Things change: The early identification of patients with an unfavourable prognosis

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Chapter 5

Development and validation of personalized prediction to estimate future risk of severe exacerbations and uncontrolled asthma in patients with asthma, using clinical parameters and early treatment response.

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ABSTRACT

Current level of asthma control can be easily assessed by validated instruments, but it is currently difficult to assess individuals' level of future risk. Our objective is to develop, and validate, a risk prediction score for level of future risk, including patient characteristics and information on early treatment response.

We used data of 304 adult patients with asthma from a 12-month primary care randomized controlled trial with 3-monthly assessments. With logistic regression we modeled the association between the level of future risk and patient characteristics including early treatment response. Future risk was defined as Asthma Control Questionnaire (ACQ) score of 1.5 or more at 12 months or the experience of at least 1 exacerbation during the final 6 months. We developed a risk prediction score on the basis of regression coefficients.

Performance of the risk prediction score improved, taking into account data on early treatment response (area under receiver-operating curve [AUROC] = 0.84) compared with a model containing only baseline characteristics (AUROC = 0.78). The score includes 6 easy-to-obtain predictors: sex, ACQ score and exacerbations in the previous year at baseline and at first follow-up, and smoking status and exacerbations in the previous 3 months (indicating early treatment response). External validation yielded an AUROC of 0.77. The risk prediction score classified patients into 3 risk groups: low (absolute risk, 11.7%), intermediate (47.0%), and high (72.7%).

We developed and externally validated a risk prediction score, quantifying both level of current asthma control and the guideline-defined future risk. Patients' individual risk can now be estimated in an easy way, as proposed but not specified, by asthma management guidelines.

INTRODUCTION

According to asthma management guidelines, clinicians should assess the current level of control of asthma symptoms, alongside the level of guideline-defined future risk of adverse outcomes, while taking into account individual patient characteristics. The goal is to obtain and/or maintain controlled asthma, as opposed to partly controlled or uncontrolled asthma, and treatment should be adjusted if necessary.[1,2,3,4] The rationale for this goal is that uncontrolled asthma increases the risk of experiencing asthma exacerbations, has an increased mortality ratio, and is associated with higher health care utilization and costs, including more hospital admissions, unscheduled doctor visits, and use of emergency services.[5,6,7] Despite this, currently 50% to 60% of patients with asthma are not controlled.[8,9]

Although the current level of asthma control can be easily assessed by validated instruments such as the Asthma Control Questionnaire (ACQ),[10] guideline-defined future risk is difficult to assess in clinical practice. In asthma management guidelines, future risk is usually defined as the occurrence of (severe) exacerbations in the (near) future, fixed airflow limitation, and/or side effect of medications.[1,2,3] The main focus has been on identifying which patient characteristics increase the likelihood of experiencing a future exacerbation.[8,11,12] Predictive factors that have been identified include smoking, lower socioeconomic status, poor medication adherence, comorbidities, and race.

The development of fixed airflow limitation is hard to predict, especially at regular structured review visits in primary care. However, it is associated with long-term uncontrolled asthma, which can be monitored.[13] For this reason, guideline-defined future risk should not only involve the occurrence of exacerbations but also incorporate the risk domain of uncontrolled asthma. Specifically predicting the occurrence of side effects might be possible, but it will be highly correlated to medication dosage.[14,15,16] Therefore, reducing the risk of side effects of medications could be accomplished, especially in patients with a low guideline-defined future risk, by safely downtitrating medication. Therefore, we aimed to analyze which patient characteristics predict guideline-defined future risk, defined as a combination of exacerbations and uncontrolled asthma, and create a prediction model on the basis of these outcomes defining patients as having a low, medium, or high risk.

In addition, several studies of long-term outcomes suggest that whether controlled asthma will be achieved may already be judged at a 3-month review.[17,18] Therefore, we believe that adding an assessment of early treatment response after 3 months of

treatment aids in the prediction of guideline-defined future risk.

Overall, the aim of this study was to develop, and externally validate, an easy-to-use prediction model enabling clinicians to identify patients with an increased guideline-defined future risk, based on patient characteristics and early treatment response.

METHODS

Study design

We analyzed potential predictors of guideline-defined future risk, described as level of asthma control and the occurrence of exacerbations, using data from 2 previous studies. The derivation data set was obtained from a pragmatic cluster-randomized controlled trial comparing 3 asthma management strategies in primary care. We analyzed data of only the 2 strategies that aimed at the same treatment goal, controlled asthma. The third strategy aimed at partly controlled asthma, and was therefore excluded. Patients' first assessment originated from 87 general practices in the areas of Leiden, Nijmegen, and Amsterdam from June 2009 until 2010. A detailed description of study procedures and participants of the randomized controlled trial has been published elsewhere.[18,19] The validation data set was obtained from another randomized controlled trial in primary care, aiming at achieving controlled asthma. In this study, 37 general practices in the Leiden and the Hague area participated, and the Outpatient Clinic of the Department of Pulmonology at the Leiden University Medical Centre recruited from September 2005 to September 2006.[17] In both studies, clinicians provided treatment according to the principle of stepped-care, based on (inter)national evidence-based treatment guidelines, supported by an internet-based decision support tool (see this article's Online Repository at www.jaci-inpractice.org). To our knowledge, there was no overlap in general practices or patients between both data sets.

Study population

In the derivation cohort, patients were aged 18 to 50 years, with a diagnosis of asthma and prescribed inhaled corticosteroids. Follow-up was 12 months and patients filled out online questionnaires at approximately 3-month intervals. We limited our selection to patients with a complete ACQ score at 12 months, and we excluded patients if no data were available at either baseline, 3 months, or 12-month follow-up. For the validation cohort, the same inclusion criteria and follow-up intervals applied.

Outcome

Our primary outcome of interest was guideline-defined future risk. We classified patients as having an increased level of future risk if patients experienced uncontrolled asthma at 12 months, defined as an ACQ score of greater than or equal to 1.5,[13] or if they experienced at least 1 severe asthma exacerbation during the final 6 months of the trial.

