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Original Article

IL-33 as a biomarker for disease severity in COPD with lung cancer comorbidity

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Abstract: Objective: To investigate the differences in peripheral blood levels of interleukin-1β (IL-1β), IL-6, IL-17, and IL-33 between patients with chronic obstructive pulmonary disease (COPD) and lung cancer (Comorbidity Group) and those with COPD alone (COPD Group), as well as to explore their clinical significance. Methods: Samples were collected from 133 patients with both COPD and lung cancer (Comorbidity Group) and 91 patients with COPD alone (COPD Group), diagnosed at Affiliated Hospital of Inner Mongolia Medical University between January 2022 and January 2024. Baseline data from both groups were analyzed, and peripheral blood levels of IL-1β, IL-6, IL-17, and IL-33 were measured using enzyme-linked immunosorbent assay (ELISA). The levels of these inflammatory cytokines were compared between the two groups to assess their correlation with disease severity. Results: Significant differences were observed between the Comorbidity Group and the COPD Group in terms of age (P<0.001), sex (P=0.012), duration of COPD (P=0.001), smoking history (P=0.006), glucocorticoid treatment (P=0.014), and GOLD Staging (P<0.001). IL-1β was positively correlated with RV/TLC (P=0.036), and IL-17 with FEV1 (P=0.027) in both groups. IL-6 was positively correlated with TLC in the Comorbidity Group (P=0.021). In the COPD Group, IL-33 was negatively correlated with FEV1 (P<0.001), FVC (P=0.001), FEV1/FVC (P<0.001), RV (P<0.001), and RV/TLC (P<0.001), and positively correlated with GOLD Staging (P=0.046). Multivariate logistic regression identified smoking history (P=0.045, OR=2.891), GOLD staging (P=0.028, OR=0.363), IL-33 (P=0.001, OR=27.369), FEV1/FVC (P=0.012, OR=4.291), RV (P=0.002, OR=5.429), and RV/TLC (P=0.002, OR=6.113) as independent factors distinguishing patients with comorbid COPD and lung cancer from those with COPD alone. Interaction analysis revealed no significant interaction between IL-33 and other risk factors. Conclusion: IL-33 levels were significantly higher in patients with comorbid COPD and lung cancer than in those with COPD alone. IL-33 was negatively correlated with lung function and positively correlated with GOLD Staging, suggesting its potential as a biomarker for disease severity.

Keywords: Chronic obstructive pulmonary disease, lung cancer, interleukin-17, interleukin-33, inflammatory cytokines

Introduction

Chronic obstructive pulmonary disease (COPD) and lung cancer are two leading causes of morbidity and mortality worldwide, significantly contributing to the global disease burden [1, 2]. COPD, a progressive disease characterized by persistent airflow limitation, is primarily caused by long-term exposure to harmful particles, such as tobacco smoke and environmental pollutants [3]. The Global Burden of Disease Study ranks COPD as the third leading cause of death globally, with its incidence and mortality rates continuing to rise annually, posing a major public health concern [4]. In contrast, lung cancer is one of the most prevalent cancers, with a five-year survival rate of only 10-20%, often due to late diagnosis and the aggressive nature of the disease [5].

Epidemiological studies have consistently shown a significant overlap between COPD and lung cancer, with COPD patients exhibiting a 2 to 5 times higher risk of developing lung cancer compared to the general population [6]. The coexistence of these two conditions, known as comorbidity, presents major clinical challenges by complicating diagnosis, treatment, and prognosis. Chronic inflammation in COPD, involving neutrophils, macrophages, and T lymphocytes,

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contributes to the pathological changes that increase the risk of malignancy, such as bronchial epithelial degeneration and subsequent carcinogenesis [7]. Moreover, the inflammatory microenvironment in lung cancer not only promotes tumor growth but also aids in tumor progression and metastasis [8]. Therefore, the coexistence of COPD and lung cancer reflects a complex, bidirectional interaction, necessitating a deeper understanding of their shared mechanisms.

The inflammatory response plays a central role in the pathogenesis of both COPD and lung cancer, with several pro-inflammatory cytokines involved in their development and progression. Among these cytokines, interleukins (ILs), such as IL-1β, IL-6, IL-17, and IL-33, play critical roles. IL-1β, produced by macrophages and other immune cells, promotes inflammation and airway remodeling in COPD while contributing to tumor progression in lung cancer by modulating immune responses [9, 10]. Similarly, IL-6 is elevated in COPD and has been implicated in tumor growth and angiogenesis in lung cancer [11]. IL-17, predominantly secreted by Th17 cells, is involved in both lung inflammation and tumor progression [12]. However, IL-33, a member of the IL-1 family, has a less well-understood role, especially in the context of comorbid COPD and lung cancer. Studies suggest that IL-33 may exacerbate airway inflammation in COPD by promoting Th2-type immune responses [13], while in lung cancer, IL-33 may play a dual role by enhancing tumor growth and metastasis [14]. Despite increasing recognition of these inflammatory cytokines, the specific relationship between IL-33 levels and disease severity in COPD patients with lung cancer comorbidity remains underexplored.

This study is innovative in providing a comprehensive analysis of the peripheral blood levels of IL-1β, IL-6, IL-17, and IL-33 in patients with COPD and lung cancer comorbidity (Comorbidity Group) compared to patients with COPD alone (COPD Group). By examining the correlation between these inflammatory markers and disease severity, we aim to uncover new insights into the shared pathophysiological mechanisms of COPD and lung cancer. More importantly, this study highlights the potential of IL-33 as a significant biomarker for assessing disease severity in patients with both COPD and lung cancer, an area that remains underexplored. Given the growing prevalence of COPD and lung cancer comorbidity, understanding the role of inflammatory cytokines like IL-33 could lead to improved diagnostic, prognostic, and therapeutic strategies, ultimately enhancing patient outcomes.

Methods and materials

Clinical data

A total of 224 COPD patients treated at Affiliated Hospital of Inner Mongolia Medical University between January 2022 and January 2024 were included in this study. Among them, 133 patients with both COPD and lung cancer were assigned to the comorbidity group, while 91 patients with COPD alone were assigned to the COPD group. The study was approved by the ethics committee of the Affiliated Hospital of Inner Mongolia Medical University (**Figure 1**).

Inclusion and exclusion criteria

Inclusion criteria: 1. COPD patients must meet the diagnostic criteria outlined in the "Global Initiative for Chronic Obstructive Lung Disease (GOLD 2021)" [15]. 2. Lung cancer patients must meet the AJCC 8th edition TNM staging criteria and be pathologically diagnosed with non-small cell lung cancer [16]. 3. Patients with both COPD and lung cancer must meet the diagnostic criteria for both diseases. 4. Patients must have complete clinical data.

Exclusion criteria: 1. Patients with multiple hospital admissions, with only data from the first admission retained; 2. Patients who were previously diagnosed and treated at other hospitals; 3. Patients diagnosed with metastatic lung cancer or other malignancies; 4. Patients with suspected lung tumors lacking pathological evidence; 5. Patients with other respiratory diseases that might affect lung function or cancer risk; 6. Patients who died within 24 hours of admission; 7. Patients with severe hematologic, hepatic, renal, or systemic diseases.

Data collection

Patient information was obtained from the hospital's electronic medical record system and outpatient follow-up records. Baseline data included age, sex, body mass index (BMI), COPD duration, residence, smoking history, alcohol consumption, diabetes history, acute exac-

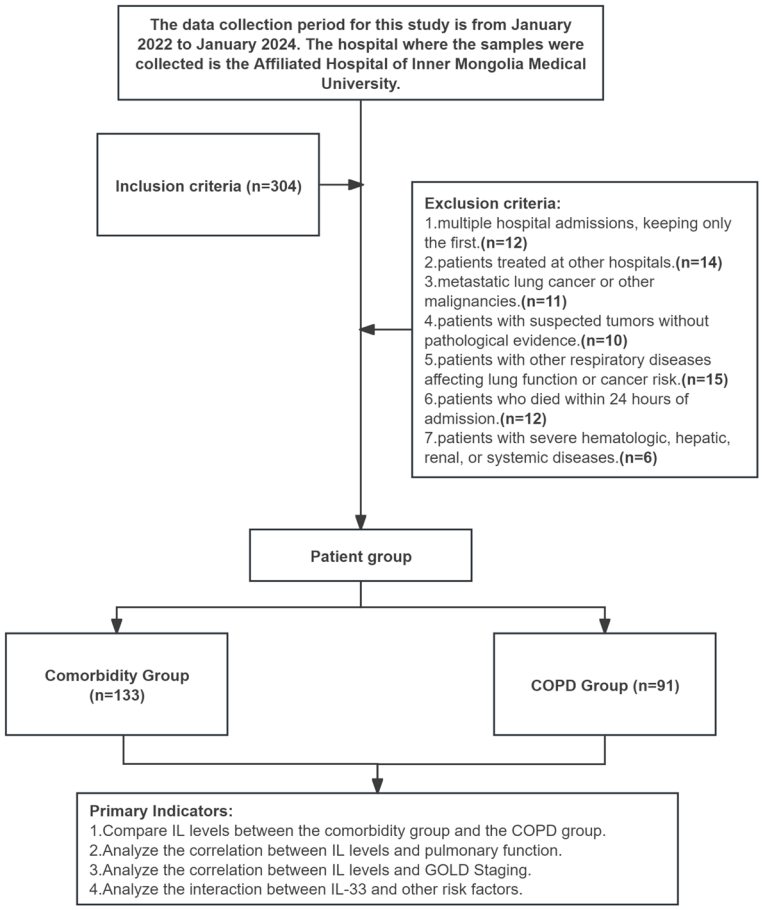


Figure 1. Flow diagram of study procedures.

erbations in the past year, corticosteroid treatment, and GOLD staging. Interleukin (IL) levels included IL-1β, IL-6, IL-17, and IL-33. Pulmonary function parameters measured included Forced Expiratory Volume in 1 second (FEV1), Forced Vital Capacity (FVC), FEV1/FVC ratio, Residual Volume (RV), Total Lung Capacity (TLC), and the RV/TLC ratio. All laboratory indicators were assessed before treatment, following pathological diagnosis.

