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ORIGINAL RESEARCH

Predictive Value of Smoking Index Combined with NT-proBNP for Patients with Pulmonary Hypertension Due to Chronic Lung Disease: A Retrospective Study

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Purpose: Smoking is a major risk factor for the group 3 PH. NT-proBNP is a biomarker for risk stratification in PH. This study aims to investigate the effects of smoking status and smoking index (SI) on group 3 PH and to evaluate the value of SI and SI combined with NT-proBNP in early diagnosis and prediction of disease severity.

Patients and Methods: Four hundred patients with group 3 PH at the First Hospital of Shanxi Medical University between January 2020 and December 2021 were enrolled and divided into two groups: mild (30 mmHg ≤ pulmonary artery systolic pressure (PASP)≤50 mmHg) and non-mild (PASP >50 mmHg). The effect of smoking on group 3 PH was analyzed using univariate analysis, and logistic analysis was conducted to evaluate the risk of group 3 PH according to smoking status and SI. Spearman correlation coefficient was used to test the correlation between SI and the index of group 3 PH severity. The predictive value of SI was evaluated using a receiver operating characteristic (ROC) curve.

Results: Correlation and logistic analyses showed that SI was associated with PH severity. Smoking status (*P*=0.009) and SI (*P*=0.039) were independent risk factors for non-mild group 3 PH, and ROC showed that the predictive value of SI (AUC:0.596) for non-mild PH was better than that of the recognized pro-brain natriuretic peptide (NT-proBNP) (AUC:0.586). SI can be used as a single predictive marker. SI and NT-proBNP can be formulated as prediction models for screening non-mild clinical cases (AUC:0.628).

Conclusion: SI is a potentially ideal non-invasive predictive marker for group 3 PH. SI and NT-proBNP could be used to develop a prediction model for screening non-mild PH cases. This can greatly improve the predictive specificity of the established PH marker, NT-proBNP.

Keywords: smoking index, NT-proBNP, pulmonary hypertension, chronic lung disease, predictive value

Introduction

Pulmonary hypertension (PH) is a disease characterized by pulmonary vascular remodeling and a progressive increase in pulmonary arterial resistance, which eventually leads to right heart failure and death.[1,2] PH is classified into five groups

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according to the 5th World Pulmonary Hypertension Symposium. PH frequently results from left heart disease (group 2) and lung diseases (group 3).[3] Symptoms of PH are nonspecific so that the early detection is difficult.[4] The research has suggested that PH incident is about 1% among the global population and the number of it is up to 10% in the people who are over 65.[5] The characteristics of this disease include high disability and mortality rate,[5] without promptly therapy. Furthermore, progressive right heart dysfunction, which leads to escalating symptoms, is often fatal.[6–8] This is partly due to the lack of understanding of the biological behavior of PH, limited treatment optionsand ineffective screening for this disease. Therefore, effective screening and early diagnosis can prevent or delay disease progression and improve the outcomes of affected individuals.

Smoking is a risk factor for various health conditions and is recognized as a significant source of multiple pollutants.[9] It is closely associated with chronic lung diseases and cardiovascular diseases.[10,11] Cigarette smoke has been found to act directly on blood vessels and promote smooth muscle cell proliferation, affecting both systolic and diastolic phases of the blood vessels, leading to pulmonary hypertension and right ventricular remodeling.[12,13] In addition, Higher systolic right ventricular pressure, inner wall thickening and right ventricular hypertrophy were observed in the smoking group of rats in animal experiments, but smoking cessation may prevent further vascular remodeling.[14] Thus smoking is a risk factor for PH,[15,16] can directly exacerbate PH severity,[17] and is closely associated with the development of group 3 PH.[18]

Currently, smoking status, cigarette exposure, and duration of abstinence can predict pulmonary fibrosis and pulmonary emphysema,[19] and smoking index (SI) is an important indicator for assessing smoking status. SI provides a quantitative measure of an individual's cumulative smoking and is used as a measure of smoking history and frequency, helping to understand an individual's level of smoking and potential health effects.[20] However, the effect of smoking on the level of laboratory indices and their correlation with the severity of group 3 PH remains largely overlooked, and whether smoking index (SI) can be used as a non-invasive marker of the group 3 PH is unclear. NT-proBNP is a biomarker for risk stratification in PH and is associated with relevant pulmonary haemodynamic indices.[21,22] There are significant differences in the expression of NT-proBNP in different stages and progression of lung disease.[23] Researches indicate that raised NT-proBNP levels have been found in patients with chronic lung diseases and Pulmonary heart disease as a consequence of pulmonary hypertension,[24] suggesting that NT-proBNP is strongly associated with group 3 PH.

In this study, we aimed to investigate the effects of smoking and SI on the severity of PH in group 3 and its related laboratory parameters. We sought to understand the underlying mechanisms involved and assess the predictive value of SI and SI combined with NT-proBNP for early diagnosis and prediction of disease severity.

Material and Methods

Study Design

This retrospective observational study was conducted at the First Hospital of the Shanxi Medical University. All adult inpatients (18–90 years old) with PH who underwent echocardiography between January 1, 2020, and December 31, 2021, were screened. This study has been approved by the ethics committee of the First Hospital of Shanxi Medical University (Approval Number K-138), and the application for scientific research exemption for informed consent has been approved. For patients with multiple admissions during the study period, the first hospital admission has been examined.

