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A Two-Staged, Risk-Stratified Strategy Combining FEV_1/FEV_6 and COPD Diagnostic Questionnaire Acts as an Accurate and Cost-Effective COPD Case-Finding Method

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Keywords: combined modality | diagnostic accuracy | FEV_1/FEV_6 | handheld lung function device | peak expiratory flow rate | predictive performance | symptom-based questionnaire

ABSTRACT

Background and Objective: Symptom-based questionnaires and handheld lung function devices are widely used for COPD case finding, but the optimal combination remains unclear. This study aimed to compare the diagnostic accuracy (DA) of various combinations of handheld lung function devices and questionnaires and develop a COPD case-finding strategy.

Methods: This cross-sectional, prospective, observational study enrolled participants aged ≥40 years with respiratory symptoms and ≥10 smoking pack-years. Participants completed three questionnaires (COPD diagnostic questionnaire [CDQ], lung function questionnaire; COPD Population Screener) and 2 handheld lung function devices (peak flow meter, microspirometer), followed by spirometry to confirm COPD (post-bronchodilation $FEV_1/FVC < 0.7$). DA is assessed using the area under the ROC curve (AUROC).

Results: Among 224 participants, COPD incidence was 29%. Individually, handheld devices showed significantly higher DA than questionnaires (AUROC 0.678–0.69 for questionnaires vs. 0.807 for peak expiratory flow rate [PEFR] and 0.888 for FEV_1/FEV_6; all pairwise $p < 0.05$). FEV_1/FEV_6-based combinations outperformed PEFR-based combinations (all $n = 224$; AUROC 0.897–0.903 vs. 0.810–0.818; $p < 0.05$). The CDQ and FEV_1/FEV_6 combination reached the highest DA (AUROC 0.903). $FEV_1/FEV_6 < 0.76$ was the optimal cutoff value. A two-staged strategy (sensitivity/specificity 0.82/0.84) was proposed: low-risk participants (CDQ ≤13) need no further testing; middle-risk (CDQ 14–26) should undergo FEV_1/FEV_6; and high-risk (CDQ ≥27) and middle-risk with $FEV_1/FEV_6 < 0.76$ require confirmatory spirometry. This approach would reduce misdiagnoses and save costs and time compared to FEV_1/FEV_6 alone.

Conclusion: FEV_1/FEV_6 and CDQ combination achieves the highest DA. A two-staged, risk-stratified strategy combining CDQ and FEV_1/FEV_6 can be accurate and cost-effective to detect at-risk, undiagnosed COPD subjects. External validation is required.

Abbreviations: BD, bronchodilation; CAT, COPD assessment test; COPD, chronic obstructive lung disease; FEV_1, forced expiratory volume in the first second; FEV_6, forced expiratory volume in six seconds; FVC, forced vital capacity; NPV, negative predictive value; %PEFR, percent predicted peak expiratory flow rate; PEFR, peak expiratory flow rate; PPV, positive predictive value.

Summary

- COPD case-finding tools that integrate handheld lung function devices and questionnaires demonstrate superior accuracy compared to individual approaches.
- Combining FEV_1/FEV_6 with COPD Diagnostic Questionnaire (CDQ) achieves the highest accuracy (area under ROC = 0.903).
- We propose a two-stage, risk-stratified strategy utilising FEV_1/FEV_6 and CDQ for accurate, cost-effective identification of at-risk, undiagnosed individuals.

1 | Introduction

Chronic obstructive pulmonary disease (COPD) is an important cause of morbidity and mortality and has been the third leading cause of death worldwide [1–3]. COPD burden is increasing. However, COPD remains largely underdiagnosed worldwide at an estimate of around 20%–80% [4–8], and a substantially high proportion of underdiagnosis occurs in primary care (PC) [7, 9, 10]. Underuse or unavailability of spirometry are significant factors for underdiagnosis. In addition, younger age, non-smoker, lower education, less severe airflow limitation, lack of symptom perception, and low disease awareness are also attributable factors [8, 11, 12]. In Taiwan, a recent nationwide telephone interview survey of the general population revealed that COPD was largely underdiagnosed due to low COPD awareness and spirometry underuse [13]. Hence, we urgently need an effective COPD case-finding strategy to identify at-risk subjects who require a spirometric diagnosis.

Currently, the US Preventive Services Task Force recommends against screening COPD in asymptomatic adults [14, 15]. By contrast, case-finding to detect COPD in those with respiratory symptoms or exposure risks is advocated [15, 16]. These symptomatic cases often present in PC, which are optimal occasions to catch COPD early. COPD case-finding tools include questionnaires, handheld lung function devices, or a combination of both [17, 18]. The COPD diagnostic questionnaire (CDQ), lung function questionnaire (LFQ), and COPD Population Screener (COPD-PS) appear to be the most commonly used questionnaires in PC [17, 19]. Overall, these questionnaires corresponded to a wide range of diagnostic accuracy (DA, represented by the area under the receiver operating characteristic curve, AUROC 0.65–0.81), and predictive performance in terms of sensitivity (49%–91%), and specificity (37%–90%) [18, 20–25]. Even using the same questionnaire in different studies, the AUROC values, sensitivity, and specificity also largely varied in CDQ (0.71–0.80, 0.63–0.91, 0.37–0.72) [20, 22, 23, 25], COPD-PS (0.65–0.79, 0.56–0.8, 0.48–0.9) [20, 21], and LFQ (0.72–0.81, 0.49–0.73, 0.58–0.68) [20, 24], respectively. The varying performances may be related to different populations, such as clinical settings or symptom prevalence. Spyratos et al. compared CDQ, LFQ, and COPD-PS in the same PC population, finding similar AUROC values (0.794–0.809). However, COPD-PS showed the highest sensitivity (0.9 vs. 0.72 and 0.68 for CDQ and LFQ) but the lowest specificity (0.56 vs. 0.74 and 0.79) [20]. This highlights that even similar questionnaires in the same population can differ in diagnostic characteristics. Thus, validating questionnaires for specific regions is crucial to ensure reliable and consistent application across diverse settings.

