Impulse oscillometry-derived equation for prediction of abnormal FEV_1/FVC ratio for COPD screening in Chinese population: a multicenter cross-sectional study

Meishan Liu,[a,t] Xin Yao,[b,t] Yiwei Shi,[c,r,s,t] Huiguo Liu,[d,t] Liang Chen,[e,t] Yong Lu,[a,t] Chunmei Zhang,[f,t] Xinran Zhang,[g,n,o,p,q] Lirong Liang,[a,h] Xiaohong Chang,[a] Li An,[a] Kian Fan Chung,[i] Janwillem W. H. Kocks,[j,k,l,m] and Kewu Huang[a,*]

[a]Department of Respiratory and Critical Care Medicine, Beijing Institute of Respiratory Medicine and Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China
[b]Department of Respiratory Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China
[c]NHC Key Laboratory of Pneumoconiosis, China
[d]Tongji Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology, Wuhan, China
[e]Beijing Jingmei Group General Hospital, Beijing, China
[f]Department of Pulmonary and Critical Care Medicine, Beijing Luhe Hospital, Capital Medical University, Beijing, China
[g]National Center for Respiratory Medicine, China
[h]Department of Clinical Epidemiology, Beijing Institute of Respiratory Medicine and Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China
[i]National Heart & Lung Institute, Imperial College London & Royal Brompton & Harefield Hospital, London, UK
[j]General Practitioners Research Institute, Groningen, the Netherlands
[k]Observational and Pragmatic Research Institute, Singapore
[l]Groningen Research Institute Asthma and COPD (GRIAC), University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
[m]Department of Pulmonology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
[n]State Key Laboratory of Respiratory Health and Multimorbidity, China
[o]Institute of Respiratory Medicine, Chinese Academy of Medical Sciences, China
[p]National Clinical Research Center for Respiratory Diseases, China
[q]Department of Clinical Research and Data Management, Center of Respiratory Medicine, China-Japan Friendship Hospital, Beijing, China
[r]Shanxi Key Laboratory of Respiratory Diseases, China
[s]Department of Pulmonary and Critical Care Medicine, The First Hospital of Shanxi Medical University, Taiyuan, Shanxi, China

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Summary

Background The diagnosis of chronic obstructive pulmonary disease (COPD) is based on spirometry that requires a forced expiratory manoeuvre, which is laborious and difficult for mass screening. Impulse oscillometry (IOS) is easier than spirometry and performed with tidal breathing. We sought to develop an equation for predicting forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) and screening COPD using IOS parameters.

Methods Data from patients who simultaneously underwent spirometry and IOS were obtained from databases at five tertiary hospitals in China. Multivariable linear regression analysis was used to develop a predictive model for pre-bronchodilator (BD) FEV_1/FVC. Model performance was analyzed against spirometric criteria of airflow obstruction (AO, defined as pre-BD $FEV_1/FVC < 0.7$) and COPD (post-BD $FEV_1/FVC < 0.7$).

Findings Using 15,113 patients and externally validated with 9586 patients, the model estimated FEV_1/FVC ratio could identified AO and spirometry-defined COPD in internal (AUC = 0.822 and 0.849, respectively) and external (AUC = 0.790 and 0.828, respectively) validation. A clinical algorithm was constructed to classify patients into three different groups: estimated $FEV_1/FVC < 0.7$: likely COPD; estimated $FEV_1/FVC \geq 0.7$ and ≤ 0.73: suspicious for COPD; estimated $FEV_1/FVC > 0.73$: unlikely COPD. The sensitivity and specificity for detecting spirometry-defined COPD were 88.0% and 77.0%, respectively, while the negative predictive value ranged from 93.7% to 98.6% and positive predictive value ranged from 26.5% to 62.1% across different COPD prevalence groups in the Chinese population.

Interpretation This equation could be useful to screen for COPD particularly in community and primary care settings.

*Corresponding author. Department of Respiratory and Critical Care Medicine, Beijing Institute of Respiratory Medicine and Beijing Chao-Yang Hospital, Capital Medical University, No 8, Gongti South Road, Chaoyang District, Beijing 100020, China.
E-mail address: kewuhuang@126.com (K. Huang).
[t]These authors contributed equally to this work.

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Keywords: Airflow obstruction; Chronic obstructive pulmonary disease; Impulse oscillometry; Prediction model

Research in context

Evidence before this study

We searched PubMed and the China National Knowledge Infrastructure for articles published up to September, 2024, using the terms "chronic obstructive pulmonary disease/COPD", "airflow obstruction/AO", "Impulse oscillometry/IOS", "Forced Oscillation Technique/ FOT", "screening", "case-finding" and "prediction model" in English and Chinese. We screened papers by reviewing abstracts to identify full-text reports that were relevant to the study aims. Some studies have preliminarily explored the association between IOS and the presence of COPD or COPD symptoms, but these studies just analyzed the one-to-one relationship between IOS parameters and COPD. The overall relationship between oscillometric parameters and spirometric criteria for the diagnosis of COPD is still not clear. A previous study (n = 88) has constructed a diagnostic model using IOS parameters for detecting CT-defined emphysema, which is an early manifestation of COPD. However, no studies have combined the IOS parameters as an overall equation for predicting FEV_1/FVC ratio and assisting in COPD screening or case-finding.

Added value of this study

To our knowledge, this study is the first one to develop and validate a predictive equation using basic demographic information and IOS parameters to estimate the FEV_1/FVC ratio, and evaluate the equation's performance for detecting COPD. The model showed a good predictive accuracy and a good performance in identifying AO and spirometry-defined COPD in internal validation (AUC = 0.822 and 0.849, respectively) and external validation (AUC = 0.790 and 0.828, respectively). We further constructed a practical algorithm based on the model to classify subjects into different risk groups: estimated FEV_1/FVC < 0.7: likely COPD; estimated FEV_1/FVC $\geq$ 0.7 and $\leq$0.73: suspicious for COPD; estimated FEV_1/FVC > 0.73: unlikely COPD. The sensitivity and specificity of the algorithm for detecting spirometry-defined COPD were 88.0% and 77.0%, respectively, while the negative predictive value ranged from 93.7% to 98.6% across different COPD prevalence groups in the Chinese population.

