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THE DIAGNOSTIC VALUE OF sST-2, GDF-15 AND THE NLR IN PULMONARY HYPERTENSION ASSOCIATED WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

DIJAGNOSTIČKA VREDNOST sST-2, GDF-15 I NLR KOD PLUĆNE HIPERTENZIJE POVEZANE SA HRONIČNOM OPSTRUKTIVNOM BOLEŠĆU PLUĆA

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Summary

Background: To explore the diagnostic efficacy of serum soluble tumorigenic factor-2 (sST-2), growth differentiation factor-15 (GDF-15), and the neutrophil/lymphocyte ratio (NLR) for the poor prognosis of pulmonary hypertension (PH) associated with chronic obstructive pulmonary disease (COPD).
Methods: The COPD mixed with PH group consisted of 121 patients who received a diagnosis of COPD combined with PH at our hospital between January 2023 and December 2024. Patients with COPD and PH were further separated into two groups: those with a fair prognosis (93 patients) and those with a bad prognosis (28 patients). Forty-five healthy people who had physical examinations were chosen as the healthy control group, and another 75 patients with uncomplicated COPD within the same time period were chosen as the COPD group. Multivariate analysis of the effects of serum sST-2 and GDF-15 levels and the NLR on the prognosis of COPD combined with PH in each group, the relationships between serum sST-2 and GDF-15 levels and the NLR and the severity of COPD combined

Kratak sadržaj

Uvod: Cilj je bio da se ispita dijagnostička efikasnost serumskog rastvorljivog tumorigenskog faktora-2 (sST-2), faktora diferencijacije rasta-15 (GDF-15) i odnosa neutrofila i limfocita (NLR) u proceni loše prognoze kod plućne hipertenzije (PH) udružene sa hroničnom opstruktivnom bolešću pluća (HOBP).
Metode: Grupu HOBP zajedno sa PH je činio 121 pacijent kojima je u našoj ustanovi u periodu od januara 2023. do decembra 2024. postavljena dijagnoza HOBP sa PH. Pacijenti sa HOBP i PH su dodatno podeljeni u dve grupe: sa povoljnom prognozom (93 pacijenta) i sa nepovoljnom prognozom (28 pacijenata). Četrdeset pet zdravih osoba koje su obavile sistematski pregled je odabrano kao zdrava kontrolna grupa, dok je dodatnih 75 pacijenata sa HOBP bez PH, u istom vremenskom periodu, uključeno kao grupa HOBP. Izvršena je multivarijantna analiza uticaja nivoa sST-2 i GDF-15 u serumu i NLR na prognozu HOBP udružene sa PH u svakoj grupi, kao i analiza odnosa ovih parametara sa težinom HOBP udružene sa PH i njihove dijagnostičke vrednosti u proceni nepovoljne prognoze.

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with PH, and the diagnostic value of COPD combined with PH for poor prognosis.

Results: The COPD combined with the PH group's serum sST-2, GDF-15, and NLR levels were noticeably higher. Compared with the healthy control group, the COPD group showed significantly greater differences ($P<0.05$) that increased with increasing PH severity. The group with a good prognosis had a considerably higher level of left ventricular ejection fraction (LVEF) than the group with a poor prognosis, whereas the levels of serum sST-2, GDF-15 and NLR in the poor prognosis group were significantly greater than those in the good prognosis group, and the differences were statistically significant ($P<0.05$). There were no statistically significant differences in age, sex, disease duration, hypertension status, diabetes status, triglyceride, cholesterol, high-density lipoprotein or low-density lipoprotein levels ($P>0.05$).

Conclusions: The levels of serum sST-2, GDF-15 and the NLR are indicators reflecting the severity of COPD combined with PH. The combined detection of these three indicators helps improve diagnostic efficacy in patients with COPD and PH at high risk of a poor prognosis.