Compared with questionnaires, case-finding using handheld lung function devices, such as the commonly used microspirometers (indicated by the ratio of forced expiratory volume in first over six seconds, FEV_1/FEV_6) [22, 25] or peak expiratory flow meters [26, 27] exhibited a higher and constant DA (AUROC 0.82–0.88), sensitivity (0.76–0.88) and specificity (0.71–0.78). A combined modality using a questionnaire and a handheld lung function device further improved DA (AUROC 0.866–0.906) [18, 25–27]. COPD case-finding tools applying questionnaires alone are simple but less reliable. By contrast, using a handheld lung function device alone elevates accuracy but requires more time, effort, and costs. A combined modality might balance their drawbacks. However, the best-combined modality has not been identified by directly comparing different combinations. In this study, we aimed to investigate which combination can achieve the best accuracy and establish a case-finding strategy. Additionally, the optimal cutoff ratio of FEV_1/FEV_6 will be determined.

2 | Methods

2.1 | Study Design

This prospective, cross-sectional, observational study was conducted in a medical centre from January 2018 to January 2020. The primary objective was to compare the DA of various combinations of handheld lung function devices and questionnaires for identifying COPD. The other objectives included the predictive performance of different diagnostic modalities and establishing an effective case-finding strategy accordingly. Eligible participants were invited in pulmonary outpatient clinics. During their visit, demographic information, responses to four questionnaires, including CDQ (8 items, score range 0–38), LFQ (5 items, score range 5–25, licensed from the Mapi Research Trust), COPD-PS (5 items, score range 0–10, licensed from the QualityMetric Inc., the 3 questionnaires detailed in the Supporting Information), and COPD assessment test (CAT, traditional Chinese version, permitted from the GSK Inc.), measurements of pre-bronchodilation FEV_1, FEV_6 (by the microspirometer- COPD-6, model 4000, Vitalograph Inc., Lenexa, Kansas, USA), peak expiratory flow rate (PEFR, model 4300, Vitalograph Inc., Lenexa, Kansas, USA), and confirmatory post-bronchodilation spirometry were obtained (See Figure S1 for study flow in the Supporting Information). Since the three questionnaires have not been officially translated into Chinese versions, we performed a simplified linguistic validation with a small pilot test to minimise misunderstandings for Chinese population (see Supporting Information for details). The items and scores of CDQ, LFQ, and COPD-PS are summarised in Table S1 in the Supporting Information. All participants completed the study flow in a single day. This study was approved by the Institutional Review Board (approval number: 2017-07-006C). All participants signed informed consent.

2.2 | Study Participants

Participants attending our pulmonary clinics with chronic respiratory symptoms were enrolled if they met all of these criteria: age ≥ 40 years, no prior COPD diagnosis, current or former smokers with ≥ 10 pack-years, and at least one chronic respiratory symptom (cough, dyspnoea, or phlegm lasting

≥4 weeks). They might come from the community without any referrals or being referred by non-pulmonologists. The following participants were excluded if they: (1) coincided with asthma (Supporting Information), clinically overt bronchiectasis (Supporting Information), lung cancer, active tuberculosis, or other known specific pulmonary disease; (2) presented with comorbidity that might significantly interfere with lung function measurements (e.g., neuromuscular disease, thoracic cage deformity, uncontrolled medical disease, post lung resection, etc.); (3) underwent active infection 3 weeks before enrollment; (4) were unwilling or unable to perform lung function tests. The measurement of PEFR and spirometry followed the standards of the American Thoracic Society/European Respiratory Society (Supporting Information). The performance of the microspirometer was based on the manufacturer's recommendations. Measurements were repeated to obtain three technically satisfactory efforts, and the best values were recorded. The diagnosis of COPD (defined by post-bronchodilation $FEV_1/FVC < 0.7$) and stages of airflow limitation were based on the 2017 Global Initiative for Chronic Obstructive Lung Disease (GOLD) report [28].

2.3 | Statistical Analysis

The sample size was calculated by comparing the AUROC values of different diagnostic modalities. Previous studies showed that the AUROC value was between 0.64 and 0.71 for questionnaires (CDQ, COPD-PS, LFQ) [21, 29–32] or between 0.83 and 0.88 for PEFR [26, 27] and FEV_1/FEV_6 [22, 33]. In the present study, we supposed the AUROC value was 0.7 for questionnaires and 0.8 for PEFR or FEV_1/FEV_6, respectively. Given a type I error of 0.05, a type II error of 0.2, and the ratio of subjects with versus without COPD of 3, the minimal required sample size was 212 (Figure S2 in the Supporting Information).

Data are presented as means ± SD or median (interquartile) or number (%), as appropriate. Continuous variables are compared using a *t*-test or Mann–Whitney *U* test. Categorical data were evaluated by a Chi-square test. The performance of different diagnostic modalities was determined and compared using AUROC analysis. The best cutoff value of different modalities was calculated using the Youden index to determine the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and numbers needed to screen (NNS). The agreement between COPD diagnoses based on pre-bronchodilation FEV_1/FEV_6 and post-bronchodilation FEV_1/FVC was evaluated using the Kappa coefficient. Statistical analysis was performed using SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). AUROC values were compared using MedCalc version 17.5.5 (MedCalc Software, Ostend, Belgium). A two-sided *p* value < 0.05 was considered significant.

