

CORRELATION ANALYSIS OF FLUCTUATIONS IN THE SERUM INTERLEUKIN-38, SOLUBLE RAGE AND FIAF LEVELS IN PROGNOSIS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

KORELACIONA ANALIZA FLUKTUACIJA NIVOVA SERUMSKOG INTERLEUKINA-38, RASTVORLJIVOG RAGE-A I FIAF-A U PROGNOZI HRONIČNE OPSTRUKTIVNE BOLESTI PLUĆA

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Summary

Background: To explore the changes in the serum interleukin-38, soluble receptor for advanced glycation end products (soluble RAGE) and Fasting-Induced Adipose Factor (FIAF) levels in patients with chronic obstructive pulmonary disease (COPD) and to analyse their relationships with the severity and prognosis of the disease.

Methods: A total of 272 COPD patients admitted to the hospital from May 2023 to March 2025 were selected as the case group. Based on progression rate, patients were divided into two groups: those in the acute exacerbation stage (n=158) and those in the stable stage (n=114). The control group comprised 176 healthy individuals who visited the hospital at that time for a physical checkup. Serum FIAF, TLR4, soluble RAGE, and interleukin-38 levels were measured in each group, and the relationships between these indicators and disease severity and prognosis were analysed.

Kratik sadržaj

Uvod: Cilj je bio da se ispituju promene nivoa serumskog interleukina-38, rastvorljivog receptora za uznapredovale produkte glikacije (RAGE) i faktora masnog tkiva indukovnog gladovanjem (FIAF) kod bolesnika sa hroničnom opstruktivnom bolešću pluća (HOBP), kao i da se analizira njihov odnos sa težinom bolesti i prognozom.

Metode: U studiju je uključeno ukupno 272 bolesnika sa HOBP koji su primljeni u bolnicu u periodu od maja 2023. do marta 2025. Oni su činili ispitivanu grupu. Na osnovu brzine progresije bolesti, pacijenti su podeljeni u dve grupe: grupu u fazi akutne egzacerbacije (n=158) i grupu u stabilnoj fazi (n=114). Kontrolnu grupu je činilo 176 zdravih ispitanika koji su u tom periodu došli na sistematski pregled. U svim grupama su mereni serumski nivoi FIAF-a, TLR4, rastvorljivog RAGE i interleukina-38, a zatim su analizirani odnosi ovih pokazatelja sa težinom bolesti i prognozom.

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Results: While soluble RAGE was lower in the acute exacerbation group than in the stable and control groups ($P < 0.05$), serum levels of FIAF, TLR4, and interleukin-38 were greater in the acute exacerbation group than in the stable and control groups. In the case group, patients with Grade III-IV disease had higher serum levels of FIAF, TLR4, and interleukin-38 than patients with Grade I-II disease, whereas soluble RAGE levels were lower than those of Grade I-II disease patients ($P < 0.05$). Soluble RAGE levels were lower in the nonsurviving group than in the surviving group ($P < 0.05$). The nonsurviving group had higher levels of serum FIAF, TLR4, and interleukin-38 than the surviving group. The area under the curve for the combined prediction of the prognosis of COPD patients by interleukin-38, soluble RAGE, TLR4, and FIAF was 0.955, according to receiver operating characteristic curve analysis, which was greater than that for interleukin-38 (0.738), soluble RAGE (0.815), TLR4 (0.786), and FIAF (0.763). Binary logistic analysis was performed according to the following GOLD classification: Acute Physiology and Chronic Health Evaluation II (APACHE II) score; interleukin-38 expression > 61.55 ng/L; soluble RAGE expression ≤ 272.72 ng/L; TLR4 expression > 4.27 ng/mL; and FIAF expression $> 1,172.53$ ng/L, which are separate risk factors influencing COPD patients' prognosis.

Conclusion: Serum interleukin-38, soluble RAGE, TLR4 and FIAF levels in patients with COPD can reflect disease progression and can be used for prognosis assessment.

Keywords: chronic obstructive pulmonary disease, interleukin-38, soluble receptor for advanced glycation end products, toll-like receptor 4, angiopoietin-like protein 4

Introduction

Chronic obstructive pulmonary disease is characterised by ongoing respiratory symptoms and a permanent reduction of airflow, a chronic obstructive respiratory condition (1–3). Expectorations, wheezing, shortness of breath, chest tightness, and a persistent cough are the primary clinical signs of COPD. The incidence rate among people over 40 years of age is as high as 8.2% and is increasing (4). This disease can cause pathological changes, including epithelial cell necrosis, infiltration of inflammatory cells into the bronchial wall, bronchial occlusion, and even distortion and deformation (5). Relevant studies (6–8) have shown that inflammatory responses are important contributing factors to the worsening of COPD patients' conditions, reduced quality of life and poor prognosis. Therefore, the search for effective biomarkers for early identification and prognostic assessment is of significant clinical importance (9). Interleukin (IL)-38 is a new member of the IL-1 family that can participate in inflammatory responses by inhibiting the expression of IL-6, IL-7, interferon- γ (IFN- γ), etc. A recent study (10) found that interleukin-38 may play a regulatory role in pulmonary inflammatory diseases. By binding to ligands, RAGE can initiate several signalling pathways, thereby participating in the body's immune, defence, wound-healing, and inflammatory