Potential predictors

Demographic and clinical variables that potentially predict guideline-defined future risk were obtained at baseline including age, sex, body mass index, previous smoking, age of asthma onset, level of education, having a pet, symptoms of allergy, allergic rhinitis, and fractional exhaled nitric oxide (Feno) concentration.[1,2,3,12,20] At baseline and every 3 months, current smoking status was updated, lung function was measured by spirometry (prebronchodilator absolute FEV1), the level of asthma control with the 6-item ACQ, and quality of life with the Asthma-related Quality of Life Questionnaire (AQLQ). In addition, current medication usage was assessed by the practice nurse and medication adherence with the Medication Adherence Report Scale (MARS) as a potential predictor. The results obtained 3 months after the baseline visit were used as a measure of early treatment response. A severe asthma exacerbation was defined as a course of oral prednisolone prescribed for worsening asthma for 3 or more days, or an emergency department visit/hospitalization due to asthma.[21] At baseline, the occurrence of at least 1 severe exacerbation over the previous year was assessed. Experiencing an exacerbation within the first 3 months after the baseline visit was also assessed as a potential measure of early treatment response.

Model development

With logistic regression we studied the association between guideline-defined future risk and baseline characteristics plus information on early treatment response. Baseline variables univariably associated with future risk ($P < .10$) were selected for multivariable logistic regression, and then backward selection was performed ($P < .10$). The final selection of variables with comparable predictive properties was based on clinical feasibility. Second, we studied the additional contribution of information on early treatment response by adding variables, assessed at 3 months, to the first model. Performance of all multivariable models was assessed with the area under the receiver-operating curve (AUROC) and for calibration we used the Hosmer-Lemeshow test.[22] The AUROC was internally validated and corrected for optimism using internal bootstrap resampling (2000 bootstrap samples). A correction for optimism is needed because the performance of a model in a derivation data set will be better than the performance of a model in another data set. Based on the regression coefficients

of our final model, a risk prediction score was developed (see Tables E1 and E2 in this article's Online Repository at www.jaci-inpractice.org) and risk categories were established, to facilitate clinical application of the model.[23] Cutoffs were based on absolute risks, as mentioned in previous literature, approximately 10% in the low-risk category and 48% in the high-risk category.[24]

Model external validation

We applied our risk prediction model, obtained from the derivation data set, to the validation data set (n = 195) and calculated the AUROC. Furthermore, we computed the absolute risk for patients, per risk prediction score.

Sensitivity analysis

First, as a sensitivity analysis we compared our results to solely using the ACQ to decide whether and how to adjust treatment, which is proposed as an interpretation of current clinical practice. Second, we performed the same statistical analysis as described, for solely an ACQ score of 1.5 or more or at 12 months as outcome measure, and for solely the experience of at least 1 severe asthma exacerbation during the final 6 months of the trial. As a third sensitivity analysis, we compared results on self-reported questionnaires at baseline (MARS, ACQ, and AQLQ), between participants from this study and people who were excluded.

For analyses, STATA statistical software version 14 (Statacorp, College Station, Texas) and SPSS version 20.0 for Windows (SPSS Inc, Chicago, III) were used.

RESULTS

Baseline characteristics

The derivation data set consisted of 304 patients (Figure 1), of which 83 (27.3%) experienced an event at 12 months, 52 scored above 1.5 on the ACQ, 19 experienced a severe exacerbation, and 12 had both events. Demographic and clinical patient characteristics (Table I) demonstrated a study population with a mean age of 40.2 ± 8.5 years and 69.0% being women. The mean score for the baseline ACQ was 0.93 ± 0.74, and the mean baseline AQLQ score was 5.87 ± 0.88. The validation data set consisted of 195 patients with a mean age of 36.3 ± 8.6 years and 69.0% being women. The baseline ACQ had a mean score of 1.09 ± 0.72, and the mean baseline AQLQ score was 5.77 ± 0.81.

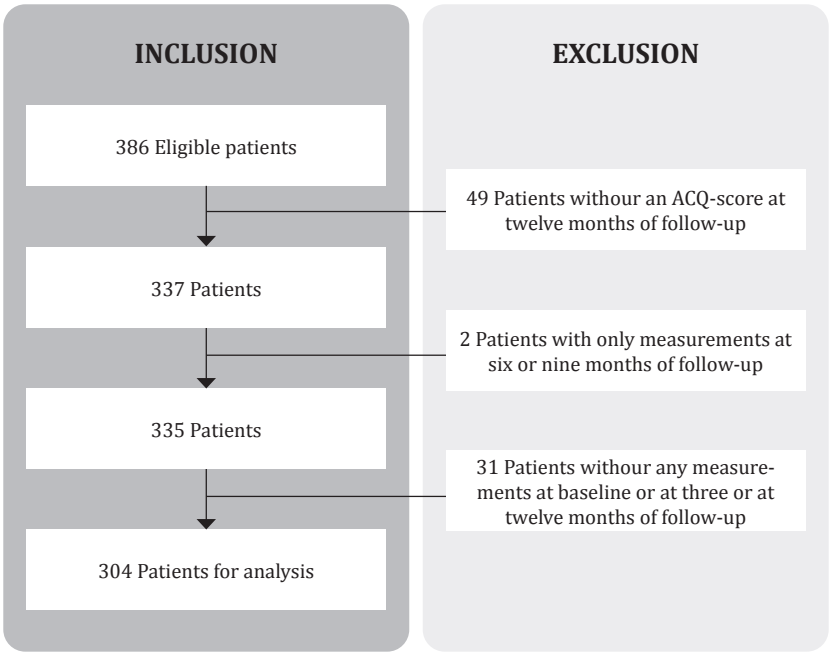

FIGURE 1. *Flowchart of inclusion and exclusion of patients with a diagnosis of asthma in the derivation data set. In the validation cohort, only 5 patients were excluded without any measurement at baseline, or at 3 or 12 months of follow-up. ACQ = Asthma Control Questionnaire.*