3 | Results

3.1 | Patient Characteristics

Two hundred sixty-three consecutive participants were invited, and 224 completed the study (Figure S1 in the Supporting Information). Sixty-six of 224 (29%) were newly diagnosed COPD patients, who were categorised by GOLD stage I (38, 58%), II (25, 38%), and III (3, 4%). None of the participants had used any COPD-specific medication. Compared with non-COPD cases, COPD patients were older and had a lower BMI, higher symptom burdens (indicated by the questionnaire scores), and lower lung function parameters (Table 1). Additionally, the majority of participants (161, 72%) directly came from the community without any referrals, followed by referrals from PC (47, 21%) and institutional non-pulmonary clinics (16, 7%), respectively.

3.2 | Diagnostic Accuracy and Predictive Performance in a Single Modality

When used alone, the three questionnaires showed similar DA, but each outperformed the CAT (Figure 1A). The best cutoff values for questionnaires are shown in Table 2. Even with similar DA, the three questionnaires exhibited various predictive performances (Table 2), such as high sensitivity/low specificity for CDQ and low sensitivity/high specificity for LFQ. Compared with LFQ, CDQ identified fewer cases with corrected diagnoses (true positives plus true negatives, 130 vs. 164 cases) but vastly reduced misdiagnosed COPD patients (false negatives, 9 vs. 40 cases) (Figure 2A,B). As to pre-bronchodilation handheld lung function devices alone, the AUROC value in every single parameter (PEFR, percent predicted PEFR [%PEFR], FEV_1, FEV_6, or FEV_1/FEV_6) was significantly higher than that in any questionnaire ($p < 0.05$ for any pairwise comparisons). The microspirometer is more accurate than the peak flow meter (AUROC: $FEV_1 >$ PEFR; $FEV_1/FEV_6 >$ PEFR and %PEFR; all $p < 0.05$), and the FEV_1/FEV_6 reached the highest DA (Figure 1B). The best cutoff values for handheld lung function device parameters are shown in Table 2. Compared with PEFR, the FEV_1/FEV_6 showed better predictive performance (Table 2) and reduced misdiagnosed COPD patients (Figure 2C,D). The optimal FEV_1/FEV_6 cutoff of < 0.76 effectively predicts post-bronchodilation $FEV_1/FVC < 0.7$, with fair to good agreement (Kappa: 0.644) and a concordance rate of 84.8% (Table S2 in the Supporting Information).

3.3 | Diagnostic Accuracy in Different Combinations

Figure 1C illustrates the DA and comparisons by combining different questionnaires and handheld lung function device parameters. There was no difference among PEFR-based or FEV_1/FEV_6-based combinations, but FEV_1/FEV_6-based combinations were significantly better than PEFR-based combinations. Combining CDQ and FEV_1/FEV_6 reached the highest DA, and CDQ had the best sensitivity. Thus, this combined modality was applied to our two-staged case-finding strategy.

3.4 | Development of a Two-Staged, Risk-Stratified Combined Modality

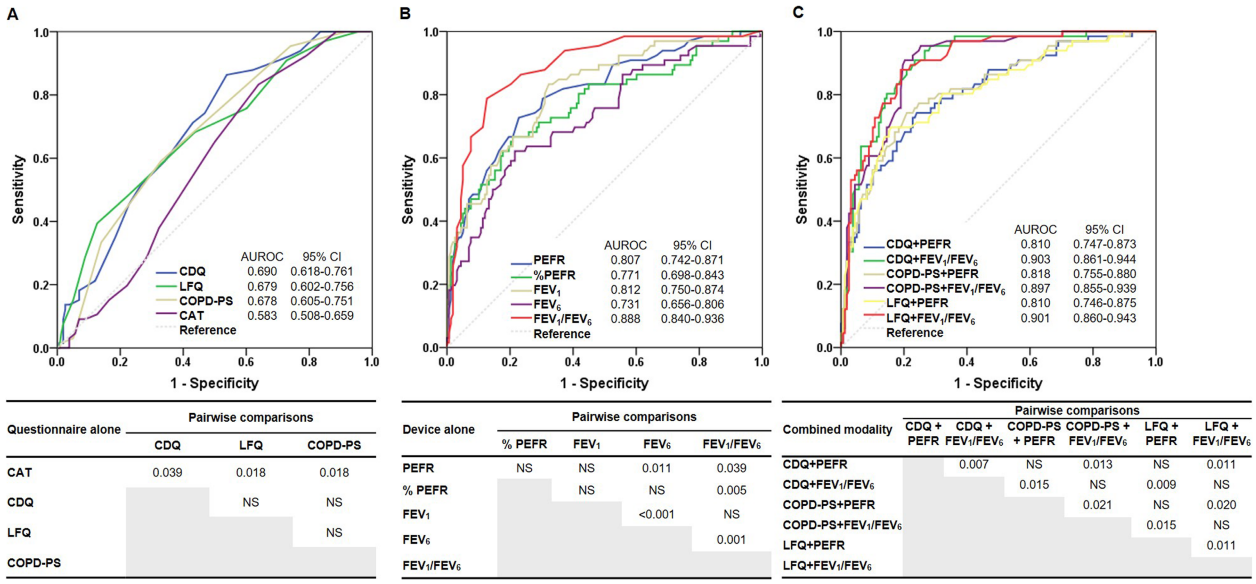
Based on the distribution of participants' CDQ scores, we first reported that the CDQ can differentiate risk levels for COPD diagnosis (see Figure S3 in the Supporting Information for details on the development of risk stratification). Participants

TABLE 1 | Baseline characteristics.