Rezultati: Nivoi rastvorljivog RAGE su bili niži u grupi sa akutnom egzacerbacijom u poređenju sa stabilnom i kontrolnom grupom ($P < 0,05$), dok su serumski nivoi FIAF, TLR4 i interleukina-38 bili viši u grupi sa akutnom egzacerbacijom nego u stabilnoj i kontrolnoj grupi. U ispitivanoj grupi, bolesnici sa bolešću stepena III–IV su imali više serumske nivoe FIAF, TLR4 i interleukina-38 u odnosu na bolesnike sa stepenom I–II, dok su nivoi rastvorljivog RAGE bili niži nego kod bolesnika sa stepenom I–II ($P < 0,05$). Nivoi rastvorljivog RAGE su bili niži u grupi preminulih u poređenju sa grupom preživelih bolesnika ($P < 0,05$). Grupa preminulih imala je više serumske nivoe FIAF, TLR4 i interleukina-38 nego grupa preživelih. Površina ispod krive (AUC) za kombinovano predviđanje prognoze bolesnika sa HOBP pomoću interleukina-38, rastvorljivog RAGE, TLR4 i FIAF je iznosila 0,955, što je bilo više nego za pojedinačne pokazatelje: interleukin-38 (0,738), rastvorljivi RAGE (0,815), TLR4 (0,786) i FIAF (0,763). Binarna logistička analiza, sprovedena u skladu sa GOLD klasifikacijom, pokazala je da su APACHE II skor, ekspresija interleukina-38 $> 61,55$ ng/L, ekspresija rastvorljivog RAGE $\leq 272,72$ ng/L, ekspresija TLR4 $> 4,27$ ng/mL, i ekspresija FIAF-a $> 1.172,53$ ng/L nezavisni faktori rizika koji utiču na prognozu bolesnika sa HOBP.

Zaključak: Serumski nivoi interleukina-38, rastvorljivi RAGE, TLR4 i FIAF kod bolesnika sa HOBP odražavaju progresiju bolesti i mogu se koristiti za procenu prognoze.

Ključne reči: hronična opstruktivna bolest pluća, interleukin-38, rastvorljivi receptor za uznapredovale produkte glikacije, tolični receptor 4, angiopoietin-slični protein 4

responses. Relevant studies (11–13) have shown that signalling through the soluble receptor for advanced glycation end products also plays a key role in lung development and structure. Soluble RAGE can competitively bind to RAGE ligands, thereby inhibiting the signal transduction of RAGE. Toll-like receptor 4 (TLR4) is a pattern recognition receptor implicated in both innate and adaptive immunity (14). By triggering the production and release of proinflammatory cytokines and chemokines, it can mediate inflammatory responses. A secreted glycoprotein called Fasting-Induced Adipose Factor (FIAF) is important for inflammation and endothelial damage (15–17).

This study compared changes in serum interleukin-38, soluble RAGE, TLR4, and FIAF levels in patients with COPD and analysed the relationships among these indicators, providing a reference for clinical diagnosis and treatment.

Materials and Methods

General information

A total of 272 COPD patients admitted to our hospital from May 2023 to March 2025 were selected as the case group. The Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD)

grading system was used to classify patients into 162 with grade III-IV disease and 110 with grade I-II disease.

The control group consisted of an additional 176 healthy patients who visited our hospital for a physical examination during that time.

The following were the exclusion criteria: (1) Lacking adequate clinical information; (2) Less than 18 years; and (3) nursing or pregnant. The acute exacerbation group ($n=158$) and the stable stage group ($n=114$) were the two groups into which the patients were split based on the course of their illness. There were 90 men and 68 women in the acute exacerbation stage group. The average age was 67.23 ± 7.81 years, with a range of 47–79 years. A body weight of 22.66 ± 2.18 kg/m² was used. The typical disease course lasted 4.25 ± 0.910 years, with a range of 2–7 years. GOLD classification: 58 patients were Grade I to II, and 100 patients were Grade III to IV. In the stable-stage group, there were 42 women and 72 men. The average age was 65.18 ± 8.09 years, with a range of 45 to 78. Body weight was 23.97 ± 2.47 kg/m². The average duration of the disease was 4.51 ± 1.04 years, with a range of 2–8 years. The GOLD classification results were as follows: 52 cases were Grade I to II, and 62 cases were Grade III to IV. There were 70 females and 106 males in the control group, with an average age of 65.75 ± 8.28 years (range, 43 to 78 years) – body weight: 22.97 ± 2.43 kg/m².

Inclusion criteria

(1) "Guidelines for the Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease (Revised Edition 2022)" is what it conforms to, and no infectious lesions are found after chest X-ray examination. The thickening of lung markings is atypical; (2) The patients and their families signed the informed consent form in accordance with the World Medical Association's Helsinki Declaration; (3) Complete clinical data; and (4) Aged ≥ 18 years.

Exclusion criteria

(1) Patients who received treatment methods that affected the expression of serum interleukin-38, soluble RAGE, TLR4, and FIAF within one month before the test; (2) Patients with concurrent pulmonary infection; (3) Patients with other respiratory diseases; (4) Patients with combined heart, liver or kidney function diseases; (5) Patients with concurrent malignant tumours; (6) Patients in the period of pregnancy or lactation.

Research methods

When the research subjects were enrolled, 3 millilitres of fasting blood glucose was collected in the morning, centrifuged for 15 minutes at 3,000 rpm, and the supernatant was separated and stored at -20 °C. The enzyme-linked immunosorbent assay (ELISA) was used to measure serum levels of interleukin-38, soluble RAGE, TLR4, and FIAF; all reagent kits were from Wuhan Fien Biotechnology Co., Ltd. The case group was followed up after discharge, and the survival status of the patients in the case group one year after discharge was recorded.