TABLE 1. *Baseline characteristics of patients in the derivation dataset (n = 304) and the validation dataset (n = 195). For continuous variables; values are stated as the mean (standard deviation). For categorical variables; values are numbers (percentages).*

	Derivation dataset	**Validation dataset**
Continuous variables		
Age years	40.2 (8.5)	36.3 (8.6)
Age of onset years	21.7 (14.9)	not available**
Body mass index kg/m^2	25.8 (5.0)	not available**
FEV_1	3.25 (0.87)	3.12 (0.76)
Fe_{NO}	24.1 (20.7)	29.5 (29.5)
ACQ score	0.93 (0.74)	1.09 (0.72)
AQLQ	5.87 (0.88)	5.77 (0.81)
Categorical variables		
Female sex	210 (69.1)	136 (69.7)
Current smokers	40 (13.2)	24 (12.3)
Previous smokers	127 (41.8)	62 (31.8)
Severe exacerbation(s) in the previous year	98 (32.2)	24 (12.3)*

* Exacerbation(s) in the previous six months.
** These variables were not assessed in the original trial of the validation data set.
FEV_1 = Forced Expiratory Volume in one second. Fe_{NO} = Fractional exhaled nitric oxide.
ACQ = Asthma Control Questionnaire. AQLQ = Asthma Quality of Life Questionnaire.

Model development

The results of our univariable analyses are presented in Table II. An increase of half a point on the baseline ACQ (defined as the clinically meaningful minimal important difference) resulted in an odds ratio (OR) of 1.87 (95% CI, 1.53-2.28) for guideline-defined future risk to be present. Compared with men, women had an OR of 2.34 (95% CI, 1.27-4.30) and FEV1 an OR of 0.63 (95% CI, 0.45-0.88) per additional liter, and no association was found for Feno concentration. The occurrence of at least 1 severe exacerbation in the previous year showed an OR of 3.17 (95% CI, 1.86-5.39).

TABLE 2. *Univariable odds ratios (95% confidence interval) and corresponding p-values in the derivation dataset.**

Continuous variables	**Odds ratio (CI95%)**	**p-value**
Age years	1.01 (0.98-1.04)	0.41
Age of onset years	1.00 (0.99-1.02)	0.77
Body mass index kg/m^2	1.02 (0.98-1.08)	0.35
FEV_1	0.63 (0.45-0.88)	< 0.01
Fe_{NO}	0.99 (0.97-1.01)	0.19
ACQ-score per 0.5	1.87 (1.53-2.28)	< 0.001
AQLQ per 0.5	0.60 (0.50-0.71)	< 0.001
MARS	0.70 (0.45-1.09)	.12
Categorical variables		
Female sex	2.34 (1.27-4.30)	< 0.01
Current smokers	1.92 (0.96-3.83)	0.06
Previous smokers	1.34 (0.80-2.23)	0.27
Symptoms of allergy	0.99 (0.53-1.84)	0.99
Allergic rhinitis	1.47 (0.74-2.92)	0.26
Having a pet	1.14 (0.68-1.91)	0.62
Severe exacerbation(s) in the previous year	3.17 (1.86-5.39)	< 0.001
Level of education		.47
Low	1.00	
Medium	0.76 (0.38-1.52)	
High	0.64 (0.32-1.29)	
Beclomethasone equivalent dose in ?g		.08
Low (0-400)	1.00	
Medium (400-800)	1.38 (0.66-2.89)	
High (>800)	1.95 (1.07-3.56)	

* Measurements that showed no (significant) univariable association are not presented in this table. These include the MARS questionnaire, allergic symptoms, allergic rhinitis, having a pet, current medication use and level of education. FEV_1 = Forced Expiratory Volume in one second. Fe_{NO} = Fractional exhaled nitric oxide. ACQ = Asthma Control Questionnaire. AQLQ = Asthma Quality of Life Questionnaire.

As shown in Table III, the variables selected in the first multivariable model, with only baseline predictors, were sex, current smoking status, the ACQ score and the

occurrence of an exacerbation in the previous year. The corresponding AUROC was 0.78 (95% CI, 0.72-0.84), and the Hosmer-Lemeshow test yielded no indication of poor fit (P = .45). In the second model, when information on early treatment response was added and current smoking status was updated, the AUROC increased to 0.84 (95% CI, 0.79-0.89), and there was no indication of poor fit (Hosmer-Lemeshow test P = .32); for the calibration plots, see Figure E1 in this article's Online Repository at www.jaci-inpractice.org. Internal validation yielded a correction for optimism of 0.01 decrease in both AUROCs. Final measurements on early treatment response included the first follow-up ACQ assessment with an OR of 1.93 (95% CI, 1.49-2.51) and the occurrence of an exacerbation in the initial 3 months of treatment (OR = 6.40; 95% CI, 1.36-30.06).

TABLE 3. *Multivariable odds ratios (95% confidence interval) and corresponding p-values in the derivation dataset; at baseline (AUROC of 0.78 (CI95% 0.72-0.84)) and after three months of treatment at follow-up (AUROC of 0.84 (CI95% 0.79-0.89).*

	Baseline (last visit)		**Follow-up (current visit)**	
Continuous variables	**Odds ratio (CI95%)**	**p-value**	**Odds ratio (CI95%)**	**p-value**
ACQ score per 0.5, baseline	1.74 (1.41-2.14)	< 0.001	1.27 (0.98-1.63)	0.07
ACQ score per 0.5, after three months as measure of early treatment response	-		1.93 (1.49-2.51)	<0.001
Categorical variables				
Women	2.05 (1.06-3.98)	0.03	2.03 (0.97-4.27)	0.06
Current smokers	1.49 (0.64-3.43)	0.35	1.27 (0.49-3.30)	0.62
Exacerbation(s) in the previous year at baseline	2.45 (1.37-4.38)	< 0.01	2.43 (1.27-4.64)	< 0.01
Exacerbation(s) in the previous three months as measure of early treatment response	-		6.40 (1.36-30.06)	0.02

. ACQ = Asthma Control Questionnaire.