Keywords: soluble tumorigenic factor-2, growth differentiation factor-15, chronic obstructive pulmonary disease, pulmonary arterial hypertension, diagnostic efficacy

Rezultati: Nivoi sST-2, GDF-15 i NLR u serumu su bili značajno viši u grupi HOBP udružene sa PH. U poređenju sa zdravom kontrolnom grupom, grupa HOBP pokazala je značajno veće vrednosti ($P<0,05$), koje su dodatno rasle s porastom težine PH. Grupa sa povoljnom prognozom imala je značajno višu vrednost ejekcione frakcije leve komore (LVEF) u poređenju sa grupom s nepovoljnom prognozom, dok su nivoi sST-2, GDF-15 i NLR u grupi s lošom prognozom bili značajno viši nego u grupi sa dobrom prognozom, pri čemu je razlika bila statistički značajna ($P<0,05$). Nije bilo statistički značajnih razlika u pogledu starosti, pola, trajanja bolesti, prisustva hipertenzije, dijabetesa, nivoa triglicerida, holesterola, lipoproteina visoke i niske gustine ($P>0,05$).

Zaključak: Nivoi sST-2, GDF-15 i NLR u serumu predstavljaju pokazatelje koji odražavaju težinu HOBP udružene sa PH. Kombinovano određivanje ova tri parametra može doprineti poboljšanju dijagnostičke efikasnosti kod pacijenata sa HOBP i PH koji su u visokom riziku od nepovoljne prognoze.

Ključne reči: rastvorljivi tumorigenski faktor-2, faktor diferencijacije rasta-15, hronična opstruktivna bolest pluća, plućna arterijska hipertenzija, dijagnostička efikasnost

Introduction

A prevalent illness that poses a serious risk to human health, chronic obstructive pulmonary disease (COPD) is defined by ongoing respiratory symptoms and airflow restrictions, endangers people's lives and health, and significantly burdens families and society (1–3). As COPD progresses, it often leads to pulmonary hypertension (PH) and eventually develops into pulmonary heart disease, which is an important factor in poor patient prognosis. Early assessment of the condition of patients with COPD and PH is of great clinical significance for improving patient prognosis. Traditional cardiopulmonary exercise tests, echocardiography, and right heart catheterisation are highly valuable for determining disease severity (4–6). However, the above indicators cannot reflect the pathophysiological process and clinical prognosis of PH in COPD patients. Therefore, the search for sensitive biological markers has become a research hotspot in COPD combined with PH (7). Soluble tumorigenic factor-2 (sST-2) plays a key role in pulmonary arterial vascular endothelial remodelling by binding to interleukin-33, triggering PH (8). Growth differentiation factor-15 (GDF-15) is an immunomodulatory cytokine primarily involved in cell proliferation, vascular remodelling, and angiogenesis (9). It is involved in the pathogenesis of various types of PH and can be used as an indicator for risk stratification and prognosis assessment of PH diseases (10). The body's inflammatory response is intimately linked to the neutrophil/lymphocyte ratio (NLR). In patients with COPD complicated with PH, the level increases and is positively correlated with the degree of PH. It serves as a reference index for the assessment of COPD combined with PH (11–13).

In this study, the levels of serum sST-2, GDF-15, and NLR were measured in patients with COPD and PH, and the diagnostic value of these parameters for predicting poor prognosis in this population was determined.

Materials and Methods

General information

A total of 121 patients who were diagnosed with COPD combined with PH from January 2023 to December 2024 were selected for the COPD combined with PH group; they had 41 females and 80 males. The age range was 42 to 82 years, with an average of 63.03±10.15 years. Eighty-one individuals had hypertension, while 35 patients had diabetes.

Inclusion criteria: (1) fulfilled the requirements for COPD diagnosis; (2) had a pulmonary artery pressure greater than 25 mmHg at rest and greater than 30 mmHg during exercise. Exclusion criteria: (1) pneumonia or other infectious diseases; (2) interstitial lung diseases, pulmonary thrombosis and cardiac insufficiency; (3) hematological and immune diseases; (4) malignant tumors; (5) dysfunction of vital organs such as the heart, liver and kidneys; (6) portal hypertension and splenectomy; (7) intellectual disability and mental disorders.