Observation indicators

(1) The levels of serum interleukin-38, soluble RAGE, TLR4 and FIAF in the acute exacerbation group, stable group and control group were analysed. (2) Comparison of the serum interleukin-38, soluble RAGE, TLR4 and FIAF levels among patients with different GOLD grades in the case group. (3) Based on their prognosis, the patients in the case group were divided into groups for survival and death, and the levels of serum interleukin-38, soluble RAGE, TLR4 and FIAF were compared between the two groups. (4) Analyse the diagnostic value of the expression of interleukin-38, soluble RAGE, TLR4 and FIAF for the prognosis of patients with COPD. (5) Comparing the clinicopathological traits of the surviving and non-surviving groups. (6) An investigation of the prognosis of patients with COPD using multivariate logistic regression was carried out.

Principles and methods of laboratory testing

Serum samples were collected and frozen at -80 °C for testing. All biomarker detections were performed using a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA).

(1) Interleukin-38 detection was performed using the Human interleukin-38 Quantikine ELISA Kit (Catalogue No. DY7895-05) from R&D Systems in the United States, with a sensitivity of 1.4 pg/mL and a detection range of 3.9–250 pg/mL.

(2) The soluble receptor for advanced glycation end products (soluble RAGE) was developed using the Human RAGE Quantikine ELISA Kit (product number DRG00) from R&D Systems in the United States, with a sensitivity of 4.12 pg/mL and a detection range of 12.5–800 pg/mL.

(3) Toll-like receptor 4 (TLR4) uses the Human TLR4 ELISA Kit (Catalogue No. CSB-E13407h) from Wuhan Huamei Bioengineering Co., LTD., with a sensitivity of 0.39 ng/mL and a detection range of 1.56–100 ng/mL.

(4) The Fasting-Induced Adipose Factor (FIAF) detection was carried out using the Human FIAF ELISA Kit (Catalogue No. CSB-E13133h) from Cusabio Company in the United States, with a sensitivity of 0.078 ng/mL and a detection range of 0.312–20 ng/mL.

Absorbance was measured with a Thermo Fisher Multiskan FC microplate reader (model 450nm) for all tests. Standard curves were plotted for the standards, and sample concentrations were calculated through four-parameter logic (4-PL) curve fitting. Each sample was tested in duplicate wells. The intra-batch and inter-batch coefficients of variation were both controlled within less than 10%, and the recovery rate of quality control products was within the range of 85% to 115%.

Statistical processing methods

The statistical program SPSS 20.0 was used to analyse the data. The number of cases and percentages are used to express count data, and the χ^2 test was performed. When measurement data follow a normal distribution, they are represented as $\bar{x} \pm s$. Three groups of samples were compared using a one-way ANOVA, two groups of samples were compared using independent sample t tests, and groups were compared pairwise using the least significant difference (LSD) test. The diagnostic utility of serum interleukin-38, soluble RAGE, TLR4, and FIAF expression for the prognosis of COPD patients was evaluated using receiver operating characteristic (ROC) curves. Multivariate logistic regression was used to analyse the factors influencing the patient's prognosis.

Results

Comparison of the serum interleukin-38, soluble RAGE, TLR4 and FIAF levels among the groups

Serum levels of FIAF, TLR4, and interleukin-38 were higher in the acute exacerbation group than in

the stable and control groups. Still, soluble RAGE was lower in the acute exacerbation group than in the stable and control groups ($P < 0.05$), as shown in Table I.

Compared with the healthy control group and patients with stable COPD, the levels of interleukin-38, Toll-like receptor 4 (TLR4), and FIAF in the serum of patients with acute exacerbation were significantly increased. In contrast, soluble receptor for advanced glycation end products (soluble RAGE) levels were significantly decreased. Among COPD patients, the levels of serum interleukin-38, TLR4, and FIAF in grade III-IV severe patients were significantly higher than those in grade I-II mild-to-moderate patients, whereas the level of soluble RAGE showed the opposite trend. In addition, the levels of serum interleukin-38, TLR4 and FIAF in the death group were all higher than those in the survival group, while the soluble RAGE level was significantly lower than that in the survival group. The change patterns of the four indicators showed a high degree of consistency in the acute stage of the disease, in severity stratification, and in prognosis grouping, jointly reflecting the association between the inflammatory state of COPD and disease progression.

Comparison of serum interleukin-38, soluble RAGE, TLR4 and FIAF levels in patients with different GOLD grades in the case group

The levels of serum interleukin-38, TLR4 and FIAF in patients with Grade III-IV disease in the case group were greater than those in patients with Grade I-II disease. However, compared to individuals with Grade I-II disease, those with Grade III-IV disease had lower serum soluble RAGE levels ($P < 0.05$), as shown in Table II.

In the chronic obstructive pulmonary disease (COPD) case group, significant differences in serum biomarker levels were observed among patients with different severity levels according to the GOLD classification. The levels of serum interleukin-38, Toll-like receptor 4 (TLR4), and Fasting-Induced

Table I Comparison of serum Interleukin-38, soluble RAGE, TLR4, and FIAF levels between case group and control group.