Implications of all the available evidence

Worldwide, there is a large underdiagnosis of COPD especially in primary care settings. COPD requires spirometry for its diagnosis, which is a laborious process for mass screening. COPD screening questionnaires focus mainly on symptoms, thereby may not be sensitive enough to identify asymptomatic individuals at the early stage of disease. IOS is easier and faster to perform in the assessment of lung function compared to spirometry, making it suitable for COPD screening. Taking advantage of the prediction model that we developed in the present study, we are able to triage individuals into likely COPD, suspicious for COPD, or unlikely COPD groups, leaving a small number of individuals who have to undergo further spirometry tests in primary care clinics. The study strongly indicates that the algorithm that we have developed can potentially enhance the efficiency of COPD screening and case-finding, can optimize resource allocation, and can be beneficial for the optimal early detection of COPD. Further studies are warranted to test the performance of this model in the community and primary care population in different regions of the world.

Introduction

Chronic obstructive pulmonary disease (COPD) is a significant global public health challenge owing to its widespread prevalence and associated morbidity and mortality.[1] However, many COPD cases are undiagnosed owing to the lack of obvious symptoms and testing in the early stage of the disease, underscoring the importance of early screening for airflow obstruction (AO), especially among community dwellings in the early stages of disease.[2]

Global Initiative for Chronic Obstructive Lung Disease (GOLD) advocates performing spirometry in patients with positive COPD screening questionnaire results.[3] However, screening questionnaires may not be sensitive enough for asymptomatic or mild symptoms patients.[4,5] In particular, one should be aware of the drawback of screening questionnaires, considering that more than one-third of people with spirometry-defined COPD in China and 29% of those in Denmark were asymptomatic.[6,7] Spirometry is the gold standard for the diagnosis of COPD.[3] However, spirometry requires rigorous inspiratory and forceful expiratory breaths, which can be difficult, especially for the old, or weak. Moreover, spirometry is not routinely used in primary care and technical quality is poor.[8,9] These factors hinder the screening and diagnosis of COPD in primary care and community settings.

Impulse oscillometry (IOS) is a convenient and time-efficient technique for measuring respiratory resistance and compliance of the respiratory system, requiring

only quiet tidal breathing.[10] These features allow oscillometry to be suitable for use in multiple clinical scenarios, especially primary care and community settings. Some studies have preliminarily elaborated the one-to-one relationship between IOS parameters and the presence of COPD or COPD symptoms[11–13]; however, no studies have combined IOS parameters into an overall equation for predicting forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio and assisting in COPD screening or case-finding.

In an ideal screening scenario, most non-COPD patients would be ruled out, while a minority of suspected COPD patients would be ruled in for further confirmation, saving many unnecessary spirometry tests. This may enhance the implementation of screening or case-finding programs, facilitating earlier identification and appropriate care for many patients with undiagnosed COPD. This study aimed to develop and validate an equation for predicting FEV_1/FVC using basic demographic information and IOS parameters, and construct an algorithm for identifying COPD based on this equation.

Methods

Study design and population

This cross-sectional study used electronic pulmonary function test databases from five tertiary hospitals in China, which collect data as part of routine clinical practice. Patients who underwent pulmonary function testing at these hospitals for any reason were included in this study. Two independent data sets were established: one for the development of the predictive equation (derivation set), and one for the validation of the predictive equation (external validation set). The derivation data set consisted of patients who simultaneously underwent IOS measurements and spirometry between January 2020 and December 2022 at two hospitals in northern China (Beijing Chao-Yang Hospital and Beijing Jingmei Group General Hospital), and one hospital in southern China (Tongji Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology). The external validation data set consisted of patients who simultaneously underwent IOS measurements and spirometry between January 2020 and December 2023 at a hospital in northern China (the First Hospital of Shanxi Medical University) and a hospital in eastern China (the First Affiliated Hospital of Nanjing Medical University). The derivation set was split into a training set and an internal validation set, in a ratio of 7:3, using a random sampling method (Fig. 1). All patients with both spirometry and IOS results were included. Patients were excluded if they were younger than 20 years old or if they were not Chinese. If a patient underwent multiple pulmonary function tests, only data from the first test were used in this analysis. All data were checked by study coordinators for integrity and accuracy. Incomplete and unreliable data were excluded from our analysis.

The study protocol was approved by the Ethics Committee of Beijing Chao-Yang Hospital (No. 2024-KE-95) in accordance with the Declaration of Helsinki. We performed data anonymization before data analysis, so patients could not be identified at the individual level. Given the anonymous and retrospective nature of the data, informed consent was waived for this study by the reviewing ethics committee.

Impulse oscillometry

IOS was measured during tidal breathing according to the European Respiratory Society (ERS) guideline,[10] using a Jaeger MasterScreen IOS device (Viasys Healthcare, Höchberg, Germany). Impedance verification was performed daily and a criterion of error ≤10% or 0.01 $kPa.s.L^{-1}$ was adopted. During the procedure, participants were required to breathe normally for 30–60 s with their nose clipped and their cheeks supported by their hands while sitting with the neck in a comfortable, neutral posture. The mean value of three technically acceptable measurements under the requirements of the ERS 2020 guideline[10] was used in the analysis.

Spirometry

Spirometry was performed according to the method described in the American Thoracic Society (ATS)/ERS guidelines,[14] using a Jaeger MasterScreen PFT device (Viasys Healthcare, Höchberg, Germany). All spirometry was performed after the IOS test. All patients underwent pre-bronchodilator (BD) spirometry, and a subgroup of individuals also underwent a bronchodilator test by inhalation of 400 μg salbutamol aerosol through a spacer and repeated spirometry 20 min later. The decision about whether a patient underwent a bronchodilator test was made by the physicians in each hospital according to routine clinical diagnosis and treatment requirements (mostly because the patient showed pre-BD AO). Pulmonary function parameters, including vital capacity (VC), FVC, and FEV_1 were collected. The predicted FEV_1 values were calculated using the European Coal and Steel Community 1993 spirometry reference value equations.[15] Experienced respiratory technicians conducted quality control analyses using ATS and ERS criteria.[14]