Laboratory tests

IL detection: Enzyme-linked immunosorbent assay (ELISA) was used to measure serum levels of IL-1β (KE10003), IL-6 (KE10007), IL-17 (KE00203), and IL-33 (KE10054). Five milliliters of peripheral blood were collected from patients upon their first admission, centrifuged, and the supernatant was used for testing. The kits were purchased from Wuhan Three Eagles Biotechnology Co., Ltd.

Pulmonary function tests: Pulmonary function was measured using a spirometer (CareFusion Germany 234 GmbH, MasterScreen model). Patients performed exhalation and inhalation exercises in a seated position, ensuring no air leakage during the test. FEV1, FVC, and the FEV1/FVC ratio were recorded.

Diaphragm function tests: Diaphragm function was assessed using an ultrasound diagnostic instrument (Mindray Medical International Limited, M9 model). Diaphragm mobility and thickness were measured using a 2-5 MHz convex probe (C5-1s) and a 6-13 MHz linear probe (L12-1s), respectively. Measurements were repeated three times, averaged, and diaphragm function parameters were recorded.

Interaction analysis

To examine the interaction effects between different clinical features on the outcome, we constructed a logistic regression model incorporating interaction terms. All independent variables and their interactions were simultaneously included in the regression model to account for potential interaction effects, ensuring a comprehensive and interpretable analysis. The dependent variable, “type”, was converted into a binary variable, mapping the “P” category to 1 and others to 0. A logistic regression model was fitted using the binomial distribution, and all independent variables (including interaction effects) were included. The model was fitted using the glm() function, and estimated coefficients, standard errors, Z-values, and *P*-values for each independent variable and interaction term were obtained. The significance of interaction effects was assessed based on *P*-values. Predicted probabilities for each sample were calculated, and interaction curves were plotted using the ggplot2 package, distinguishing different outcome categories (e.g., type =1 vs. type =0). Interaction plots for each

independent variable were created and combined into a comprehensive display to illustrate the influence patterns.

Observation indicators

Primary outcomes: 1. IL levels in the comorbidity group and the COPD group. 2. The correlation between IL levels and pulmonary function. 3. The correlation between IL levels and GOLD Staging. 4. The interaction between IL-33 and other risk factors.

Secondary outcomes: 1. Comparison of baseline data between the comorbidity group and the COPD group. 2. Comparison of pulmonary function parameters between the two groups. 3. Evaluation of the diagnostic value of IL and pulmonary function in COPD patients with lung cancer. 4. Screening for independent diagnostic factors for COPD combined with lung cancer using logistic regression analysis.

Statistical analysis

Statistical analysis was performed using SPSS 26.0 software. The Kolmogorov-Smirnov (K-S) test was used to analyze the distribution of measurement data. Normally distributed data were expressed as mean (standard deviation), with between-group comparisons made using independent sample t-tests, and paired t-tests used for within-group comparisons. Rank data were analyzed using the rank-sum test (Z), and categorical data were analyzed using the chi-square test. Count data were represented by chi-square test using [n (%)]. The diagnostic value of IL and pulmonary function in diagnosing COPD with lung cancer was assessed using receiver operating characteristic (ROC) curves. Logistic regression was used to identify independent risk factors for COPD with lung cancer. Correlation and interaction analyses were conducted using R (4.4.0). The "rcorr" function from the Hmisc package was used for Pearson correlation testing, and interaction analysis was conducted using the "glm()" function and the interactions package. Visualization was performed using the "ggplot2" package, and significance markers were added using the "ggsignif" package. Data manipulation and visualization were conducted using the "dplyr" and patchwork packages, with semi-symmetric plots created using the "gghalves" package. A *p*-value <0.05 was considered statistically significant.

Results

Comparison of baseline data between comorbidity group and COPD group

We compared baseline data between the comorbidity group and the COPD group. Significant differences were found between the two groups in age (P<0.001), gender (P=0.012), COPD duration (P=0.001), smoking history (P=0.006), corticosteroid treatment (P=0.014), and GOLD staging (P<0.001). However, no significant differences were observed in BMI (P=0.989), residence (P=0.574), alcohol consumption history (P=0.231), diabetes history (P=0.861), or acute exacerbations in the past year (P=0.201) (**Table 1**).

Comparison of IL levels between comorbidity group and COPD group

No significant differences were found between the comorbidity and COPD groups in IL-1β (P=0.469) and IL-6 (P=0.108). However, IL-17 (P=0.033) and IL-33 (P<0.001) levels were significantly higher in the comorbidity group (**Table 2**; **Figure 2**).

Comparison of pulmonary function between comorbidity group and COPD group

Significant differences were found in FEV1 (P<0.001), FVC (P=0.008), FEV1/FVC% (P<0.001), RV (P<0.001), and RV/TLC% (P<0.001), with lower values for these parameters in the COPD group. No significant difference was found in TLC (P=0.082) (**Table 3**; **Figure 3**).

Correlation analysis between IL and pulmonary function

Correlation analysis revealed that IL-1β was positively correlated with RV/TLC (P=0.036), while IL-17 was positively correlated with FEV1 (P=0.027). However, no significant correlations were found for other pulmonary function parameters (P>0.05). In the comorbidity group, IL-6 was positively correlated with TLC (P=0.021). In the COPD group, IL-33 was negatively correlated with FEV1 (P<0.001), FVC (P=0.001), FEV1/FVC (P<0.001), RV (P<0.001), and RV/TLC (P<0.001, **Table 4**; **Figure 4**) (Supplementary Tables 1, 2; Supplementary Figures 1, 2).

Table 1. Comparison of baseline characteristics between the comorbidity group and COPD group

Variable	Comorbidity Group (n=133)	COPD Group (n=91)	Z/t/χ^2 Value	*P*-Value
Age	66.00 (63.00, 71.00)	64.00 (62.50, 66.00)	3.505	<0.001
≥65 years	89	41	9.259	0.002
<65 years	47	50		
Gender			6.351	0.012
Male	122	73		
Female	11	18		
BMI (kg/m^2)	22.91 (3.20)	22.90 (3.35)	0.014	0.989
<18.5	11	10	0.569	0.752
18.5-24	75	48		
>24	47	33		
COPD Duration (years)	11.00 (7.00, 16.00)	8.00 (5.00, 12.00)	3.197	0.001
<10	55	56	11.038	0.004
45585	65	33		
>20	13	2		
Residence			0.316	0.574
Urban	65	41		
Rural	68	50		
Smoking History			7.63	0.006
Present	108	59		
Absent	25	32		
Drinking History			1.436	0.231
Present	29	14		
Absent	104	77		
Diabetes History			0.031	0.861
Present	8	6		
Absent	125	85		
Acute Exacerbation in Past Year			1.632	0.201
Present	90	54		
Absent	43	37		
Corticosteroid Treatment			6.065	0.014
Present	20	26		
Absent	113	65		
GOLD Staging			24.804	<0.001
I	18	2		
II	79	37		
III	34	46		
IV	2	6		

Note: BMI: Body Mass Index, COPD: Chronic Obstructive Pulmonary Disease, GOLD: Global Initiative for Chronic Obstructive Lung Disease.

Table 2. Comparison of IL levels between the comorbidity group and COPD group

Variable	Comorbidity Group (n=133)	COPD Group (n=91)	t Value	*P*-Value
IL-1β (pg/mL)	7.68 (1.18)	7.82 (1.70)	-0.726	0.469
IL-6 (pg/mL)	5.88 (1.05)	5.66 (0.98)	1.616	0.108
IL-17 (pg/mL)	7.14 (0.88)	6.79 (1.36)	2.155	0.033
IL-33 (pg/mL)	6.43 (1.05)	5.17 (1.28)	7.728	<0.001

Note: IL-1β: Interleukin-1 Beta, IL-6: Interleukin-6, IL-17: Interleukin-17, IL-33: Interleukin-33.

