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# Haemoptysis as a prognostic factor in lung adenocarcinoma after curative resection

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**Background:** Haemoptysis is a common symptom of lung cancer. Its prognostic role and mechanisms are still poorly understood.

**Methods:** We retrospectively reviewed 666 consecutive patients with primary lung adenocarcinoma who underwent complete resection. The prognostic value of haemoptysis with respect to overall survival (OS), disease-specific survival (DSS) and disease-free survival (DFS) was analysed. To further explore the possible mechanisms of haemoptysis, we evaluated vascular endothelial growth factor (VEGF) expression, tumour necrosis, vascular invasion and extratumoural microvessel density (MVD) in 112 randomly selected patients.

**Results:** Haemoptysis predicted poor OS, DSS and DFS in operable lung adenocarcinoma (all  $P < 0.001$ ). In addition, haemoptysis was associated with high white blood cell (WBC) count ( $P = 0.032$ ), high fibrinogen (Fib;  $P < 0.001$ ), high tumour greatest dimension ( $P < 0.001$ ), severe vascular invasion ( $P = 0.002$ ) and central tumour location ( $P < 0.001$ ). We obtained no statistically significant differences of VEGF expression, tumour necrosis and extratumoural MVD in haemoptysis and non-haemoptysis groups.

**Conclusion:** Our study demonstrates that haemoptysis predicts poor OS, DSS and DFS in lung adenocarcinoma after curative resection. Vascular invasion rather than angiogenesis or tumour necrosis could be the most important mechanism of haemoptysis in lung adenocarcinoma.

Lung cancer is the leading cause of cancer death worldwide (Dela Cruz *et al*, 2011; Kimman *et al*, 2012; Siegel *et al*, 2013), and has had very little improvement in survival during the past 30 years compared with leukaemia and non-Hodgkin's lymphoma (Siegel *et al*, 2013). Without regard to histology, most patients suffer from one or more symptoms at the time of diagnosis (Soni *et al*, 2002). The most common symptoms include weakness, cough, dyspnoea, haemoptysis, chest pain and fever. Haemoptysis, defined as bleeding from lower respiratory tract, is a common complication of lung cancer. It varies from bloody sputum to fatal pulmonary haemorrhage. According to a prospective evaluation in a tertiary referral hospital, cancer was the most common cause of haemoptysis, and was usually associated with mild to moderate amounts of haemorrhage (Uzun *et al*, 2010).

Based on the amount of haemorrhage per day, haemoptysis was divided into four categories: mild (<30 ml, including blood

sputum or less than two tablespoons), moderate (30–100 ml), severe (100–600 ml) and massive (> 600 ml) (Fidan *et al*, 2002).

Although haemoptysis is one of the most frequent clinical manifestations of lung cancer, few robust data have been reported about its incidence in patients before treatment, and the mechanisms of haemoptysis are poorly understood, especially for mild or moderate haemoptysis. Possible mechanisms include neovascularisation, vascular invasion, tumour necrosis, trauma due to invasive procedures or cough and so on.

Lung adenocarcinoma accounts for the most common type of lung cancer in many countries (Drilon *et al*, 2012), and the presence of baseline gross haemoptysis was identified as a potential risk factor associated with severe pulmonary haemorrhage in using bevacizumab (Sandomenico *et al*, 2012). Thus, we hypothesised that haemoptysis played a more important role than a common clinical symptom.

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The purpose of this study was to identify the prognostic value of haemoptysis in lung adenocarcinoma and to further explore the possible mechanism.

## MATERIALS AND METHODS

**Patients and specimens.** A retrospective study was carried out on consecutive patients with primary lung adenocarcinoma undergoing complete resection between January 2006 and December 2011 at Provincial Hospital Affiliated to Shandong University. Clinical data were collected from individual cases. This study protocol was approved by the Ethical Committee of Provincial Hospital affiliated to Shandong University. Eligibility criteria included histological diagnosis of lung adenocarcinoma, complete resection of the primary lesion and untreated before surgery. Patients were excluded if they died within 30 days of surgery or with positive margins.

Staging was determined based on the seventh edition TNM classification (Goldstraw *et al*, 2007). The following information including sex, age, smoking status, final pathologic TNM stage, tumour grade, tumour lobar location (tumour located in which lobe) and the greatest dimension of primary tumour were collected.

In order to detect whether there were any significant differences between the central and peripheral lung cancers, we reviewed imaging findings (chest radiographs and computed tomographic scans), bronchoscopy findings and medical records to classify tumours into central type and peripheral type.

