Applicable predictive factors extracted from peak flow trajectory for the prediction of asthma exacerbation

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Conflict of Interest

I.Y. received research fund by Nihon Medi-Physics, and speaker fees from Chugai Pharmaceutical Co, and AstraZeneca, outside the submitted work. M.N received research funding from AstraZeneca K.K., Kyorin Pharmaceutical Ltd., and MSD. The rest of the authors declare that they have no relevant conflicts of interest. None of these companies had a role in the design or analysis of the study or in the writing of the manuscript.

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Clinical Trial Registration

The Hokkaido-based Investigative Cohort Analysis for Refractory Asthma (Hi-CARAT) was registered in the UMIN Clinical Trials Registry (UMIN ID: 000003254). https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000003917

Keywords

airflow ability; airway inflammation; acute asthma attack; lung function; prediction

Abbreviations/Acronyms

Abbreviations	Definitions
PEF	Peak expiratory flow
%predPEF	Percentage predicted PEF
CV	Coefficient of variation
Min/Max	The highest PEF over the lowest PEF within specific periods
ΔMA	Delta moving average
%ΔMA	Delta percentage predicted PEF moving average
Hi-CARAT	Hokkaido-based Investigative Cohort Analysis for Refractory Asthma

SD	Standard deviation
%bestPEF	Percentage best PEF
ROC	Receiver operating characteristic
AUC	Area under the curve
PBE	Peripheral blood eosinophils
FeNO	Fractional exhaled nitric oxide

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Abstract

Background: Real-time asthma exacerbation prediction and upcoming acute asthma attack detection are essential for patients with severe asthma. Among several potential predictors, peak expiratory flow (PEF) exhibits a potential for use in long-term asthma self-monitoring; However, the method for processing PEF calculations remains to be clarified.

Objective: Present research was conducted to develop clinically applicable novel exacerbation predictors calculated using PEF records.

Methods: Previously proposed exacerbation predictors, including the decreasing trend of PEF, percentage predicted PEF, percentage best PEF, the highest PEF over the lowest PEF within specific periods, and PEF coefficient of variation, as well as a novel indicator delta PEF moving average (ΔMA), defined as the difference between 14-day and 3-day average PEF values along with ΔMA adjusted for PEF reference (%ΔMA), were verified using the Hokkaido-based Investigative Cohort Analysis for Refractory Asthma data of 127 patients with severe asthma from whom 73,503 PEF observations were obtained. Receiver operating characteristic curves for all predictors were drawn and the corresponding areas under the curve (AUCs) were computed. Regression analysis for ΔMA and %ΔMA were conducted.

Results: The most outstanding performance was demonstrated by ΔMA and %ΔMA, with AUC values of 0.659 and 0.665 in the univariate model, respectively. When multivariate models incorporated with random intercepts for individual participants, the AUC for ΔMA and %ΔMA soared to 0.907 and 0.919, respectively.

Conclusion: The ΔMA and %ΔMA are valuable indicators that should be considered when deriving predictors from the PEF trajectory for monitoring exacerbations in patients with severe asthma.

Introduction

Asthma is a common respiratory disease that leads to the narrowing of the bronchus, resulting in wheezing, excess mucus production, and breathing difficulties [1]. Globally, asthma-related deaths have barely decreased despite the increase in asthma care [2]. Regardless of the therapy applied, a minority of patients with asthma, including those with severe (or refractory) asthma, continuously present with uncontrolled symptoms and are threatened by acute exacerbation, which may be fatal [3,4]. Asthma surveillance and exacerbation prediction for patients with severe asthma are topics of great interest to researchers.

Because of the heterogeneity of asthma and the acute exacerbation algorithm [5,6], previous studies have used several methods to identify asthma attack triggers and establish methods for asthma exacerbation prediction. The proposed predictive factors of real-time asthma exacerbation include, but are not limited to, weather, air pollution, exhaled chemical substances, blood biomarkers, and questionnaires [7–12]. These studies provide valuable insights into exacerbation management. However, some of the abovementioned predictors cannot be calculated by the patients themselves; moreover, blood tests and exhaled component analysis cannot be performed at home, thus preventing the use of these factors in asthma self-monitoring. Although patients can access information on weather and air pollution without support from healthcare workers, these data only represent the external environment of the patients and not their internal health condition. Applying the Asthma Control Questionnaire [13], Asthma Quality of Life Questionnaire [14] or Asthma Symptom Utility Index [15] can be considered; however, it inevitably involves patient subjectivity and can be time-consuming.

