

Predicting future risk of asthma exacerbations using individual conditional probabilities

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Background: Determination of future risk of exacerbations is a key issue in the management of asthma. We previously developed a method to calculate conditional probabilities (π) of future decreases in lung function by using the daily fluctuations in peak expiratory flow (PEF).

Objective: We aimed to extend calculation of π values to individual patients, validated by using electronically recorded data from 2 past clinical trials.

Methods: Twice-daily PEF data were analyzed from 78 patients with severe (study A) and 61 patients with poorly controlled (study B) asthma. For each patient, the π value was calculated from 5000 PEF data points simulated based on the correlation and distribution properties of observed PEF. Given an initial PEF, the π value was defined as the probability of a decrease in PEF to less than 80% of predicted value on 2 consecutive days within a month. These probabilities were then compared with actual occurrences of such events and clinically defined exacerbations within the following month.

Results: π Values were related to actual occurrences of decreases in PEF (adjusted $R^2 > 0.800$ for both studies). Every increase of 10% in π value was associated with an odds ratio of having a future exacerbation of 1.24 (95% CI, 1.07-1.43) for study A and 1.13 (95% CI, 1.02-1.26) for study B, with better sensitivity and specificity than clinic-measured FEV₁.

Conclusion: These results from 2 independent datasets with differing asthmatic populations and differing exacerbation criteria provide support that clinically relevant quantification of individual future risk of exacerbations is possible. (J Allergy Clin Immunol 2011;■■■:■■■-■■■.)

Key words: Peak expiratory flow rate, pulmonary function tests, patient monitoring, risk assessment

Recent guidelines have highlighted the importance of determining future risk of deterioration in the management of asthma.^{1,2} Monitoring strategies exist to assess asthma severity and control, but it is notoriously difficult to predict exacerbation risk.²⁻⁵ The latter is important not only in the quality of life for the patient but also crucially influences treatment strategies. Several studies have identified lung function as an independent predictor of subsequent asthma exacerbations.⁶⁻⁸ However, although current levels of lung function and other measures, such as symptoms, airway hyperresponsiveness, and exhaled nitric oxide, can be assessed during clinic visits, the past values of these measures are often not taken into account or at least assessed in a limited manner. From clinical experience, the general practitioner knows the history of his or her patient and judges the stability of the patient's asthma and exacerbation risk based on past events^{5,9-13}; a complex disease such as asthma follows a dynamic course that relates to both past and current patient status. It is therefore proposed that any concept of asthma control needs to incorporate an assessment of individual patient history, as well as future potential for experiencing poor asthma outcomes.¹ Although assessing asthma control at a single point in time is of some value, multiple measurements of lung function, symptoms, or β_2 -agonist use over time are required to adequately determine asthma control and to more reliably predict future response in clinical trials.¹⁴

Home monitoring of peak expiratory flow (PEF) offers one avenue to obtain multiple observations over time, but studies of PEF variability in the past have yet to produce a clear and clinically relevant parameter that can quantify past history or assess risk of exacerbation.^{15,16} We have previously developed a method that uses daily fluctuations in PEF to calculate conditional probabilities (π) of a future decrease or sudden deterioration in lung function^{17,18} given a patient's current lung function. The daily fluctuations in PEF exhibit fractal-type long-range correlation properties, which implies that there are deterministic components in daily lung function variability that can be used to predict future behavior in a probabilistic manner.¹⁸ However, these predictions were calculated for treatment groups rather than for individual patients.

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Abbreviations used

ICP:	Individual conditional probabilities
PEF:	Peak expiratory flow
%predFEV ₁ :	Percent predicted FEV ₁
%predPEF:	Percent predicted peak expiratory flow
π :	Conditional probabilities
ROC:	Receiver operating characteristic

There is thus far no statistical method that can estimate the risk of exacerbations for individual patients because most risk-assessment strategies have been based on population statistics (eg, increased risk of smokers in comparison with nonsmokers). Medicine is moving toward individualized phenotyping, risk assessment, and treatment strategies, and there is an urgent need for better statistical prediction methods for individual risks.

In this study we introduce and validate a novel method of calculating individual conditional probabilities (ICP) to determine future risk of exacerbation in asthmatic patients using data from 2 past studies in which lung function was monitored electronically.^{19,20}

METHODS

The following represents a summarized version of the methodology. Detailed methods can be found in this article's Online Repository at www.jacionline.org.

Original datasets

In study A¹⁹ 309 adult patients with asthma for 3 or more years and uncontrolled severe asthma for 1 or more years^{21,22} were randomized to receive placebo or different doses of a trial drug for 52 weeks. From weeks 0 to 24, a constant dosage of inhaled corticosteroids with or without oral corticosteroids was maintained. From weeks 24 to 52, downtitration of corticosteroid treatment was attempted. For the present study, twice-daily electronically recorded PEF data (Jaeger AM2+; Viasys Healthcare, Hoechst, Germany) from weeks 0 to 52 of the trial were used from patients in the placebo group who had completed 24 or more weeks and had entered the downtitration phase ($n = 77$).

In study B²⁰ 61 adult patients with poorly controlled asthma²³ were randomized to receive 8 weeks of either 1600 $\mu\text{g}/\text{d}$ or 3200 $\mu\text{g}/\text{d}$ budesonide treatment, followed by 8 weeks of 1600 $\mu\text{g}/\text{d}$ and 14 months of downtitration. For the present study, twice-daily electronically recorded PEF data (MicroMedical DiaryCard, Rochester, United Kingdom) from weeks 0 to 72 of the trial were used from all patients who had completed 16 or more weeks ($n = 58$).

Details of both studies have been published previously,^{19,20} and they were approved by the relevant ethics committees.

Calculation of conditional probabilities

Briefly, of the original time series (Fig 1, A), the first 64 days of PEF data served as a reference observation period (Fig 1, B) for each patient. A PEF quality control criterion was used whereby patients with 10% or more data missing from the completed monitoring period were excluded from the main analyses. Fluctuation analysis was performed as previously described^{18,24} to obtain the time correlation properties of PEF from this period. The distribution properties of PEF (mean, SD, and skewness) were also calculated. Both properties were subsequently used to simulate a new time series of 5,000 PEF data points for each patient with the same correlation and distribution properties as the original data (Fig 1, C). This was done as previously described^{17,18} but based on data from each patient.