Another 75 patients with simple COPD in our hospital during the same period were selected as the

COPD group, including 54 males and 21 females. The ages ranged from 41 to 81 years, with an average of 61.91±9.23 years. The three groups' general data, including age and sex, were equivalent and did not differ statistically significantly ($P>0.05$). Every research subject provided informed consent by signing the consent form, and the ethics committee approved this study [No. HKYS-2025-A0216].

Treatment methods

Patients with COPD are given conventional symptomatic and supportive treatments such as oxygen inhalation, anti-infectives, expectorants, mechanical ventilation, aminophylline and prednisone during the acute exacerbation period. For patients in the remission stage of COPD, salmeterol/fluticasone and tiotropium bromide powder inhalation are combined for treatment, and cardiopulmonary exercise therapy is provided. All 121 patients with COPD and PH were followed for 1 year. Patients in the bad prognosis group were those who died from COPD or were readmitted. Otherwise, they were in the good prognosis group based on the primary follow-up data.

Cardiac ultrasound examination

Colour echocardiography was used to identify echocardiograms and the left ventricular ejection fraction (LVEF), while the tricuspid valve pressure difference method was used to detect the pulmonary artery systolic pressure (PASP). The patients were split into three groups: mild (36–50 mmHg), moderate (51–60 mmHg), and severe (>60 mmHg).

Blood sample collection and testing

After the patient was admitted to the hospital and during the physical examination of healthy individuals, approximately 5 mL of venous blood from the elbow was collected. A centrifuge was used at 3,000 r/min with a 9 cm radius for 10 minutes. The supernatant was placed in a -70 °C refrigerator for testing. Serum sST-2 and GDF-15 levels were measured by enzyme-linked immunosorbent assay. The kit was manufactured by Wuhan Saipei Biotechnology Co., Ltd. and was used strictly in accordance with the instructions. An automatic biochemical analyser was used to measure triglycerides, cholesterol, high-density lipoprotein, and low-density lipoprotein. The routine blood test was conducted via the Mindray fully automatic blood analyser. All tests were conducted via the accompanying reagent kits.

sST-2 and GDF-15 were detected by enzyme-linked immunosorbent assay or electrochemiluminescence immunoassay using certified commercial kits as per the instructions. To reduce batch effects, samples should be processed in the same batch whenever possible. High- and low-concentration quality control and blank Wells should be set up with double-well repetition. The detection limit and linear range should be recorded, and the intra-batch and inter-batch coefficient of variation should be controlled at 10%. Samples with hemolysis, lipemic blood or severe jaundice were excluded.

Laboratory testing reagents and equipment

(1) sST-2 (Soluble Growth Stimulation Expression Gene 2 Protein)

Method: Enzyme-linked immunosorbent assay (ELISA)

Kit: Presage® ST2 Detection Kit (Item No. 93500)

Manufacturer: Critical Diagnostics (currently under Roche Diagnostics)

Equipment:

- Microplate reader – BioTek Synergy H1
- Plate washer – BioTek ELx405

(2) GDF-15 (Growth Differentiation Factor-15)

Method: ELISA

Kit: Human GDF-15 Quantikine ELISA Kit (Item No. DGD150)

Manufacturer: R&D Systems (currently under Bio-Techne)

Equipment: Same as above (BioTek Synergy H1 microplate reader and BioTek ELx405 washer)

(3) Neutrophil-to-Lymphocyte Ratio (NLR)

Method: Complete blood count (CBC) using an automated haematology analyser

Parameters:

- Absolute neutrophil count (NEUT#)
- Absolute lymphocyte count (LYMPH#)

Calculation: NLR = NEUT# / LYMPH#

Equipment: Sysmex XN-9000 fully automatic haematology analysis line

Manufacturer: Sysmex Corporation

Reagents: Sysmex original reagents (diluents, hemolysins, cleaning solutions, etc. – daily batch dependent)

(4) Other Equipment and Consumables

Low-temperature high-speed centrifuge – Eppendorf 5424R (Eppendorf)