Patient Enrolment

In this study, 2360 patients were screened. Based on the inclusion and exclusion criteria, 400 patients were enrolled in this study. Four hundred cases of 3 group PH were categorized in this study according to the 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension.[25] There were 277 cases of PH due to obstructive lung disease or emphysema, 82 cases of PH due to restrictive lung disease, 13 cases of PH due to Lung disease with mixed restrictive/obstructive pattern, 26 cases of PH due to hypoventilation syndromes, and 2 cases of PH due to developmental lung disorders. Inclusion criteria: a. patients who were 18–90 years old; b. patients who had chronic lung disease based on clinical symptoms, signs, risk factors, chest X-rays, and other tests; and c. patients who were diagnosed with PH based on echocardiographic findings. Exclusion criteria: a. PH complicating pregnancy; b. complications with certain forms of malignant diseases (such as cancer), silicosis, or pneumoconiosis; c. patients who smoked other tobacco products; and

d. Patients in other PH groups. The severity of PH was divided into two groups: mild (30 mmHg ≤ pulmonary artery systolic pressure (PASP) ≤ 50 mmHg) and non-mild (PASP > 50 mmHg) according to the degree of increased pulmonary artery systolic pressure (PASP).[26]

Data Collection

The clinical data were collected by two independent reviewers using an electronic medical record system. These data were obtained from the patients before PH-specific treatment initiation, including sociodemographic characteristics (age, sex, diabetes, hypertension, smoking status, alcohol consumption status, body mass index (BMI), length of stay), blood cell count, serum cardiac markers, arterial blood gas analysis indicators, coagulation indices, and echocardiography indicators.

In this study, smokers were defined as those who smoked at least 5 cigarettes per day for 6 or more consecutive months. (Smoking Index ≥ 5). The remaining patients were classified as non-smokers. Smoking Index (SI) = number of cigarettes smoked per day × number of years smoked.

Statistical Analysis

The study data were analyzed using SPSS (version 25.0). Continuous variables are presented as median (inter-quartile range). Categorical variables are presented as counts (percentages). Comparisons between the two groups were performed using the Mann–Whitney *U*-test and chi-square test. Correlation analyses were performed using Spearman correlation coefficients for SI and 3 groups of PH severity-related variables. To correct for potential confounders, correlations between variables were further assessed by multiple linear regression analysis ($P < 0.05$). Binary logistic regression was used to analyse independent risk factors for non-mild group 3 PH. Receiver operating characteristic (ROC) curve analysis was performed on the predictive performance of SI and SI combined with NT-proBNP for non-mild PH. Statistical significance was set at $\alpha = 0.05$.

Results

Baseline Characteristics of the Study Population and Mild and Non-Mild Patients

A total of 2360 patients with PH were hospitalized in the institution from January 1, 2020, to December 31, 2021. One patient smoked other tobacco products, and 1190 patients had malignant diseases, silicosis, pneumoconiosis, or pregnancy. Out of 1169 patients who were not excluded, 400 were 3group PH cases. Thus, 400 patients formed the study cohort (Figure 1).

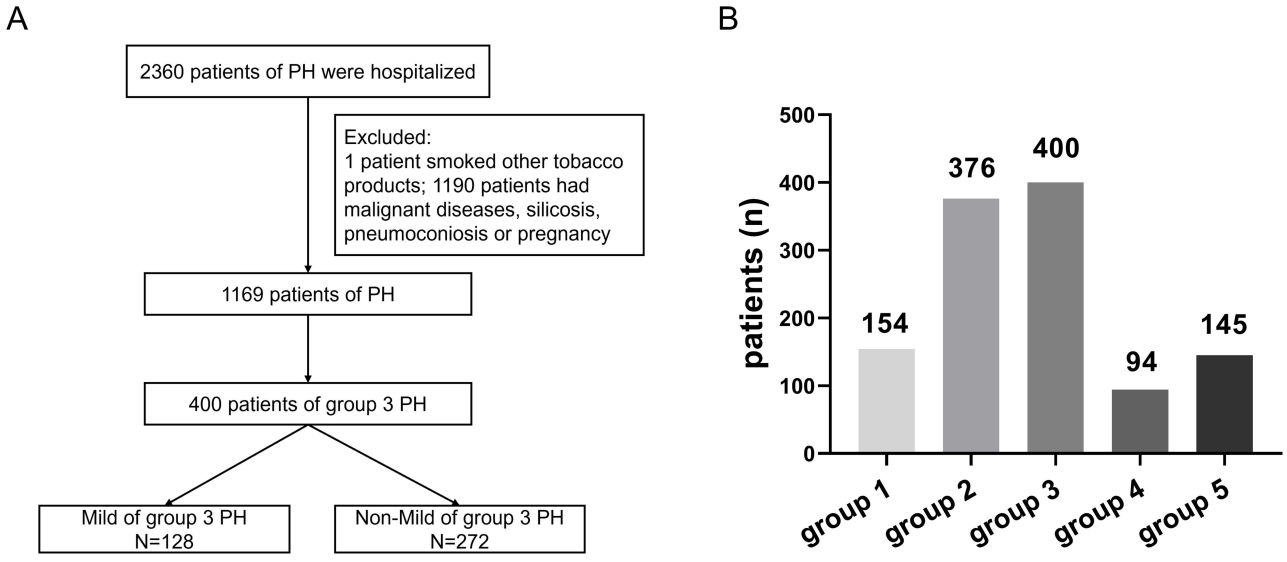

Figure 1 Study population. (**A**) Flow chart. (**B**) Distribution of PH patients in 5 groups.

