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ORIGINAL RESEARCH

The Impact of Different Smoking Behavior on Pulmonary Function and Pulmonary Hypertension Among Chinese Male Patients with Chronic Obstructive Pulmonary Disease

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Purpose: Cigarette smoking is the most recognized risk factor of chronic obstructive pulmonary disease (COPD) in China. However, there are no studies analyzing the impact of different smoking behaviors on pulmonary function and pulmonary hypertension (PH) among Chinese male patients with COPD.

Patients and Methods: Chinese male smokers with COPD performed pulmonary function tests. Clinical characteristics, smoking behavior features, spirometry and echocardiographic results were compared between the two groups stratified by initial smoking age (18 years old) or complicated PH.

Results: The early-smoking group had more respiratory symptoms, more severe smoking behavior, worse pulmonary function with lower FEV1%pre (38.5% vs 70.2%) and FEV1/FVC% (47.5% vs 63.8%), and higher systolic pulmonary artery pressure (sPAP: 38.6 vs 33.9 mmHg) than the late-smoking group. Initiating smoking before adulthood was an independently contributing factor of ventilatory dysfunction and Global Initiative for Obstructive Lung Disease (GOLD) stage escalation. It also had a significant interaction with long smoking duration (≥30 years), characterized by markedly decreased lung volumes (VC%pre: 64.0% vs 84.5%), impaired diffusing capacity (DLCO%pre: 58.0% vs 76.8%) and severe emphysema (RV/TLC%pre: 145.2% vs 130.2%). COPD patients complicated with PH exhibited worse ventilatory function (FEV1%pre: 43.2% vs 56.2%), impaired diffusion capacity (DLCO%pre: 56.7% vs 77.1%) and decreased lung volume (VC%pre: 67.67% vs 75.38%). Both severe smoking behaviors and impaired pulmonary function had close correlations with sPAP.

Conclusion: The early-smoking group exhibited predominantly ventilation dysfunction and had complex interactions with long smoking duration to further affect lung volume and diffusion capacity. Different smoking behaviors influenced variations of pulmonary dysfunction and comorbid PH in patients with COPD.

Keywords: chronic obstructive pulmonary disease, pulmonary function, smoking behavior, initial smoking age, pulmonary hypertension

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow obstruction and multiple comorbidities due to exposure to inhaled noxious particles, notably tobacco smoke.[1,2] According to forecasts by the World Health Organization, COPD will become one of the three leading causes of death worldwide by 2030.[3] The China Pulmonary Health study found that the direct medical cost of COPD accounted for 33.33−118.09% of the average annual income.[4]

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However, only 2.6% of the patients are aware of having COPD and 12% undergo pulmonary function tests.[5] The mortality rate of COPD will keep increasing unless urgent action is taken to reduce underlying risk factors, particularly tobacco use.[6]

Cigarette smoking is the most recognized risk factor of COPD with an estimated 312 million Chinese who are smoking.[7] Compared to smoking-related COPD, non-smokers have predominantly small airway dysfunction with less emphysema, and slower rates of decline in ventilatory (FEV1) and diffuse function (DLCO/VA).[7,8] The pathogenesis of smoking-related COPD includes the protease, anti-protease, oxidant-antioxidant hypotheses, and abnormal repair processes.[9] The factors of smoking behavior (smoking habit, initial smoking age, smoking duration) influence the occurrence of COPD.[9] Since the decline in lung function occurs progressively after 25–35 years of age, the age factor in the case of COPD plays a critical role in increased cell aging, increased oxidative stress, and protective pathways such as autophagy.[10,11] Smoking duration and pack-years may have negative impacts on FEV1%pre.[12] Smoking causes serious destruction of the lung parenchyma such as alveolar tissue. Thus, the variability of structural lung changes and pulmonary dysfunction may be obvious among patients with different smoking behavior.

Perceptions about the risk and management of COPD differ between physicians and patients.[13] Patients may underestimate the role of smoking in COPD, and relatively little is known about the impact of different smoking behavior on COPD. Therefore, our study was designed to focus on the smoking behavior features, pulmonary function and echocardiographic data in order to identify whether lung function impairments and pulmonary hypertension differ by the impact of different smoking behaviors in Chinese male patients with COPD.

Materials and Methods

Study Design and Population

This cross-sectional study was conducted at the Department of Pulmonary Medicine, Xiamen Branch, Zhongshan hospital, Fudan University between January 2019 and June 2022. All enrolled participants were Chinese male smokers, who had persistent respiratory symptoms or a history of risk factors combined with an initial diagnosis of COPD based on the 2023 Global Initiative for Obstructive Lung Disease (GOLD) diagnostic criteria.[1] The inclusion criterion included: 1) male current smokers ≥18 years of age; 2) smoking duration ≥one year; 3) effective data of pulmonary function tests (PFTs) at Zhongshan Hospital; 4) forced expiratory volume at one second/forced vital capacity (FEV1/FVC) <70% after inhalation of a bronchodilator. Exclusion criteria were as follows: 1) pneumonia, lung cancer, acute respiratory failure, active pulmonary tuberculosis, bronchiectasis, pulmonary embolism, pneumoconiosis, pulmonary edema, interstitial lung disease or other comorbid lung diseases; 2) only asthma or restrictive ventilatory disorder; 3) previous thoracic surgery; 4) severe heart, liver or kidney dysfunction; 5) history of malignant diseases; 6) systemic steroid use within the last two weeks or immunocompromised status; 7) idiopathic or secondary pulmonary hypertension (PH) caused by congenital/valvular heart diseases or heart failure. All participants were provided written informed consent, and this study was approved by the ethics review committee of Xiamen Branch, Zhongshan Hospital, Fudan University (No. B2022-047) in accordance with the Declaration of Helsinki.

Measurement of Pulmonary Function

Two experienced physicians independently collected spirometry data (VC, VC%pre, FVC, FVC%pre, FEV1, FEV1%pre, FEV1/FVC%, FEV1/FVC%pre, PEF%pre, PEF25%pre, PEF50%pre, PEF75%pre, MMEF%pre, RV%pre, TLC%pre, RV/TLC%pre, DLCO%pre, KCO%pre, bronchodilator reversibility (BDR)) and echocardiographic data (left atrium diameter, interventricular septal thickness, systolic pulmonary artery pressure (sPAP), left ventricular ejection fractions). PFTs were conducted for at least three manoeuvres in a standing position following standard procedures using the Jaeger Master Screen PFT System spirometer (CareFusion, Germany) until FVC and FEV1 were repeatable within 150 mL with the best measure recorded.[14] Spirometry was performed before bronchodilation and 15 minutes after inhalation of 400 μg of salbutamol to assess postbronchodilator FEV1/FVC. BDR was defined as an increase of at least 12% and 200 mL in FEV1 or FVC. When a patient underwent multiple spirometry measurements, the first test result was used to exclude the possible treatment effect on spirometry results. All spirometry data were centrally reviewed by an expert panel to determine whether they fulfilled the reproducibility and acceptability criteria of the American Thoracic Society/European Respiratory Society Task Force.[15] The European Community of Coal and Steel predicted equations were used to calculate predicted values.[16]