Peak expiratory flow (PEF), an objective indicator of airway function assessing airway obstruction, has been used in daily practice for asthma monitoring [16]. As portable PEF meters have become easily available, it has become possible for patients to estimate PEF at home and perform self-monitoring, which is vital for asthma symptom control [17]. However, a limited number of studies have been conducted to determine the capability of PEF as a real-time asthma exacerbation predictor. Previous research suggests that the percentage predicted PEF (%predPEF) was related to airway obstruction [18]. A previous study explored whether PEF statistics, including the mean, coefficient of variation (CV), or autocorrelation, can be used to predict the loss of asthma control, and found that CV is a potential choice as a predictor of loss of asthma control [19]. Some studies have suggested that the highest PEF over the lowest PEF within specific periods (Min/Max) is associated with asthma symptoms and exacerbation [11,20]. Furthermore, decreases in PEF have been reportedly associated with upcoming asthma attacks [21]. Nevertheless, these statistics calculated using the PEF trajectory enable the assessment of exacerbation risk at the price of a high calculation burden. The complexity involved in calculating variation and decreasing trends of PEF make the clinical application of PEF difficult.

Regardless of these successful previous studies, extracting information from PEF records and performing real-time asthma exacerbation prediction at an individual level are challenging for researchers and healthcare workers. Therefore, an easily accessible statistic for asthma self-monitoring is required. We suggested novel prediction predictors, i.e., the delta moving average (ΔMA) and the delta percentage predicted PEF moving average (%ΔMA) of PEF, and univariate prognostic models for asthma exacerbation prediction targeting adult patients with severe asthma. Using this model, individualized

action time points for a medical visit or the administration of medications can be identified.

Methods

Study resources

PEF records were collected from the Hokkaido-based Investigative Cohort Analysis for Refractory Asthma (Hi-CARAT, UMIN ID: 000003254). Hi-CARAT is a multicenter observation study that included adult patients with severe asthma with or without smoking history in Hokkaido Prefecture, Japan. This study was approved by the ethics committee of Hokkaido University Hospital (approval number, 009-0205). All participants provided written informed consent. This study was registered in the University Hospital Medical Information Network Clinical Trials Registry system (https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000003917).

The study protocol and other details are as per our previous study [22]. All participants were recruited from the Hokkaido University Hospital and its 29 affiliated clinics and hospitals [22]. The inclusion criteria for patients with severe asthma were based on the American Thoracic Society criteria for refractory asthma 2000 version [23], with slight modifications. The following two additional inclusion criteria were added: 1) a severe asthma diagnosis with one or both major criteria and two minor criteria being met and 2) patients receiving medication and in a well-controlled condition were asked if they needed urgent medical care visits and short-acting bronchodilators or experienced episodic deterioration of symptoms when the dose of the current medication was reduced within the last year [24]. The cohort study was conducted from February 2010 to March 2019 and the airway function monitoring was conducted from February 2010 to

September 2015. Airway function data of 127 patients with severe asthma included in the Hi-CARAT study were used in the present study. The length of the follow-up period varied, ranging from 2 to 42 months. As the entry time varied for each participant, the first participant completed the airway function monitoring on April 23, 2010, while the last participant completed it on September 11, 2015.

PEF values were recorded using Piko-1 (nSpire Health, Inc. USA), an electronic peak flow meter. Its reliability has been proven in previous research studies [25,26]. Each participant measured their PEF twice daily (morning and evening) every 3 months for 30 days, leading to a total of 73,503 PEF observations. For the initial period of the study, we set the first and second measurement sessions (about 2 months) as practice for the participants to ensure they correctly applied the PEF technique. All data were electronically analyzed using a PC after 30 days of measurement. Three physicians independently evaluated the analyzed data; if two of the three physicians judged any data as an outlier, the data were not adopted. The PEF trajectories as well as the exacerbation periods were recorded. In Hi-CARAT, asthma exacerbation was defined as the use of systemic corticosteroids for >3 days and/or severe exacerbation requiring hospitalization [24]. A total of 467 exacerbations were recorded. For instance, Figure 1 illustrates a part of the PEF record of patient number 98 from Hi-CARAT in a time-series manner. The vertical axis denotes the PEF value (L/min), whereas the horizontal axis represents the calendar date. The measurement time was set at once per 3 months on average, with a gap of 2 months between two measurements between two groups of data points. Pink panels denote exacerbation periods when symptoms relief drugs are administered. The light blue points were recorded during the daytime, whereas the black points were recorded at night. PEF data collected during or after exacerbation periods were excluded from the analysis

for each measurement month because the increasing trend of PEF caused by medication may interfere with the natural asthma PEF trajectories.