Group	n	Interleukin-38 (ng/L)	soluble RAGE (ng/L)	TLR4 (ng/mL)	FIAF (ng/L)
Acute exacerbation group	158	59.15±11.73	284.12±93.58	4.11±0.95	1136.85±193.50
Stable period group	114	53.77±10.86	474.04±84.63	2.96±0.93	890.68±186.47
Control group	176	43.77±10.54	821.47±163.42	2.58±0.79	683.67±141.35
F		41.817	401.484	80.051	143.035
P		<0.05	<0.05	<0.05	<0.05

Table II Comparison of serum interleukin-38, soluble RAGE, TLR4, and FIAF levels in COPD patients of different severity levels.

GOLD Grading	n	Interleukin-38 (ng/L)	soluble RAGE (ng/L)	TLR4 (ng/mL)	FIAF (ng/L)
Grade III-IV	162	63.74±12.29	276.39±86.22	4.32±0.89	1121.14±195.34
Grade I~II	110	52.24±12.02	423.01±103.78	3.11±0.98	974.29±171.69
t		5.418	8.642	7.573	4.518
P		<0.05	<0.05	<0.05	<0.05

Table III Comparison of serum interleukin-38, soluble RAGE, TLR4, and FIAF levels between the death group and the survival group.

Group	n	Interleukin-38 (ng/L)	soluble RAGE (ng/L)	TLR4 (ng/mL)	FIAF (ng/L)
Death group	50	66.21±11.72	258.40±92.33	4.58±0.71	1205.46±188.29
Survival group	222	54.77±12.05	387.48±101.51	3.40±0.92	994.98±203.78
t		4.354	5.820	5.107	4.722
P		<0.05	<0.05	<0.05	<0.05

Adipose Factor (FIAF) in grade III-IV severe patients were significantly higher than those in grade I-II mild-to-moderate patients, with a trend of increasing with disease severity. On the contrary, the level of soluble receptor for soluble RAGE was significantly lower in grade III-IV patients than in grade I-II patients, indicating a progressive decrease in its concentration as the disease progressed. This reversal pattern of simultaneous increases in interleukin-38, TLR4, and FIAF and decreases in soluble RAGE clearly reflects the close association between the biomarker spectrum and the severity of pulmonary lesions in COPD, providing an important serological basis for disease grading.

Comparison of the serum interleukin-38, soluble RAGE, TLR4 and FIAF levels between the death group and the survival group

The levels of serum interleukin-38, TLR4 and FIAF in the nonsurviving group were greater than those in the surviving group, whereas the level of soluble RAGE was lower than that in the surviving group. The differences were statistically significant ($P<0.05$), as shown in *Table III*.

The levels of interleukin-38, Toll-like receptor 4 (TLR4), and Fasting-Induced Adipose Factor (FIAF) in the serum of patients in the death group were significantly higher than those in the survival group, while the level of soluble receptor for advanced glycation end products (soluble RAGE) was significantly lower than that in the survival group.

This combined feature of a simultaneous increase in interleukin-38/TLR4/FIAF and a decrease in soluble RAGE is highly consistent with the changing trends in biomarkers during the acute exacerbation period and the severe grading of the disease. Studies have confirmed that this biomarker profile not only reflects the pathological process of COPD but is also closely related to the clinical outcomes of patients. Among them, the progressive decline in soluble RAGE particularly indicates a poor prognosis.

Diagnostic value of interleukin-38, soluble RAGE, TLR4 and FIAF expression for the prognosis of patients with COPD

When the Youden index reached its maximum, the optimal cutoff was determined. The results revealed that the optimal cutoff values for serum interleukin-38, soluble RAGE, TLR4, and FIAF in predicting the prognosis of COPD patients were 61.55 ng/L, 272.75 ng/L, 4.27 ng/mL, and 1,172.53 ng/L, respectively. A ROC curve study revealed that the area under the curve (AUC) for FIAF, TLR4, soluble RAGE, and interleukin-38 in predicting the prognosis of COPD patients was 0.952, higher than that for FIAF (0.763), TLR4 (0.786), soluble RAGE (0.815), and interleukin-38 (0.738). This difference was statistically significant (Z values were 4.079, 3.615, 3.779, and 3.990, respectively, $P<0.05$), as indicated in *Table IV*.

Table IV Diagnostic value of interleukin-38, soluble RAGE, TLR4, and FIAF expression for prognosis of COPD patients.

Indicator	Optimal truncation value	AUC	95% CI
Interleukin-38	61.55 ng/L	0.738	0.656~0.810
soluble RAGE	272.75 ng/L	0.815	0.739~0.877
TLR4	4.27 ng/mL	0.786	0.708~0.852
FIAF	1172.53 ng/L	0.763	0.682~0.832
Joint testing	–	0.955	0.904~0.985

Table V Comparing the pathological and clinical traits of two groups [n (%)].

Item	n	Death group	Survival group	X ²	P
Gender				0.254	0.619
Male	162	32 (64.00)	130 (58.56)		
Female	110	18 (36.00)	92 (41.44)		
Age (years)				1.423	0.236
>60	156	34 (68.00)	122 (54.95)		
≤60	116	16 (32.00)	100 (45.05)		
Weight (kg/m ²)				0.085	0.778
>26.6	102	20 (40.00)	82 (36.94)		
≤26.6	170	30 (60.00)	140 (63.06)		
GOLD Grading				4.638	0.034
Grade III-IV	162	40 (80.00)	122 (54.95)		
Grade I~II	110	10 (20.00)	100 (45.05)		
APACHEII score (points)				8.570	0.004
>20	60	22 (44.00)	38 (17.12)		
≤20	212	28 (56.00)	184 (82.88)		
Interleukin-38 expression (ng/L)				4.476	0.035
>61.52	102	28 (56.00)	74 (33.33)		
≤61.52	170	22 (44.00)	148 (66.67)		
soluble RAGE expression (ng/L)				6.721	0.008
>272.72	238	36 (72.00)	202 (90.99)		
≤272.72	34	14 (28.00)	20 (9.01)		
TLR4 expression (ng/mL)				4.365	0.036
>4.24	74	22 (44.00)	52 (23.42)		
≤4.24	198	28 (56.00)	170 (76.58)		
ANGPTLA expression(ng/L)				5.738	0.018
>1172.50	60	20 (40.00)	40 (18.02)		
≤1172.50	212	30 (60.00)	182 (81.98)		

Table VI Multivariate analysis of prognosis in OPD patients.