Next the simulated data were used to calculate π values; given an initial percent predicted PEF (%predPEF), the π value was defined as the

probability of encountering a decrease in PEF to less than a set threshold of 80% on 2 consecutive days within 30 days calculated over multiple overlapping windows moved progressively over the simulated data.¹⁸ The end point of this procedure is a reference curve (Fig 1, D) relating π values to initial %predPEF for each patient, which predicts the probability of a lung function decrease within 30 days as a function of the initial %predPEF on the first day of that period.

Calculation of actual events of PEF decrease

A testing window of 30 days after the 64-day observation period in the original PEF data was used to validate the predictive ability of the calculated π values (Fig 2, A). Here the initial %predPEF was determined, and the corresponding π value was obtained from the reference curve previously calculated for that patient (Fig 2, B). This π value was then compared with the number and occurrence of actual events of decrease in %predPEF to less than the threshold within the future testing window (Fig 2, C).

The above calculations were repeated for multiple pairs of observation periods and testing windows within the entire study period used for analysis (Fig 2, D). Thus we could determine the relationship of actual events of a decrease in %predPEF versus π values averaged over all windows for each patient (Fig 2, E).

Determination of clinically defined exacerbations

The π values were also compared with occurrences of actual exacerbations defined clinically as per the original studies (Table I) as outcome. Because the numbers of events, clinically defined exacerbations, or both were low for some patients, when looking at occurrences of outcome, the observation period and testing window were moved progressively in an overlapping manner to increase the number of observation periods relevant to an event or exacerbation. This would be analogous to a patient's lung function history being continually updated to renew his or her assessment of risk.

Statistical analysis

Associations between π values and actual future numbers of PEF events (count outcome) were made by examining the adjusted R^2 value in a nonlinear regression between the π value and the number of PEF events averaged for each patient.

Associations between π values and occurrence of PEF events (binary outcome) were examined by using logistic regression. Because of the use of overlapping windows, the effect of adjusting for clustering at the patient level was examined, whereby robust SEs in the regression were recalculated, allowing for correlation of multiple observations within the same patient. In addition, receiver operating characteristic (ROC) curves were used to compare the predictive ability of π values with that of the closest available clinic-recorded prebronchodilator FEV₁ measurement before each analysis window expressed as a percentage of predicted value (percent predicted FEV₁ [%predFEV₁]). The direction of %predFEV₁ was reversed to be consistent with the expected direction of a higher π value (higher risk).

Associations between π values and the occurrence of clinically defined exacerbations (binary outcome) were examined in a similar manner as for the PEF events above.

In all analyses the standard period in which PEF events were counted and the testing window used was 30 days (ie, 60 data points) because this window size has been shown to yield stable π for most patients (see this article's Fig E1 in the Online Repository at www.jacionline.org), and a threshold of a decrease to less than 80% of predicted PEF was used to determine the occurrence of a PEF event. We also examined the effect of using a shorter testing window size of 15 days (ie, 30 data points) and of using a lower threshold at 60% of predicted PEF.

All statistical analyses were performed with Intercooled Stata version 11 software (StataCorp, College Station, Tex).

RESULTS

Subjects' demographics and baseline characteristics can be found in Table II. In summary, 35 of 78 patients in study A (with

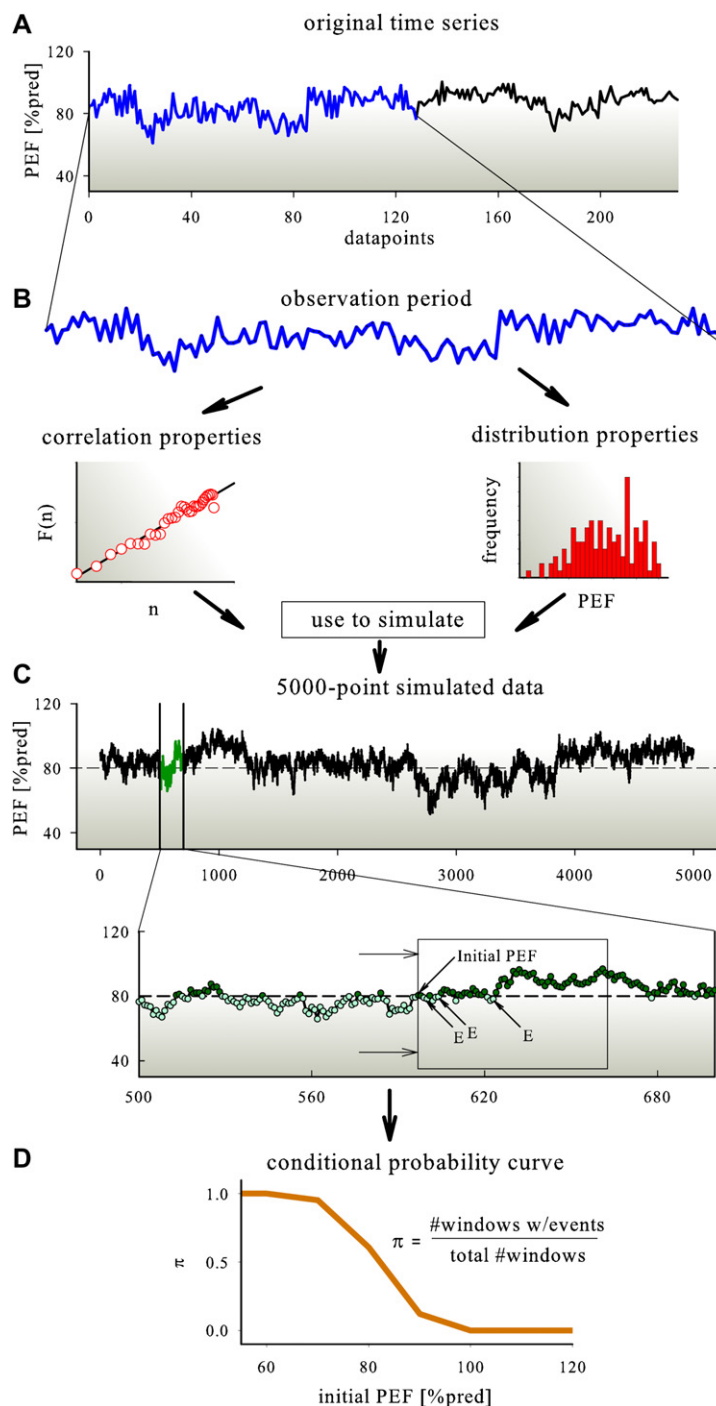


FIG 1. Summary of procedure for calculating π values. **A**, Sample twice-daily PEF time series from a patient. **B**, Reference 64-day observation period, from which correlation and distribution properties were extracted. $F(n)$, Fluctuations in PEF (as a function of window size n ¹⁸). **C**, Simulated series from which PEF events were determined. E , PEF event. **D**, Reference curve of π versus initial PEF. Please refer to the Methods section for details.

severe persistent asthma uncontrolled by high-dose inhaled ($\pm$ oral) corticosteroid and long-acting β_2 -agonist treatment) and 34 of 61 patients in study B (with uncontrolled asthma and not necessarily taking any inhaled corticosteroids at entry [maximum dose, 1200 μ g/d]) had sufficient data for analysis satisfying the quality control criterion.

