ORIGINAL RESEARCH

Increased Serum Soluble Interleukin-2 Receptor Associated with Severity of Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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Background: This study aimed to reveal the correlation between serum soluble interleukin-2 receptor (sIL-2R) and prognosis in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD).

Methods: A total of 315 patients diagnosed with AECOPD between December 2017 and June 2020 were enrolled. The patients were divided into the good and adverse groups based on the outcomes. An adverse outcome in COPD exacerbation was defined by the presence of at least one of the following: (1) death from a respiratory cause during hospitalisation or within 1 month of follow-up; (2) intensive care unit admission; (3) invasive or non-invasive mechanical ventilation; and (4) COPD-related emergency visit or readmission within 1 month of follow-up. A good outcome was considered as the absence of all the aforementioned issues. The patients underwent lung function (spirometry) assessment, and clinical and inflammatory profiles were collected. Univariate and multivariate analyses were performed to identify the correlation between serum sIL-2R concentration and other variables related to adverse outcomes of AECOPD. The receiver operating characteristic curve was used to show the predictive ability of sIL-2R for adverse outcomes of AECOPD.

Results: We enrolled 315 patients, of whom 161 and 154 had good and adverse outcomes, respectively. We demonstrated that patients with adverse outcomes of AECOPD had a higher concentration of serum sIL-2R than patients with good outcomes ($p < 0.001$). The increased serum sIL-2R was positively associated with mMRC scores ($p < 0.001$), GLOD grades ($p < 0.001$), frequent exacerbation ($p < 0.001$), and smoking ($p < 0.001$) in patients with AECOPD and negatively correlated with pulmonary function ($p < 0.001$). An elevated sIL-2R level was a predictor for the risk of adverse outcomes in AECOPD with a cut-off value of 860 U/mL.

Conclusion: Increased serum sIL-2R concentration correlated with the risk of the adverse outcomes in AECOPD, indicating that it can be a predictive factor contributing to the diagnosis and assessment of adverse outcomes in patients with AECOPD.

Keywords: chronic obstructive pulmonary disease, acute exacerbation, soluble interleukin-2 receptor, predictive factor

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Background

Chronic obstructive pulmonary disease (COPD) is characterised by persistent airflow limitation, which is ranked as a leading cause of death and disability globally.[1] Acute exacerbation of COPD (AECOPD), punctuating the natural history of COPD, is a major clinical risk factor for increased morbidity and mortality rates in the future.[2,3] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has

stated that the prevention and treatment of exacerbations should be a key goal in COPD management.[4]

Severity, evolutionary process, and results of AECOPD may differ significantly between patients. Several patients have favourable outcomes, in whom the disease can be controlled within a short period, while others may be hospitalised for long periods or may even die. Therefore, the identification of risk factors for unfavourable outcomes could help in distinguishing patients who require more intense management, consequently reducing disability and mortality rates of COPD and improving the patients' quality of life.

Although several clinical factors associated with frequent AECOPD have been identified,[5] the reasons for adverse outcomes in patients with AECOPD remain unclear. This is because COPD is a complex and heterogeneous disease. In addition to causing local pulmonary inflammation, COPD is a systemic inflammatory disease involving a variety of inflammatory factors.[6,7] Several studies concerning these inflammatory factors provided various novel ideas regarding the pathogenesis of AECOPD; however, to date, there are no objective biomarkers that can predict the disease activity or adverse outcomes in AECOPD.

Soluble interleukin-2 receptor (sIL-2R) are present at low levels in the sera of healthy individuals, but are further increased in patients with infections, inflammation and autoimmune diseases, so it has been reported and primarily considered as effective markers for measuring disease activity. However, there are few concerns related to the correlation between sIL-2R and COPD exacerbation. This study aimed to determine whether changes in serum sIL-2R concentrations are related to the severity of disease and may be a predictive factor of disease exacerbations, helping clinicians to distinguish the risk of AECOPD and develop targeted interventions.

Methods
Ethics Statement
The study protocol was approved by the Human Research Ethics Committee of the Xinhua Hospital affiliated to Shanghai Jiaotong University Medical College (XHEC-C-2017-085). Written informed consent was obtained from each participant. This study was conducted in accordance with the Declaration of Helsinki.

Study Subjects
A total of 315 patients diagnosed with AECOPD between December 2017 and June 2020 from the emergency department or outpatient department of Xinhua Hospital in Shanghai were enrolled, of whom 161 and 154 had good and adverse outcomes, respectively. All the patients enrolled in this study met the diagnostic criteria of the GOLD:[4] (a) symptoms of cough and dyspnoea; (b) individual susceptibility factors and environmental factors; and (c) forced expiratory volume in the first second/forced vital capacity (FEV_1/FVC) < 70% after inhalation of 400 µg of salbutamol. According to the GOLD document, AECOPD was defined as a recent worsening of respiratory symptoms that required a change in the domiciliary therapy, with the need for hospitalisation based on the severity of COPD exacerbation and presence of indicators.

The exclusion criteria were as follows: documented history of other concomitant chronic respiratory diseases, such as asthma and interstitial lung disease, and pneumonia, tuberculosis, lung cancer, pulmonary embolism, or acute heart failure identified by clinical signs, chest radiograph, or computed tomography at admission.

All patients discharged from our institution following treatment of AECOPD were scheduled for a follow-up visit after 1 month. For reasons concerning the statistical power, we conducted our analysis using data from the first exacerbation in each patient, despite the possibility of more than one admission during the observation period.

An adverse outcome in COPD exacerbation was defined by the presence of at least one of the following: death from a respiratory cause during hospitalisation or within 1 month of follow-up; intensive care unit admission; invasive or non-invasive mechanical ventilation; and COPD-related emergency visit or readmission within 1 month of follow-up. A good outcome was considered as the absence of all the aforementioned issues. The sample number and division are detailed in Figure 1.

