Predicting asthma-related crisis events using routine electronic healthcare data

ABSTRACT

Background: There is no published algorithm predicting asthma crisis events (Accident and Emergency (A&E) attendance, hospitalisation or death) using routinely available electronic health record (EHR) data.

Aim: To develop an algorithm to identify individuals at high risk of an asthma crisis event.

Design and Setting: Database analysis from primary care EHRs.

Method: Multivariable logistic regression was applied to a dataset of 61,861 people with asthma from England and Scotland using the Clinical Practice Research Datalink. External validation was performed using the Secure Anonymised Information Linkage databank of 174,240 patients from Wales. Outcomes were one or more hospitalisation (development dataset) and asthma-related hospitalisation, A&E attendance or death (validation dataset) within a 12-month period.

Results: Risk factors for asthma-related crisis events included previous hospitalisation, older age, underweight, smoking and blood eosinophilia. The prediction algorithm had acceptable predictive ability with a Receiver Operating Characteristic (ROC) of 0.71 (0.70, 0.72) in the validation dataset. Using a cut-point based on the 7% of the population at greatest risk results in a positive predictive value of 5.7% (95% CI 5.3 – 6.1) and a negative predictive value of 98.9% (98.9 – 99.0), with sensitivity of 28.5% (26.7 – 30.3) and specificity of 93.3% (93.2 – 93.4); they had an event risk of 6.0% compared 1.1% for the remaining population. Eighteen people would be “needed to follow” to identify one admission.

Conclusions: This externally validated algorithm has acceptable predictive ability for identifying patients at high risk of asthma-related crisis events and excluding individuals not at high risk.

246 words

Keywords

Asthma, asthma attack, risk, prediction, algorithm.

How this fits in

Risk stratification is commonly undertaken in primary care but there are no validated prediction algorithms for people with asthma using routine data. An algorithm was developed using a primary care dataset and externally validated showing acceptable predictive ability with a Receiver Operating Characteristic (ROC) of 0.71 (95% CI 0.70 – 0.72). The 7% of the population most at risk had an event rate of 6.0% compared 1.1% for the remaining population. This algorithm can be used to identify individuals at high risk of an asthma-related crisis event from primary care electronic health records.

INTRODUCTION

The challenge of reducing unplanned hospital admissions and avoidable deaths in common chronic conditions, such as asthma, remains unresolved. Despite effective treatments, evidence-based guidelines(1) and financially incentivised community-based chronic disease management (via the Quality and Outcomes Framework(2)), each year in the UK an average of 1500 people die(3) and 93,000 are hospitalised due to asthma(4). Identification of those at increased risk of these events is beneficial both at an individual level to tailor disease management, and at a population level to inform and modify processes of care.

Many risk factors for poor asthma outcomes have been identified,(5-8) some of which have been combined into risk algorithms including the Asthma UK “Asthma attack risk checker”(9), Asthma Disease Activity Score(10) and Wheeze frequency, Admissions, Reliever use and Step on BTS medication guidelines (WARS) score(11). Recently an algorithm has been developed to identify children at risk of life-threatening asthma(12). These have been derived from small datasets including those from clinical trials or the variables used in the prediction tools have required up-to-date personal characteristics including psychosocial characteristics or adherence to medication for which comprehensive data are difficult to obtain in large populations(13). An algorithm to identify patients at greatest risk of poor outcomes using electronic healthcare data would overcome this problem and enable a register of high-risk patients to be generated efficiently.

Most prediction algorithms have defined a severe asthma attack as one that requires oral corticosteroid therapy or hospital attendance/admission(14). However, this

composite scoring includes variables which are not necessarily co-linear. Early treatment with prednisolone may stop the deterioration and prevent an Accident and Emergency (A&E) attendance and as such this composite definition may mask the benefits of prompt management of an attack, with increased prednisolone treatment and reduced hospitalisations(13). Therefore, it is important to develop algorithms that identify these two risks separately.

We aimed to develop and validate a prediction tool to identify individuals at high risk of an asthma related crisis event (A&E attendance, hospital admission or death due to asthma) during the following 12 months, calculated from routinely captured electronic health records (EHR).

METHODS

Data Sources

(i) Derivation dataset

An analytical dataset was used from a published cohort study(15) which used a database of people with physician diagnosed and recorded asthma (with no subsequent code for asthma resolved) aged between 12 and 80 years and measurement of full blood count (FBC) at any time in the past, with two years of continuous data, registered at 650 primary care practices in the United Kingdom. The dataset comprised data from the Clinical Practice Research Datalink (CPRD, www.cprd.com) (16) between 2001 and 2012. Although the CPRD database contains record-linked primary and secondary care data, including reason for admission to hospital, only data from primary care were used to derive the algorithm because EHRs in UK primary care do not consistently code secondary care events.