The mean $\pm$ SD number of exacerbations per patient was 3.1 ± 3.0 for the first 24 weeks of study A and 0.9 ± 1.2 for the first 16

weeks of study B. The ranges of π values obtained were 7.8% to 99.7% for study A and 0.2% to 99.9% for study B. To interpret π values, for a threshold of 80% of predicted PEF, a π value of 75% indicates that there is a 75% chance that the patient will experience a PEF event (ie, a decrease in PEF to less than this threshold for 2 days in a row) within the following month. Summary of observation and testing window pairs, as well as calculated π values, PEF events, and clinical exacerbations, are provided in Table III.

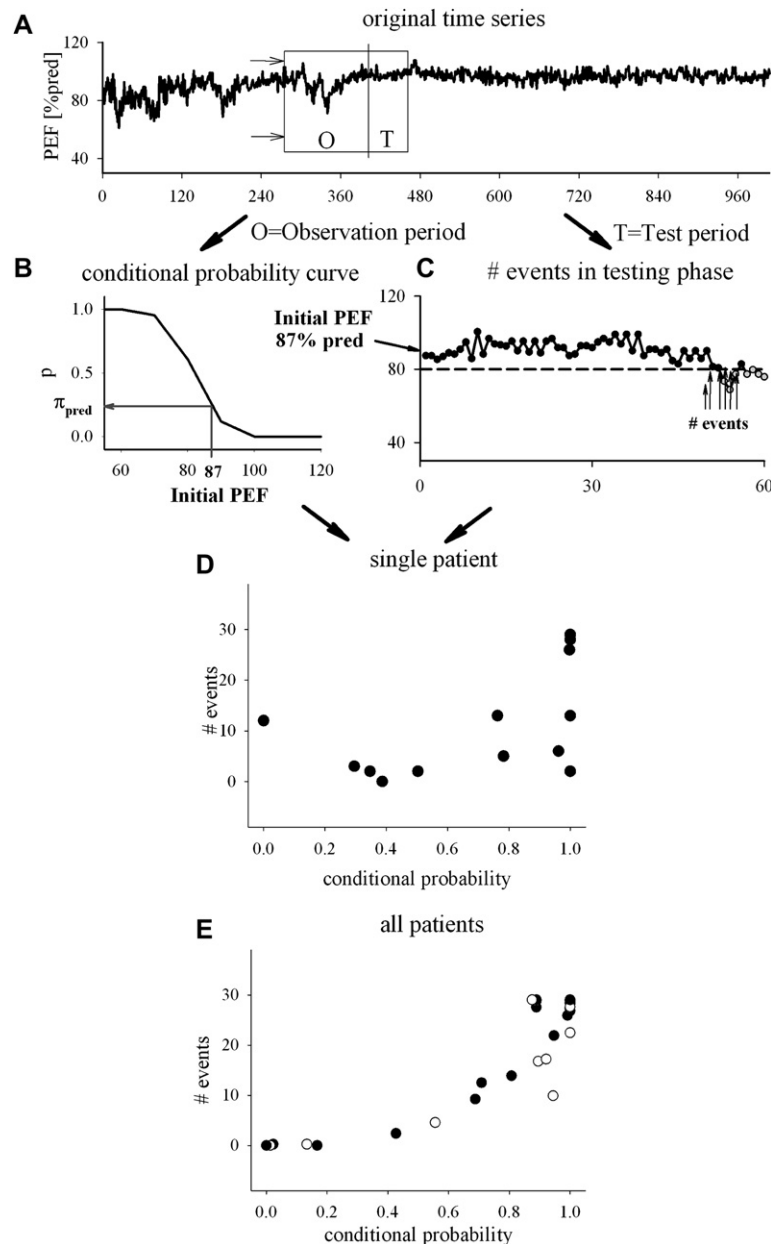


FIG 2. Summary of the procedure for validating the π values calculated. **A**, Sample original time series. **B**, Conditional probability reference plot as shown in Fig 1. **C**, Testing window from which initial PEF and thus π values from the reference curve were obtained. The actual number of PEF events was also counted. **D**, Actual number of PEF events against π values for all windows for each patient. **E**, Actual number of PEF events against π values averaged per patient for all patients (see Fig 3). Please refer to the Methods section for details.

Validation with patient-averaged number of PEF events

An increase in π values corresponded to an increasing number of occurrences of decreases in %predPEF to less than the threshold in subjects from both studies. Fig 3 shows this relationship as averaged probabilities and events per patient, for a threshold of 80%. R^2 values for studies A and B were 0.929 and 0.807, respectively. When patients not meeting the quality control criterion were included, R^2 values became 0.904 and 0.905, respectively. Note that 3 patients in study B had only 1 window; however, their inclusion did not significantly change the regression analysis.

With a shorter window size of 15 instead of 30 days and a lower threshold at 60% of predicted PEF, the general increasing relationship between π values and numbers of PEF events persisted (R^2 range = 0.883-0.945).

Validation with occurrence of actual PEF events

For study A, every increase of 10% in π values was associated with an odds ratio of 1.62 (95% CI, 1.36-1.94; $P < .001$) of having a PEF event in the testing window. Similarly for study B, every increase of 10% in π values was associated with an odds ratio

TABLE I. Exacerbation definitions as per original studies

	Study A ¹⁹	Study B ²⁰
Severe exacerbation	An episode of worsening asthma requiring treatment with intravenous or oral steroids (increase of oral steroids ≥ 20 mg/d from baseline)	- A decrease in morning PEF to $<80\%$ of recent best measurement on 2 consecutive days and β_2-agonist use on ≥ 3 occasions OR - a decrease in morning PEF to $<70\%$ of recent best measurement These exacerbations were treated with oral steroids.
Mild exacerbation	- A decrease of $>20\%$ in morning PEF or >3 additional inhalations of rescue medication per 24 h on 2 consecutive days compared with baseline OR - an increase in nocturnal awakenings caused by asthma on 2 consecutive nights compared with baseline	A decrease in morning PEF to $<85\%$ of recent best measurement on 2 consecutive days
Other		An exacerbation could also be determined at the investigator's discretion when not all criteria were fulfilled.

of 1.50 (95% CI, 1.32-1.72; $P < .001$). Adjusting for within-patient clustering yielded similar results for both studies.

