

Elevated Pulmonary Artery Systolic Pressure is Associated with Poor Survival of Patients with Non-Small Cell Lung Cancer

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Purpose: Pulmonary hypertension (PH) is an important comorbidity of lung cancer, PH in lung cancer patients is gradually gaining interest because of its apparent high prevalence, but the impact of PH on the outcomes of lung cancer remains uncertain and had rarely been discussed. We aimed to evaluate the prevalence, determinants and prognosis value of elevated pulmonary artery systolic pressure (PASP) in non-small cell lung cancer patients.

Patients and Methods: In this retrospective study, subjects with a new and pathological confirmed diagnosis of lung cancer were enrolled. All patients underwent transthoracic echocardiography before received treatment. Pulmonary artery systolic pressure was measured by transthoracic echocardiography. Lung cancer subtypes were categorized by WHO classification of lung tumors. Hazard ratios (HR) were estimated by using Cox regression models.

Results: Among 612 non-small cell lung cancer (NSCLC) patients, 19.8% coexisted with PH. After adjustment for age, symptom, coagulation disorders, lymph node metastasis, distant metastasis, histological type, clinical stage, PASP ≥ 35 mmHg was significantly associated with the decreased overall survival (OS) of NSCLC ($P=0.028$). Moreover, PASP ≥ 45 mmHg was an independent predictor for perioperative death. Independent factors of comorbid elevated PASP were age, the presence of intrapulmonary metastasis and coagulation disorders.

Conclusion: These findings suggest that PASP is an independent prognostic risk factor for NSCLC patients. Main determinants of elevated PASP are age, the presence of intrapulmonary metastasis and coagulation disorders.

Keywords: pulmonary hypertension, non-small cell lung cancer, tumoral pulmonary hypertension, overall survival

Introduction

Lung cancer is still the most common type of cancer worldwide, and being the leading cause of cancer death, its 5-year relative survival rates is currently 18%.¹ While there is a 20% reduction in lung cancer mortality and the death rate for lung cancer dropped steadily because early diagnosis through low-dose computed tomography screening and developments in the therapy,² however, survivors of lung cancer have the worse quality of life (QoL) than other cancer survivors.³ Among the reasons, dyspnea and asthenia had a significant impact on QoL, and cardiovascular diseases (CVD) and chronic obstructive pulmonary disease are the two most prevalent comorbidities among lung cancer patients.^{4,5} A recent study found that 48% (250/519) of lung cancer patients had a mean PA diameter of ≥ 28 mm,

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suggestive of PH, as assessed by high-resolution computed tomography (CT) of the chest. However, few studies have discussed the prognosis in these population.

Lung cancer and PH are closely related and previous studies have discussed in autopsy specimens and animal models, in which pulmonary tumor thrombotic microangiopathy (PTTM) is increasingly recognized as an important cause in which underlying mechanism is believed to be microscopic tumor cell emboli and intimal proliferation.⁶ Other agents are implicated in the development of PH in cancer patients, including chronic thromboembolism pulmonary hypertension complicating venous thromboembolism. Chemotherapeutic drugs may also cause PH⁷ and pulmonary veno-occlusive disease (PVOD).⁸ Besides, histopathological evidence of lung vascular remodeling was found in human lung cancer tissue and mouse models of lung cancer suggested that lung cancer might trigger PH.⁹ From the perspective of metabonomics, pulmonary vascular cells of PH and extravascular tissue of PH patients exhibit a glycolytic switch similar to the Warburg effect in cancer, featuring increased aerobic glycolysis and decreased glucose oxidation,¹⁰ which provides intermediates for the synthesis of amino acids, lipids, and nucleotides, required for the demand of enhanced proliferation and apoptosis resistance in cells of PH.¹¹

PH is defined as an elevation in the mean pulmonary artery pressure (mPAP) that is greater than 20 mmHg,¹² which was measured at rest via right heart catheterization (RHC). The gold standard for the diagnosis of PH is right heart catheterization (RHC). However, RHC is invasive and costly. A good correlation has been found between RHC and echocardiography and the threshold of 35 mmHg is most commonly used to estimate PH.^{12,13}

The aims of our study are to analyze the prevalence of elevated PASP in non-small cell lung cancer (NSCLC) patients and its adverse prognosis value for OS and to elucidate the risk factor associated with PH.

