An accurate prediction model to identify undiagnosed at-risk patients with COPD: a cross-sectional case-finding study

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Underuse or unavailability of spirometry is one of the most important factors causing underdiagnosis of COPD. We reported the development of a COPD prediction model to identify at-risk, undiagnosed COPD patients when spirometry was unavailable. This cross-sectional study enrolled subjects aged ≥40 years with respiratory symptoms and a smoking history (≥20 pack-years) in a medical center in two separate periods (development and validation cohorts). All subjects completed COPD assessment test (CAT), peak expiratory flow rate (PEFR) measurement, and confirmatory spirometry. A binary logistic model with calibration (Hosmer-Lemeshow test) and discrimination (area under receiver operating characteristic curve [AUROC]) was implemented. Three hundred and one subjects (development cohort) completed the study, including non-COPD (154, 51.2%) and COPD cases (147; stage I, 27.2%; II, 55.8%; III–IV, 17%). Compared with non-COPD and GOLD I cases, GOLD II–IV patients exhibited significantly higher CAT scores and lower lung function, and were considered clinically significant for COPD. Four independent variables (age, smoking pack-years, CAT score, and percent predicted PEFR) were incorporated developing the prediction model, which estimated the COPD probability (P_{COPD}). This model demonstrated favorable discrimination (AUROC: 0.866/0.828; 95% CI 0.825–0.906/0.751–0.904) and calibration (Hosmer-Lemeshow P = 0.332/0.668) for the development and validation cohorts, respectively. Bootstrap validation with 1000 replicates yielded an AUROC of 0.866 (95% CI 0.821–0.905). A P_{COPD} of ≥0.65 identified COPD patients with high specificity (90%) and a large proportion (91.4%) of patients with clinically significant COPD (development cohort). Our prediction model can help physicians effectively identify at-risk, undiagnosed COPD patients for further diagnostic evaluation and timely treatment when spirometry is unavailable.

npj Primary Care Respiratory Medicine (2019) 29:22; https://doi.org/10.1038/s41533-019-0135-9

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a key cause of morbidity and mortality worldwide.1,2 However, the disease has been considerably underdiagnosed.3 The causes of underdiagnosis include low awareness regarding COPD in the general population and among doctors in charge, as well as the low use of spirometry.4 The absence of patients in clinics is probably the leading cause because they might lack symptom perception and disease knowledge. In addition, a high proportion of under-diagnosis occurs in primary care settings.5–7 Underuse or unavailability of spirometry is the most common cause of underdiagnosis in primary care settings.4,8–7 Underuse or unavailability of spirometry is one of the most important factors causing underdiagnosis of COPD. We reported the development of a COPD prediction model to identify at-risk, undiagnosed COPD patients when spirometry was unavailable. This cross-sectional study enrolled subjects aged ≥40 years with respiratory symptoms and a smoking history (≥20 pack-years) in a medical center in two separate periods (development and validation cohorts). All subjects completed COPD assessment test (CAT), peak expiratory flow rate (PEFR) measurement, and confirmatory spirometry. A binary logistic model with calibration (Hosmer-Lemeshow test) and discrimination (area under receiver operating characteristic curve [AUROC]) was implemented. Three hundred and one subjects (development cohort) completed the study, including non-COPD (154, 51.2%) and COPD cases (147; stage I, 27.2%; II, 55.8%; III–IV, 17%). Compared with non-COPD and GOLD I cases, GOLD II–IV patients exhibited significantly higher CAT scores and lower lung function, and were considered clinically significant for COPD. Four independent variables (age, smoking pack-years, CAT score, and percent predicted PEFR) were incorporated developing the prediction model, which estimated the COPD probability (P_{COPD}). This model demonstrated favorable discrimination (AUROC: 0.866/0.828; 95% CI 0.825–0.906/0.751–0.904) and calibration (Hosmer-Lemeshow P = 0.332/0.668) for the development and validation cohorts, respectively. Bootstrap validation with 1000 replicates yielded an AUROC of 0.866 (95% CI 0.821–0.905). A P_{COPD} of ≥0.65 identified COPD patients with high specificity (90%) and a large proportion (91.4%) of patients with clinically significant COPD (development cohort). Our prediction model can help physicians effectively identify at-risk, undiagnosed COPD patients for further diagnostic evaluation and timely treatment when spirometry is unavailable.