Variables and Definitions

Trained interviewers, blinded to the spirometry measurements, collected data from face-to-face interviews and electronic medical records. Candidate variables included age, body mass index (BMI), smoking behavior, respiratory symptoms (cough, phlegm, wheezing, dyspnea) and comorbid PH. The variable of age was grouped into two categories: adult (≥18 to <65 years old) and elderly (≥65 years old). BMI was divided into three groups: <18.5 kg/m^2, 18.5–23.9 kg/m^2 and ≥24 kg/m^2. Respiratory symptoms were combined into a three-level variable: no, one and ≥two respiratory symptom(s). PH was defined by a resting mean pulmonary arterial pressure >25 mmHg. Ventilatory dysfunction included obstructive, restrictive and mixed ventilatory disorder. Obstructive ventilatory disorder was defined as post-bronchodilator FEV1/FVC <0.70.[1] Restrictive ventilatory disorder was defined based on pre-bronchodilator spirometry as FEV1/FVC ≥0.70 and FVC%pre <80%.[17] The severity of COPD was categorized as GOLD stage I (FEV1 ≥80% predicted), GOLD stage II (FEV1 ≥50% to <80% predicted), GOLD stage III (FEV1 ≥30% to <50% predicted) and GOLD stage IV (FEV1 <30% predicted).[1]

Smokers were defined as smoking ≥100 cigarettes within one year, or smoking at least weekly two cigarettes for more than one year in a row. Smoking behavior includes initial smoking age, smoking duration, cigarettes/day and pack-years (packs/day multiplied by years of smoking). The variables of initial smoking age and smoking duration were respectively divided into two groups: patients who initiated smoking at ≤18 years old (early-smoking) or >18 years old (late-smoking) , and smokers with a history for <30 years or ≥30 years. Both cigarettes/day and pack-years were divided into two groups: patients smoking <20 cigarettes/day or ≥20 cigarettes/day, and patients smoking <50 pack-years or ≥50 pack-years. Physicians collected these variables and analyzed the relationship between candidate variables and pulmonary function or echocardiographic data.

Statistical Analysis

The baseline characteristics of the study population were described and compared, such as early-smoking group versus late-smoking group, and patients with PH versus without PH. Categorical data expressed as frequencies or percentages were compared by the chi-squared test. Measurement data were tested for normality, and then normally distributed data were expressed as mean ± standard deviation and compared by *t*-test between groups. Nonnormally distributed measurement data were expressed as median (interquartile range) and compared by the Mann–Whitney *U*-test or Wilcoxon rank sum test. We sought to explore the impact of different smoking behavior on pulmonary function and identify potential factors that were associated with comorbid PH. As such, we analyzed the linearity relationship between variables (such as smoking behavior) and spirometry measurements by the Pearson's product-moment correlation for bivariate normal distribution data or the Spearman's rank correlation for ranked data or data without bivariate normal distribution. In order to screen independent predictors for pulmonary function indexes or sPAP, we carried out multiple linear regression analysis for continuous variables and multivariable logistic regression analysis for categorical variables after adjusting for age, BMI and other variables. Furthermore, subgroup analysis was performed based on clinical variables and smoking behavior to examine their interactions on pulmonary function indexes. The difference was considered statistically significant at $P < 0.05$, and data were analyzed using R, version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics and Clinical Features

Of the total 356 participating adults, 272 eligible male participants undergoing PFTs were included in the analysis, of whom 127 patients (46.7%) initiated smoking ≤18 years old (early-smoking group) and 145 (53.3%) initiated smoking >18 years old (late-smoking group) (Supplementary Figure 1). Eighty-four patients were excluded because of improper spirometry, comorbid diseases or failing to meet the 2023 GOLD diagnostic criteria. Table 1 shows the clinical features of the two groups separated by initial smoking age without statistical differences in terms of age and BMI. The initial smoking age of the two groups was 15.9±2.6 years old and 28.2±8.7 years old, respectively. The earlier the patients initiated smoking, the higher the probability of developing no less than two respiratory symptoms (37.0% vs 13.8%, $P < 0.001$). The early-smoking group underwent more severe smoking status than the late-smoking group based on smoking duration (48.6±10.8 vs 34.0±10.9 years, $P < 0.001$) and tobacco exposure (72.7 ± 42.9 vs 46.9±28.2 pack-years, $P < 0.001$).

Table 1 Comparison of the Baseline Characteristics Between Early-Smoking Group and Late-Smoking Group in Chinese Male Smokers with COPD

Clinical features, PFTs and echocardiographic data	All (n = 272)	Initial smoking age		Statistic	P-value
		≤18 (n = 127)	>18 (n = 145)		
Age (years old)	65.57±10.07	68.15±8.37	66.32±10.9	2.128	0.313
BMI (kg/m2)	22.39±3.42	22.19±3.77	22.56±3.09	−0.857	0.392
Respiratory symptoms				21.297	<0.001
No	172 (63.2)	62 (48.8)	110 (75.9)		
Yes	100 (36.8)	65 (51.2)	35 (24.1)		
Number of respiratory symptoms				23.46	<0.001
0	172 (63.2)	62 (48.8)	110 (75.9)		
1	33 (12.1)	18 (14.2)	15 (10.3)		
≥ 2	67 (24.6)	47 (37)	20 (13.8)		
Duration of respiratory symptoms (years)	3.43±5.75	4.91±6.07	2.14±5.13	4.028	<0.001
Cigarettes/day	28.78±15.08	30.21±16.52	27.52±13.63	1.474	0.142
Smoking duration (years)	40.83±13.04	48.58±10.81	34.03±10.87	11.039	<0.001
Pack-years	58.96±37.97	72.73±42.85	46.9±28.17	5.784	<0.001
VC (L)	2.86±0.83	2.43±0.66	3.24±0.78	−9.234	<0.001
VC%pre	75.36±18.6	64.4±15.4	84.97±15.64	−10.899	<0.001
RV%pre	116.61±27.88	116.3±33.32	116.83±23.48	−0.104	0.917
TLC%pre	83.87±13.39	78.24±11.95	87.8±13	−4.443	<0.001
RV/TLC%pre	137.01±23.06	145.64±24.32	130.99±20.19	3.896	<0.001
FVC (L)	2.71±0.85	2.24±0.63	3.12±0.81	−10.103	<0.001
FVC%pre	74.93±20.17	62.15±15.14	86.12±17.17	−12.133	<0.001
FEV1 (L)	1.6±0.78	1.1±0.48	2.05±0.71	−13.074	<0.001
FEV1%pre	55.37±23.56	38.48±14.64	70.17±19.62	−15.21	<0.001
FEV1/FVC%	56.18±13	47.52±10.13	63.77±10.21	−13.144	<0.001
FEV1/FVC%pre	72.2±16.18	61.89±13.66	81.23±12.41	−12.231	<0.001
PEF%pre	50.84±23	37.94±17.15	62.15±21.5	−10.322	<0.001
PEF25%pre	35.36±24.96	19.14±14.15	49.56±23.7	−13.029	<0.001
PEF50%pre	27.38±19.19	14.52±9.28	38.64±18.55	−13.809	<0.001
PEF75%pre	31.09±16.49	21.55±9.45	39.38±16.84	−10.924	<0.001
MMEF%pre	27.7±16.07	16.79±8	37.17±15.31	−13.93	<0.001
DLCO% pre	70.46±23.46	59.2±20.67	78.33±22.14	−5.19	<0.001
KCO%pre	78.02±21.42	70.18±21.28	83.5±19.87	−3.805	<0.001

(*Continued*)

Table 1 (Continued).

