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Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire

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Summary The 7-item Asthma Control Questionnaire (ACQ) has been validated to measure the goals of asthma management as defined by international guidelines (minimisation of day- and night-time symptoms, activity limitation, β_2-agonist use and bronchoconstriction). Responses are given on a 7-point scale and the overall score is the mean of the responses (0 = totally controlled, 6 = severely uncontrolled). The aim of this analysis was to determine the cut-point on the ACQ that best differentiates between 'well-controlled' and 'not well-controlled' for (a) clinical practice (low risk of missing 'not well-controlled') and (b) clinical trials (low risk of including 'well-controlled'). All 1323 patients who provided data sets at week 12 in the Gaining Optimal Asthma Control (GOAL) clinical trial were included in the analysis. The gold standard for 'well-controlled' was a composite based on the GINA/NIH guidelines and derived from data collected in the clinical trial diaries and clinic records. The analysis showed that the crossover point between 'well-controlled' and 'not well-controlled' is close to 1.00 on the ACQ. However, to be confident that a patient has well-controlled asthma, the optimal cut-point is 0.75 (negative predictive value = 0.85). To be confident that the patient has inadequately controlled asthma, the optimal cut-point is 1.50 (positive predictive value = 0.88). In conclusion, knowledge of these cut-points will enhance practising clinicians ability to identify patients whose asthma requires additional treatment, enable investigators to enroll poorly controlled patients into studies and for both clinicians and investigators to evaluate whether treatment goals are being achieved.

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Introduction

The Asthma Control Questionnaire (ACQ)[1] was developed to measure the primary goals of asthma management as identified by international guidelines.[2–5] All guidelines indicate that to achieve good control, treatment should minimise day- and night-time symptoms, activity limitation, airway narrowing and rescue bronchodilator use and thus reduce the risk of life-threatening exacerbations and long-term morbidity. Three independent studies have provided evidence that the ACQ is valid for measuring asthma control and has strong measurement properties for use both in clinical practice and research.[1,6,7] In addition, the smallest change in score that can be considered clinically important has been determined.[6]

The aim of this analysis was to determine the cut-points on the ACQ that give the best definition between adequate and inadequate control. In clinical practice it is important not to miss patients whose asthma is inadequately controlled whereas in clinical trials investigators usually want to enrol patients with poorly controlled asthma which can benefit from an intervention. Therefore, there cannot be a single cut-point to serve all purposes. In this study, we have used the database generated by the Gaining Optimal Asthma Control (GOAL) clinical trial[8] to determine the probabilities of patients having well- or not well-controlled asthma for different cut-points of the ACQ. Although it is considered most beneficial to use the full 7-item ACQ for clinical practice, shorter 6- and 5-item versions have been validated for use in clinical trials and epidemiological surveys.[6,7,9] In addition, some clinical practices use the shorter versions either because they are unable to measure airway calibre or because some patients do not use an inhaled short-acting β_2-agonist as rescue medication. In this study we have examined whether the cut-points for control are similar in all versions.

Methods

Patients

This analysis was conducted using data collected during the GOAL clinical trial. A full description of the study design and patients has been published elsewhere.[7] In brief 3421 patients, 12–80 years, with uncontrolled asthma were randomised to either to fluticasone propionate or salmeterol/fluticasone for 1 year. Patients with diary, clinic and ACQ data at week 12 post-randomisation were included in this analysis.

Outcome measures

Asthma control questionnaire

Ninety-one asthma clinicians, who were members of international asthma guideline committees,[2–5] participated in the development of the ACQ.[1] They identified the 7 items in the questionnaires as being the most important for determining the adequacy of asthma control. Patients are asked to recall their experiences during the previous week and to respond to the first 6 questions (night-time waking, symptoms on waking, activity limitation, shortness of breath, wheeze and rescue short-acting β_2-agonist use) on a 7-point scale (0 = no impairment; 6 = maximum impairment). Clinic staff score FEV_1% predicted pre-bronchodilator on a similar 7-point scale. The items are equally weighted and the ACQ score is the mean of the 7 items and therefore between 0 (totally controlled) and 6 (severely uncontrolled). The ACQ has been validated and has strong measurement properties for use in both clinical practice and clinical trials.[1,6,7]

Data for the gold standard

In a daily diary, patients scored the severity of day-time and night-time asthma symptoms (0 = none, 5 = severe), amount of night-time awakening, daily rescue β_2-agonist use and morning peak expiratory flow (PEF) rates. The clinic form recorded whether patients experienced treatment-related adverse events, exacerbations requiring oral corticosteroid, emergency department visits and hospitalisation.

Analysis

Gold standard

Patients who provided diary and clinic data at week 12 were categorised as having either 'well-controlled' asthma (negative) or 'not well-controlled' asthma (positive) according to the definition shown in Table 1. For patients who provided incomplete diaries, the algorithm shown in Table 1 was used for categorisation. Once patients had been categorised, 2×2 tables were constructed for cut-points of the ACQ at intervals of 0.25. For each cut-point (from 0.25 upwards) the positive and negative predictive values have been calculated. An example of a 2×2 table and the calculation of the predictive values are shown in Fig. 1.