However, both primary and secondary care data were used when assessing the outcome.

(ii) Validation dataset.

A separate dataset of patients from the Secure Anonymised Information linkage (SAIL) databank (17, 18) who were registered at 340 general practices in Wales was used to validate the algorithm. Record-linked data from primary and secondary care were available for individual patients and included reason for admission to hospital. Data on asthma outcomes, healthcare interactions (including GP consultations) and prescribed medications were obtained from the SAIL Databank.

Eligibility.

Patients included in the existing analytical dataset for the derivation of the at-risk algorithm comprised those with ‘active asthma’ (i.e. with a coded diagnosis of asthma and a prescription for asthma treatment in the previous 12 months(19)), no diagnosis of any other chronic respiratory disease, a valid blood eosinophil count (≤ 5,000 blood eosinophils/microlitre (μL)) and complete data for the baseline and outcome years (the year prior to and the year following the last eosinophil count).

Patients included in the SAIL validation dataset comprised those with at least one “asthma diagnosis” code before 31/12/2011, no “asthma resolved” codes between 1/1/2010 and 31/12/2011, and at least one asthma prescription (bronchodilator, corticosteroid or leukotriene receptor antagonist) code between 1/1/2010 and 31/12/2010. Patients were continuously registered at one general practice between

1/1/2010 and 31/12/2010 (baseline data collection year) and continually registered (or died) between 1/1/2011 and 31/12/2011 (outcome year).

Predictors.

Details of all variables considered as potential predictors for the at-risk algorithm are shown in Supplementary Table S1. These included age, sex, smoking history, comorbidities, respiratory related medication, healthcare contacts and blood eosinophil count. For diagnostic variables (e.g. ischaemic heart disease, diabetes), Read Codes (coded clinical terms) were queried anytime up to the end of the baseline year (i.e. from 'ever' to '31/12/2010') from the validation and derivation databases. Similarly, for eosinophil count, body mass index (BMI), and smoking status, the most recent codes any time before 31/12/2010 were used. For the rest of the variables (prescriptions for asthma, allergic rhinitis, diabetes, anxiety and depression, as well as paracetamol use (which is positively associated with asthma(20)), lower respiratory tract infection (LRTI) consultations, allergic rhinitis diagnosis), the codes were queried between 01/01/2010 and 31/12/2010.

Outcome.

The outcome was defined as one or more hospitalisations within 12 months for the development of the algorithm. For the validation of the algorithm we defined the outcome as a crisis event which comprised an asthma-related hospitalisation, A&E attendance or death within a 12-month period.

Statistical analysis.

Univariate logistic regression models were used to identify baseline measures of disease severity, patient demographics and comorbidities predictive of one or more future events. Variables showing an association ($p<0.05$) with an asthma exacerbation resulting in hospital admission in univariable analyses were entered into a multivariable model, which was reduced using backward elimination to produce a final list of predictors of hospital admission. No model updating was undertaken.

The final model was used to create ‘at-risk’ scores indicating the risk of an asthma-related crisis event for each patient in the dataset. To do this, coefficients for those factors present in each patient were summed, along with the intercept, to obtain the risk score (x) which is the logit of the probability of asthma-related attendance at A&E or hospital admission; the probability is given by $e^x/(1+e^x)$. We did not investigate internal validation, as we used a separate dataset to perform external validation. The calibration slope coefficient was estimated by splitting the predicted risk into 10 groups, based on quintiles, and calculating the percentage of people with the outcome in these estimating a linear regression model with the predicted risk group against the actual risk.

We assessed discrimination (the ability to distinguish between those who do and do not experience the outcome) by calculating the Receiver Operating Characteristic (ROC) for the risk scores. In addition, we calculated the specificity, sensitivity, positive predictive values (PPV) and negative predictive values (NPV) for five different ’at-risk’ cut-offs (top 1%, 2%, 5%, 7% and 10%) for the risk scores for both

the derivation and the validation datasets. The overall goodness of fit of the score was assessed by estimating the pseudo R^2 from the logistic regression model. Assuming an asthma prevalence of 6-7%, a 7% cut-off would, on average, identify the most at risk 42-49 individuals from a practice of 10,000 patients. A sensitivity analysis was undertaken for the validation cohort including only data related to hospitalisation.