The baseline characteristics of the included patients and mild and non-mild patients in group 3 PH are presented in Table 1. Among the 400 patients with group 3 PH, 128 were categorized into the mild group and 272 into the non-mild group. The mean age of the patients was 71 years, and the majority of patients are male patients (68.3%). The median length of hospital stay was 11 days (IQR, 8.00–14.00 days), and 39.8% of the patients had hypertension. SI was significantly higher in non-mild patients (median [IQR],[27],200 [0.00–800.00]) than in mild patients (median [IQR], 0.00 [0.00–600.00]) ($P = 0.009$), and there were more smokers in the non-mild group (55.5%) than in the mild group (41.4%) ($P = 0.008$). There were no significant differences in the average age and sex between the two groups (age: median [IQR], 72.00 [65.25–81.00] vs 71.00 [63.00–79.00], $P = 0.443$; male proportion: 61.7% versus 71.3%, $P = 0.054$). No significant differences were observed between the two groups with respect to BMI, drinking habits, or basic diseases.

Baseline Characteristics of Different Smoking Status Patients

The baseline characteristics of the non-smokers and smokers are presented in Table 2. Patients in the smoking group were younger than those in the non-smoking group (median [IQR], 74.00 [64.00–81.00] vs 70.00 [62.00–77.75], $P = 0.029$). Non-smokers had a significantly higher BMI than smokers (median [IQR], 22.00 [19.10–25.70] vs 21.25 [18.50–24.35], $P = 0.044$). Male and drinkers of smokers group were more than the non-smokers group (male: 69.2% vs 30.8%, $P <$

Table 1 Basic Characteristics of Mild Patients and Non-Mild Patients with Group 3 PH

Index	Total (n=400)	Mild (n=128)	Non-Mild (n=272)	*P* value
Age(y), Median(IQR)	71.00(63.00–80.00)	72.00(65.25–81.00)	71.00(63.00–79.00)	0.443
BMI, Median(IQR) (kg/m^2)	21.40(18.80–25.00)	21.20(18.73–24.88)	21.20(18.00–25.00)	0.757
SI, Median(IQR)	42.5(0–600)	0.00(0.00–600.00)	200.00(0.00–800.00)	0.009
LOS(d), Median(IQR)	11.00(8.00–14.00)	13.50(8.75–16.25)	11.00(8.00–15.00)	0.128
Sex, No. (%)				0.054
Male	273(68.3)	79(61.7)	194(71.3)	
Female	127(31.8)	112(38.3)	15(28.7)	
Drinkers, No. (%)	96(24.0)	24(18.8)	72(26.5)	0.092
Diabetes, No. (%)	48(12.0)	15(11.7)	33(12.1)	0.905
Hypertension, No. (%)	159(39.8)	52(40.6)	107(39.3)	0.806
Smokers, No. (%)	204(51)	53(41.4)	151(55.5)	0.008

Abbreviations: *BMI, body mass index; SI, smoking index; LOS, length of stay.*

Table 2 Basic Characteristics of Non-Smokers and Smokers Patients with Group 3 PH

Index	Non-smokers (n=196)	Smokers (n=204)	*P* value
Age(y), Median(IQR)	74.00(64.00–81.00)	70.00(62.00–77.75)	0.029
BMI, Median(IQR) (kg/m^2)	22.00(19.10–25.70)	21.25(18.50–24.35)	0.044
SI, Median(IQR)	0.000	600.00(412.50–1000.00)	<0.001
LOS(d), Median(IQR)	11.00(8.00–15.00)	10.00(8.00–14.00)	0.724
Sex, No. (%)			<0.001
Male	84(30.8)	189(69.2)	
Female	112(88.2)	15(11.8)	
Drinkers, No. (%)	8(4.1)	88(43.1)	<0.001
Diabetes, No. (%)	26(13.3)	22(10.8)	0.445
Hypertension, No. (%)	87(44.4)	72(35.3)	0.063
Severity of illness, No. (%)			0.008
Mild PH	75(38.3)	53(26.0)	
Non-Mild PH	121(61.7)	151(74.0)	

Abbreviations: *BMI, body mass index; SI, smoking index; LOS, length of stay.*

0.001; drinkers: 43.1% vs 4.1%, $P < 0.001$), and the SI of the smoking group was concentrated at 600 (IQR, 412.50–1000.00). No significant differences were observed between the two groups with respect to basic diseases.

The Relationship Between the Severity of Group 3 PH, Smoking Status and Various Indicators

The Relationship Between the Severity of Group 3 PH, Smoking Status and Blood Cell Indices

Table 3 summarizes the relationship between the severity of PH in group 3, smoking status, and blood cell indices. The red cell volume distribution width (RDW) level was significantly higher in non-mild patients than in mild patients ($P < 0.001$). The levels of red blood cells (RBC) and hemoglobin in smokers were significantly higher than those in non-smokers ($P < 0.001$); however, no significant difference was found between mild and non-mild patients ($P > 0.05$). In addition, the remarkably higher level of hematocrit in non-mild patients and smoker patients than these in mild patients and non-smoker patients. The platelet count was significantly lower in non-mild patients and smokers than in mild patients ($P < 0.001$) and non-smokers ($P = 0.023$). Regarding LYMPH, percentage of neutrophils (NEUT) and white blood cell (WBC), no significant differences were found in disease severity and smoking status ($P > 0.05$).