The first end point was overall survival (OS), defined as the time from operation to the date of death, the date lost to follow-up or the date of latest follow-up. The second end point was disease-specific survival (DSS), and failure was defined as death from lung cancer or treatment-related complications. Additional end point included disease-free survival (DFS), defined as time from operation to the first event of either confirmed recurrence or death.

**Laboratory data.** Laboratory data including white blood cell (WBC) count, red blood cell (RBC) count, platelet count, prothrombin time (PT), prothrombin time-international normalised ratio (PT-INR), activated partial thromboplastin time (APTT) and fibrinogen (Fib) were recorded at baseline, before surgery.

**Sample size estimation.** Further studies were conducted on randomly selected paraffin-embedded specimens. To determine the sample size for further immunostaining, PASS software (Version 11.0; NCSS Statistical Software, Kaysville, UT, USA) was used. Estimation of the least total sample size was performed using the 'Logrank Test Power Analysis' based on Lakatos Edward's method (Lakatos, 1988, 2002).

**Immunohistochemistry.** Tissue sections of 4  $\mu$ m thickness were used for staining, and only those containing the leading edge of the tumour were used. Immunohistochemistry (IHC) for vascular endothelial growth factor (VEGF) was performed with rabbit polyclonal anti-human VEGF antibody (1:100 dilution, Abcam, Cambridge, UK). Mouse monoclonal anti-CD34 antibody (working solution, Zhongshan Biotechnology, Beijing, China) was used to stain blood vessels. Immunohistochemistry was performed on paraffin-embedded sections. The detail procedures of IHC have been described previously (Wang *et al*, 2013). Water-bath heating antigen retrieval was conducted with citrate buffer solution (pH 6.0) for VEGF and CD34. The streptavidin-peroxidase-biotin (SP) technique was adopted to detect the expression of antigens by using SP kit (Zhongshan Biotechnology, Beijing, China). Negative controls were performed by omitting the primary antibody.

**Scoring of IHC.** Each specimen was evaluated independently by two pathologists who were blinded to the patients' clinical features and outcomes. For VEGF, only cytoplasmic VEGF expression was evaluated (Figure 3A). Evaluation of the IHC was performed

according to the immunoreactive score (Friedrichs *et al*, 2006). The intensity of staining was defined as 0, negative; 1, weak; 2, moderate; and 3, strong. The extension was determined as percentage of positive cells, that is: 0, negative; 1, <10% positive cells; 2, 11–50%; 3, 51–80%; and 4, >80%. A final score was calculated by multiplying the staining intensity by the extension.

## Assessment of microvessel density and blood vessel invasion.

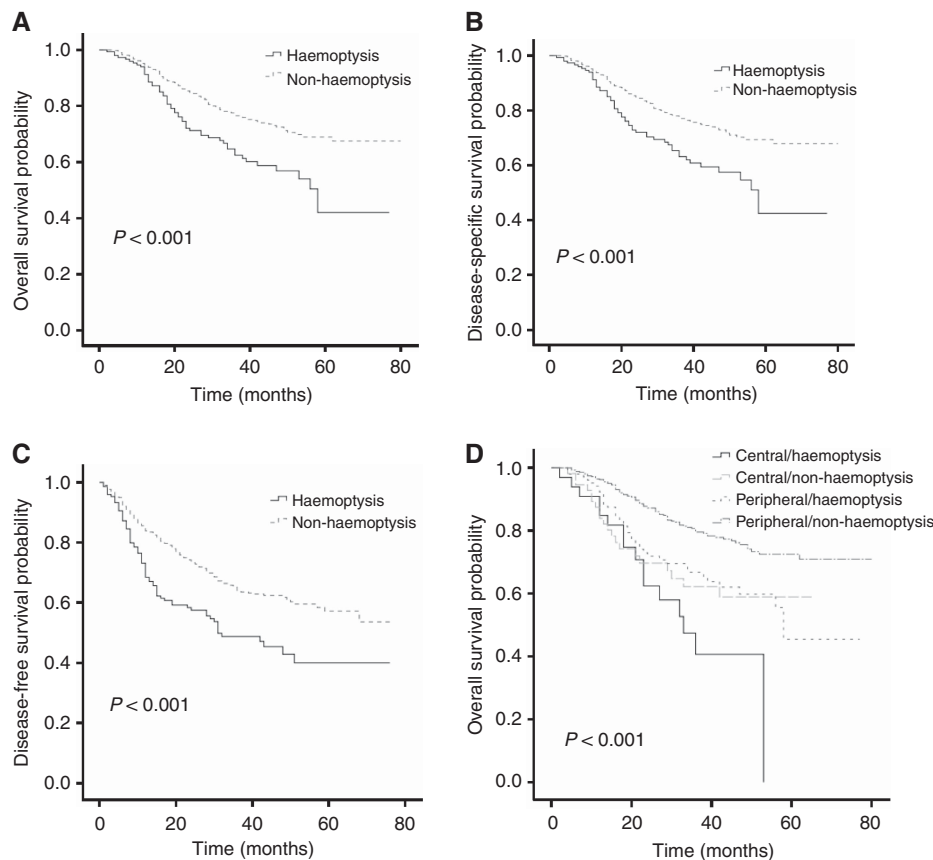
Extratumoural microvessel density (MVD) was assessed by CD34 immunohistochemical staining. To determine the MVD, sections were scanned under light microscopy at low power ( $\times 100$ ), and