Predictors and calculation of estimated FEV_1/FVC

We identified parameters predictive of pre-BD FEV_1/FVC using basic anthropometric variables (age, sex, height, body weight) and pre-BD IOS parameters. All oscillometric parameters routinely measured in respiratory clinics were included in this analysis, including resistance at 5 Hz (R5), resistance at 20 Hz (R20), reactance at 5 Hz (X5), resonant frequency (Fres), and the area of reactance (AX). Parameters with potential multicollinearity with others, such as the difference between R5 and R20 (R5 – R20) and total

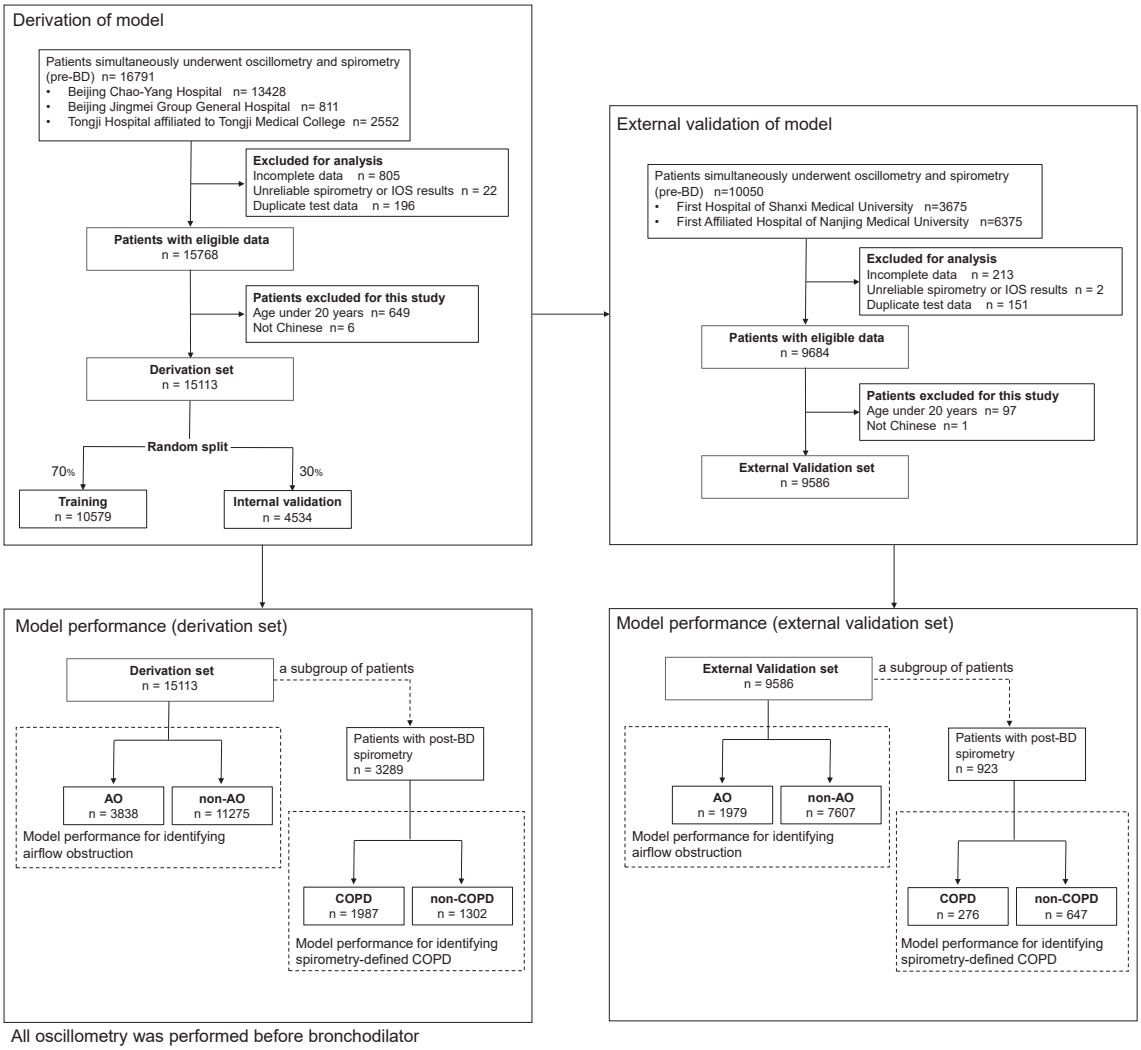

Fig. 1: Study flowchart. Abbreviations: AO, airflow obstruction; BD, bronchodilator; COPD, chronic obstructive pulmonary disease.

respiratory impedance (Z5, $Z5 = \sqrt{R5^2 + X5^2}$), were not included in the model. A multivariable linear regression model was generated and the equation for estimated pre-BD FEV_1/FVC was: pre-BD FEV_1/FVC = (regression coefficient of age) × age (years) + (regression coefficient of sex) × sex (0 if male, 1 if female) + (regression coefficient of height) × height (cm) + (regression coefficient of body weight) × body weight (kg) + (regression coefficient of R5) × R5 ($kPa.s.L^{-1}$) + (regression coefficient of R20) × R20 ($kPa.s.L^{-1}$) + (regression coefficient of Fres) × Fres (Hz) + (regression coefficient of X5) × X5 ($kPa.s.L^{-1}$) + (regression coefficient of AX) × AX ($kPa.L^{-1}$) + numeric constant.

Definition of AO and COPD

We defined patients with a pre-BD $FEV_1/FVC < 0.7$ as having AO. The severity of AO was categorized based on the pre-BD FEV_1 % predicted (pre-BD $FEV_1 \geq 80\%$ predicted; $50\% \leq$ pre-BD $FEV_1 < 80\%$ predicted; $30\% \leq$ pre-BD $FEV_1 < 50\%$ predicted; and pre-BD $FEV_1 < 30\%$ predicted).

Patients were classified as having spirometry-defined COPD when post-bronchodilator (post-BD) FEV_1/FVC was <0.7. The severity of spirometry-defined COPD was categorized according to the GOLD criteria based on the post-BD FEV_1 % predicted.[3]

Statistical analysis

All analyses were performed using SPSS version 26.0 (IBM, Armonk, NY, USA) and R version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria). *P*-values were two-sided, and $P < 0.05$ was considered statistically significant. Our analysis included all patients for whom the relevant variables of interest were

available. Missing values were handled through list-wise deletions.