The Relationship Between the Severity of Group 3 PH, Smoking Status and Serum Cardiac Markers

Table 4 shows that there were no significant differences in calcitonin, creatine kinase-MB (CK-MB), or cardiac troponin T (cTnT) levels among the patients. Non-mild patients presented significantly higher cardiac troponin I (cTnI) levels than mild patients ($P = 0.033$) but not in smokers than in non-smokers ($P > 0.05$). Moreover, NT-proBNP levels were

Table 3 Effects of Group 3 PH Severity and Smoking Status on Blood Cell Analysis Indicators

Group (n)	LYMPH %	NEUT %	RDW %	WBC 10^9/L	RBC 10^12/L	Hemoglobin g/L	Hematocrit %	Platelet 10^9/L
Mild	19.95 (12.03–27.88)	67.90 (57.15–76.08)	14.10 (13.35–15.10)	6.15 (4.60–7.28)	4.42 (4.16–5.18)	139.00 (129.50–159.75)	42.85 (39.66–50.13)	204.00 (130.00–261.00)
Non-Mild	16.30 (11.30–22.30)	69.50 (63.50–69.50)	15.00 (13.70–17.20)	6.50 (4.80–9.10)	4.43 (3.95–4.99)	137.00 (117.00–158.00)	43.90 (35.90–49.40)	170.00 (120.00–222.00)
***P* value**	0.142	0.380	<0.001	0.815	0.109	0.183	0.031	<0.001
Non-Smoker	16.30 (11.00–25.90)	70.80 (61.73–78.30)	14.35 (13.30–16.10)	6.25 (4.83–8.30)	4.26 (3.70–4.82)	130.50 (108.00–145.00)	40.70 (33.55–44.80)	186.50 (138.25–245.75)
Smoker	19.00 (12.70–25.60)	68.05 (61.50–74.88)	14.30 (13.23–15.90)	6.30 (4.90–8.00)	4.61 (4.10–5.27)	144.00 (129.00–164.75)	44.50 (38.95–51.95)	169.50 (127.25–224.50)
***P* value**	0.078	0.076	0.546	0.885	<0.001	<0.001	<0.001	0.023

Abbreviations: LYMPH, Percentage of lymphocytes; NEUT, percentage of neutrophils; RDW, red cell volume distribution width; WBC, white blood cell; RBC, red blood cell.

Table 4 Effects of Group 3 PH Severity and Smoking Status on Serum Cardiac Markers

Group (n)	Procalcitonin ng/mL	NT-proBNP pg/mL	cTnT ng/mL	cTnI ng/mL	CK-MB U/L
Mild	0.06 (0.05–0.11)	572.31 (135.00–2703.15)	0.02 (0.01–0.03)	0.03 (0.01–0.05)	0.86 (0.53–6.43)
Non-Mild	0.06 (0.05–0.247)	913.12 (323.60–2978.16)	0.02 (0.01–0.04)	0.04 (0.02–0.06)	1.30 (0.71–9.00)
***P* value**	0.301	0.010	0.109	0.033	0.505
Non-Smoker	0.08 (0.05–0.21)	1439.29 (358.74–3785.65)	0.03 (0.01–0.05)	0.04 (0.02–0.07)	1.14 (0.68–13.75)
Smoker	0.06 (0.05–0.33)	848.41 (321.92–3070.74)	0.02 (0.01–0.04)	0.04 (0.02–0.06)	1.56 (0.70–12.00)
***P* value**	0.643	0.021	0.290	0.988	0.256

Abbreviations: NT-proBNP, N-terminal pro-brain natriuretic peptide; cTnT, cardiac troponin T; cTnI, cardiac troponin I; CK-MB, creatine kinase-MB.

significantly higher in non-mild patients than in mild patients ($P = 0.010$) but were much lower in smokers than in non-smokers ($P = 0.021$).

The Relationship Between the Severity of Group 3 PH, Smoking Status and Arterial Blood Gas Indices

There were no significant differences in oxygen saturation (SaO_2), pondus hydrogenii (ph), pressure of oxygen (PaO_2), GLU, or Lac among patients ($P > 0.05$). The study showed a significantly higher $PaCO_2$ level in non-mild patients and smokers than in mild patients ($P = 0.002$) and non-smokers ($P = 0.027$), respectively (Table 5).

The Relationship Between the Severity of Group 3 PH, Smoking Status and Blood Coagulation Function Indicators

Patients with non-mild disease presented a significantly higher prothrombin time (PT) level than patients with mild disease ($P = 0.026$), but not in smokers than in non-smokers ($P > 0.05$). There was the significantly higher level of APTT in non-mild patients and smokers patients than in mild patients ($P = 0.004$) and non-smokers patients ($P = 0.005$), respectively. There were no significant differences in thrombin time (TT) or D-dimer levels among the participants ($P > 0.05$) (Table 6).