Clinical features, PFTs and echocardiographic data	All (n = 272)	Initial smoking age		Statistic	P-value
		≤18 (n = 127)	>18 (n = 145)		
Bronchodilator reversibility				9.565	0.023
Suspicious positive	20 (7.4)	14 (11)	6(4.1)		
Positive	32 (11.8)	20 (15.7)	12 (8.3)		
Negative	152 (55.9)	66 (52)	86 (59.3)		
Types of pulmonary ventilation dysfunction				102.493	<0.001
Obstructive	132 (48.5)	20 (15.7)	112 (77.2)		
Mixed	140 (51.5)	107 (84.3)	33 (22.8)		
GOLD stage				122.551	<0.001
I	56 (20.6)	2 (1.6)	54 (37.2)		
II	87 (32)	21 (16.5)	66 (45.5)		
III	83 (30.5)	62 (48.8)	21 (14.5)		
IV	46 (16.9)	42 (33.1)	4(2.8)		
Left atrium diameter (mm)	35.03±4.67	34.68±4.44	35.38±4.9	−0.93	0.354
Interventricular septal thickness (mm)	9.88±1.69	9.81±1.92	9.95±1.42	−0.508	0.612
Systolic pulmonary artery pressure (mmHg)	36.28±12.97	38.62±14.94	33.86±10.08	2.336	0.021
Left ventricular ejection fractions (%)	0.65±0.05	0.65±0.04	0.65±0.05	−0.044	0.965
Pulmonary hypertension				3.412	0.065
No	101 (37.1)	46 (36.2)	55 (37.9)		
Yes	54 (19.9)	33 (26)	21 (14.5)		

Abbreviations: COPD, chronic obstructive pulmonary disease; PFTs, pulmonary function tests; BMI, body mass index; GOLD, Global Initiative for Obstructive Lung Disease.

Pulmonary Function Features Differ in Patients with Different Smoking Behavior

Table 1 shows lower FEV1%pre (38.5% vs 70.2%, P < 0.001) and FEV1/FVC% (47.5% vs 63.8%, P < 0.001) in the early-smoking group, and significant results in the distribution of GOLD stage between the early-smoking group versus the late-smoking group (GOLD stage III: 48.8% vs 14.5%; GOLD stage IV: 33.1% vs 2.8%; P < 0.001). Other ventilatory function indicators (FEV1, FVC, FVC%pre, FEV1/FVC%pre) were also significantly lower among early-smoking subjects. They exhibited decreased lung volume with lower VC%pre (64.4% vs 85.0%, P < 0.001), more severe emphysema with higher RV/TLC%pre (145.6% vs 131.0%, P < 0.001), and worse diffusion capacity with lower DLCO%pre (59.2% vs 78.3%, P < 0.001) than late-smoking subjects. Thus, the prevalence of mixed ventilatory dysfunction increased from 22.8% in the late-smoking group to 84.3% in the early-smoking group. The rate of the bronchodilator response in the early-smoking group was higher than in the late-smoking group. When comparing the echocardiographic data, no differences were found between the two groups except for sPAP which was higher in the early-smoking group (38.6 vs 33.9 mmHg, P = 0.021). Early-smoking subjects experienced more severe airway obstruction and emphysema with decreased lung volume and diffusion capacity, suggesting the significant impact of initial smoking age on pulmonary function.

Supplementary Table 1 shows the correlation analysis between clinical variables and pulmonary function indexes. FEV1%pre was negatively correlated with age (r = −0.333), respiratory symptoms (r = −0.388), smoking duration (r =

−0.454) and pack-years (r = −0.25), but positively correlated with BMI (r = 0.181) and initial smoking age (r = 0.458) with P < 0.001 (Figure 1A–E). Similar results were detected between smoking behavior and other spirometry parameters such as VC%pre, TLC%pre, FEV1/FVC% and FEV1/FVC%pre (Supplementary Figure 2). Meanwhile, both RV/TLC% pre (r = -0.279) and GOLD stage (r = −0.571) were negatively correlated with initial smoking age (Figure 1F and G). These results demonstrated that the earlier the smokers initiated heavy tobacco exposure, the worse the lung function would be, especially for lung volume and ventilation function.

Smoking Behavior Has a Predicted Value in Pulmonary Function Among COPD Patients

In the regression analysis, initial smoking age was positively associated with FEV1%pre, FEV1/FVC%, TLC%pre, MMEF %pre, and DLCO%pre, but negatively correlated with RV/TLC%pre and GOLD stage (Supplementary Tables 2 and 3). Similar positive correlations were observed in the analysis of BMI. Conversely, smoking duration and pack-years had a positive impact on decreased lung volume, impaired ventilatory function and GOLD stage escalation, with the same effect as age and respiratory symptoms. We adjusted age, BMI, respiratory symptoms and smoking behavior in the multiple linear/ logistic regression analysis (Table 2). The initial smoking age was a significant influencing factor of VC%pre (0.625 [0.338, 0.912]), TLC%pre (0.347 [0.072, 0.621]), FVC%pre (0.821 [0.523, 1.119]), FEV1%pre (1.043 [0.711, 1.375]), FEV1/FVC % (0.494 [0.313, 0.675]), MMEF%pre (0.566 [0.330, 0.802]) and GOLD stage (−0.115 [−0.154, −0.075]). The variable of age exhibited an adverse effect compared to initial smoking age, while smoking duration and pack-years were not significantly associated with pulmonary function indexes. BMI affected ventilatory function indexes, including FEV1% pre and FEV1/FVC%, but not lung volume indexes. Therefore, the variable of initial smoking age has an independently predicted value in the occurrence and severity of COPD, as well as age and BMI.

Table 3 shows the results of our subgroup analysis. VC%pre in patients with smoking duration <30 years was not statistically different between the early-smoking versus the late-smoking groups. However, when the subjects were exposed to cigarette smoking ≥30 years, the early-smoking group had significantly lower VC%pre than the late-smoking group (64.0% vs 84.5%, P < 0.001). Similar results were observed in TLC%pre, RV/TLC%pre and DLCO%pre. For ventilatory function indexes (FVC%pre, FEV1%pre, FEV1/FVC%, MMEF%pre), significant differences existed between the two groups no matter how long they were exposed to cigarette smoking. These results indicate that initial smoking age is closely associated with ventilatory function, while smoking duration exhibits a significant interaction with initial smoking age in affecting lung volume, diffusion capacity and emphysema. The late-smoking group with a BMI ≥18.5 showed a significantly greater increase in VC%pre and TLC%pre compared to the early-smoking group, suggesting BMI ≥18.5 was a potential protective factor of lung volume in the late-smoking group. Both elderly (≥65 years old) and heavy-smoke exposure (≥20 cigarettes/day) could exacerbate emphysema with greater RV/TLC%pre among the early-smoking group. Overall, smoking behaviors take effect independently and interact with each other to influence pulmonary function among COPD patients.

Smoking Behaviors Impact Comorbid Pulmonary Hypertension in COPD Patients

The characteristics of patients with PH were somewhat different from those without PH (Supplementary Table 4). COPD patients with PH were older with lower BMI, more respiratory symptoms and longer smoking duration. Initial smoking age, cigarettes/day and pack-years had no significant differences between the two groups. Patients with PH exhibited significantly worse ventilatory function with lower FVC%pre (65.1% vs 74.7%), FEV1%pre (43.2% vs 56.2%), FEV1/FVC% (49.6% vs 57.3%) and MMEF%pre (21.1% vs 28.1%) than the other group, as well as worse diffusion capacity with lower DLCO%pre. The parameters of VC%pre and TLC%pre were found to be markedly lower in patients with PH, resulting in more mixed ventilatory disorder than patients without PH (72.2% vs 53.5%). No statistical differences were found in terms of echocardiographic data except for sPAP between the two groups.