Table 1. Characteristics of patients and correlation between haemoptysis and clinicopathological characteristics

Characteristics	No. of patients (%)	Haemoptysis	Non-haemoptysis	P-value
Overall number	666	149	517	
Sex				0.136 <sup>a</sup>
Female	305 (45.8)	60	245	
Male	361 (54.2)	89	272	
Age				1.000 <sup>a</sup>
≤65	506 (76.0)	113	393	
>65	160 (24.0)	36	124	
N status				0.058 <sup>a</sup>
N0	399 (59.9)	79	320	
N+	267 (40.1)	70	197	
Tumour node metastasis (TNM) stage				0.007 <sup>a</sup>
I	342 (51.4)	61	281	
II	127 (19.1)	39	88	
III	197 (29.6)	49	148	
Smoking status				0.120 <sup>a</sup>
Current smokers	236 (35.4)	60	176	
Ex-smokers	44 (6.6)	13	31	
Nonsmokers	386 (58.0)	76	310	
Degree of tumour differentiation				0.018 <sup>a</sup>
Grade 1–2	473 (71.0)	94	379	
Grade 3–4	193 (29.0)	55	138	
Tumour lobar location				0.613 <sup>b</sup>
Right upper lobe	190 (28.5)	37	153	
Right middle lobe	54 (8.1)	11	43	
Right lower lobe	124 (18.6)	28	96	
Left upper lobe	164 (24.6)	38	126	
Left lower lobe	121 (18.2)	30	91	
Hilus of the lung	13 (2.0)	5	8	
Central or peripheral tumour				<0.001 <sup>a</sup>
Central tumour	89 (13.4)	33	56	
Peripheral tumour	533 (80.0)	104	429	
Not classified	44 (6.6)	12	32	

<sup>a</sup>P-value for Pearson's  $\chi^2$ .

<sup>b</sup>P-value for Fisher's exact test.



**Figure 1.** Overall survival (A, log-rank test,  $P < 0.001$ ), disease-specific survival (B, log-rank test,  $P < 0.001$ ) and disease-free survival (C, log-rank test,  $P < 0.001$ ) in patients with operable lung adenocarcinoma related to haemoptysis. (D) Combined influence of haemoptysis and central/peripheral tumours on survival (log-rank test,  $P < 0.001$ ).

three most vascular areas (vascular hot spots) were chosen. Afterwards, extratumoural MVD of these three areas were counted under high power ( $\times 200$ ) as described by Weidner *et al* (1991). The quantification was performed using the image analysis software (Image Pro Plus 6.0; Media Cybernetics, Bethesda, MD, USA). The average number of microvessels was used for the statistical analysis. Vascular invasion is defined as definite tumour cells in the vascular lumen (Figure 3B).

**Evaluation of necrosis.** The extent of tissue necrosis on the section was assessed in accordance with previously reported criteria (Pollheimer *et al*, 2010). The degree of necrosis was recorded at low magnification ( $\times 40$ ) and scored as 0, absent; 1, focal ( $\leq 10\%$  of the tumour area); 2, moderate ( $10\%–30\%$  of the tumour area); 3, extensive ( $\geq 30\%$  of the tumour area). An average of 10 low-power fields was assessed based on the size of the sections.

**Statistical analysis.** SPSS software program (version 20.0; SPSS Inc, Chicago, IL, USA) was used for data analysis. For the analysis of relation with haemoptysis, categorical variables were compared using Pearson's  $\chi^2$  test or Fisher's exact test. Kolmogorov–Smirnov test was used to check for normal distribution of continuous variables. Continuous variables that were not normally distributed were compared using Mann–Whitney  $U$ -test. Overall survival, PFS and DSS analyses were performed using the Kaplan–Meier method, and the differences between groups were analysed by using the log-rank test. Univariate Cox proportional hazard model was used to evaluate each potential predictor, and  $P$ -values  $\leq 0.10$  were enrolled in multivariate analysis. All the  $P$ -values were two sided, and  $P \leq 0.05$  was considered to have a significant statistical difference.