Clinical Characterisation
Demographic and clinical data, including laboratory findings, were collected within 3 h of admission. The data included the patients' demographic variables, body mass index, smoking habit (former smokers were defined as those who stopped smoking for ≥6 months prior to their participation in this study), and comorbidities (using the Charlson index).[8] Cigarette smoking history was collected as the smoking index (SI = pack per day × smoking years). Furthermore, data on the number of AECOPD in the preceding year was collected. Frequent exacerbation was defined as ≥2 exacerbations per year. Dyspnoea of patients
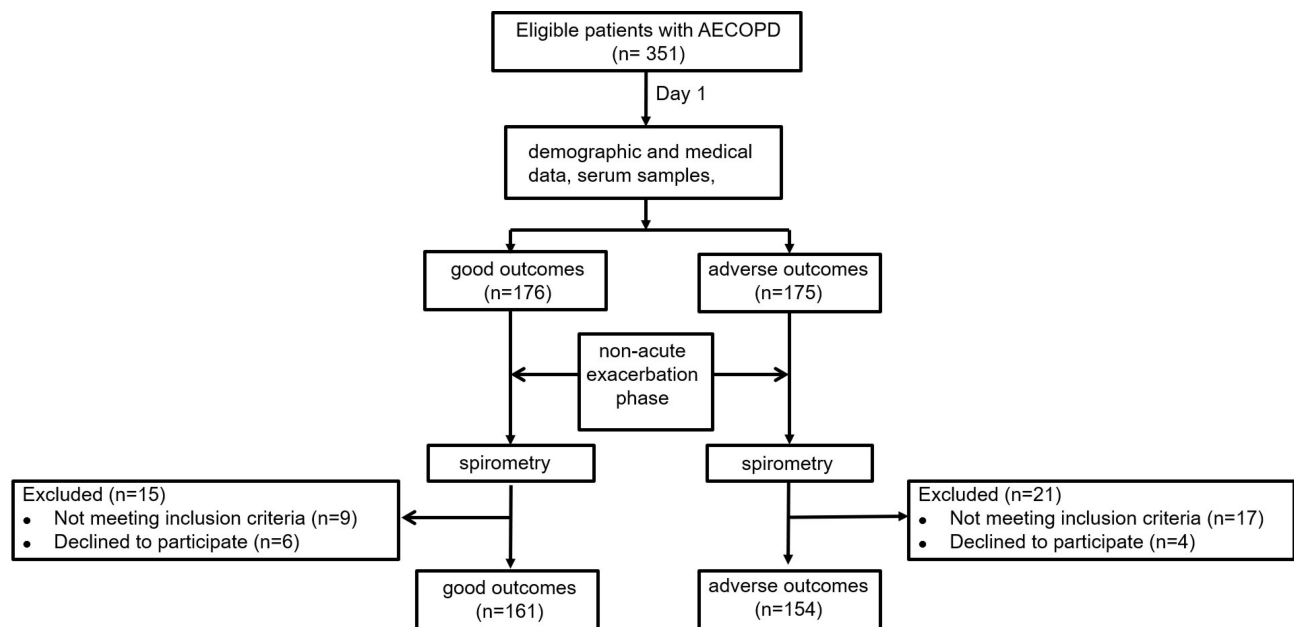
Figure 1 Flow diagram of patients with AECOPD.

was evaluated by the modified British Medical Research Council (mMRC) scale.

Spirometry Measurements

Spirometry measurement was based on the American Thoracic Society/European Respiratory Association guidelines.[9] Data were collected with 6 months prior to enrolment (during the stable phase) or 3 months after AECOPD. Classification of COPD severity followed the GOLD diagnostic criteria.[4]

Sample Collection

Venous blood samples were obtained from the cubital vein of all the subjects within 3 hours of admission and were centrifuged immediately at 3000 rpm for 15 min at 4°C. Subsequently, the plasma and serum samples were stored at −80°C until analysis. The concentration of serum sIL-2R was analysed using a chemiluminescence immunoassay (Siemens, Erlangen, Germany). All the samples from each patient were measured in the same assay to reduce inter-assay variability.

Statistical Analysis

We calculated the frequency and percentage for categorical variables and mean ± standard deviation for normal continuous variables or median (1st and 3rd quartiles) for non-normal distributed continuous variables. To explore the possible relationship of sIL-2R with AECOPD, we classified the participants into three groups according to the tertile of

sIL-2R. Categorical variables in different sIL-2R groups were compared by using the chi-square test or Fisher's exact test. Continuous variables were compared using one-way analysis of variance. Comparisons of parameters with skewed distributions used the Wilcoxon test. Pearson's correlation coefficient was used to analyse the correlation between serum sIL-2R concentration and other variables related with adverse outcomes of AECOPD. Multivariable logistic regression models were used to calculate the odds ratio (OR) (95% confidence interval [CI]) of AECOPD after adjusted for potential confounders. We conducted three models: crude model, model adjusted for age, gender, smoking status, BMI and CRP; and model adjusted for age, gender, smoking status, BMI, CRP, history of congestive heart disease, chronic kidney failure, hypertension and diabetes. The receiver operating characteristic (ROC) curve was used to show the predictive ability of sIL-2R for adverse outcomes of AECOPD. SAS software (version 9.4; SAS Institute) was used for data analysis. *P*-value < 0.05 for two-tailed tests was considered statistically significant.

Results

Comparison of Patients with Good and Adverse Outcomes in Terms of Clinical and Laboratory Variables

Three hundred and fifteen patients, with an average age of 71.82 ± 8.44 years, diagnosed with AECOPD between