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Received: 9 July 2018 Accepted: 2 May 2019
Published online: 28 May 2019

Published in partnership with Primary Care Respiratory Society UK
management of COPD. The CAT evaluates the severity of respiratory symptoms as well as the impact on the quality of life. Thus, the CAT might potentially serve as a case-finding tool. Both the PEFR and CAT are common tools in real-life practice. Combining the PEFR and CAT may provide a new and precise tool for identifying COPD cases. This possibility is worthy of further investigation.

Previous studies have applied two-stage approaches, using various screening questionnaires to select high-risk cases and then, conducted PEFR measurement with these cases. These studies concluded that the aforementioned strategy improved the accuracy of COPD identification. However, the strategy may potentially miss COPD cases in groups categorized as low-risk by the questionnaires, who might be unaware of the disease or be less perceptive to its symptoms. Thus, we initiated a one-step COPD case-finding study by inviting all at-risk subjects to complete the CAT, PEFR measurement, and confirmatory spirometry. We aimed to develop a logit model by using easily assessed variables, including the age, smoking status, PEFR, and CAT score, to estimate the probability of COPD (P_COPD) and clinically significant COPD. Moreover, the robustness of the final model was examined through sensitivity analysis.

RESULTS
Patient characteristics
In the development cohort, 373 consecutive subjects were invited and 301 completed the study (Supplementary Fig. 1a). Most of the development cohort subjects (242, 80.4%) directly came from the community without any referrals, and the others were referred from non-pulmonary clinics (39, 13%) at our hospital and from general practitioners (GPs) (20, 6.6%) in the community. The subjects were categorized into the non-COPD (154, 51.2%) and newly diagnosed COPD (147, 48.8%) groups (Table 1). Of the 147 COPD cases, 40 (27.2%) were categorized as stage I (post-bronchodilator [BD] forced expiratory volume in first second [FEV1] ≥80%), 82 (55.8%) were stage II (50% ≤ post-BD FEV1 < 80%), and 25 (17%) were stage III–IV (post-BD FEV1 <50%) as per the severity classification proposed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD). Compared with the non-COPD subjects and COPD GOLD stage I patients, GOLD stages II–IV COPD patients had significantly higher symptoms (CAT score) and lower lung function variables (including the PEFR, pre-BD, and post-BD FEV1), and forced vital capacity (FVC). By contrast, GOLD stage I patients were similar to non-COPD subjects in terms of the symptoms and lung function (Table 1). Thus, GOLD stages II–IV COPD patients were considered clinically significant for COPD. For all the subjects, the CAT score was weakly and negatively associated with the percent predicted PEFR (%PEFR) and post-BD percent predicted FEV1 (%FEV1) (Pearson’s r = −0.379 and −0.409, respectively; both P < 0.001). However, the post-BD %FEV1 was strongly correlated with the %PEFR (Pearson’s r = 0.332 and 0.668, respectively), which indicated accurate calibration. The discrimination was also favorable in terms of the AUROC for both the development (0.866) and validation (0.828) cohorts (Fig. 1). Bootstrap validation revealed similar discrimination (AUROC: 0.865, 95% confidence interval [CI] 0.821–0.905).

Predictive performance and cutoffs
The mean estimated P_COPD was 0.75 and 0.23 for the COPD patients and non-COPD subjects, respectively (Table 3). P_COPD ≥0.44 exhibited favorable diagnostic accuracy for identifying cases with COPD. The cut-off of P_COPD ≥0.44 correctly identified 77.6% of total COPD cases, with the missing COPD cases (false negatives; those with P_COPD <0.44 but actually had COPD) having a few symptoms (mean CAT score 6.3) and preserved lung function (mean post-BD FEV1, 90%; Supplementary Table 2). In comparison to P_COPD ≥0.44, P_COPD ≥ 0.65 identified COPD patients with higher specificity (90 vs. 79%; Table 4), a lower false-positive rate (13.9 vs. 21.9%; Fig. 2) and a higher proportion of clinically significant COPD patients (GOLD II/IV, 91.4 vs. 86.0%; Fig. 2). A cut-off CAT score of <7 and <10 resulted in 40.1 and 59.2% missing COPD cases, respectively, with a mean post-BD %FEV1 of 79 and 77%, respectively (Supplementary Table 2).