	Total	Non-COPD	COPD	*p* value
Numbers (%)	224	158 (71)	66 (29%)	
Age, year	64.9 ± 11.8	61.9 ± 10.9	71.9 ± 11.1	< 0.001[a]
BMI	25.5 (22.8–28.1)	26 (23.9–28.7)	23.8 (22.2–26.3)	0.001[b]
Male, *N* (%)	200 (89)	140 (89)	60 (91)	0.612[c]
Current smoker, *N* (%)	86 (38.4)	64 (40.5)	22 (33.3)	0.314[c]
Smoking pack-years	30 (18–50)	30 (17.5–45)	42.5 (20–53)	0.065[b]
Questionnaires				
CDQ	21 (17–24)	19 (15–23)	23 (19–25)	< 0.001[b]
LFQ	16 (15–18)	17 (16–19)	15 (13–17)	< 0.001[b]
COPD-PS	4 (4–5)	4 (3–5)	5 (4–6)	< 0.001[b]
CAT	4 (2–7)	4 (2–7)	5 (3–7)	0.048[b]
Peak flow meter (Pre-BD)				
PEFR, L/min	495 (400–560)	515 (450–580)	400 (280–460)	< 0.001[b]
PEFR, % pred.	96 (84–108)	101 (91–111)	82 (55–96)	< 0.001[b]
Microspirometer (Pre-BD)				
FEV_1, L	2.49 ± 0.8	2.74 ± 0.7	1.9 ± 0.71	< 0.001[a]
FEV_6, L	3.18 ± 0.96	3.39 ± 0.88	2.66 ± 0.96	< 0.001[a]
FEV_1/FEV_6	0.78 ± 0.08	0.81 ± 0.06	0.71 ± 0.07	< 0.001[a]
Pre-BD spirometry				
FEV_1, L	2.52 ± 0.77	2.76 ± 0.66	1.93 ± 0.7	< 0.001[a]
FEV_1, % pred.	95 ± 20	101 ± 15	81 ± 22	< 0.001[a]
FVC, L	3.25 ± 0.88	3.4 ± 0.84	2.9 ± 0.9	< 0.001[a]
FVC, % pred.	91 ± 17	92 ± 16	86 ± 19	0.013[a]
FEV_1/FVC	0.77 ± 0.1	0.82 ± 0.05	0.66 ± 0.08	< 0.001[a]
Post-BD spirometry				
FEV_1, L	2.59 ± 0.77	2.83 ± 0.66	2.02 ± 0.7	< 0.001[a]
FEV_1, % pred.	98 ± 19	103 ± 16	85 ± 21	< 0.001[a]
FVC, % pred.	3.37 ± 0.86	3.48 ± 0.82	3.1 ± 0.92	0.002[a]
FVC, % pred.	94 ± 17	95 ± 15	92 ± 19	0.302[a]
FEV_1/FVC	0.77 ± 0.09	0.82 ± 0.05	0.65 ± 0.06	< 0.001[a]
BDR (+), *N* (%)[d]	11 (4.9)	2 (1.3)	9 (13.6)	< 0.001[c]

Note: Data are presented as numbers (%) for categorical variables, or median (interquartile range) for non-parametric variables, or mean ± SD for parametric variables.
Abbreviations: % pred., % of predicted value; BD, bronchodilation; BMI, body mass index; CAT, COPD assessment test; CDQ, COPD diagnostic questionnaire; COPD-PS, COPD population screener questionnaire; FEV_1, forced expiratory volume in first second; FEV_6, forced expiratory volume in 6 s; FVC, forced vital capacity; LFQ, lung function questionnaire; PEFR, peak expiratory flow rate.
[a]Independent *t*-test, COPD versus non-COPD.
[b]Mann–Whitney *U* test, COPD versus non-COPD.
[c]Chi-Square test, COPD versus non-COPD.
[d]BDR indicates brochoreversibility, defined by an increase in $FEV_1 \geq 200$ mL and ≥ 12% from baseline after inhalation of 400 μg of salbutamol.

were categorised into low (score 0–13), middle (score 14–26), and high (score 27–38) risk groups, with a corresponding COPD incidence of 0% (0/26), 31% (54/175), and 52% (12/23), respectively (Figure 3A). Additionally, the middle-risk group had a similar portion of non-COPD and COPD cases (77% vs. 82%), indicating the need for a secondary tool to improve case discrimination. Applying a microspirometer in the middle-risk group correctly identified 78% (42/54) of COPD cases but



Questionnaire alone	Pairwise comparisons		
	CDQ	LFQ	COPD-PS
CAT	0.039	0.018	0.018
CDQ		NS	NS
LFQ			NS
COPD-PS			

Device alone	Pairwise comparisons			
	% PEFR	FEV_1	FEV_6	FEV_1/FEV_6
PEFR	NS	NS	0.011	0.039
% PEFR		NS	NS	0.005
FEV_1			<0.001	NS
FEV_6				0.001
FEV_1/FEV_6				

Combined modality	Pairwise comparisons					
	CDQ + PEFR	CDQ + FEV_1/FEV_6	COPD-PS + PEFR	COPD-PS + FEV_1/FEV_6	LFQ + PEFR	LFQ + FEV_1/FEV_6
CDQ+PEFR		0.007	NS	0.013	NS	0.011
CDQ+FEV_1/FEV_6			0.015	NS	0.009	NS
COPD-PS+PEFR				0.021	NS	0.020
COPD-PS+FEV_1/FEV_6					0.015	NS
LFQ+PEFR						0.011
LFQ+FEV_1/FEV_6						