Table 1 Baseline Clinical and Laboratory Characteristics of Study Population

Characteristics	Total Population n=315	Good Outcomes n=161	Adverse Outcomes n= 154	P-value
Demographics				
Male, n (%)	269 (85.4)	142 (88.2)	127 (82.47)	0.1499
Age, year	71.82 ± 8.44	71.11 ± 8.82	72.56 ± 7.98	0.1251
BMI, kg/m^2	22.49 ± 3.16	22.67 ± 3.14	22.29 ± 3.17	0.2864
Smoking status, n (%)				0.6444
Current smoker	133 (42.22)	70 (43.48)	63 (40.91)	
Former smoker	182 (57.78)	91 (56.52)	91 (59.09)	
Smoking index, pack-years	41.04 ± 24.18	37.26 ± 23.96	44.98 ± 23.85	0.0044
Clinical variables				
mMRC, n (%)				< 0.0001
mMRC 0–1, n (%)	64 (20.32)	56 (34.78)	8 (5.19)	
mMRC 2, n (%)	67 (21.27)	47 (29.19)	20 (12.99)	
mMRC 3–4, n (%)	184 (58.41)	58 (36.02)	126 (81.82)	
FEV$_1$, %pred	42.17 ± 17.33	50.52 ± 17.62	33.44 ± 11.89	< 0.0001
FEV$_1$/FVC	51.6 ± 10.52	55.54 ± 10.11	47.49 ± 9.32	< 0.0001
GOLD 2017 stages, n (%)				< 0.0001
GOLD 1–2	98 (31.11)	84 (52.17)	14 (9.09)	
GOLD 3–4	217 (68.89)	77 (47.83)	140 (90.91)	
Cerebrovascular disease, n (%)	16 (5.08)	4 (2.48)	12 (7.79)	0.0590
Chronic kidney failure, n (%)	17 (5.4)	5 (3.11)	12 (7.79)	0.0657
Hypertension, n (%)	137 (43.49)	62 (38.51)	75 (48.7)	0.0682
Diabetes, n (%)	51 (16.19)	23 (14.29)	28 (18.18)	0.3481
Congestive heart disease, n (%)	132 (41.9)	53 (32.92)	79 (51.3)	0.0010
Frequent COPD exacerbation, n (%)	156 (49.52)	49 (30.43)	107 (69.48)	< 0.0001
Laboratory variables				
pH	7.38 ± 0.06	7.41 ± 0.04	7.36 ± 0.07	< 0.0001
PaCO$_2$, mmHg	54.53 ± 19.7	42.19 ± 7.47	67.44 ± 20.24	< 0.0001
PaO$_2$/FiO$_2$	239.20 ± 54.51	256.95 ± 44.44	220.65 ± 57.91	< 0.0001
WBC, 10^9/L	8.3 (6.3, 11.3)	8.2 (6, 11.1)	8.6 (6.8, 11.3)	0.1916
CRP, mg/L	31 (8, 85)	28 (8, 79)	37.5 (9, 88)	0.1591
PCT, ng/mL	0.06 (0.04, 0.14)	0.06 (0.04, 0.1)	0.08 (0.05, 0.25)	0.0085
ESR, mm/h	34 (17, 57)	33 (17, 54)	35 (18, 62)	0.4551
IL-8, pg/mL	28.4 (16.5, 53.1)	23.5 (14, 48)	33.5 (20, 53.9)	0.0036
IL-6, pg/mL	14.59 (6.91, 24.17)	12.5 (5, 19.5)	17.36 (8.9, 27.2)	0.0006
IL-10, pg/mL	5 (5, 5.5)	5(5,5.0)	5(5,6.2)	0.0066

(*Continued*)

Table 1 (Continued).

Characteristics	Total Population n=315	Good Outcomes n=161	Adverse Outcomes n= 154	P-value
TNF-α,pg/mL	18.4(11.5,32.4)	16.7(9.86,28.7)	22.8(14.2,35.7)	0.001
sIL-2R, U/mL	813(550,1096)	688 (472, 886)	927 (679, 1279)	< 0.0001

Note: Data are shown as n (%), mean ± standard deviation (SD) or median (interquartile range).
Abbreviations: GOLD, Global Initiative for Chronic Obstructive Lung Disease; COPD, chronic obstructive pulmonary disease; BMI, body mass index; Smoking index, number of cigarettes smoked per day × years of smoking; mMRC score, modified Medical Research Council dyspnoea score; FEV_1, forced expiratory volume in 1 second; FEV_1/FVC, forced expiratory volume in 1 second/force Vital Capacity; WBC, white blood cells; CRP, C-reactive protein; PCT, procalcitonin; ESR, erythrocyte sedimentation rate; IL, interleukin; TNF-α,tumor necrosis factor-α; sIL-2R, soluble interleukin-2 receptor.

December 2017 and June 2020 were recruited to the observation group, of whom 161 and 154 had good and adverse outcomes, respectively. Patients with adverse outcomes had a higher SI, more severe dyspnoea, significantly lower FEV_1% pred (%pred) and FEV_1/FVC ratio, higher GOLD stage, and more frequent exacerbations within the previous year than patients with good outcomes (Table 1).

As shown in Table 1, the signs of respiratory failure at admission in terms of lower pH, lower ratio of partial arterial oxygen pressure to the fraction of inspired oxygen (PaO_2/FiO_2), and higher partial arterial carbon dioxide pressure ($PaCO_2$) were associated with adverse outcomes ($p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively). Serum procalcitonin ($p = 0.0085$), interleukin-6 (IL-6) ($p = 0.0006$), interleukin-8 (IL-8) ($p = 0.0036$), interleukin-10 (IL-10) ($p = 0.0066$), tumour necrosis factor-α (TNF-α) ($p = 0.001$), and sIL-2R ($p < 0.0001$) were higher in the adverse outcomes group than in the good outcomes group.

Correlation of Serum sIL-2R with mMRC Score

Patients were divided into three groups according to the tertile of the serum concentration of sIL-2R at admission: group 1, < 619 U/mL; group 2, 619–947 U/mL; and group 3, > 948 U/mL. As shown in Table 2, in the group with a high concentration of sIL-2R, the number of patients with an mMRC score of 3–4 was more than those with an mMRC score of 0–1 and 2 ($p = 0.0002$). Subgroup analysis (Table 3) showed that the risk of adverse outcomes in patients with AECOPD increased gradually with the increase of sIL-2R concentration in either the mMRC score of 0–1, 2, or 3–4 group. By adjusting the analysis, the statistical results showed that serum sIL-2R concentration was more closely associated with adverse outcomes of AECOPD in the mMRC score of 3–4 group. In the mMRC score of 0–1, 2, and 3–4 groups, serum sIL-2R

concentration was higher in patients with adverse outcomes than in those with good outcomes (Table 4, Figure 2A).

Correlation of Serum sIL-2R with GOLD Stages

Subgroup analysis (Table 3) showed that the risk of adverse outcomes in patients with AECOPD increased gradually with the increase of sIL-2R concentration in either the GOLD 1–2 or GOLD 3–4 group. By adjusting the analysis, the statistical results showed that concentration of serum sIL-2R was more closely associated with adverse outcomes of AECOPD in the GOLD 1–2 group. In both GOLD 1–2 and GOLD 3–4 groups, the serum sIL-2R concentration was higher in patients with adverse outcomes than in those with good outcomes (Table 4, Figure 2B).

Correlation of Serum sIL-2R with Frequent Exacerbation

As shown in Table 3, the risk of adverse outcomes of AECOPD increased gradually with the increase of sIL-2R concentration in either the non-frequent or frequent exacerbation group. By adjusting analysis, the statistical results showed that serum sIL-2R concentration was more closely associated with adverse outcomes of AECOPD in the frequent exacerbation group. In both the frequent and non-frequent exacerbation groups, the concentration of sIL-2R was higher in patients with adverse outcomes than in those with good outcomes (Table 4, Figure 2C).