The sensitivity and specificity of the π value to detect future PEF events were demonstrated by using area under the ROC curves, as shown in Fig 4. For the standard testing window of 30 days and a threshold of 80%, we obtained areas of 0.8505 (study A) and 0.7853 (study B). Also, π value as a predictor performed better than clinic-recorded %predFEV₁ for both study A (area for FEV₁ = 0.5422, P value for the comparison $< .001$) and study B (area for FEV₁ = 0.5771, P value for the comparison $< .001$).

Validation with occurrence of clinically defined exacerbations

For study A, every increase of 10% in π values was associated with an odds ratio of 1.24 (95% CI, 1.07-1.43; $P = .003$) of having a clinically defined exacerbation in the testing window. For study B, exacerbations were examined only over weeks 1 to 16, but similarly, every increase of 10% in π values was associated with an odds ratio of 1.13 (95% CI, 1.02-1.26; $P = .02$) of having a clinically defined exacerbation in the testing window. Adjusting for within-patient clustering weakened the significances, but the increasing trends remained for both studies. We attempted to examine mild and severe exacerbations separately; unfortunately, the small numbers prevented meaningful analysis.

With a shorter window size but not with a lower threshold, the relationship between π values and clinically defined exacerbations remained strongly significant for study A. There were no significant associations with changing window size, threshold, or both for study B.

The ROC curves for the detection of future clinically defined exacerbations are shown in Fig 5. For the standard testing window of 30 days and a threshold of 80%, we obtained areas of 0.6604 (study A) and 0.6102 (study B). The area under the curve for the π value was higher than for FEV₁ in the direction of change studied for both study A (area for FEV₁ = .5426, although the comparison was not significant [$P = .13$]) and study B (area for FEV₁ = 0.1542, $P < .001$ for the comparison); however, for the latter, a higher FEV₁ was paradoxically more predictive of an exacerbation. In other words, when the direction of FEV₁ was

TABLE II. Subjects' demographics and baseline characteristics for the 2 datasets

	Study A ¹⁹	Study B ²⁰
No. of subjects	78	61
Female sex	42 (54%)	28 (46%)
Age (y [range])	49.4 (22-77)	39.5 (18-67)
Patients with history of smoking*	19 (24%)	13 (21%)
Disease duration (y)	1-5 (n = 7) 6-10 (n = 11) >10 (n = 60)	1-5 (n = 1) 6-10 (n = 7) >10 (n = 52)
FEV ₁ (L)	1.98 $\pm$ 0.63	2.43 $\pm$ 0.85
FEV ₁ (% predicted)	60.9 $\pm$ 11.1	71.7 $\pm$ 17.3
Baseline PEF (L/min)	303 $\pm$ 124	393 $\pm$ 109
Baseline PEF (% predicted)	57.4 $\pm$ 20.0	70.8 $\pm$ 16.0
FEV ₁ reversibility (%)	15.6 $\pm$ 15	—
PD ₂₀ FEV ₁ (μ mol of histamine)†	—	0.36 $\pm$ 0.70
Rescue medication use per day	4.5 $\pm$ 3.7 puffs	3.2 $\pm$ 1.9 occasions
Patients taking inhaled corticosteroids at entry	78 (100%)	27 (44%)
Corticosteroid dose in these patients (mg/d)	1,279 $\pm$ 461	630 $\pm$ 322

Values are presented as means $\pm$ SDs unless otherwise indicated.

*In study A all patients who had smoked for at least 1 year before entry or who had a smoking history of greater than 10 pack-years were excluded. In study B all current smokers were excluded.

†Provocative dose of histamine causing a 20% decrease in FEV₁.

reversed from that studied, FEV₁ was a better predictor than π value.

DISCUSSION

Summary of results

We found good association between our novel method (ICP) of quantifying individual risk of future exacerbation and the number of actual events of a decrease in PEF based on data from 2 different populations of asthmatic patients studied by using 2 different time windows of observation and 2 different thresholds for defining a PEF decrease. The probabilities calculated by using

TABLE III. PEF events and exacerbations per patient and window for the 2 datasets

	Study A ¹⁹	Study B ²⁰
No. of patients included in main analyses*	35/78	34/61
Comparison with patient-averaged number of PEF events		
Median (range) no. of windows	9 (2-9)	13 (1-13)
Median (range) no. of windows containing a PEF event	9 (1-9)	10 (1-13)
Mean $\pm$ SD no. of PEF events	25 $\pm$ 8	18 $\pm$ 12
Mean $\pm$ SD of conditional probability π (%)	92.5 $\pm$ 19.6	76.7 $\pm$ 36.5
Comparison with occurrence of PEF events [†]		
Median (range) no. of windows, overlapping [§]	54 (15-57)	18 (12-25)
Mean $\pm$ SD of conditional probability π (%)	92.3 $\pm$ 20.4	69.4 $\pm$ 40.5
Median (range) no. of windows containing a PEF event	54 (7-57)	18 (0-23)
Mean $\pm$ SD no. of PEF events	25 $\pm$ 8	14 $\pm$ 13
Comparison with occurrence of clinical exacerbations [‡]		
No. of patients with an exacerbation	27 (77%)	20 (59%)
Median (range) no. of windows containing an exacerbation	13 (0-57)	10 (0-25)

Note that the number of windows per patient within each study was variable because of different follow-up times within the examined study periods.

*Patients who had 10% or greater missing data were excluded from main analyses.

[†]A PEF event was defined as a decrease in PEF to less than a set threshold on 2 consecutive days within a specified testing window. Numbers shown in the table are for a threshold of 80% of predicted PEF and a window size of 30 days (ie, 60 data points).

[‡]See Table I for definition of exacerbations. For study B, only weeks 1 to 16 were analyzed for prediction of exacerbations.

[§]Overlapping windows were moved by 10 days for study A and 2 days for study B.

