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Association between clinical and pulmonary function features and diagnosis of cough variant asthma: a case–control study

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ABSTRACT

Objectives To compare physical information, such as age, sex, height, weight, body mass index (BMI) and pulmonary function test (PFT) results, between cough variant asthma (CVA) and chronic cough (CC) and establish a diagnostic model of CVA.

Design A case–control study of patients with suspected CVA enrolled at The First Affiliated Hospital of Zhejiang Chinese Medical University.

Setting One leader unit of the National Key Specialised Pulmonary Disease Cooperation Group in China.

Participants Enrolled 545 patients who underwent PFT and bronchial provocation tests.

Outcome measures We obtained physical information and pulmonary test data and established the model using logistic regression analysis. The Hosmer-Lemeshow goodness-of-fit test, area under the receiver operating characteristic curve (AUC), calibration plot and decision curve analysis were used to evaluate this model. All data were analysed using SPSS V.27 and RStudio software.

Results The CVA group had more female patients (%) (68.12% vs 51.48%, p value<0.001) and lower height (m) (1.61 (0.40) vs 1.65 (3.26), p value<0.001), weight (kg) (60 (56) vs 63 (85), p value<0.001) and BMI (kg/m^2) (22.59 (17.91) vs 23.28 (21.81), p value=0.016) than the CC group. Differences between CVA and CC in forced vital capacity (FVC) in percent predicted values (FVC% pred) (94.4 (57.3) vs 91.60 (94.10), p value=0.006), forced expiratory volume in 1 s/FVC (FEV1/FVC) (%) (84.65±6.82 vs 86.91±6.71, p value<0.001), peak expiratory flow in per cent predicted values (PEF% pred) (93.00 (81.10) vs 98.00 (108.00), p value=0.005), maximal mid-expiratory flow in percent predicted values (MMEF% pred) (74.50 (100.60) vs 90.85 (170.30), p value<0.001), forced expiratory flow (FEF) at 50% of FVC in per cent predicted values ($FEF_{50\%}$ pred) (78.9(113.50) vs 93.10(169.80), p value<0.001) and FEF at 75% of FVC in per cent predicted values ($FEF_{75\%}$ pred) (69.70 (137.60) vs 85.60 (225.80), p value<0.001) were significant. Patients with CVA were more in number compared with patients with CC at a lower degree (<65%) of MMEF% pred (32.37% vs 14.50%, p value<0.001), $FEF_{50\%}$ pred (26.09% vs 13.02%, p value<0.001) and $FEF_{75\%}$ pred (39.13% vs 23.67%, p value<0.001). FVC% pred, FEV1/FVC, BMI and MMEF% pred aided in establishing a model with an AUC of 0.733 (95% CI: 0.6829 to 0.7831). The model was tested using internal and external data (p value=0.2865 and p value=0.3197, respectively).

Conclusion BMI, FVC% pred, FEV1/FVC (%) and MMEF% pred were used to establish the diagnostic model. Our model potentially indicates CVA.

Trial registration number NCT06199830.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The model construction method is simple and easily operable.
⇒ Most medical centres that perform pulmonary function tests have the items included in this model.
⇒ We did not perform external verification based on data from other medical centres.
⇒ Instead, we completed external verification using data from the same medical centre 3 years later.
⇒ Another limitation is that our model did not include more clinical characteristics, such as symptom scores and history of allergy.

INTRODUCTION

Chronic cough (CC) is defined as a cough lasting for more than 8 weeks in adults.[1] CC affects approximately 10% of the general population worldwide[2] and 3.6% of Chinese adults.[3]

Over one-third of the patients with CC have cough variant asthma (CVA).[4] A persistent cough associated with bronchial hyperresponsiveness (BHR) is the principal or only symptom that characterises CVA.[5] Although most CVA patients present with typical symptoms and high heterogeneity, some develop typical asthma over time.[6] Distinguishing CVA from CC is crucial because improper or delayed diagnosis can lead to insufficient treatment, an inability to relieve cough symptoms and worsening health.[7] However, clinicians may find it challenging to differentiate patients with CVA from those with CC based on respiratory symptoms and history of the disease. BHR is a hallmark of CVA and can

be considered a predictor of CVA in non-smoking adults with CC.[8] Physicians diagnose CVA largely based on a positive bronchial provocation test (BPT). However, this method is expensive and time-consuming. In addition, the requirements of professional technicians and equipment[9] and the potential risk of severe bronchospasm make it difficult to apply BPT widely in primary clinics.