-80 °C ultra-low temperature storage freezer – Thermo Scientific Forma 900 Series (Thermo Fisher Scientific)

-20 °C refrigerator – Haier (for short-term reagent storage)

Micropipettes (10 μL–1000 μL range) – Eppendorf Research® plus

Blood collection tubes:

- Sterile EDTA anticoagulant tubes–BD Vacutainer® (Item No. 368861) Used for NLR

- Serum separation tubes–BD Vacutainer® (Item No. 367812) Used for sST-2 and GDF-15

Observation indicators

Multivariate analysis of the prognosis of COPD combined with PH, comparison of serum sST-2 and GDF-15 levels and the NLR in each group, the relationships between serum sST-2 and GDF-15 levels and the NLR and between the severity of COPD combined with PH, and the diagnostic value of combined detection of the three indicators for poor prognosis of COPD combined with PH were performed.

Statistical processing methods

Data analysis and processing were conducted using SPSS 21.0. Measurement data that conform to a normal distribution are expressed as $\bar{x}\pm s$. The t-test was used for comparisons between two groups, analysis of variance for comparisons among multiple groups, and the least significant difference (LSD) test for pairwise comparisons among multiple groups. Numbers of cases or percentages are used to express count data. The diagnostic effectiveness of blood sST-2 and GDF-15 levels, as well as the NLR, for predicting poor prognosis in patients with COPD and PH was examined using ROC curves.

Results

Comparison of serum sST-2 and GDF-15 levels and the NLR in the COPD combined with PH group, COPD group and healthy control group

The COPD with PH group had significantly higher serum sST-2, GDF-15, and NLR levels than both the COPD and healthy control groups. The difference between the COPD group and the healthy control group was statistically significant ($P<0.05$), see *Table I*.

Comparison of serum sST-2 and GDF-15 levels and the NLR among the mild group, moderate group and severe group

There were 38 patients in the severe group, 50 in the moderate group, and 33 in the mild group. Compared with the mild and moderate groups, the severe group's serum sST-2, GDF-15, and NLR levels were significantly higher. However, compared with the mild group, the moderate group's levels were noticeably higher. The differences were statistically significant ($P<0.05$) (*Table II*).

Comparison of the general data and various test indices between the good prognosis group and the poor prognosis group

There were 28 patients in the poor-prognosis group and 93 in the good-prognosis group. The LVEF was significantly higher in the good-prognosis group than in the poor-prognosis group, even though serum sST-2, GDF-15, and NLR levels were significantly lower in the good-prognosis group than in the poor-prognosis group. Age, sex, length of illness, hypertension, diabetes, triglycerides, cholesterol, and levels of high-density lipoprotein or low-density lipoprotein did not differ significantly between the groups with excellent and poor prognoses ($P>0.05$; see *Table III*).

Multivariate logistic regression analysis of the prognosis of COPD combined with PH

The LVEF, sST-2, GDF-15, and NLR, which were significantly different (Table III), were included in the multivariate logistic regression analysis. In patients with COPD and PH, the NLR, elevated serum sST-2 and GDF-15 levels, and reduced LVEF were independent risk factors for a poor prognosis ($P<0.05$), see *Table IV.*

Diagnostic efficacy of serum sST-2 and GDF-15 levels and the NLR for the poor prognosis of COPD patients with PH

Based on multivariate logistic analysis findings of poor prognosis, the equation $Y=0.27\times X$sST-

Table I Comparison of serum sST-2, GDF-15 levels and NLR between the COPD combined with PH group, COPD group and healthy control group ($\bar{x}\pm s$).

Group	n	sST-2 (ng/mL)	GDF-15 (pe/L)	NLR
Healthy control group	45	11.73±2.74	0.85±0.21	1.43±0.36
COPD group	75	37.32±4.25	2.48±0.73	2.78±0.54
COPD combined with the PH group	121	42.93±5.40	3.79±0.99	3.92±0.84
F		884.299	264.105	267.906
P		<0.001	<0.001	<0.001

Table II Comparison of serum sST-2, GDF-15 levels and NLR between mild, moderate and severe groups ($\bar{x}\pm s$).