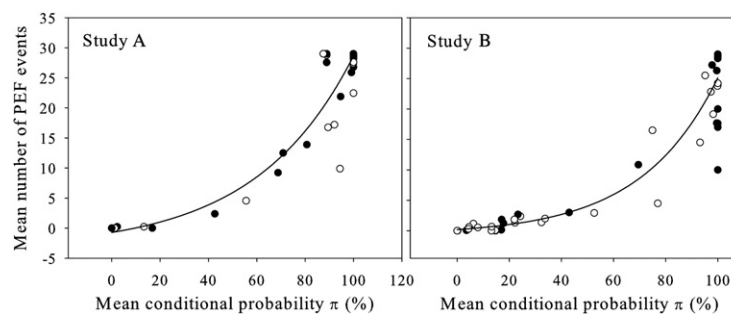


FIG 3. Mean number of actual events of decreases in PEF to less than a threshold of 80% of predicted value versus a mean π value of such a decrease per patient in asthmatic subjects from study A (left panel) and study B (right panel). Open symbols indicate patients not meeting the PEF quality control criterion of less than 10% missing data. The curve represents the best nonlinear fit.

this method were also well associated with whether future decreases in PEF and clinically defined exacerbations occurred in both studies and in general offered even better prediction than clinic-measured lung function.

Significance and clinical implications

Our results suggest that fluctuations in past lung function should be considered in the assessment of future behavior. As mentioned, it is intuitive to the clinician that past information should be used in assessing asthma status or future risk,^{9,17} but to date, methods have been inadequate in incorporating this information into an objective parameter. Previous studies examining daily PEF in a conventional manner have not found any value in predicting exacerbations in asthma additional to other measures.^{25,26} The application of statistics to assess lung function for the purpose of asthma diagnostics and care has been examined in case studies with some promise,²⁷⁻²⁹ but a definitive parameter with useful predictive power is still lacking.^{2,3,15} From previous simulations, we have shown that past correlations play a significant role in the conditional probability, so long as PEF was not

so low as to completely dominate the risk, in which case the distribution properties of PEF *per se* would be just as predictive.¹⁷ The results from this study seem to show good accuracy with practical utility.

ICP was found to be highly predictive not only for future PEF decrease (which is not surprising because of its basis on past PEF events), but its predictive power was also shown for the first time for future clinically defined exacerbations. This is significant because recent American Thoracic Society/European Respiratory Society guidelines² defined severe exacerbations on the basis of systemic corticosteroid use or emergency department or hospital admission because of a lack of validated lung function criteria for exacerbations and reduced the emphasis on lung functional changes to define moderate exacerbations. The results from the present study might help in developing appropriate tools for identifying exacerbations.

To use study A as an example, if a patient attending the clinic can report his or her home-monitored lung function from the last 64 days, a clinician can choose a cutoff π value (eg, 80%) and then predict the probability of an exacerbation occurring within the next month with a sensitivity of up to 68.8% and a specificity of up

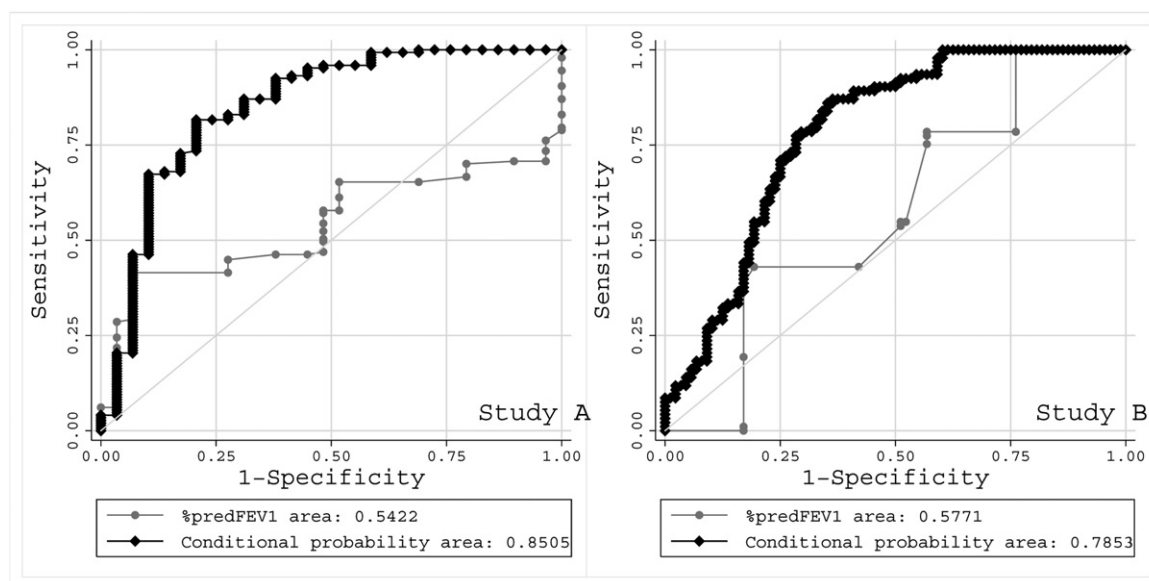


FIG 4. ROC curves of calculated π values of a decrease in PEF to less than a threshold of 80% of predicted value (black curve) compared against %predFEV₁ (gray curve) in asthmatic subjects from study A (left panel) and study B (right panel) for the prediction of actual events of decreases in %predPEF.

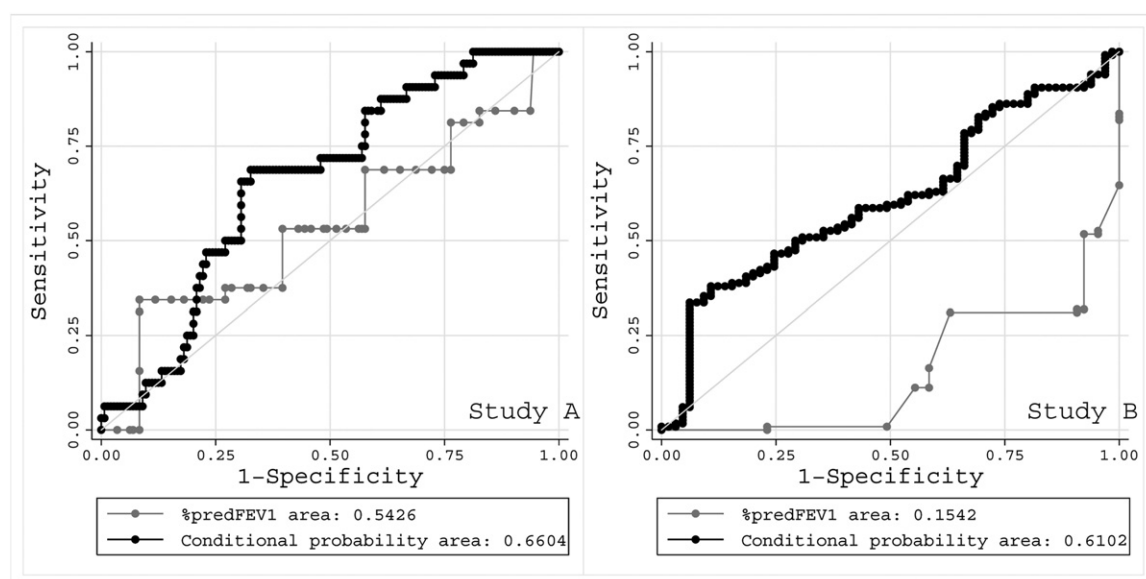


FIG 5. ROC curves of calculated π values of a decrease in PEF to less than a threshold of 80% of predicted value (black curve) compared against %predFEV₁ (gray curve) in asthmatic subjects from study A (left panel) and study B (right panel) for the prediction of occurrence of clinically defined exacerbations (see Table I).