The split of training set and internal validation set was performed using the 'sample' R function with a random seed of 1234. Continuous variables were expressed as means (standard deviations), and categorical data were expressed as numbers (percentages). Comparisons among groups used one-way ANOVA for continuous variables and Chi–Square Test for categorical variables. Correlations between IOS parameters and FEV_1/FVC were determined using Pearson's correlation analyses. Classical ordinary least squares (OLS) regression, shrinkage models (ridge, LASSO, and elastic net), and stepwise regression were used for selecting model predictors. Subsequently, multivariable linear regression analysis was used to develop a predictive model for FEV_1/FVC. Mean absolute error (MAE) and root-mean-square error (RMSE) were calculated to evaluate the bias of the equations. Using the model-estimated FEV_1/FVC ratio, the area under the receiver operating characteristic curve (AUC) was calculated for discriminating between patients with and without AO, as well as patients with and without spirometry-defined COPD. Comparisons between the AUC values between the predictive model and individual IOS parameters in all patients, and the AUC values of the predictive model in patients stratified by age, sex, BMI, and severity of AO were performed using the Delong test. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), balanced accuracy, positive likelihood ratio (+LR), and negative likelihood ratio (–LR) were calculated at various cut-offs for the two outcomes. The Youden index was used to identify the optimal cutoff value based on sensitivity and specificity. Fagan's nomogram was used for estimating the clinical value of our model across various disease prevalences.[16]

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had final responsibility for the decision to submit for publication.

Results

Participant characteristics

The study flowchart is shown in Fig. 1. 15,768 patients who simultaneously underwent spirometry and oscillometry tests were identified to constitute the derivation data set. Of these, 649 patients aged < 20 years and six patients who were not Chinese were excluded. The remaining 15,113 patients were randomly allocated into separate training and internal validation sets for the identification of the predictive equation. In addition, 9586 patients from the two other hospitals were identified for the external validation set.

Comparisons of demographic and clinical variables among the training, internal validation, and external validation sets are shown in Table 1. The mean pre-BD FEV_1/FVC ratio was 0.74 (standard deviation [SD], 0.11) in the training set, 0.74 (0.11) in the internal validation set, and 0.76 (0.11) in the external validation set.

Development of a predictive equation for FEV_1/FVC

Correlation analyses were performed between each oscillometric parameter and pre-BD FEV_1/FVC (Supplementary Fig. E1). The strongest positive correlation was between X5 and FEV_1/FVC (r = 0.521, $P < 0.0001$), and the strongest negative correlation was between AX and FEV_1/FVC (r = –0.549, $P < 0.0001$).

The prediction model for pre-BD FEV_1/FVC generated using different methods (OLS, stepwise, LASSO, ridge, and elastic net) showed similar performance (Supplementary Table E1, and Supplementary Fig. E2). A stepwise regression model including all predictors was used to build the final model (R-squared: 0.435, Adjusted R-squared: 0.435), with a MAE of 0.061 and a RMSE of 0.083, and the estimated pre-BD FEV_1/FVC correlated well with actual values (Supplementary Fig. E3). The β coefficients and 95% confidence interval of the stepwise linear regression model are shown in Table 2. Based on these results, we generated regression equations for pre-BD FEV_1/FVC: Estimated pre-BD FEV_1/FVC = –0.00137 × age (years) + 0.0364 × sex (0 if male, 1 if female) – 0.00304 × height (cm) + 0.00138 × weight (kg) + 0.0858 × R5 ($kPa.s.L^{-1}$) – 0.107 × R20 ($kPa.s.L^{-1}$) – 0.00334 × Fres (Hz) + 0.182 × X5 ($kPa.s.L^{-1}$) – 0.0254 × AX ($kPa.L^{-1}$) + 1.303. To allow for easy use by clinicians, we constructed a calculator in the form of an Excel file, which can be found in Supplementary File S2.

Model performance for identifying AO

For identifying AO using model-estimated pre-BD FEV_1/FVC, the AUC was 0.816 (95% CI 0.806–0.825) in the training set and 0.822 (95% CI 0.808–0.836) in the internal validation set (Fig. 2a and b). The AUC of the prediction model was significantly higher than that of any single IOS parameter (Supplementary Table E2).

We further compared the diagnostic accuracy of our model among patients categorized into different subgroups (Supplementary Table E3). The AUC value of the prediction model was significantly higher in patients with pre-BD FEV_1% predicted <50% compared with those with pre-BD FEV_1% predicted ≥50% (AUC = 0.886 vs 0.782, $P = 0.0034$). No significant differences were observed across various age, sex, and BMI groups.

The sensitivities and specificities of the predictive equation at various cut-offs for identifying AO are shown in Table 3. Using the GOLD-recommended cut-off value (estimated FEV_1/FVC < 0.70), our model

Variable	Training set	Internal validation set	External validation set	*P*-value[a]
n	10,579	4534	9586	
Age, years	58.5 (13.6)	58.4 (13.6)	60.8 (13.4)	<0.0001
Sex (n, %)				
Male	5688 (53.8)	2464 (54.3)	5732 (59.8)	<0.0001
Female	4891 (46.2)	2070 (45.7)	3854 (40.2)	
Height, cm	163.0 (8.5)	163.0 (8.5)	164.0 (8.1)	<0.0001
Weight, kg	67.4 (12.9)	67.3 (12.8)	66.1 (13.5)	<0.0001
BMI, kg/m^2	25.2 (4.0)	25.2 (4.0)	24.4 (4.1)	<0.0001
Spirometry (pre-bronchodilator)				
FEV_1, L	2.44 (0.82)	2.45 (0.82)	2.34 (0.77)	<0.0001
FVC, L	3.30 (0.95)	3.30 (0.95)	3.06 (0.89)	<0.0001
FEV_1% predicted	93.7 (23.4)	93.7 (23.2)	89.0 (21.7)	<0.0001
FEV_1/FVC	0.74 (0.11)	0.74 (0.11)	0.76 (0.11)	<0.0001
Oscillometry (pre-bronchodilator)				
R5, kPa.s.L^{-1}	0.41 (0.16)	0.41 (0.16)	0.39 (0.15)	<0.0001
R20, kPa.s.L^{-1}	0.33 (0.09)	0.32 (0.09)	0.29 (0.09)	<0.0001
Fres, Hz	15.6 (6.9)	15.5 (6.7)	17.1 (5.6)	<0.0001
X5, kPa.s.L^{-1}	−0.14 (0.10)	−0.14 (0.11)	−0.14 (0.11)	0.0139
AX, kPa.L^{-1}	0.86 (1.27)	0.87 (1.34)	0.95 (1.05)	<0.0001
Airflow obstruction (n, %)				
Yes	2671 (25.2)	1167 (25.7)	1979 (20.6)	<0.0001
No	7908 (74.8)	3367 (74.3)	7607 (79.4)	