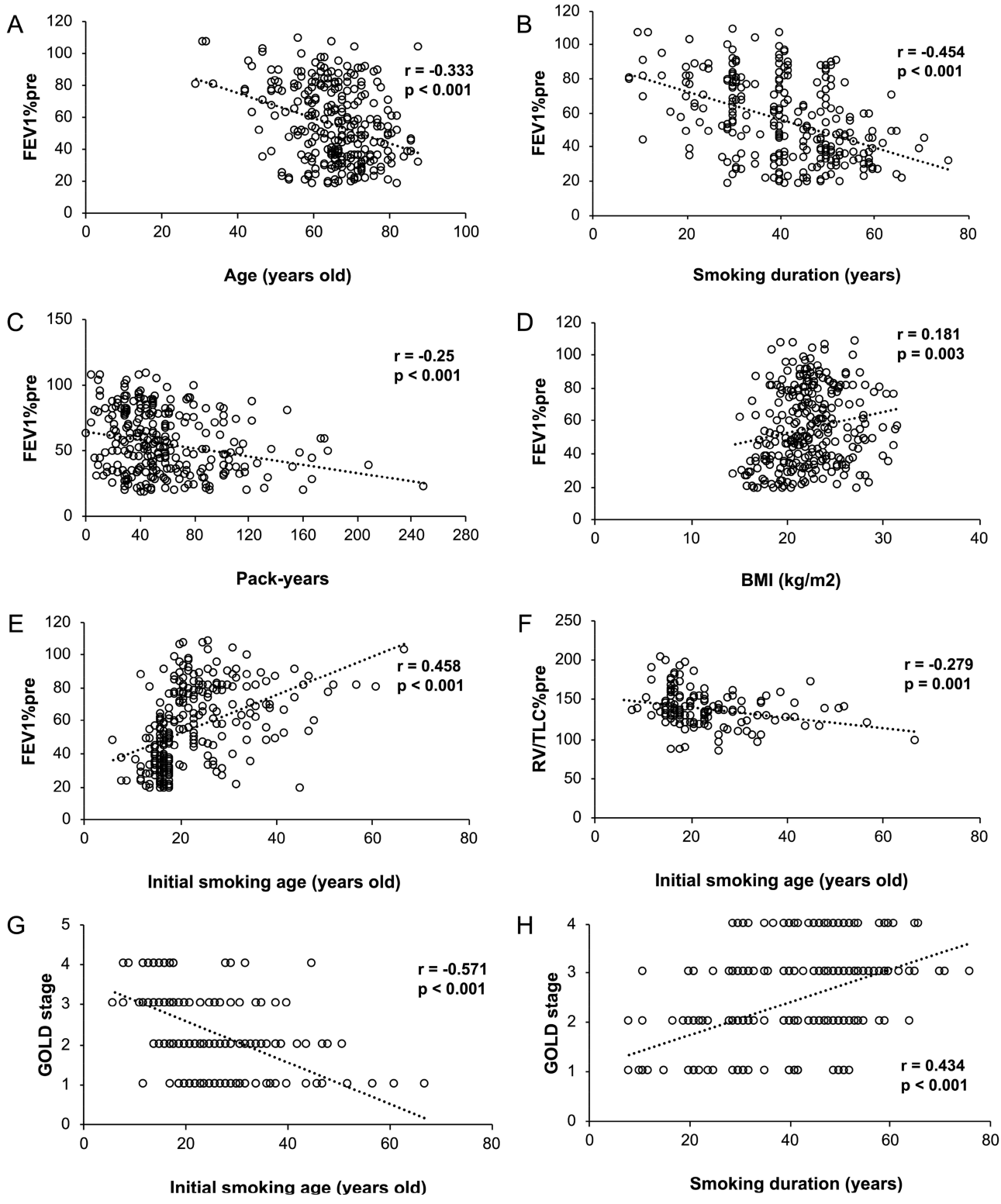

Figure 1 The correlations between spirometry parameters or GOLD stage and clinical characteristics. The correlation analysis has shown the relationship between FEV1% pre and age (**A**), smoking duration (**B**), pack-years (**C**), BMI (**D**), and initial smoking age (**E**); between RV/TLC%pre and initial smoking age (**F**); and between GOLD stage and initial smoking age (**G**) or smoking duration (**H**).

Abbreviations: BMI, body mass index; GOLD, Global Initiative for Obstructive Lung Disease.

Table 2 Regression Analysis of Independent Variables Associated with Pulmonary Function Indexes in COPD Patients

PFTs	Variables	β	Std. error	Statistic	P-value	95% CI	R^2	Adjust R^2
FVC%pre	Age (years old)	−0.713	0.137	−5.194	<0.001	(−0.983,-0.442)	0.353	0.33
	BMI (kg/m2)	−0.245	0.298	−0.822	0.412	(−0.831,0.341)		
	Initial smoking age (years old)	0.821	0.151	5.421	<0.001	(0.523,1.119)		
	Smoking duration (years)	0.036	0.195	0.185	0.853	(−0.348,0.42)		
	Pack-years	0.03	0.104	0.291	0.771	(−0.174,0.234)		
FEV1%pre	Age (years old)	−0.651	0.153	−4.266	<0.001	(−0.952,-0.351)	0.412	0.392
	BMI (kg/m2)	0.896	0.331	2.703	0.007	(0.243,1.548)		
	Initial smoking age (years old)	1.043	0.169	6.187	<0.001	(0.711,1.375)		
	Smoking duration (years)	0.038	0.217	0.176	0.861	(−0.389,0.465)		
	Pack-years	−0.011	0.115	−0.093	0.926	(−0.238,0.217)		
FEV1/FVC%	Age (years old)	−0.29	0.083	−3.483	0.001	(−0.455,-0.126)	0.424	0.405
	BMI (kg/m2)	1.133	0.181	6.258	<0.001	(0.776,1.489)		
	Initial smoking age (years old)	0.494	0.092	5.364	<0.001	(0.313,0.675)		
	Smoking duration (years)	0.061	0.119	0.513	0.608	(−0.173,0.294)		
	Pack-years	−0.054	0.063	−0.858	0.391	(−0.178,0.07)		
FEV1/FVC%pre	Age (years old)	−0.164	0.105	−1.57	0.118	(−0.37,0.042)	0.415	0.395
	BMI (kg/m2)	1.73	0.227	7.617	<0.001	(1.283,2.177)		
	Initial smoking age (years old)	0.636	0.116	5.507	<0.001	(0.409,0.864)		
	Smoking duration (years)	0.098	0.149	0.66	0.51	(−0.195,0.391)		
	Pack-years	−0.072	0.079	−0.904	0.367	(−0.227,0.084)		
MMEF%pre	Age (years old)	−0.444	0.108	−4.091	<0.001	(−0.657,-0.23)	0.374	0.352
	BMI (kg/m2)	0.671	0.235	2.853	0.005	(0.208,1.135)		
	Initial smoking age (years old)	0.566	0.12	4.723	<0.001	(0.33,0.802)		
	Smoking duration (years)	−0.027	0.154	−0.172	0.863	(−0.33,0.277)		
	Pack-years	−0.016	0.081	−0.195	0.846	(−0.176,0.145)		
VC%pre	Age (years old)	−0.62	0.132	−4.699	<0.001	(−0.88,-0.36)	0.296	0.272
	BMI (kg/m2)	−0.165	0.286	−0.578	0.564	(−0.729,0.398)		
	Initial smoking age (years old)	0.625	0.146	4.29	<0.001	(0.338,0.912)		
	Smoking duration (years)	−0.063	0.188	−0.336	0.737	(−0.432,0.306)		
	Pack-years	0.07	0.1	0.704	0.482	(−0.126,0.267)		
TLC%pre	Age (years old)	−0.507	0.129	−3.926	<0.001	(−0.763,-0.252)	0.232	0.179
	BMI (kg/m2)	−0.077	0.301	−0.256	0.798	(−0.672,0.518)		
	Initial smoking age (years old)	0.347	0.139	2.497	0.014	(0.072,0.621)		
	Smoking duration (years)	−0.168	0.176	−0.955	0.341	(−0.517,0.18)		
	Pack-years	0.151	0.099	1.529	0.129	(−0.044,0.346)		

(*Continued*)

Table 2 (Continued).