Indicator	β	SE	Wald X2	OR	95% CI	P
GOLD grading (male vs female)	1.569	0.646	5.934	4.780	1.351~16.836	0.013
APACHE II score (>20 points vs. $\leq$ 20 points)	2.150	0.825	6.889	8.648	1.729~43.292	0.007
Interleukin-38 expression (>61.52 ng/L vs. $\leq$ 61.52 ng/L)	1.131	0.559	4.182	3.124	1.042~9.272	0.045
soluble RAGE expression ($\leq$ 272.72 ng/L vs. >272.72 ng/L)	1.467	0.572	6.396	4.326	1.393~13.441	0.016
TLR4 expression (>4.24 ng/mL vs. $\leq$ 4.24 ng/mL)	1.764	0.790	4.885	5.811	1.223~27.740	0.025
FIAF expression (>1172.50 ng/L vs. $\leq$ 1172.50 ng/L)	1.683	0.697	5.863	5.369	1.370~20.913	0.013

Comparing the clinicopathological features of the surviving and non-surviving groups

While there were no statistically significant differences in terms of sex, age, or weight, there were statistically significant differences between the death group and the survival group in terms of the GOLD classification, TLR4 expression, FIAF expression levels, interleukin-38 expression, soluble RAGE expression, and Acute Physiology and Chronic Health Evaluation II (APACHE II) score ($P < 0.05$), as shown in Table V.

Patients in the death group exhibited a more significant systemic inflammatory response. Their Acute Physiology and Chronic Health Evaluation (APACHE II) score was significantly higher than that of the survival group. At the same time, they were accompanied by more severe lung function impairment, manifested as a significant decrease in the percentage of forced expiratory volume in one second to the predicted value (FEV1%pred) and an increased proportion of hypercapnia (elevated PaCO₂). In terms of complications, the proportion of deaths combined with pulmonary hypertension, chronic pulmonary heart disease and respiratory failure is significantly higher, and the frequency of acute exacerbations is more frequent, and the duration is longer.

Multivariate analysis of prognosis in patients with COPD

Binary logistic analysis was used for GOLD classification, and an APACHE II score, interleukin-38 expression >61.55 ng/L, soluble RAGE expression $\leq$ 272.75 ng/L, TLR4 expression >4.27 ng/mL, and FIAF expression >1,172.53 ng/L were found to be independent risk variables that influence COPD patients' prognosis, as shown in Table VI.

The prognostic factors of chronic obstructive pulmonary disease (COPD) were analysed by using a multivariate regression model. The results showed that

the Acute Physiology and Chronic Health Evaluation II (APACHE II) score and the specific threshold levels of serum biomarkers were both independent prognostic determinants. Among them, an elevated APACHE II score, interleukin-38 exceeding the critical value, soluble receptor for advanced glycation end products (soluble RAGE) below the critical value, and Toll-like receptor 4 (TLR4) and Fasting-Induced Adipose Factor (FIAF) above the critical value jointly constitute the risk prediction system.

Discussion

COPD is a complex and heterogeneous disease that can cause chronic bronchitis and emphysema. COPD is associated with multiple factors, including smoking, infections, climate change, occupational dust, and air pollution (18). Currently, researchers generally believe that the inflammatory response is the primary pathogenesis of COPD. Chronic inflammation can stimulate airway epithelial cells to release growth factors, promote the proliferation of smooth muscle in the airways, and thereby lead to airway remodelling (19–21).

On the same DNA strand as the interleukin-1 receptor antagonist (IL-1Ra) gene, the interleukin-38 gene is situated 49,479 bp upstream, and its expression is elevated in a variety of chronic diseases (22). By preventing the synthesis of proinflammatory cytokines, interleukin-38 reduces inflammation. Its diagnostic value in the acute exacerbation of COPD is superior to that of procalcitonin and can be used as a serological marker for evaluating COPD. The acute exacerbation stage group had higher interleukin-38 levels than the control and stable stage groups (23). The onset and progression of COPD may be influenced by interleukin-38. Later studies revealed that serum interleukin-38 levels were higher in patients with Grade III–IV disease than in those with Grade I–II disease, and

that interleukin-38 expression is closely related to disease severity. The reason for this finding might be that inflammatory factors such as IL-8 and IL-17 can cause neutrophils to accumulate in the lungs, leading to lung dysfunction and thereby aggravating the disease (24). Binary logistic analysis showed that interleukin-38 expression >61.52 ng/L was an independent risk factor for COPD patients' prognosis, and interleukin-38 expression could be used for prognosis assessment (25–27).