DISCUSSION
Four variables were employed in this study, namely the age, smoking pack-years, CAT, and %PEFR to form an accurate
symptoms, and air.

Diagnosis of COPD is based on exposure risks, respiratory identifying cases of COPD. A prediction model can serve as a clinically practical strategy for sensitivity when using the %PEFR alone than when using the CAT alone. The four-variable model demonstrated the highest sensitivity, offering a one-step, rapid estimation of COPD cases. To our knowledge, this study is unique that the aforementioned four variables have been employed as a one-step approach to identify COPD in at-risk subjects. \( P_{\text{COPD}} \) can be calculated immediately by entering the four variables into an equation by using a software program. The satisfactory accuracy and simplicity of our model offer the potential for wide application. The model could help physicians identify patients at risks of COPD, particularly in primary care settings where confirmatory spirometry is unavailable.

Confirmation of airflow limitation by spirometry is required for COPD diagnosis. After considering the benefits of improving patient outcomes and altering the disease process, the US Preventive Services Task Force did not recommend screening for COPD in asymptomatic subjects through questionnaires and pulmonary function tests of improving patient outcomes and altering the disease process, the US Preventive Services Task Force did not recommend screening for COPD in asymptomatic subjects through questionnaires and pulmonary function tests.

\[ \text{Spirometry, pre-BD} \]

|                  | All   | Total subjects | COPD | Non-COPD | \( P^a \) | COPD patients divided by GOLD stage | \( P^a \) |
|------------------|-------|----------------|------|----------|--------|------------------------------------|--------|
| Numbers          | 301   | 147            | 154  |          |        | GOLD I                             | 40     |
| Age, years       | 70.7 ± 13.2 | 75.2 ± 11.3 | 66.5 ± 13.5 | <0.001 | 77.9 ± 9.9 | 7.50 ± 11.2 | 72.3 ± 10.8 | <0.001 |
| Gender, male (%) | 287 (95) | 139 (95) | 148 (96) | 0.524 | 39 (98) | 77 (94) | 23 (92) | 0.652 |
| Current smoker (%) | 128 (43) | 56 (38) | 72 (47) | 0.129 | 14 (35) | 30 (37) | 12 (48) | 0.315 |
| Smoking pack-years | 45.4 ± 25.0 | 50.6 ± 26.0 | 40.3 ± 20.1 | <0.001 | 52.3 ± 29.9 | 49.5 ± 25.9 | 51.7 ± 19.8 | 0.004 |

COPD assessment test, COPD chronic obstructive pulmonary disease, FEV\(_1\), forced expiratory volume in the first second, FVC forced expiratory capacity, PEFR peak expiratory flow rate

\( ^a \) Independent \( t \)-test, COPD vs. non-COPD

\( ^b \) One-way ANOVA test, compare 4 groups: non-COPD, GOLD I, GOLD II, and GOLD III-IV

\( ^c \) Chi-square test

\( ^d \) Post-hoc Bonferroni test, \( P < 0.05 \), vs. non-COPD

\( ^e \) Post-hoc Bonferroni test, \( P < 0.05 \), vs. GOLD I

\( ^f \) Post-hoc Bonferroni test, \( P < 0.05 \), vs. GOLD II

prediction model for identifying undiagnosed COPD. The favorable model performance indicates that the prediction model is robust and accurate. When using only a single variable to identify COPD, the CAT is inadequate. A higher accuracy was obtained when using the %PEFR alone than when using the CAT alone. However, the four-variable model demonstrated the highest accuracy, offering a one-step, rapid estimation of \( P_{\text{COPD}} \). Moreover, with a tight cut-off, the prediction model could identify clinically significant COPD with a high degree of specificity. Therefore, the prediction model can serve as a clinically practical strategy for identifying cases of COPD.