The Relationship Between the Severity of Group 3 PH, Smoking Status on Echocardiography Indicators

It was observed that there was significantly higher level of right room area (RAA), tricuspid regurgitant jet velocity (TRV) and PASP in non-mild patients than in mild patients ($P < 0.001$). In contrast, there was no statistically significant

Table 5 Effects of Group 3 PH Severity and Smoking Status on Arterial Blood Gas Analysis Indicators

Group (n)	SaO_2 %	PH	PaO_2 mmHg	$PaCO_2$ mmHg	GLU mmol/L	Lac mmol/L
Mild	91.80 (83.45–95.05)	7.42 (7.37–7.44)	65.20 (53.15–77.60)	44.95 (37.60–54.68)	6.90 (5.78–8.88)	1.65 (1.20–2.13)
Non-Mild	91.20 (85.90–95.10)	7.40 (7.38–7.45)	64.00 (55.15–77.60)	48.20 (38.60–59.20)	7.10 (5.90–8.60)	1.60 (1.30–2.30)
***P* value**	0.174	0.214	0.180	0.002	0.684	0.349
Non-Smoker	92.00 (86.60–95.25)	7.41 (7.38–7.44)	66.50 (54.45–79.40)	43.10 (37.60–52.15)	7.20 (6.05–9.45)	1.60 (1.30–2.20)
Smoker	90.80 (86.10–93.80)	7.41 (7.38–7.44)	62.30 (54.60–73.80)	46.70 (38.80–56.30)	7.00 (5.70–8.70)	1.60 (1.30–2.20)
***P* value**	0.232	0.783	0.254	0.027	0.079	0.564

Abbreviations: SaO_2, oxygen saturation; GLU, glucose; Lac, lactate.

Table 6 Effects of Group 3 PH Severity and Smoking Status on Blood Coagulation Function Indicators

Group (n)	PT S	APTT S	TT S	D-Dimer μg/L
Mild	12.75 (11.98–14.10)	29.30 (25.13–32.18)	17.30 (16.13–18.25)	1.27 (0.55–18.48)
Non-Mild	13.20 (12.30–15.20)	31.00 (27.10–34.40)	17.20 (15.30–18.10)	2.62 (0.76–116.00)
***P* value**	0.026	0.004	0.336	0.261
Non-Smoker	12.90 (12.20–15.00)	29.00 (26.20–33.30)	16.90 (15.30–18.00)	2.52 (0.71–143.00)
Smoker	13.20 (12.20–15.20)	30.80 (27.20–34.50)	16.90 (15.00–18.00)	1.85 (0.59–110.00)
***P* value**	0.814	0.005	0.777	0.145

Abbreviations: PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time.

difference between the smoking and non-smoking patients ($P > 0.05$). Smokers showed significantly lower left atrial diameter (LAD) levels than non-smokers ($P = 0.008$); however, mild PH patients had higher LAD levels than non-mild PH patients ($P > 0.05$). Moreover, a significantly higher level of right ventricular internal dimension (RVID) in non-mild patients and smokers than in mild patients ($P < 0.001$) and non-smokers ($P = 0.050$), respectively. Regarding left ejection fraction (EF) and fractional shortening (FS), no significant differences were found in disease severity or smoking status ($P > 0.05$) (Table 7).

Echocardiography findings showed that smokers with mild PH in group 3 had pericardial effusion, while smokers with non-mild PH in group 3 had a more significant decrease in right ventricular function than non-smokers, and the degree of cardiac function damage in non-smokers was less than that in smokers (Figure 2), indicating that smoking may promote the development of group 3 PH.

Correlations Between SI and the Severity of Group 3 PH

The relationship between the severity of PH, smoking status and the indicators in the 3 group PH has been introduced above. These six indicators (hematocrit, platelet, NT-proBNP, PaCO2, APTT, and RVID) were obtained from the above tables, with statistical significance, and were used for correlation analysis with SI. As shown in Table 8, SI was positively correlated with hematocrit, $PaCO_2$, APTT, and RVID, and negatively correlated with platelet and NT-proBNP levels.

In the Multiple linear regression analysis (enter method), we further assessed the correlations between SI and hematocrit, platelet, NT-proBNP, $PaCO_2$, APTT, and RVID by adjusting for sex, BMI, and diabetes. The results showed that SI was still positively correlated with hematocrit and $PaCO_2$, and negatively correlated with NT-proBNP. Additionally, SI tended to correlate with APTT ($r = 0.073$, $P = 0.072$) and RVID ($r = 0.079$, $P = 0.058$). No collinearity was detected in the multivariate linear regression analysis.

Combination of SI and NT-proBNP in Predicting Non-Mild Group 3 PH

Univariate logistic analysis showed that smoking status (95% *CI*:1.15417–2.70201) and SI (95% *CI*:1.00002–1.00087) were independent risk factors for non-mild group 3 PH (Table 9), which can be a significant predictor of non-mild group 3 PH. ROC curve analysis was performed to evaluate the predictive value (Figure 3). The sensitivity of SI alone to differentiate non-mild from mild cases was 52.8%, with an area under the curve (AUC) of 0.596 and a specificity of 66.7%. To provide better insight into the predictive value of SI for non-mild group 3 PH, it was evaluated against the established PH biomarker NT-proBNP.[28] A dichotomous logistic regression model was also established to evaluate the prediction value of SI combined with NT-proBNP in group 3 PH (Table 10). The results showed that the area under the curve for SI (AUC: 0.596) was larger than that for NT-proBNP (AUC: 0.586). SI is a potential predictive marker. Furthermore, the AUC of SI + NT-proBNP was significantly higher than that of NT-proBNP or SI alone, and the AUC

Table 7 Effects of Group 3 PH Severity and Smoking Status on Echocardiography Indicators