Materials and Methods

Patients

We performed a retrospective cohort study including newly diagnosed NSCLC patients underwent transthoracic echocardiography within 1 month before the therapy from January 2009 to January 2015 at a single center in Beijing. Inclusion criteria were age \geq 18 years, cytology or histology confirmed NSCLC, clinical stability (defined as Zubrod performance status of 2 or less). The exclusion criteria

were as follows: patients with clinical instability, inability to understand the study or rejection to personal data record and processing, patients with poor echocardiography quality or pulmonary artery systolic pressure (PASP) not correctly reported, the pregnancy, patients with a definite history of idiopathic PAH, chronic obstructive pulmonary disease, obstructive sleep apnea, other pulmonary diseases with mixed restrictive or obstructive patterns, left heart diseases, chronic thromboembolism, HIV infection, portal hypertension, drug and toxic exposure, connective tissue disease, or any other obvious identified cause of PH, patients less than 18 years old. The final eligible cohort encompassed 612 NSCLC patients divided into clinical subgroups (stages IA–IIB, IIIA and IIIB–IV). The study was undertaken in accordance with international guidelines on Good Clinical Practice and the Declaration of Helsinki. It was approved by the ethics committee of Peking University First Hospital. Informed written consent was obtained from all participating individuals.

Echocardiographic Measurements

PASP was measured by transthoracic echocardiography (TTE) that was performed by two experienced cardiologists. All the reading cardiologist was blinded to the clinical characteristics of the study participants. The estimation of PASP by echocardiograph derived from the application of the modified Bernoulli equation: $PASP = 4 \times (TRV)^2 + RAP$,¹⁴ TRV is the maximum tricuspid regurgitation jet speed and RAP is the right atrium pressure, which is estimated by inferior vena cava diameter.¹⁵ Elevated PASP is defined as a PASP value above or equal to 35 mm Hg.¹⁴ We considered moderate to severe PH when PASP was above or equal to 45 mm Hg.

Laboratory Tests

Laboratory parameters were routine tests, and coagulation test including thrombin time (TT), activated partial thromboplastin time (APTT), prothrombin time (PT), fibrinogen (FIB), fibrinogen-degradation products (FDP), D-Dimer. All measurements were performed according to standard methods.

Follow-Up and Outcomes Definitions

All patients were followed up to determine their survival status. Follow-up was conducted by telephone to obtain information on survival (date and cause of death). To evaluate the burden in relation to mortality, the main end point was overall survival (time until death from any cause or last follow-up).

Statistical Methods

All statistical analyses were performed using SPSS version 23. Continuous variables were expressed as means and standard deviation if the data was normally distributed, and vice versa by median and interquartile range. Comparison between the groups was done using Student's *t*-test or a Mann–Whitney *U*-test. Categorical variables were compared using the chi-squared test. Univariate analysis was performed using logistic regression to assess factors associated with PH. The prognosis value of PH for predicting the study outcomes was assessed by the Kaplan–Meier analysis (survival curves were compared using a Log-rank test) and Cox regression. In multivariate Cox models, we included all variables that showed significant association with the study outcomes at univariate Cox analyses. The models also included those considered confounders factors. Differences were considered statistically significant when *p* value was <0.05. Survival time was defined as the interval between the date of lung cancer diagnosis and the date of death, or end of follow-up (1 December 2019).

Results

Elevated PASP and Baseline Data

A total of 956 patients with newly diagnosed lung cancer were enrolled in this study. Among these patients, 346 were not included: 189 patients with COPD or Interstitial lung disease, 74 patients with PS score greater than 2, 30 patients with systolic dysfunction, 23 patients with connective tissue disease, 21 patients with valvular disease, 9 patients were diagnosed with pulmonary embolism. A flow chart of patient selection is shown in Figure 1. The characteristics of the

patients are provided in Table 1. The age of lung cancer patients was 66 (59,73) years. Among 612 enrolled patients, 381 (62.3%) were male and 303 (49.5%) were current smokers or ex-smokers. Two hundred and two (33.0%) were squamous carcinoma, 379 (61.9%) adenocarcinoma and 31 (5.1%) other histologic types (including large cell lung cancer, carcinoid, sarcomatoid carcinoma, adenosquamous carcinoma, lymphoepithelial carcinoma). Moreover, 270 (44.1%) lung cancers were at an early stage (stage IA–IIB) and 520 (85.0%) of all lung cancers had eventually undergone surgery.