Statistical analyses

PEF slope, standard deviation (SD), maximum PEF value, minimum PEF value, and mean PEF values in 3-, 7-, and 14-day intervals were calculated from the PEF trajectories for each calendar date. The slope represents the time coefficient in a univariate linear model setting PEF estimates as the outcome and time as an explanatory variable. It represents the evolving trend of PEF. If the PEF value increases over a specific period, the slope is positive; otherwise, the slope is zero or negative. Because of the twice-daily PEF recording rule, the unit of time was half a day. The CV was determined using the following equation.

$$CV = \frac{SD}{Mean},$$

that is, SD divided by the means within a specified period. It illustrates the variability of the PEF trajectory regardless of the mean PEF value. Period maximum and minimum PEF values were extracted to calculate Min/Max using the following equation:

$$Min/Max = \frac{Period\ minimum\ PEF}{Period\ maximum\ PEF}.$$

Min/Max is also an indicator associated with PEF variability.

$$\%predPEF = \frac{PEF}{PEF\ ref}.$$

The %predPEF was calculated as PEF measurement divided by the PEF reference calculated using sex, height, and age. A recently developed equation for PEF reference calculation for eastern Asia was applied.

$$Males\ PEF\ ref\ =\ exp[-7.0972 + 1.6544 \times ln(h) + 0.2314 \times ln(y) + spline]$$

$$Females\ PEF\ ref\ =\ exp[-6.63189 + 1.61459 \times ln(h) + 0.08976 \times ln(y) + spline],$$

where h denotes the participant's height in cm, and the y represents the age in years. The spline is the age-specific contribution of the spline function. More details regarding this equation have been given previously [27]. Our sample included two patients aged >81 years for whom the spline values were not reported. Therefore, we applied the spline corresponding to 81 years of age for these two participants.

$$\%bestPEF = \frac{PEF}{personal\ best\ PEF}.$$

Other than setting the PEF reference as the denominator, we also calculated the %bestPEF (percentage best PEF) dividing PEF by the patients best recorded PEF.

In addition to these indicators introduced in previous studies, a novel explanatory variable, ΔMA, was evaluated. It reflects not only the trend of PEF after smoothing but also the variation in the observations. ΔMA applied in the present study was calculated using the following equation:

$$\Delta MA\ =\ 14\ day\ PEF\ average\ -\ 3\ day\ PEF\ average.$$

The equation above only requires the calculation of average and difference PEF, making it applicable in self-monitoring.

$$\%\Delta MA\ =\ 14\ day\ \%predPEF\ average\ -\ 3\ day\ \%predPEF\ average.$$

Furthermore, we calculated the $\%\Delta MA$ to check if the performance improved.

To evaluate the discriminative ability of PEF slope, CV, Min/Max, %predPEF, $\%bestPEF$, ΔMA, and %ΔMA, receiver operating characteristic (ROC) curve, a graphic tool using 1 − specificity as the horizontal axis and sensitivity as the vertical axis, was applied [28]. The area under the curve (AUC) was used to compare discriminant performance between each independent variable. Prediction curves with prediction intervals were drawn to demonstrate how the risk of exacerbation varies with the changes in ΔMA or %ΔMA.

We used logistic regression analysis to predict real-time asthma exacerbations with a dichotomic outcome: whether a particular patient will experience exacerbation the next day. Two univariate logistic regression models were constructed, and the novel predictors ΔMA and %ΔMA were set as the independent variables respectively. Hosmer–Lemeshow test and subgroup analysis were conducted to ascertain model calibration [29]. The subgroups were categorized according to patients' age, sex, atopy status and smoking status. We expanded our initial univariate analyses to multivariate models by incorporating several factors as covariates: sex, body mass index, waist circumference, serum immunoglobulin E levels, peripheral blood eosinophils (PBE), fractional exhaled nitric oxide (FeNO), atopy status, smoking status, and air pollutants, namely nitrogen dioxide, sulfur dioxide, and suspended particulate matter. To account for individual variations not captured by these covariates, we also constructed mixed-effects models for both ΔMA and %ΔMA. All statistical analyses were conducted using R version 4.2.2 [30].