Correlation of Serum sIL-2R with Smoking Status

As shown in Table 3, the risk of adverse outcomes in patients with AECOPD increased gradually with the increase of sIL-2R concentration in patients in the

Table 2 Clinical and Laboratory Characteristics According to the Tertile of sIL-2R

Characteristics	sIL-2R			P-value
	Tertile 1 < 619 U/mL	Tertile 2619–947 U/mL	Tertile 3 ≥ 948 U/mL	
No. of participants	103	104	108	
Demographics				
Male, n (%)	91 (88.35)	86 (82.69)	92 (85.19)	0.5244
Age, year	68.8 ± 7.63	72.48 ± 8.6	74.06 ± 8.24	**< 0.0001**
BMI, kg/m^2	22.96 ± 3.47	22.49 ± 3.01	22.04 ± 2.93	0.1041
Smoking status, n (%)				0.0919
Current smoker	48 (46.6)	47 (45.19)	38 (35.19)	
Former smoker	55 (53.4)	57 (54.81)	70 (64.81)	
Smoking index, pack-years	42.39 ± 25.6	39.31 ± 19.72	41.41 ± 26.68	0.6455
Clinical variables				
mMRC, n (%)				**0.0002**
mMRC 0–1, n (%)	30 (29.13)	22 (21.15)	12 (11.11)	
mMRC 2, n (%)	24 (23.3)	24 (23.08)	19 (17.59)	
mMRC 3–4, n (%)	49 (47.57)	58 (55.77)	77 (71.3)	
FEV$_1$, %pred	45.38 ± 18.72	42.09 ± 16.97	39.19 ± 15.84	**0.0340**
FEV$_1$/FVC	52.84 ± 10.77	52.84 ± 10.57	49.23 ± 9.89	**0.0147**
GOLD 2017 stages, n (%)				0.2619
GOLD 1–2	34 (33.01)	36 (34.62)	28 (25.93)	
GOLD 3–4	69 (66.99)	68 (65.38)	80 (74.07)	
Cerebrovascular disease, n (%)	3 (2.91)	4 (3.85)	9 (8.33)	0.0720
Chronic kidney failure, n (%)	3 (2.91)	3 (2.88)	11 (10.19)	**0.0187**
Hypertension, n (%)	42 (40.78)	41 (39.42)	54 (50)	0.1730
Diabetes, n (%)	15 (14.56)	17 (16.35)	19 (17.59)	0.5516
Congestive heart disease, n (%)	27 (26.21)	48 (46.15)	57 (52.78)	**0.0001**
Frequent COPD exacerbation, n (%)	48 (46.6)	47 (45.19)	61 (56.48)	0.1171
Laboratory variables				
pH	7.38 ± 0.05	7.39 ± 0.06	7.37 ± 0.08	0.1194
PaCO$_2$, mmHg	52.25 ± 18.12	53.02 ± 20.32	58.17 ± 20.19	0.0579
PaO$_2$/FiO$_2$	241.61 ± 50.31	239.21 ± 54.24	236.9 ± 58.84	0.8222
WBC, 10^9/L	7.7 (5.9, 9.6)	8 (6.2, 10.85)	10 (7.2, 12.4)	**0.0005**
CRP, mg/L	9 (5, 29)	46.5 (10, 87)	63.5 (26, 103)	**< 0.0001**
PCT, ng/mL	0.05 (0.03, 0.07)	0.07 (0.04, 0.15)	0.09 (0.05, 0.27)	**< 0.0001**
ESR, mm/h	24 (11, 40)	36 (18, 56.5)	41 (23, 66.5)	**< 0.0001**
IL-8, pg/mL	23.2 (12.6, 53.7)	28.5 (16.95, 48.1)	30.4 (19.6, 60)	0.1195
IL-6, pg/mL	5.88 (2.94, 10.5)	16.14 (10.6, 22.4)	23.93 (15.99, 33.3)	**< 0.0001**
IL-10, pg/mL	5 (5, 5)	5 (5, 5.51)	5 (5, 7.67)	**< 0.0001**
TNF-α, pg/mL	14.3 (7.98, 29.1)	16.5 (11.0, 27.8)	21.55 (16.3, 33.45)	**< 0.0001**

Notes: Data are shown as n (%), mean ± standard deviation (SD) or median (interquartile range). Bold font indicates P<0.05.
Abbreviations: GOLD, Global Initiative for Chronic Obstructive Lung Disease; COPD, chronic obstructive pulmonary disease; BMI, body mass index; Smoking index, number of cigarettes smoked per day × years of smoking; mMRC score, modified Medical Research Council dyspnoea score; FEV$_1$, forced expiratory volume in 1 second; FEV$_1$/FVC, forced expiratory volume in 1 second/force Vital Capacity; WBC, white blood cells; CRP, C-reactive protein; PCT, procalcitonin; ESR, erythrocyte sedimentation rate; IL, interleukin; TNF-α, tumor necrosis factor-α; sIL-2R, soluble interleukin-2 receptor.

Table 3 Association Between sIL-2R and Adverse Outcomes in Overall Patients with AECOPD and Subgroups Stratified by Related Factors