to 67.4%. The predictive value was found to be better than clinic-measured lung function (%predFEV₁) in both studies. The paradoxical association between increased lung function and occurrence of clinical exacerbation in study B might be attributable to the definition of exacerbation used in that study, which was based on recent best lung function over the previous 2 weeks, whereas clinic-measured FEV₁ was only recorded every 8 weeks, during which time any changes in treatment dose would have taken effect. It should be noted here that better predictive power

is not likely attributable to the use of PEF over FEV₁ but rather the use of lung function history quantified from multiple measurements over time over single measurements.

We believe that ICP is the first statistical method that can be used to calculate the exacerbation risk of an individual patient. It is fundamentally different from population-based risk assessments (eg, whether a patient belongs to a smoking population) because the risk is derived from the history of the patient's individual past lung function fluctuations. The novelty of the method

in comparison to the previously described conditional probability method¹⁸ lies in the simulation of individual datasets. In previous computer simulation studies we have demonstrated the possibility of numerically generating PEF series based on grouped data.^{17,18} Because the reference PEF series in an individual is limited in length, the number of events of PEF decrease within the reference period and hence the prediction accuracy are limited. By simulating an series of 5000 PEF values with identical correlation and distribution properties from the reference period, we dramatically increase the number of hypothetical events, and the conditional probabilities can be better estimated.

A further advantage of ICP is the relative ease of measurement of PEF home monitoring; twice-daily PEF or FEV₁ series can be assessed by the patient himself or herself, is observer independent, and does not require clinic visits, offering an advantage over clinic-performed spirometry³⁰ and exhaled nitric oxide measurement^{25,30} as predictors of risk. The area under the ROC curve obtained in this study is similar to that recently described by Forno et al³¹ using a promising clinical decision score comprising various measures obtained in the outpatient ambulatory setting. Our method, in contrast, is based on measures that can be obtained at home and that can be updated every day. Furthermore, our method provides assessment of risk within the following month. Theoretically, an even shorter period of prediction would be possible when correlations are strong, although we are unable to validate this because the number of clinical exacerbations within a shorter period would be too low. The PEF measurement technique is standardized; data can be electronically recorded, therefore avoiding data fabrication; the calculation can be automated, potentially aiding the doctor in treatment decisions regarding the patient's asthma stability through telemonitoring; and the computations would not be difficult to incorporate into a standard PEF measurement device.

A strength of the present study is that electronic monitoring of PEF both prevented data fabrication and facilitated good adherence with monitoring.³² Fabricated data might not necessarily have the same correlation patterns as real data. This new approach also bears ethical significance in light of the substantial effort and commitment on the part of the patient during monitoring because it considers all PEF data collected. This is in contrast to current use of PEF in which the patient's status is assessed at different time points (mainly at the end) and the rest of the data are left largely untouched, except in the increasing use of mixed-model analysis.

Finally, in this analysis we adopted a conservative approach to quality control by excluding all patients who did not record 90% or more of scheduled PEF data. However, in practical terms the similarity of results with and without application of this quality control criterion also suggests that the method is not strongly dependent on complete adherence with monitoring. This is in contrast to using fluctuation analysis *per se* to assess asthma status, in which correlation properties, as well as predictive value, are altered, with more than 10% missing data.^{18,24}

Future studies would be needed to establish how treatment should be changed in response to a signal from ICP and whether such a change in treatment would prevent a predicted exacerbation from occurring.

Limitations

Being a retrospective analysis of 2 past clinical trials, the present analysis is constrained by the design of the 2 original

studies: a change from constant dosage treatment to downtitration in study A (with 63% of included patients completing the downtitration phase with varying degrees of corticosteroid reduction) and a higher dose of treatment than commonly used and downtitration with a clinical algorithm in study B (with 24% completing the downtitration phase, again with varying degrees of reduction). Also, in study A all patients took high-dose inhaled ($\pm$ oral) corticosteroids and long-acting β_2 -agonists, whereas in study B all patients took high-dose inhaled corticosteroids but none took long-acting β_2 -agonists during the study period. Despite these heterogeneous circumstances, similar results were found in the 2 datasets in terms of relationships with PEF events and clinically defined exacerbations, providing support for the robustness and applicability of our method. Variable conditions and treatment strategies are common in daily practice, and thus the different designs in studies A and B are reflective of real patient scenarios, at least for patients with severe or poorly controlled asthma. It remains to be seen whether the method would have equal or better predictive ability in patients with mild-to-moderate or well-controlled asthma, including those who have less history of significant exacerbations. Subgroup analyses showed that the associations between π values and actual future numbers of PEF events were independent of inhaled corticosteroid use or of asthma control status in the current population of patients with severe asthma, as defined by the Global Initiative for Asthma (data not shown). It is likely that more constant or controlled conditions would improve the predictive ability of the technique. The results of the present study open up the possibility of a prospectively designed trial allowing the flexibility to examine optimum observation periods, prediction windows, and thresholds for PEF decreases.

Note that the simulation of 5000 data points assumes a stationary process that is equivalent to assuming that the disease condition within the reference period and the prediction period remains approximately constant. Furthermore, it has to be kept in mind that the information content is still limited to the length of the reference period; the estimation of the conditional probability is merely improved by basing it on the simulated time series. Although the assumption might not always apply, the deduction of correlation properties makes use of a method that is relatively robust to local nonstationarities.³³

Another limitation is the minimum period required to characterize the correlation properties of the PEF (64 days) and how this relates to potential changes from external influences, such as seasonality. For this study, we were able to ascertain that the calculated π values for each reference period were not related to the month of the year at the start of the period, and the relationship between calculated π values and actual occurrence of PEF events remained strongly significant when month of the year was taken into account (data not shown). There could be other situations in which an external event caused an exacerbation but might have had no bearing on the patient's previous PEF status. Such exacerbations might not be predicted by the present method.