Results

Table 1 lists the characteristics of the study participants. Countable variables, including the number of men, patients with a positive atopy test result, those with a

smoking history, and those who received oral corticosteroids, are presented as values and percentage. Eosinophil and neutrophil counts are presented as geometric mean with log10 SD. Continuous variables are presented as mean ± SD or median (interquartile range). All patients were adults with an average age of 58 years. Of the 127 participants, 51 were men and 76 were women. A never-smoker was defined as an individual whose Brinkman Index was 0, i.e., an individual who had never smoked before [31]. Furthermore, 75 participants had smoking history at the end of the tracing, and 45 patients had received oral corticosteroids. Patients with asthma participating in this study exhibited a relatively low blood eosinophil count, with a geometric mean of 203.4 cells/μl. The median of rare PEF estimates and %prePEF were 307.0 L/min and 78.6%, respectively. More details regarding participant demographic characteristics, pulmonary function status, serum biomarker levels, sputum cells, and corticosteroids are available in our previous study [32].

ROC graphs were drawn for all previously proposed indicators, including PEF slope, %predPEF, %bestPEF, Min/Max, and CV; the outcomes are presented in Figure 2. The axes of these subgraphs are the same, with X and Y axes representing 1 − specificity and sensitivity, respectively. Panel A, is the ROC for the PEF slope. The PEF slope within 3, 7, and 14 days are illustrated using different colors, and their AUCs are listed in the graph legend. The 14-day slope exhibited the best discriminant performance, and the AUC decreases with the period. Panel B represents the ROC curve for %predPEF and %bestPEF, AUC = 0.566 and 0.537 respectively. Panel C illustrates the ROC curves for Min/Max within 3, 7, and 14 days. The discriminant performance of Min/Max was undesirable, regardless of the period. Panel D presents the ROC curve of CV for the different periods. Similarly, the indicator CV, which also reflects variability in the PEF trajectory, yielded low AUCs at 0.479, 0.561, and 0.563 for 3, 7, and 14 days, respectively.

These results reveal that the indicators reflect a varying trend, i.e., the slope exhibited higher AUCs than other indicators like CV.

Figure 3 presents the ROC curves for ΔMA and % ΔMA. The AUC of %ΔMA was 0.665, indicating the best discriminant performance compared with other indicators. The AUC of ΔMA is 0.659, which is slightly lower than that of %ΔMA. We did not optimize the cutoff value using the Youden index [33] because it included the equality assumption for sensitivity and specificity, which is not convincing in exacerbation prediction. It is assumed that providing medical attention to a patient whose symptoms are effectively controlled is equivalent to ignoring a patient with severe asthma with an impending exacerbation in terms of exacerbation prediction. We proposed five reference cutoff values for ΔMA and %ΔMA. These cutoff values were marked on the ROC curves (Figure 3A) and can be used to identify action time points for patients with severe asthma to have a medical visit. Table 2 shows the discriminant performance for various cutoffs, including sensitivity and specificity. When the cutoff value increased, the sensitivity decreased. In contrast, the specificity increased while the chosen cutoff increased. As illustrated in Figure 3B, by extending the univariate models to multivariate models and incorporating sex, body mass index, waist circumference, serum immunoglobulin E levels, PBE, FeNO, atopy status, smoking status, and air pollutants as covariates, the AUC for ΔMA and %ΔMA improved to 0.710 and 0.707 respectively. We calculated a baseline AUC by using these covariates as independent variables without including ΔMA or %ΔMA. This yielded an AUC of 0.632 for the multivariate model framework. Thus, ΔMA and %ΔMA added an additional discriminative power of 0.078 and 0.075 (0.710 - 0.632 and 0.707 – 0.632). Replacing ΔMA or %ΔMA with other previously proposed

PEF indicators in the multivariate models, such as PEF slope, CV, Min/Max, and %predPEF, resulted in comparatively lower AUC values (for instance, 14-day slope at AUC = 0.641 and 3-day Min/Max at AUC = 0.666). When we further advanced these multivariate models into a mixed model framework, incorporating individual participant effects as random terms, the AUCs for ΔMA and %ΔMA impressively rose to 0.907 and 0.919, respectively.

The Hosmer–Lemeshow goodness-of-fit test was conducted to evaluate model calibration for the univariate models (Table 3). Although the model appeared to be weakly calibrated in the subgroups defined by allergy or smoking status, it was well-calibrated across the whole population. We obtained the predicted risk of exacerbation using ΔMA or %ΔMA (Figure 4). The graph revealed that exacerbation risk increased steadily when the value of ΔMA or %ΔMA increased. This means that the prediction of exacerbation risk calculated using ΔMA or %ΔMA is reliable.

Discussion

The present study examined PEF data from Hi-CARAT in patients with severe asthma to identify optimal predictors of asthma exacerbation. We verified the discriminative ability for several candidate predictors proposed in previous researches, including the PEF slope, %predPEF, Min/Max, and CV. We also suggested two novel predictors, ΔMA and %ΔMA, which can be easily calculated and demonstrate better prediction performance than other indicators.