PFTs	Variables	β	Std. error	Statistic	P-value	95% CI	R^2	Adjust R^2
	Variables	**estimate**	**std.error**	**statistic**	**p-value**	**95% CI**		
GOLD stage	Age (years old)	0.049	0.016	8.934	0.003	(0.017,0.081)		
	BMI (kg/m2)	−0.114	0.035	10.64	0.001	(−0.182,-0.045)		
	Initial smoking age (years old)	−0.115	0.02	32.875	<0.001	(−0.154,-0.075)		
	Smoking duration (years)	0	0.023	0	0.991	(−0.044,0.044)		
	Pack-years	−0.001	0.012	0.007	0.934	(−0.025,0.023)		

Abbreviations: COPD, chronic obstructive pulmonary disease; PFTs, pulmonary function tests; BMI, body mass index; GOLD, Global Initiative for Obstructive Lung Disease; CI, confidence interval.

Table 3 Subgroup Analysis of Pulmonary Function Indexes According to Smoking Behavior and Clinical Variables

PFTs	Smoking duration (years)	Early-smoking	Late-smoking	P-value
VC%pre	<30	72.18±12.17	86.23±17.85	0.053
	≥30	63.95±15.48	84.5±14.81	<0.001
TLC%pre	<30	82.47±7.85	90.37±15.56	0.334
	≥30	77.93±12.19	86.7±11.71	<0.001
RV/TLC%pre	<30	151.89±19.72	132.93±18.87	0.074
	≥30	145.17±24.72	130.15±20.83	0.001
FVC%pre	<30	71.59±12.51	87.83±18.81	0.034
	≥30	61.6±15.15	85.49±16.57	<0.001
FEV1%pre	<30	51.19±9.33	72.92±21.71	<0.001
	≥30	37.74±14.57	69.16±18.8	<0.001
FEV1/FVC%	<30	56.36±2.71	65.65±10.97	<0.001
	≥30	47±10.17	63.08±9.88	<0.001
FEV1/FVC%pre	<30	72.79±3.49	82.58±13.21	0.06
	≥30	61.26±13.76	80.73±12.13	<0.001
MMEF%pre	<30	21.78±5.6	40.7±17.26	<0.001
	≥30	16.49±8.04	35.85±14.39	<0.001
DLCO%pre	<30	75.91±28.64	81.81±20.13	0.61
	≥30	57.96±19.76	76.84±22.95	<0.001
KCO%pre	<30	83.55±30.15	85.87±21.64	0.851
	≥30	69.19±20.52	82.48±19.17	0.001
PFTs	**BMI (kg/m2)**	**Early-smoking**	**Late-smoking**	**P-value**
VC%pre	<18.5	64.38±13.9	72.87±18.16	0.121

(*Continued*)

Table 3 (Continued).

PFTs	Smoking duration (years)	Early-smoking	Late-smoking	P-value
	18.5~23.9	66.12±16.91	86.92±14.73	<0.001
	≥24	61.32±13.02	85.01±15.01	<0.001
TLC%pre	<18.5	81.47±9.56	84.44±13.19	0.541
	18.5~23.9	76.85±12.99	88.33±12.28	<0.001
	≥24	78.32±11.79	88.28±14.88	0.031
PFTs	**Cigarettes/day**	**Early-smoking**	**Late-smoking**	**P-value**
RV/TLC%pre	<20	139.92±18.13	134.71±31.55	0.685
	≥20	146.55±25.2	130.47±18.37	<0.001
PFTs	**Age (years old)**	**Early-smoking**	**Late-smoking**	**P-value**
RV/TLC%pre	<65	146.37±26.04	133.6±19.51	0.057
	≥65	145.41±24.06	128.3±20.76	0.001

Abbreviations: PFTs, pulmonary function tests; BMI, body mass index.

sPAP was positively correlated with age, respiratory symptoms, smoking duration and GOLD stage, and negatively correlated with VC%pre, FVC%pre, FEV1%pre, FEV1/FVC% and FEV1/FVC%pre (Supplementary Table 5, Figure 2). The regression analysis on influencing factors associated with sPAP was similar with the correlation analysis (Supplementary Table 6). Multiple linear regression analysis by adjusting those variables yielded only one statistically independent factor, duration of respiratory symptoms, with a R^2 of 0.386 (data not shown). In the subgroup analysis according to initial smoking age (Table 4), FEV1/FVC%pre was significantly lower in patients with PH than those without PH (72.6% vs 81.7%, P = 0.004) among the late-smoking population rather than the early-smoking population. Similar results were detected in FEV1%pre, FEV1/FVC% and MMEF%pre. Significant differences of pulmonary function indicators were also found between patients with and without PH in the subgroups with heavier cigarette-smoking exposure or longer smoking duration. Notably, the proportion of patients with initial smoking age ≤18 years old and cigarette exposure ≥50 pack-years in patients with PH was higher than those without PH (42.6% vs 32.7%). Thus, smoking behavior, pulmonary function and their significant interactions consistently impact sPAP and complicated PH in COPD patients.

Discussion

To the best of our knowledge, this is the first analysis of the impact of smoking behavior on pulmonary function and PH among Chinese male smokers with COPD. The main findings of this study include: (1) Pulmonary function features differ in patients with different smoking behaviors. (2) Initial smoking age has significant predicted value in the occurrence and severity of COPD. (3) Smoking duration exhibits a significant interaction with initial smoking age, further affecting lung volume, diffusion capacity and emphysema. (4) Smoking behavior, pulmonary function and their significant interactions impact sPAP and complicated PH in COPD patients.

Current smokers and pack-years were selected as significant variables for identifying a high-risk population of patients with COPD.[18,19] Male (odds ratio (OR) = 6.333), smoking (OR = 5.1318), initial smoking age <15 years old (OR = 12) or ≥15 years old (OR = 3.647), and smoking for ≥30 years (OR = 8.857) influenced the incidence of COPD.[9] Severe smoking behavior, including early initial smoking, long smoking duration and heavy cigarette-smoking exposure, may further promote pulmonary function decline. However, there are no studies analyzing the differences stratified by initial smoking age and explaining the contributions of smoking behavior features in the severity of airway obstruction