FIGURE 1 | Diagnostic accuracy according to the ROC curve analysis. The ROC curves and pairwise comparisons are shown in the upper and lower panels based on the questionnaires alone (A), handheld lung function devices alone (B), and systemic combinations of questionnaires and handheld lung function devices (C), respectively. Statistical evaluations were performed using MedCalc. %PEFR, percent predicted peak expiratory flow rate; %PEFR, percent predicted PERR; AUROC, area under the ROC; CAT, COPD assessment test; CDQ, COPD diagnostic questionnaire; CI, conference interval; COPD-PS, COPD population screener; FEV_1, forced expiratory volume in the first second; FEV_6, forced expiratory volume in six seconds; LFQ, lung function questionnaire; PEFR, peak expiratory flow rate; ROC, receiver operating characteristic curve.

missed 22% (12/54) of COPD cases (Figure 3B). Based on this observation, we proposed a two-staged, risk-stratified combined modality (Figure 3C): first, submit all cases to CDQ. Second, the low-risk group requires no further workup; the middle-risk group should be tested using a microspirometer, then submit those with $FEV_1/FEV_6 < 0.76$ to confirmatory spirometry; the high-risk group directly undergoes confirmatory spirometry. This strategy resulted in high predictive performance (Figure 3D and Table 2), similar to FEV_1/FEV_6. Moreover, compared with a single modality (Table 3), this combined modality accurately diminished misdiagnosed COPD patients (vs. LFQ or FEV_1/FEV_6). Additionally, using a single modality significantly reduced costs and lung function test time compared to regular spirometry for all participants but risked missing some COPD cases depending on the tool. FEV_1/FEV_6 provided the best balance of benefits and limitations. Combining modalities further improved cost-effectiveness and reduced test time compared to FEV_1/FEV_6 alone (Table 3).

4 | Discussion

This study performed systemic comparisons of DA among the five COPD case-finding tools. We first identified that the DA was significantly higher in FEV_1/FEV_6 (vs. PEFR) or FEV_1/FEV_6-based (vs. PEFR-based) combinations, respectively. CDQ exhibited the highest sensitivity, while the FEV_1/FEV_6 presented the largest specificity among the five case-finding tools. Based on these findings, we showed that a two-staged, risk-stratified combined modality using CDQ and FEV_1/FEV_6 could be an accurate and cost-effective case-finding strategy. In addition, $FEV_1/FEV_6 < 0.76$ can serve as the optimal cutoff value for using a microspirometer in Taiwan.

Recently, Schnieders et al. reported that LFQ acted as a slightly more robust tool, followed by CDQ and COPD-PS in a systemic review; however, the meta-analysis demonstrated the contrary despite a lack of statistical significance [19]. Direct comparisons can help clarify this issue, and currently available comparisons are summarised in Table S3 in the Supporting Information. As to the DA, our data showed indiscriminative AUROC values among the three questionnaires, which is consistent with the reports from Spyratos et al. in Greece (AUROC 0.794–0.809) [20] and Bastidas et al. in Columbia (AUROC 0.65–0.68) [34]; in contrast, Zhou found a slightly higher DA in LFQ (AUROC 0.785) than that in CDQ (AUROC 0.731) and COPD-PS (AUROC 0.745) in China [35]. Although the statistical significance varies across these four studies, the AUROC values are very close in each individual study. These observations might be expected because all three questionnaires evaluate four common aspects- age, smoking intensity, phlegm, and dyspnoea- the key clues suggesting COPD diagnosis based on the GOLD recommendation [28]. Regarding the predictive performance, our data showed that CDQ had the highest sensitivity, whereas LFQ exerted the best specificity. However, these results were inconsistent with previous studies (Table S3 in the Supporting Information [20, 34, 35]). Surprisingly, the sensitivity, specificity, PPV, and NPV in each questionnaire (CDQ, LFQ, or COPD-PS) largely varied across these studies. The different clinical settings (community- vs. hospital-based participants) and COPD incidence (10.9%–36.3%) might broadly impact the questionnaires' predictive performance. Taken together, CDQ, LFQ, and COPD-PS exhibit similar but unsatisfactory DA and largely variable predictive performance. A secondary tool, such as a handheld lung function device, is needed to improve DA, and the selected questionnaire should be validated before being widely used in their country.

TABLE 2 | Predicted performance of different diagnostic modalities to detect undiagnostic COPD patients.

	Best cutoff value[a]	Sensitivity	Specificity	PPV	NPV	Youden index	NNS	% correct classification[b]
Questionnaire alone								
CDQ	≥19	0.86	0.46	0.40	0.89	0.33	3.4	58
LFQ	≤14	0.39	0.87	0.57	0.78	0.27	2.9	73
COPD-PS	≥5	0.59	0.67	0.43	0.80	0.26	4.4	65
CAT	≥3	0.83	0.36	0.35	0.84	0.19	5.2	50
Handheld lung function device alone								
PEFR, L/min	<450	0.73	0.77	0.57	0.87	0.50	2.3	76
FEV_1/FEV_6	<0.76	0.79	0.87	0.72	0.91	0.66	1.6	85
Combined modality (a proposed two-staged strategy)								
CDQ plus FEV_1/FEV_6	Algorism in Figure 3C	0.82	0.84	0.68	0.92	—	1.7	83

Note: Refer to Table 1 for other abbreviations.
Abbreviations: NNS, numbers needed to screen; NPV, negative predictive value; PEFR, peak expiratory flow rate; PPV, positive predictive value.
[a]Indicates the best cutoff value determined by the Youden index.
[b]Indicates true positive plus true negative rate.