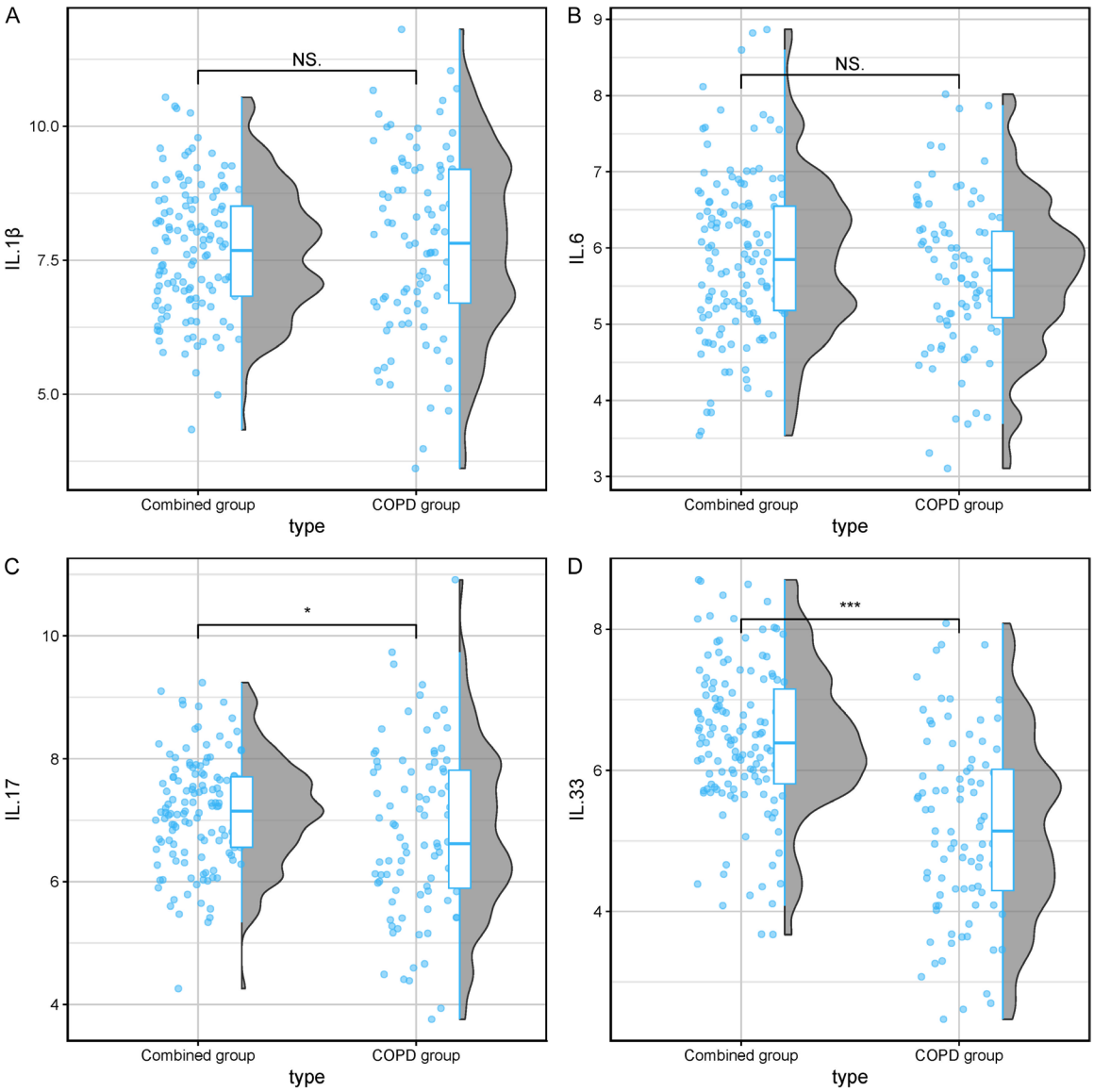


Figure 2. Comparison of interleukins levels between the Comorbidity Group and COPD Group. A. Comparison of IL-1β levels between comorbidity and COPD groups. B. Comparison of IL-6 levels between comorbidity and COPD groups. C. Comparison of IL-17 levels between comorbidity and COPD groups. D. Comparison of IL-33 levels between comorbidity and COPD groups. Note: IL: Interleukin; NS P>0.05, *P<0.05, ***P<0.001; unit (pg/mL).

Table 3. Comparison of pulmonary function between the comorbidity group and COPD group

Variable	Comorbidity Group (n=133)	COPD Group (n=91)	Z/t Value	*P*-Value
FEV1 (L)	1.19 (1.04, 1.34)	1.48 (1.33, 1.80)	-8.399	<0.001
FVC (L)	2.36 (2.13, 2.70)	2.53 (2.22, 2.92)	-2.659	0.008
FEV1/FVC (%)	0.50 (0.42, 0.61)	0.63 (0.54, 0.68)	-6.047	<0.001
RV (L)	2.28 (0.46)	2.75 (0.42)	-7.989	<0.001
TLC (L)	5.32 (4.53, 6.05)	5.11 (4.48, 5.45)	1.742	0.082
RV/TLC (%)	0.43 (0.37, 0.50)	0.54 (0.50, 0.60)	-8.325	<0.001

Note: FEV1: Forced Expiratory Volume in 1 second, FVC: Forced Vital Capacity, FEV1/FVC%: Ratio of FEV1 to FVC, RV: Residual Volume, TLC: Total Lung Capacity, RV/TLC%: Ratio of Residual Volume to Total Lung Capacity.

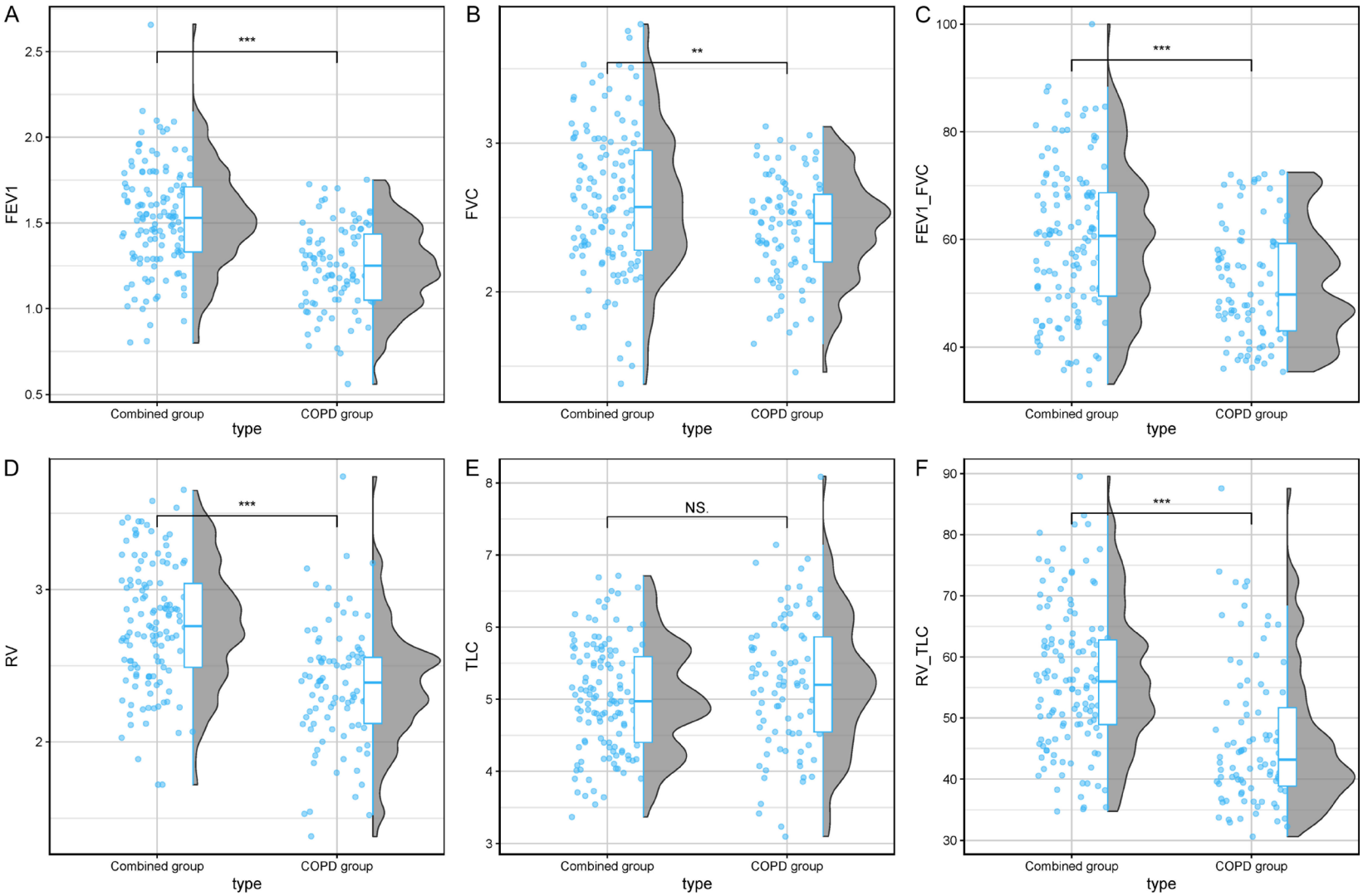


Figure 3. Comparison of pulmonary function parameters between the comorbidity and COPD groups. A. FEV1 levels in comorbidity and COPD groups. B. FVC levels in comorbidity and COPD groups. C. FEV1/FVC levels in comorbidity and COPD groups. D. RV levels in comorbidity and COPD groups. E. TLC levels in comorbidity and COPD groups. F. RV/TLC levels in comorbidity and COPD groups. Note: FEV1: Forced Expiratory Volume in 1 second, FVC: Forced Vital Capacity, FEV1/FVC%: Ratio of FEV1 to FVC, RV: Residual Volume, TLC: Total Lung Capacity, RV/TLC%: Ratio of Residual Volume to Total Lung Capacity. ***P<0.001, **P<0.01, NS P>0.05.