## RESULTS

**Baseline clinical and laboratory features.** A total of 666 patients were included in the analysis, including 361 males and 305 females. Mean age was 58.13 (range, 20 to 83). Of these, 236 were current smokers, 44 were ex-smokers and 386 were nonsmokers.

Haemoptysis was observed in 149 patients (22.4%) at the time of diagnosis. The duration of haemoptysis ranged from 1 day to a maximum of 600 days (median 30 days). In all, 127 patients presented with mild haemoptysis, 21 with moderate haemoptysis and 1 with severe haemoptysis; none of the patients presented with massive haemoptysis.

In the whole cohort, 89 (13.4%) tumours were classified as central lesions and 533 (80.0%) as peripheral lesions; detailed information was not available for 44 (6.6%) tumours and hence they could not be classified. The main characteristics of patients are listed in Table 1.

**Survival analysis.** Median follow-up (until December 2011) was 34 months, including 68.2% of patients with over 24 months, 45.3% with over 36 months and 9.2% with over 60 months, excluding 89 patients (13.4%) lost to follow-up. Progression was observed in 252 (37.8%) patients among the whole cohort, with 75 (50.3%) patients in the haemoptysis group and 177 (34.2%) in the nonhaemoptysis group. A total of 178 patients died at the end of follow-up, among whom 171 (96.1%) patients died of cancer and 7 (3.9%) died of noncancer-related causes. Haemoptysis group accounted for 32% (57 out of 178) of the total deaths and nonhaemoptysis group accounted for 68% (121 out of 178) of the total deaths. At the end of follow-up, the survival rates were 41%

Table 2. Cox proportional hazard analysis of whole cohort

	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
<b>Overall survival</b>				
Sex		0.081		<sup>a</sup>
Male	1			
Female	1.305 (0.968–1.761)			
Age		0.003		<0.001
> 65	1		1	
≤ 65	0.627 (0.460–0.856)		0.482 (0.343–0.677)	
Smoking status		0.023		<sup>a</sup>
Never smokers	1			
Current smokers	1.336 (0.978–1.824)			
Ex-smokers	1.918 (1.143–3.221)			
TNM		<0.001		<0.001
I	1		1	
II	4.036 (2.654–6.137)		3.915 (2.521–6.080)	
III	5.470 (3.748–7.982)		6.716 (4.473–10.085)	
Grade		<0.001		<sup>a</sup>
1–2	1			
3–4	1.971 (1.455–2.671)			
Haemoptysis		<0.001		<0.001
Absent	1		1	
Present	1.821 (1.329–2.496)		1.838 (1.321–2.556)	
Central or peripheral tumour		<0.001		<sup>a</sup>
Central tumour	1			
Peripheral tumour	0.448 (0.309–0.649)			
<b>Disease-specific survival</b>				
Sex		0.046		<sup>a</sup>
Male	1			
Female	1.362 (1.005–1.844)			
Age		0.006		<0.001
> 65	1		1	
≤ 65	0.643 (0.469–0.881)		0.495 (0.350–0.699)	
Smoking status		0.014		<sup>a</sup>
Never smokers	1			
Current smokers	1.381 (1.009–1.890)			
Ex-smokers	1.983 (1.179–3.334)			
TNM		<0.001		<0.001
I	1		1	
II	4.247 (2.775–6.498)		4.135 (2.644–6.467)	
III	5.689 (3.868–8.366)		6.947 (4.587–10.520)	
Grade		<0.001		<sup>a</sup>
1–2	1			
3–4	1.930 (1.420–2.624)			
Haemoptysis		<0.001		<0.001
Absent	1		1	
Present	1.817 (1.322–2.497)		1.828 (1.310–2.550)	
Central or peripheral tumour		<0.001		<sup>a</sup>

Table 2. (Continued)