In this study, either the PEFR or microspirometer alone exerted higher DA than any questionnaire alone (Figure 2), consistent with recent reviews' reports [17, 19]. The meta-analysis by Zhou et al. reported a high pooled DA (AUROC 0.91) and predictive performance (sensitivity 0.85, specificity 0.85) from 31 studies that applied various handheld lung function devices to measure PEFR, FEV_1/FEV_6, and FEV_1/FVC [36]. However, only scarce studies (summarised in Table S4 in the Supporting Information) concurrently examined PEFR and FEV_1/FEV_6 in an individual study, and direct compassions of DA are lacking to date [37, 38]. Similar to questionnaires, PEFR and FEV_1/FEV_6 exhibited significant variations in sensitivity and specificity in these studies (Table S4 in the Supporting Information). Again, this inconsistency might result from different clinical settings and COPD incidence. In this study, we first demonstrated that the FEV_1/FEV_6 had higher DA than PEFR, which is consistent with the results of indirect comparisons in a meta-analysis [36]. Although PEFR, FEV_1, and FEV_6 are all effort-dependent, PEFR examines the maximal flow rate soon (usually <0.5 s) after initiating a forced expiration, which may not fully capture the degree of airflow limitation and easily leads to considerable variability. In contrast, the FEV_1/FEV_6 provides a more comprehensive assessment of airflow obstruction by measuring the proportion of exhaled volume during different periods. Moreover, a reduced PEFR has less discrimination between obstructive and restrictive lung abnormalities, and the diagnosis of COPD remains dependent on post-bronchodilation FEV_1/FVC <0.7 based on the GOLD recommendation [16]. Recently, the FEV_6 has been regarded as a simplified alternative to an FVC manoeuvre [39, 40]. The FEV_1/FEV_6 could be as reliable as the FEV_1/FVC ratio to detect airway obstruction, but the pre-bronchodilation FEV_1/FEV_6 cutoff values largely varied, ranging from 0.70 to 0.80 across different studies [17, 19, 36]. Overall, a handheld lung function device measuring the FEV_1/FEV_6 effectively detects undiagnosed COPD, but every country should establish its cutoff value. FEV_1/FEV_6 <0.76 is validated in Taiwan for future clinical application.

Indirect comparisons across studies have been reviewed regarding the DA of combining different tools [17, 19]. Lin et al. found that combining PEFR and different questionnaires had higher DA than either alone [17], and Schnieders et al. reported that combining a microspirometer and a questionnaire was as capable as a microspirometer alone [19]. In this study, we first demonstrated discriminative DA by directly comparing different combined modalities (Figure 2C). Interestingly, no difference existed among the different PEFR-based or FEV_1/FEV_6-based combinations, but FEV_1/FEV_6 ratio-based combinations are superior to PEFR-based combinations. These results indicate a handheld lung function device, irrespective of any combined questionnaire, plays an essential role in determining DA, and applying a device measuring FEV_1/FEV_6 rather than PEFR can improve DA.

In addition to DA, the cost-effectiveness of a diagnostic modality is another concern. Soriano et al. reported that a diagnostic modality using the COPD-PS and PEFR could reduce 90% of spirometry tests if they only submit those with either or both tests positive to spirometry [41]. In this study, since the FEV_1/FEV_6-based combined modality can improve DA, choosing an adequate questionnaire based on its diagnostic characteristics becomes an important issue. A higher-sensitivity questionnaire has fewer misdiagnosed cases but at a higher cost of confirmatory tests, such as CDQ, in our data (Figure 2A, Table 3). In contrast, a questionnaire with higher specificity results in more misdiagnosed cases but saves more diagnostic costs, such as LFQ (Figure 2B, Table 3). Although the FEV_1/FEV_6 alone can somewhat balance questionnaires' drawbacks by reducing misdiagnosed cases (vs. LFQ) and saving more spirometry costs (vs. CDQ) (Figure 2C, Table 3), this strategy still needs lots of effort and expenses in submitting

