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اصول تنظیم قراردادها

آموزش مهارت های کاربردی در تدوین و چاپ مقاله
Logistic Regression Model for Prediction of Airway Reversibility Using Peak Expiratory Flow

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Background: Using peak expiratory flow (PEF) as an alternative to spirometry parameters (FEV1 and FVC), for detection of airway reversibility in diseases with airflow limitation is challenging. We developed logistic regression (LR) model to discriminate bronchodilator responsiveness (BDR) and then compared the results of models with a performance of >18%, >20%, and >22% increase in ΔPEF% (PEF change relative to baseline), as a predictor for bronchodilator responsiveness (BDR).

Materials and Methods: PEF measurements of pre-bronchodilator, post-bronchodilator and ΔPEF% of 90 patients with asthma (44) and chronic obstructive pulmonary disease (46) were used as inputs of model and the output was presence or absence of the BDR.

Results: Although ΔPEF% was a poor discriminator, LR model could improve the accuracy of BDR. Sensitivity, specificity, positive predictive value, and negative predictive value of LR were 68.89%, 67.27%, 71.43%, and 78.72%, respectively.

Conclusion: The LR is a reliable method that can be used clinically to predict BDR based on PEF measurements.

Key words: Peak expiratory flow; Spirometry; Airway reversibility; Logistic regression

INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are respiratory diseases that are increasing in rate all over the world especially in developing countries (1). Assessing the presence and degree of airflow limitation and reversibility in airways is critical, especially in the elderly with asthma or COPD (2, 3). Spirometry is a standard tool that is used for the diagnosis of airflow limitation and its severity. The bronchodilator responsiveness (BDR) test is carried out by performing baseline spirometric evaluation, with repeated spirometry after administration of a short-acting bronchodilator, and assessing the change in forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), or vital capacity. However, spirometry is not widely available and its use is limited in primary care clinics (4-9). Moreover, a general practitioner, who may not have access to a spirometer, visits patients with asthma or COPD. In this regard, both physician and patient need a cheaper, simpler and more accessible method with high levels of reliability. Peak expiratory flow (PEF) is maximal expiratory flow that is utilized clinically in asthma monitoring (10-15). PEF measures large airways’ (diameter>2mm) function, which is effort dependent whereas FEV1 mirrors large and intermediate airways (15). It is assumed that FEV1 is moderately dependent on PEF and there is a high correlation between them within and between patients (16, 17). Thus, measurement of PEF is suggested as an...
alternative for spirometry and meets those criteria (3, 4, 18-20).

Since bronchodilator response in asthmatic patients occurs first in large airways and to a lesser extent with delay in small airways, PEF may have some correlations with FEV1 after bronchodilator administration. Although there is evidence regarding the correlation of PEF and spirometry parameters (16, 17), there are controversies in previous findings and this correlation is questioned in airway limitation (9, 15). We need more accurate evidence regarding validity of measuring peak flow to assess airflow limitation and reversibility in asthmatics or COPD patients.

The aim of this study was to evaluate the efficacy of PEF measurement as an alternative to spirometry in predicting airway reversibility and developing logistic regression (LR) model, based on PEF values, to predict BDR in patients with asthma and COPD.

MATERIALS AND METHODS

Our prospective study was carried out from September 2010 to May 2011 in a teaching hospital. After the approval of institutional review board and ethics committee (Tehran University) an informed consent was obtained from patients. We prospectively studied patients with asthma and COPD. All examinations were done by the same pulmonologist to keep the diagnosis reliable and prevent variations according to ATS criteria (21). After doing examinations and taking history, patients with the following criteria were excluded from the study: other pulmonary diseases, upper respiratory tract infection in the previous six weeks, cardiac or brain infarction in the previous one month, aortic, abdominal or brain aneurism, dementia, abdominal or thoracic surgery, and occupational exposure. Moreover, Short acting bronchodilator medications had to be discontinued 8 hours and long acting bronchodilators, corticosteroids and theophylline had to be withheld 48 hours prior to lung function tests. Additionally, patients had to avoid smoking 1 hour, food intake 4 hours, exercise 1 hour and food or drinks that have caffeine or alcohol 4 hours before the tests.

Confirmed asthmatic and COPD patients who had used bronchodilators and steroids and were able to do lung function maneuvers were selected and entered the study consecutively. Patients’ demographic data and clinical conditions were obtained by means of examinations and interview and entered into standard forms. FEV1, FVC and FEV1/FVC were measured using a Jaeger SpiroPro hand-held spirometer (Viasys Healthcare, Hoechberg, Germany) and PEF was measured by mean of peak flow meter (PFM20; OMRON Healthcare Ltd; UK). As a routine activity, spirometer was calibrated each day using a 3-liter syringe.