Recently, an increasing number of studies have focused on the pulmonary characteristics of patients with CVA to distinguish CVA from CC more conveniently and safely. One study indicated that fractional exhaled nitric oxide (FeNO) and maximum mid-expiratory flow (MMEF) may have substantial potential as negative parameters for differentiating CVA from CC.[10] Another study implied that a combination of $FeNO_{200}$ with MMEF, forced expiratory flow (FEF) at 75% of forced vital capacity (FVC) ($FEF_{75\%}$) and FEF at 50% of FVC ($FEF_{50\%}$) contributed strongly to differentiate CVA from CC.[11] However, FeNO tests are expensive, and in some countries, such as the UK, FeNO is available in specialist centres but not in primary care centres where most asthma cases are diagnosed.[12] Thus, we need a new CVA diagnostic model that is more suited for primary care and with a broad application range. This study aimed to establish a model for CVA diagnosis based on the differences in physical information and pulmonary ventilation data between patients with CVA and those with CC.

METHODS

Study design

This was a case–control study (NCT06199830) of patients with CC or CVA who underwent pulmonary tests between January 2019 and December 2019, while the time-external test data were collected from January 2023 to April 2023. We recruited all CVA and CC participants in collaboration with The First Affiliated Hospital of Zhejiang Chinese Medical University, a tertiary medical institute of traditional Chinese medicine in Zhejiang province. The patients and the public were not involved in designing, conducting, reporting or disseminating our research plans.

Inclusion criteria for CVA included: (1) age 18–65 years; (2) CC (≥8 weeks) as the sole or predominant symptom; (3) variable airway limitation evaluated by BHR test; (4) positive response to anti-asthma therapy.[13] Inclusion criteria for CC included: (1) age 18–65 years; (2) CC (≥8 weeks) as the sole or predominant symptom; (3) no radiographic evidence of lung disease; (4) no fever, blood-stained sputum or other active respiratory infection.[10 14]

Exclusion criteria for CVA were as follows: (1) history of chronic obstructive pulmonary disease (COPD), bronchiectasis, bronchitis, cystic fibrosis or pneumonia, interstitial lung disease (ILD), pulmonary tuberculosis, lung cancer and cough caused by drugs or treatments; (2) upper airway cough syndrome (UACS), gastro-oesophageal reflux-related cough (GERC) or other apparent causes of cough; (3) use of inhaled corticosteroids in the previous 4weeks. The exclusion criterion for CC was history of variable airway limitation, confirmed by methods such as a positive BHR test result. The study protocol can be accessed from online supplemental file 1. Patients with missing data on age, sex, height, weight and pulmonary function tests (PFTs) were filtered out.

Assessments and spirometry

Professional technicians used a computerised spirometer (MasterScreen PFT system, Jaeger, Germany) for PFTs and another computerised spirometer (ASTOGRAPH Jupiter 21, CHEST, Japan) for the methacholine (MCh) challenge test (BHR test); these tests were performed according to the 2014 Guideline for Pulmonary Function of the Chinese Respiratory Society.[15] The FVC, forced expiratory volume in 1 s (FEV1), FEV1/FVC (%), MMEF and FEF were recorded during the PFT.

The BHR test was performed after PFT. Patients were asked to inhale gradually increasing doses of MCh, and FEV1 was measured after each inhalation. This test was stopped when the baseline FEV1 reduced by over 20%. A quantitative nebulisation inhalation method was used. These tests were not performed in real-time; however, the data were retrospectively collected from an existing lung function measurement database.

