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Cribriform pattern in lung invasive adenocarcinoma correlates with poor prognosis in a Chinese cohort

Yang Qu, Haifeng Lin, Chen Zhang, Kun Li, Haiqing Zhang*

Department of Pathology, Beijing Chest Hospital, Capital Medical University, Beijing, 101149, China

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ABSTRACT

The 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) lung adenocarcinoma classification and the following 2015 WHO classification have both been validated for their predictive values of histologic subtypes for prognosis. We sought to investigate the clinicopathological and prognostic significance of the cribriform pattern in lung adenocarcinomas. Histologic subtypes were evaluated in 395 patients who underwent complete resection for invasive lung adenocarcinomas between 2011 and 2013. Cribriform pattern was correlated with clinicopathological factors as well as molecular and survival data. One hundred and thirty cases (33%) were present with cribriform pattern (5–100%; mean ± SD, 24% ± 22%). Thirty two (8%) of those were reclassified into cribriform predominant tumors. Presence of cribriform pattern (≥5%) was significantly associated with lymph/vascular invasion ($P < 0.001$), nodal positivity ($P = 0.003$), higher T stage($P = 0.005$) and higher TNM stage ($P = 0.001$). Cribriform pattern (≥10%) was highly associated with worse disease-free survival (DFS) and overall survival (OS) (mean DFS: 42.6 months, $P < 0.001$; mean OS: 64.1 months, $P = 0.012$). The DFS or OS for cribriform predominant tumors was similar to that for solid or micropapillary tumors. In multivariate analysis, cribriform pattern (≥10%) or cribriform predominant subtype was an independent predictor for DFS. Cribriform pattern was a specific pattern compared to other acinar patterns, presenting with more aggressive behavior. Moreover, presence of cribriform pattern was a strong predictor for worse prognosis and should be considered a high grade pattern. Our study provides further evidence for cribriform pattern to be acknowledged as an independent subtype in the future classification.

1. Introduction

Lung cancer is the leading cause of cancer-related death worldwide [1]. Adenocarcinoma is a common subtype of lung cancer. The 2011 IASLC/ATS/ERS lung adenocarcinoma classification and the following 2015 WHO classification have both been validated for their predictive value of histologic subtypes on prognosis [2,3]. In the new classification, lung invasive adenocarcinoma is reclassified into five predominant subtypes: lepidic, acinar, papillary, solid and micropapillary. Semiquantitative assessment of each subtype in 5% increments is also recommended to identify all patterns present in each tumor. Several independent studies have demonstrated the predictive value of the new classification system for both prognosis and treatment [4–7].

As one type of glandular pattern, cribriform pattern has been identified to predict survival in several organs, including prostate, breast and lung [8,9]. Based on criteria of the new classification system, cribriform pattern is included in acinar subtype. However, several studies have demonstrated that cribriform pattern could further stratify prognosis in lung adenocarcinomas [10–13]. The aim of our study was to investigate the clinicopathological significance of cribriform pattern in lung adenocarcinomas in a Chinese cohort. We analyzed a cohort of 395 surgically resected cases with available clinicopathological and follow up information.

2. Materials and methods

2.1. Cohort

In the present study, we retrospectively identified 395 patients with invasive lung adenocarcinomas (stage I-III) who underwent complete resection between 2011 and 2013. Patients who had received neoadjuvant chemotherapy or radiotherapy or had a history of other malignant tumors were excluded. The last follow up date was June 30, 2018. Correlative clinicopathological data were reviewed from patient

* Corresponding author at: Department of Pathology, Beijing Chest Hospital, Capital Medical University, 97# Machang, Tongzhou District, Beijing, 101149, China.
E-mail address: zhqing56@sina.com (H. Zhang).

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archives in our hospital. Approval for this study was obtained from the review board of Beijing Chest Hospital and written informed consent was assigned by all the patients, the ethics committees approved the consent procedure. Tumors were restaged in accordance with the 8th edition of TNM classification [14].