RESULTS

Participants

The derivation and validations data sets comprised 58,619 and174,240 people respectively (Figure 1) The average age of participants in the derivation dataset was 50 years and 44 years in the validation dataset, with more females in both datasets (Table 1). There were proportionally more people receiving Global Initiative for Asthma (GINA) treatment step 4 or 5 (medium or high dose inhaled corticosteroid and long acting beta agonist/muscarinic antagonist +/- add on therapies) and more with a diagnosis of or treatment for rhinitis in the derivation database. There were differences in the dataset in terms of smoking status, BMI, anxiety and depression and paracetamol usage. The outcome was present in 1.65% of individuals in the derivation and 1.40% in the validation dataset.

The results of the logistic regression are presented in Table 2, which gives the estimated weight of each variable and describes the algorithm used to predict asthma crisis events. The overall ability of the algorithm to discriminate between patients who subsequently had an asthma-related crisis event and those who did not was acceptable (Table 3) and similar in the derivation data (ROC = 0.72 (95% CI: 0.71, 0.74) to the validation data (ROC = 0.71 (95% CI: 0.70, 0.72). Using a cut-point based on the 7% of the population at greatest risk results in a positive predictive value of 5.7% (95% CI 5.3 – 6.1) and a negative predictive value of 98.9% (98.9 – 99.0), with 28.5% (26.7 – 30.3) sensitivity of 28.5% (26.7 – 30.3) and specificity of 93.3% (93.2 – 93.4) (Table 3). The discriminative ability of the algorithm was similar in the validation cohort when the outcome was confined to hospitalisation only (Table S2). These individuals had a risk of event of 5.68% (Table 4) and 3.31%

when considering hospitalisation only (Table S3). The at-risk algorithm showed acceptable prognostic performance in the validation data with a 5.4 -fold higher asthma-related crisis event rate in the high risk-group (6.0%) versus the rest of the population (1.1%) at the 7% cut-off (Table 5) or an absolute difference of 4.9%.

The calibration slopes showed acceptable agreement between deciles of mean risk score and proportions of people experiencing asthma-related crisis events within each decile group, with data points close to the line of equality. The slope coefficient for the development dataset was 0.99 (95%CI 0.92 to 1.05), while that for the validation was 0.85 (95%CI 0.75 – 0.96).

Discussion

Summary

We have derived and externally validated an algorithm, containing hospitalisation, older age, underweight, smoking and blood eosinophilia, to identify individuals at increased risk of experiencing an asthma-related crisis event using data that are routinely available in UK primary care EHRs. This had acceptable overall characteristics with ROC of 0.72 in the derivation and 0.71 in the validation cohorts respectively. Using the top 7% of the score as a cut-off, our algorithm correctly identified 28.5% of the asthma population most at risk and 93.3% of those not at risk. A practice can expect a crisis event to occur in 6.0% of the 'high risk' group compared to 1.1% of the rest of the asthma population. Eighteen people would be "needed to follow" to identify one admission. The algorithm can identify people who are at a 5-fold increased risk (absolute difference of 5%) of an asthma-related crisis event compared to those not at-risk.

Strengths and Limitations

The main strength of this study is that we used two separate large databases capturing people from different geographical areas with record linkage between primary and secondary care data. The generalisability of the algorithm is illustrated by its similar behaviour in two different datasets. We deliberately ignored the data on cause (asthma related or not) for hospital admission when deriving the algorithm as this information, although predictive of future events, is not routinely available in primary care datasets. However, by linking primary care with secondary care data for the purposes of assessing the outcome, we were able to confirm that our algorithm identifies people at risk of an asthma related crisis event.

The limitations were that patients in the derivation, but not validation, cohort needed to have had a valid FBC to be entered into the database (although specific values such as eosinophil counts were not required). This is likely to have resulted in differences in some of the characteristics for example age, gender, asthma severity, number of comorbidities. We do not believe that there is any difference in the diagnosis or management of people with asthma between Wales and England as both countries follow National Guidelines(1). The databases contained data which are now a decade old (validation 2001-2012, validation 2011-2012) and asthma guidelines have been update in this time(1). These modifications have included the use of high dose inhaled corticosteroids to abort an asthma attack(21), vitamin D monitoring and therapy(22) as well as the use of monoclonal antibody therapies(23). However, there have been no significant changes to the understanding of the aetiology of asthma crises or deaths since the data were collected and the software systems and determinants of coding decisions in day to day practice remain comparable. We did not have access to information on medication adherence or social circumstances. Socioeconomic status has been shown to be a risk factor for hospitalisation(24) and also independent predictor for life threatening asthma in children(12). Unfortunately, routine data do not contain this information although algorithms have been developed for assessing prescription uptake(25) and socioeconomic status is available from postcode data(26) both of which may be applied to future algorithms. We did not have death or A&E data in the derivation cohort, but we did in the validation cohort. However, we have shown that the performance of the prediction algorithm is similar when considering hospitalisation or hospitalisation, A&E attendance or death. Whilst the number of short-acting beta-

agonist scripts were included in our list of potential variables, long-acting beta-agonist as monotherapy, which has been described as a risk factor in asthma deaths(27), was not as this regime is rarely prescribed(28). This algorithm does not predict community-based asthma attacks requiring oral prednisolone.