	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Central tumour	1			
Peripheral tumour	0.448 (0.309–0.649)			
<b>Disease-free survival</b>				
Sex		0.023		<sup>a</sup>
Male	1			
Female	1.339 (1.041–1.722)			
Age		0.023		<0.001
> 65	1		1	
≤ 65	0.731 (0.558–0.958)		0.582 (0.435–0.779)	
Smoking status		0.004		<sup>a</sup>
Never smokers	1			
Current smokers	1.364 (1.050–1.772)			
Ex-smokers	1.944 (1.247–3.031)			
TNM		<0.001		<0.001
I	1		1	
II	3.515 (2.521–4.902)		3.419 (2.417–4.835)	
III	3.970 (2.944–5.352)		4.428 (3.216–6.097)	
Grade		<0.001		<sup>a</sup>
1–2	1			
3–4	1.830 (1.416–2.364)			
Haemoptysis		<0.001		<0.001
Absent	1		1	
Present	1.751 (1.336–2.296)		1.789 (1.349–2.372)	
Central or peripheral tumour		0.001		<sup>a</sup>
Central tumour	1			
Peripheral tumour	0.578 (0.415–0.806)			

Abbreviations: CI = confidence interval; HR = hazard ratio; TNM = tumour node metastasis.  
<sup>a</sup>Not in the final step of multivariate analysis.

and 67% for patients with or without haemoptysis, respectively. We evaluated the prognostic value of haemoptysis related to three end points: OS, DSS and DFS. Kaplan–Meier curves of the two patient groups for OS, DSS and DFS are shown in Figure 1A–C, respectively. Statistically significant differences were found between these two groups, with  $P < 0.001$  consistently, demonstrating that haemoptysis is an important marker for poor prognosis.

Further study was performed to identify the combined influence of haemoptysis and tumour location within each lobe on survival. The patients were divided into four groups: central/haemoptysis (central tumours with haemoptysis), central/nonhaemoptysis (central tumours without haemoptysis), peripheral/haemoptysis (peripheral tumours with haemoptysis) and peripheral/nonhaemoptysis (peripheral tumours without haemoptysis). Our data showed that the peripheral/nonhaemoptysis group had the best OS, although whereas the central/haemoptysis group had the poorest OS ( $P < 0.001$ , Figure 1D).

To determine the independent predictors of OS, DSS and DFS, the Cox proportional hazards regression models were used. In univariate Cox analysis, age, smoking status, TNM classification, tumour grade, central tumour and haemoptysis were all statistically significant predictors for OS ( $P = 0.003$ , 0.023, <0.001, <0.001, <0.001, <0.001, respectively). Then, multivariate Cox analysis

was performed, in which variables were tested in a step-forward logistic regression approach, and only age, TNM classification and haemoptysis were proved to be independent predictors (all  $P < 0.001$ ). In the following analysis, haemoptysis was related to poor DSS and DFS in both univariate and multivariate Cox regression analyses. The hazard ratios (HRs) were 1.817 ( $P < 0.001$ ) by univariate analysis and 1.828 ( $P < 0.001$ ) by multivariate analysis for DSS; and 1.751 ( $P < 0.001$ ) by univariate and 1.789 ( $P < 0.001$ ) by multivariate analysis for DFS (Table 2).

#### Relationship between haemoptysis and clinicopathological data.

To analyse the relationship between haemoptysis and clinicopathological parameters, we collected data on WBC count, RBC count, PT, PT-INR, APTT and Fib before operation; the greatest dimension of primary tumour specimen was also evaluated. All these values were not normally distributed by using Kolmogorov–Smirnov test, and Mann–Whitney *U*-test was used for further analysis. Comparison of the clinicopathologic characteristics between haemoptysis and nonhaemoptysis groups disclosed haemoptysis was significantly associated with high WBC count ( $P = 0.032$ ), high Fib ( $P < 0.001$ ) and high tumour greatest dimension ( $P < 0.001$ ), whereas no significant association was found with RBC count, platelet count, PT, PT-INR or APTT (Figure 2).