Characteristics or Subgroups	OR of Adverse Outcomes (95% CI)	Adjusted OR of Adverse Outcomes (95% CI)*	Adjusted OR of Adverse Outcomes (95% CI)#	P-value for Trend
Overall patients				
sIL-2R, per 100U/mL	1.21 (1.13, 1.30)	1.24 (1.15, 1.34)	1.22 (1.13, 1.32)	
Tertile 1	Referent	Referent	Referent	0.0001
Tertile 2	1.90 (1.08, 3.36)	2.02 (1.09, 3.72)	1.94 (1.04, 3.63)	
Tertile 3	4.83 (2.70, 8.65)	5.24 (2.70, 10.16)	4.73 (2.41, 9.27)	
mMCR subgroups				
Patients with mMCR 0–1				
sIL-2R, per 100U/mL	1.26 (1.04, 1.54)	1.40 (1.07, 1.83)	1.43 (1.07, 1.90)	
Tertile 1	Referent	Referent	Referent	0.0193
Tertile 2	1.40 (0.18, 10.79)	1.27 (0.33, 4.89)	2.13 (0.97, 4.70)	
Tertile 3	7.00 (1.08, 45.44)	3.42 (0.90, 12.99)	3.66 (1.67, 8.03)	
Patients with mMCR 2				
sIL-2R, per 100U/mL	1.12 (0.99, 1.27)	1.17 (0.99, 1.39)	1.21 (1.00, 1.46)	
Tertile 1	Referent	Referent	Referent	0.0178
Tertile 2	1.25 (0.27, 5.87)	3.44 (1.35, 8.79)	2.20 (0.18, 26.48)	
Tertile 3	5.50 (0.90, 33.81)	5.89 (2.24, 15.51)	19.43 (1.35, 279.79)	
Patients with mMCR 3–4				
sIL-2R, per 100U/mL	1.21 (1.10, 1.34)	1.31 (1.16, 1.49)	1.30 (1.14, 1.48)	
Tertile 1	Referent	Referent	Referent	0.0124
Tertile 2	3.38 (1.28, 8.96)	15.23 (0.32, 726.91)	0.73 (0.11, 4.72)	
Tertile 3	5.33 (1.98, 14.41)	90.28 (1.45, 1000)	21.03 (1.68, 263.65)	
Patients with GOLD stage 1–2				
sIL-2R, per 100U/mL	1.24 (1.07, 1.43)	1.30 (1.09, 1.55)	1.30 (1.06, 1.60)	
Tertile 1	Referent	Referent	Referent	0.0102
Tertile 2	5.32 (0.59, 48.13)	4.85 (0.47, 50.48)	3.46 (0.28, 42.13)	
Tertile 3	13.20 (1.54, 113.48)	17.28 (1.62, 184.05)	19.21 (1.42, 260.55)	
Patients with GOLD stage 3–4				
sIL-2R, per 100U/mL	1.29 (1.17, 1.43)	1.33 (1.19, 1.49)	1.33 (1.18, 1.49)	
Tertile 1	Referent	Referent	Referent	0.0043
Tertile 2	2.11 (1.06, 4.18)	2.30 (1.09, 4.81)	2.41 (1.13, 5.11)	
Tertile 3	5.78 (2.74, 12.19)	6.10 (2.63, 14.18)	5.88 (2.50, 13.85)	
Non-Frequent AECOPD patients				
sIL-2R, per 100U/mL	1.21 (1.09, 1.33)	1.24 (1.11, 1.38)	1.22 (1.09, 1.37)	
Tertile 1	Referent	Referent	Referent	0.0244
Tertile 2	2.24 (0.87, 5.79)	2.42 (0.87, 6.73)	2.23 (0.78, 6.37)	
Tertile 3	5.51 (2.14, 14.16)	6.27 (2.20, 17.84)	4.86 (1.62, 14.53)	
Frequent AECOPD patients				

(Continued)

Table 3 (Continued).

Characteristics or Subgroups	OR of Adverse Outcomes (95% CI)	Adjusted OR of Adverse Outcomes (95% CI)*	Adjusted OR of Adverse Outcomes (95% CI)#	P-value for Trend
sIL-2R, per 100U/mL	1.23 (1.11, 1.37)	1.39 (1.19, 1.62)	1.43 (1.20, 1.69)	
Tertile 1	Referent	Referent	Referent	0.0015
Tertile 2	2.13 (0.93, 4.91)	3.43 (1.26, 9.29)	4.07 (1.42, 11.66)	
Tertile 3	5.10 (2.11, 12.33)	9.69 (2.95, 31.83)	12.90 (3.48, 47.72)	
Former smoker				
sIL-2R, per 100U/mL	1.17 (1.08, 1.26)	1.20 (1.09, 1.31)	1.18 (1.08, 1.30)	
Tertile 1	Referent	Referent	Referent	0.0077
Tertile 2	1.98 (0.92, 4.27)	2.40 (1.03, 5.55)	2.41 (1.02, 5.73)	
Tertile 3	3.70 (1.76, 7.80)	4.42 (1.85, 10.53)	4.23 (1.74, 10.28)	
Current smoker				
sIL-2R, per 100U/mL	1.31 (1.16, 1.49)	1.34 (1.16, 1.54)	1.36 (1.16, 1.60)	
Tertile 1	Referent	Referent	Referent	0.0034
Tertile 2	1.80 (0.77, 4.21)	1.73 (0.67, 4.43)	1.57 (0.57, 4.31)	
Tertile 3	7.83 (2.96, 20.7)	8.51 (2.83, 25.6)	7.29 (2.25, 23.62)	
FEV_1, %pred > 40				
sIL-2R, per 100U/mL	1.19 (1.08, 1.32)	1.24 (1.10, 1.39)	1.24 (1.10, 1.40)	
Tertile 1	Referent	Referent	Referent	0.0020
Tertile 2	2.41 (0.87, 6.64)	2.73 (0.89, 8.36)	1.59 (0.62, 4.07)	
Tertile 3	4.57 (1.7, 12.33)	5.25 (1.68, 16.43)	6.63 (2.03, 21.65)	
FEV_1, %pred ≤ 40				
sIL-2R, per 100U/mL	1.3 (1.15, 1.46)	1.32 (1.14, 1.52)	1.32 (1.13, 1.53)	
Tertile 1	Referent	Referent	Referent	0.0363
Tertile 2	1.70 (0.77, 3.75)	1.60 (0.65, 3.90)	1.59 (0.62, 4.07)	
Tertile 3	7.36 (2.79, 19.39)	6.84 (2.23, 21.03)	6.63 (2.03, 21.65)	
FEV_1/FVC > 45				
sIL-2R, per 100U/mL	1.16 (1.08, 1.26)	1.18 (1.08, 1.28)	1.17 (1.08, 1.28)	
Tertile 1	Referent	Referent	Referent	0.0064
Tertile 2	1.83 (0.92, 3.63)	1.94 (0.91, 4.13)	1.84 (0.86, 3.95)	
Tertile 3	3.27 (1.61, 6.62)	3.32 (1.49, 7.36)	3.13 (1.39, 7.03)	
FEV_1/FVC ≤ 45				
sIL-2R, per 100U/mL	1.38 (1.17, 1.62)	1.49 (1.21, 1.83)	1.53 (1.20, 1.95)	
Tertile 1	Referent	Referent	Referent	0.0113
Tertile 2	2.25 (0.76, 6.65)	2.49 (0.75, 8.26)	3.08 (0.71, 13.3)	
Tertile 3	12.2 (3.39, 43.8)	19.5 (3.94, 97.1)	23.0 (3.47, 152)	

Notes: *Adjusted for age, gender, smoking status, BMI and CRP; #Adjusted for age, gender, smoking status, BMI, CRP, history of congestive heart disease, chronic kidney failure, hypertension and diabetes.
Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval; sIL-2R, soluble interleukin-2 receptor; mMRC score, modified Medical Research Council dyspnoea score; GOLD, Global Initiative for Chronic Obstructive Lung Disease; FEV_1, forced expiratory volume in 1 second; FEV_1/FVC, forced expiratory volume in 1 second/force Vital Capacity.

current or former smoker groups. By adjusting the analysis, the statistical results showed that concentration of serum sIL-2R was more closely associated with adverse outcomes of AECOPD in patients in the current smoker group. In both the current and former smoker groups, the concentration of serum sIL-2R was higher in patients with adverse outcomes than in those with good outcomes (Table 4, Figure 2D).