The prevalence of elevated PASP was 19.8% and 3.1% of the population presented PASP \geq 45mmHg. The PASP in the whole group was 28.3 (24.0, 33.0) mmHg, while in the elevated PASP group it was 39.0 (36.9, 42.8) mmHg. Data analysis according to the presence or absence of PH showed that patients with elevated PASP were significantly older, with coagulation disorders and were more likely to have intrapulmonary as well as distant metastasis.

Elevated PASP and Risk of Death

The median follow-up period of 77 months, with a follow-up rate of 91.8% (562 of 612 NSCLC patients), and 273 patients died (48.6%), 199 in the non-elevated PASP group (44.6%) and 74 in the elevated PASP group (63.8%). The 3-/5-year OS rates of NSCLC were 57.1%/49.5% in elevated PASP patients and were 91.3%/84.4% in non-elevated PASP patients. The main causes of death were cancer (80.2%). The Kaplan–Meier survival curves indicated that elevated PASP was significantly associated with the worse OS of lung cancer (Figure 2).

The HRs of factors related to lung cancer prognosis are shown in Table 2. In univariate analysis, the presence

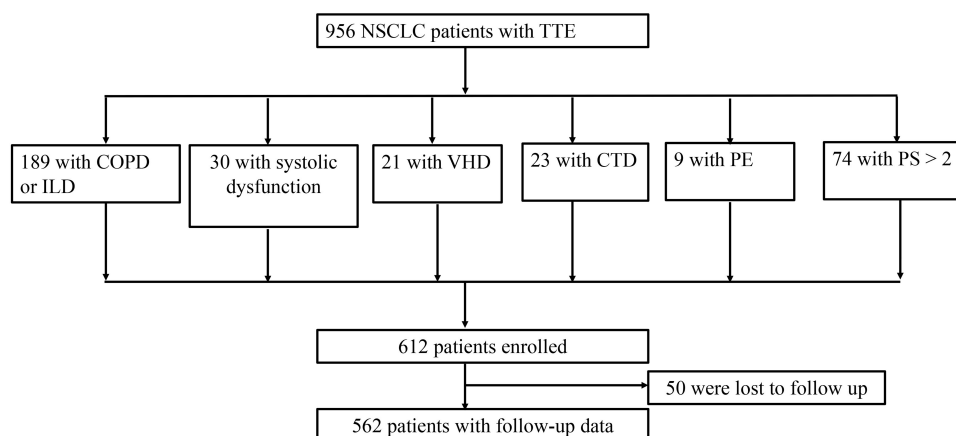


Figure 1 Flow chart of patients inclusion and diagnosis.

Abbreviations: NSCLC, non-small cell lung cancer; TTE, transthoracic echocardiography; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; VHD, valvular heart diseases; CTD, connective tissue disease; PE, pulmonary embolism; PS, Zubrod performance status.