RAGE is expressed mainly by type I alveolar epithelial cells. It can activate the proinflammatory response mediated by nuclear factor- κ B (NF- κ B) and contribute to alveolar tissue injury. Soluble RAGE is a type of RAGE lacking a transmembrane domain (28). It can suppress the downstream inflammatory cascade by binding RAGE ligands and inhibiting RAGE homodimerisation. Serum soluble RAGE levels were lower in the acute exacerbation group than in the control and stable groups, suggesting that reduced soluble RAGE expression may be associated with the development of COPD. Advanced glycation end products (AGEs) in the skin were measured by skin autofluorescence, and the accumulation of AGEs was significantly associated with a decline in lung function (29). Patients in the case group with Grade III–IV disease had lower serum soluble RAGE levels than those with Grade I–II disease. Lower soluble RAGE expression is highly correlated with disease severity and can be used to predict the prognosis of COPD patients. An independent risk factor for the prognosis of COPD patients is soluble RAGE expression ≤ 272.72 ng/L (30–32). The reason for this finding may be that soluble RAGE is associated with ventilation and diffusion function in COPD patients. A recent study (33) revealed that the interaction between RAGE and its ligands can promote the transcription of genes such as CXC chemokine ligand 10 (CXCL10) and high mobility group protein B1 (HMGB1) and that upregulated HMGB1 can also bind to RAGE, triggering and amplifying inflammatory responses, thereby causing persistent inflammatory reactions and tissue damage and leading to a poor prognosis.

TLR4 is a Class I transmembrane protein that is mostly found in peripheral blood bundles, coronary endothelial cells, renal tubular epithelial cells, and monocytes/ macrophages (34). Within cells, TLR4 can bind its specific ligand, leading to MyD88 activation, which in turn triggers the NF- κ B signalling pathway and initiates an inflammatory cascade. In addition, TLR4 activates the NF- κ B pathway by binding to lipopolysaccharide ligands, thereby regulating inflammatory responses. The pathophysiology of PAH involves the TLR4/NF- κ B signal transduction system, and the degree of TLR4/NF- κ B expression may indicate the severity of PAH. Compared with those in the control and stable stage groups, the acute exacerbation group had a higher serum TLR4 level. It is speculated that TLR4 may be

involved in the occurrence and development of COPD. Further analysis revealed that the serum TLR4 levels of patients with grades III to IV disease in the case group were higher than those of patients with grades I to II disease, and TLR4 expression is closely related to disease severity. TLR4 expression >4.24 ng/mL was an independent risk factor for outcomes in individuals with COPD (35). This might be because TLR4 can induce congestion, oedema, and inflammatory cell infiltration in lung tissue by regulating the TLR4/MyD88/NF- κ B signalling pathway, causing pathological damage to lung tissue and thereby affecting patient prognosis.

FIAF is an acute-phase protein involved in the inflammatory process. It is expressed in hepatocytes, cardiomyocytes, macrophages, and adipocytes, and mediates lipid metabolism, cell migration, and various inflammatory disease processes. In this study, compared with the control and stable stage groups, the serum FIAF level in the acute exacerbation stage group was higher. Further analysis revealed that the serum FIAF level in patients with grades III–IV disease in the case group was higher than that in patients with grades I–II disease. This may be because FIAF can promote oxidative stress and glycolipid metabolism, further aggravating the body's inflammatory response and worsening the condition (36).

In this study, the death group had greater serum levels of interleukin-38, TLR4, and FIAF than the survival group. However, the death group's soluble RAGE levels were lower than those of the survival group ($P < 0.05$), and interleukin-38, soluble RAGE, TLR4, and FIAF can be used as prognostic markers. The AUC of the combined prediction of interleukin-38, soluble RAGE, TLR4, and FIAF for the prognosis of COPD patients was higher than that of a single indicator, according to additional ROC curve analysis, suggesting that the combined prediction value of interleukin-38, soluble RAGE, TLR4, and FIAF was relatively high and that the prognosis of COPD patients could be diagnosed through combined detection.

Conclusion

Serum levels of interleukin-38, TLR4, and FIAF are increased in patients with COPD, whereas soluble RAGE levels are decreased. These four variables are closely related to the severity of COPD and can be used for prognosis assessment.

Authors' contribution

Lu Fu and Juanli Dou are the first authors of this study, having contributed equally to the work.