Table IV presents the risk prediction scores corresponding to the second model, with higher scores indicating a higher future risk of uncontrolled asthma and/or exacerbations (see Tables E1 and E2). We established 3 risk categories: low (ranging from 0-4), intermediate (ranging from 5-8), and high (ranging from 9-16). The absolute risk for the low-risk category was 11.7%, for the intermediate-risk category 47.0%, and for the high-risk category 72.7%. In the derivation data set, 64.2% of patients were classified as having a low risk, 23.6% as having an intermediate risk, and 12.2% as having a high risk.

Figure 2a and 2b plot the absolute risk of patients having a guideline-defined future risk per risk prediction score.

TABLE 4. *Construction of the asthma risk prediction score. A total score ranging from 0 to 4 is classified as low level of future risk (11.7%), a total score ranging from 5 to 8 as intermediate level of future risk (47.0%), and a total score ranging from 9 to 16 is classified as high level of future risk (72.7%). The risk prediction score is assessed on the basis of 2 points in time: current visit and visit ~3 months previously.*

Factor	Points
Current visit	
Current smoking	
No	0
Yes	1
Sex	
Men	0
Women	1
ACQ-6 score	
< 0.75	0
0.75-1.50	2
> 1.50	6
Exacerbation(s) since the previous visit (±three months)	
No	0
Yes	4
Previous visit	
ACQ-6 score	
< 0.75	0
0.75-1.50	1
> 1.50	2
Exacerbation(s) in the previous year	
No	0
Yes	2
Total score (range)	**0-16**

ACQ = Asthma Control Questionnaire.

Model external validation

In the validation data set, the risk prediction model, including early treatment response, showed a discriminative AUROC of 0.77 (95% CI, 0.68-0.86), whereas the baseline risk prediction model showed an AUROC of 0.72 (95% CI, 0.64-0.81). The absolute risks per category were, respectively, 14.5%, 33.3%, and 68.0%. Furthermore, 66.7% of patients were classified as having a low risk, 19.4% as having an intermediate risk, and 13.9% as having a high risk.

Sensitivity analysis

First sensitivity analysis, with the use of solely the ACQ as a predictor, resulted in an AUROC of 0.73 (95% CI, 0.66-0.80); see Figure E2 in this article's Online Repository at www.jaci-inpractice.org. Second sensitivity analysis, with solely an ACQ score of greater than or equal to 1.5 as an outcome measure with the developed model, resulted

in an AUROC of 0.87 (95% CI, 0.81-0.90), and with solely the experience of at least 1 severe exacerbation in an AUROC of 0.76 (95% CI, 0.67-0.85). Also, for both outcome measures, we performed the same statistical analysis as for our combined measure; see Table E3 and Table E4, in this article's Online Repository at www.jaci-inpractice.org. Third sensitivity analysis showed no significant difference between included and excluded people: ACQ (0.12; 95% CI, −0.07 to 0.31), AQLQ (−0.13; 95% CI, −0.36 to 0.09), and MARS (−0.03; 95% CI, −0.17 to 0.11).

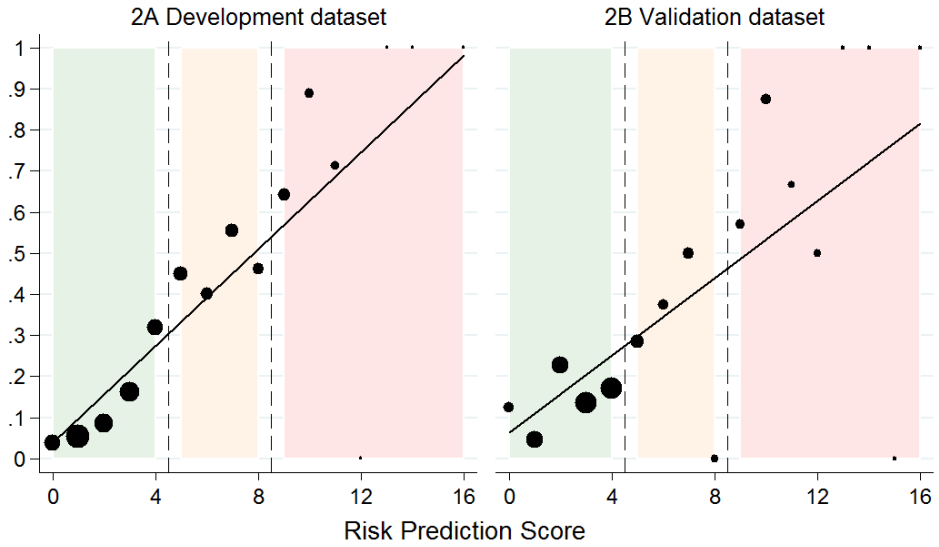

FIGURE 2. *The risk prediction score is on the x-axis, and the absolute risk in the data set is on the y-axis: derivation data set (A) and validation data set (B). Circles represent the number of patients; the larger the circle, the more patients with the same risk prediction score. The green area represents the low-risk category (11.7%), followed by the orange intermediate-risk category (47%) and on the right side the high-risk category (72.7%) as the red area. A regression line was fitted; the absolute risk increases with the increasing risk prediction score (derivation data set, 0.0602x – 0.0259; validation data set 0.047x + 0.017).*