Table I Characteristics of the Included Patients

Characteristics	All Participants (n= 612)	PASP < 35mmHg (n= 491, 80.2%)	PASP ≥ 35mmHg (n= 121, 19.8%)	P value
Age, y (median, range)	66 (59, 73)	65 (59, 71)	72 (63, 77)	< 0.001
Sex, n (%)				0.328
Male	381 (62.3)	301 (61.3)	80 (66.1)	
Female	231 (37.7)	190 (38.7)	41 (33.9)	
BMI, kg/m ² (mean ± SD)	24.1 ± 3.5	24.2 ± 3.4	23.8 ± 3.6	0.324
Symptom, n (%)				0.257
Negative	240 (39.2)	198 (40.3)	42 (34.7)	
Positive	372 (60.8)	293 (59.7)	79 (65.3)	
CCI, n (%)				0.434
≤ 2	457 (75.2)	370 (75.4%)	87 (71.9)	
> 2	155 (25.3)	121 (24.6%)	34 (28.1)	
History of other cancer, n (%)	20 (3.3)	15 (3.1)	5 (4.1)	0.551
Smoking history, n (%)				0.065
No	309 (50.5)	257 (52.3)	52 (43.0)	
Yes	303 (49.5)	234 (47.7)	69 (57.0)	
Alcohol history, n (%)				0.781
No	501 (81.9)	403 (82.1)	98 (81.0)	
Yes	111 (18.1)	88 (17.9)	23 (19.0)	
Coagulation function, n (%)				< 0.001
Normal	499 (81.5)	424 (86.4)	75 (62.0)	
Abnormal ^a	113 (18.5)	67 (13.6)	46 (38.0)	
Hb, g/L (median, range)	135.8 (127.0, 146.0)	136 (128.0, 146.0)	134 (122.0, 144.0)	0.077
IBIL, μmol/L (median, range)	9.0 (7.1, 11.4)	9.1 (7.3, 11.4)	8.8 (6.8, 10.8)	0.119
Platelets, ×10 ⁴ /L (median, range)	212.0 (176.0, 257.8)	212 (176.0, 257.0)	209 (171.5, 264.5)	0.930
GGO ^b , n (%)	94 (15.4)	75 (15.3)	19 (15.7)	0.907
Clinical stage, n (%)				0.132
I	222 (36.3)	186 (37.9)	36 (29.8)	
II	48 (7.8)	40 (8.1)	8 (6.6)	
III–IV	342 (55.9)	265 (54.0)	77 (63.6)	
Echocardiographic parameter				
PASP, mmHg (median, range)	28.3 (24.0, 33.0)	26.3 (23.0, 30.0)	39.0 (36.9, 42.8)	< 0.001
LVEF, % (median, range)	71.0 (65.0, 76.0)	71.0 (65.8, 76.0)	71.0 (63.5, 75.9)	0.403
Histological type, n (%)				0.160
Adenocarcinoma	379 (61.9)	302 (61.5)	77 (63.6)	
Squamous-cell carcinoma	202 (33.0)	160 (32.6)	42 (34.7)	
Other types ^c	31 (5.1)	29 (5.9)	2 (1.7)	
Intrapulmonary metastasis, n (%)	43 (7.0)	24 (4.9)	19 (15.7)	< 0.001
Lymph node metastasis, n (%)	241 (39.4)	185 (37.7)	56 (46.3)	0.083
Distant metastasis, n (%)	96 (15.9)	69 (14.1)	27 (22.3)	0.025
Treatment types, n (%)				< 0.001
Surgery	520 (85.0)	432 (88.0)	88 (72.7)	
Chemotherapy	62 (10.1)	41 (8.4)	21 (17.4)	

(Continued)

Table 1 (Continued).

Characteristics	All Participants (n= 612)	PASP < 35mmHg (n= 491, 80.2%)	PASP ≥ 35mmHg (n= 121, 19.8%)	P value
Radiotherapy	5 (0.8)	5 (1.0)	0	
Other	25 (4.1)	13 (2.6)	12 (9.9)	
Perioperative death, n (%)	12 (2.5)	4 (4.8)	8 (2.0)	
Surgical types, n (%)				0.988
Thoracotomy	219 (42.1)	182 (42.1)	37 (42.0)	
VATS	301 (57.9)	250 (57.9)	51 (58.0)	

Notes: ^aAbnormal coagulation function was defined as the presence of D-dimer >0.24mg/L or FDP > 5mg/L. ^bChest scan shows ground-glass opacity, ^cOther subtypes include large cell lung cancer, carcinoid, sarcomatoid carcinoma, adenosquamous carcinoma, lymphoepithelial carcinoma.

Abbreviations: PASP, pulmonary artery systolic pressure; BMI, body mass index; CCI, Charlson comorbidity index; Hb, hemoglobin; IBIL, indirect bilirubin; GGO, ground gross opacity; PASP, pulmonary artery systolic pressure; LVEF, left ventricular ejection fraction; VATS, video-assisted thoracic surgery.

of elevated PASP and PASP values was both associated with the decreased OS of lung cancer (hazard ratio [HR] 1.705, 95% CI 1.296–2.243; 1.039, 95% CI 1.023–1.054). Multivariate Cox regression analysis showed that, after adjustment for age, sex, respiratory symptoms, smoking status, GGO, Charlson comorbidity index (CCI), coagulation dysfunction, lymph node metastasis, distant metastasis, pathological type, elevated PASP and PASP value remained as independent predictors. Moreover, perioperative death rates were 2.5% in the whole group and PASP ≥ 45mmHg was an independent predictor of perioperative death, as shown in Table 3. Further, we found the independent predictors of PH were age, coagulation disorder and intrapulmonary metastasis as shown in Table 4.