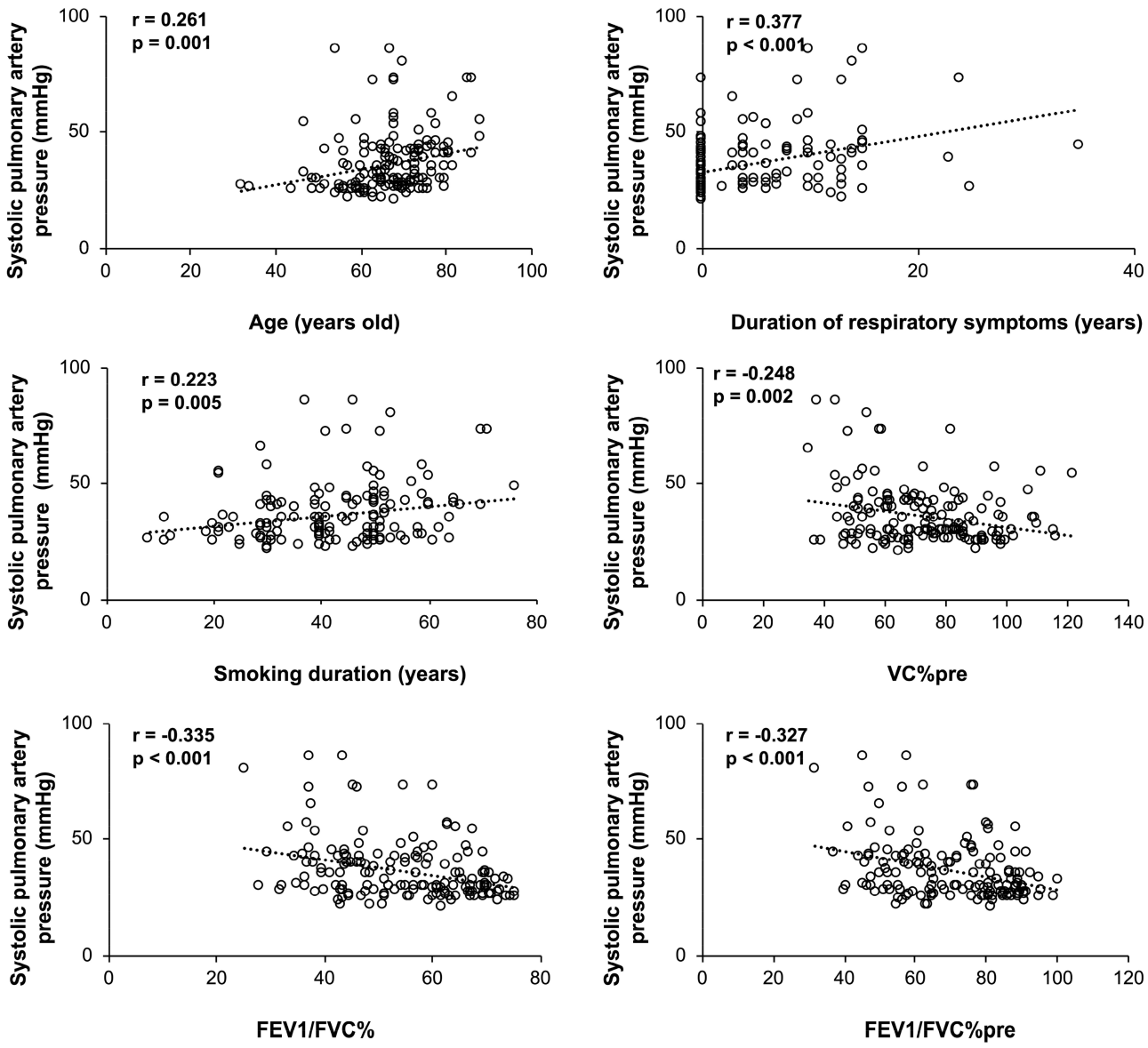

Figure 2 The correlations between systolic pulmonary artery pressure and smoking behavior or spirometry parameters.

among COPD patients. Our study found that early-smoking subjects had more severe airway obstruction and emphysema with decreased lung volume and diffusion capacity. Initiating smoking before adulthood had an independently predicted value in the occurrence and severity of COPD. Since the lungs still develop until 20 years old, smoking in childhood and adolescence caused irreversible lung damage which could not be dramatically decreased through quitting smoking.[20] The damage caused by smoking included emphysema, severe lung parenchymal and diffusion damage through inflammation, oxidative stress and elevated protease activity.[21] Emphysematous destruction of the lung parenchyma involved narrowing with an obliteration of the small airways.[22] Thus, governments should reinforce the role of tobacco control campaigns and policies regarding age restrictions on the purchase of cigarettes.

Our study showed that initial smoking age had a predictive value in the development of COPD. However, the relationship between smoking behavior and pulmonary function is not a simple linear relationship, reflecting the heterogeneity and complexity of COPD pathogenesis. We also found that significant differences of VC%pre, DLCO% pre and VC/TLC%pre were observed between early-smoking and late-smoking groups in patients who smoked ≥30 years but not those <30 years. That is to say, long-term exposure to cigarette smoking exhibited a significant interaction with

Table 4 Subgroup Analysis of Pulmonary Function Indexes According to Smoking Behavior and Complicated Pulmonary Hypertension

	Initial smoking age (years old)	Without PH	With PH	P-value
FEV1%pre	≤18	38.64±13.16	33.17±10.56	0.052
	>18	70.78±19.31	58.93±24.35	0.029
FEV1/FVC%	≤18	49.55±10.18	45.21±9.93	0.063
	>18	63.76±9.31	56.37±9.92	0.003
FEV1/FVC%pre	≤18	64.67±13.33	59.09±13.9	0.075
	>18	81.68±11.78	72.55±12.41	0.004
MMEF%pre	≤18	16±7.18	16.84±8.67	0.645
	>18	38.07±14.78	27.61±14.05	0.007
	Cigarettes/day	**Without PH**	**With PH**	**P-value**
VC%pre	<20	78.52±17.14	65.42±18.29	0.132
	≥20	75.11±18.3	68.25±18.91	0.046
FVC%pre	<20	76.06±19.22	62.34±20.58	0.159
	≥20	74.59±20.34	65.76±19.76	0.019
FEV1%pre	<20	51.26±17.92	42.25±22.99	0.37
	≥20	56.57±23.62	43.43±21.06	0.002
FEV1/FVC%	<20	51.67±12.18	49.65±10.33	0.701
	≥20	57.77±11.93	49.53±11.61	0
FEV1/FVC%pre	<20	67.29±12.97	65.56±14.01	0.788
	≥20	74.5±15.17	64.01±15.12	0
MMEF%pre	<20	23.98±11.88	22.86±9.95	0.826
	≥20	28.5±16.57	20.65±12.8	0.003
	Smoking duration (years)	**Without PH**	**With PH**	**P-value**
VC%pre	<30	83.54±17.92	87.82±33.75	0.702
	≥30	73.62±17.82	65.61±15.57	0.01
TLC%pre	<30	89.37±16.46	93.94±14.53	0.621
	≥30	84.31±11.85	77.78±13.34	0.021
FVC%pre	<30	82.67±19.53	88.59±35.35	0.622
	≥30	72.98±20	62.66±16.25	0.002
FEV1%pre	<30	65.39±23.83	70.76±35.84	0.693
	≥30	54.14±22.71	40.37±17.44	0
FEV1/FVC%	<30	61.99±11.76	59.22±13.22	0.654
	≥30	56.27±11.88	48.57±10.71	0

(*Continued*)

Table 4 (Continued).