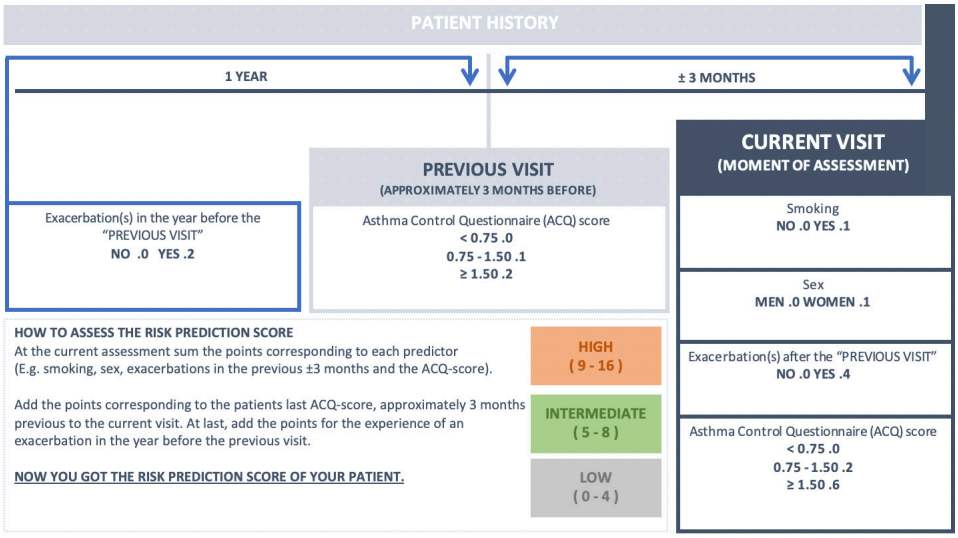

FIGURE 3. *The risk prediction score in clinical practice: simplified users guide. ACQ = Asthma Control Questionnaire.*

DISCUSSION

We developed and externally validated a clinical prediction tool that provides clinicians with an easy-to-use risk prediction score that quantifies both the level of current asthma control and guideline-defined future risk of uncontrolled asthma or exacerbations, by assessing 6 easily accessible variables. Furthermore, including measures of early treatment response improved the predictive properties.

Comparisons with literature

Our study is in line with current asthma management guidelines, focusing on current control and future risk.[1,2,3] In contrast to most studies, our study not only defined future risk by whether or not a severe exacerbation occurs, but we also included the future level of asthma control.[25,26] In clinical practice this is an important addition, because these are patients who should be assessed more regularly. Therefore, a clinical prediction model that combines these outcomes is clinically more relevant than those capturing exacerbations solely.[12] In our study, the derivation data set consisted of 304 patients, of which 83 experienced an event at 12 months; 14% of the patients with an event experienced both a severe asthma exacerbation and scored above 1.5 on the ACQ. Furthermore, 63% solely scored above 1.5 on the ACQ and 23% experienced solely a severe asthma exacerbation; the incidence of events is in line with previous studies (see

Table E3 and Table E4).

In our model we included, at first, the level of asthma control (ACQ score), current smoking status, the occurrence of severe exacerbations in the previous year, and sex, with the ACQ score and the occurrence of severe exacerbations in the previous year as the strongest predictors. This is in line with several other longitudinal studies assessing prediction of future risk.[10,27,28,29,30] Also, an increased future risk for women was found in several other studies; a possible explanation is that women tend to have late onset of asthma, which is a subgroup with more severe asthma.[31,32,33,34]

In our study, we have added predictors representing early treatment response and updated current smoking status; only a few other studies have assessed the change in asthma control over time as a predictor.[35,36] Comparable to our results, those studies showed that this change does indeed predict future risk. An increase of 1 point over 2 weeks on the ACQ increased the risk of an exacerbation by 50% the following 2 weeks.[35] Bateman et al[36] reviewed several studies and showed that the better the level of asthma control, the lower the risk of uncontrolled asthma for the following week; furthermore, the probability of an exacerbation was related to current state of control. Blakey et al[30] found that a combination of 16 predictors gave a similar AUC score as ours (AUROC, 0.87; 95% CI, 0.86-0.87). These included nasal polyps and blood eosinophilia, which are not easily assessed in primary care. Recently, Loymans et al[15] predicted the occurrence of future exacerbations on the basis of patient characteristics in the same data set. Compared with that study we changed the outcome to guideline-defined future risk and added early treatment effect. These changes resulted in an AUROC of 0.84 (95% CI, 0.79-0.89), compared with the AUROC of 0.80 (95% CI, 0.78-0.81) in the study of Loymans et al.

For this study, we assessed early treatment response after approximately 3 months, which is comparable to findings of earlier studies.[10,17,18] Those studies showed that, for the mainstay of patients, analyzing treatment response after the first 3 months will show whether they are on track toward controlled asthma. By using our analysis, we singled out those patients who are not on track. Specifically targeting individuals who appear to be off track greatly improves efficiency of asthma management. We included the occurrence of an exacerbation in the previous 3 months of treatment as an outcome of early treatment response, despite the large upper bound. In our development data set only few patients (n = 15) experienced a severe exacerbation during the specified period; however, because of the clinical importance, we included this predictor in our final risk model.

In sensitivity analysis, we compared our results to solely the use of the ACQ. We are aware that the ACQ does not cover the entire aspect of monitoring a patient in clinical practice. However, it is as close to current practice as possible.

