Original Article

Association between the Dietary Inflammatory Index and lung function in exacerbated chronic obstructive pulmonary disease: The mediating role of inflammatory indicators

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Background and Objectives: This study explored the association between the dietary inflammatory index (DII) and lung function in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD), and the potential mediating role of blood inflammatory markers. **Methods and Study Design:** In this cross-sectional study of 507 patients with AECOPD, dietary intake was assessed through 24-hour dietary recalls, and the DII was determined. Generalized linear models, logistic regression and mediation analysis were used to evaluate associations between DII, inflammatory markers [white blood cell count (WBC), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune inflammation index (SII), and systemic inflammatory response index (SIRI)], and lung function [forced expiratory volume in one second (FEV1), forced vital capacity (FVC)]. **Results:** DII was 2.81and showed a significant negative linear correlation with FVC (p <0.05) and with FEV1 (p <0.05). After adjusting for confounding factors, each unit increase in DII was associated with a decrease of 0.053 L in FEV1 and 0.078 L in FVC. Additionally, FEV1 showed negative associations with SII, SIRI, NLR, PLR, and WBC (all p <0.05). Mediation analysis revealed that WBC exerted a statistically significant mediating effect between DII and FEV1 (ACME = -7.54×10^{-3}, p <0.05). **Conclusions:** It was indicated that a pro-inflammatory diet is associated with reduced lung function in AECOPD patients, with lung function showing a significant negative correlation with inflammatory markers. WBC serves as a key mediator between the DII and FEV1.

Key Words: AECOPD, DII, lung function, blood inflammatory markers, mediating roles

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the most prevalent respiratory disorder worldwide. Reports indicate that over 3 million people die from COPD annually,[1] which is the third leading cause of death globally.[2] Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are important events in the natural progression of the disease,[3] episodes of worsening respiratory symptoms, which contribute substantially to the burden of COPD.[4] In addition, AECOPD is a significant contributor to increased hospitalization rates,[5] with the risk of death escalating as the frequency of severe exacerbations rises.[6] Therefore, identifying and managing modifiable risk factors is paramount for preventing or delaying the onset of AECOPD.

COPD is an inflammatory disease that is characterized by irreversible and progressive airflow limitation and lung function decline.[7] Inflammation is significantly associated with pulmonary dysfunction.[8] Elevated levels of pro-inflammatory cytokines have been observed in the airways of patients with COPD, indicating a persistent state of inflammation.[9,10] Airway viral or bacterial infections, pollution, or other insults to the airways are often associated with increased airway inflammation, a significant mechanism in AECOPDs.[11] Frequent AECOPDs are

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associated with systemic inflammation. Systemic inflammation can be quantified using a variety of biochemical or hematological indicators, which are usually determined in routine blood tests or calculated from these measurements. White blood cell (WBC) is common markers to assess inflammation. And it is the most common prognostic biomarkers for patients with AECOPD, supported by previous studies and clinical experience.[12,13] A high WBC count is related to poorer lung function and lower quality of life in COPD patients.[14] The presence of the neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR) are recognized as a marker for systemic inflammation.[15,16] Some studies have suggested that elevated levels of the NLR and PLR may be associated with an increased risk of deterioration in COPD patients.[16,17] The systemic immune-inflammation index (SII), originally developed as a prognostic marker for adverse outcomes in cancer patients, has emerged as a novel and robust indicator of systemic inflammation.[18] In recent years, studies have shown that higher SII levels may be linked to a higher prevalence of COPD.[19] Systemic inflammation response index (SIRI) is also a new systemic inflammatory biomarker, which was positively associated with the prevalence of COPD.[20] Therefore, WBC, NLR, PLR, SII, and SIRI may become promising serological indicators for predicting lung function decline.

In addition, previous studies have shown that diet can influence inflammatory lung disease and affect lung function.[21,22,23] For example, red or processed meats, refined grains, saturated fats, and sweets were linked to an increased risk of developing COPD,[24] which had pro-inflammatory effects.[25,26] Conversely, fruits, vegetables, oily fish, and whole grains were associated with preserved lung function, anti-inflammatory and antioxidant effects.[27] Considering these factors, the DII, a quantitative tool that generates an overall inflammatory effect score by calculating pro-inflammatory and anti-inflammatory scores for each food parameter, is used to assess the impact of diet on inflammation.[28] Higher DII scores are associated with a greater potential of the diet to promote inflammation, whereas lower DII scores suggest a diet more likely to exert anti-inflammatory effects.[29] In 2016, Iowa Women's Health investigative indicates that a pro-inflammatory diet, as evidenced by higher DII scores, may be associated with total mortality as well as mortality of COPD.[30] In recent years, many other studies have also found that DII scores are associated with an increased risk of COPD,[31-35] and higher DII scores may contribute to lower lung function.[32,35] AECOPD negatively impacts patients' quality of life and accelerates the deterioration of the lung function.[19] There is a need to systematically explore the relationship between DII and lung function in AECOPD patients.

Consequently, this study aimed to investigate the association between the DII and lung function in patients with AECOPD, as well as the relationships between WBC and other relevant factors and lung function. Given that diet-induced inflammation is closely linked to systemic inflammation, and considering that the dietary patterns in COPD patients are typically pro-inflammatory, we hypothesize that dietary inflammation may exacerbate systemic inflammatory responses, thereby contributing to the decline in lung function. The primary aim of this study is to explore the relationships between DII and lung function, and between WBC, NLR, PLR, SII, and SIRI in AECOPD patients, and to explore the mediating role of inflammatory indicators in influencing lung function. This will provide clues for the prevention or treatment of AECOPD and for future dietary approaches to the decline in lung function.