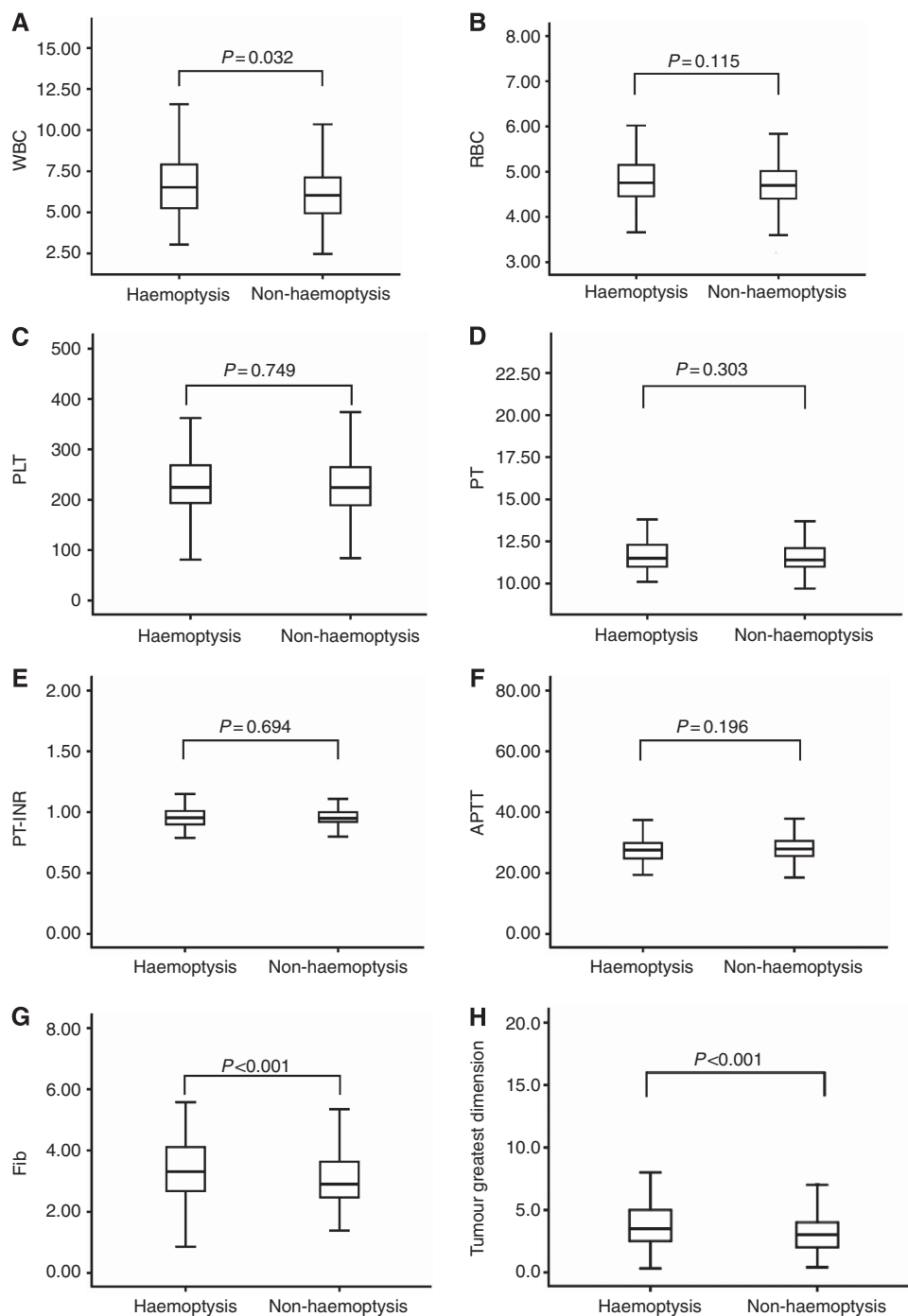


Figure 2. Relationship between haemoptysis and clinicopathological data. (A–H) The distribution of WBC, RBC, platelet, PT, PT-INR, APTT, Fib before operation, and the greatest dimension of primary tumour specimens in the haemoptysis and nonhaemoptysis group, respectively, are shown.

Categorical variables including sex, age, smoking status, degree of tumour differentiation, tumour lobar location, central or peripheral tumour, lymph node metastasis and TNM stage were also analysed. Only degree of tumour differentiation, TNM stage and central tumour were associated with haemoptysis ( $P=0.018$ ,  $P=0.007$ ,  $P<0.001$ , respectively; Table 1). There was a higher incidence of haemoptysis in central tumours than in peripheral tumours (37.1% vs 19.5%; odds ratio, 2.43; 95% confidence interval, 1.50–3.93).

**Relationship between haemoptysis and VEGF expression, tumour necrosis, vessel invasion and extratumoural MVD.** The minimal sample size estimated by PASS was 110 (55 in the control

group and 55 in the treatment group), achieving 80.3% power at a 0.100 significance level. Therefore, we randomly selected 112 patients (56 in haemoptysis group and 56 in nonhaemoptysis group) for further IHC (Figure 3).

The median values for VEGF expression, tumour necrosis and extratumoural MVD were 0, 0 and 25; and the highest quartile values were 4, 3 and 34, respectively. All the variables were dichotomised into low and high levels according to their median and highest quartile values. We obtained no statistically significant differences of VEGF expression, tumour necrosis and extratumoural MVD in the two groups when neither median nor highest quartile values were used as cutoff points (all  $P>0.05$ , Table 3).