Strengths and weaknesses

The heterogeneous and relatively large study population is a strength of this study, with a variety in baseline characteristics including the degree of asthma control and with limited use of exclusion criteria. Therefore, the study population is representative for the population in general practice. Our study is strengthened by external validation of our developed risk prediction score, which showed an AUROC of 0.77. Furthermore, by adding the ACQ as a predictor in our model, it is possible for the clinician to estimate the current level of control and the level of guideline-defined future risk, all within the same risk model. Eight or less potential predictors were considered at the same time; with 83 patients classified as having an increased future risk, we fulfil the criterion of a minimum of 10 events per variable for prediction research.[37] Although also mentioned as a strength of our study, the ACQ is as yet not routinely used in primary care, because other questionnaires are also available; so it is simultaneously a limitation. However, we assume that the result would not differ greatly from other asthma symptom scores, because outcomes are correlated.[38,39] A second limitation of our study could be the exclusion of patients without an ACQ assessment at 12 months and patients without complete data at either baseline, 3 months, or 12 months of follow-up. Potentially, included patients have a better adherence, because they adhere more to study requirements as well, which would result in selection. However, because of the heterogeneity of the study population, it is not likely to be the case here. In addition, we compared results of a questionnaire on self-reported adherence between participants from this study and people who were excluded and results were similar: mean difference, −0.03 (95% CI, −0.17 to 0.11). However, overall patients willing to participate in a clinical trial may be more compliant. In this study, we added the MARS questionnaire on adherence and this showed no association. Potentially, patients might not have been completely honest about adherence, but asking them is the best we can do in current clinical practice. A third limitation is the choice of cutoff values at approximately 10% and 48% absolute risk of experiencing uncontrolled asthma or exacerbations in the future. Evidence regarding appropriate cutoff values is scarce, and these are the only cutoffs suggested by previous literature.[24] However, because treating physicians might want to apply more or less strict criteria, we have supplied an overview of absolute risks per risk prediction score (see Table E2).

Another limitation is the use of baseline predictors in combination with measurements

of early treatment response after approximately 3 months of treatment, and thereby the delayed risk estimation in clinical practice. However, it is possible to estimate the risk prediction score at one moment in time if there is a known history of ACQ scores and occurrence of exacerbations. To promote, and simplify, the use of the risk prediction score, we developed an online application (see Online Risk Prediction Tool, in this article's Online Repository at www.jaci-inpractice.org).

From previous literature, we know that in general practice up to a third of patients might not be properly diagnosed.[40] The risk prediction score is developed and externally validated in samples representing the population in general practice, so it might have been influenced by wrongly diagnosed patients. However, the problems with physician-diagnosed asthma have not yet been resolved in general practice, so our sample is valid, although of course it would be preferable if diagnosis was more precise. For the application of the risk prediction score in another population, it should be external validated separately.

Clinical interpretation

The developed risk model should be used alongside other important components of a structured asthma review; for example, inhaler technique, adherence, and patient education. The risk prediction score provides the clinician, and patients, with a clear estimate for the guideline-defined future risk; it includes information on the level of asthma control and on treatment response (Figure 3). With the inclusion of early treatment response in the model, a review of effectiveness of treatment is included, thereby minimizing exposure to ineffective treatment. Because a clinician is always short on time, an easy-to-obtain risk prediction score requiring no additional measurements other than questions is quite helpful. Also, especially in general practice, it is useful to know which patients have a high risk; our risk prediction score classifies 57.7% of the patients as having a low risk. These patients could be safely assessed less frequently or, for example, could safely be reviewed by the practice nurse. This allows the clinician more time for an extensive review and medication changes, in the smaller subgroup of patients in the highest risk category.[41,42,43]

Furthermore, we defined the guideline-defined future risk as a combination of exacerbations and uncontrolled asthma, where asthma symptom control is an important outcome for patients themselves. Both outcomes may need different treatment approaches. However, with the risk prediction score we classify patients, and it is up to the clinician to decide on treatment approach, especially in high-risk patients.

CONCLUSION

We developed and externally validated a clinical tool that provides clinicians with 6 easy accessible parameters to quantify guideline-defined future risk, including the assessment of current level of asthma control as a parameter.

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ONLINE SUPPLEMENT APPENDIX 1

SUPPLEMENT TABLE 1. *Based on the regression coefficients of our final model the risk prediction score was developed.*[23]

Variable	Beta	Categories	Reference (W)	Beta * ($W-W_{REF}$)	Points†	Rounded points
Sex	0.719	Male	$\mathbf{0}_{REF}$	0	0	0
		Female	1	0.719	1.455	1
Current smokers	0.247	No	$\mathbf{0}_{REF}$	0	0	0
		Yes	1	0.247	0.5	1
Exacerbation(s) in the previous year at baseline	0.887	No	$\mathbf{0}_{REF}$	0	0	0
		Yes	1	0.886	1.796	2
ACQ score per 0.5, baseline	0.471	< 0.75	$\mathbf{0.37}_{REF}$	0	0	0
		0.75 - 1.50	1.13	0.358	0.725	1
		> 1.50	2.50	1.003	2.031	2
Exacerbation(s) in the previous three months at follow-up	1.878	No	$\mathbf{0}_{REF}$	0	0	0
		Yes	1	1.878	3.802	4
ACQ score per 0.5, follow-up	1.314	< 0.75	$\mathbf{0.37}_{REF}$	0	0	0
		0.75 - 1.50	1.13	0.999	2.022	2
		> 1.50	2.50	2.799	5.666	6
Intercept	-3.714					

† Constant B = 0.494

Variable. The remaining variables of the risk prediction model.

Beta. The regression coefficients corresponding to the variables.

Categories. Variables are categorized into meaningful categories.

Reference (W). The reference value for each category was determined; for the ACQ -score we used the midpoint of each category (range 1st to 90th percentile). Furthermore, we determined the base category for each variable, for the referent ($_{REF}$) profile, with the lowest expected risk.

Beta * ($W-W_{REF}$). We determined how far each category is from the base category in regression units; multiplying the beta by the difference between reference value for the specific category and the reference value for the base category.

Points. In order to compute the risk prediction points, we had to set a constant B for the point system, or the number of regression units that will correspond to one point. We set the constant as the smallest beta (current smokers) and multiplied it by two; we multiplied the constant by two in order to keep the total risk prediction score in a feasible range without loss of accuracy. Points were computed by (*Beta * ($W-W_{REF}$)) * constant B*.

Rounded. Risk prediction points were rounded to the nearest integer.