Table 4 Relationship Between Clinical Parameters and the Serum Concentration of sIL-2R in Each Group

Variable	Good Outcomes Group	Adverse Outcomes Group	P-value
mMRC 0–1	648.26 ± 247.41	869.32 ± 321.79	< 0.05
mMRC 2	667.8 ± 241.92	902.86 ± 395.41	< 0.05
mMRC 3–4	692.17 ± 323.04	1179.49 ± 411.26 *	< 0.001
GOLD 1–2	606.48 ± 213.14	904.66 ± 414.47#	< 0.001
GOLD 3–4	784.57 ± 382.09	1126.24 ± 433.68	< 0.001
Non-Frequent AECOPD	661.14 ± 217.96	912.38 ± 389.16	< 0.05
Frequent AECOPD	720.66 ± 349.13	1090.54 ± 416.12	< 0.001
Former smoker	670.13 ± 264.72	936.63 ± 437.15	< 0.05
Current smoker	720.4 ± 308.15	1184.26 ± 424.31	< 0.001
FEV_1, %pred > 40	634.51 ± 243.9	917.71 ± 458.81	< 0.001
FEV_1, %pred ≤ 40	746.27 ± 313.62	1120.06 ± 412.73	< 0.001
FEV_1/FVC > 45	637.08 ± 217.14	872.33 ± 321.64	< 0.05
FEV_1/FVC ≤ 45	763.46 ± 362.91	1210.51 ± 427.44$	< 0.001

Notes: Data are shown as mean ± standard deviation (SD); *Serum concentration of sIL-2R was higher in patients with mMRC 3–4 than in those with mMRC 0–1 in adverse outcomes group ($P<0.05$); #Serum concentration of sIL-2R was higher in patients of adverse outcomes group than in those of good outcomes group in GOLD 1–2 ($P<0.05$); $Serum concentration of sIL-2R was higher in patients with FEV_1/FVC ≤ 45 than in those with FEV_1/FVC > 45 in adverse outcomes group ($P<0.05$).
Abbreviations: sIL-2R, soluble interleukin-2 receptor; mMRC score, modified Medical Research Council dyspnoea score; GOLD, Global Initiative for Chronic Obstructive Lung Disease; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FEV_1/FVC, forced expiratory volume in 1 second/force vital capacity.

Correlation of Serum sIL-2R with FEV_1% pred and FEV_1/FVC

Table 2 shows that with an increase in the sIL-2R concentration, the FEV_1%pred and FEV_1/FVC ratio decreased gradually ($p < 0.05$ and $p < 0.05$, respectively). Subgroup analysis (Table 3) showed that an increase in the sIL-2R concentration in both high and low FEV_1%pred groups, the risk of developing adverse outcomes of AECOPD significantly increased. Similarly, with the increase of sIL-2R concentration in both the high and low FEV_1/FVC groups, the risk of developing adverse outcomes of AECOPD significantly increased. By adjusting the analysis, the statistical results showed that concentration of serum sIL-2R was more closely associated with adverse outcomes of AECOPD in the low FEV_1%pred and low FEV_1/FVC groups.

Statistical results showed (Table 4, Figure 3A) that in both high and low FEV_1%pred groups, the serum sIL-2R concentration was higher in patients with adverse outcomes than in those with good outcomes. Additionally, in both the high and low FEV_1/FVC groups, the concentration of serum sIL-2R was higher in patients with adverse outcomes than in those with good outcomes (Table 4, Figure 3B).

Correlation of Serum sIL-2R with Other Laboratory Variables

As shown in Table 5, sIL-2R was positively correlated to $PaCO_2$, whole blood leukocyte counts (WBC), C-reactive protein (CRP), erythrocyte sedimentation rate, and IL-6, IL-10, and TNF-α levels and negatively correlated with serum pH and PaO_2/FiO_2.

Determination of Serum sIL-2R Concentration Contributes to the Differential Diagnosis of Adverse Outcomes in AECOPD

Table 3 shows that as sIL-2R concentration increased, the association with adverse outcomes of AECOPD became stronger in all the subjects (OR = 1.21; 95% CI, 1.13–1.3; $p < 0.05$). By adjusting the analysis, the serum sIL-2R concentration was still positively correlated with the adverse outcomes of AECOPD in all the subjects.

The ROC curve analysis indicated that the area under the curve (AUC) of sIL-2R to distinguish adverse outcomes in AECOPD was 0.6887 (95% CI, 0.6304–0.7470) (Figure 4). With a cut-off value of 860 U/mL, the sensitivity and specificity were 62.0% and 73.9%, respectively.

Discussion

COPD is associated with the chronic inflammation of the airways and lung parenchyma, which increases during acute exacerbations and is associated with systemic inflammation. Inflammatory biomarkers can be used to supplement clinical data and determine the health status of patients before, during, and after the occurrence of COPD exacerbation.[10,11] Over the past decade, various inflammatory biomarkers associated with COPD exacerbation have been investigated.[12–14] However, whether sIL-2R is associated with the exacerbation of COPD has not been reported. Our study found that the serum sIL-2R concentration in patients with adverse outcomes of AECOPD was higher than in those with good outcome,
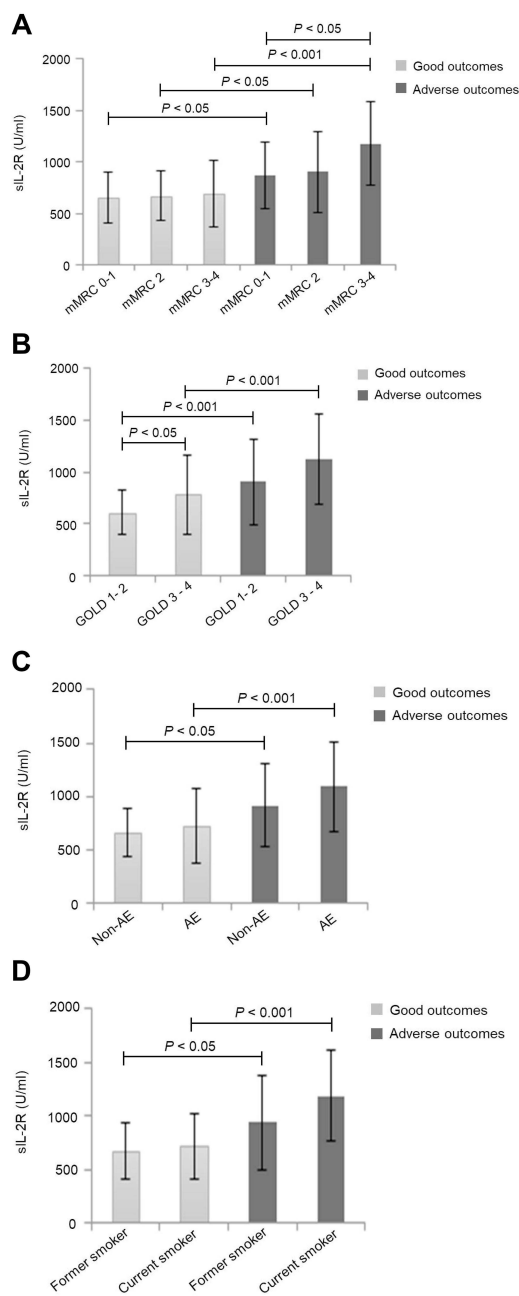
Figure 2 Relationship between clinical parameters and serum concentration of sIL-2R in good and adverse outcomes of AECOPD.