The prevalence of COPD among older adults is high, and the diagnosis of COPD is based on exposure risks, respiratory symptoms, and airflow limitations according to the guideline. Previous epidemiological studies have reported that increasing age and smoking pack-years are strongly associated with COPD. Similarly, case-finding studies have found that COPD cases have significantly higher CAT scores and lower PEFRs than non-COPD cases. To our knowledge, this study is unique that the aforementioned four variables have been employed as a one-step approach to identify COPD in at-risk subjects.
Currently, PEFR reduction was one of the most common criteria for COPD cases with compromised lung function (Supplementary Table 2). Thus, the CAT alone is inadequate as a screening tool for identifying undiagnosed COPD cases. It may be argued that this study was conducted in a medical center, where the patient population may differ from those in primary care settings. However, outpatients in medical centers in Taiwan are atypical of those in other countries, which is ascribed to the unique healthcare system in Taiwan. This government-run, single-payer health insurance system is characterized by compulsory coverage for all citizens, convenient accessibility, and low costs with almost all medically necessary services covered. The system has a weak gatekeeper role and no restrictive referral regulations. Thus, outpatients have freedom to choose any specialist in any hospital, including a medical center, without a referral.33 This loose regulation results in most Taiwanese people visiting a doctor directly at a medical center. The Taiwan National Health Insurance Administration announced that a substantially lower percentage of outpatient visits accounted for over 80% of the subjects in both primary care settings. However, outpatients in medical centers sought specialist care without any referrals. In this study, those without referrals and with similar results reported in previous studies.31,32 A CAT score of ≥7 yielded an optimal cut-off for the diagnostic accuracy in this study. The GOLD strategy considers that COPD cases with CAT scores ≥10 are symptomatic.16 However, both a CAT score ≤7 or <10 resulted in a high proportion of missing COPD cases with compromised lung function (Supplementary Table 2). Thus, the CAT alone is inadequate as a screening tool for identifying undiagnosed COPD cases.

Table 2. Variables associated with the diagnosis of COPD in the development cohort

| Table 2. Variables associated with the diagnosis of COPD in the development cohort |
|-----------------------------------------------|
| **Univariate** | **Multivariate** |
| β | Odds ratio | 95% CI | Pβ | β | Odds ratio | 95% CI | Pβ |
|---|---|---|---|---|---|---|---|
| Age, years | 0.055 | 1.06 | 1.04–1.08 | <0.001 | 0.045 | 1.05 | 1.02–1.07 | <0.001 |
| Sex, male | – 0.35 | 0.71 | 0.24–2.08 | 0.526 | – | | | |
| Current smoker | – 0.355 | 0.7 | 0.44–1.11 | 0.129 | – | | | |
| Smoking pack-years | 0.017 | 1.02 | 1.01–1.03 | 0.001 | 0.015 | 1.02 | 1.00–1.03 | 0.016 |
| Best PEFR (L/min) | – 0.012 | 0.99 | 0.98–0.99 | <0.001 | – | | | |
| Predicted PEFR (%) | – 0.056 | 0.95 | 0.93–0.96 | <0.001 | – 0.049 | 0.95 | 0.94–0.97 | <0.001 |
| CAT score Total | 0.103 | 1.11 | 1.06–1.16 | <0.001 | 0.056 | 1.06 | 1.00–1.12 | 0.037 |
| Cough | 0.213 | 1.24 | 1.05–1.46 | 0.012 | – | | | |
| Phlegm | 0.282 | 1.33 | 1.12–1.57 | 0.001 | – | | | |
| Chest tightness | 0.289 | 1.34 | 1.11–1.61 | 0.003 | – | | | |
| Breathlessness | 0.469 | 1.6 | 1.33–1.92 | <0.001 | – | | | |
| Activity limitation | 0.447 | 1.56 | 1.24–1.97 | <0.001 | – | | | |
| Confidence | 0.506 | 1.66 | 1.21–2.28 | 0.002 | – | | | |
| Sleep | 0.154 | 1.17 | 0.96–1.41 | 0.116 | – | | | |
| Energy | 0.416 | 1.52 | 1.23–1.86 | <0.001 | – | | | |

β regression coefficient, CAT COPD assessment test, CI confidence interval, COPD chronic obstructive pulmonary disease, PEFR peak expiratory flow rate