METHODS

Study design

A cross-sectional study was conducted among patients diagnosed with AECOPD at Weifang No. 2 People's Hospital, Shandong Province, China, from August 1, 2022 to October 1, 2024. Initially, 517 patients were identified, however, those not meeting the inclusion and exclusion criteria were excluded, resulting in a final sample size of 507 patients. This study adhered to the ethical principles outlined in the Declaration of Helsinki and was reviewed and approved by the Ethics Committees of Qingdao University (QDU-HEC-2022277) and Weifang Second People's Hospital (KY2023-030-01). Additionally, it was registered with the Chinese Clinical Trial Registry (ChiCTR2300069658). All patients signed the informed consent form.

Participants

All AECOPD patients received standard treatment. Participants were eligible for inclusion if they met the following criteria: 1) aged 45 years or older; 2) diagnosed with COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines; 3) experiencing an AECOPD, defined as a worsening of respiratory symptoms, including increased dyspnea, cough, and sputum production within 14 days, potentially accompanied by tachypnea and/or tachycardia; and 4) provided informed consent.

Exclusion criteria included: 1) a history of oncological disease or tuberculosis within the past five years; 2) a history of severe cardiovascular conditions such as myocardial infarction, angina pectoris, or heart failure; 3) uncontrolled blood pressure (systolic BP >170 mmHg or diastolic BP >100 mmHg) or blood glucose levels (fasting glucose >7.0 mmol/L or postprandial glucose >10.0 mmol/L); 4) a history of liver diseases or coagulation disorders within the past two years; 5) substance abuse or dependence (including alcohol) within the past two years; and 6) incomplete dietary data or energy intake outside the range of 500 to 3500 kcal/day.

Questionnaires

Structured questionnaires were used to investigate the demographic information and living habits of the research subjects. Such as age, sex, place of residence, marital status, educational level, family annual income, smoking status and drinking status. The modified Medical Research Council Dyspnea Scale (mMRC)[36] grades and the COPD assessment test (CAT)[37,38] were assessed by questionnaire. Information on the patient's clinical case was collected, including clinical symptoms and comorbidities.

Prior to the start of the study, a preliminary survey was conducted to familiarize with the interview process and to

understand the local dialect. To ensure good compliance and quality of the questionnaire, the two investigators discussed and standardized the criteria and used a uniform standard to record the questionnaire results. Data collation was carried out by two investigators who reviewed the data with each other.

Physical examination

Professionally trained staff performed a physical examination of the patients, measuring height, weight, waist and hip circumference. Body mass index (BMI) was calculated as follows: BMI = weight (kg)/height $(m)^2$, and the standard classification of BMI in China was: <18.5 kg/m^2 for underweight, 18.5-23.9 kg/m^2 for normal weight, 24.0-27.9 kg/m^2 for overweight and ≥28.0 kg/m^2 for obese.[39] Waist Hip Ratio (WHR) was calculated by dividing waist circumference by hip circumference.

Blood inflammation indicators

Fasting venous blood samples (2 mL and 5 mL) were collected from each research subject using EDTA anticoagulant tubes and procoagulant tubes, respectively. Plasma was isolated by centrifuging the anticoagulated blood at 3000 rpm for 5 minutes using a CTK80 centrifuge, while serum was obtained from the procoagulant tubes by centrifugation at 4000 rpm for 8 minutes. Following onsite analysis of routine blood and biochemical parameters, the remaining samples were aliquoted and stored at -80°C. All hematological parameters were measured using a fully automated hematology analyzer (Laboman assembly line). Data on WBC, PLR, NLR, SIRI, and SII were derived from peripheral blood cell counts. SIRI was calculated as neutrophils × monocytes / lymphocytes, and SII as platelets × neutrophils / lymphocytes.

Lung function indicators

In the Special Examination Department, a physician conducted lung function tests on the patient in Testing Room II, utilizing a JAEGER (Germany) lung function instrument. The following parameters were recorded: forced expiratory volume in one second (FEV1), forced vital capacity (FVC), the FEV1/FVC ratio, and the percentage of predicted FEV1 (FEV1% predicted).

Dietary survey and DII calculation

On the day the patient was admitted for treatment, a 24-hour dietary review questionnaire was used to investigate the date and number of meals consumed by the patients (breakfast, lunch, dinner, and additional meals or snacks), including the name of the dish, the composition of the food, and the weight (g). Basic nutrients (energy, protein, total fat, carbohydrates, dietary fiber, cholesterol, dietary fiber and dietary fiber) were calculated by the Dietary Nutrition Survey and Intelligent Analysis Software V1.0. The basic nutrients (energy, protein, total fat, carbohydrates, dietary fiber, cholesterol, β-carotene, vitamin A, thiamin, riboflavin, niacin, vitamin C, vitamin E, magnesium, iron, and zinc, selenium), fatty acids (SFA, monounsaturated fatty acids, PUFA, n-3 PUFA, and n-6 PUFA), and phytochemicals (isoflavones and anthocyanins) per day consumed, and the amount of alcohol consumed per person per day was calculated based on the amount of alcohol consumed and the number of different types of alcoholic beverages.

The DII calculations were performed based on the method of Nitin Shivappa et al with the following results. The specific results of the calculations are as follows: (1) DII calculations are based on dietary intake data then linked to a regionally representative world database, providing a robust estimated mean and standard deviation for each parameter, the Z-scores and center percentiles for the corresponding food parameters are then obtained; (2) Multiply the central percentile of each food parameter by the respective Food Parameter Specific Inflammatory Effect Score (Supplementary Table 1) to calculate the Food Parameter Specific DII Score; (3) Sum the Food Parameter Specific DII Scores to obtain the overall DII Score for an individual diet.