Data are mean (standard deviation) unless otherwise indicated. Airflow obstruction was defined as a pre-bronchodilator FEV_1/FVC < 0.7. AX, reactance area; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; Fres, resonant frequency; R5, resistance at 5 Hz; R20, resistance at 20 Hz; X5, reactance at 5 Hz. [a]The *P*-value among three groups was calculated using one-way ANOVA for continuous variables and Chi-square tests for categorical variables.

Table 1: **Comparison of demographic and clinical characteristics among the training, internal validation, and external validation sets.**

Variable	β-coefficient	SE	95% Confidence interval	*P*-value
Age (years)	−0.00137	0.00007	−0.00150, −0.00125	<0.0001
Sex (female)	0.0364	0.0024	0.0317, 0.0411	<0.0001
Height (cm)	−0.00304	0.00016	−0.00335, −0.00273	<0.0001
Weight (kg)	0.00138	0.00008	0.00122, 0.00153	<0.0001
R5 (kPa.s.L^{-1})	0.0858	0.0212	0.0443, 0.127	<0.0001
R20 (kPa.s.L^{-1})	−0.107	0.023	−0.152, −0.0613	<0.0001
Fres (Hz)	−0.00334	0.00023	−0.00379, −0.00290	<0.0001
X5 (kPa.s.L^{-1})	0.182	0.020	0.143, 0.222	<0.0001
AX (kPa.L^{-1})	−0.0254	0.0023	−0.0298, −0.0209	<0.0001

AX, reactance area; FEV_1/FVC, forced expiratory volume in 1 s/forced vital capacity; Fres, resonant frequency; R5, resistance at 5 Hz; R20, resistance at 20 Hz; SE, standard error; X5, reactance at 5 Hz.

Table 2: **Multivariable linear regression results for pre-bronchodilator FEV_1/FVC ratio.**

exhibited high specificity (90.8%) but relatively low sensitivity (51.2%). The optimal cut-off value for detecting AO was achieved at model-estimated FEV_1/FVC < 0.73, with the maximum Youden index. Sensitivity, specificity, balanced accuracy, +LR, –LR, PPV, and NPV were 72.6%, 76.6%, 75.5%, 3.10, 0.36, 51.8%, and 89.0%, respectively.

Model performance for identifying spirometry-defined COPD

For identifying spirometry-defined COPD using model-estimated FEV_1/FVC, we analyzed a subgroup of patients in the derivation set who underwent post-BD spirometry (n = 3,289, characteristics are shown in Supplementary Table E4). Using the model-estimated pre-BD FEV_1/FVC, the AUC for detecting spirometry-defined COPD was 0.849 (95% CI 0.836–0.862, Supplementary Fig. E4), which was significantly higher than that of any single IOS parameter (Supplementary Table E5). Comparing the diagnostic accuracy of our model among different age, sex, BMI, and GOLD stages did not reveal significant differences (Supplementary Table E6). The sensitivities and specificities at different cut-offs for identifying spirometry-defined COPD are shown in Table 4. Based on the highest Youden Index, the optimum cut-off value for detecting spirometry-defined COPD was model estimated FEV_1/FVC < 0.70, with a sensitivity and specificity of 67.0% and 85.2%, respectively (Table 4).

Construction of the COPD screening algorithm

To exclude individuals without AO and include individuals with potential spirometry-defined COPD as much as possible, a clinical algorithm based on dual cut-offs was developed for the model. The optimal cut-off for excluding AO (estimated FEV_1/FVC > 0.73) and the optimal cut-off for detecting spirometry-defined COPD (estimated FEV_1/FVC < 0.70) were used as the exclusion and inclusion cut-offs, respectively, while individuals with an estimated FEV_1/FVC between the two cutoffs (0.70–0.73) were in the grey zone. The clinical algorithm based on our prediction model for the triage of individuals at risk of COPD is presented in Fig. 3 and includes three outcomes: (1) Model-estimated FEV_1/FVC < 0.7: likely COPD. Diagnosis and treatment should be conducted, with the patient referred to a specialist clinic for further assessment if primary care cannot provide guideline-based diagnosis; (2) Model-estimated FEV_1/FVC ≥ 0.7 and ≤0.73: suspicious for COPD. The patient needs a further spirometry test to confirm the diagnosis of COPD; (3) Model-estimated FEV_1/FVC > 0.73: unlikely COPD. The patient should be considered normal or alternative diagnosis to COPD.

External validation of the predictive equation

The equation produced a MAE of 0.076 and a RMSE of 0.099 for predicting pre-BD FEV_1/FVC in the external validation set. The estimated pre-BD FEV_1/FVC was moderately correlated with actual pre-BD FEV_1/FVC (r = 0.499, P < 0.0001) (Fig. 4a). The AUC of the estimated pre-BD FEV_1/FVC for detecting AO was 0.790 (95% CI 0.779–0.801, Fig. 4b), which was similar to that in the training and internal validation sets.