	Initial smoking age (years old)	Without PH	With PH	P-value
FEV1/FVC%pre	<30	78.49±14.5	75.96±16.33	0.74
	≥30	72.95±15.1	63.14±14.27	0
MMEF%pre	<30	35.3±19.13	34.19±19.63	0.91
	≥30	26.57±15.23	19.74±10.58	0.003
	Pack-years	**Without PH**	**With PH**	**P-value**
VC%pre	<50	80.6±18.83	72.76±20.59	0.109
	≥50	71.36±16.67	62.94±15.56	0.028
FVC%pre	<50	80.06±21.09	70.07±23.4	0.07
	≥50	70.57±18.56	60.42±14.64	0.013
MMEF%pre	<50	32.42±18.32	24.73±13.61	0.052
	≥50	24.78±13.66	17.87±9.96	0.01
Initial smoking age	<50			
≤18 years old		13 (29.5)	10 (38.5)	0.443
>18 years old		31 (70.5)	16 (61.5)	
	≥50			
≤18 years old		33 (57.9)	23 (82.1)	0.027
>18 years old		24 (42.1)	5 (17.9)	

Abbreviation: PH, pulmonary hypertension.

initial smoking age, further damaging lung volume and diffuse capacity, and exacerbating emphysema. The mechanism behind these results could be a sequence of events that first cause bronchial inflammation, small airway stenosis and alveolar rupture leading to emphysema due to long smoking duration. Secondly, changes in the network of curled collagen fibers surrounding the alveoli led to alveolar enlargement, alveolar compliance decrease and a severe reduction in the amounts of functional alveolar-capillary units. Thirdly, an increase of age and smoking duration was associated with decreased diaphragm curvature, causing decreased respiratory muscle mass and airway function due to extrathoracic causes.[23] Ji et al also found that patients with tobacco smoke exposure exhibited predominantly emphysema, while patients with biomass smoke and tobacco smoke exposure exhibited predominantly airway obstruction.[24] These findings provide insights into variations of pulmonary function disorders under different exposure factors or smoking behaviors, which are valuable in providing clinicians with better evidence for treatment decisions.

Approximately 40% of COPD patients continue to smoke despite knowing they have the disease.[25] These patients seeking medical advice were at advanced stages and actively smoke despite severe symptoms and functional impairment.[12] Smoking cigarettes over a long period could deplete the antioxidant mechanism, inhibit alveolar macrophage function and lead to hypertrophy and hyperplasia of the mucus excreting gland.[9] Long-term cigarette smoking ultimately result in tissue damage and disease progression with a negative impact on prognosis of COPD. Our study demonstrated that long smoking duration resulted in impaired ventilatory function and GOLD stage escalation, interacting with early initial smoking age in damaging lung volume and diffusion capacity. These results emphasize the influential effect of a long duration of tobacco habit on functional parameters. Since smoking habit is closely related to lung function decline and symptoms worsening, smoking cessation allows an improvement of clinical and functional

parameters.[26] Pezzuto et al found that smoking cessation confirmed its efficacy leading to an improvement of all respiratory functional parameters including symptoms (mMRC test) and obstructive parameters in both large and small airways (FEV1, FEF25/75) in the short term.[26] For COPD patients with smoking, both pharmacological therapy and non-pharmacological measures should be described, starting with smoking cessation. The GOLD 2023 report recommends that healthcare providers should strongly enforce the need for smoking cessation at all times for patients who continue to smoke.[1] Government should spread the message about the dangers of smoking and the necessity of quitting smoking, especially in adolescence.

Patients with PH in our analysis had longer smoking duration and worse pulmonary function compared to those without PH, consistent with the correlation analysis between sPAP and pulmonary function indicators. Elderly, male and long-term exposure to cigarette smoking were reported to be the most important risk factors for COPD complicated with PH.[27] In our study, patients with heavy cigarette exposure (≥50 pack-years) and early initial smoking age (≤18 years old) had the highest probability of developing PH, suggesting the significant impact and interactions between different smoking behavior on sPAP. Long-term exposure to cigarette smoking from an early age induced diverse inflammatory responses and oxidative stress, which might influence lung development, pulmonary hypertension or remodeling, and vascular permeability.[28] This could explain why initiating smoking in adulthood could be a potential protective factor of pulmonary function among patients without PH in our analysis. Severe smoking behavior and their significant effect on pulmonary function may affect sPAP and promote the development of PH.

Clinical variables, including advanced age, male sex, the absence of overweight, and dyspnea, were predictors of airflow obstruction.[29–32] In our analysis, elderly, lower BMI and respiratory symptoms showed negative effect on pulmonary function and sPAP in male smokers, which was in line with previous studies. We found that the early-smoking group had a higher possibility of developing ≥two respiratory symptoms with advanced GOLD stages. A reasonable explanation was that chronic smoking from an early age caused irreversible small airway obstruction, tissue injury and epithelial remodeling, resulting in chronic cough, expectoration and impaired ventilatory function.[8,33] Inadequate dietary intake and malnutrition were prevalent in COPD patients.[34] BMI ≥18.5 was a potential protective factor of lung volume in late-smoking subjects of our study. BMI <18.5 indicated airway disease-predominant pattern and great increase in residual volume, suggesting severe small airways obstruction and gas trapping.[24] The worse lung function observed among patients with lower BMI could be explained by smaller lungs and more emphysema whose presence has been shown to be a strong determinant of rapid decline in lung function. Use of other early predictive markers appeared to be promising in analyzing the association between nicotine metabolites and COPD diagnosis.[35] Fast metabolizers with greater CYP2A6 activity had a higher occurrence of COPD, so that they could be aware of an increased "personal" risk and consistently strengthen the self-commitment to smoke cessation.[35]

The present study has some limitations. First, this study only analyzed the effect of several factors due to realistic conditions. Further analysis should involve as many potential influencing factors as possible including occupational exposure which are critical for pulmonary function. Secondly, this study did not analyze these results based on the clinical phenotypes of COPD (non-exacerbators, asthma-COPD overlap syndrome, exacerbators with emphysema, exacerbators with chronic bronchitis), which were closely associated with disease severity and comorbidities. Thirdly, we failed to involve comorbidities of COPD (eg, lung cancer, infection) as cofactors due to the exclusion criteria of our study and incomplete data. The participants with missing spirometry data were not included, and our analysis focused on male current smokers, which might not be applicable to female patients. As the importance of risk factors for COPD differs in variable economic and cultural context, our study population may be different from that of primary or secondary care settings. Finally, owing to cross-sectional design, the recall bias and defect in causal inference are inevitable The association between smoking behavior and prognosis of COPD has not been explored, as well as the causal relationship between smoking cessation and pulmonary function. Further longitudinal follow-up studies are required to clarify these associations.

Conclusion

This study revealed the impact of different smoking behaviors on pulmonary function and PH in Chinese male patients with COPD. Compared to the late-smoking group, the early-smoking group has more respiratory symptoms, more severe smoking

behaviors, and worse pulmonary function. Initiating smoking before adulthood is a significant influencing factor of ventilatory function, predicting the occurrence and severity of COPD. Smoking duration exhibits a significant interaction with initial smoking age, further affecting lung volume, diffusion capacity and emphysema. COPD patients with PH exhibit longer smoking duration and worse pulmonary function than those without PH. Severe smoking behaviors and their significant effect on pulmonary function impact sPAP and comorbid PH. Variations of pulmonary function disorders under different smoking behaviors may provide useful evidence for treatment decisions and tobacco control.

Abbreviations

COPD, chronic obstructive pulmonary disease; PH, pulmonary hypertension; GOLD, Global Initiative for Obstructive Lung Disease; PFTs, pulmonary function tests; BMI, body mass index; BDR, bronchodilator reversibility; sPAP, systolic pulmonary artery pressure; OR, odds ratio.

Data Sharing Statement

The raw data supporting the conclusions of this article will be made available from the corresponding authors upon reasonable request.

Ethics Statement

All participants were provided written informed consent, and the ethics review committee of Xiamen Branch, Zhongshan Hospital, Fudan University (No. B2022-047) approved this work.

Consent for Publication

All authors have read and approved the revised version submitted and published.