All data were obtained from The First Affiliated Hospital of Zhejiang Chinese Medical University and have been reviewed by data checkers. The doctors determined the cause of the CC.

Sample size

The sample size for this study was calculated using PASS V.15.0.5 with a 1:1 ratio between CVA and CC group. Based on studies by Chen *et al*,[10] considering a 20% drop in this research, the final sample size is 28 patients in each group.

Statistical analysis

All data analysed using SPSS V.27 (IBM Corporation, Armonk, New York, USA) and RStudio software. P value<0.05 was considered statistically significant. Normal statistical variables were expressed as mean±SD. The Student's t-test was used to compare the two groups of patients with CVA and CC. Classification variables are characterised as N(%) and analysed using the χ^2 test. Non-normal data are expressed as medians (range), and comparisons between groups were performed using the Mann-Whitney U test. A model for the outcomes was established using logistic regression analysis. After model establishment, the Hosmer-Lemeshow goodness-of-fit test was applied (p value>0.05, good calibration). The area under the receiver operating characteristic curve (AUC) greater than 0.7 considerably has good discrimination validity and is verified using internal and external data. Calibration plots and decision curve analyses were performed to assess the accuracy and clinical effectiveness of this model. RStudio software (V.4.2.1) and SPSS (V.27)

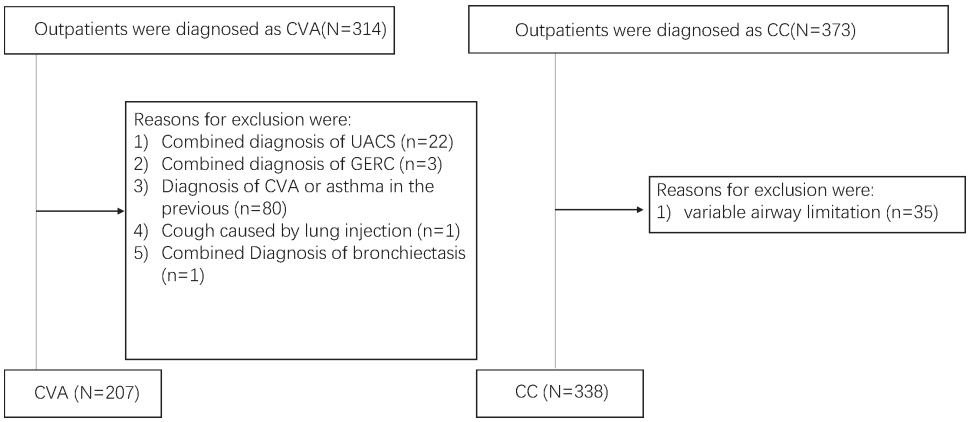

Figure 1 The strategies of flow-chart with CVA or CC patient. CC, chronic cough; CVA, cough variant asthma; GERC, gastro-oesophageal reflux-related cough; n, number of subjects; UACS, upper airway cough syndrome.

were used for statistical analyses. Internal and external verification was performed using RStudio software.

RESULTS

Pulmonary and critical care physicians diagnosed 545 patients with CVA or CC based on clinical manifestations, examinations and positive response to therapy.

Of these, we enrolled and analysed 207 patients with CVA. The reasons for exclusion were as follows: (1) combined diagnosis of UACS (n=22); (2) combined diagnosis of GERC (n=3); (3) diagnosis of CVA or asthma in a previous study (n=80); (4) cough caused by lung infection (n=1); (5) combined diagnosis of bronchiectasis (n=1). Overall, 338 patients with CC were enrolled and analysed. The reason for exclusion was variable airway limitation (n=35). Figure 1 shows the flow chart depicting the strategies used.