A subgroup of 923 patients with both pre-BD and post-BD spirometry results in the external validation set

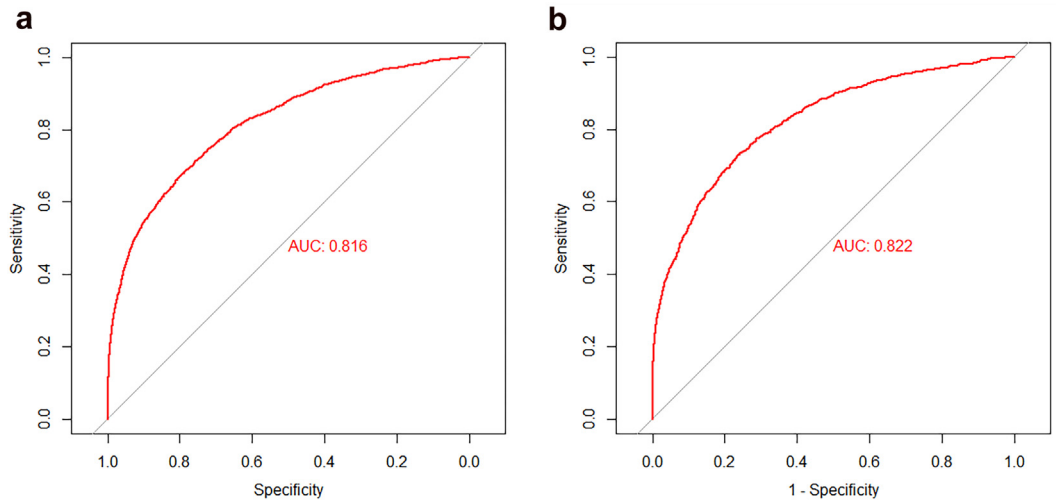

Fig. 2: Receiver operating characteristic (ROC) curve for identifying airflow obstruction (AO) using the model-estimated FEV_1/FVC. (a) ROC curves for identifying AO in the training set. (b) ROC curves for identifying AO in the internal validation set. Abbreviations: FEV_1/FVC, forced expiratory volume in 1 s/forced vital capacity.

were analyzed to externally validate the performance of the model for identifying spirometry-defined COPD (Supplementary Table E7). Using the model-estimated FEV_1/FVC, the AUC for detecting spirometry-defined COPD was 0.828 (95% CI 0.800–0.856, Fig. 4c) in external validation. When applying the clinical algorithm, the proportions of AO in likely COPD, suspicious for COPD, and unlikely COPD groups were 60.4%, 31.8%, and 13.3%, respectively (Supplementary Fig. E5); and the proportions of spirometry-defined COPD in likely COPD, suspicious for COPD, and unlikely COPD groups were 58.1%, 23.4%, and 8.0%, respectively (Supplementary Fig. E6). Sensitivity, specificity, PPV, and NPV for detecting spirometry-defined COPD in the external validation set were 88.0%, 77.0%, 58.1%, and 92.0%, respectively (Supplementary Table E8).

Model application in the general population

To explore how the model could be utilized in community or primary care clinics for COPD screening, sensitivity and specificity for detecting spirometry-defined COPD in the external validation set were analyzed by Fagan's nomogram to calculate the post-test probability. Table 5 shows that, using the prevalence of spirometry-defined COPD in a Chinese general population aged 20 years or older of 8.6%[3] as the pre-test probability, the NPV of the prediction model at exclusion cut-off (estimated $FEV_1/FVC > 0.73$) was 98.6%, whereas the PPV of the prediction model at inclusion cut-off (estimated $FEV_1/FVC < 0.70$) was 26.5%. With differing prevalences of spirometry-defined COPD in a Chinese general population and primary care population across different age groups, which increased from 8.6% to about 30%,[2] the NPV ranged from 93.7% to 98.6% and PPV ranged from 26.5% to 62.1%, respectively (Table 5).

Discussion

In this study, we developed and validated an equation using IOS parameters to predict FEV_1/FVC based on multicenter, large-sample spirometry and oscillometry data of tertiary hospital patients in China. The equation exhibited good predictive accuracy, with a MAE and RMSE of 0.061 and 0.083, respectively. The predicted FEV_1/FVC ratio correlated well with actual values in internal and external validations. In addition, the model estimated FEV_1/FVC performed well in identifying AO and spirometry-defined COPD. To our knowledge, this

Cut-off	Sensitivity (%)	Specificity (%)	Youden Index (%)	Balanced accuracy (%)	+LR	−LR	PPV (%)	NPV (%)
0.68	41.8	95.0	36.8	81.3	8.43	0.61	74.5	82.5
0.69	46.1	92.9	39.0	80.8	6.47	0.58	69.2	83.2
0.70	51.2	90.8	42.0	80.6	5.56	0.54	65.8	84.3
0.71	58.1	87.6	45.7	80.0	4.67	0.48	61.8	85.8
0.72	64.6	82.7	47.3	78.1	3.74	0.43	56.5	87.1
0.73[a]	72.6	76.6	49.2	75.5	3.10	0.36	51.8	89.0
0.74	78.2	69.7	47.9	71.9	2.58	0.31	47.2	90.2
0.75	83.7	61.5	45.2	67.2	2.18	0.26	43.0	91.6
0.76	88.4	52.6	41.0	61.8	1.87	0.22	39.3	92.9
0.77	91.6	42.9	34.5	55.4	1.60	0.20	35.7	93.6

The indexes represent the performance of the prediction model at various cut-offs in the internal validation set. PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; −LR, negative likelihood ratio. [a]Cut-off value with maximum Youden index.

Table 3: **Model performance at various cut-offs for identifying airflow obstruction.**

Cut-off (%)	Sensitivity (%)	Specificity (%)	Youden Index (%)	Balanced accuracy (%)	+LR	−LR	PPV (%)	NPV (%)
0.68	57.9	90.7	48.6	70.9	6.23	0.46	90.5	58.6
0.69	62.6	88.3	50.9	72.8	5.36	0.42	89.1	60.7
0.70[a]	67.0	85.2	52.2	74.2	4.52	0.39	87.3	62.9
0.71	71.5	80.4	51.9	75.0	3.65	0.35	84.8	64.9
0.72	76.8	75.2	52.0	76.2	3.10	0.31	82.5	68.0
0.73	81.6	68.4	50.0	76.4	2.58	0.27	79.7	70.9
0.74	85.9	62.5	48.4	76.6	2.29	0.23	77.8	74.3
0.75	90.0	55.5	45.5	76.4	2.02	0.18	75.5	78.5
0.76	92.9	46.9	39.8	74.7	1.75	0.15	72.8	81.1
0.77	95.5	37.9	33.4	72.7	1.54	0.12	70.1	84.6

The indexes represent the performance of the prediction model at various cut-offs in the internal validation set. PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; −LR, negative likelihood ratio. [a]Cut-off value with maximum Youden index.