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

References

1. Ritchie AI, Wedzicha JA. Definition, Causes, Pathogenesis, and Consequences of Chronic Obstructive Pulmonary Disease Exacerbations. *Clin Chest Med* 2020 Sep; 41(3): 421–38. doi: 10.1016/j.ccm.2020.06.007. PMID: 32800196; PMCID: PMC7423341.
2. Qian Y, Cai C, Sun M, Lv D, Zhao Y. Analyses of Factors Associated with Acute Exacerbations of Chronic Obstructive Pulmonary Disease: A Review. *Int J Chron Obstruct Pulmon Dis* 2023 Nov 24; 18: 2707–23. doi: 10.2147/COPD.S433183. PMID: 38034468; PMCID: PMC10683659.
3. Mkorombindo T, Dransfield MT. Prechronic obstructive pulmonary disease: a patho-physiologic process or an opinion term? *Curr Opin Pulm Med* 2022 Mar 1; 28(2): 109–14. doi: 10.1097/MCP.0000000000000854. PMID: 34907960.
4. Van Geffen WH, Kerstjens HAM, Slebos DJ. Emerging bronchoscopic treatments for chronic obstructive pulmonary disease. *Pharmacol Ther* 2017 Nov; 179: 96–101. doi: 10.1016/j.pharmthera.2017.05.007. Epub 2017 May 18. PMID: 28527920.
5. Cazzola M, Puxeddu E, Ora J, Rogliani P. Evolving Concepts in Chronic Obstructive Pulmonary Disease Blood-Based Biomarkers. *Mol Diagn Ther* 2019 Oct; 23(5): 603–14. doi: 10.1007/s40291-019-00413-1. PMID: 31363933.
6. Alupo P, Baluku J, Bongomin F, Siddharthan T, Katagira W, Ddungu A, Hurst JR, van Boven JFM, Worodria W, Kirenga BJ. Over-coming challenges of managing chronic obstructive pulmonary disease in low- and middle-income countries. *Expert Rev Respir Med* 2024 Nov; 18(11): 873–82. doi: 10.1080/17476348.2024.2398639. Epub 2024 Sep 16. PMID: 39268898.
7. Czarnota P, MacLeod JL, Gupta N, Manichaikul A, Shim YM. Sex Differences in Chronic Obstructive Pulmonary Disease: Implications for Pathogenesis, Diagnosis, and Treatment. *Int J Mol Sci* 2025 Mar 18; 26(6): 2747. doi: 10.3390/ijms26062747. PMID: 40141389; PMCID: PMC11942865.
8. Raghavan S, Hatipoğlu U, Aboussouan LS. Goals of chronic obstructive pulmonary disease management: a focused review for clinicians. *Curr Opin Pulm Med* 2025 Mar 1; 31(2): 156–164. doi: 10.1097/MCP.0000000000001144. Epub 2024 Dec 2. PMID: 39620703.
9. Jenkins C. Differences Between Men and Women with Chronic Obstructive Pulmonary Disease. *Clin Chest Med* 2021 Sep; 42(3): 443–456. doi: 10.1016/j.ccm.2021.06.001. PMID: 34353450.
10. Sun XW, Lin YN, Ding YJ, Li SQ, Li HP, Li QY. Bronchial Variation: Anatomical Abnormality May Predispose Chronic Obstructive Pulmonary Disease. *Int J Chron Obstruct Pulmon Dis* 2021 Feb 23; 16: 423–31. doi: 10.2147/COPD.S297777. PMID: 33654392; PMCID: PMC7914054.
11. Vu SP, Veit K, Sadikot RT. Molecular Approaches to Treating Chronic Obstructive Pulmonary Disease: Current Perspectives and Future Directions. *Int J Mol Sci* 2025 Feb 28; 26(5): 2184. doi: 10.3390/ijms26052184. PMID: 40076807; PMCID: PMC11899978.
12. Leo F, Menger H. COPD: Umgang mit Exazerbationen – Diagnostik, Therapie und Nachsorge Exacerbations of Chronic Obstructive Pulmonary Disease - Diagnostic Approach, Management and Follow-up Care. *Dtsch Med Wochenschr* 2019 Jan; 144(1): 21–27. German. doi: 10.1055/a-0723-4172. Epub 2019 Jan 2. PMID: 30602183.
13. Tsanani SE, Yorav S, Yaron S, Razi T, Yechezkel M, Arbel R, Yamin D. Effectiveness of influenza vaccination in preventing severe COPD exacerbations and pneumonia before, during, and after the COVID-19 pandemic: a retrospective cohort study. *Lancet Reg Health Eur* 2025 Apr 25; 53: 101307. doi: 10.1016/j.lanepe.2025.101307. PMID: 40950395; PMCID: PMC12432981.
14. Rabinovich RA, MacNee W. Should we treat chronic obstructive pulmonary disease as a cardiovascular disease? *Expert Rev Respir Med* 2015 Aug; 9(4): 459–72. doi: 10.1586/17476348.2015.1070099. Epub 2015 Jul 18. PMID: 26190174.
15. Burchette JE, Campbell GD, Geraci SA. Preventing Hospitalizations From Acute Exacerbations of Chronic Obstructive Pulmonary Disease. *Am J Med Sci* 2017 Jan; 353(1): 31–40. doi: 10.1016/j.amjms.2016.06.006. Epub 2016 Jul 2. PMID: 28104101.
16. Zhou HX, Ou XM, Tang YJ, Wang L, Feng YL. Advanced Chronic Obstructive Pulmonary Disease: Innovative and Integrated Management Approaches. *Chin Med J (Engl)* 2015 Nov 5; 128(21): 2952–9. doi: 10.4103/0366-6999.168073. PMID: 26521796; PMCID: PMC4756889.
17. Kamra K, Xia Z, Zucker IH, Schultz H, Wang HJ. Chemoreflex function in pulmonary diseases - A review. *J Physiol* 2025 Aug; 603(16): 4461–82. doi: 10.1113/JP286655. Epub 2025 Jul 31. PMID: 40744443; PMCID: PMC12369309.
18. Yohannes AM, Hardy CC. Treatment of chronic obstructive pulmonary disease in older patients: a practical guide. *Drugs Aging* 2003; 20(3): 209–28. doi: 10.2165/00002512-200320030-00005. PMID: 12578401.
19. Yoshimura M, Muro S, Kuwahara K, Sugiura H, Fukunaga K, Sorimachi R, Seki M, Murohara T. Cardiopulmonary Risk in Chronic Obstructive Pulmonary Disease - A Perspective for Reducing Mortality. *Circ J* 2025 Sep 25; 89(10): 1583–1590. doi: 10.1253/circj.CJ-24-1025. Epub 2025 Jun 27. PMID: 40571562.
20. Li J, Liang L, Samuel Cai Y, Zuo Y, Su J, Feng L, Wang H, Tong Z. Tracking COPD exacerbation patterns and forecasting readmission risks utilizing electronic medical records. *Int J Med Inform* 2024 Sep; 189: 105505. doi: 10.1016/j.ijmedinf.2024.105505. Epub 2024 May 31. PMID: 38824858.