Table 1 presents the demographic parameters of the enrolled patients. A significant difference was found in the female ratio between the CVA and CC groups (68.12% for CVA and 51.48% for CC, p value<0.001). Height, weight and body mass index (BMI) were lower in the CVA group than in the CC group (p value<0.001, p value<0.001, p value=0.016, respectively). Furthermore,

Table 1 Baseline characteristics, pre-BPT spirometry of patients with CVA and CC

Demographic parameter	CVA	CC	P value
N	207	338	
Age, years	40 (47)	39 (43)	0.575
Female, n (%)	141 (68.12)	174 (51.48)	<0.001
Height, m	1.61 (0.40)	1.65 (3.26)	<0.001
Weight, kg	60 (56)	63 (85)	<0.001
BMI, kg/m^2	22.59 (17.91)	23.28 (21.81)	0.016
FVC% pred	94.4 (57.3)	91.60 (94.10)	0.006
FEV1	2.72 (3.25)	2.93 (4.27)	0.002
FEV1% pred	93.00 (64.90)	94.55 (118.00)	0.320
FEV1/FVC (%)	84.65±6.82	86.91±6.71	<0.001
PEF% pred	93.00 (81.10)	98.00 (108.00)	0.005
MMEF% pred	74.50 (100.60)	90.85 (170.30)	<0.001
$FEF_{50\%}$ pred	78.9(113.50)	93.10(169.80)	<0.001
$FEF_{75\%}$ pred	69.70 (137.60)	85.60 (225.80)	<0.001
MMEF% pred (<65%), n (%)	67 (32.37)	49 (14.50)	<0.001
$FEF_{50\%}$ pred (<65%), n (%)	54 (26.09)	44 (13.02)	<0.001
$FEF_{75\%}$ pred (<65%), n (%)	81 (39.13)	80 (23.67)	<0.001

N refers to the total patients.
The difference between groups was analysed by Student's t-test or χ^2 or Mann-Whitney U test. Significant p value<0.05.
BMI, body mass index; CC, chronic cough; CVA, cough variant asthma; FEF, forced expiratory flow; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; MMEF, maximal mid-expiratory flow.

we found significant differences in FVC to predicted value ratio (FVC% pred) (p value=0.006), FEV1/FVC (%)(p value<0.001), the peak expiratory flow (PEF) in per cent predicted values (PEF% pred) (p value=0.005), MMEF in per cent predicted values (MMEF% pred) (p value<0.001), $FEF_{50\%}$ predicted (p value<0.001) and $FEF_{75\%}$ predicted (p value<0.001) between CVA and CC. We did not observe any difference in the FEV1% predicted. Patients with CVA showed significant differences in MMEF% pred (<65%), $FEF_{50\%}$ pred (<65%)and $FEF_{75\%}$ pred (<65%) (p value<0.001, p value<0.001, p value<0.001, respectively) compared with the CC group.

Model establishment

Based on table 1, sex, height, weight, BMI, FVC% pred, FEV1/FVC (%), FEF% pred, MMEF% pred, $FEF_{50\%}$ pred, $FEF_{75\%}$ pred, MMEF% pred (<65%), $FEF_{50\%}$ pred (<65%) and $FEF_{75\%}$ pred (<65%) showed significant differences between the CVA and CC groups. The CVA group had more female patients than the CC group, which might explain the significant differences in FEV1, height and weight. Thus, the FEV1, height and weight were not considered when establishing the model. MMEF% pred (<65%), $FEF_{50\%}$ pred (<65%) and $FEF_{75\%}$ pred (<65%) were calculated based on MMEF% pred, $FEF_{50\%}$ pred and $FEF_{75\%}$ pred, respectively. To avoid multiple linear relationships and obtain a lower −2 log-likelihood, we used MMEF% pred, $FEF_{50\%}$ pred and $FEF_{75\%}$ pred to establish the model. Using SPSS, we selected BMI, FEV1/FVC, FVC%pred and MMEF% pred for model establishment (online supplemental table 1) and conducted a logistic regression model using RStudio.

Enrolled patients were randomly divided into a 7:3 ratio of training and internal test groups by setting random seeds with R. Overall, 384 and 161 patients were used for model construction and the internal test, respectively. The differences were not significant between the two groups (online supplemental table 2). Based on the logistic regression analysis, we constructed a nomogram prediction model for CVA, as shown in figure 2. MMEF% pred showed the highest influence, ranging from 0–100, whereas, BMI contributed the least to this model. This model indicated that a patient with a lower MMEF% pred, higher FEV1/FVC ratio, FVC% pred and normal BMI would be more likely to be diagnosed with CVA.