Table 4. Correlation analysis between IL and pulmonary function parameters

Interleukin	Lung Function	Pearson R	*P*-Value
IL-1β (pg/mL)	FEV1 (L)	-0.044	0.513
IL-1β (pg/mL)	FVC (L)	-0.05	0.458
IL-1β (pg/mL)	FEV1/FVC	0.008	0.905
IL-1β (pg/mL)	RV (L)	-0.077	0.252
IL-1β (pg/mL)	TLC (L)	0.103	0.126
IL-1β (pg/mL)	RV/TLC (%)	-0.14	0.036
IL-6 (pg/mL)	FEV1 (L)	0.027	0.692
IL-6 (pg/mL)	FVC (L)	0.044	0.512
IL-6 (pg/mL)	FEV1/FVC	0.016	0.808
IL-6 (pg/mL)	RV (L)	0.047	0.485
IL-6 (pg/mL)	TLC (L)	0.109	0.105
IL-6 (pg/mL)	RV/TLC (%)	-0.049	0.469
IL-17 (pg/mL)	FEV1 (L)	0.148	0.027
IL-17 (pg/mL)	FVC (L)	0.103	0.125
IL-17 (pg/mL)	FEV1/FVC	0.08	0.233
IL-17 (pg/mL)	RV (L)	0.038	0.571
IL-17 (pg/mL)	TLC (L)	-0.083	0.216
IL-17 (pg/mL)	RV/TLC (%)	0.071	0.293
IL-33 (pg/mL)	FEV1 (L)	0.052	0.436
IL-33 (pg/mL)	FVC (L)	0.033	0.62
IL-33 (pg/mL)	FEV1/FVC	-0.006	0.928
IL-33 (pg/mL)	RV (L)	0.075	0.263
IL-33 (pg/mL)	TLC (L)	-0.026	0.694
IL-33 (pg/mL)	RV/TLC (%)	0.058	0.384

Note: IL: Interleukin, IL-1β: Interleukin-1 Beta, IL-6: Interleukin-6, IL-17: Interleukin-17, IL-33: Interleukin-33, FEV1: Forced Expiratory Volume in 1 second, FVC: Forced Vital Capacity, FEV1/FVC%: FEV1 to FVC Ratio, RV: Residual Volume, TLC: Total Lung Capacity, RV/TLC%: RV to TLC Ratio.

Correlation analysis between IL and GOLD staging

IL-33 showed a significant positive correlation with GOLD Staging in both the comorbidity and COPD groups (P<0.001). Specifically, in the COPD group, IL-33 was significantly correlated with GOLD Staging (P=0.046). No significant correlations were observed for IL-1β, IL-6, and IL-17 (**Table 5**; **Figure 5**).

Diagnostic value of IL and pulmonary function parameters in COPD with lung cancer

In the diagnostic analysis, IL-33, FEV1, FEV1/FVC, RV, and RV/TLC all demonstrated high diagnostic ability, with AUCs greater than 0.7. Specifically, the AUCs for IL-33, FEV1, FEV1/FVC, RV, and RV/TLC were 0.774, 0.831, 0.738, 0.781, and 0.828, respectively. These indicators demonstrated high discriminatory power in diagnosing COPD with lung cancer (**Table 6**; **Figure 6**).

Logistic regression analysis for independent diagnostic factors of COPD with lung cancer

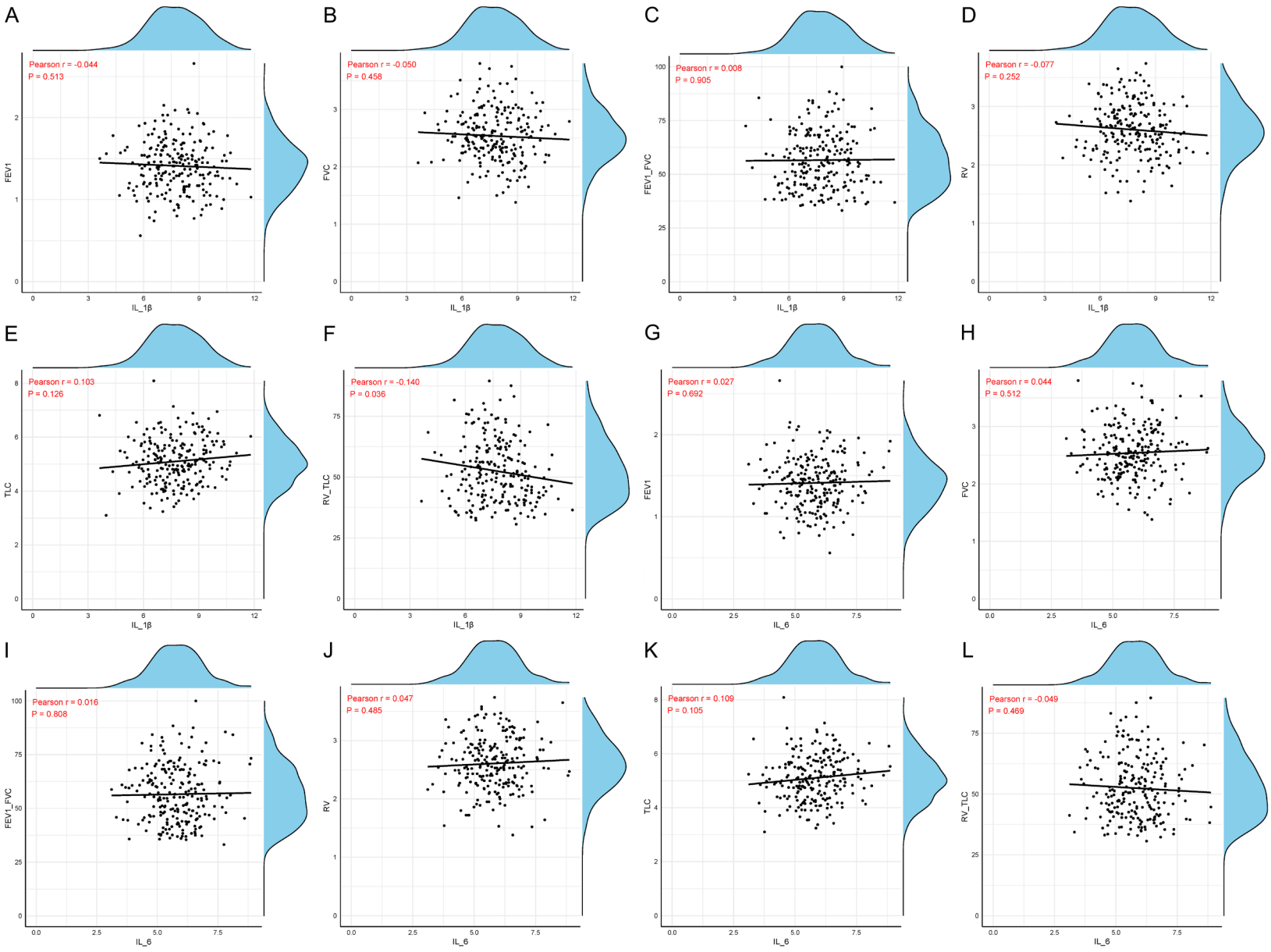
Multivariate logistic regression analysis identified smoking history (P=0.045, OR=2.891), GOLD staging (P=0.028, OR=0.363), IL-33 (P=0.001, OR=27.369), RV (P=0.002, OR=5.429), and RV/TLC (P=0.002, OR=6.113) as significant factors distinguishing comorbid COPD and lung cancer patients from those with COPD alone. GOLD staging was used as a single variable for regression analysis to avoid multicollinearity (**Tables 7**, **8**).

Interaction analysis between IL-33 and other risk factors

Interaction analysis using a logistic regression model showed no significant interactions between IL-33 and other risk factors, including smoking history (P=0.211), FEV1/FVC (P=0.428), RV (P=0.359), RV/TLC (P=0.983), and GOLD Staging (P=0.179) (**Table 9**; **Figure 7**).

Discussion

COPD and lung cancer are major contributors to respiratory disease-related mortality worldwide [17]. Lung cancer is the second most common cancer and the leading cause of cancer-related deaths, posing a significant threat to human health and quality of life. It also places a considerable economic burden on healthcare systems, even in developed countries [18]. Despite various treatment options, mortality rates among COPD and lung cancer patients continue to rise [19]. Studies have shown that COPD is an independent risk factor for lung cancer, and lung cancer is a leading cause of death in COPD patients. As more lung cancer patients are diagnosed with COPD, the comorbidity has garnered increasing attention [20]. While research on COPD and lung cancer has intensified, their shared pathogenesis remains unclear, highlighting the need for further studies to explore their associations and distinctions, which could guide diagnosis and treatment for patients with both conditions.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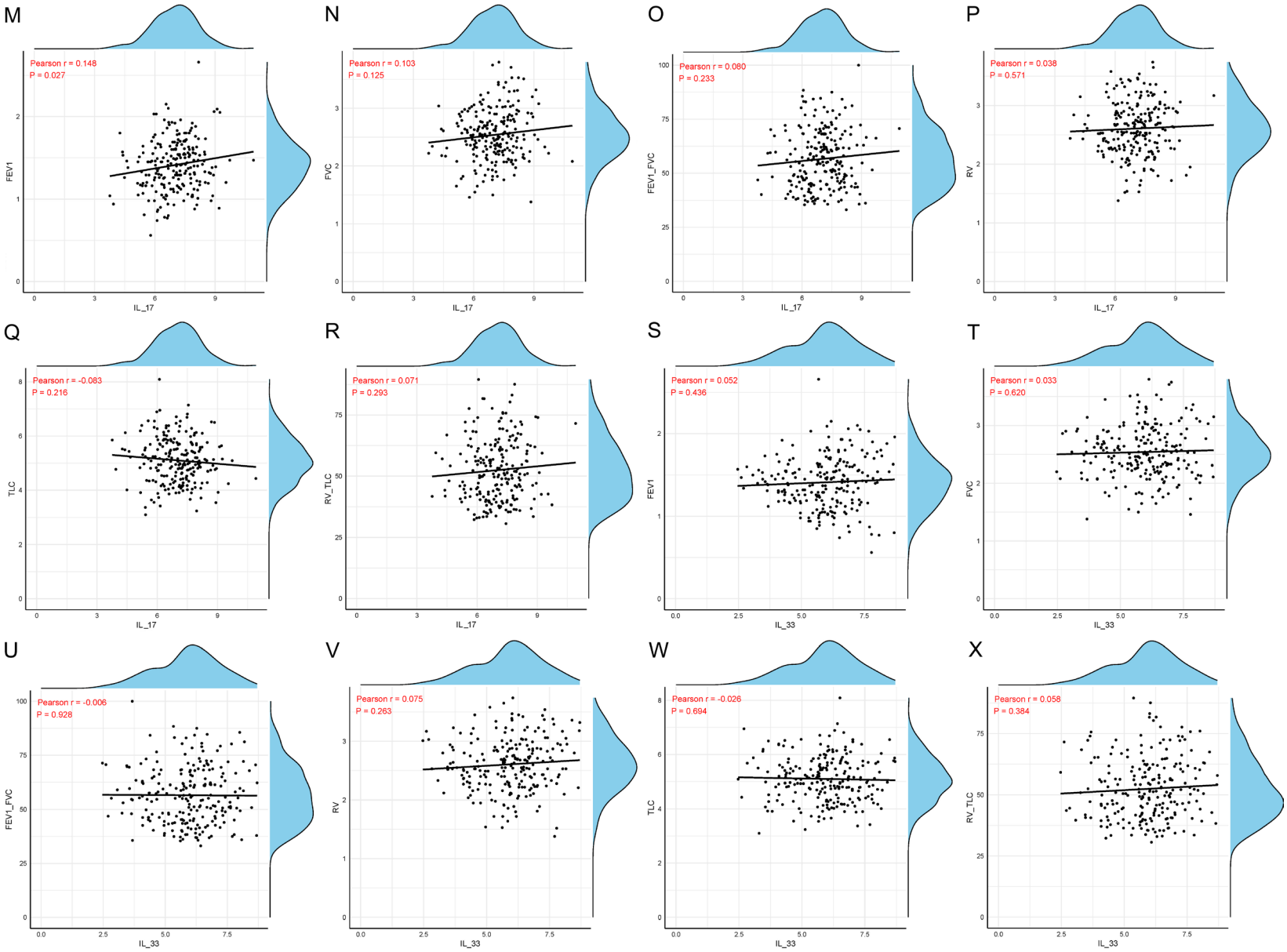
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Pearson r = -0.026
P = 0.694
TLC
IL_33
X
Pearson r = 0.058
P = 0.384
RV_TLC
IL_33