Comparison with existing literature

The WARS score had a ROC of 0.83 for prednisolone use (11) but the performance of the score in terms of crisis events is unknown. Likewise, the performance measurements of the Risk Score developed by Bateman et al(10) for asthma attacks are not published. However the Respiratory Effectiveness Group Initiative published an algorithm to predict risk of two or more attacks in the subsequent two years with an ROC of 0.79 (95% CI 0.78-0.79)(29). Recent evidence (27), suggests that disease severity is an unreliable measure of risk and, indeed, our results confirmed that GINA treatment step 'no therapy' was as significant a risk factor as step 4-5.

In terms of non-respiratory hospitalisation prediction algorithms, the QRISK2 score which is widely used within the NHS to predict cardiovascular events has a R^2 of 43.5 and 38.4, and ROC statistic of 0.82 and 0.79 in females and males, respectively(30). A systematic review of risk prediction models to predict emergency admission in community dwelling adults(31) identified 27 different risk prediction models and showed that models using clinical data (as in our algorithm) out-performed those using self-reported data with C-statistics ranging from 0.63 to 0.83. Our algorithm, which utilised clinical data, had a comparable level of calibration (C-statistic 0.72) to other clinically useful algorithms.

We collected our outcome data as events over a 12-month period in order to avoid seasonal variations. Our algorithm therefore predicts hospitalisation within the following year. However, an individual's risk status can change if, for example, they had a hospitalisation just within or out with a 365-day period. Different algorithms can show substantial variation in risk at the individual level (32) and should complement physician assessment based on knowledge about individuals. Nevertheless, the growing workloads on primary care clinicians and the ongoing challenge of rising unplanned admissions and avoidable deaths makes accurate identification and targeting of the highest risk individuals an essential part of primary care strategy.

Implications for research and/or practice

Primary care software systems routinely use prompts to alert clinicians to overdue asthma reviews and the over-ordering, and by implication over-use, of short acting beta agonists (SABA). Both are helpful markers of risk which are not always recognised as such(13, 33, 34), but they do not reflect the range and complexity of factors found in patients most at risk of adverse outcomes(27, 35). Guidelines(1) recommend that patients are assessed for risk of future attacks. The indicators recommended include a history of previous attacks, SABA use and other markers of disease control, atopy and environmental tobacco exposure in children, and in adults, smoking, obesity and depression. In April 2020, Quality and Outcome Framework (QOF) indicators for disease control were changed from the Three Royal Colleges of Physicians Questions to the Asthma Control Test Score plus the number of exacerbations in the previous twelve months. Achieving these new indicators requires more clinician time and greater participation from patients. Failure to attend appointments is in itself a risk factor for poor outcomes(35).

Our algorithm simplifies the collection and weights the significance of multiple risk factors. It has the potential to save clinicians' time and provide accurate real-time assessments of patients' risk. It does not require patients to attend and therefore also by-passes the dangers of inverse care associated with poor attendance at appointments. It also concurs with, and provides a mechanism to identify, important markers highlighted in the National Review of Asthma Deaths (NRAD) report such as patients on no treatment for their asthma at all (27). It can be used to generate alerts or prompts to identify patients, at high risk of asthma crisis events (A&E attendance, hospitalisation or death), when their EHRs are accessed so that care can be targeted appropriately.

The algorithm is currently being used in a study to validate the role of at-risk asthma registers in primary care(36). Further work is also needed to explore some of the unexpected findings such as low BMI, and to find a way to incorporate important social and behavioural determinants not currently captured in primary care EHRs.

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Ethical Approval

The study protocol was approved by the CPRD Independent Scientific Advisory Committee (ISAC approval number 10_087).

Competing Interests

David Price has board membership with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Mylan, Mundipharma, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, Teva Pharmaceuticals, Thermofisher; consultancy agreements with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mylan, Mundipharma, Novartis, Pfizer, Teva Pharmaceuticals, Theravance; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Mylan, Mundipharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Respiratory Effectiveness Group, Sanofi Genzyme, Teva Pharmaceuticals, Theravance, UK National Health Service;

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