5]. Potential RAG users were involved from the beginning in the development and implementation process and stated their motivation to include patients. Nevertheless, to retain users' interest, the burden of participation was kept as low as possible and features wanted by the physicians were implemented.

RAG was designed to comply with security and data protection standards, including key challenges of the new European GDPR. No individually identifiable information of the patient is recorded in the database. Only the his/her physician can link the recorded data to the patient that remains the owner of the data. RAG's data sharing policies allow the use of data for research, requiring the consent of the physician that recorded the data and a simple process to gather this consent was implemented.

5. Conclusions

The Portuguese Severe Asthma Registry is a national web-based disease registry of adult and pediatric severe asthma patients. The development and implementation of the RAG was a multistep consensus process. RAG includes automatic assessment of eligibility, easy data input, and features for exporting and sharing data. It allows prospective clinical data collection, promotes standardized clinical records, and creates a secure virtual setting for collaborative clinical research. RAG database is prepared for future data exchange with international databases. In the future, the analysis of RAG data may contribute to inform evidence-based healthcare policies for severe asthma.

Data Availability

Data sharing is not applicable to this article.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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