Figure 4. Correlation analysis between interleukins and pulmonary function parameters. A-F: Correlation between IL-1β and pulmonary function parameters. G-L: Correlation between IL-6 and pulmonary function parameters. M-R: Correlation between IL-17 and pulmonary function parameters. S-X: Correlation between IL-33 and pulmonary function parameters. Note: IL: Interleukin, IL-1β: Interleukin-1 Beta, IL-6: Interleukin-6, IL-17: Interleukin-17, IL-33: Interleukin-33, FEV1: Forced Expiratory Volume in 1 second, FVC: Forced Vital Capacity, FEV1/FVC%: FEV1 to FVC Ratio, RV: Residual Volume, TLC: Total Lung Capacity, RV/TLC%: RV to TLC Ratio.

Table 5. Correlation analysis between IL and GOLD staging

Group	GOLD staging	Interleukin	Pearson R	*P*-Value
Comorbidity + COPD Group	GOLD staging	IL-1β (pg/mL)	-0.022	0.745
		IL-6 (pg/mL)	-0.090	0.180
		IL-17 (pg/mL)	-0.087	0.194
		IL-33 (pg/mL)	0.131	0.050
Comorbidity Group	GOLD staging	IL-1β (pg/mL)	-0.019	0.529
		IL-6 (pg/mL)	-.0104	0.234
		IL-17 (pg/mL)	-0.051	0.556
		IL-33 (pg/mL)	0.033	0.709
COPD Group	GOLD staging	IL-1β (pg/mL)	-0.036	0.737
		IL-6 (pg/mL)	-0.010	0.927
		IL-17 (pg/mL)	-0.043	0.685
		IL-33 (pg/mL)	0.704	<0.001

Note: IL: Interleukin, IL-1β: Interleukin-1 Beta, IL-6: Interleukin-6, IL-17: Interleukin-17, IL-33: Interleukin-33, COPD: Chronic Obstructive Pulmonary Disease, GOLD: Global Initiative for Chronic Obstructive Lung Disease.

The inflammatory response plays a central role in the development and progression of both COPD and lung cancer [21]. Interleukins (ILs) are key mediators in the pathogenesis of both COPD and lung cancer [22]. In our study, we found no significant differences in IL-1β and IL-6 levels between the comorbidity and COPD-only groups. However, IL-17 and IL-33 levels were significantly higher in the comorbidity group. This finding suggests that while IL-1β and IL-6 are fundamental inflammatory factors in both diseases, they may not distinctly differentiate between the two conditions.

The significant elevation of IL-17 suggests a more intense inflammatory response in COPD and lung cancer comorbidity patients, potentially linked to disease complexity and severity. Previous studies, such as those by Yang et al. [23], found significantly higher IL-17 expression in the lung tissue of COPD with lung cancer patients compared to healthy controls. This suggests that IL-17 may play a crucial pro-inflammatory role and contribute to disease progression in this patient group. Similarly, Wang et al. [24] observed that IL-17 levels significantly decreased following treatment in COPD with lung cancer patients, indicating that IL-17 may also be involved in the therapeutic response in this patient group. Additionally, Chen et al. [25] reported that smoking exacerbates lung inflammation, leading to increased IL-17 expression in the airways and lung parenchyma, further emphasizing IL-17's role in the pathogenesis of both COPD and lung cancer. Our results align with these findings, showing elevated IL-17 levels in the comorbidity group, reinforcing the idea that IL-17 could serve as a useful biomarker for assessing inflammation and disease progression in COPD with lung cancer comorbidity.

The significant increase in IL-33 underscores its pivotal role in the shared inflammatory environment of both diseases. IL-33 promotes Th2-type immune responses and inflammation, exacerbating airway inflammation in COPD while also contributing to tumor progression in lung cancer [13]. Xia et al. reported increased IL-33 expression in COPD, associated with both airway and systemic inflammation [26]. Our findings corroborate this, showing higher IL-33 levels in the comorbidity group. Studies have also demonstrated that IL-33 expression in monocyte-derived dendritic cells in COPD patients is regulated by epithelial cells, indicating that complex cellular interactions influences airway inflammation and play a critical role in COPD

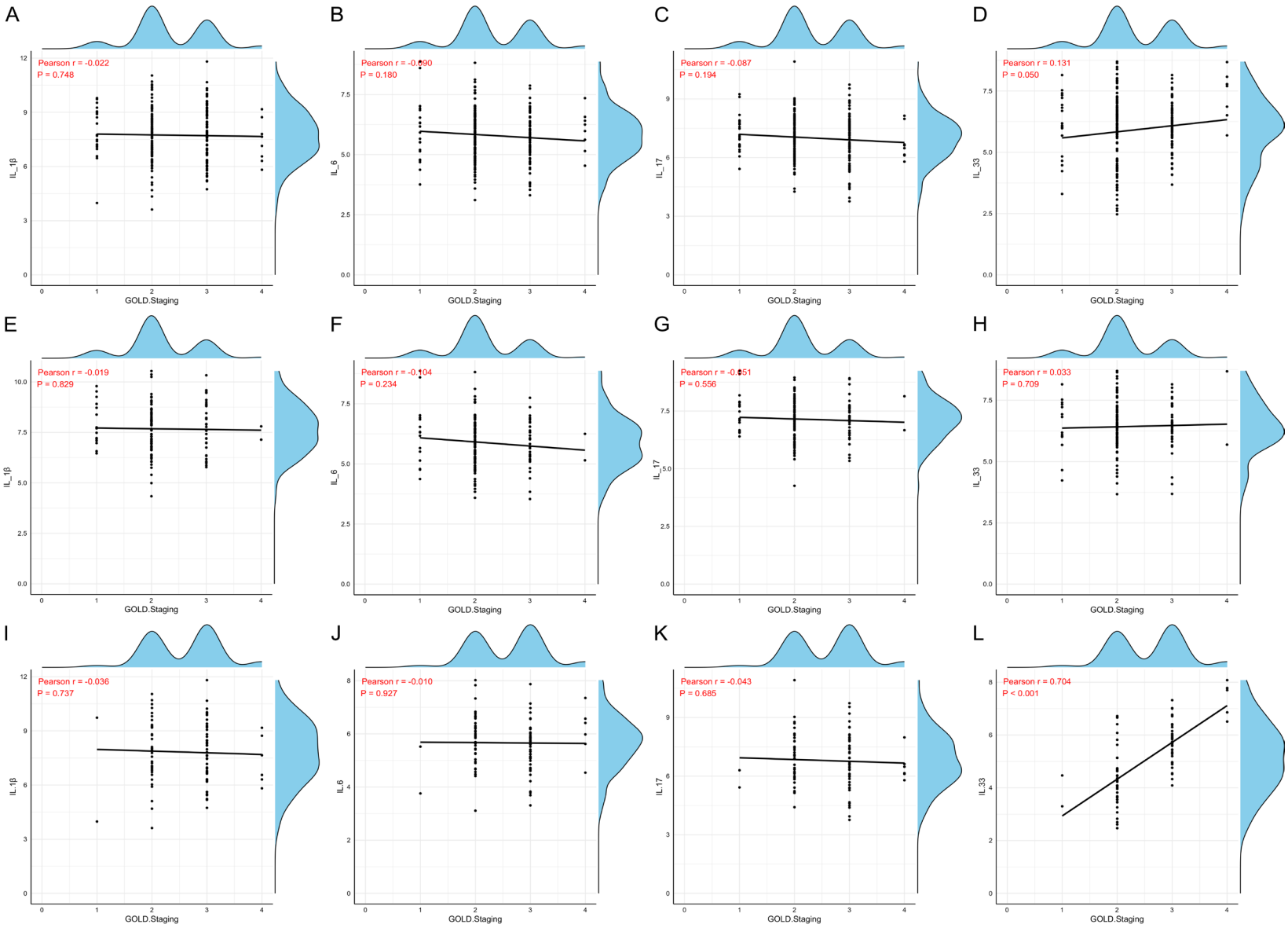

Figure 5. Correlation analysis between interleukins and GOLD staging. A-D: Correlation between IL and GOLD staging in comorbidity and COPD groups. E-H: Correlation between IL and GOLD staging in comorbidity group. I-L: Correlation between IL and GOLD staging in COPD group. Note: IL: Interleukin, IL-1β: Interleukin-1 Beta, IL-6: Interleukin-6, IL-17: Interleukin-17, IL-33: Interleukin-33, COPD: Chronic Obstructive Pulmonary Disease, GOLD: Global Initiative for Chronic Obstructive Lung Disease.