Conclusions

A novel method of ICP has been introduced that makes use of information from the history of past fluctuations in lung function for predicting individual risk of future deterioration in asthma control. In this respect ICP performed better in general than one of the strongest previously known predictors, clinic-based spirometry. The ability of ICP to predict asthma exacerbations has been

validated in 2 independent datasets of patients of differing asthma populations. Thus the method offers clinically relevant prediction of future exacerbations. It is a step toward individualized medicine.

Key messages

- Recent research and guidelines have identified the importance of assessing future risk of deterioration in asthma control. Studies of fluctuations in home-monitored PEF have suggested value in prediction of future exacerbation risk, but this has only been calculated from grouped data.
- The novel method of analyzing past fluctuations in PEF can now be extended to quantify the risk of future asthma exacerbation in the individual patient, as validated in 2 independent datasets of adult asthmatic subjects; this represents a step toward computer-aided personalized medicine.

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METHODS

Original datasets

Study A was a phase II, multicenter, randomized, double-blind, placebo-controlled study assessing the safety and efficacy of a trial of mAb asthma treatment.^{E1} Patients were required to have had a diagnosis of asthma for 3 or more years and uncontrolled severe asthma for 1 or more years, according to the 2002 Global Initiative for Asthma/National Heart, Lung, and Blood Institute guidelines.^{E2,E3} Three hundred nine adult patients were randomized to receive monthly subcutaneous injections of placebo or study drug at 50, 100, or 200 mg for 52 weeks. From weeks 0 to 24, the same dosage of inhaled corticosteroids with or without oral corticosteroids as during a prior 2-week run-in phase was maintained. From weeks 24 to 52, downtitration of corticosteroid treatment was attempted. Throughout weeks 0 to 52, patients were given 50 µg of salmeterol for use twice daily in addition to corticosteroids and were assessed at study visits every 4 weeks. For the present study, all available twice-daily electronically recorded PEF data (Jaeger AM2+, VIASYS Healthcare) from weeks 0 to 52 of the trial were used from patients in the placebo treatment group ($n = 78$) who had completed at least 24 weeks and had entered the downtitration phase ($n = 77$).

Study B was a single-center, randomized, parallel-group study to determine whether a very high starting dose of inhaled budesonide could improve patients' outcomes.^{E4} Patients were defined as having poorly controlled asthma according to 1992 National Heart, Lung, and Blood Institute guidelines.^{E5} Sixty-one adult patients were randomized to receive 8 weeks of either 1600 or 3200 µg/d budesonide treatment, followed by 8 weeks of 1600 µg/d treatment and a 14-month period of downtitration of treatment. During the study, use of long-acting or oral β_2 -agonists, theophyllines, and long-acting antihistamines was not permitted, and patients were assessed at study visits every 8 weeks. For the present study, all available twice-daily electronically recorded PEF data (MicroMedical DiaryCard) from weeks 0 to 72 of the trial were used from all patients who had completed at least 16 weeks ($n = 58$).

Details of both studies have been published previously^{E1,E4} and were approved by the relevant ethics committees.

PEF measurement

In study A subjects were instructed to attempt to collect PEF readings before any use of inhaled short-acting β -agonist in the morning or at least 4 hours after any use of inhaled short-acting β -agonist in the evening and before taking their morning and evening doses of long-acting β -agonist. Twice-daily PEF measurements were still to be collected regardless of inability to withhold treatment as suggested. Subjects received appropriate training on the use of the electronic PEF meter at the screening visit. At each clinic visit, the study coordinator downloaded the data from the PEF device, printed out the information, and reviewed the data with the subject for completeness and consistency.

In study B subjects were asked to collect PEF readings while standing, recording the morning session immediately on waking and the evening session around dinner time. β -Agonist was inhaled on demand, and subjects were asked to use the electronic diary device before medication. After answering the diary questions, subjects were then prompted to perform 3 spirometric maneuvers. The on-screen instruction was "Spirometry – blow now," but verbal and written instructions emphasized the instruction to "blow all the way out as fast as you can." At the initial visit, subjects were shown how to use the device and were issued an instruction booklet that was written specifically for the study. Subjects were encouraged to use the device as many times as they wished during the first 2 days of the run-in period to become familiar with its use; these data were not used for analysis. Technique with the device was checked at each visit by the investigators.

Calculation of conditional probabilities

The procedure for calculation of π values is shown in Fig 1. In both studies the first 64 days of PEF data served as a reference observation period for each patient. This length of period is required to adequately quantify the correlation properties of the PEF data, as described later to within an error of 4%.^{E6} A PEF quality control criterion was used whereby patients with 10% or more data missing from the completed monitoring period were excluded from the main analyses. (In a secondary analysis we evaluated the effect of including

these patients; however, the criterion applies to all results unless otherwise reported.) Fluctuation analysis was performed as previously described^{E7,E8} to obtain the time correlation properties of PEF from this period. The distribution properties of PEF (mean, SD, and skewness) were also calculated. Both properties were subsequently used to simulate a new time series of 5,000 PEF data points with the same correlation and distribution properties as the original data. This was done as previously described^{E7,E9} but based on data from each patient.

Next the simulated data were used to calculate the π values; given an initial %predPEF, the π value was defined as the probability of encountering a decrease in PEF to less than a set threshold on 2 consecutive days within 30 days calculated over multiple overlapping windows moved progressively over the simulated data.^{E10} Three consecutive days with low PEF would constitute 2 events, such that there is a maximum of 29 possible events within 30 days. The end point of this procedure is a reference curve relating the π value to the initial %predPEF for each patient, which predicts the probability of a lung function decrease within 30 days as a function of the initial %predPEF on the first day of that period.

Calculation of actual events of PEF decrease

A testing window of 30 days after the 64-day observation period in the original PEF data was used to validate the predictive ability of the calculated π values. The procedure is shown in Fig 2. Here the initial %predPEF was determined, and the corresponding π value obtained from the reference curve was previously calculated for that patient. This π value was then compared with the number and occurrence of actual events of decrease in %predPEF to less than the threshold within the future testing window.

The above calculations were repeated for multiple pairs of observation periods and testing windows within the entire study period used for analysis. Thus we could determine the relationship of actual events of decrease in %predPEF versus π values averaged over all windows for each patient. Note that the number of windows per patient within each study was variable because of different follow-up times within the examined study periods.