SUPPLEMENT TABLE 2. *Risk prediction score*

The risk prediction score and the associated guideline-define risk estimate is computed by the following formula:[23]

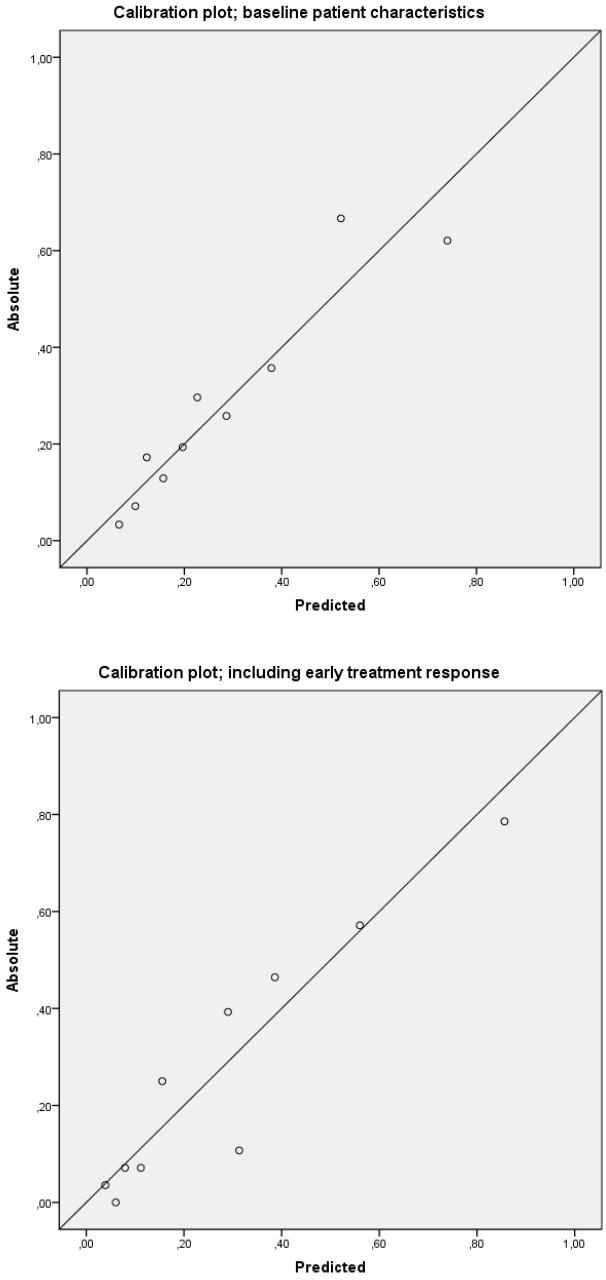
$$\hat{p} = \frac{1}{1 + \exp\left(-\sum_{i=0}^{P} \beta_i X_i\right)}$$

Risk prediction score	Future risk estimate	No future risk in derivation dataset	Future risk in derivation dataset	Absolute risk of future risk based on the derivation dataset
1	0.045	3	0	0
2	0.072	32	1	0.03
3	0.112	51	4	0.073
4	0.172	27	4	0.129
5	0.254	34	5	0.128
6	0.358	14	9	0.391
7	0.478	11	9	0.45
8	0.600	8	6	0.429
9	0.711	6	10	0.625
10	0.801	8	9	0.529
11	0.868	4	9	0.692
12	0.915	2	4	0.667
13	0.947	2	4	0.667
14	0.967	0	1	1
15	0.979	0	1	1
16	0.987	0	1	1

Risk prediction category	Risk prediction score	No future risk in derivation dataset	Future risk in derivation dataset	Absolute risk of future risk based on the derivation dataset
Low	≤ 4	144	14	0.089
Intermediate	5 - 8	39	34	0.466
High	≥ 9	16	29	0.644

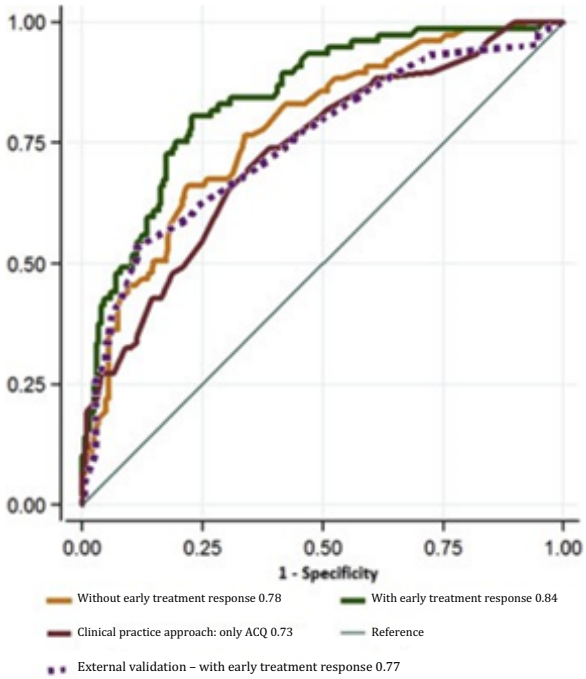
N = 279; complete cases in the derivation dataset.

APPENDIX 2



SUPPLEMENT FIGURE 1. *Calibration plots in the derivation dataset.*

APPENDIX 3



SUPPLEMENT FIGURE 2. *AUROC comparing the models with and without early treatment response to the approach of clinical practice (in the derivation data set). The model with early treatment response differs significantly from the model without early treatment response (P < .01) and from the model representing clinical practice approach (P < .001).*

APPENDIX 4

Sensitivity analysis.