Three efforts of patients (<5% difference) were measured for all lung function tests and the highest levels were written down in forms. For PEF, the highest (PEFH) and lowest (PEFL) levels were chosen among three best tests. Acquaintance FEV1 values were marked as FEV1H and FEV1L respectively. After recording the baseline FEV1 and PEF, bronchodilator (BD) was administered for the patients. Salbutamol (Abureihan Pharmaceutical Co. Tehran, Iran), which is a short acting BD and available as a metered dose spray was administered for patients by means of a spacer (Tehran Fanavar Teb Co., Tehran, Iran) to gain the highest bronchodilation. Fifteen minutes after BD inhalation, lung function tests were repeated. Within this period, patients must be sitting and avoiding any activities that may affect the respiratory tests. Acceptability and reproducibility of spirometry were evaluated according to ATS criteria (21). The change in PEF, FEV1 and FVC, both absolute (ΔPEF, ΔFEV1 and ΔFVC) and relative to baseline (ΔPEF%, ΔFEV1% and ΔFVC%), were calculated. Bronchodilator responsiveness and reversibility were defined by at least 12% improvement over baseline in either FEV1 or FVC, along with an absolute minimal volume increment of 200ml, based on ATS guidelines (21). Performance of >18, >20, and >22 increase in ΔPEF% in subjects correctly identified with airway reversibility was assessed. All recordings were verified by the referrer pulmonologist.
**Logistic regression model:** LR is useful for situations where researcher wants to be able to predict the presence or absence of a characteristic or outcome based on values of a set of predictor variables. LR regresses a dichotomous dependent (target) variable on a set of independent (predictor) variables. It is similar to a linear regression model but is suited to models where the dependent variable is dichotomous. LR model was developed using SPSS software (for windows, V.16, SPSS Inc., Chicago, IL). We used PEF values (before and after BD) and ΔPEF% as inputs of model and the output was the presence or absence of the BDR.

**Statistical analysis:**
Correlation between changes in PEF and a corresponding change in FEV1 or FVC were assessed by Pearson’s correlation coefficient. Accuracy (the number of correct predictions divided by total predictions), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), likelihood ratio positive (LR+) and likelihood ratio negative (LR−) of ΔPEF% and LR were calculated. The discriminating power of these methods to predict BDR can be measured by receiver operating characteristic (ROC) curves.

**RESULTS**
Of the 133 participants in this Study, 43 subjects were excluded because they did not meet ATS acceptability and reproducibility criteria. Data from 90 subjects (44 asthmatics and 46 COPD patients) were analyzed. The mean age of patients was 47.3±12.4 years (range 20-69 yrs). Gender distribution was 63% males and 37% females, 23.4% of patients reported being active smokers, 23.3% reported being former smokers (quitted more than a year ago), and 53.3% mentioned that they never smoked. BDR was documented by standard spirometric criteria in 55 (61.1%) of these patients.

The mean values of respiratory parameters: FEV1, FVC and PEF were 2.103±0.286 (L), 2.593±0.296 (L), and 296±85 (L/min), respectively; the changes in FEV1 (ΔFEV1%), FVC (ΔFVC%) and PEF (ΔPEF%) after BD were 0.941±0.114 L (12.09±1.35), 0.254±0.045 L (11.18±3.16), and 39.74±27.1 L/min (20.49±4.88), respectively. Although ΔPEF and ΔPEF% significantly correlated with corresponding changes in FEV1 and FVC (p<0.001), the absolute values of the correlation coefficients were low.

Table 1 shows the performance indices of ΔPEF% and LR in predicting BDR, compared to the standard spirometric criteria. ΔPEF% was a poor discriminator for estimating BDR. In contrast, the LR model could improve the accuracy of BDR. Since accuracy of ΔPEF%>20 for estimating airway reversibility was better than the other two cut-off values (>18 and >22 increase in ΔPEF%), we used ΔPEF%>20 for data analysis.

Table 1. Comparison of predictive performance of ΔPEF% and LR for predicting BDR

<table>
<thead>
<tr>
<th></th>
<th>ΔPEF%&gt;18</th>
<th>ΔPEF%&gt;20</th>
<th>ΔPEF%&gt;22</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy (%)</td>
<td>56.67</td>
<td>63.33</td>
<td>55.56</td>
<td>68.89</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>67.27</td>
<td>60.13</td>
<td>43.64</td>
<td>67.27</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>40.30</td>
<td>67.57</td>
<td>74.09</td>
<td>71.43</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>63.79</td>
<td>77.50</td>
<td>72.07</td>
<td>70.27</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>43.75</td>
<td>52.17</td>
<td>45.61</td>
<td>58.14</td>
</tr>
<tr>
<td>LR+</td>
<td>1.12</td>
<td>1.91</td>
<td>1.70</td>
<td>2.35</td>
</tr>
<tr>
<td>LR−</td>
<td>0.82</td>
<td>0.58</td>
<td>0.76</td>
<td>0.46</td>
</tr>
</tbody>
</table>

PPV positive predictive value, NPV negative predictive value, LR+ likelihood ratio positive, LR− likelihood ratio negative.