Table 1 Gold standard criteria for defining patients with 'well-controlled' asthma.

2 or more per week of:
(a) $\leqslant$2 days with symptom score $>$1
(b) rescue β_2-agonist use on $\leqslant$2 days and $\leqslant$4 occasions
(c) PEF $\geqslant$80% predicted every day

And all of the following criteria
No night-time awakenings
No exacerbations (need for oral corticosteroids)
No emergency department visits/hospitalisations
No treatment-related adverse events enforcing a change in asthma therapy

Gold standard categorisation for diaries with missing data

Number of days of data available	Classification
$<$7 days complete data+control criteria failed	Not well-controlled
5–6 days complete data+control criteria achieved	Well-controlled
$<$5 days complete data	Excluded

		Asthma Control Gold Standard		
		Positive = Not well-controlled	Negative = Well-controlled	
Asthma Control Questionnaire	Positive ≥1.5	394 a	55 b	Positive predictive value a/a+b = 394/449 =0.88
	Negative <1.5	c 297	d 577	Negative predictive value d/c+d = 577/874 = 0.66

a = true positive ; b = false positive; c = false negative; d = true negative
If a patient has an ACQ score of 1.5 or greater, there is an 88% chance that their asthma is **not** well controlled.
If a patient has an ACQ score of less than 1.5, there is a 66% chance that their asthma is well controlled

Figure 1 Calculation of positive and negative predictive values for ACQ cut point of 1.5.

Positive predictive value (*PPV*): If a patient has a score greater than the cut-point on the ACQ, the PPV is the probability of the patient having 'not well-controlled asthma'.

Negative predictive value (*NPV*): If a patient has a score less than the cut-point on the ACQ, the NPV is the probability of the patient having 'well-controlled asthma'.

Results

At week 12, 1323 patients of the 3421 randomised, provided either complete data or diary/clinic data to which the algorithm for missing gold standard data could be applied. The majority of patients were excluded because, at that time (2000), the ACQ was not yet available in their language.

Positive and negative predictive values for a range of cut-points on the ACQ are shown in Tables 2–4. For all three versions of the ACQ, the crossover point between well-controlled and not well-controlled is close to 1.00. This means that below 1.00 patients are more likely to have well-controlled asthma and above 1.00 they are more likely to have not well-controlled asthma. Concordance at crossover was 0.76–0.77 for all 3 versions and therefore patients with a score close to 1.00 can probably be considered borderline in either direction.

If one is using the ACQ to identify patients whose asthma is well-controlled (i.e. minimal risk of being uncontrolled), a judicious cut-point is 0.75

Table 2 Summary of 2 × 2 tables for the complete ACQ (7 items).

Asthma control questionnaire cut points	Number of true positives (*a*)	Number of false positives (*b*)	Number of false negatives (*c*)	Number of true negatives (*d*)	Positive predictive value	Negative predictive value
0.25	686	522	5	110	0.57	0.96
0.5	665	375	26	257	0.64	0.91
0.75	621	235	70	397	0.73	0.85
1	525	146	166	486	0.78	0.75
1.25	486	107	205	525	0.82	0.72
1.5	394	55	297	577	0.88	0.66
1.75	297	23	394	609	0.93	0.61
2	225	10	466	622	0.96	0.57
2.25	190	8	501	624	0.96	0.55
2.5	125	3	566	629	0.98	0.53

a–*d* = cells of the 2 × 2 tables (see Table 2).

Table 3 Summary of 2 × 2 tables for the ACQ6 (no FEV_1).

Asthma control questionnaire cut points	Number of true positives (*a*)	Number of false positives (*b*)	Number of false negatives (*c*)	Number of true negatives (*d*)	Positive predictive value	Negative predictive value
0.25	676	424	15	208	0.61	0.93
0.5	625	264	66	368	0.7	0.84
0.75	589	193	102	439	0.75	0.81
1	486	102	205	530	0.83	0.72
1.25	429	82	262	550	0.84	0.68
1.5	325	46	366	586	0.87	0.62
1.75	295	25	396	607	0.92	0.61
2	212	11	479	621	0.95	0.56
2.25	171	7	520	625	0.96	0.54
2.5	110	6	581	626	0.94	0.52

Table 4 Summary of 2 × 2 tables for the ACQ5 (no FEV_1 or *bd*).

Asthma control questionnaire cut points	Number of true positives (*a*)	Number of false positives (*b*)	Number of false negatives (*c*)	Number of true negatives (*d*)	Positive predictive value	Negative predictive value
0.25	663	406	28	226	0.62	0.89
0.5	633	320	58	312	0.66	0.84
0.75	595	228	96	404	0.72	0.81
1	474	123	217	509	0.79	0.7
1.25	419	88	272	544	0.83	0.67
1.5	356	70	335	562	0.84	0.63
1.75	305	49	386	583	0.86	0.6
2	217	18	474	614	0.92	0.56
2.25	186	13	505	619	0.93	0.55
2.5	144	10	547	622	0.94	0.53

(NPV = 0.85) (Table 2). This means that if a patient has an ACQ score of 0.75 or less, there is an 85% chance that his/her asthma is well-controlled.