The main highlights of our research are listed as follows. First, %ΔMA and ΔMA demonstrated superior discriminant performance in terms of real-time asthma exacerbation prediction based on AUC regardless of whether a univariate or multivariate

model was employed. The computation burden for %ΔMA and ΔMA was significantly lower than that for the PEF slope, for which a linear regression analysis was required. This implies that %ΔMA and ΔMA are potential choices for the development of asthma exacerbation prediction model in the future. Second, in real-time asthma exacerbation prediction, the changing trend in the PEF trajectory may be a more accurate predictor compared with other predictors associated with PEF variability in univariate model frameworks. Predictors focusing on PEF variability, such as CV, showed relatively lower discriminant performance and seemed to conflict with the results of a previous study [19]. This may be because of the heterogeneity of the research population. In the present study, we only included Asian patients with severe asthma living in Hokkaido Prefecture, Japan. Third, determining discriminant performance using only one predictor from PEF records is undesirable even while using the %ΔMA, ΔMA, or 14-day slope. This implies the need of a multivariate predictive approach for asthma exacerbation prediction. Fourth, because of the complexity of exacerbation onset, univariate prediction models based on independent variables calculated from the PEF trajectory are insufficient to accurately predict the onset of exacerbation. The findings of the subgroup analysis supported this point through the results of the Hosmer–Lemeshow test for the atopy-negative and never-smoker subgroups. Our multivariate regression analysis further substantiated this result. By integrating covariates such as atopy and smoking status, the AUC of the prediction model exhibited a marked increase. Compared to the univariate models, both the multivariate and mixed models demonstrated superior discriminative performance. However, constructing both the multivariate and mixed models necessitated the use of a computer, leading to a compromise in calculation simplicity. Furthermore, to establish

individual random terms in the mixed model, the patient's previous exacerbation history was essential.

We previously reported asthma exacerbations to be associated with PBE and FeNO [24,34]. However, these indicators were not for daily monitoring but for determining clinical phenotypes. Therefore, although PBE and FeNO have helped identify populations prone to asthma exacerbations, they have not been able to predict the time of exacerbations without a time-dependent variable. Using indices that can be measured daily, such as PEF, the timing of exacerbations is expected to be predicted. Prioritizing the measurement of PEF in patients with clinical phenotypes prone to exacerbations may result in the development of strategies to prevent exacerbations.

There are certain limitations to our study. The PEF values were obtained by measuring once in the morning and once in the evening each day, with the raw measurements being recorded. These observations of PEF may be susceptible to operational errors that could potentially influence the data. The success of exacerbation prediction, derived from predictors calculated from PEF monitoring data, hinges on the patient's consistent and accurate recording of PEF values. However, study has demonstrated that real-world adherence to this practice can be low, with rates falling below 50% [35]. Also, the computational burden of utilizing a multivariate regression model for exacerbation prediction has constrained its adoption in clinical settings. We believe that the proliferation of smartphone-based portable PEF meters could offer a viable solution to these challenges [36]. These innovative devices are capable to automatically record and validate PEF data, as well as calculate the risk of exacerbation, thereby mitigating the issues associated with operational errors and patient non-adherence. The

gathering of evidence and developing the exacerbation prediction model are integral to elevating predictive capabilities of smartphone-based portable PEF meters. The Hi-CARAT study did not document the specific timing of fast-acting bronchodilator administration. Instead, it defined an exacerbation based on the use of systemic corticosteroids for more than three days and/or the need for hospitalization due to a severe exacerbation. Consequently, this approach restricted our ability to explore additional potential predictive indicators, such as the percentage of post-bronchodilator PEF response. Given that daily symptom diaries were not longitudinally recorded in the Hi-CARAT study, a direct comparison of the predictive abilities between our proposed model and symptom diary-based asthma control tools, such as the Asthma Symptom Utility Index, cannot be made. Developing a predictive model for asthma exacerbation that incorporates both subjective and objective indicators is one of our research objectives in the future. Our results may require external validation because the present study included patients with severe asthma from Japan. The covariance of exacerbation was ignored to simplify the model for the facilitation of self-monitoring; however, exacerbations are recurrent events, and some patients may be more likely to have exacerbation onset. A joint model-extended version that can handle event covariance structure and endogenous longitudinal covariates simultaneously is desirable over logistic regression models. Despite these limitations, our research provides significant information on real-time asthma exacerbation prediction using predictors extracted from the PEF trajectory. In subsequent research, we aim to employ a joint model that integrates both the longitudinal PEF record and the exacerbation period, leveraging the full potential of Hi-CARAT data. Our goal is to devise a more clinically pertinent prediction model for patients with severe asthma.