Statistical analyses

Statistical analyses were conducted using SPSS version 27.0. Quantitative data were evaluated for normality. Normally distributed data are presented as mean ± standard deviation, with differences between groups analyzed via One-way ANOVA. Post-hoc pairwise comparisons among three groups were performed using Bonferroni's method. Skewed data are reported as median (interquartile range), and group differences were assessed using the Kruskal-Wallis nonparametric test. Categorical data are presented as frequencies and analyzed using chi-square tests or non-parametric tests as appropriate. The relationships between the DII and mMRC subgroups, CAT scores, lung function indices, and inflammatory markers in patients with AECOPD were examined using Spearman correlation analysis. The correlation regression graph between DII and lung function indicators was plotted using GraphPad Prism 9. Generalized linear model and logistic regression model were employed to investigate the associations between DII and CAT subgroups, GOLD classification, and lung function indices (FEV1, FVC, FEV1/FVC, and FEV1%pred). The correlation between inflammatory indicators and lung function indicators was analyzed by multiple linear regression. The mediating role of inflammatory indicators between DII and lung function was analyzed by R 4.5.1. A p-value 0.05 was considered statistically significant.

RESULTS

Baseline characteristics stratified by DII levels

Among the 507 study subjects, the average age and BMI were 68.3±7.5years and 22.9±3.8 kg/m^2, with 81.5% (413) male. DII was 2.8 (2.1, 3.5) for pro-inflammatory status. The participants' characteristics were presented in Table 1 based on tertiles of DII (T1: DII ≤1.8; T2: 1.8 <DII ≤2.8; T3: 2.8 <DII ≤3.7). Compared to the T1, the patients in the T3 were older, and had a lower weight, waist, hipline, BMI, WBC and SII (all p <0.05). Also compared to the T2 group, the patients in the T3 group were older, more living alone, and had a lower weight, waist and hipline (all p <0.05). Among the three DII categories, there were no statistical difference in other basic information, lifestyle habits and lung function (all p >0.05).

Table 1. General characteristics, inflammatory biomarkers, and lung function parameters by DII levels of AECOPD participants

Characteristics	Total (n=507)	DII			*p*
		T1 (n=169)	T2 (n=169)	T3 (n=169)	
Age (years)	68.3±7.5	67.8±7.4	67.6±7.3	69.6±7.8†,‡	0.031
Gender, n (%)					0.798
Men	413 (81.5)	138 (81.7)	135 (79.9)	140 (82.8)	
Women	94 (18.5)	31 (18.3)	34 (20.1)	29 (17.2)	
Place of residence, n (%)					0.124
Rural	290 (57.2)	86 (50.9)	103 (60.9)	101 (59.8)	
Urban	217 (42.8)	83 (49.1)	66 (39.1)	68 (40.2)	
Living alone, n (%)					0.014
Yes	47 (9.3)	22 (13.0)	7 (4.1) †	18 (10.7) ‡	
No	460 (90.7)	147 (87.0)	162 (95.9) †	151 (89.3) ‡	
Marital status, n (%)					0.180
Married	464 (91.7)	154 (91.1)	160 (94.7)	150 (88.8)	
Widowed	38 (7.5)	13 (7.7)	7 (4.1)	18 (10.7)	
Other	5 (0.8)	2 (1.2)	2 (1.2)	1 (0.5)	
Current smoking status, n (%)					0.109
Yes	127 (25.1)	37 (21.9)	38 (22.5)	52 (30.8)	
No	380 (74.9)	132 (78.1)	131 (77.5)	117 (69.2)	
Current drinking status, n (%)					0.647
Yes	350 (69.0)	40 (23.1)	48 (28.4)	42 (24.9)	
No	157 (31.0)	129 (76.9)	121 (71.6)	127 (75.1)	
Weight (kg)	62.9±11.5	63.5±11.3	64.7±11.2	60.5±11.6†,‡	0.003
BMI (kg/m^2)	22.9±3.8	23.1±3.7	22.6±3.6	22.3±3.7†	0.008
Waist (cm)	89.1±10.8	90.0±10.8	90.4±11.3	86.9±9.9†,‡	0.005
Hipline (cm)	97.6±10.4	99.0±10.2	98.3±10.7	95.8±9.9†,‡	0.010
WHR	0.9±0.1	0.9±0.6	0.9±0.6	0.9±0.6	0.147
Inflammatory					
WBC (×10^{9}L)	6.7 (5.4, 8.5)	7.1 (5.9, 9.1)	6.5 (5.3, 7.9)	6.6 (5.3, 8.4)	0.003
HsCRP (mg/L)	2.7 (0.5, 14.4)	2.7 (0.5, 20.5)	2.7 (0.7, 11.7)	2.9 (0.5, 14.3)	0.972
SII	714.4 (439.9, 1250.2)	820.0 (475.7, 1522.1)	655.1 (399.9, 1052.8)	743.2 (453.2, 1297.4)	0.028
SIRI	1.5 (0.9, 2.9)	1.5 (1.0, 3.5)	1.4 (0.8, 2.5)	1.6 (0.9, 2.8)	0.050
PLR	156.4 (116.1, 229.3)	164.7 (116.8, 233.8)	146.9 (112.4, 221.5)	157.8 (118.1, 236.9)	0.379
NLR	3.2 (2.1, 5.5)	3.4 (2.3, 6.9)	2.9 (1.9, 5.1)	3.3 (2.1, 5.5)	0.057
Lung function parameters					
FEV1/FVC, %	48.1±12.8	48.0±12.6	48.7±12.5	47.4±13.2	0.616
FEV1, %pre	50.6±22.3	52.1±22.9	50.5±21.1	49.2±23.0	0.501
FEV1, L	1.1 (0.8,1.6)	1.1 (0.9,1.7)	1.1 (0.9,1.6)	1.1 (0.8,1.6)	0.085
FVC, L	2.6±0.8	2.7±0.8	2.6±0.9	2.5±0.8	0.062
GOLD Stage					0.455
I	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
II	226 (44.6)	81 (47.9)	77 (45.6)	68 (40.2)	
III	246 (48.5)	74 (43.8)	83 (49.1)	89 (52.7)	
IV	35 (6.9)	14 (8.3)	9 (5.3)	12 (7.1)	
CAT					0.114
≤20	316 (62.3)	116 (68.6)	99 (58.6)	101 (59.8)	
>20	191 (37.7)	53 (31.4)	70 (41.4)	68 (40.2)	
mMRC					0.138
0	39 (7.6)	13 (7.7)	14 (8.3)	12 (7.1)	
1	72 (14.2)	31 (18.3)	19 (11.2)	22 (13.0)	
2	118 (23.3)	38 (22.5)	38 (22.5)	42 (24.9)	
3	196 (38.7)	67 (39.6)	59 (34.9)	70 (41.4)	
4	82 (16.2)	20 (11.8)	39 (23.1)	23 (13.6)	
DII	2.8 (2.1,3.5)	1.8 (1.2,2.1)	2.8 (2.6,3.1)	3.7 (3.5,4.0)	<0.001