Group (n)	LAD mm	RVID mm	RAA mm^2	EF %	FS %	TRV cm/s	PASP mmHg
Mild	36.00 (30.00–40.50)	24.00 (21.00–27.00)	2099.00 (1404.25–2757.00)	63.50 (55.25–69.00)	34.00 (29.75–39.00)	303.00 (287.25–318.25)	46.00 (42.75–48.00)
Non-Mild	34.00 (30.00–40.00)	27.00 (24.00–31.00)	2350.00 (1887.00–3080.00)	64.00 (58.00–69.00)	34.00 (30.00–39.00)	373.00 (347.00–418.00)	65.00 (58.00–82.00)
***P* value**	0.399	<0.001	<0.001	0.351	0.354	<0.001	<0.001
Non-Smoker	36.50 (31.00–42.00)	24.00 (20.00–29.00)	2160.00 (1558.50–2860.00)	64.00 (58.00–68.00)	35.00 (31.00–39.00)	339.00 (312.00–383.75)	56.00 (47.00–69.00)
Smoker	33.00 (30.00–39.00)	26.00 (22.00–29.00)	2120.00 (1638.50–2673.00)	64.00 (57.75–69.00)	34.00 (30.00–38.25)	354.50 (328.00–395.00)	60.00 (50.75–72.00)
***P* value**	0.008	0.050	0.911	0.264	0.409	0.054	0.132

Abbreviations: LAD, left atrial diameter; RVID, right ventricular internal dimension; RAA, right room area; EF, left ejection fraction; FS, fractional shortening; TRV, tricuspid regurgitant jet velocity; PASP, pulmonary artery systolic pressure.

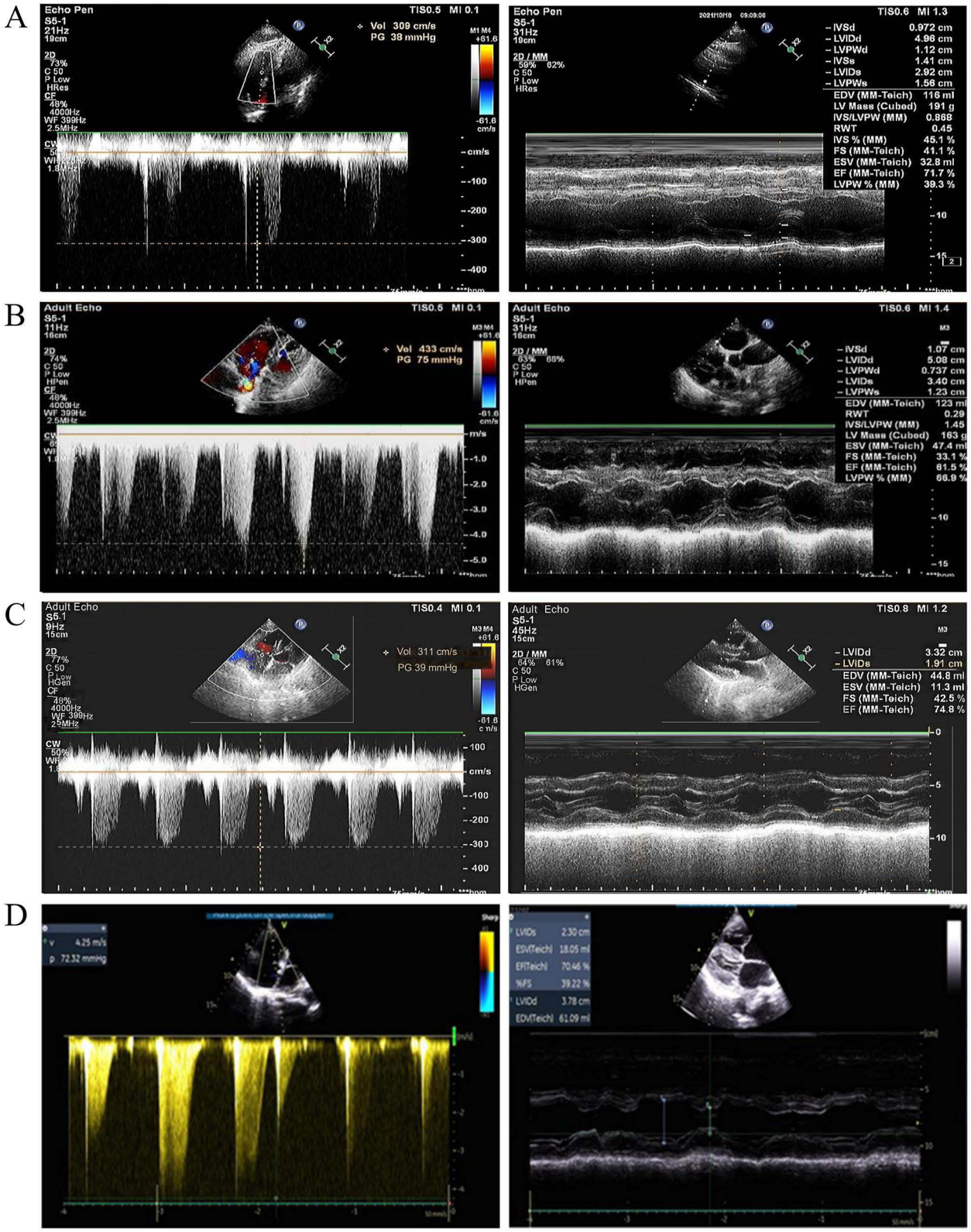

Figure 2 Echocardiography of mild and non-mild group 3 PH patients with different smoking status. (**A**) 70 years old male non-smokers with mild symptoms had a PASP of 43. (**B**) 70 years old male non-smokers with non-mild symptoms had a PASP of 85. (**C**) 70 years old male smokers with mild symptoms had a PASP of 44. (**D**) 70 years old male smokers with non-mild symptoms had a PASP of 82.