Determination of clinically defined exacerbations

The π values described above were also compared with occurrences of actual exacerbations defined clinically as per the original studies (Table I) as outcome, combining mild and severe exacerbations for this analysis. Note that in study B during the downtitration phase patients experiencing more than 2 exacerbations in 2 consecutive 8-week periods were withdrawn from the original study. Thus only data from weeks 1 to 16 were included in the validation of clinically defined exacerbations.

Because the numbers of events, clinically defined exacerbations, or both were low for some patients, when looking at occurrences of outcome, the observation period and testing window were moved progressively in an overlapping manner to increase the number of observation periods relevant to an event or exacerbation. This would be analogous to a patient's lung function history being continually updated to renew his or her assessment of risk. Overlapping windows were moved by 10 days for study A and 2 days for study B to account for the differences in trial periods.

Statistical analysis

Associations between π values and actual future numbers of PEF events (count outcome) were made by examining the adjusted R^2 value in a nonlinear regression between the π value and the number of PEF events averaged for each patient. An exponential model ($y = a * e^{bx} + y_0$) was used based on observation of the data.

Associations between π values and occurrence of PEF events (binary outcome) were examined by using logistic regression. Because of the use of overlapping windows, the effect of adjusting for clustering at the patient level was examined, whereby robust SEs in the regression were recalculated, allowing for correlation of multiple observations within the same patient. In addition, ROC curves were used to assess the predictive ability of π values. At very high or very low PEF, it can arise that the method is unable to find PEF events (yielding $\pi = 0\%$) or the entire testing window consists of only

PEF events (yielding $\pi = 100\%$). Thus calculations yielding a π value of 0% or 100% were treated as artifacts and excluded from the analyses. The predictive ability of π values was also compared with that of the closest available clinic-recorded prebronchodilator FEV₁ measurement before each analysis window expressed as %predFEV₁. Note that in the ROC curves the direction of %predFEV₁ was reversed to be consistent with the expected direction of a higher π value (higher risk).

Associations between π values and occurrence of clinically defined exacerbations (binary outcome) were examined in a similar manner as for the PEF events above.

In all analyses the standard period in which PEF events were counted and the testing window used was 30 days (ie, 60 data points) because this window size has been shown to yield stable π values for most patients (Fig E1), and a threshold of a decrease to less than 80% of predicted PEF was used to determine the occurrence of a PEF event. We also examined the effect of using a shorter testing window size of 15 days (ie, 30 data points) and of using a lower threshold at 60% of predicted PEF.

All statistical analyses were performed with Intercooled Stata version 11 software (StataCorp, College Station, Tex).

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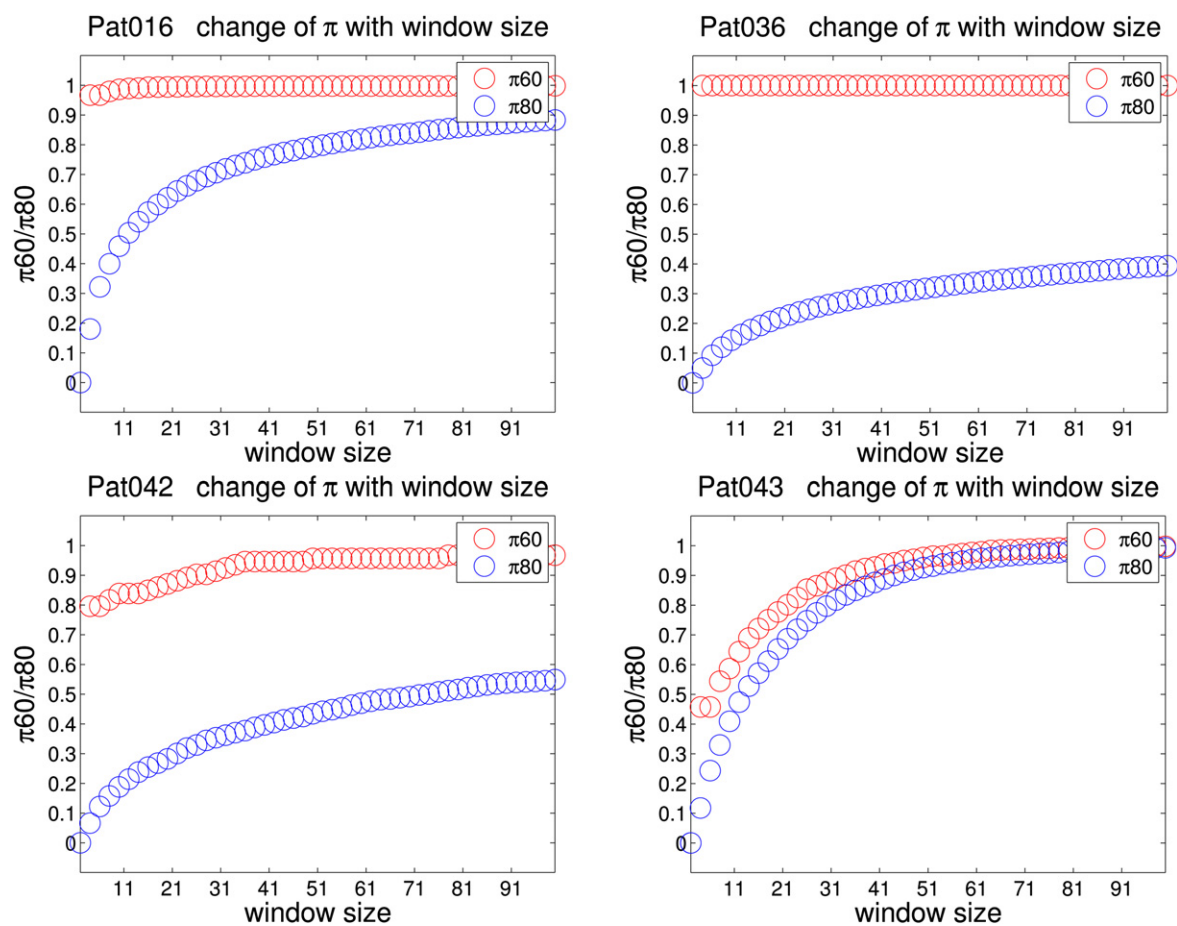


FIG E1. Plots of the variation in calculated conditional probabilities (π_{60} for an initial PEF of 60% of predicted PEF and π_{80} for an initial PEF of 80% of predicted PEF) with window size in 4 patients.