COPD, chronic obstructive pulmonary disease; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BMI, body mass index; WHR, waist to hip ratio; CAT, COPD assessment test; mMRC, the modified medical research council dyspnea scale; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; FEV1/FVC, the ratio of forced expiratory volume in 1 s and forced vital capacity; GOLD, Global Initiative for chronic obstructive pulmonary disease; DII, dietary inflammatory index. T1, low DII scores group; T2, middle DII scores group; T3, high DII scores group.

Data are presented as n (%), mean±SD or median (P25, P75).

†compared to T1, $p<0.05$

‡compared to T2, $p<0.05$.

Associations of DII with lung function of AECOPD participants

As shown in Figure 1, A and B indicated a strong negative linear relationship between DII and both FVC and FEV1(r = -0.11, r = -0.12; p <0.05); however, C and D showed no significant association between the DII and FEV1/FVC, FEV1%pre (p >0.05). Generalized linear models was used to evaluate the association between lung function of AECOPD participants and DII was shown in Table 2. It was indicated that FEV1 and FVC negatively correlated with DII, each unit of increased DII score was associated with 0.053L decrease in FEV1 and 0.078L decrease in FVC in Model 3. In a multivariable analysis of tertile of DII, the second tertile of the DII had significantly lower of FVC and FEV1%pre than those in the first tertile (FVC, T2 vs. T1, the β = -0.17, p = 0.041; FEV1%pre, T2 vs. T1, the β = -3.29, p = 0.037). Ordinal logistic regression was used to evaluate the association between GOLD and mMRC of AECOPD participants and DII is shown in Table 2. And the association between CAT and DII was used binary logistic regression. In model 3, indicated that CAT positively correlate3.3d with DII. And the second tertile of the DII had significantly associated with 1.617 times increased risk of CAT than those in the first tertile (T2 vs. T1, p = 0.044).

Association between lung function and blood inflammatory markers in AECOPD patients

The correlation heatmap (Figure 2A) visualized the pairwise association between WBC, PLR, NLR, SII, SIRI and lung function indicator (FEV1, FVC, FEV1/FVC and FEV1%). Strong negative correlations were evident between WBC and FEV1%pre (p <0.05), PLR and FEV1%pre, FVC, FEV1, FEV1/FVC (all p <0.05), SII and FEV1%pre, FVC, FEV1, FEV1/FVC (all p <0.05), SIRI and FEV1%pre, FVC, FEV1, FEV1/FVC (all p <0.05). Variables within others showed weak intercorrelations. Multiple linear regression was used to evaluate the association between lung function of AECOPD participants and inflammatory indicators were shown in Figure 2(B, C, D, E). After adjusted for age, gender, marital status, residence, career, smoking, BMI, diabetes, hyperlipidemia and hypertension, FEV1 showed negative associations with SII, SIRI, NLR, PLR, and WBC (β = -0.006, -0.019, -0.014, -0.001, and -0.014, respectively; all p <0.05). Similarly, FEV1% predicted was inversely associated with SII, SIRI, NLR, PLR, and WBC (β = -0.003, -0.994, -0.974, -0.648, and -0.024, respectively; all p <0.05). FVC was negatively correlated with SII, SIRI, and PLR (β = -0.009, -0.029, and -0.001, respectively; all p <0.05). Additionally, the FEV1/FVC ratio was inversely related to SII and NLR (β = -0.001 and -0.218, respectively; both p <0.05).

Mediation analysis

The mediation analysis revealed distinct roles of WBC, SII, SIRI, NLR and PLR in the association between DII and lung function. Figure 3 demonstrated that WBC had a statistically significant mediating effect (ACME = 7.54 × 10^{-3}, p <0.05). However, the mediation proportion was negative (-10.6%).