2.2. Histological evaluation

All specimens were formalin fixed immediately after resection and stained with hematoxylin and eosin (H&E). All tumor slides for each patient were reviewed independently by two pathologists (Y.Q. and H.L.) who were blinded to the clinical data. Histologic subtypes were evaluated according to the 2015 WHO classification. Briefly, the percentage of each histologic component (lepidic, acinar, papillary, solid and micropapillary) and cribriform pattern was recorded in 5% increments in each case. The component occupying the majority of the tumor was defined as predominant subtype. For the non-predominant components, presence of solid, micropapillary or cribriform component with no less than 5% was defined as minor component. In addition, we also considered each of these three subtypes to be absent when it was not observed or less than 5%.

The criteria for the cribriform pattern was in accordance with Kadota et al. [10], who defined it as invasive back-to-back fused tumor glands with poorly formed glandular spaces lacking intervening stroma, or invasive tumor nests of tumors cells that produce glandular lumina without solid components (Fig. 1).

2.3. Mutation analysis

EGFR (18–21 exons) and *KRAS* (exons 2–3) mutations were identified by use of an amplification refractory mutation system, as described previously [15]. *ALK* rearrangements were identified through detection of *ALK* protein expression. Sections were stained using a Ventana Discovery XT automated immunohistochemical stainer (Ventana Medical Systems, Tucson, AZ, USA), in accordance with the manufacturer's guidelines [16]. The rabbit *ALK* monoclonal antibody (*D5F3*) (Cell Signaling Technology, Danvers, MA, USA) was used and a rabbit monoclonal antibody raised against immunoglobulin G (Roche, Bael, Switzerland) was used as a negative control. Intensive brown staining with granular texture in the cytoplasm was considered positive for *ALK*, while faint cytoplasmic staining was considered negative.

2.4. Statistical analysis

Correlation of clinicopathological factors with cribriform pattern was examined by Chi-square or Fisher's exact tests. OS was defined from the first day after surgery until patient death from any cause. DFS was defined from the first day after surgery until the first time of recurrence. OS and DFS were estimated using the Kaplan-Meier method, with a log-rank test to probe for significance. Univariate and multivariable analyses were performed using the Cox regression hazards model. All statistical analyses were performed using SPSS Statistics 17 (IBM, Ehningen, Germany). Statistical significance was set at $P<0.05$.

3. Results

3.1. Patient and tumor characteristics

Important clinicopathological findings for all patients are summarized in Table 1. A total of 395 patients (203 male, 192 female) diagnosed with lung adenocarcinoma were enrolled in our study. The median age was 59 years (range, 23–80 years). In total, 29% of patients were current smokers, 11% were former smokers, and 60% were never smokers.Ninety-five percent of patients received a lobectomy and 5% received a pneumonectomy, accompanied by systematic lymph node dissection in all cases. Based on the 8th edition of the cancer staging system, 52% of patients were stage I, 16% were stage II, and 32% were stage III.