Table 8 Correlations Between Smoking Index and Index of PH Severity

Index	Coefficient (*r*)	*P* value	Adjusted coefficient (*r*)*	*P* value
Hematocrit	0.255	<0.001	0.191	<0.001
Platelet	−0.105	0.036	−0.059	0.121
NT-proBNP	−0.129	0.015	−0.096	0.035
$PaCO_2$	0.139	0.009	0.108	0.021
APTT	0.131	0.009	0.073	0.072
RVID	0.103	0.040	0.079	0.058

Abbreviations: SI, smoking index; NT-proBNP, N-terminal pro-brain natriuretic peptide; APTT, activated partial thromboplastin time; RVID, right ventricular internal dimension.
*Each variable is adjusted for gender, body mass index, diabetes by multivariate linear regression analysis.

Table 9 Univariate Logistic Analysis of Smoking Status, SI and Non-Mild Group 3 PH

Index	*B*	*P* value	*OR* (95% CI)
Smoking status	0.5687	0.009	1.76594(1.15417,2.70201)
SI	0.0004	0.039	1.00045(1.00002,1.00087)

Abbreviation: SI, smoking index.

increased to 0.628 (Table 11). The final regression equation for this joint prediction model was as follows logit (P) = 0.474 + 0.00057× SI + 0.00006×NT-proBNP level.

Discussion

Group 3 PH is a kind of disease with high morbidity and mortality rate.[29] Clinical symptoms and somatic symptoms are difficult to identify, and currently there is no specific therapy for group 3 PH.[28] Despite the apparent progress in the study of PH, many clinical and scientific issues remain incompletely defined, and early prevention and early diagnosis are essential.[30] Smoking is a known risk factor for lung diseases and may directly promote the development and progression

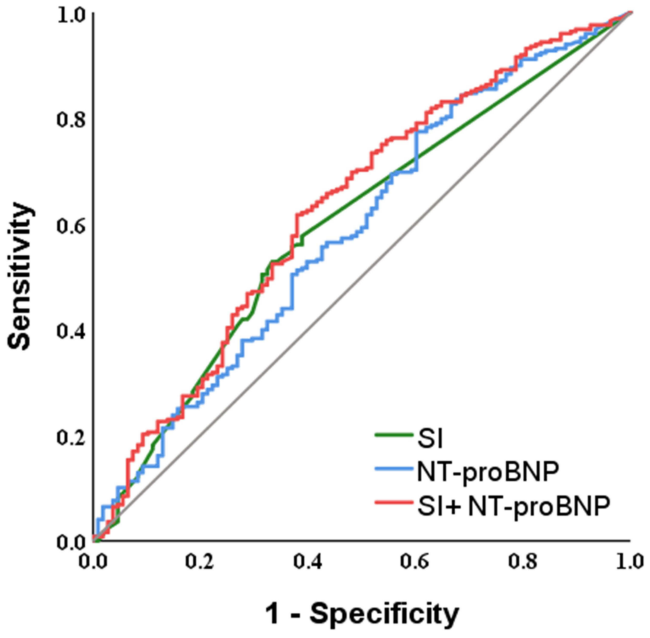

Figure 3 Prediction value of SI in non-mild group 3 PH.

Table 10 Multivariate Logistic Analysis of NT-proBNP, SI and Non-Mild Group 3 PH

Index	*B*	*P* value	*OR* (95% CI)
NT-proBNP	0.00006	0.087	1.00006(1.00000,1.00014)
SI	0.00057	0.018	1.00057(1.00010,1.00104)

Abbreviations: SI, smoking index; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Table 11 Test Characteristics for Prediction of Non-Mild Group 3 PH

Index	AUC	95% CI	Sensitivity	Specificity
SI	0.596	0.532–0.660	0.528	0.667
NT-proBNP	0.586	0.521–0.652	0.774	0.398
SI+ NT-proBNP	0.628	0.564–0.692	0.617	0.620

Abbreviations: SI, smoking index; NT-proBNP, N-terminal pro-brain natriuretic peptide.

of group 3 PH. Therefore, we have studied the influence of smoking status and SI on group 3 PH patients, so as to promote the prevention and diagnosis of this disease.

The study showed that the severity of PH was only related to smoking status and was not influenced by other sociodemographic characteristics. We found that the incidence of smokers in the non-mild group 3 PH was higher, age at diagnosis was lower, and degree of cardiac injury in smoking patients was greater than that in non-smoking patients, suggesting that smoking could be a risk factor and play a pathogenic role in non-mild group 3 PH patients.