Notes: (**A**) In the mMRC score of 0–1, 2 and 3–4 groups, sIL-2R concentration was higher in patients with adverse outcomes than in those with good outcomes ($P<0.05$, $P<0.05$, $P<0.001$, respectively); Serum sIL-2R concentration was higher in patients with mMRC 3–4 than in those with mMRC 0–1 in adverse outcomes group ($P<0.05$); (**B**) In both GOLD 1–2 and GOLD 3–4 groups, sIL-2R concentration was higher in patients with adverse outcomes than in those with good outcomes ($P<0.001$, $P<0.001$, respectively); Serum sIL-2R concentration was higher in patients of adverse outcomes group than in those of good outcomes group in GOLD 1–2 ($P<0.05$); (**C**) In both the frequent and non-frequent exacerbation groups, the concentration of sIL-2R was higher in patients with adverse outcomes than in those with good outcomes ($P<0.05$, $P<0.001$, respectively); (**D**) In both the current and former smoker groups, the concentration of serum sIL-2R was higher in patients with adverse outcomes than in those with good outcomes ($P<0.05$, $P<0.001$, respectively).

Abbreviations: sIL-2R, soluble interleukin-2 receptor; mMRC score, modified Medical Research Council dyspnoea score; GOLD, Global Initiative for Chronic Obstructive Lung Disease; AECOPD, acute exacerbation of chronic obstructive pulmonary disease.

indicating that sIL-2R may play a potential role in the development of AECOPD.

The sIL-2R comprises of α (CD25), β (CD122), and common γ (CD132) chains expressing on the surface of T cells and is released by T cells in a soluble form as sIL-2R.[15,16] Furthermore, sIL-2R is present in vivo, at low levels in the sera of healthy individuals, but are further increased in patients during the acute or aggravated phase of the disease and decreased during the convalescence period or after treatment,[17,18] such as in patients with cancer;[19] inflammatory bowel disease;[17] IgG4-related disease;[20] autoimmune inflammation, including rheumatoid arthritis;[21] systemic lupus erythematosus;[22] sarcoidosis;[23] and severe asthma.[24]

Cigarette smoke exposure is a significant risk factor for the occurrence and development of a variety of airway diseases. Inflammation caused by cigarette smoke plays a key role in bronchospasm airway remodelling and lung tissue damage. Even after smoking cessation, pulmonary inflammation continues to occur; hence, it is speculated that there are autoimmune factors in COPD. Several studies have found[25,26] that the increased number of T cells in the lungs and airways of patients with COPD correlated with disease severity, and the proportion of T cells in sputum was significantly increased during AECOPD compared to that in the stable phase.[27,28] Serum sIL-2R expression is increased with T-cell activation. Our study showed that the AECOPD patients with adverse outcomes who still smoked had a significantly higher serum concentration of sIL-2R than those patients with good outcomes, suggesting that cigarette smoke may promote the occurrence and development of COPD by activating T cells.

The lung function test is an indicator of the degree of airflow limitation in patients with COPD. Our study found that serum concentration of sIL-2R in AECOPD was negatively correlated with the rate of decline in $FEV_1\%$ pred and FEV_1/FVC, both in the total population and in the subgroups. Serum sIL-2R concentration in patients with AECOPD at the GOLD 3–4 stage was higher than that in patients at the GOLD 1–2 stage, both in the total population and subgroups, indicating that the serum sIL-2R concentration can reflect the severity of airflow limitation in AECOPD.

It has been proven that the mMRC scale is of great value in assessing the severity of dyspnoea in patients with COPD. Our data showed that the serum concentration of sIL-2R in adverse outcome of AECOPD with an mMRC score of 3 and 4 was higher than that in patients with an
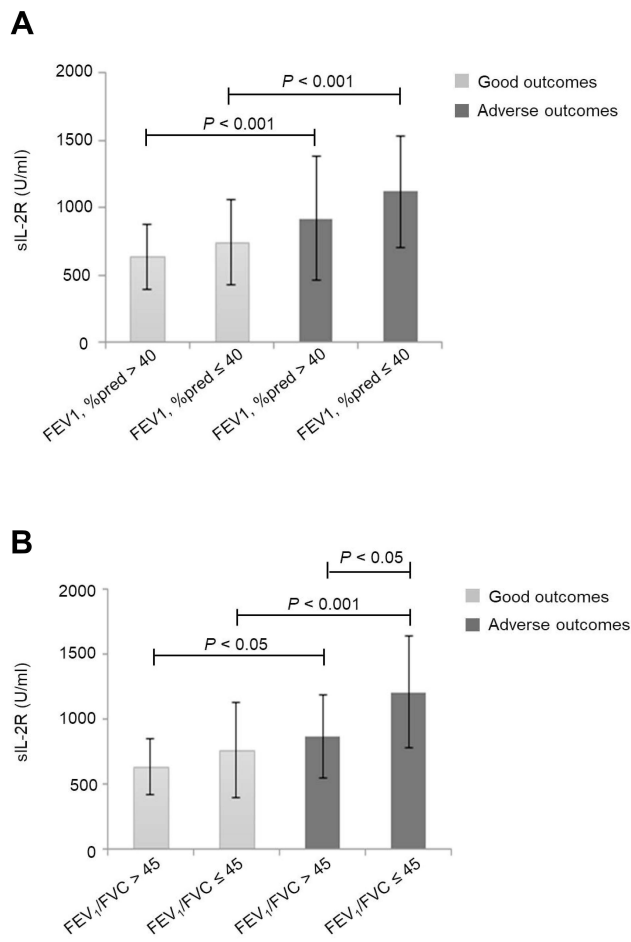
A