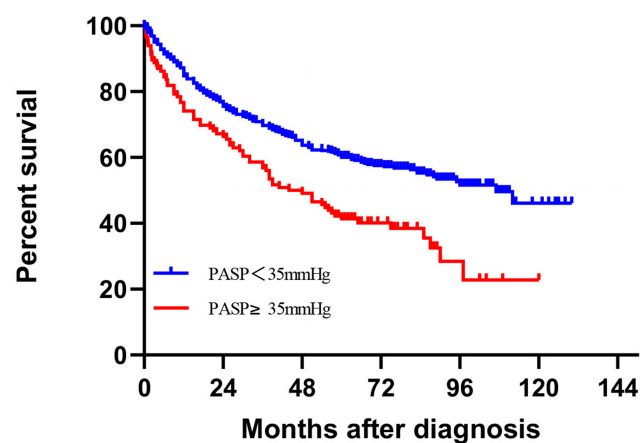


Figure 2 Kaplan–Meier curves of overall survival rate of NSCLC cancer. Elevated PASP is associated with all-cause mortality in NSCLC patients. P value are shown for the Log-rank test.

Discussion

In an analysis of 562 participants of lung cancer with long-term follow-up, we found that elevated PASP was common in an unselected cohort of lung cancer patients (19.8%), whereas its prevalence varies from 11 to 26 cases per million adults.¹⁶ Our study explored insight into the association between elevated PASP and the prognosis of lung cancer. These associations persisted after adjusting for several covariates, including pathological type, clinical stages. Moreover, PASP≥45mmHg, smoking history, distant metastasis and coagulopathy are independent predictors of perioperative mortality in NSCLC patients. Further, we found the main predictors of elevated PASP in NSCLC lung cancer patients are age, coagulation disorder and intra-pulmonary metastasis.

In recent decades, the treatment of lung cancer has achieved great medical advances, but the survival rate of lung cancer is still very low.¹⁷ It is therefore important to identify factors related to the prognosis of lung cancer. Our study supported the results of previous investigators who found that the prevalence of PH among lung cancer patients was high.⁹ Several studies have reported that approximately 1.4% of cancer coexist with pulmonary tumor thrombotic microangiopathy (PTTM) which eventually results in pulmonary hypertension, among this lung cancer accounts for 16.7% and the most frequent histological type was adenocarcinoma (93.3%).¹⁸ However, our study found no difference in tumor histological typing between the two groups. Moreover, some studies have reported that PH was closely related to the occurrence of lung cancer. A prospective multicenter study has revealed that the cancer incidence in pre-capillary PH was 14.45%, and lung cancer was the most common frequent.¹⁹ The

Table 2 HRs for Overall Survival Among NSCLC Patients

	Univariate Analysis		Multivariate Cox Regression ^a	
	HR (95% CI)	p value	HR (95% CI)	p value
PASP (increase)	1.039 (1.023–1.054)	<0.001	1.018 (1.003–1.034)	0.020 ^b
PASP ≥ 35mmHg (present)	1.705 (1.296–2.243)	<0.001	1.386 (1.036–1.853)	0.028 ^c
Age (increase)	1.029 (1.015–1.042)	<0.001	1.030(1.017–1.044)	< 0.001 ^c
Sex (female)	0.622 (0.478–0.810)	<0.001		0.179 ^c
Symptom (yes)	2.852 (2.147–3.788)	<0.001	1.720(1.270–2.329)	< 0.001 ^c
Smoke (yes)	1.412 (1.148–1.735)	0.001		0.540 ^c
GGO (yes)	0.679 (0.467–0.987)	0.042		0.692 ^c
CCI (>2)	1.514 (1.169–1.960)	0.002		0.598 ^c
Coagulopathy (yes)	2.857 (2.204–3.703)	<0.001	1.363(1.030–1.804)	< 0.001 ^c
Intrapulmonary metastasis (yes)	2.892 (2.024–4.133)	<0.001		0.148 ^c
Lymph node metastasis (yes)	2.848 (2.237–3.626)	<0.001	1.698(1.272–2.266)	< 0.001 ^c
Distant metastasis (yes)	3.696 (2.825–4.836)	<0.001	2.077(1.469–2.936)	< 0.001 ^c
Histological type		<0.001		0.004 ^c
Adenocarcinoma	0.400 (0.253–0.633)	<0.001	0.447(0.279–0.718)	0.001 ^c
Squamous-cell carcinoma	0.638 (0.400–1.019)	0.06	0.476(0.292–0.776)	0.003 ^c
LVEF (increase)	0.979 (0.966–0.993)	0.003		0.123 ^c