Verification of nomogram prediction model

A clinical prediction model was established using RStudio, and the ROC was delineated. As presented in figure 3A, AUC was 0.733 (95% CI: 0.6829 to 0.7831). The Hosmer-Lemeshow goodness-of-fit test showed no significant difference (p value=0.9625); 30% of the data were randomly separated and used as the internal test group. The AUCs were not significantly different (p value=0.2865, figure 3B). External test group data were collected at The First Affiliated Hospital of Zhejiang Chinese Medical University from January 2023 to April 2023. The AUCs between the training and external test groups also showed no significant differences (p value=0.3197, figure 3C). The calibration plot revealed good predictive accuracy between the actual and predicted probabilities (figure 4A). Decision curve analysis showed that the nomogram performed well in terms of net benefit (figure 4B), indicating good clinical effectiveness.

DISCUSSION

In this study, we found that sex, height, weight, BMI, FVC% pred, FEV1/FVC (%), PEF% pred, MMEF% pred, $FEF_{50\%}$ pred, $FEF_{75\%}$ pred, MMEF% pred (<65%), $FEF_{50\%}$ pred (<65%) and $FEF_{75\%}$ pred (<65%) were significantly different between the CVA and CC groups. BMI, FVC% pred, FEV1/FVC (%) and MMEF% pred were used to establish a diagnostic model for CVA. The BMI was lower in the CVA group than in the CC group. One study focusing on obesity and asthma illustrated that a high BMI was associated with a high risk of wheezing without asthma but not with a high risk of asthma without wheezing.[16] The difference between CVA and typical asthma was that patients with CVA exhibited no wheezing

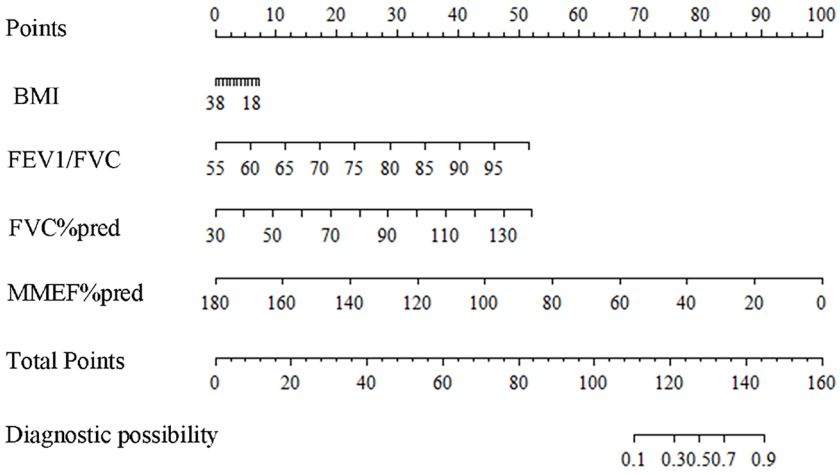

Figure 2 A nomograph model for predicting cough variant asthma. BMI, body mass index; FEV, forced expiratory volume; FEV1, FEV in 1 s; FVC, forced vital capacity; MMEF, maximal mid-expiratory flow.