We identified the novel applicable predictive factors for exacerbation in severe asthma. We hope the results of this study help in the construction of a clinically applicable exacerbation prediction model in the future.

Table 1. Patient characteristics (N = 127)

Characteristics	N (%) / Mean ± standard deviation
Male	51 (40.2%)
Age, y	58.0 ± 13.1
Age at onset of asthma, y	38.2 ± 17.7
Body mass index, kg/m^2	25.6 ± 5.5
Atopy positivity	81 (63.8%)
Smoking status	N (%) / Median (interquartile range)
Current	13 (10.2%)
Previous	62 (48.8%)
Never	52 (40.9%)
Pack-years	5.0 (0, 22.7)
Peripheral blood/serum	Geometric mean (log10 standard deviation)
Eosinophils, cells/μl	203.4 (0.5)
Neutrophils, cells/μl	4,554.4 (0.17)
Corticosteroid use	N (%) / Mean ± standard deviation
Inhaled corticosteroid dose, μg	1649 ± 574
Oral corticosteroid use	45 (35.4%)
Pulmonary function	Mean ± standard deviation/median (interquartile range)
FEV_1 % predicted (prebronchodilator)	82.8 ± 19.4
FEV_1/FVC	67.1 ± 13.0
PEF, L/min	307.0 (247.0, 397.0)
%prePEF	78.6% (61.7%, 96.4%)
Number of exacerbation onsets	1 (0, 4)

Overall, 127 patients with severe asthma were included. FEV_1 was measured when participants were hospitalized in the Hokkaido University Hospital, whereas PEF data were collected by longitudinal self-monitoring.

Table 2. Discriminant performance of each potential cutoff value

	Cutoff	Sensitivity	Specificity
ΔMA	1.250	0.692	0.529
	2.500	0.673	0.577
	3.750	0.673	0.621
	5.000	0.615	0.662
	6.250	0.577	0.700
%ΔMA	0.010	0.654	0.630
	0.014	0.615	0.680
	0.018	0.596	0.724
	0.022	0.519	0.762
	0.026	0.481	0.796

Serial potential cutoff values of PEF ΔMA and $\%\Delta$MA and their discriminant performance indicators, including sensitivity and specificity are listed. Sensitivity decreases with the increase in cutoff. In contrast, specificity increases as the cutoff increases.

Table 3. Model calibration and subgroup analysis

	Participants		AUC		Hosmer–Lemeshow p-value	
	N	%	ΔMA	%ΔMA	ΔMA	%ΔMA
All	127	100%	0.659	0.665	0.654	0.483
Age (y)						
≥65	47	0.370	0.632	0.643	0.696	0.566
< 65	80	0.630	0.670	0.674	0.419	0.518
Sex						
Male	51	0.402	0.599	0.597	0.391	0.445
Female	76	0.598	0.686	0.687	0.134	0.125
Atopy						
Positive	81	0.638	0.663	0.664	0.737	0.630
Negative	46	0.362	0.657	0.666	0.026*	0.017*
Smoking						
Yes	75	0.591	0.604	0.611	0.542	0.501
No	52	0.409	0.757	0.754	0.034*	0.049*

Statistical significance is set at 0.05. The significances are shown in subgroup analysis when sample data are categorized by atopy or smoking status, suggesting that on comparing with the univariate logistical models, more comprehensive models may be preferable considering atopy and smoking statuses.

Figure 1. Data demonstration and exclusion criteria

A part of participant number 98's PEF values recorded between September 2011 and April 2012 were demonstrated. The y-axis represents PEF (L/min) and the x-axis represents the recording date. The pink areas are the exacerbation periods.