Group	n	sST-2 (ng/mL)	GDF-15 (μg/L)	NLR
Mild group	33	36.99±1.92	2.70±0.42	2.97±0.41
Moderate group	50	42.86±1.85	3.79±0.41	3.97±0.35
Severe group	38	48.19±5.18	4.74±0.91	4.67±0.77
F		102.221	98.322	90.187
P		<0.001	<0.001	<0.001

Table III General information and comparison of various detection indicators levels between the good prognosis group and the poor prognosis group [n (%) or $\bar{x}\pm s$].

Group	n	Gender		Age (years)	Disease duration (years)	Hypertension	Diabetes
		Male	Female				
Good prognosis group	93	64 (68.82)	29 (31.18)	62.71±10.19	5.32±1.42	60(64.52)	25(26.88)
Poor prognosis group	28	16 (57.14)	12 (42.86)	64.11±10.12	5.57±1.91	21 (75.00)	10 (35.71)
x^2/t		0.840		-0.637	-0.746	0.648	0.444
P		0.359		0.525	0.457	0.421	0.505

Group	n	LVEF (%)	Triglycerides (mmol/L)	Cholesterol (mmol/L)	High density lipoprotein (mmol/L)
Good prognosis group	93	64.13±8.18	1.15±0.31	3.91±1.06	1.33±0.45
Poor prognosis group	28	59.71±10.06	1.26±0.46	4.19±1.50	1.33±0.29
x^2/t		2.370	-1.259	-1.084	0.040
P		0.019	0.217	0.280	0.968
Good prognosis group	93	2.42±0.62	41.47±4.27	3.55±0.86	3.74±0.77
Poor prognosis group	28	2.64±0.80	47.78±5.95	4.59±0.98	4.50±0.82
x^2/t		-1.543	-5.214	-5.449	-4.541
P		0.125	<0.001	<0.001	<0.001

Table IV Multivariate logistic regression analysis of OPD combined with PH prognosis.

Indicator	β	SE	Wald x^2	P	OR (95%CI)
LVEF	-0.095	0.038	6.135	0.013	0.909 (0.843 0.980)
sST-2	0.289	0.079	13.520	0.001	1.335 (1.144 1.557)
GDF-15	1.363	0.392	12,068	0.001	3.909 (1.812 8.437)
NLR	1.522	0.451	11.392	0.002	4.581 (1.893 11.087)

Table V Diagnostic efficacy of serum sST-2, GDF-15 levels, and NLR in predicting poor prognosis of COPD complicated with PH.

Indicator	Best Truncation Value	Sensitivity (%)	Specificity (%)	AUC (95%CI)
sST-2	45.53 ng/mL	67.9	86.0	0.801 (0.718~0.868)
GDF-15	3.56p μg/L	92.9	57.0	0.798 (0.715~0.865)
NLR	3.90	75.0	64.5	0.753 (0.666~0.827)
Joint Projects	-	78.6	93.5	0.916 (0.852~0.959)