Figure 1 depicts the ROC curves for the %ΔPEF>20 and LR model. Results of the comparison of the ROC curves are shown in Table 2. ROC analysis estimates a curve that describes the inherent trade-off between sensitivity and specificity of a prediction tool. Discriminatory power is measured by area under the curve (AUC), which is a particularly important metric for evaluating prediction tools because it is the average sensitivity over all possible specificities. AUC may range from 0 to 1, with area of 1.0 representing perfect discrimination and an area of 0.5 representing what is expected by chance alone. According to Figure 1 and Table 2, the LR model significantly outperformed the %ΔPEF>20 (p<0.05).
**DISCUSSION**

In this study, we developed LR model in order to predict BDR based on PEF values in patients with asthma and COPD. Although $\Delta$PEF% was a poor discriminator, the LR model could improve the accuracy of BDR finding using PEF values (preBD and postBD) and its changes as inputs.

In a clinical setting, FEV1, FVC and FEV1/FVC before and after BD are the main parameters in airway reversibility diagnosis. However, spirometer is an expensive apparatus and is inaccessible in most primary care centers and physician offices. Alternatively, we suggest peak flow meter for substitution which is a portable and cheap tool. Multiple investigations have been performed to show the relationship between PEF, FEV1 and FVC and the predictability of PEF in airflow limitation. Some studies have shown significant correlations between PEF and spirometry parameters. However, this correlation was reported non-significant in some investigations (9, 15), while the absolute coefficient values were low (3, 24-27), which are in agreement with our finding. Therefore, there are controversies in findings and this correlation is questioned in airflow limitation.

Thus, the question is whether the PEF is a reliable alternative for spirometry and the important challenge is using PEF for predicting BDR, especially in airflow limitation. Aggarwal and colleagues showed that $\Delta$PEF and $\Delta$PEF% had poor discrimination power in identifying BDR (24). The highest specificity of 88% was found with $\Delta$PEF increase of 80 l/min versus a 12% improvement over baseline in either FEV1 or FVC, along with an absolute volume increase of 200ml. Dekker et al. could detect BDR (>9% increase in FEV1) in patients with asthma and COPD based on PEF (60 l/min increase in PEF) with a sensitivity, specificity and PPV of 68%, 93%, and 87%, respectively (27). In another study on asthmatic patients, a >18% increase in the PEF predicted FEV1 >15% with a sensitivity, specificity, PPV and NPV of 85%, 79%, 77%, and 86%, respectively (28). Since the patients and the definition of BDR were different in previous studies, it is difficult to compare their results with our findings. However, our results confirmed previous investigations regarding the fact that PEF was a poor predictor of airway reversibility. In this research, BDR (>12% increase in FEV1 or FVC) was detected using a $\geq$20% increase in $\Delta$PEF% with a sensitivity, specificity, PPV and NPV of 60%, 68.57%, 75%, and 52.17%, respectively.

The AUC is a measure of a model’s discriminatory power. According to the observation by Swets et al. (29), an AUC of $\geq$0.7 is diagnostically useful. In our study, LR model could discriminate BDR well (Table 2). The LR model significantly outperform the $\Delta$PEF%>20 (AUC=0.694 vs. 0.643, p<0.05) in the test setting. The LR model also had better simultaneous accuracy (68.89%), sensitivity (67.27%), and specificity (71.43%).
To our knowledge, there is no study using mathematical model to reveal BDR based on PEF values. Our findings show that the LR has a good ability to predict airway reversibility by using different values of PEF as input.

The real time use of the LR is not difficult. The number of hospitals that have an electronic medical record is increasing rapidly. Once trained, the LR could reside in the background of the clinical information systems. The data used by our LR is the standard information routinely collected from the patients. Once entered into the electronic record, these data could then be used by the LR to generate the probability of the predicted outcome. LR accuracy can be continuously improved over time because it can constantly be retrained as more patients are added to the system (23, 30).

Some limitations to this study need to be addressed. First, the LR was not tested in real time. It is not clear how physicians will respond if they are provided with LR predicted outcome of BDR. However, a reliable second opinion is often helpful in medical decision making with or without a detailed understanding of how it works. Secondly, this study was carried out at a single institution. These findings must be corroborated on patients from multiple locations.

CONCLUSION

Our results indicated that ΔPEF% is a poor discriminator of BDR. However, the LR model could improve the accuracy of BDR finding using PEF values, and can be used clinically as an inexpensive and rapid method.

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