In our study, significantly increased levels of RBC, hemoglobin, hematocrit, and $PaCO_2$ were observed in smokers, consistent with the findings of Adel Qlayel Alkhedaide and Nadia.[31] We hypothesized that inflammatory mediators and oxidative stress are involved in the pathogenesis of smoking group 3 PH. Long-term smoking can cause inflammatory responses in the lungs and even the whole body,[27,32] reduced oxygen-carrying capacity of the blood, increased $PaCO_2$, and decreased oxygen supply to tissues. These results could cause oxidative stress and release a large number of reactive oxygen species for compensation, resulting in an increase in RBC and hemoglobin levels and progression to respiratory failure.[33,34]

In the study of this paper, smoking and non-mild patients had lower platelet counts, higher activated partial APTT, and significantly decreased coagulation function. This is consistent with the findings of Eleni Vrigkou.[35] This finding suggests that most smoking patients in group 3 PH have coagulopathy. Park JM's study proposed that cigarette smoke extract (CSE) inhibited thrombin-induced platelet aggregation.[36] Since the toxic substances in cigarette smoke disturb the internal environment of the body, disrupting homeostasis, and since long-term smoking causes inflammatory reactions in the lungs and even the whole body.[27,32] These reactions trigger oxidative stress, releasing large amounts of reactive oxygen species (ROS), which also include oxidants produced by inflammation. These oxidative stress processes modulate platelet function and alter coagulation.[36] However, the role of coagulation deficits in the development and progression of PH has not yet been elucidated, and whether smoking causes group 3 PH coagulopathy and thus promotes the development of PH requires further investigation.

Cardiac troponin can indicate ongoing myocardial damage,[37] and NT-proBNP has diagnostic value in the differential diagnosis of acute dyspnea and possibly congestive heart failure.[38] They are markers of myocardial injury and positively correlate with disease severity.[39] In this study, it was found that there was a higher level of NT-proBNP in non-mild patients than in mild patients, and this result was consistent with Lorena Maries and Michael.[38–40] It is suggested that elevated NT-proBNP is associated with increased PH severity. Interestingly, smoking is a risk factor for group 3 PH, but smoking patients had lower NT-proBNP levels than non-smokers in this study. This is in contrast to Welsh P's study, which showed that smoking was associated with elevated NT-proBNP.[41] Since the pathogenetic processes of group 3 PH

have not been clarified to date and the role of myocardial markers in the development and progression of smoking-induced PH has not been elucidated, it could be difficult to speculate whether these findings are characteristic of group 3 PH in smoking patients or an epiphenomenon. Whether smoking causes a decrease in NT-proBNP levels and obscures the severity of the disease further increases the difficulty of diagnosis need to be discussed. The effect of smoking on myocardial markers in group 3 patients with PH remains to be studied in the future.

With elevated pulmonary vascular resistance, this can lead to right ventricular dilatation, right ventricular dysfunction, and increased tricuspid regurgitation.[30] Second, as right ventricular load increases, it can lead to left ventricular underfilling and atrophy.[42] These are consistent with the findings that RVID, RAA, TRV, and PASP were higher in non-mild patients compared with mild disease, and right heart failure was more severe in patients with non-mild PH. Meanwhile, echocardiographic results showed pericardial effusion in the 3 groups of smokers with mild PH, whereas the decline in right ventricular function was more pronounced in the 3 groups of smokers with non-mild PH than in non-smokers, and the degree of cardiac impairment was greater in smokers than in non-smokers. In addition, RVID was greater in PH smokers, and SI and RVID were positively correlated, further suggesting that smoking was a risk factor for group 3 PH and affected the severity of the disease.

Correlation and logistic analyses revealed that SI was associated with PH severity. Smoking status and SI were independent risk factors for non-mild group 3 PH. Smokers were 1.766 times more likely to develop non-mild PH than non-smokers, and for each additional cigarette smoked per year, the probability of developing non-mild PH increased by 0.045%.

NT-proBNP is a recognized diagnostic marker for PH. ROC curve analysis showed that the predictive value of SI for the severity of group 3 PH was better than that of NT-proBNP, which further suggested that SI was a potential non-invasive predictor for the severity of group 3 PH. Furthermore, SI provided additional predictive value in addition to NT-proBNP, which can greatly improve the specificity of predicting the severity of group 3 PH. SI combined with NT-proBNP could be formulated as a prediction model for screening non-mild group 3 PH for its accurate specificity and sensitivity.

Conclusion

SI is a potentially eligible and ideal non-invasive predictive marker for group 3 PH. SI and NT-proBNP could be formulated as a prediction model for screening non-mild clinical cases. This approach greatly improves the predictive specificity of the established PH marker NT-proBNP and has good value in clinical practice.

Abbreviations

PH: Pulmonary hypertension; SI: Smoking Index; PASP: Pulmonary artery systolic pressure; RHC: Right heart catheterization; BMI: Body mass index; SI: Smoking index; LOS: Length of stay; LYMPH: Percentage of lymphocytes; NEUT: Percentage of neutrophils; $PaCO_2$: Partial pressure of arterial carbon dioxide; RD: Red cell volume distribution width; WBC: White blood cell; RBC: Red blood cell; NT-proBNP: N-terminal pro-brain natriuretic peptide; cTnT: Cardiac troponin T; cTnI: Cardiac troponin I; CK-MB: Creatine kinase-MB; SaO_2: Oxygen saturation; GLU: Glucose; Lac: Lactate; PT: Prothrombin time; APTT: Activated partial thromboplastin time; TT: Thrombin time; LAD: Left atrial diameter; RVID: Right ventricular internal dimension; RAA: Right room area; PH: Pondus Hydrogenii; EF: Left ejection fraction; FS: Fractional shortening; TRV: Tricuspid regurgitant jet velocity; AUC: area under the curve.

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Ethics Approval and Informed Consent

This study was conducted in accordance with the Declaration of Helsinki and approved by the First Hospital of Shanxi Medical University Research Ethics Committee (Approval Number K-138). The Research Ethics Committee of the First Hospital of Shanxi Medical University waived the need for informed consent due to its retrospective design. This study states that all data collected was confidential and was reported in a way that ensures the privacy of participants.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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