According to asthma management guidelines, clinicians should assess the current level of asthma control alongside the level of guideline-defined future risk of adverse outcomes, while taking into account individual patient characteristics. In practice, it can be difficult to combine all these separate assessments into a single treatment advice, especially if outcomes point to different directions (eg, a patient can have poor asthma control but rarely exacerbate). Therefore, it would be relevant to make a single combined assessment of both current control and risk of future uncontrolled asthma and exacerbations. For this study, we classified patients as having an increased level of future risk if patients experienced uncontrolled asthma at 12 months, defined as an ACQ score of 1.5 or more, or if they experienced at least 1 severe asthma exacerbation during the final 6 months of the trial. A severe asthma exacerbation was defined as a course of oral prednisolone prescribed for worsening asthma for 3 or more days, or an emergency department visit/hospitalization due to asthma.E4

In this Online Repository, we report 2 prediction models for the 2 outcomes, uncontrolled asthma and exacerbations, separately. We performed exactly the same statistical analyses as described in the article, but for solely an ACQ score of 1.5 or more at 12 months as outcome measure, and for solely the experience of at least 1 severe asthma exacerbation during the final 6 months of the trial. The results of all models (models including information on early treatment response) can be found in Table E3 and Table E4.

Furthermore, we assessed model performance (AUROC) of our developed model for the separate outcome measures. For an ACQ score of 1.5 or more at 12 months, the AUROC was 0.87 (95% CI, 0.81-0.90) and for the experience of at least 1 severe asthma exacerbation during the final 6 months of the trial, the AUROC was 0.76 (95% CI, 0.67-0.85).

TABLE 1A. *Multivariable odds ratios (95% confidence interval) and corresponding p-values for different outcome measures, at baseline. Our combined outcome measure with an ACQ score ≥ 1.5 after twelve months, or if they experienced at least one severe asthma exacerbation during the final six months of the trial (AUROC 0.84 (CI95% 0.79 - 0.89). Solely an ACQ score ≥ 1.5 after twelve months as an outcome measure (AUROC 0.84 (CI95% 0.79 - 0.89). Solely the experience of at least one severe asthma exacerbation during the final six months of the trial (AUROC 0.85 (CI95% 0.79 - 0.91).*

	Combined		**Solely ACQ**		**Solely Exacerbations**	
Continuous variables	**Odds ratio (CI95%)**	**p-value**	**Odds ratio (CI95%)**	**p-value**	**Odds ratio (CI95%)**	**p-value**
ACQ score per 0.5, baseline	1.74 (0.41 - 2.14)	< 0.001	1.87 (1.49 - 2.35)	< 0.001	1.35 (0.97 - 1.89)	0.08
ACQ score per 0.5, early treatment response (±3 months)	-		-		-	
Peak flow, early treatment response (±3 months)	-		-		-	
Categorical variables						
Women	2.05 (1.06 - 3.98)	0.03	3.59 (1.54 - 8.33)	0.06	-	
Current smokers	1.49 (0.64 - 3.43)	0.35	2.03 (0.84 - 4.93)	0.12	-	
Rhinitis	-		-		8.23 (1.04 - 65.16)	0.05
Exacerbation(s) in the previous year at baseline	2.45 (1.37 - 4.38)	< 0.01	2.06 (1.07 - 3.96)	0.03	3.05 (1.05 - 8.84)	0.04
Exacerbation(s) in the previous three months as measure of early treatment response	-		-		-	
Beclomethasone equivalent dose in mcg						0.66
Low (0-400)	-		-		1.00	
Medium (400-800)	-		-		4.47 (0.43 - 46.79)	
High (>800)	-		-		11.65 (1.46 - 93.18)	
AUROC	**0.78 (0.72 - 0.84)**		**0.81 (0.76 - 0.87)**		**0.84 (0.74 - 0.94)**	

TABLE 1B. *Multivariable odds ratios (95% confidence interval) and corresponding p-values for different outcome measures, after approximately three months of treatment. Our model with the combined outcome measure, with an ACQ score ≥ 1.5 after twelve months, or if they experienced at least one severe asthma exacerbation during the final six months of the trial, had an AUROC of 0.84 (CI95% 0.79 - 0.89). The model with for solely an ACQ score ≥ 1.5 after twelve months as an outcome measure had an AUROC of 0.84 (CI95% 0.79 - 0.89), and the model with solely the experience of at least one severe asthma exacerbation during the final six months of the trial as an outcome measure had an AUROC of 0.85 (CI95% 0.79 - 0.91).*

	Combined		**Solely ACQ**		**Solely Exacerbations**	
Continuous variables	**Odds ratio (CI95%)**	**p-value**	**Odds ratio (CI95%)**	**p-value**	**Odds ratio (CI95%)**	**p-value**
ACQ score per 0.5, baseline	1.27 (0.98 - 1.63)	0.07	1.27 (0.98 - 4.32)	0.07	1.28 (0.96 - 1.70)	0.09
ACQ score per 0.5, early treatment response (±3 months)	1.93 (1.49 - 2.51)	< 0.001	1.93 (1.49 - 2.51)	< 0.001	1.87 (1.38 - 2.53)	< 0.001
Peak flow, early treatment response (±3 months)	-		-		0.49 (0.29 - 0.81)	< 0.01
Categorical variables						
Women	2.03 (0.97 - 4.27)	0.06	2.05 (0.98 - 4.32)	0.06	-	
Current smokers	1.27 (0.49 - 3.30)	0.62	1.29 (0.48 - 3.42)	0.62	-	
Rhinitis	-		-		2.33 (0.94 - 5.78)	0.07
Exacerbation(s) in the previous year at baseline	2.43 (1.27 - 4.64)	< 0.01	2.43 (1.27 - 4.64)	< 0.01	3.28 (1.47 - 7.30)	< 0.01
Exacerbation(s) in the previous three months as measure of early treatment response	6.40 (1.36 - 30.06)	0.02	6.54 (1.40 - 30.55)	0.02	-	
Beclomethasone equivalent dose in mcg						0.66
Low (0-400)	-		-		1.00	
Medium (400-800)	-		-		1.04 (0.35 - 3.08)	
High (>800)	-		-		1.45 (0.59 - 3.58)	
AUROC	**0.84 (0.79 - 0.89)**		**0.84 (0.79 - 0.89)**		**0.85 (0.79 - 0.91)**	