Table 3. The correlation between haemoptysis and IHC results

	Cutoff	Category	Haemoptysis	Nonhaemoptysis	Pearson's $\chi^2$	P-value
Total			56	56		
VEGF	Median	High	29	24	0.895	0.449
		Low	27	32		
	Highest quartile	High	26	21	0.917	0.444
		Low	30	35		
Necrosis	Median	High	29	24	0.895	0.449
		Low	27	32		
	Highest quartile	High	17	14	0.401	0.673
		Low	39	42		
Extratumoural MVD	Median	High	33	25	2.289	0.185
		Low	23	31		
	Highest quartile	High	15	13	0.190	0.828
		Low	41	43		
Vascular invasion		Positive	24	9	9.666	0.002
		Negative	32	47		

Abbreviations: IHC = immunohistochemistry; MVD = microvessel density; VEGF = vascular endothelial growth factor.

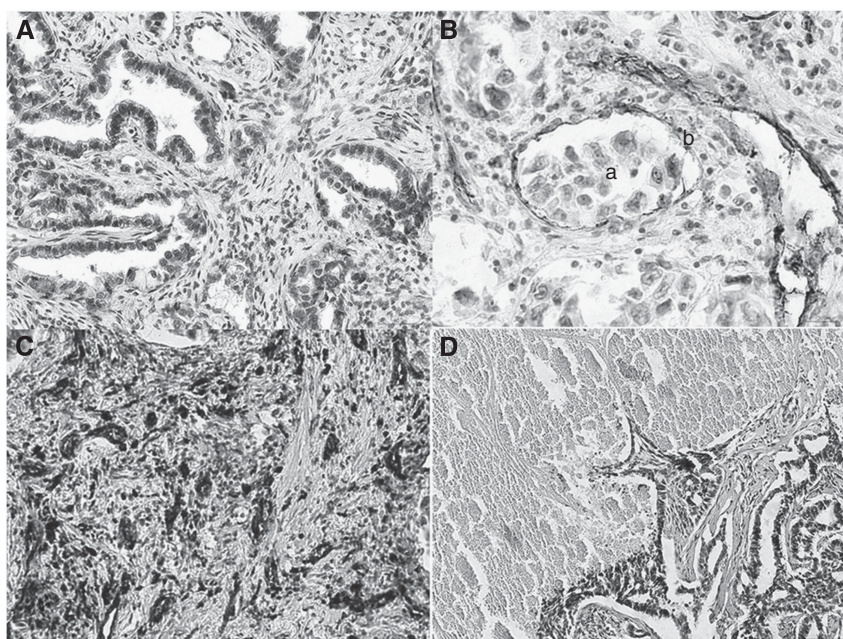


Figure 3. Representative images of immunohistochemical staining. (A) Immunohistochemical staining of VEGF ( $\times 200$ ). (B) Blood vessel invasion staining with CD34 ( $\times 400$ ). The alphabet 'a' indicates tumour cells in the vascular lumen, and the alphabet 'b' indicates blood vessel, identified by CD34 staining positive. (C) Immunohistochemical staining of extratumoural MVD ( $\times 200$ ). (D) Tumour necrosis ( $\times 100$ ).

Vascular invasion was seen in 33 (29.5%) samples, including 24 (42.9%) from the haemoptysis group and 9 (16.1%) from the nonhaemoptysis group. There was a significant correlation between vascular invasion and haemoptysis ( $P = 0.002$ ).

## DISCUSSION

Haemoptysis is among the most common respiratory symptoms in lung cancer. It was reported in  $\sim 30\%$  to  $60\%$  of patients (Reck *et al*, 2012). Generally, depending on the severity, haemoptysis is divided into massive haemoptysis and submassive haemoptysis (nonlife-threatening haemoptysis). According to one retrospective case series, the incidence rates of submassive and massive haemoptysis in lung cancer were 16.0% and 3.3%,

respectively (Miller and McGregor, 1980). Massive haemoptysis was proved to be related to tumour type (squamous-cell lung cancer) and location (central tumours). However, such correlations were not found in nonlife-threatening haemoptysis (Miller and McGregor, 1980). One previous study reported that 98% haemoptysis of lung cancer was submassive (Uzun *et al*, 2009). Different from squamous carcinomas, most adenocarcinomas arise from the peripheral lung (Gazdar and Minna, 1997). In the present study, the incidence of haemoptysis was lower in peripheral lesions; although central lesions accounted for only a small proportion of lung adenocarcinomas, it was still a risk factor for submassive haemoptysis.