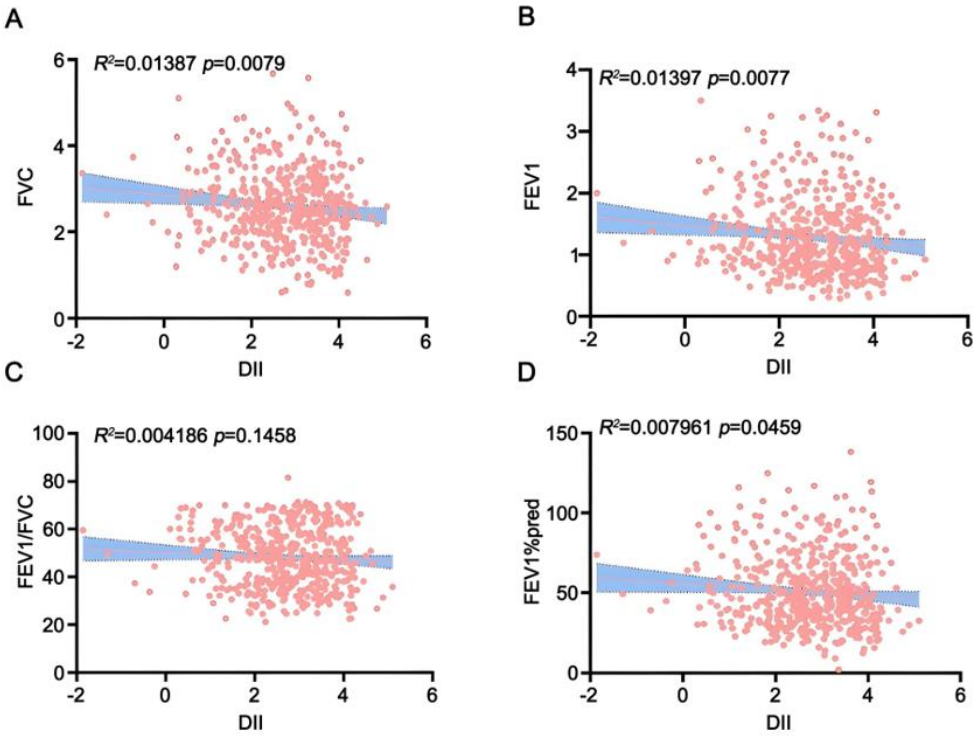

Figure 1. Simple linear regression of DII and FVC, FEV1, FEV1/FVC, FEV1%pred. (A) Association between DII and FVC; (B) Association between DII and FEV1; (C) Association between DII and FEV1/FVC; (D) Association between DII and FEV1%pre. DII, Dietary Inflammatory Index; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; FEV1/FVC, the ratio of forced expiratory volume in 1 s and forced vital capacity.

Table 2. Generalized linear models and logistic regression of DII with lung function of AECOPD participants

	Model 1		Model 2		Model 3	
	OR/β (95%*CI*)	*p*	*OR/β* (95%*CI*)	*p*	*OR/β* (95%*CI*)	*p*
FEV1						
DII	-0.07 (-0.12, -0.02)	0.007	-0.06 (-0.11, -0.01)	0.024	-0.05 (-0.10, -0.00)	0.035
T1	ref	-	ref	-	ref	-
T2	-0.06 (-0.19, 0.08)	0.403	-0.10 (-0.23, 0.03)	0.118	-0.10 (-0.23, 0.02)	0.904
T3	-0.14 (-0.27, -0.01)	0.036	-0.09 (-0.22, 0.03)	0.147	-0.09 (-0.21, 0.04)	0.918
FVC						
DII	-0.10 (-0.17,-0.03)	0.008	-0.08(-0.15,-0.02)	0.011	-0.08(-0.14, -0.02)	0.015
T1	ref	-	ref	-	ref	-
T2	-0.13 (-0.31, 0.04)	0.141	-0.16 (-0.32, 0.00)	0.047	-0.17 (-0.33, -0.01)	0.041
T3	-0.21 (-0.39, -0.04)	0.019	-0.15 (-0.31, 0.01)	0.073	-0.14 (-0.30, 0.02)	0.084
FEV1/FVC						
DII	-0.80 (-1.88, 0.28)	0.144	-0.52 (-1.53, 0.50)	0.317	-0.43 (-1.45, 0.59)	0.404
T1	ref	-	ref	-	ref	-
T2	0.69 (-2.02, 3.41)	0.614	-0.37 (-2.93, 2.20)	0.781	-0.33 (-2.90, 2.23)	0.799
T3	-0.07 (-3.40, 2.04)	0.628	-0.08 (-2.64, 2.47)	0.948	0.14 (-2.43, 2.71)	0.917
FEV1%pre						
DII	-0.19 (-3.84, -0.04)	0.045	-1.62 (-3.45, 0.12)	0.081	0.11 (-3.33, 0.33)	0.222
T1	ref	-	ref	-	ref	-
T2	-1.54 (-6.33,3.24)	0.527	-3.31 (-7.92, 1.31)	0.160	-3.29 (-7.89, 1.32)	0.037
T3	-2.88 (-7.66,1.90)	0.238	-2.37 (-6.96, 2.22)	0.311	-2.25 (-6.86, 2.36)	0.105
GOLD						
DII	-	-	-	-	-	-
T1	1	-	1	-	1	-
T2	1.02 (0.68, 1.55)	0.910	1.17 (0.75, 1.82)	0.498	1.17 (0.75, 1.83)	0.488
T3	1.28 (0.84, 1.94)	0.247	1.15 (0.74, 1.78)	0.545	1.12 (0.72, 1.75)	0.609
mMRC						
DII	-	-	-	-	-	-
T1	1	-	1	-	1	-
T2	1.45 (0.87, 2.42)	0.155	1.70 (0.97, 2.97)	0.065	1.66 (0.95, 2.91)	0.076
T3	1.40 (0.84, 2.33)	0.198	1.20 (0.70, 2.05)	0.518	1.18 (0.69, 2.03)	0.551
CAT						
DII	-	-	-	-	-	-
T1	1	-	1	-	1	-
T2	1.55 (0.99, 2.42)	0.055	1.59 (0.99, 2.54)	0.051	1.62 (1.01, 2.58)	0.044
T3	1.47 (0.94, 2.31)	0.089	1.39 (0.88, 2.22)	0.160	1.37 (0.86, 2.19)	0.198

Model 1, no adjustment; Model 2, adjusted for age, gender, marital status, residence, career, smoking, BMI; Model 3, adjusted for age, gender, marital status, residence, career, smoking, BMI, diabetes, hyperlipidemia, hypertension. FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; FEV1/FVC, the ratio of forced expiratory volume in 1 s and forced vital capacity; GOLD, Global Initiative for chronic obstructive pulmonary disease; DII, dietary inflammatory index; CAT, COPD assessment test; mMRC, the modified medical research council dyspnea scale.
-: not suitable for calculations in this model.