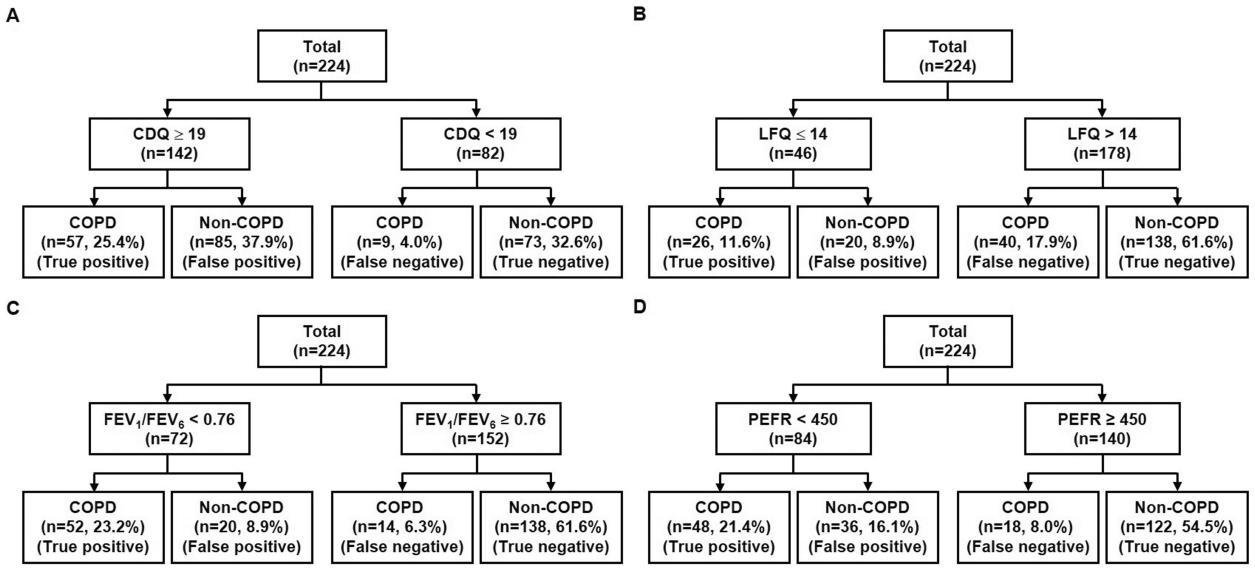
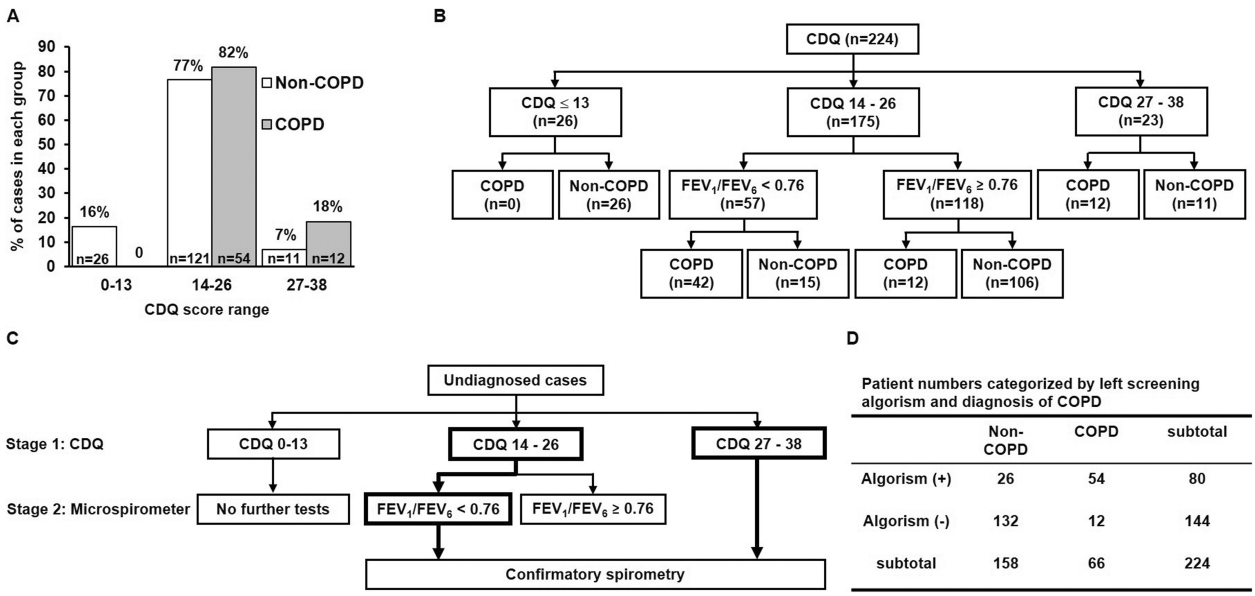


FIGURE 2 | Distributions of study participants based on the cutoff values and COPD diagnosis in CDQ (A), LFQ (B), FEV_1/FEV_6 (C), and PEFR (D). Refer to Figure 1 for abbreviations.



	Non-COPD	COPD	subtotal
Algorism (+)	26	54	80
Algorism (-)	132	12	144
subtotal	158	66	224

FIGURE 3 | Development of the two-staged, risk-stratified COPD case-finding strategy based on the study findings. The distributions of study participants are shown based on the CDQ score alone (A) or combined CDQ score and FEV_1/FEV_6 (B). Therefore, we propose the two-staged, risk-stratified diagnostic flow (C) and tabulate the diagnostic results following this algorithm (D).

all participants to a microspirometer. Compared with the FEV_1/FEV_6 alone, our two-staged risk-stratified combined modality further reduced misdiagnosed COPD patients and saved more lung function medical expense and operating time (Table 3). Our risk-stratified concept is similar to another combined modality reported by Martinez et al. in the US [27]. They developed the novel CAPTURE questionnaire and classified the risk levels by the CAPTURE scores (low: 0–1; middle: 2–4; high 5–6) or by PEFR (high: males < 350 L/min, females < 250 L/min) to identify clinically significant COPD (those with FEV_1 < 60% predicted and/or exacerbation risk). They concluded that those with middle scores should measure PEFR and those presenting high or middle scores with low PEFR should undergo spirometry.

Regular spirometry, although accurate, often consumes significant medical resources and yields a low diagnostic rate, making it inefficient for widespread COPD detection [14]. Case-finding strategies utilising single tools, such as questionnaires or handheld lung function devices, offer cost-effective alternatives with optimal or suboptimal diagnostic accuracy depending on the tool used, and handheld lung function devices generally outperform questionnaires in this regard [18, 38, 42, 43]. Notably, compared to single-tool approaches, combined modalities further enhance diagnostic performance and cost-effectiveness by improving the identification of undiagnosed COPD cases [38, 43]. Our findings (Table 3) align with these reports. Consequently, the proposed strategy provides feasibility for broader implementation, particularly in resource-limited settings.

TABLE 3 | Comparing the cost-effectiveness of microspirometer and confirmatory spirometry with different case-finding modalities.