We explored the association between haemoptysis and clinicopathologic parameters as well as patients' outcome, and demonstrated that haemoptysis predicted poor OS, DSS and DFS

in lung adenocarcinoma. Therefore, patients with lung adenocarcinoma who present with haemoptysis can be expected to have a worse outcome on the average. Our data also showed that central tumour with haemoptysis group had the poorest outcome, which might be because the tumours in this group more easily invaded larger blood vessels, despite a potentially countervailing effect of central tumour location yielding earlier detection and treatment. This information might be important for judgement on disease severity and treatment decision making. Of note, in our previous study (Pingping Hu *et al*), haemoptysis did not predict poor outcome in lung squamous carcinoma (HR, 1.105; 95% confidence interval, 0.808–1.512;  $P = 0.531$ ).

Despite the high incidence and importance of haemoptysis in lung carcinoma, its mechanisms have not been elucidated. Few research studies have focussed on haemoptysis from lung cancer, especially submassive haemoptysis from adenocarcinoma. In a study of haemorrhage in lung cancer, autopsies of patients who had had massive haemoptysis disclosed extensive inflammation and necrosis of vascular walls within the tumour bed, but only slight tumour invasion of arterial walls (Miller and McGregor, 1980). In contrast to this study, vascular invasion by carcinoma was the immediate cause of pulmonary haemorrhage-related death in another recent study (Nichols *et al*, 2012). Inoue *et al* (2001) demonstrated that VEGF level was significantly higher in patients with pulmonary haemorrhage (PH) than in those without PH in pulmonary aspergilloma. Our study first explored the possible mechanisms of haemoptysis in adenocarcinoma; we analysed the expression of VEGF, extratumoural MVD, tumour necrosis, vascular invasion as well as coagulation function, and demonstrated that vascular invasion could be the most important mechanism of haemoptysis in lung adenocarcinoma. Our study showed that patients with haemoptysis had poor prognosis and a high frequency of vascular invasion. It can be inferred that cancer cells in haemoptysis patients may have higher invasive potential. Further studies are required to address this question.

Extratoural blood vessels take part in the pulmonary vascular circuit and are assumed to be functional vasculature, whereas intratumoural blood vessels are usually occluded by surrounding cells, and might not always be functional blood vessels (Shimada *et al*, 2010). Therefore, only extratumoural MVD were evaluated in our study. We have demonstrated that the greatest dimension of tumour was larger in haemoptysis group, which was in line with the former result that with the augment of tumour size, the frequency of blood vessel invasion increased (Yano *et al*, 2010; Arame *et al*, 2012).

The level of Fib was higher in haemoptysis group than nonhaemoptysis group. Generally, high levels of Fib indicate high risk of thrombosis (Wang *et al*, 2011; Reck *et al*, 2012); thus, the elevated Fib level may reflect the enhanced coagulation associated with haemoptysis. Elevated WBC count was found in haemoptysis group in the present study. Circulating inflammatory cells correlate with patients' outcome, as has been demonstrated in a range of tumours. Different inflammatory cell subtypes may play different prognostic roles. Zhu *et al* (2011) reported that high levels of peripheral CD4+ CD69+ CD25- T cells in hepatocellular carcinoma patients were significantly correlated with vascular invasion. Distinct subsets of tumour-infiltrating myeloid-derived suppressor cells (MDSCs) including monocytic-MDSC and granulocytic-MDSC favoured tumour progression and dissemination, and granulocytic MDSC subset was shown to be greatly increased in the blood of xenotransplantation model and was also shown to be upregulated in renal cell carcinoma patients (Ko *et al*, 2009; Toh *et al*, 2011; Toh and Abastado, 2012). Thus, several lines of evidence suggest that there may be some relationship between tumour invasion, tumour-infiltrating inflammatory cells

and circulating inflammatory cells, which need further experiments to determine.

## CONCLUSIONS

In conclusion, this is the first study to quantitate the prognostic value of haemoptysis in patients with lung primary adenocarcinoma. It highlights haemoptysis as an independent predictor of poor OS, DSS and DFS in lung adenocarcinoma after curative resection. In addition, vascular invasion rather than angiogenesis or tumour necrosis could be the most important mechanism of haemoptysis. Therefore, studies of the invasive ability of lung adenocarcinoma in patients presenting with haemoptysis could supply important information for therapeutic strategy. Such information may help to predict patient's outcome early and to provide a rationale for individual treatment.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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