Table 6. ROC curve parameters for IL and pulmonary function parameters in differentiating comorbidity from COPD alone

Marker	AUC	Specificity	Sensitivity	Youden Index	Cut-off
IL-1β (pg/mL)	0.532	0.2857	0.8947	0.1805	9.14
IL-6 (pg/mL)	0.553	0.7692	0.3835	0.1527	6.26
IL-17 (pg/mL)	0.592	0.5055	0.7368	0.2423	6.635
IL-33 (pg/mL)	0.774	0.615	0.85	0.465	5.635
FEV1 (L)	0.763	0.7253	0.6842	0.4095	1.405
FVC (L)	0.611	0.9231	0.2857	0.2088	2.905
FEV1/FVC (%)	0.668	0.7912	0.5113	0.3025	60.05
RV (L)	0.766	0.8022	0.6767	0.4789	2.625
TLC (L)	0.57	0.5934	0.5714	0.1648	5.075
RV/TLC (%)	0.745	0.6923	0.7669	0.4592	48.23

Note: IL: Interleukin, IL-1β: Interleukin-1 Beta, IL-6: Interleukin-6, IL-17: Interleukin-17, IL-33: Interleukin-33, FEV1: Forced Expiratory Volume in 1 second, FVC: Forced Vital Capacity, FEV1/FVC%: FEV1 to FVC Ratio, RV: Residual Volume, TLC: Total Lung Capacity, RV/TLC%: RV to TLC Ratio, COPD: Chronic Obstructive Pulmonary Disease.

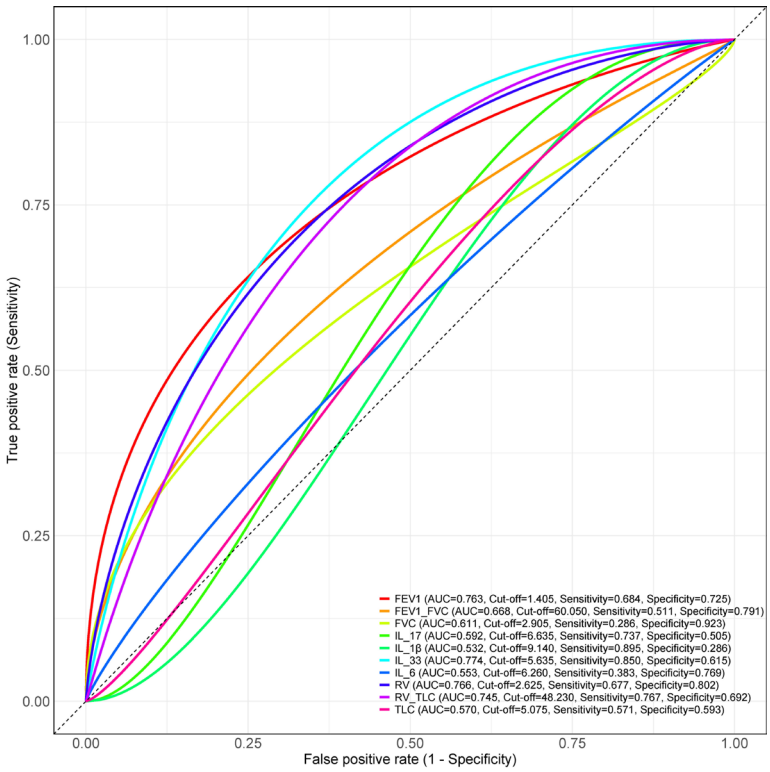

Figure 6. ROC curves for interleukins and pulmonary function parameters in diagnosing comorbidity in COPD patients. Note: IL: Interleukin, IL-1β: Interleukin-1 Beta, IL-6: Interleukin-6, IL-17: Interleukin-17, IL-33: Interleukin-33, FEV1: Forced Expiratory Volume in 1 second, FVC: Forced Vital Capacity, FEV1/FVC%: FEV1 to FVC Ratio, RV: Residual Volume, TLC: Total Lung Capacity, RV/TLC%: RV to TLC Ratio, COPD: Chronic Obstructive Pulmonary Disease.

pathobiology [27]. Taken together, these results suggest that both IL-17 and IL-33 may serve as important biomarkers for diagnosing COPD and lung cancer comorbidity, offering valuable insights for further research and clinical applications.

To better understand the role of ILs in COPD and lung cancer comorbidity, we analyzed the correlation between IL levels, pulmonary function parameters, and GOLD Staging. We found that IL levels correlated with both pulmonary function parameters and GOLD Staging. Specifically, in the COPD group, IL-33 was significantly negatively correlated with FEV1, FVC, FEV1/FVC, RV, and RV/TLC, and positively correlated with GOLD Staging. These findings are consistent with studies by others [28, 29], which highlight IL-33's critical role in airway inflammation and remodeling, contributing to significant declines in lung function and greater disease severity in COPD. The complexity and diversity of IL-mediated mechanisms in COPD and lung cancer are noteworthy. While IL-1β and IL-6 are essential pro-inflammatory cytokines in both diseases, their levels were similar in the comorbidity and COPD groups, possibly due to a balanced inflammatory response that does not show a significant correlation with pulmonary function

Table 7. Variable assignment

Variable	Assignment
Age	≥65 years =1, <65 years =0
Gender	Male =1, Female =0
COPD Duration (years)	<10=0, 10-20=1, >20=2
Smoking History	Present =1, Absent =0
Corticosteroid Treatment	Present =1, Absent =0
GOLD Classification	I =0, II =1, III =2, IV =3
IL-17 (pg/mL)	≤6.635=0, >6.635=1
IL-33 (pg/mL)	≤5.78=0, >5.78=1
FEV1 (L)	≤1.405=0, >1.405=1
FVC (L)	≤2.905=0, >2.905=1
FEV1/FVC (%)	≤60.05=0, >60.05=1
RV (L)	≤2.625=0, >2.625=1
RV/TLC (%)	≤48.23=0, >48.23=1

Note: IL-17: Interleukin-17, IL-33: Interleukin-33, FEV1: Forced Expiratory Volume in 1 second, FVC: Forced Vital Capacity, FEV1/FVC%: FEV1 to FVC Ratio, RV: Residual Volume, RV/TLC%: RV to TLC Ratio, COPD: Chronic Obstructive Pulmonary Disease, GOLD: Global Initiative for Chronic Obstructive Lung Disease.

parameters. In contrast, IL-33's negative correlation with pulmonary function and positive correlation with GOLD Staging in the COPD group suggests its critical role in driving airway inflammation and remodeling, which significantly impairs lung function and exacerbates disease severity [28, 29].

The correlation analysis between IL levels and pulmonary function parameters in this study highlighted the diagnostic potential of ILs in COPD and lung cancer comorbidity. IL-33, along with FEV1, FEV1/FVC, RV, and RV/TLC, exhibited high AUC values of 0.774, 0.831, 0.738, and 0.828, respectively, demonstrating strong discriminatory power for diagnosing COPD with lung cancer. IL-33 promotes airway inflammation and remodeling, leading to substantial declines in lung function and reflecting disease severity [30]. Additionally, multivariate logistic regression analysis identified IL-33 as an independent diagnostic factor for COPD with lung cancer, suggesting that its role in airway inflammation and the tumor microenvironment may involve multiple mechanisms. These findings emphasize the unique role of IL-33 in COPD and lung cancer comorbidity. However, we found no significant interactions between IL-33 and other risk factors such as smoking history, FEV1/FVC, and RV. This indicates that, although IL-33 is highly expressed in both COPD and lung cancer, its role may be independent of traditional risk factors. This result suggests that IL-33 contributes to disease progression primarily through its direct influence on inflammation and immune responses, rather than interactions with other risk factors.

However, there are several limitations to this study. The limited sample size restricts the external validity of the results. Future studies should include larger samples to enhance representativeness and statistical power. Multicenter research can increase sample diversity and provide broader data, improving the generalizability of the findings. Moreover, this study's cross-sectional design reveals only correlations, not causal relationships between variables. Longitudinal studies are needed to observe the dynamic relationship between IL levels, lung function, and disease progression in patients with COPD and lung cancer comorbidity over time. Additionally, as this study was conducted at a single medical center, it may introduce regional and institutional biases. Future studies should involve multiple centers from different regions and hospitals to reduce these biases. Finally, the lack of long-term follow-up limits our understanding of how IL levels impact patient prognosis. Long-term follow-up studies are needed to assess how IL levels influence survival rates and quality of life. Addressing these limitations will enable more comprehensive insights into the role of ILs in COPD and lung cancer comorbidity and their potential clinical applications.

Conclusion

This study found higher IL-33 levels in COPD patients with lung cancer compared to those with COPD alone, with a negative correlation to lung function and a positive correlation with GOLD Staging. These findings suggest that IL-33 may serve as a potential biomarker for disease severity. However, the study's limited sample size and cross-sectional design prevent definitive conclusions. Larger, longitudinal studies are needed to confirm these results and further explore the role of IL-33 in COPD with lung cancer comorbidity.