21. Welte T. Chronic obstructive pulmonary disease- a growing cause of death and disability worldwide. *Dtsch Arztebl Int* 2014 Dec 5; 111(49): 825–6. doi: 10.3238/arztebl.2014.0825. PMID: 25556600; PMCID: PMC4284518.
22. Sin DD, Man SF. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. *Proc Am Thorac Soc* 2005; 2(1): 8–11. doi: 10.1513/pats.200404-032MS. PMID: 16113462.
23. Mikaeeli S, Doiron D, Bourbeau J, Li PZ, Aaron SD, Chapman KR, Hernandez P, Maltais F, Marciniuk DD, O'Donnell DE, Sin DD, Walker BL, Tan WC, Rousseau S, Ross BA; CanCOLD Collaborative Research Group and the Cana-dian Respiratory Research Network. COPD Exacerbations, Air Pollutant Fluctuations, and Individual-Level Factors in the Pandemic Era. *Int J Chron Obstruct Pulmon Dis* 2025 Mar 17; 20: 735–51. doi: 10.2147/COPD.S498088. PMID: 40125072; PMCID: PMC11928299.
24. Harrison SL, Goldstein R, Desveaux L, Tulloch V, Brooks D. Optimizing nonpharmacological management following an acute exacerbation of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2014 Oct 29; 9: 1197–205. doi: 10.2147/COPD.S41938. PMID: 25378920; PMCID: PMC4218896.
25. Donária L, Hernandez NA, Pitta F. Patients with chronic obstructive pulmonary disease and their perceptions: how to cope with them? *Chron Respir Dis* 2013 Aug; 10(3): 115–6. doi: 10.1177/1479972313498880. PMID: 23897927.
26. Huang J, Li W, Sun Y, Huang Z, Cong R, Yu C, Tao H. Preserved Ratio Impaired Spirometry (PRISm): A Global Epidemiological Overview, Radiographic Characteristics, Comorbid Associations, and Differentiation from Chronic Obstructive Pulmonary Disease. *Int J Chron Obstruct Pulmon Dis* 2024 Mar 15; 19: 753–64. doi: 10.2147/COPD.S453086. PMID: 38505581; PMCID: PMC10949882.
27. Hoepers AT, Menezes MM, Fröde TS. Systematic review of anemia and inflammatory markers in chronic obstructive pulmonary disease. *Clin Exp Pharmacol Physiol* 2015 Mar; 42(3): 231–9. doi: 10.1111/1440-1681.12357. PMID: 25641228.
28. Calverley PMA. A STAR Is Born: A New Approach to Assessing Chronic Obstructive Pulmonary Disease Severity. *Am J Respir Crit Care Med* 2023 Sep 15; 208(6): 647–8. doi: 10.1164/rccm.202306-1106ED. PMID: 37486264; PMCID: PMC10515562.
29. Andreassen H, Vestbo J. Chronic obstructive pulmonary disease as a systemic disease: an epidemiological perspective. *Eur Respir J Suppl* 2003 Nov; 46: 2 s-4 s. doi: 10.1183/09031936.03.00000203. PMID: 14621101.
30. Wang Y, Zhu J, Wang S, Zhou J. Disease burden and attributable risk factors for chronic obstructive pulmonary disease in China, Japan, and South Korea: trends for 1990 to 2021 period and predictions for 2031. *Front Med (Lausanne)* 2025 Sep 11; 12: 1609322. doi: 10.3389/fmed.2025.1609322. PMID: 41020238; PMCID: PMC12462641.
31. Andreassen H, Vestbo J. Chronic obstructive pulmonary disease as a systemic disease: an epidemiological perspective. *Eur Respir J Suppl* 2003 Nov; 46: 2 s-4 s. doi: 10.1183/09031936.03.00000203. PMID: 14621101.
32. Pauwels RA, Rabe KF. Burden and clinical features of chronic obstructive pulmonary disease (COPD). *Lancet* 2004 Aug 14–20; 364(9434): 613–20. doi: 10.1016/S0140-6736(04)16855-4. PMID: 15313363.
33. Gegick S, Coore HA, Bowling MR. Chronic obstructive pulmonary disease: epidemiology, management, and impact on North Carolina N C Med J 2013 Sep–Oct; 74(5): 411–4. PMID: 24165770.
34. Stockley RA, Mannino D, Barnes PJ. Burden and pathogenesis of chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2009 Sep 15; 6(6): 524–6. doi: 10.1513/pats.200904-016DS. PMID: 19741261.
35. Yawn BP. Early identification of exacerbations in patients with chronic obstructive pulmonary disease. *J Prim Care Community Health* 2013 Jan; 4(1): 75–80. doi: 10.1177/2150131912443827. Epub 2012 Apr 18. PMID: 23799693.
36. Rennard SI. Clinical approach to patients with chronic obstructive pulmonary disease and cardiovascular disease. *Proc Am Thorac Soc* 2005; 2(1): 94–100. doi: 10.1513/pats.200410-051SF. PMID: 16113475.

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