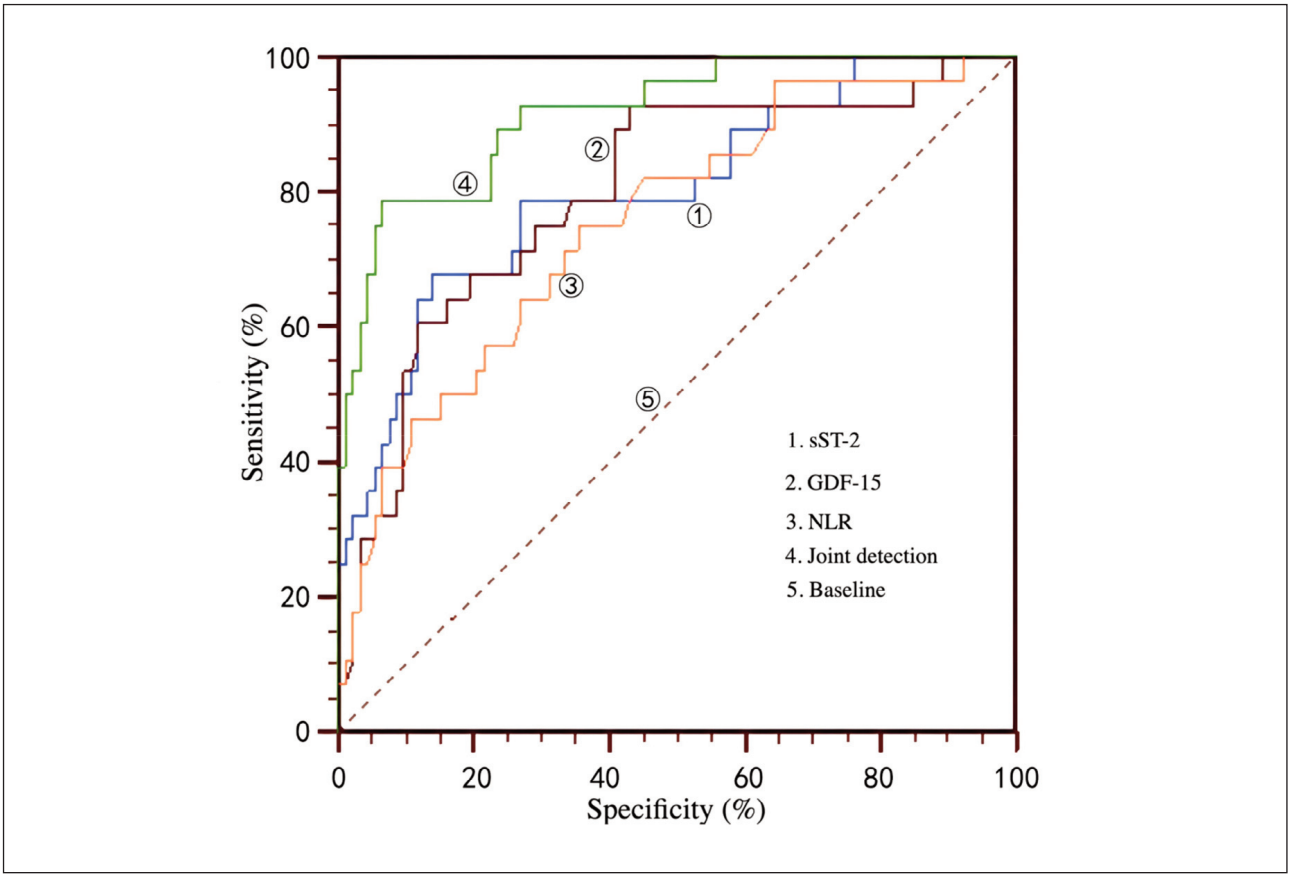

Figure 1 ROC curves of serum sST-2 and GDF-15 levels and the NLR in the poor prognosis of COPD patients complicated with PH.

2+1.20×XGDF-15+1.40×XNLR-23.65 was established as the combined detection model. The sensitivity of the combined detection method was 78.6%, the specificity was 93.5%, and the AUC was 0.916, which were significantly greater than those of the individual indicators sST-2 (Z=2.486, P=0.013), GDF-15 (Z=2.542, P=0.011), and NLR (Z=2.902, P=0.004), while among the three indicators, A was not significantly different in UC (P>0.05), see *Figure 1* and *Table V*.

Discussion

The pathogenesis of COPD combined with PH is rather complex. Generally, inflammatory responses and hypoxemia lead to abnormal contraction of pulmonary blood vessels, resulting in proliferation of vascular endothelial cells and abnormal fibrosis of the vascular intima, which, in turn, causes thickening of the vessel wall, vascular stiffness, and PH formation. Once COPD is combined with PH, it not only accelerates the progression of the disease but also increases the risk of death in patients (14–16). Therefore,

understanding the prognosis of COPD combined with PH at an early stage and implementing appropriate interventions early are highly clinically important for improving patient outcomes (17).

sST-2 competitively binds to the interleukin-33 receptor, inhibiting the interleukin-33/sST-2 signalling pathway and promoting the onset and progression of inflammatory responses (18–20). Some studies have reported that serum sST-2 levels are negatively correlated with lung function in COPD patients. By detecting serum sST-2 levels, the severity of the disease and lung function can be assessed (21).