The correlation between the CAT score and the lung function variables (%PEFR or %FEV1) was weak, and the predictive performance of CAT were not satisfactorily observed in this study.
Table 3. Estimating the probability of COPD in the development cohort

| Data source used in this modela | Independent variables | Estimated P<sub>COPD</sub> | COPD yes/no | Post-BD FEV1/FVC | Pre-BD %FEV1 |
|--------------------------------|-----------------------|-----------------------------|-------------|----------------|-------------|
| From means of our cohort       | Age | Pack-years | CAT | %PEFR | COPD yes/no | Post-BD FEV1/FVC | Pre-BD %FEV1 |
| Non-COPD subjects              | 67  | 40         | 6   | 95    | 0.23        | No               | 79             |
| COPD subjects                   | 75  | 51         | 10  | 63    | 0.75        | No               | 82             |
| From selected study subjects   | Subject A | 71  | 53   | 3    | 79    | 0.45        | Yes             | 0.56           | 63             |
|                               | Subject B | 67  | 20   | 4    | 74    | 0.36        | No              | 0.71           | 82             |
|                               | Subject C | 49  | 86   | 13   | 63    | 0.65        | Yes             | 0.62           | 59             |
|                               | Subject D | 47  | 21   | 2    | 78    | 0.14        | No              | 0.75           | 79             |

%PEFR percent predicted peak expiratory flow rate, CAT COPD assessment test, COPD chronic obstructive pulmonary disease, P<sub>COPD</sub> probability of COPD

aEntering the values of the four variables into a preset computer program immediately calculates the probability of COPD

limited patient numbers, and the CAT might have varied over time. Thus, these results should be individualized and cautiously applied for initiating COPD treatment. Finally, whether subjects with high P<sub>COPD</sub> but without spirometric confirmation should start treatment requires further investigation.

In conclusion, we developed and validated an accurate COPD prediction model using the age, smoking-pack years, %PEFR, and CAT score. The model can accurately and rapidly estimate the P<sub>COPD</sub> in at-risk subjects or undiagnosed COPD patients who may require further diagnostic evaluation and timely treatment when spirometry is unavailable. The developed prediction model may be a cost-effective tool for use in COPD case-finding strategies.

METHODS

Study design

This cross-sectional, observational study was conducted at a medical center, namely Taipei Veterans General Hospital, Taiwan, from November 2011 to March 2014 for the development cohort and from December 2017 to December 2018 for the validation cohort. The subjects were invited in pulmonary outpatient clinics, where their demographic information, chest X-rays, CAT questionnaires (Chinese version34), PEFR measurements, and diagnostic spirometry (Supplementary Fig. 1 for the study flow) were obtained. All the participants completed the study flow on the same day. This study was approved by the Institutional Review Board of Taipei Veterans General Hospital (ID: 2011-07-010IC for the development cohort and 2017-07-006C for the validation cohort). As the course of this study was part of our routine clinical service, the requirement for patient informed consent was waived in the development cohort. Subsequently, for a more rigorous study, informed consent was obtained in the validation cohort.

Study subjects

Eligible subjects were aged ≥ 40 years, had a history of smoking ≥ 20 pack-years, presented with chronic respiratory symptoms (at least one of cough, phlegm, or dyspnea), and denied a previous history of chronic respiratory illness (including COPD, asthma, bronchiectasis, lung cancer, lung fibrosis, pulmonary tuberculosis, and any neuromuscular or spinal disease that affected lung function). Subjects were excluded if they had an acute respiratory infection 2 weeks prior to enrollment, exhibited significant abnormality on chest radiographs, or were unable/unwilling to undergo peak flow meter testing and/or spirometry. Finally, the study subjects were categorized into non-COPD and COPD with distinct GOLD obstructive stages for pairwise comparisons of different variables.

Measurements of lung function

The PEFR measurement was performed using a Mini-Wright peak flow meter (Micropeak, Micro Medical Limited, Rochester, UK) according to the ERS recommendations.35 The best PEFR was adopted from three correct blows when patients exerted maximal expiratory efforts in a standing position. Following at least a 1-h break, the patients completed confirmatory spirometry for the diagnosis of COPD. Pre-BD and post-BD (20–30 min after inhalation of 400 μg of salbutamol via a Ventolin metered dose inhaler with a spacer; GlaxoSmithKline, Brentford, UK) spirometry (Spiro Medics system 2130; SensorMedics; Anaheim, CA, USA) was performed in accordance with the guideline from the American Thoracic Society/European Respiratory Society.36 The diagnosis of COPD was confirmed by a post-BD ratio (FEV1 over FVC) <0.7.16,24