DISCUSSION

This study innovatively investigated the associations between the DII, lung function parameters, and systemic inflammatory markers, and further explored the potential mediating effects of inflammatory indicators. Our findings revealed that higher DII scores were significantly associated with lower lung function, as measured by both FEV1 and FVC. Moreover, FEV1 was inversely correlated with several inflammatory markers, including WBC, SII, SIRI, NLR, and PLR. Similarly, FVC showed negative correlations with SII, SIRI, and PLR. Importantly, mediation analysis indicated that WBC partially mediated the association between DII and FEV1. It suggests that changes in inflammatory markers play a crucial role in the relationship between dietary inflammation and lung function.

Our study demonstrated significant inverse correlations between several inflammatory indices, specifically the SII, SIRI, WBC, NLR, and PLR and FEV1. Inverse correlations were also observed between SII, SIRI, and PLR with FVC. These findings align with prior research indicating a negative association between established inflammatory markers and measures of lung function, muscle strength, and exercise capacity. Progressive and largely irreversible airflow obstruction accompanied by loss of lung function represents a core pathological feature of COPD.[40] This functional impairment arises mainly from small airways disease (SAD) and chronic airway inflammation, which plays a central role in COPD pathogenesis. Persistent inflammation promotes progressive narrowing of the airways and destruction of the alveolar parenchyma.[41] Exaggerated airway inflammatory responses, often triggered by viral or bacterial infections, are key mechanisms in AECOPD.[42] The increasing levels of NLR and PLR could function as biomarkers, akin to CRP, for diagnosis and assessment of acute exacerbations among COPD patients. Prior studies have shown that plasma CRP and WBC were associated with AECOPD.[43-45]

In particular, a WBC count exceeding 9×10^9 cells/L has been correlated with higher exacerbation rates. Furthermore, WBC subtypes have shown negative correlations with lung function. One proposed mechanism