Table 4: **Model performance at various cut-offs for identifying spirometry-defined chronic obstructive pulmonary disease.**

study is the first to establish a model using IOS parameters to predict FEV_1/FVC ratio and the presence of COPD.

COPD diagnosis in primary care is challenging owing to the lack of trained technicians, insufficient equipment, limited time, and poor-quality control of spirometry testing.[17] Oscillometry is easier and more convenient to performed than spirometry. However, widespread implementation of oscillometry is limited owing to high costs of the devices and a lack of standardization of measurement and interpretation. With the construct of ATS/ERS standards,[10] more studies on IOS reference values[18] and the availability of new portable devices,[19,20] these limitations could be resolvable in the near future.

In this study, we observed that most oscillometric parameters were moderately correlated with FEV_1/FVC ratio, which is concordant with previous reports.[21,22] X5 was positively correlated with FEV_1/FVC, while R5, R20, Fres, and AX were negatively correlated with FEV_1/FVC. The significant correlations between oscillometric parameters and FEV_1/FVC support the use of oscillometry for estimating FEV_1/FVC ratio and assisting in COPD early screening.

The predictive equation developed in this study performed well in predicting FEV_1/FVC in internal and external validations. Using model estimated FEV_1/FVC, our equation showed considerable diagnostic value for identifying spirometry-defined COPD. Previous studies have analyzed the diagnostic ability of single IOS parameters for identifying COPD. Chaiwong and colleagues[23] found that an AX $\geq$ 8.66 cmH_2O/L showed an AUC of 0.79, with a sensitivity of 79.1% and a specificity of 78.0% for the diagnosis of COPD. Liu and colleagues[24] reported that Fres was the most effective IOS parameter for identifying a physician-diagnosed COPD, with AUC values ranging from 0.905 to 0.914 for different age groups. However, these studies were performed in small, single-center samples, and only analyzed the one-to-one relationship between IOS parameters and COPD. Actually, the airflow obstruction of COPD is caused by a mixture of small airways disease and large airway disorders,[25] therefore, using a single IOS parameter may not be enough to detect the presence of COPD. In contrast to previous studies,[23,24] this study used multicenter data to develop a regression equation using multiple IOS parameters to predict FEV_1/FVC ratio, and we demonstrated that the performance of this equation was superior to any single IOS parameter for identifying patients with possible COPD. Moreover, we developed an algorithm/workflow for easy and straightforward clinical use based on our derived equation. The algorithm can be applied in primary care settings or in the community for COPD screening, offering both high rule-in and rule-out values.

Several COPD screening or case-finding tools including questionnaires, microspirometry, and peak

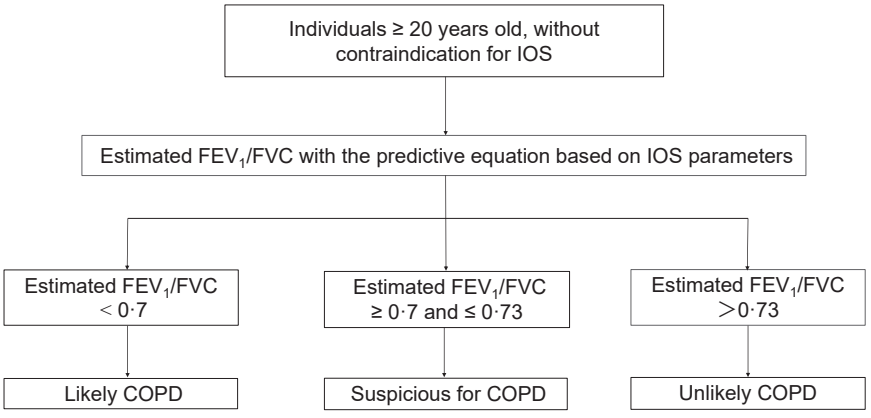

Fig. 3: Proposed clinical algorithm for the triage of patient at risk of chronic obstructive pulmonary disease using the predictive equation based on IOS parameters.

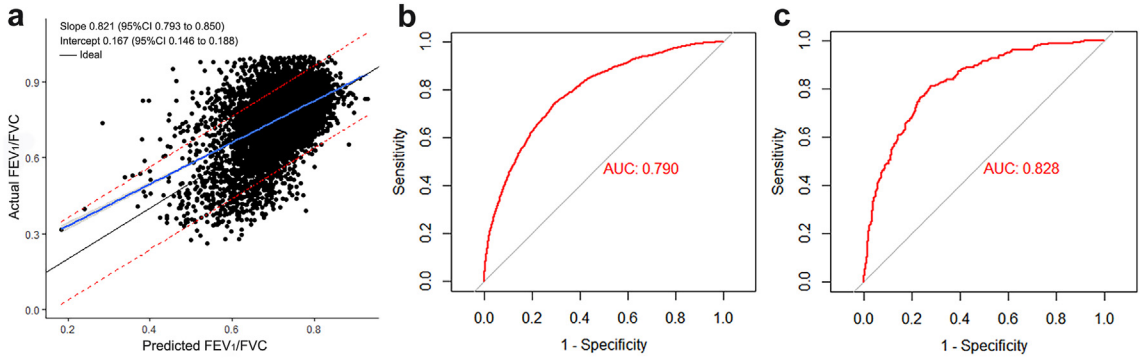

Fig. 4: Performance evaluation of the prediction model in the external validation set. (a) Correlation between actual and estimated pre-bronchodilator FEV_1/FVC. The linear regression line (blue line) is depicted together with the 95% confidence interval (shaded area) and the 95% prediction interval (red dashed lines). (b) ROC curve for identifying airflow obstruction in external validation. (c) ROC curve for identifying spirometry-defined chronic obstructive pulmonary disease in external validation. Abbreviations: FEV_1/FVC, forced expiratory volume in 1 s/forced vital capacity, ROC, receiver operating characteristic.

expiratory flow (PEF) have been developed for identifying undiagnosed COPD in primary care and the general population.[5,26] The benefits of questionnaires are their simplicity, convenience, and cost-effectiveness, whereas their drawbacks are susceptibility to individual cognitive abilities, subjectivity, and low sensitivity for asymptomatic individuals at the early stage of disease.[4,5,27] Microspirometry and PEF were reported to have higher sensitivity and specificity compared with questionnaires[5,26]; however, these tools need forced inspiratory and expiratory maneuvers which can be difficult to perform for the old and weak. Compared with microspirometry and PEF, IOS only needs quiet tidal breath, which is easier to accomplish due to the limited cooperation needed from individuals. A previous multicenter study among primary care patients in China reported that the sensitivity and specificity of COPD screening questionnaires ranged from 51.7%–63.1% and 70.3%–78.6%, respectively. Microspirometry showed 64.9% sensitivity and 89.7% specificity, while PEF had 67.3% sensitivity and 82.6% specificity.[5] The present study has shown that IOS equation has good screening properties for the detection of spirometry-defined COPD, and we think that future studies will be needed to compare the performance of our equation with COPD screening questionnaires, microspirometry, and PEF in order to find the most accurate and time-efficient screening tool for the early identification of COPD.