Sample size estimation

The best practice for sample size estimation in the development cohort is to have at least 10 outcome events per variable estimated27–39 (i.e., the ratio of COPD patients to the selected variables is 10). We selected 12 variables, including the age, sex, smoking intensity, PEFR, and eight symptoms in the CAT, which corresponded to a target number of COPD cases of 120. According to the review data in our pulmonary clinics, approximately 40% of patients who met the inclusion criteria were diagnosed as GOLD-defined COPD,16,24 irrespective of severity classification. Therefore, the estimated sample size in the development cohort had to reach a minimum value of 300. However, the required sample size in validation cohorts is not well understood.37 We calculated the required size according to the AUROC value. For a type I error of 0.05 and a power of 0.9, we assumed to reach an AUROC value of 0.7. The required minimal sample size was therefore at least 116 (estimated using MedCalc software, see Supplementary Fig. 3).

Statistical analysis

Data are presented as means ± SD or a number (%), as appropriate. Continuous variables were compared using a t-test or one-way analysis of variance, followed by a Bonferroni test for pairwise comparisons. Categorical data were evaluated using a chi-square test. The association between two continuous variables was evaluated through Pearson’s correlation. A binary logistic regression model using the enter method was applied to examine the independent variables related to the diagnosis of COPD and to generate an equation for estimating the P<sub>COPD</sub>. Therefore, the accuracy of using different modalities to diagnose COPD could be determined through ROC curve analysis. The optimal cut-off of the selected modality was calculated using the Youden index to determine the sensitivity, specificity, positive predictive value, and negative predictive value.

Subsequently, the logit model to estimate the P<sub>COPD</sub> was employed using the independent variables for the highest accuracy. Thus, the log odds ratio of subjects with or without COPD is expressed as follows:

$$
\log\left( \frac{P_{COPD}}{1 - P_{COPD}} \right) = \logit(P_{COPD}) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_n X_n,
$$

(3)

where $\beta_0$ is the coefficient of the constant and $\beta_i$ is the coefficient(s) of the independent variable(s) $X_i$. This equation can be transformed as follows:

$$
P_{COPD} = \frac{e^{\beta X}}{1 + e^{\beta X}},
$$

(4)

where $P_{COPD}$ can be directly calculated.40 We applied sensitivity analysis to
investigate the influence of dropping different variables from the prediction model (P\textsubscript{COPD}) on the diagnostic accuracy represented by the AUROC in the development cohort. We also examined the prediction model by using the AUROC for discrimination, Hosmer-Lemeshow goodness-of-fit test for calibration, and resampling bootstrap validation with 1000 replicates. Statistical analysis was performed using SPSS for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). The comparison of the AUROC values (based on the methodology from DeLong et al.\textsuperscript{41}) and sample size estimation according to the AUROC value were performed using MedCalc version 17.5.5 (MedCalc Software bvba, Ostend, Belgium). The AUROC of the resampling bootstrap was estimated using R statistical software (version 3.5.1, R Foundation for Statistical Computing, Vienna, Austria). A two-sided P<0.05 was considered significant.

**DATA AVAILABILITY**
All data generated or analyzed during this study are included in this published article (and its supplementary information files).

**ACKNOWLEDGEMENTS**
We are grateful for statistical modeling consultant Dr. Jack Chen, from the ESTAT Statistical Consulting Co., Ltd., for his assistance with statistical analysis. We also thank the Wallace Academic Editing for the work of English editing. This study was partly supported by the research grants from Taipei Veterans General Hospital (V107C-112 and V108C-072). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**AUTHOR CONTRIBUTIONS**
Conception and design: D.W. Perng and K.C. Su; acquisition, analysis, or interpretation of data: H.K. Ko, K.T. Chou, Y.H. Hsiao, and V. Y. Su; drafting of the manuscript: K.C. Su and H.K. Ko; critical revision of the manuscript for important intellectual content: D.W. Perng, and Y.R. Kou.

**ADDITIONAL INFORMATION**
Supplementary information accompanies the paper on the npj Primary Care Respiratory Medicine website (https://doi.org/10.1038/s41533-019-0135-9).

**Competing interests:** The authors declare no competing interests.

**Publisher's note:** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.
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