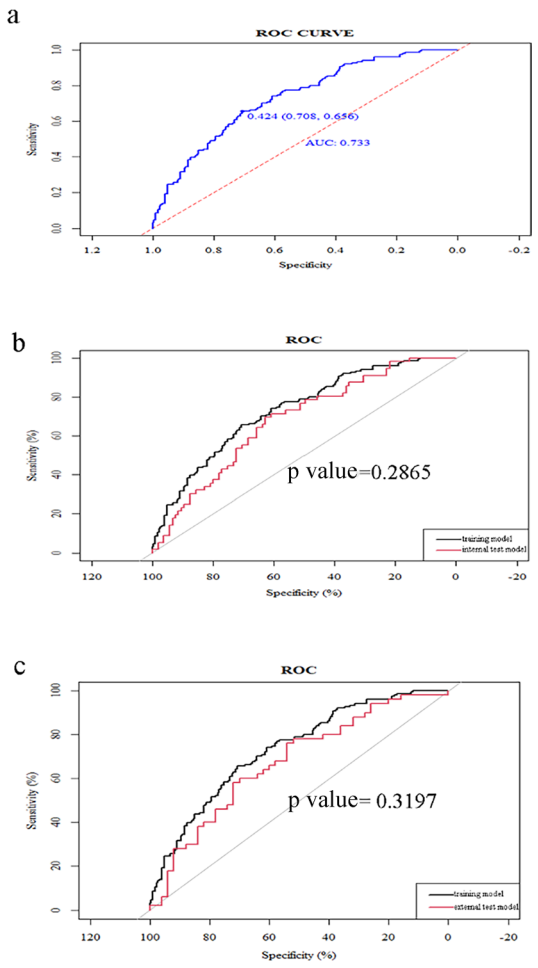

Figure 3 (A) The area under the receiver operating characteristic curve of the nomograph prediction model; (B) comparison of training model and internal test model; (C) comparison of training model and internal test model.

symptoms. Thus, a high BMI may not be associated with a high CVA risk. In contrast, Yuan *et al* found evidence for an association between obesity and an increased gastro-oesophageal reflux disease (GERD) risk.[17] GERD is one of the main types of CC.[18] that could explain the reasons for significantly higher BMI in the CC group than in the CVA group. Our study indicates that a lower BMI could be a positive indicator of CVA diagnosis when used to identify CVA and CC.

BMI was inversely associated with FVC, and higher BMI was associated with higher FEV1/FVC,[19] similar to the findings in our study. Recent trials have been using FVC to define disease progression in patients with progressive pulmonary fibrosis.[20] Reduction of FVC%≥10% of patients with ILDs was associated with significantly increased odds of an inpatient hospitalisation.[21] The strong link between the FEV1/FVC ratio and COPD was used as a threshold for defining COPD.[22] In other words, lower FVC% pred and FEV1/FVC may indicate a greater possibility of cough caused by other respiratory diseases such as ILD and COPD. Therefore, higher FEV1/FVC and FVC% pred imply greater potential for diagnosing CVA, as shown in this study. BHR is one of the main differences between CVA and CC. Patients with small airway dysfunction were more likely to develop BHR.[23] MMEF% pred, a marker of small airway function, can be used as a surrogate to predict BHR in patients with respiratory symptoms.[24] As shown in the nomograph, MMEF% pred played the most important role. Overall, this model indicates that higher FVC% pred and FEV1/FVC ratios with lower BMI and MMEF% pred imply a stronger association with CVA.

An increasing number of studies have attempted to establish diagnostic models for CVA to replace BPT. Most of these studies have considered FeNO because of its association with Th_2 cell-mediated airway inflammation and its vital role in CC aetiology.[10] Contrarily, some studies have implied that, although high FeNO levels suggest the existence of asthmatic cough (CVA and cough-predominant asthma), lower FeNO levels have limited diagnostic significance.[25] Moreover, as previously mentioned, FeNO might