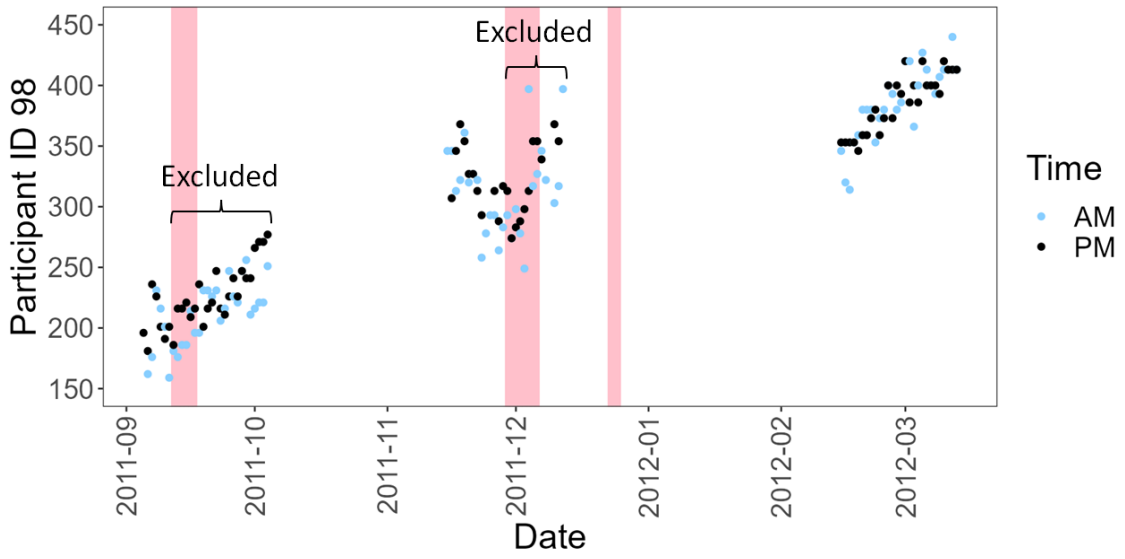


Figure 2. ROCs for slope, %predPEF, %bestPEF, Min/Max, and CV

On the panel A, C, D, variables on days 3, 7, and 14 are indicated using red, green, and blue lines, respectively. The discriminant performance is given in graph legends. The 14-day PEF slopes exhibit the best discriminant performance that AUC = 0.645.