Notes: ^aThere were two Cox regression models. PASP (continuous, increase), PASP ≥ 35mmHg (dichotomous, referent: PASP < 35mmHg) were, respectively, distributed in models 1, 2. Age (continuous, increase), sex (dichotomous, referent: male), Symptom (dichotomous, referent: without symptom), Smoke (dichotomous, referent: non-smoking), GGO (dichotomous, referent: without-GGO), CCI (dichotomous, referent: CCI ≤ 2), coagulopathy (dichotomous, referent: without coagulation disorder), Intrapulmonary metastasis (dichotomous, referent: without Intrapulmonary metastasis), Lymph node metastasis (dichotomous, referent: without lymph node metastasis), Distant metastasis (dichotomous, referent: without distant metastasis), Clinical stage (dichotomous, referent: IA-IIIB), LVEF (continuous, increase). ^bModel 1; ^cModel 2.

Table 3 Logistic Regression Analyses for Variables Associated with Perioperative Death

	Unadjusted		Adjusted ^a	
	HR (95% CI)	p value	HR (95% CI)	p value
Coagulopathy	4.313 (1.342–13.859)	0.014	3.504 (1.006–12.202)	0.115 ^d
PASP range		0.030		0.102 ^d
PASP 35–45mmHg ^b	1.368 (0.284–6.577)	0.696		0.899 ^d
PASP ≥ 45mmHg ^c	9.575 (1.799–50.958)	0.008	7.849 (1.260–48.878)	0.042 ^d
PASP	1.064 (1.013–1.116)	0.013		0.088 ^e
Age	1.088 (1.010–1.171)	0.025	1.090 (1.005–1.181)	0.038 ^d
CCI	5.170 (0.594–44.976)	0.137		
Symptom	4.043 (0.876–18.656)	0.073		
Sex		0.995		
BMI	0.841 (0.702–1.008)	0.061		
Alcohol	1.363 (0.362–5.135)	0.648		
GGO	1.051 (0.226–4.896)	0.949		
Smoke	2.607 (1.062–6.400)	0.036	3.213 (1.149–8.986)	0.026 ^d
Intrapulmonary metastasis	2.247 (0.275–18.365)	0.450		
Lymph node metastasis	2.552 (0.797–8.169)	0.114		
Distant metastasis	6.682 (1.689–26.427)	0.007	10.287 (2.230–47.445)	0.003 ^d
Histological type		0.058		
Adenocarcinoma	0.250 (0.025–2.496)	0.238		
Squamous-cell carcinoma	1.272 (0.152–10.625)	0.687		
Clinical stage	1.974 (0.586–6.647)	0.272		
Surgery types	3.614 (0.966–13.522)	0.056		

Notes: ^aThere were two logistic models, PASP range (dichotomous, referent: PASP 35–44mmHg), PASP (continuous, increase) were, respectively, distributed in models 1, 2. ^bPulmonary artery systolic pressure between 35–44mmHg. ^cPulmonary artery systolic pressure above or equal to 45mmHg. ^dModel 1; ^eModel 2.

Table 4 Logistic Regression Analyses for Variables Associated with Elevated PASP

	Unadjusted		Adjusted ^a	
	HR (95% CI)	p value	HR (95% CI)	p value
Age	1.065 (1.039–1.090)	<0.001	1.060 (1.034–1.087)	< 0.001
Sex	0.812 (0.535–1.233)	0.329		
BMI	0.969 (0.914–1.027)	0.291		
Symptom	1.271 (0.839–1.926)	0.258		
Alcohol history	1.075 (0.646–1.789)	0.781		
Smoking history	1.457 (0.976–2.177)	0.066		
GGO (yes)	1.033 (0.597–1.787)	0.907		
CCI (>2)	1.195 (0.765–1.867)	0.434		
Coagulopathy ^b	3.867 (2.468–6.057)	<0.001	3.380 (2.053–5.566)	< 0.001
Intrapulmonary metastasis (yes)	3.625 (1.913–6.866)	<0.001	3.329 (1.556–7.125)	0.002
Lymph node metastasis (yes)	1.425 (0.954–2.129)	0.084		
Distant metastasis (yes)	1.757 (1.068–2.890)	0.027	0.857 (0.455–1.614)	0.633
Histological type		0.148		
Adenocarcinoma	3.697 (0.863–15.833)	0.078		
Squamous-cell carcinoma	3.806 (0.873–16.598)	0.075		
Clinical stage ^c	1.492 (0.990–2.250)	0.056		

Notes: ^aMultivariate model included all variables that were associated with elevated PASP at univariate analyses. ^bCoagulopathy (dichotomous). ^cClinical stage (dichotomous).

risk of cancer may be increased in patients with chronic lung diseases.