	Required test numbers		Estimated medical expense (New Taiwan Dollar)[a]		Estimated operating time (min)[b]		Missing COPD patients	
	Micro-spirometer	Confirmatory spirometry	Total expense	% difference vs. microspirometer	Total time	% difference vs. microspirometer	Case numbers	% of total COPD cases
Regular spirometry	0	224	187,040	+62.6	6496	+61.8	0	0
Case finding with a single modality								
CDQ ≥ 19	0	142[c]	118,570	+3.1	4118	+2.6	9	14
LFQ ≤ 14	0	46[d]	38,410	−66.6	1334	−66.8	40	61
$FEV_1/FEV_6 < 0.76$	224[e]	72[e]	115,000	0	4014	0	14	21
Case finding with the combined modality (CDQ plus microspirometer)								
Two-staged strategy	175[f]	80[g]	109,675	−4.6	3825	−4.7	12	18

[a]The estimated medical expense was calculated based on NT$ 245 and 835 per test for the microspirometer and standard bronchodilation test, respectively. The test cost is per Taiwan's National Health Insurance policy.
[b]The estimated time for lung function measurement was based on the average time of 8.6 and 29 min per test for the microspirometer and standard bronchodilation test, respectively. The average time was obtained from 15 subjects who performed microspirometer and spirometry tests with standard quality assurance.
[c]Submit those with CDQ ≥ 19 to confirmatory spirometry based on Figure 2A.
[d]Submit those with LFQ ≤ 14 to confirmatory spirometry based on Figure 2B.
[e]Submit all participants to a microspirometer and those with $FEV_1/FEV_6 < 0.76$ to confirmatory spirometry based on Figure 2C.
[f]Submit those in the middle-risk group (CDQ 14–26) to a microspirometer based on Figure 3B.
[g]Submit those with $FEV_1/FEV_6 < 0.76$ in the middle-risk group and those in the high-risk group based on Figure 3B.

In this study, we enrolled symptomatic patients, in whom most of the newly diagnosed COPD patients had mild obstruction levels (GOLD stage I 58%). It might be argued that these case-finding tool-detected patients' medication options and benefits have not been well-established. Recently, Aaron et al. have demonstrated that in undiagnosed, symptomatic patients, CDQ-detected COPD patients might benefit from pulmonologist-directed treatment by improving symptoms, lung function, and life quality and reducing healthcare utilisation for respiratory illness compared with usual care from a PC practitioner over 1-year follow-up [44]. Therefore, a symptom-driven case-finding strategy might benefit early COPD detection and health promotion.

The strength of this study is that we performed systemic comparisons of DA among five case-finding tools and reasonably established our case-finding strategy. There are also some limitations. First, nearly 90% of study participants and COPD cases were male, reflecting Taiwan's significantly higher smoking prevalence among men (male-to-female ratio ~ 9–10:1, per a nationwide health survey) and smoking-related COPD prevalence (ratio ~ 9:1, per a nationwide COPD survey [13]). Details are in the Supporting Information. This gender imbalance may bias findings and limit the generalizability of the case-finding strategy to other countries. Second, the optimal PEFR must vary between different genders. The female participants were limited; thus, the optimal cut-off value of female PEFR requires more female participants to establish if applying PEFR as a case-finding tool. Similarly, the optimal cut-off value for the FEV_1/FEV_6 for females could also require more female participants. Third, this strategy is based on a smoking population and may overlook COPD cases in non-smokers, highlighting the need for an alternative approach. Fourth, this strategy was developed in a medical centre, where COPD prevalence may be higher than in PC, even though 93% of participants were community-based and similar to a typical PC population. This setting may introduce a bias toward higher sensitivity compared to real-world PC. Fifth, it is acknowledged that this two-staged strategy has been derived in this cohort of patients, where it seems to perform well; however external validation with a separate cohort is required.

In conclusion, this study aligns with the conclusions of a recent review by Aaron SD et al. that using combined tools has shown better DA than either tool alone. Combining a questionnaire and a handheld lung function device is a more effective strategy for identifying individuals at increased risk for COPD. However, questionnaires used alone are still valuable tools for predicting COPD [12]. Handheld lung function devices, rather than questionnaires, play a crucial role in determining DA, and the FEV_1/FEV_6 is better than PEFR. A two-staged, risk-stratified combined modality using CDQ and FEV_1/FEV_6 can be an accurate and cost-effective case-finding strategy for COPD detection. This strategy deserves further validation and implementation in PC to detect at-risk, undiagnosed COPD in Taiwan.

Author Contributions

Po-Chun Lo: conceptualization (equal), data curation (lead), formal analysis (equal), investigation (equal), writing – original draft (lead). **Hsin-Kuo Ko:** formal analysis (lead), investigation (equal), methodology (equal), writing – original draft (equal). **Kun-Ta Chou:** investigation (equal), methodology (lead), visualization (lead), writing – original draft (equal). **Yi-Han Hsiao:** data curation (equal), investigation (equal), software (equal), visualization (equal). **Diahn-Warng Perng:** conceptualization (equal), formal analysis (lead), methodology (lead), writing – review and editing (equal). **Kang-Cheng Su:** conceptualization (lead), funding acquisition (lead), investigation (lead), methodology (equal), project administration (lead), writing – review and editing (lead).

Ethics Statement

This study was performed in accordance with the Declaration of Helsinki. This human study was approved by the Institutional Review Board, Taipei Veterans General Hospital—approval: 2017-07-006C. All adult participants provided written informed consent to participate in this study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data generated or analyzed during this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.