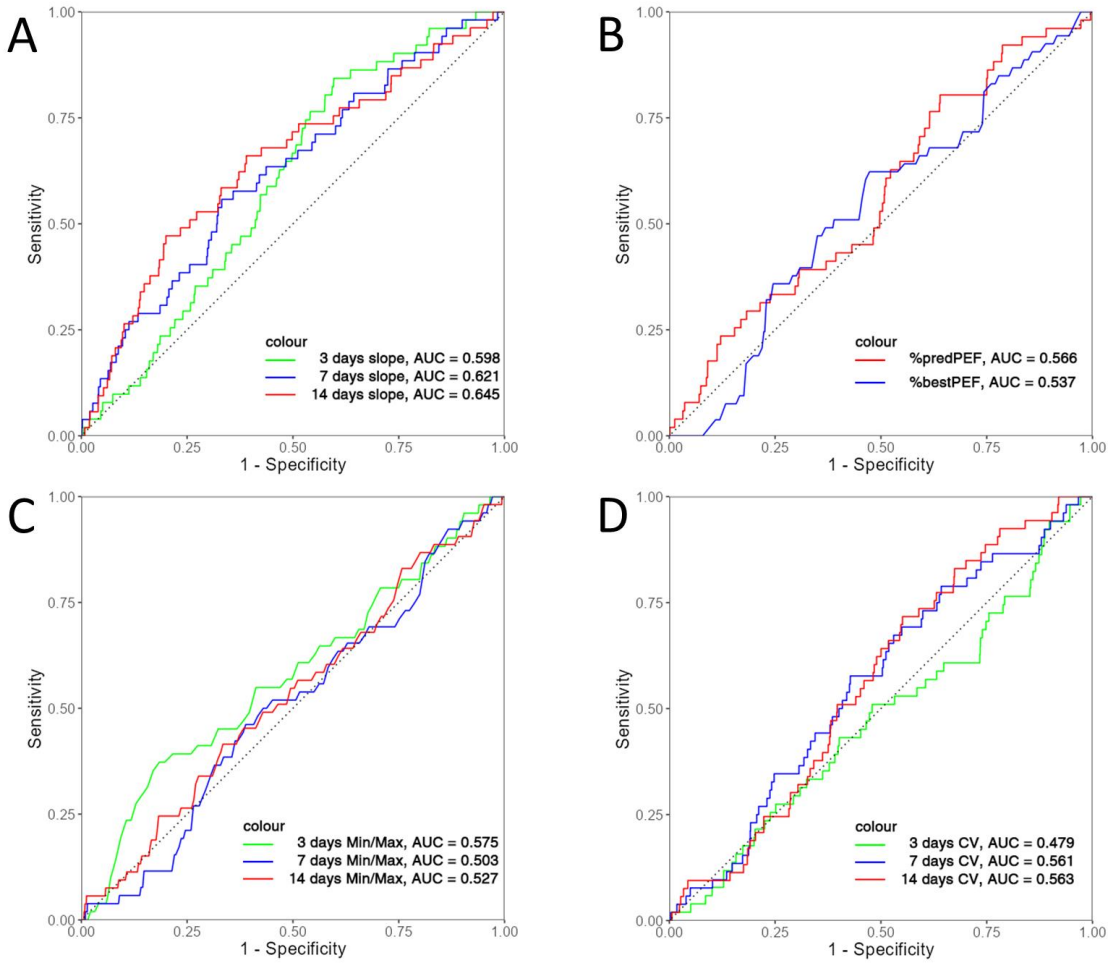


Figure 3. ROC for ΔMA and %ΔMA

ΔMA and %ΔMA deliver the top two discriminative performances. This exceptional performance is consistent within the context of multivariate regression. When models integrated random intercepts for participants, the AUC values for ΔMA and %ΔMA rose to 0.907 and 0.919, respectively.

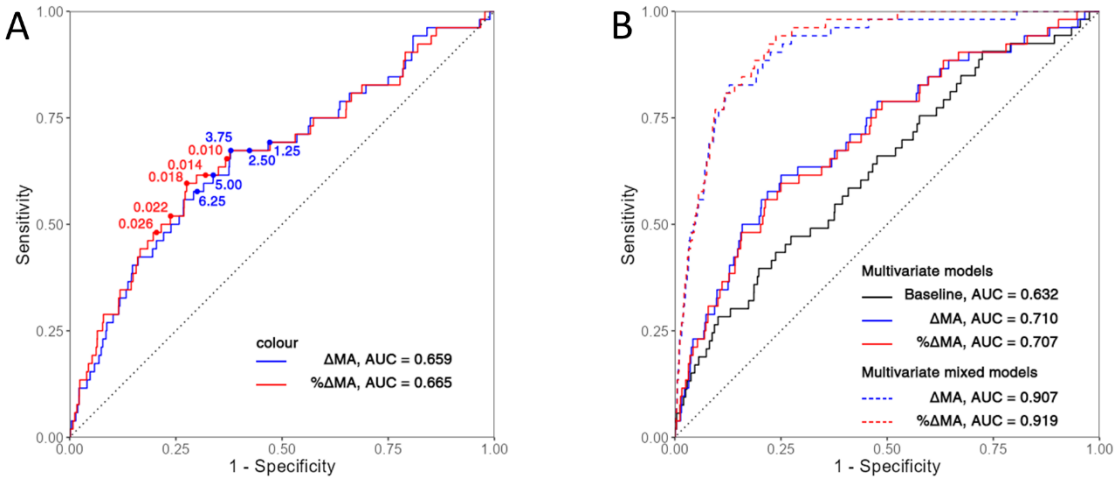
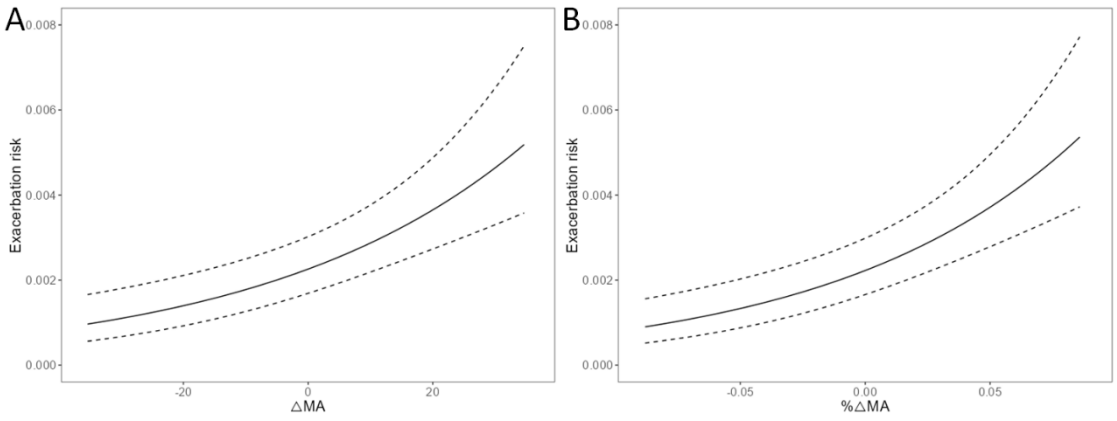


Figure 4. Prediction curves for ΔMA and %ΔMA

The vertical axis indicates the risk of exacerbation onset on the next day. The horizontal axis presents the independent variable ΔMA or %ΔMA. The broken line represents the 95% prediction interval of exacerbation risk.



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