Table 8. Multivariate analysis of comorbidity in COPD patients

Variable	Estimate	Std. Error	*P* Value	OR	Lower	Upper
Age	0.678	0.459	0.140	1.970	0.803	4.923
Gender	1.296	0.767	0.091	3.656	0.854	17.772
COPD Duration (years)	0.537	0.386	0.164	1.711	0.818	3.758
Smoking History	0.876	0.513	0.088	2.401	0.891	6.765
Corticosteroid Treatment	-0.947	0.587	0.107	0.388	0.117	1.193
GOLD Classification	-1.667	0.422	0.001	0.189	0.078	0.414
IL-17	0.690	0.459	0.133	1.994	0.812	4.974
IL-33	3.355	0.606	0.001	28.631	9.562	105.676
FVC	0.263	0.671	0.696	1.301	0.360	5.177
RV	1.667	0.538	0.002	5.299	1.903	16.035
RV/TLC	1.781	0.571	0.002	5.937	2.018	19.474

Note: IL-17: Interleukin-17, IL-33: Interleukin-33, FVC: Forced Vital Capacity, RV: Residual Volume, RV/TLC%: RV to TLC Ratio, COPD: Chronic Obstructive Pulmonary Disease, GOLD: Global Initiative for Chronic Obstructive Lung Disease.

Table 9. Interaction between IL-33 and other risk factors

Variable	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	-2.073	1.517	-1.367	0.172
Smoking history	0.403	0.322	1.251	0.211
FEV1/FVC	0.010	0.013	0.792	0.428
RV	0.427	0.466	0.917	0.359
RV/TLC	0.001	0.017	-0.022	0.983
Gold Staging	0.336	0.250	1.345	0.179

Note: FEV1: Forced Expiratory Volume in 1 second, FVC: Forced Vital Capacity, FEV1/FVC%: FEV1 to FVC Ratio, RV: Residual Volume, RV/TLC%: RV to TLC Ratio, GOLD: Global Initiative for Chronic Obstructive Lung Disease.

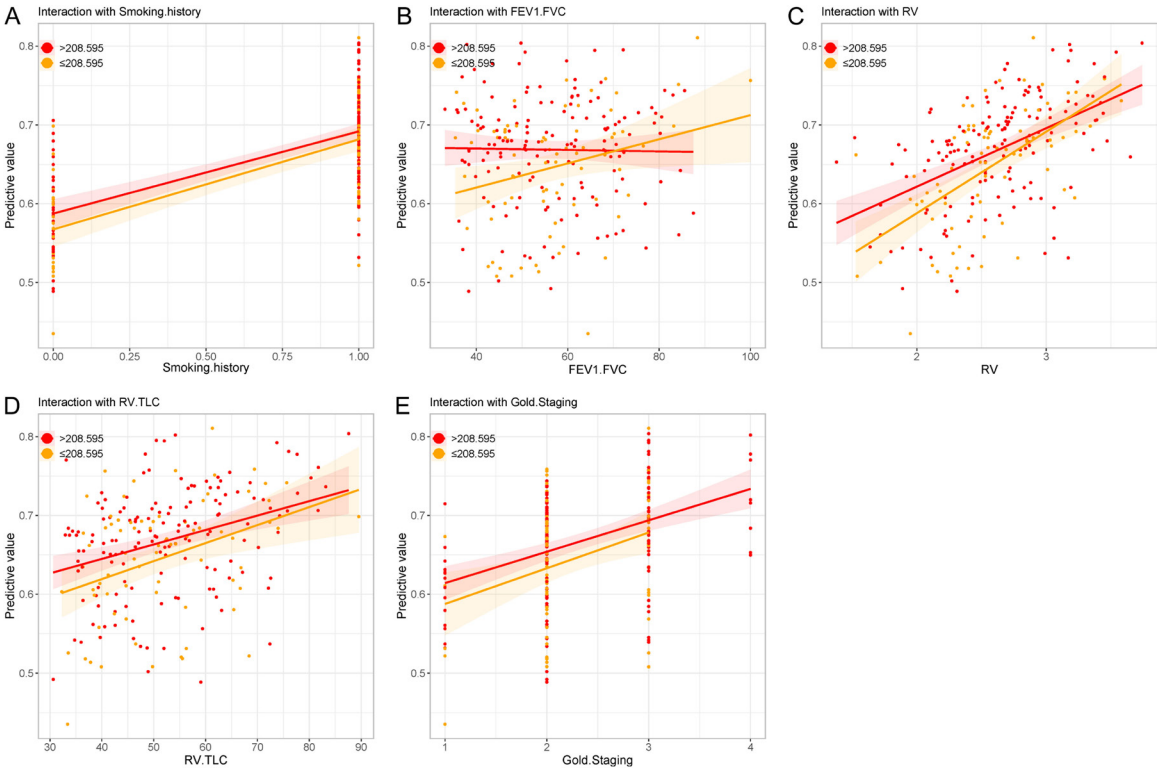

Figure 7. Interaction effects between risk factors and IL-33 level. A. Interaction between IL-33 and smoking history. B. Interaction between IL-33 and FEV1/FVC. C. Interaction between IL-33 and RV. D. Interaction between IL-33 and RV/TLC. E. Interaction between IL-33 and GOLD staging. Note: FEV1: Forced Expiratory Volume in 1 second, FVC: Forced Vital Capacity, FEV1/FVC%: FEV1 to FVC Ratio, RV: Residual Volume, RV/TLC%: RV to TLC Ratio, GOLD: Global Initiative for Chronic Obstructive Lung Disease.

Disclosure of conflict of interest

None.

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Supplementary Table 1. Correlation analysis parameters between IL and lung function in the combined group

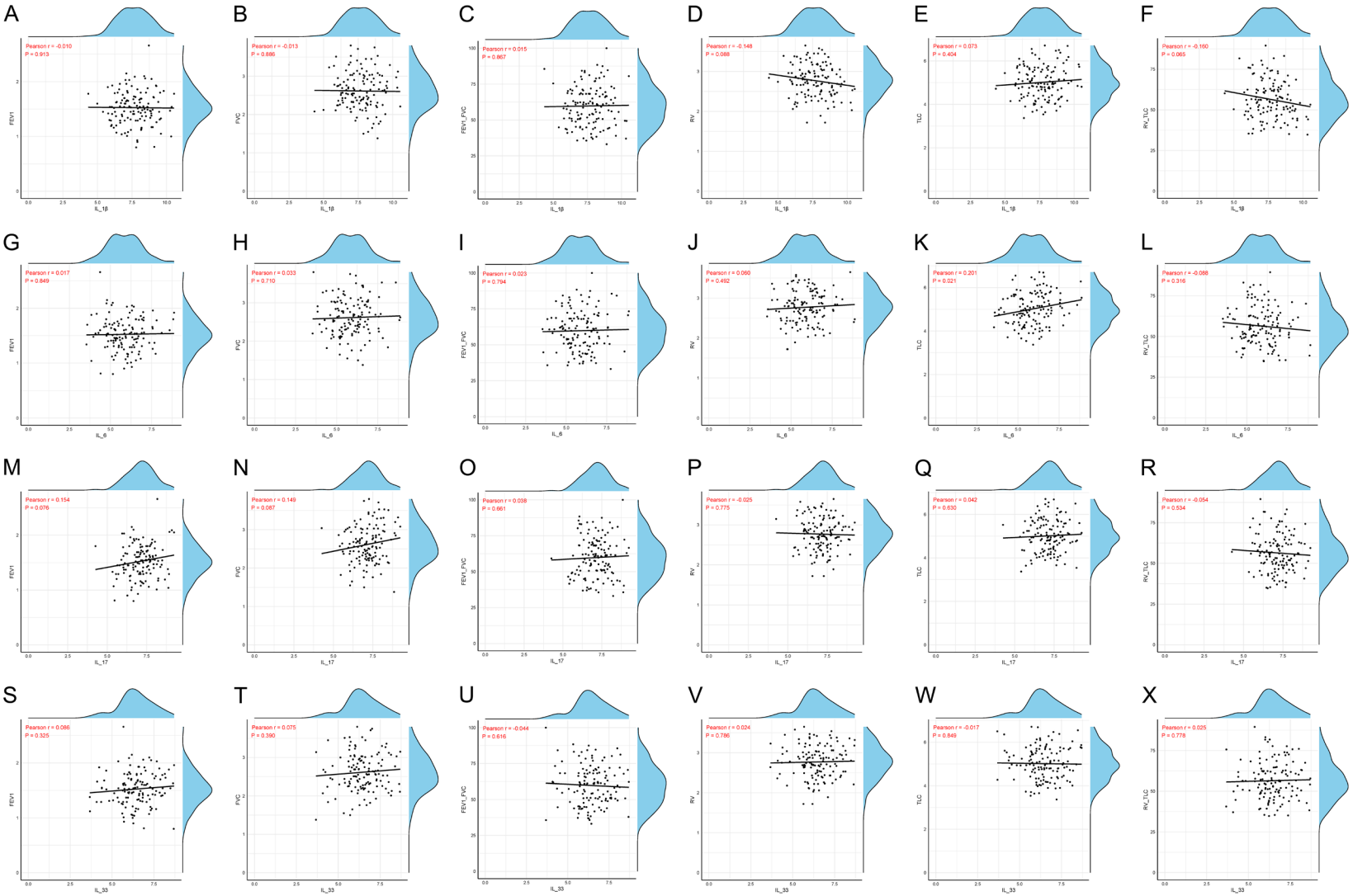
Interleukin	LungFunction	PearsonR	PValue
IL-1β (pg/mL)	FEV1(L)	-0.010	0.913
IL-1β (pg/mL)	FVC(L)	-0.013	0.886
IL-1β (pg/mL)	FEV1/FVC	0.015	0.867
IL-1β (pg/mL)	RV(L)	-0.148	0.088
IL-1β (pg/mL)	TLC(L)	0.073	0.404
IL-1β (pg/mL)	RV/TLC(%)	-0.160	0.065
IL-6 (pg/mL)	FEV1(L)	0.017	0.849
IL-6 (pg/mL)	FVC(L)	0.033	0.710
IL-6 (pg/mL)	FEV1/FVC	0.023	0.794
IL-6 (pg/mL)	RV(L)	0.060	0.492
IL-6 (pg/mL)	TLC(L)	0.201	0.021
IL-6 (pg/mL)	RV/TLC(%)	-0.088	0.316
IL-17 (pg/mL)	FEV1(L)	0.154	0.076
IL-17 (pg/mL)	FVC(L)	0.149	0.087
IL-17 (pg/mL)	FEV1/FVC	0.038	0.661
IL-17 (pg/mL)	RV(L)	-0.025	0.775
IL-17 (pg/mL)	TLC(L)	0.042	0.630
IL-17(pg/mL)	RV/TLC(%)	-0.054	0.534
IL-33 (pg/mL)	FEV1(L)	0.086	0.325
IL-33 (pg/mL)	FVC(L)	0.075	0.390
IL-33 (pg/mL)	FEV1/FVC	-0.044	0.616
IL-33 (pg/mL)	RV(L)	0.024	0.786
IL-33 (pg/mL)	TLC(L)	-0.017	0.849
IL-33 (pg/mL)	RV/TLC(%)	0.025	0.778