Tumoral PH currently lies within group 5 of the classification of PH according to the 6th World Symposium on Pulmonary Hypertension,²⁰ and the pathophysiological correlates of lung cancer with PH are numerous and complex. (i) Cohesive tumor cells occlude the small pulmonary arteries as has been defined as pulmonary tumor microembolism (PTE),²⁰ the interaction between tumor cells and endothelial cell then initiates clot formation, and releases cytokines which initiate macrophage recruitment and intimal proliferation and ultimately PH, which is the feature of pulmonary tumor thrombotic microangiopathy (PTTM).^{21–23} Pulmonary microvascular disease comprises PTE and PTTM, the tumor emboli increase pulmonary vascular resistance through mechanical obstruction and may relate to vascular remodeling.^{21–23} Half of the reported PTTM cases have features of microangiopathic haemolytic anaemia (MHAH) or disseminated intravascular coagulation, while no significant difference was found between the two groups with respect to hemoglobin, platelets, indirect bilirubin. (ii) Malignancy is a risk factor for chronic thromboembolism (CTEPH) and large tumor metastasis can mimic pulmonary embolism; however, our study did not present the evidence of such condition and the latter is more often reported in cases of breast cancer,²⁴ hepatocellular carcinoma.²⁵ (iii) Cancer therapies may induce PAH. The

tyrosine kinase inhibitors (TKIs) include dasatinib which are reported to cause direct pulmonary artery endothelial cell toxicity through the production of mitochondrial reactive oxygen species.²⁶ Besides, cytotoxic chemotherapy including gemcitabine,²⁷ mitomycin-C and irradiation, occupation organic solvent exposure is likely to relate to venous endothelial injury, which is the common mechanism of cancer treatment-related PVOD.²⁸ Nevertheless, our patients enrolled were all first diagnosed and untreated before undergoing the echocardiogram. (iv) COPD is an important comorbidity of lung cancer, and PH-COPD is classified as group III of PH.²⁰ However, patients with a definite history of COPD history are excluded from the study. (v) In vitro and in vivo experiments suggested that tumor cells interact with inflammatory cells and release of several cytokines in the tumor microenvironment promoted lung vascular cell proliferation and migration. Thus, anti-inflammatory therapies present potential in lung cancer-associated PH.

Current treatment of PH still focusing on vasodilators failed to reverse the vascular remodeling which may be related to the overlap mechanisms with lung cancer, featured by sustained proliferation and escape from apoptosis. Thus, antitumor drugs show therapeutic potential in the management of PH.²⁹ Besides, several cases have reported that imatinib was effective in patients with PTTM associated PH and remarkably improves acute right heart

failure caused by PTTM, whereas it was weaker in the case of colon and breast cancer and the mechanism may be associated with the production of growth factors varies between different tumors.²⁹ Subsequently, we can speculate that imatinib may be an effective therapeutic option for PH in some cases of PTTM.³⁰

The strengths of this study include the larger sample size and long-term follow-up. To the best of our knowledge, our work represents the first study evaluating the prognosis of lung cancers with elevated PASP. Although this cohort is the largest ever reported, our work has two main limitations. (i) We have only estimated the PASP by echocardiography instead of using right heart catheterization (RHC) which remains the gold standard for PH diagnosis. However, most of studies use the estimate PASP because of its noninvasive and economic nature, besides, it has a good relation with RHC. (ii) Another limitation in our study was a retrospective study and echocardiography was not a routine investigation in lung cancer patients at our hospital because of the unawareness of the presence of PH in this population, thus may lead to selective bias, further, well-designed prospective studies are required to solve these problems.

Conclusion

Elevated PASP was an independent prognostic risk factor for NSCLC and PASP ≥ 45 mmHg is related to perioperative death. Moreover, advanced age, with coagulation disorder and intra-pulmonary metastasis at the time of diagnosis are independent risk factors for elevated PASP in NSCLC patients. Result of this study provides important implications on the research of the mechanism between lung cancer and PH and contributed to the clinical identification of lung cancer patients with poor prognosis.

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Disclosure

The authors report no conflicts of interest in this work.

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