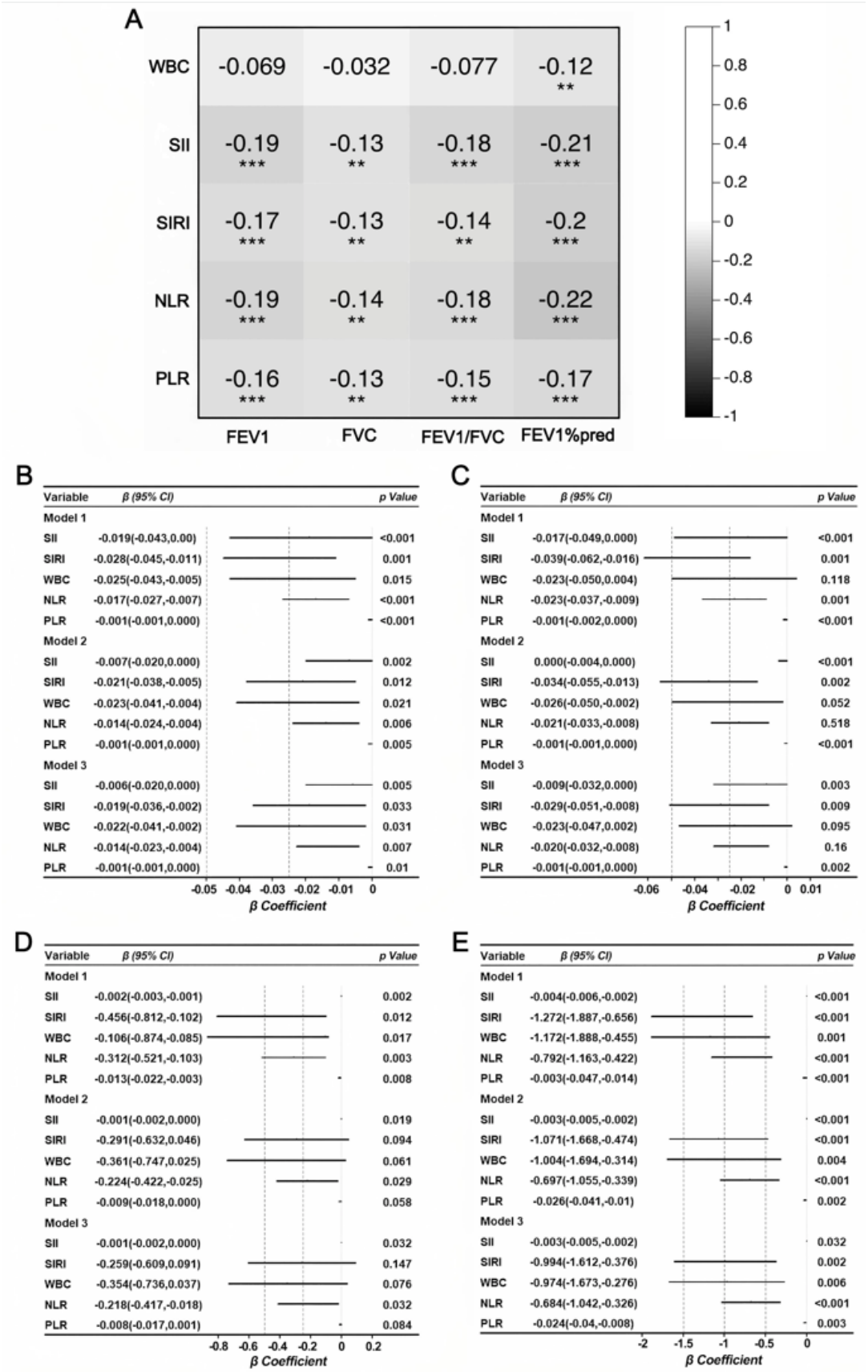

Figure 2. Association between inflammatory indicators and lung function indicators across multiple models. (A) Association between inflammatory indicators and lung function indicators, (B) Generalized linear models of inflammatory indicators and FEV1, (C) Generalized linear models of inflammatory indicators and FVC, (D) Generalized linear models of inflammatory indicators and FEV1/FVC, (E) Generalized linear models of inflammatory indicators and FEV1%pre. CRP, C-reactive protein; WBC, white blood cell; PLR, Platelet-to-Lymphocyte ratio; NLR, Neutrophil-to-Lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammatory response syndrome; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; FEV1/FVC, the ratio of forced expiratory volume in 1 s and forced vital capacity. Model 1, no adjustment; Model 2, adjusted for age, gender, marital status, residence, career, smoking, BMI; Model 3, adjusted for age, gender, marital status, residence, career, smoking, BMI, diabetes, hyperlipidemia, hypertension. Color intensity indicates the strength of correlation. *p< 0.05, **p < 0.01, ***p < 0.001.

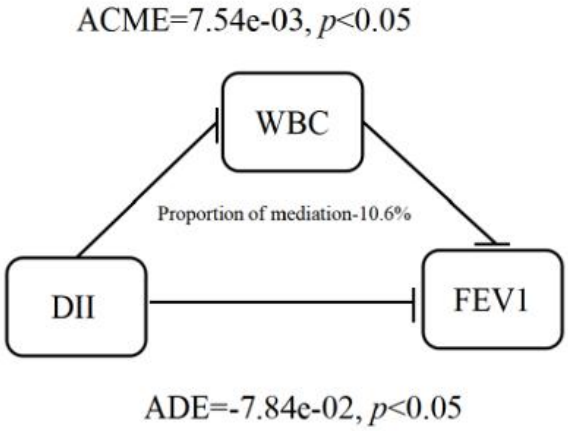

Figure 3. Mediation effects of WBC on the associations of DII with lung function parameters. Mediation effect of WBC on the associations of DII andFEV1. ACME refers to the indirect effect, ADE refers to the direct effect, and the mediation percentage represents the proportion of the indirect effect to the total effect (sum of indirect and direct effects)

involves the release of proteases by activated inflammatory cells, which may contribute to parenchymal destruction, alveolar damage, airspace enlargement, and emphysema development under conditions of protease–antiprotease imbalance.[46] The SII, integrating platelet, neutrophil, and lymphocyte counts, provides a comprehensive reflection of systemic immune-inflammatory status.[18] Elevated SII has previously been linked to COPD severity.[47-49] Previous studies support a significant correlation between SII and lung function,[50] including negative associations with FEV1/FVC%.[51] Our results further substantiate the utility of SII, WBC and related hematologic indices as accessible markers reflecting inflammatory burden in COPD.

Inflammation is a well-established mechanism contributing to lung dysfunction.8 Dietary intake plays a modulatory role, with various nutrients demonstrating anti-inflammatory (e.g., vitamin D, omega-3 fatty acids) or pro-inflammatory (e.g., saturated fatty acids) properties that have been linked to lung health.[52] The DII is a validated tool developed to quantify the overall inflammatory potential of an individual's diet by integrating intakes of a wide range of nutrients and food components with established inflammatory effects. In this study, the median DII score among AECOPD patients was 2.81, indicating a generally pro-inflammatory dietary pattern. This finding aligns with previous reports, including one study of early COPD patients showing a median DII of 3.8232 and another reporting significantly higher DII scores in COPD subjects (0.43 ± 1.81) compared to non-COPD controls (-0.19 ± 1.79).31 Among the DII food parameters, nutrients mainly derived from fruits and vegetables (such as vitamins A, C, D, E, β-carotene, polyphenols and fibre) exhibit anti-inflammatory and antioxidant effects. Anti-inflammatory dietary ingredients have antioxidant properties that can boost the immune system, fight viruses, and improve lung function.[53] In contrast, saturated fatty acids (SFAs), trans-fats, cholesterol, and omega-6 polyunsaturated fatty acids (n-6 PUFAs) are recognized as pro-inflammatory components that elevate the DII score.[54,55] Accumulating evidence supports a strong association between higher DII scores and COPD risk. A cross-sectional study of 3,962 adults found a significant positive association between DII and early COPD, as well as an inverse correlation with lung function.[32] Previous cross-sectional studies also have shown that an increased DII was associated with reduced lung function parameters, including FEV1 and FVC, among individuals with PRISm.[35] These observations suggest that a pro-inflammatory diet may increase susceptibility to early COPD and accelerate lung function decline. Consistent with these findings, our study demonstrated that in AECOPD patients, higher DII scores were significantly associated with lower FEV1 and FVC levels. Each one-unit increase in DII corresponded to a reduction of 0.053 L in FEV1 and 0.078 L in FVC. This dose-response relationship is further supported by a study of healthy older adults (≥65 years), in which individuals in the highest DII category exhibited reductions of 0.15 L in FEV1 and 0.25 L in FVC compared to those in the lowest category.[56] Collectively, these results indicate that a pro-inflammatory diet, as reflected by an elevated DII, is associated with progressive lung function decline, which may in turn contribute to the development and progression of AECOPD over time.