Note: Interleukin (IL), Interleukin-1 Beta (IL-1β), Interleukin-6 (IL-6), Interleukin-17 (IL-17), Interleukin-33 (IL-33), Forced Expiratory Volume in 1 second (FEV1), Forced Vital Capacity (FVC), FEV1 to FVC Ratio (FEV1/FVC%), Residual Volume (RV), Total Lung Capacity (TLC), and RV to TLC Ratio (RV/TLC%).

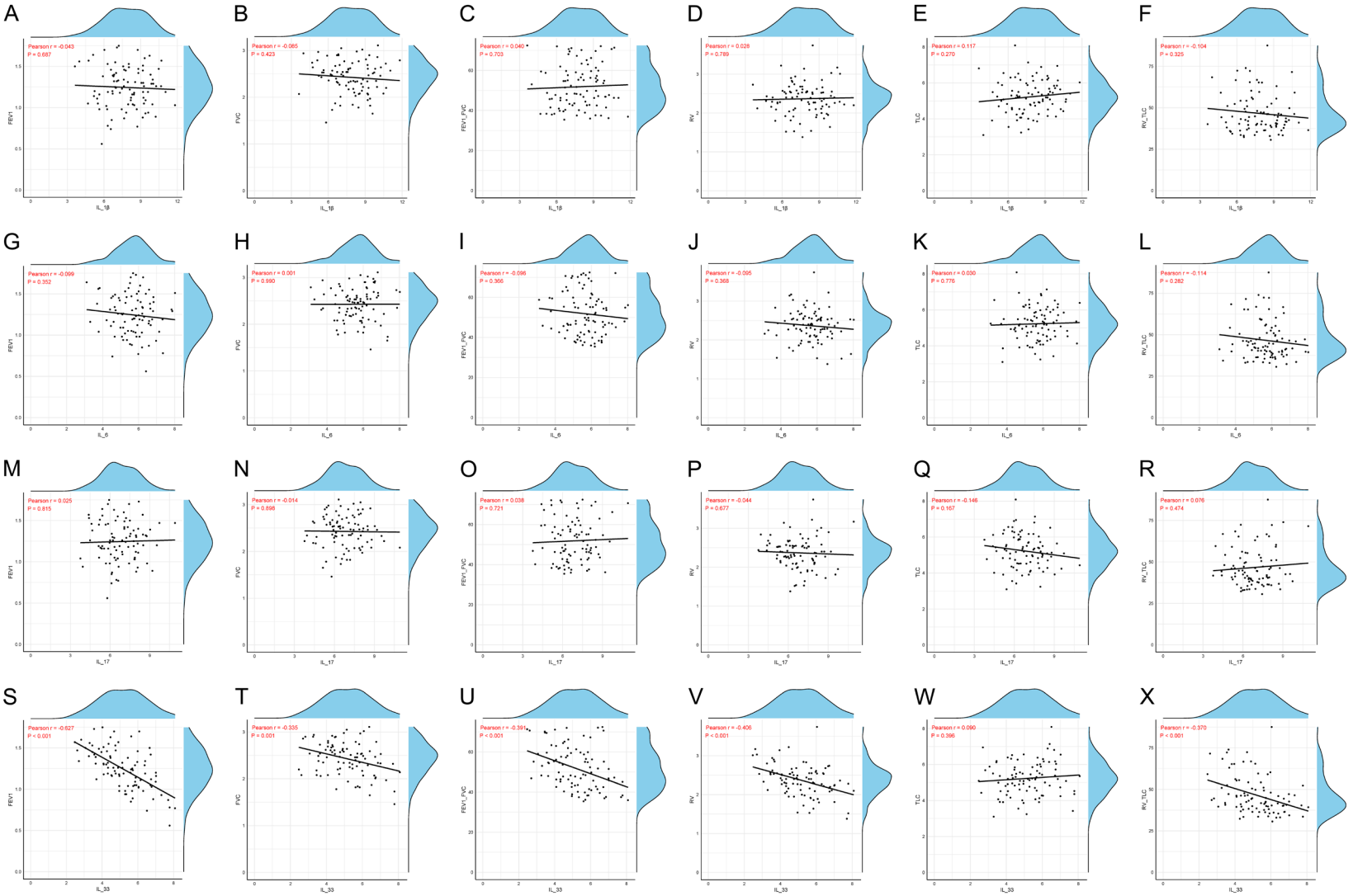
Supplementary Table 2. Correlation analysis parameters between IL and lung function in the COPD group

Interleukin	LungFunction	PearsonR	PValue
IL-1β (pg/mL)	FEV1(L)	-0.043	0.687
IL-1β (pg/mL)	FVC(L)	-0.085	0.423
IL-1β (pg/mL)	FEV1/FVC	0.040	0.703
IL-1β (pg/mL)	RV(L)	0.028	0.789
IL-1β (pg/mL)	TLC(L)	0.117	0.270
IL-1β (pg/mL)	RV/TLC(%)	-0.104	0.325
IL-6 (pg/mL)	FEV1(L)	-0.099	0.352
IL-6 (pg/mL)	FVC(L)	0.001	0.990
IL-6 (pg/mL)	FEV1/FVC	-0.096	0.366
IL-6 (pg/mL)	RV(L)	-0.095	0.368
IL-6 (pg/mL)	TLC(L)	0.030	0.776
IL-6 (pg/mL)	RV/TLC(%)	-0.114	0.282
IL-17 (pg/mL)	FEV1(L)	0.025	0.815
IL-17 (pg/mL)	FVC(L)	-0.014	0.898
IL-17 (pg/mL)	FEV1/FVC	0.038	0.721
IL-17 (pg/mL)	RV(L)	-0.044	0.677
IL-17 (pg/mL)	TLC(L)	-0.146	0.167
IL-17 (pg/mL)	RV/TLC(%)	0.076	0.474
IL-33 (pg/mL)	FEV1(L)	-0.627	< 0.001
IL-33 (pg/mL)	FVC(L)	-0.335	0.001
IL-33 (pg/mL)	FEV1/FVC	-0.391	< 0.001
IL-33 (pg/mL)	RV(L)	-0.406	< 0.001
IL-33 (pg/mL)	TLC(L)	0.090	0.396
IL-33 (pg/mL)	RV/TLC(%)	-0.370	< 0.001

Note: Interleukin (IL), Interleukin-1 Beta (IL-1β), Interleukin-6 (IL-6), Interleukin-17 (IL-17), Interleukin-33 (IL-33), Forced Expiratory Volume in 1 second (FEV1), Forced Vital Capacity (FVC), FEV1 to FVC Ratio (FEV1/FVC%), Residual Volume (RV), Total Lung Capacity (TLC), and RV to TLC Ratio (RV/TLC%).



Supplementary Figure 1. Correlation analysis between IL and lung function in the combined group. A-F. Correlation analysis between IL-1β and lung function indicators; G-L. Correlation analysis between IL-6 and lung function indicators; M-R. Correlation analysis between IL-17 and lung function indicators; S-X. Correlation analysis between IL-33 and lung function indicators. Note: Interleukin (IL), Interleukin-1 Beta (IL-1β), Interleukin-6 (IL-6), Interleukin-17 (IL-17), Interleukin-33 (IL-33), Forced Expiratory Volume in 1 second (FEV1), Forced Vital Capacity (FVC), FEV1 to FVC Ratio (FEV1/FVC%), Residual Volume (RV), Total Lung Capacity (TLC), and RV to TLC Ratio (RV/TLC%).



Supplementary Figure 2. Correlation analysis between IL and lung function in the COPD group. A-F. Correlation analysis between IL-1β and lung function indicators; G-L. Correlation analysis between IL-6 and lung function indicators; M-R. Correlation analysis between IL-17 and lung function indicators; S-X. Correlation analysis between IL-33 and lung function indicators. Note: Interleukin (IL), Interleukin-1 Beta (IL-1β), Interleukin-6 (IL-6), Interleukin-17 (IL-17), Interleukin-33 (IL-33), Forced Expiratory Volume in 1 second (FEV1), Forced Vital Capacity (FVC), FEV1 to FVC Ratio (FEV1/FVC%), Residual Volume (RV), Total Lung Capacity (TLC), and RV to TLC Ratio (RV/TLC%).