If one is using the ACQ to identify patients whose asthma is not well-controlled (i.e. minimal risk of being well-controlled), a judicious cut-point is 1.50 (PPV = 0.88). This means that if a patient has an ACQ score of 1.50 or greater, there is an 88% chance that his/her asthma is not well-controlled.

Very similar values were observed for the two shortened versions of the ACQ (Tables 3 and 4).

Discussion

This analysis has provided the positive and negative predictive values for a range of cut-points on the 7-point scale of the original ACQ and two shorter versions. These values will enable users of the questionnaire to know whether patients are likely to have either well-controlled or not well-controlled asthma as defined by the GINA guidelines.[10]

In clinical trials, investigators usually want to enrol patients whose asthma is not well-controlled so that there is room for improvement on the trial intervention. Therefore, one wants a cut-point that gives a high PPV (i.e. there is minimal risk of enrolling patients with well-controlled asthma). This means there may be some false negatives (i.e. there are patients who are inadequately controlled who are excluded from the study). If a patient has an ACQ score of 1.50 or greater, there is an 88% chance that his/her asthma is not well-controlled.

When the ACQ is used in clinical practice, we usually want things the other way round. We want to make sure that we do not miss patients whose asthma is not well-controlled. One therefore needs a cut-point that provides a high NPV which means that there is a low risk of false negatives but conversely there will be some false positives (i.e. patients whose asthma is well-controlled but their score suggests not well-controlled). To make sure that most patients with inadequately controlled asthma are not missed, the optimum cut-point is 0.75 where there is an 85% chance that his/her asthma is well-controlled.

Although international guidelines[2–5,10] indicate that the ideal treatment goal in asthma should be 'total control' with patients having no symptoms, no activity limitations, no rescue bronchodilator use and normal airway calibre, a more realistic goal is usually considered to be 'well-controlled' where patients may experience occasional minor impairments but are at minimal risk of exacerbation or long term airway damage. Although there are several definitions of well-controlled, the one chosen for the GOAL study was the one identified by Bateman et al.[11] as being the best to meet these clinical goals. The authors and the other members of the GOAL study committee identified the cut-points on the outcomes collected in the study (diary and clinic record) that should be used to meet this definition.[7] Therefore, a strength of this gold standard was that it was based on objective data rather than clinician impression.

Although a change in score of 0.5 on the ACQ can be considered clinically important,[6] the ultimate goal of management is usually to achieve well-controlled asthma. To be confident that a patient has realised this state, it would be wise to use the lower cut-point of 0.75 where 85% of patients will be well-controlled. At the higher cut-point of 1.50, the probability of having well-controlled asthma is only 66%.

In this study, both the ACQ and the diary/clinic record composite (gold standard) were developed to measure the same construct, asthma control as defined by international guidelines.[2–5,10] However, the correlation between the two instruments, although acceptable for the task, was only modest ($r = 0.76$) and the possible reasons need to be explored. Both instruments include night-time waking, day-time symptoms, rescue bronchodilator use and a measure of airway calibre. However, they differ in that the ACQ includes activity limitation (not in the composite) and the composite includes medication side effects and ER/hospitalisations (not in the ACQ). The ACQ has undergone several validation studies (reliability, responsiveness and construct validity) and shown strong measurement properties,[1,6,9] whereas the composite gold standard is considered valid by definition.

Other possible reasons for the lack of concordance between the two instruments include: (1) noise of measurement (both instruments), (2) different scoring systems: ACQ is the mean of 7 items scored on 7-point interval scale (continuous data): the gold standard is based on the total number of dichotomous events (e.g. no. of days with Sx > 1; no. of days with < 1 puff bd), (3) the ACQ is a clinic questionnaire and the composite used diaries and clinic records, (4) some diaries had missing data and an algorithm was used to estimate control, (5) the ACQ uses FEV_1% predicted (7-point scale) and the composite uses PEF ($\pm$80% predicted).

Although it is important to identify possible weaknesses, it is also important to recognise the strengths of this analysis. There was a very large sample and the majority of patients provided data sets that could be included in the analysis. The gold standard was estimated objectively which is very

important given the recent studies that have shown that clinicians may not be very good at giving a subjective estimate of asthma control.[12,13] Patients represented a wide range of asthma severity and therefore the results can be applied to all patients with asthma. The modest correlation between the two instruments, caused by the limitations mentioned above, will have only have affected the precision of the estimate, they should not have affected the accuracy. Therefore one can have confidence that the actual crossover point is close to 1.00.

In conclusion, knowledge of these cut-points will enable investigators to enroll patients whose asthma is poorly controlled into clinical trials, they will enhance practising clinicians' ability to identify patients whose asthma requires additional treatment and both investigators and clinicians will be able to evaluate the effectiveness of interventions by determining whether patients achieve the threshold of well-controlled asthma.

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