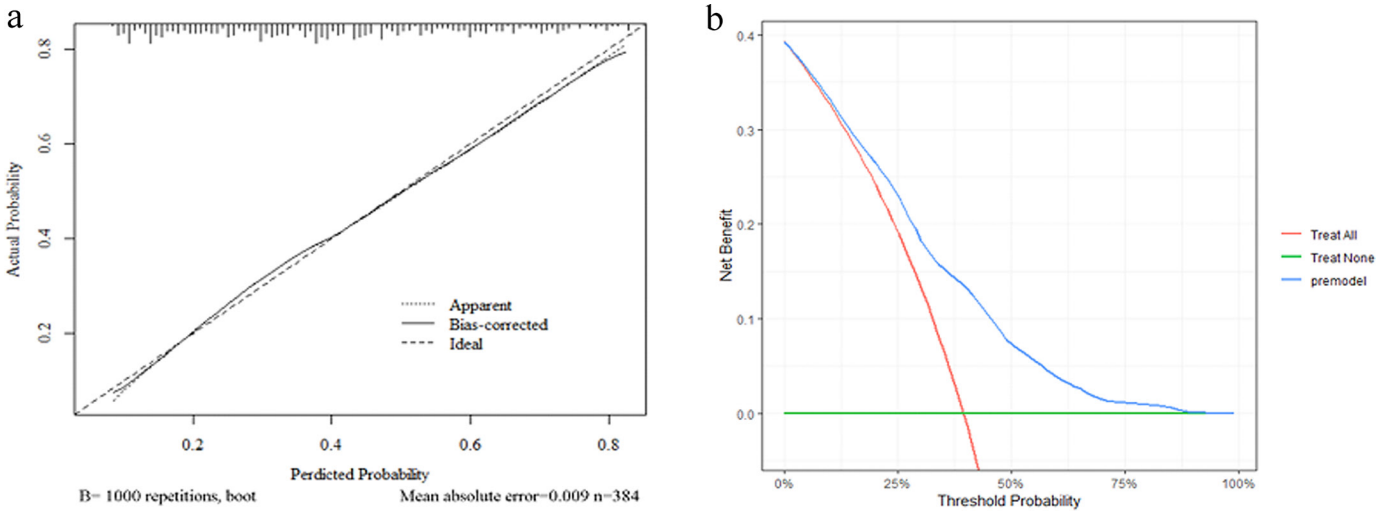

Figure 4 (A) Calibration curve of nomogram model for predicting cough variant asthma (CVA); (B) decision curve analysis of model for predicting CVA.

be unavailable in primary care.[12] Thus, our diagnostic model based on expediently available data from lower-risk examinations can be applied more conveniently.

Strengths and limitations

We did not complete the external verification based on space because of the lack of BPT in other medical centres. However, we completed external verification using data from the same medical centre 3 years later, which was similar to another retrospective study.[26] The adverse events that occurred during MCh-BPT included transient wheezing, cough, pharyngeal itching, hoarseness, sore throat and shortness of breath, and chest tightness was up to 26.32%.[27] Therefore, it could be too dangerous for some primary medical centres to operate an MCh-BPT. We performed this study to identify factors firmly connected to CVA to offer more evidence for treating CVA without verification of MCh-BPT.

The symptom scores were not assessed. The retrospective nature of this study has made it challenging to evaluate the symptoms of patients suffering from CVA, such as the cough severity visual analogue scale and Leicester Cough Questionnaire. Furthermore, they could be included in future studies to modify the model.

This model can be tested in other medical centres in future to verify its effectiveness. Since three of four parameters are from PFT, input data from incomplete PFT reports should be assessed and handled when implementing the prediction model. We can obtain all parameters contained in this model conveniently and safely. Thus, users will not be required to have a high level of expertise and obtain the results directly by using a nomogram. On the other hand, we can also enrol more patients to modify the model.

CONCLUSIONS

This study showed that more female patients, a lower BMI and severe small airway dysfunction were associated with CVA. BMI, FVC% pred, FEV1/FVC (%) and MMEF% pred were used to establish the diagnostic model. Our model potentially differentiates CVA from CC through internal and external verifications.

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Contributors KN, SW and JY designed the protocol. XZ, YZ, YL and YW collected the data and KN finished the manuscript. KN and SL analysed the data. KN and JY interpreted the data. SW and KN supervised the statistical analyses. All authors edited, read and approved the manuscript. KN and SW contributed equally to this work. JY is responsible for the overall content as the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Ethics Committee of The First Affiliated Hospital of Zhejiang Chinese Medical University, which absolved the need for written informed consent because of the retrospective study. The ethics protocol number is 2023-KLS-100-01. All personal identification data were anonymised and de-identified before analysis.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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