When the serum sST-2 concentration was >45.53 ng/mL, the sensitivity for diagnosing the poor prognosis of patients with COPD combined with PH was 67.9%, the specificity was 86.0%, and the AUC was 0.801, indicating that sST-2 has high diagnostic efficacy for the poor prognosis of patients with COPD combined with PH (22). sST-2 is involved in the processes of pulmonary fibrosis and the pulmonary inflammatory response and is associated with the body's Th2-type immune response (23). Moreover, the serum sST-2 level in patients who died of pulmonary disease was significantly higher than that in surviving patients, and it is believed that the serum sST-2 level can serve as an important predictor of death within 1 year (24–26).

The group with COPD and PH had a considerably higher serum GDF-15 level than both the COPD group and the healthy control group (27). Moreover, the serum GDF-15 level increases with the severity of PH, indicating that the serum GDF-15 level is an important indicator reflecting the severity of PH (28–30). GDF-15 is a member of the transforming growth factor- superfamily and is associated with impaired lung function (31–33). The greater the increase in its level, the more severe the impairment of lung function, which may be related to damage to airway epithelial cells, increased airway resistance, increased airway mucosal secretion, and impaired lung ventilation function caused by GDF-15 (34–36). This may be related to the activation of inflammatory signalling pathways by GDF-15, the promotion of mucin expression in airway epithelium, the increase in sputum volume, and the aggravation of airway obstruction (37). Moreover, GDF-15 can activate the inflammatory response, increase the number of local airway neutrophils, trigger a massive release of inflammatory mediators, aggravate COPD, and increase the risk of PH. This study revealed that when the serum GDF-15 concentration was >3.56 μg/L, the sensitivity for the poor prognosis of patients with COPD combined with PH was 92.9%, the specificity was 57.0%, and the AUC was 0.798, indicating that the serum GDF-15 concentration has high diagnostic value for the poor prognosis of patients with COPD combined with PH.

The COPD and healthy control groups had considerably lower NLRs than the COPD and PH groups. Moreover, the NLR increased with increasing severity of PH, indicating a significant correlation between the NLR and COPD. The NLR is the ratio of neutrophils to lymphocytes, reflecting the balanced state of the body's inflammatory response (38). When the body is infected or under stress, an inflammatory response characterised by a significant increase in neutrophil numbers occurs. Moreover, the body undergoes immunosuppression, with a significant decrease in lymphocyte counts, leading to a marked increase in NLR. A study of COPD combined with PH found that the NLR was positively correlated with PH severity, suggesting that immune changes induced by alterations in pulmonary vascular structure may be involved. This study revealed that when the NLR was >3.90, the sensitivity for diagnosing poor prognosis in patients with COPD combined with PH was 75.0%, the specificity was 64.5%, and the AUC was 0.753, proving the NLR's high diagnostic effectiveness in identifying patients with COPD and PH who have a poor prognosis.

The combined detection of sST-2 and GDF-15 levels and the NLR has greater diagnostic efficacy for predicting poor prognosis in patients with COPD and PH. The AUC was significantly greater than that of a single indicator, indicating that all three indicators are related to the inflammatory response and have some complementarity. The specific mechanism needs further study.

Conclusion

Serum sST-2, GDF-15, and NLR levels are indicators of the severity of COPD combined with PH. The combined detection of these three indicators helps improve diagnostic efficacy in patients with COPD and PH at high risk of poor prognosis.

Authors' contribution

Wei Chen and Guoling Lyu contributed equally as first authors to this work.

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Conflict of interest statement

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

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