In previous study, DII scores exhibit positive correlations with established inflammatory mediators, including IL-1β, IL-6, TNF-α, and CRP.[28] Furthermore, one study highlighted that the association between DII and systemic inflammatory markers, such as WBC and CRP, was more pronounced in COPD patients compared to non-COPD subjects.[23] It is noteworthy that our study identified a paradoxical association between a higher DII and lower levels of WBC and SII. This finding contradicts the conventional paradigm where pro-inflammatory diets elevate systemic inflammatory markers. We postulate that this inverse relationship may be primarily driven by diet-induced malnutrition and immunosuppression. A chronically pro-inflammatory dietary pattern, typically characterized by poor nutrient density, can impair bone marrow function and leukocyte production, leading to cytopenias despite an ongoing inflammatory stimulus at a molecular level.[57] In our study, although there was no difference in the DII tertiles of Hs-CRP, this does not imply that it may not indicate less inflammation. While diet can modulate chronic, low-grade inflammation, Hs-CRP levels are also

exquisitely sensitive to acute non-dietary stimuli (e.g., minor infections, tissue injury, stress) and metabolic factors (e.g., obesity, insulin resistance).[58] This high background variability can obscure the specific signal from dietary patterns in observational, cross-sectional studies, especially if the dietary effect is subtle relative to other influences.[59]

Importantly, our mediation analysis identified WBC as a significant partial mediator in the association between DII and FEV1 (ACME = $7.54e^{-03}$, p <0.05), accounting for -10.6% of the total effect. This finding suggests that diet-induced systemic inflammation, as reflected by the DII, may partly impair lung function through pathways involving WBC regulation. However, the observed inverse correlation between higher DII and lower WBC in our study (participants in the highest DII tertile had lower WBC levels) appears paradoxical at first glance, as a pro-inflammatory diet might be expected to elevate WBC. This phenomenon may be explained by several interconnected mechanisms related to chronic disease states. First, chronic low-grade inflammation induced by a long-term pro-inflammatory diet could lead to immune cell exhaustion or functional suppression, resulting in reduced WBC counts despite ongoing inflammatory stress.[60] Second, pro-inflammatory diets are often deficient in essential nutrients (e.g., antioxidants, B vitamins) crucial for hematopoiesis, potentially impairing bone marrow function and leukocyte production. The high DII diet is associated with bile acid metabolism disorders and changes in the liver transcriptome, possibly indirectly affecting the hematopoietic microenvironment and resulting in a decrease in white blood cell production.[61] Third, metabolic disturbances (e.g., insulin resistance) commonly associated with poor diets may alter cytokine profiles and disrupt immune regulation, further contributing to leukopenia.[62] Lastly, in AECOPD patients, factors such as disease severity, anorexia, reduced dietary variety, and concurrent medical treatments might synergistically drive a state where a high DII coexists with lowered WBC, reflecting an advanced or dysregulated disease phase rather than a simple acute inflammatory response.[63]

Evidence from nutritional epidemiology supports the role of diet in modulating inflammation and lung health. Higher intake of fruits and vegetables, which are the components associated with lower DII scores, has been consistently linked to reduced inflammation, lower risk of COPD,[52-54] and improved lung function.[55,56,65,66] These findings underscore the importance of dietary quality in managing AECOPD, as improving dietary patterns may help ameliorate systemic inflammation, preserve lung function, and delay disease progression. A recent prospective cohort study conducted in China reported that adherence to a "balanced dietary pattern", which was characterized by high consumption of fresh fruits and protein-rich foods such as soy products, meat, poultry, fish, eggs, and dairy, was associated with a significantly reduced risk of COPD.[67] Nonetheless, individuals with COPD often consume diets deficient in fruits and vegetables,[68] a pattern correlated with poorer lung function and increased COPD risk.[69] As a modifiable risk factor, diet represents a promising target for reducing the disease burden of AECOPD.[70] In summary, this study indicates that the dietary pattern prevalent among AECOPD patients is predominantly pro-inflammatory. Importantly, this pro-inflammatory dietary profile was correlated with poorer lung function, which in turn was associated with elevated systemic inflammatory markers. These findings highlight the potential for dietary interventions aimed at reducing inflammatory burden in AECOPD patients, particularly during acute exacerbations.

However, this study still has several limitations. First, due to its cross-sectional design, the temporal sequence and causal relationships between the DII, nutritional status, dietary intake, inflammatory markers, and lung function in AECOPD patients cannot be established. Second, dietary data were collected using a single 24-hour dietary recall, which may be subject to recall bias and may not fully represent participants' habitual intake. Third, although we adjusted for a range of potential confounders, including age, gender, marital status, residence, occupation, smoking status, BMI, and comorbidities such as diabetes, hyperlipidemia, and hypertension, the influence of unmeasured or residual confounding factors cannot be entirely ruled out. Fourth, due to the cross-sectional design, the mediation analysis cannot establish causal relationships among DII, WBC, and FEV1.Therefore, future investigations employing larger prospective cohort studies or randomized controlled trials are warranted to validate these findings, elucidate the longitudinal effects of nutritional status, specific dietary components, and overall dietary patterns on clinical outcomes in AECOPD, and ultimately establish causality.

Conclusion

In summary, the diet of AECOPD patients is in a proinflammatory state. Our study suggests that a pro-inflammatory diet is associated with lower lung function in AECOPD patients, and lung function is significantly correlated with inflammatory indicators. WBC is an important indicator that plays a mediating role between DII and lung function. Therefore, from the perspective of dietary nutrition, this study provides a scientific basis for clinicians to scientifically and reasonably guide the dietary intake level of COPD patients, reduce the risk of acute attacks, and improve the quality of life.

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DISCLOSURE ON THE USE OF AI AND AI-ASSISTED TECHNOLOGIES

The authors hereby confirm that no AI-assisted technologies were used for data collection, data analysis, or the creation of images or graphical elements in this work.

CONFLICT OF INTEREST AND FUNDING DISCLOSURES

The authors declare no conflict of interest.

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