This study created a clinical algorithm with dual cut-offs to include individuals likely to have spirometry-defined COPD and exclude those without AO. Our results in external validation set showed that, in likely COPD group (model estimated $FEV_1/FVC < 0.70$), the proportions of AO and spirometry-defined COPD were 60.4% and 58.1%, respectively. We recommend this patient group with great possibility to have COPD should be referred to a specialist clinic without additional testing in primary care clinics. Patients in unlikely COPD group (model estimated $FEV_1/FVC > 0.73$) were judged to be free from COPD according to the algorithm. Our results showed that the proportions of AO and spirometry-defined COPD in unlikely COPD group were only 13.3% and 8.0%, respectively, indicating a very low risk of the algorithm missing COPD patients. Furthermore, we recommend that only patients with model estimated FEV_1/FVC falling in the grey zone (0.70–0.73) need to undergo a diagnostic spirometry test in primary care clinics. In this study, the proportion of patients in the grey zone were only 15.5% and 16.7% in internal and external validation, which means that a large number of spirometry tests can be saved in primary care clinics through the IOS derived equation.

	Pre-test probability					
	Prevalence 8.6%	Prevalence 10%	Prevalence 15%	Prevalence 20%	Prevalence 25%	Prevalence 30%
Model-estimated $FEV_1/FVC > 0.73$	NPV 98.6%	NPV 98.3%	NPV 97.3%	NPV 96.3%	NPV 95.1%	NPV 93.7%
Model-estimated $FEV_1/FVC < 0.70$	PPV 26.5%	PPV 29.8%	PPV 40.3%	PPV 48.9%	PPV 56.1%	PPV 62.1%

FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; NPV, negative predictive value; PPV, positive predictive value.

Table 5: **Negative and positive predictive values for the prediction model according to different prevalences of spirometry-defined chronic obstructive pulmonary disease.**

Our predictive equation showed a high NPV (>90%) for spirometry-defined COPD, which indicate that the risk of missing a patient with COPD who has a negative result is low. Considering that NPV depend on disease prevalence, NPV would increase in real-world clinical practice as the prevalence of COPD is lower in the general population or primary care populations compared with our sample.[2] Consequently, using our equation in a primary care setting will incur a low to very low risk of missing a patient who has potential risk of COPD. The operating characteristics of our equation in COPD screening across various disease prevalences were further explored through a Fagan's nomogram, which showed that our equation is well-suited to rule out COPD patients (NPV 93.7%–98.6%) in community and primary care settings.

Using a dual cut-off approach, our equation could potentially enhance the efficiency of COPD diagnosis in primary care and optimize healthcare resource allocation. Only patients suspected of having COPD need to undergo further spirometry tests in primary care clinics, saving time and effort for general practitioners. However, the cut-offs in this study were established among patients from tertiary hospitals, and further research is needed to determine optimal cut-offs in primary care settings in population with large samples. Furthermore, our model was developed and validated using only data from Chinese patients, which in theory could be different to that of other populations. We also encourage other researchers to validate our equation in the future.

The strengths of this study are the large sample size, the multicentric methodology, and the use of pre- and post-BD spirometry. However, there are several limitations of our findings. First, we only recruited participants from tertiary hospitals, and the performance of our prediction model in hospital scenarios may not match that in primary care settings, thus further external validation is needed in primary care clinics. Second, in the current databases, detailed information about smoking history, environmental or occupational exposure, and clinical symptoms were missing and could not be analyzed. However, asymptomatic COPD and nonsmoking COPD are common in low- and middle-income countries,[6] and there were instances of individuals diagnosed with COPD who had no history of smoking or exposure to known risk factors.[28] This equation may be advantageous in that it is not influenced by individual symptoms or history of exposure, thereby serving as an objective physiological measurement for the detection of undiagnosed COPD. Third, a cost effectiveness analysis was not performed in this study, and the grey zone may lead to increased subsequent diagnostic costs. Further studies are needed to analyze the economic impact and resource allocation for testing patients in the grey area. Moreover, we used a fixed ratio—rather than the lower limit of normal—of Chinese reference values in defining COPD, which may overestimate COPD in elderly patients. A further limitation is that the identification of patients with COPD in this population is reliant on spirometry testing, rather than a clinical diagnosis, which potentially limit the representativeness of the COPD population.

Conclusions

We developed and validated a model for predicting FEV_1/FVC based on sex, age, height, weight, and IOS parameters. Based on this equation, we constructed a screening paradigm for COPD which could be a promising approach for optimizing the process of identifying patients with COPD in the primary and community healthcare settings.

Contributors

ML, CZ, and KH conceptualized and designed the study. XY, YS, HL, LC, YL, XC, and LA acquired the data and information for this study. ML and CZ directly accessed to all raw data and verified the underlying data reported in the study. ML, CZ, and XZ conducted data analysis. ML, CZ, and XZ interpreted the data and drafted the initial manuscript. KC, JK and KH critically revised the manuscript for important intellectual content. KH were responsible for the decision to submit the manuscript. All authors participated in preparing the manuscript and approved the final version for submission.

Data sharing statement

Anonymized individual patient data analyzed during this study are available from the corresponding author on reasonable request. Approval of such requests depends on the nature of the request, merit of the research proposed, availability of the data, and intended use of the data. Data requests should be sent to kewuhuang@126.com.

Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2025.101501.

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