B

Figure 3 Relationship between FEV_1%pred, FEV_1/FVC and serum concentration of sIL-2R in good and adverse outcomes of AECOPD.
Notes: (**A**) In both high and low FEV_1%pred groups, the concentration of serum sIL-2R was higher in patients with adverse outcomes than in those with good outcomes ($P<0.001$,$P<0.001$, respectively); (**B**) In both high and low FEV_1/FVC groups, the concentration of serum sIL-2R was higher in patients with adverse outcomes than in those with good outcomes ($P<0.05$, $P<0.001$, respectively); Serum sIL-2R concentration was higher in patients with low FEV_1/FVC group than in those with high FEV_1/FVC group of adverse outcomes ($P<0.05$).
Abbreviations: sIL-2R, soluble interleukin-2 receptor; FEV_1, forced expiratory volume in 1 second; FEV_1/FVC, forced expiratory volume in 1 second/force Vital Capacity.

mMRC score of 0–1 and 2. Frequent acute exacerbation of COPD in the preceding year is a major clinical risk factor for increased morbidity and mortality rates in the future. Our study showed that the serum concentration of sIL-2R in patients with adverse outcome of AECOPD with frequent acute exacerbations of COPD was higher than that in patients with non-frequent acute exacerbations of COPD, indicating that the serum sIL-2R concentration can be used as an indicator to predict changes in respiratory function and severity of the disease in patients with AECOPD.

Table 5 Correlation Between sIL-2R and Other Laboratory Variables in Patients with AECOPD

Variable	Correlation Coefficient	P-value
pH	−0.14774	**0.0086**
$PaCO_2$	0.15008	**0.0076**
PaO_2/FiO_2	−0.09098	0.1070
WBC	0.25015	**< 0.0001**
CRP	0.35949	**< 0.0001**
PCT	0.10383	0.0657
ESR	0.27274	**< 0.0001**
IL-8	−0.01863	0.7419
IL-6	0.45888	**< 0.0001**
IL-10	0.21242	**0.0001**
TNF-α	0.14268	**0.0112**

Note: Bold font indicates $P<0.05$.
Abbreviations: sIL-2R, soluble interleukin-2 receptor; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; WBC, white blood cells; CRP, C-reactive protein; PCT, procalcitonin; ESR, erythrocyte sedimentation rate; IL, interleukin; TNF-α,tumor necrosis factor-α.

In terms of inflammatory factors, our study found that sIL-2R was positively correlated with WBC, CRP, IL-6, IL-10, and TNF-α levels, suggesting that these inflammatory factors are associated with adverse outcomes of AECOPD, which is consistent with the results of previous studies.[29,30]
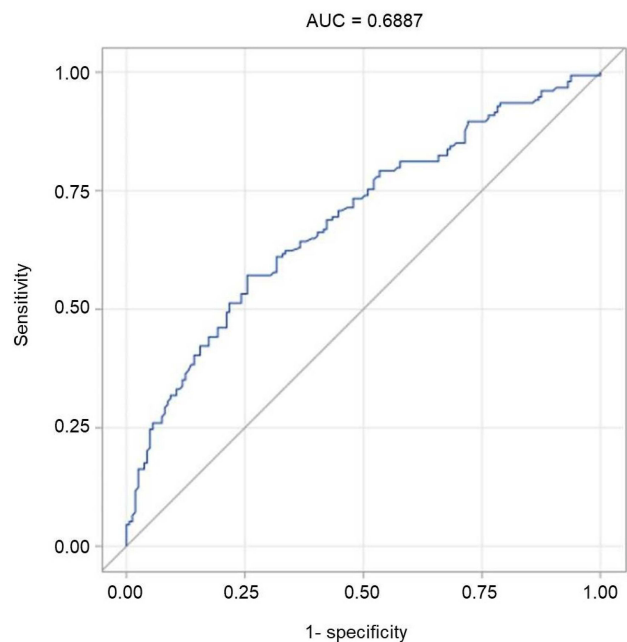

Figure 4 Diagnostic value of sIL-2R for adverse outcomes of AECOPD (AUC=0.6887).

Immediate identification of patients with adverse outcomes of AECOPD and providing accurate treatment are extremely crucial to reduce the incidence and mortality of patients with AECOPD in the future. Our study showed that the serum concentration of sIL-2R can be used to effectively screen patients at risk for adverse outcomes of AECOPD, and the ROC curve demonstrated that the sensitivity and specificity of serum concentration of sIL-2R were 62.0% and 73.9%, respectively, and the AUC reached 0.6887.

This study had a few limitations. First, the subjects included in this study were all from a tertiary hospital, which does not reflect the general population. Second, there was a high proportion of male patients (85.4%), which could affect the generalisability of the results. Finally, in future studies, we will need to analyse other samples that better reflect airway conditions, such as bronchoalveolar lavage fluid or sputum.

Conclusion

Our study found that the serum sIL-2R concentration was higher in patients with adverse outcomes of AECOPD than in patients with good outcomes. Increased serum sIL-2R concentration was positively associated with the GOLD grade, mMRC score, frequent exacerbation, and smoking in patients with AECOPD and negatively correlated with pulmonary function, indicating that serum sIL-2R concentration is a useful biomarker for predicting adverse outcomes in patients with AECOPD and a novel treatment target for AECOPD; thus, helping clinicians to stratify the risk of AECOPD and advancing clinical practice toward precision medicine.

Abbreviations

COPD, Chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; AECOPD, Acute exacerbation of COPD; %pred, Percent of predicted; FEV_1/FVC, Forced expiratory volume/forced vital capacity; SI, Smoking index; mMRC, Modified British Medical Research Council; $PaCO_2$, Partial arterial carbon dioxide pressure; PaO_2/FiO_2, Ratio of partial arterial oxygen pressure to the fraction of inspired oxygen; WBC, Whole blood leukocyte counts; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; PCT, procalcitonin; IL-6, Interleukin-6; IL-8, Interleukin-8; IL-10, Interleukin-10; TNF-α, Tumour necrosis factor-α; sIL-2R, Soluble interleukin-2 receptor; OR, Odds ratio; CI, Confidence interval; ROC, Receiver operating characteristic; AUC, Area under the curve.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The study protocol was approved by the Human Research Ethics Committee of the Xinhua Hospital affiliated to Shanghai Jiaotong University Medical College (XHEC-C-2017-085). Written informed consent was obtained from each participant. This study was conducted in accordance with the Declaration of Helsinki.

Acknowledgments

The authors thank all miner workers who participated in this study.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, agreed to the submitted journal, and agree to be accountable for all aspects of the work.

Funding

Disclosure

The authors declare that they have no competing interests in this work.

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