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Author Contributions

All authors have made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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Disclosure

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Agustí A, Celli BR, Criner GJ, et al. Global initiative for chronic obstructive lung disease 2023 report: gold executive summary. *Eur Respir J*. 2023;61(4):2300239. doi:10.1183/13993003.00239-2023
2. Christenson SA, Smith BM, Bafadhel M, Putcha N. Chronic obstructive pulmonary disease. *Lancet*. 2022;399(10342):2227–2242. doi:10.1016/S0140-6736(22)00470-6
3. World Health Organization. Chronic obstructive pulmonary disease (COPD) world health organization. Geneva, Switzerland; 2022.

4. Zhu B, Wang Y, Ming J, Chen W, Zhang L. Disease burden of COPD in China: a systematic review. *Int J Chron Obstruct Pulmon Dis*. 2018;13:1353–1364. doi:10.2147/COPD.S161555
5. Quan Z, Yan G, Wang Z, et al. Current status and preventive strategies of chronic obstructive pulmonary disease in China: a literature review. *J Thorac Dis*. 2021;13(6):3865–3877. doi:10.21037/jtd-20-2051
6. Fang L, Gao P, Bao H, et al. Chronic obstructive pulmonary disease in China: a nationwide prevalence study. *Lancet Respir Med*. 2018;6(6):421–430. doi:10.1016/S2213-2600(18)30103-6
7. Ding Q, Li J, Xu S, et al. Different smoking statuses on survival and emphysema in patients with acute exacerbation of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2022;17:505–515. doi:10.2147/COPD.S346456
8. Salvi SS, Brashier BB, Londhe J, et al. Phenotypic comparison between smoking and non-smoking chronic obstructive pulmonary disease. *Respir Res*. 2020;21(1):1–12. doi:10.1186/s12931-020-1310-9
9. Safitri W, Martini S, Artanti KD, Li CY. Smoking from a younger age is the dominant factor in the incidence of chronic obstructive pulmonary disease: case-control study. *Int J Environ Res Public Health*. 2021;18(11):6047. doi:10.3390/ijerph18116047
10. Mercado N, Ito K, Barnes PJ. Accelerated ageing of the lung in COPD: new concepts. *Thorax*. 2015;70(5):482–489. doi:10.1136/thoraxjnl-2014-206084
11. Schneider JL, Rowe JH, Garcia-de-Alba C, Kim CF, Sharpe AH, Haigis MC. The aging lung: physiology, disease, and immunity. *Cell*. 2021;184(8):1990–2019. doi:10.1016/j.cell.2021.03.005
12. de Torres JP, Campo A, Casanova C, Aguirre-Jaime A, Zulueta J. Gender and chronic obstructive pulmonary disease in high-risk smokers. *Respiration*. 2006;73(3):306–310. doi:10.1159/000090051
13. Menezes AM, Landis SH, Han MK, et al. Continuing to confront COPD International Surveys: comparison of patient and physician perceptions about COPD risk and management. *Int J Chron Obstruct Pulmon Dis*. 2015;10:159–172. doi:10.2147/COPD.S74315
14. Jensen RL, Teeter JG, England RD, White HJ, Pickering EH, Crapo RO. Instrument accuracy and reproducibility in measurements of pulmonary function. *Chest*. 2007;132(2):388–395. doi:10.1378/chest.06-1998
15. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319–338. doi:10.1183/09031936.05.00034805
16. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report working party standardization of lung function tests, European community for steel and coal. official statement of the European respiratory society. *Eur Respir J Suppl*. 1993;16(Suppl 16):5–40. doi:10.1183/09041950.005s1693
17. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J*. 2005;26(5):948–968. doi:10.1183/09031936.05.00035205
18. Wang X, He H, Xu L, et al. Developing and validating a chronic obstructive pulmonary disease quick screening questionnaire using statistical learning models. *Chron Respir Dis*. 2022;19:14799731221116585. doi:10.1177/14799731221116585
19. Zha Z, Leng R, Xu W, et al. Prevalence and risk factors of chronic obstructive pulmonary disease in Anhui Province, China: a population-based survey. *BMC Pulm Med*. 2019;19(1):102. doi:10.1186/s12890-019-0864-0
20. Let's make the next generation tobacco-free: your guide to the 50th anniversary surgeon general's report on smoking and health.
21. Corlăţeanu A, Odajiu I, Botnaru V, Cemirtan S. From smoking to COPD--current approaches. *Pneumologia*. 2016;65(1):20–23.
22. McDonough JE, Yuan R, Suzuki M, et al. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. *N Engl J Med*. 2011;365(17):1567–1575. doi:10.1056/NEJMoa1106955
23. Skloot GS. The effects of aging on lung structure and function. *Clin Geriatr Med*. 2017;33(4):447–457. doi:10.1016/j.cger.2017.06.001
24. Ji W, Lim MN, Bak SH, et al. Differences in chronic obstructive pulmonary disease phenotypes between non-smokers and smokers. *Clin Respir J*. 2018;12(2):666–673. doi:10.1111/crj.12577
25. Montes de Oca M. Smoking cessation/vaccinations. *Clin Chest Med*. 2020;41(3):495–512. doi:10.1016/j.ccm.2020.06.013
26. Pezzuto A, Ricci A, D'Ascanio M, et al. Short-term benefits of smoking cessation improve respiratory function and metabolism in smokers. *Int J Chron Obstruct Pulmon Dis*. 2023;18:2861–2865. doi:10.2147/COPD.S423148
27. Qu S, Zhu J. A nomogram for predicting cardiovascular diseases in chronic obstructive pulmonary disease patients. *J Healthc Eng*. 2022;2022:6394290. doi:10.1155/2022/6394290
28. Miele CH, Grigsby MR, Siddharthan T, et al. Environmental exposures and systemic hypertension are risk factors for decline in lung function. *Thorax*. 2018;73(12):1120–1127. doi:10.1136/thoraxjnl-2017-210477
29. Lee SC, An C, Yoo J, Park S, Shin D, Han CH. Development and validation of a nomogram to predict pulmonary function and the presence of chronic obstructive pulmonary disease in a Korean population. *BMC Pulm Med*. 2021;21(1):32. doi:10.1186/s12890-021-01391-z
30. Wang Y, Li Z, Li FS. Development and assessment of prediction models for the development of COPD in a typical rural area in Northwest China. *Int J Chron Obstruct Pulmon Dis*. 2021;16:477–486. doi:10.2147/COPD.S297380
31. Chen Z, Wang J, Wang H, et al. Machine learning reveals sex differences in clinical features of acute exacerbation of chronic obstructive pulmonary disease: a multicenter cross-sectional study. *Front Med*. 2023;10:1105854. doi:10.3389/fmed.2023.1105854
32. Pan J, Adab P, Cheng KK, et al. Development and validation of a prediction model for airflow obstruction in older Chinese: Guangzhou biobank cohort study. *Respir Med*. 2020;173:106158. doi:10.1016/j.rmed.2020.106158
33. Kim V, Criner GJ. Chronic bronchitis and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2013;187(3):228–237. doi:10.1164/rccm.201210-1843CI
34. Xiao M, Wang X, Wang H, et al. Risk factors for hyponatremia in acute exacerbation chronic obstructive pulmonary disease (AECOPD): a multicenter cross-sectional study. *BMC Pulm Med*. 2023;23(1):39. doi:10.1186/s12890-023-02328-4
35. Pezzuto A, Lionetto L, Ricci A, Simmaco M, Borro M. Inter-individual variation in CYP2A6 activity and chronic obstructive pulmonary disease in smokers: perspectives for an early predictive marker. *Biochim Biophys Acta Mol Basis Dis*. 2021;1867(1):165990. doi:10.1016/j.bbadis.2020.165990