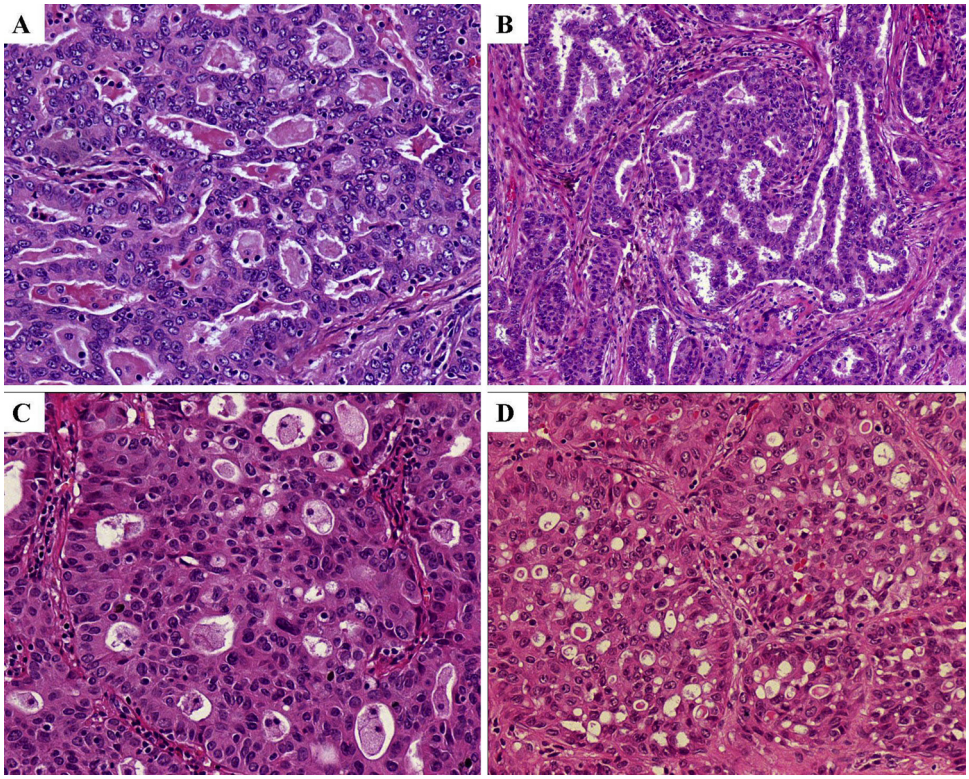

Fig. 1. Morphology of cribriform pattern in lung adenocarcinoma. A and B, cribriform pattern presenting with back-to-back tumor glands with variant size glandular spaces lacking intervening stroma. C and D, cribriform pattern showing tumor nests with poorly formed glandular lumina.

Table 1
Survival analysis for clinicopathological factors of the patients.

Parameter	N	DFS, mo Mean (SE)	*p* Value	OS, mo Mean (SE)	*p* value
Age					
≤59	206	52.6(2.6)	0.434	71.4(2.2)	0.646
>59	189	55.5(2.7)		69.5(2.3)	
Sex					
Male	203	49.5(2.7)	0.014	65.9(2.4)	0.009
Female	192	59.0(2.7)		75.3(2.1)	
pT					
1	201	65.4 (2.4)	< 0.001	79.5(1.8)	< 0.001
2	167	44.9 (2.9)		64.1(2.6)	
3	24	28.9 (6.6)		47.8(7.5)	
4	3	15.3 (7.7)		17.7(5.0)	
pN					
0	224	67.1(2.2)	< 0.001	80.5(1.4)	< 0.001
1	49	44.5(4.9)		63.8(4.5)	
2	122	33.0(3.1)		52.9(3.3)	
3	–	–		–	
pStage					
I	206	69.4(2.2)	< 0.001	82.3(1.3)	< 0.001
II	63	44.4(4.6)		64.4(4.1)	
III	126	33.1(2.9)		52.9(3.3)	
Smoking					
Nonsmoker	236	56.9(2.4)	0.072	73.9(1.9)	0.027
Current/exsmoker	159	49.8(3.0)		65.6(2.7)	
Lymph/vascular invasion					
No	211	63.5(2.4)	< 0.001	75.6(2.0)	0.001
Yes	184	43.5(2.7)		64.8(2.5)	

3.2. Distribution of the cribriform pattern

Among the 395 cases, cribriform pattern was present in 130 (33%) cases, ranging from 5 to 100% of total tumor volume (mean ± SD, 24% ± 22%) (Table 2). Based on the criteria of the 2015 WHO classification, all cases were classified as invasive adenocarcinomas, which were further divided into five predominant subtypes (cribriform pattern was included in acinar predominant subtype): lepidic (21/5%), acinar (145/37%), papillary (63/16%), solid (104/26%) and micropapillary (62/17%). Frequency of cribriform pattern was highest in acinar predominant tumors (56/38.6%), followed by solid (35/33.7%), papillary (16/25.4%), micropapillary (22/36.1%), and lepidic (1/4.8%) predominant tumors ($p < 0.001$; Fig. 2). When we defined cribriform pattern as an independent predominant subtype, the distribution of predominant subtypes were as follows: lepidic (21/5%), acinar (113/29%), papillary (63/16%), solid (105/26%), micropapillary (61/15%), and cribriform (32/8%).

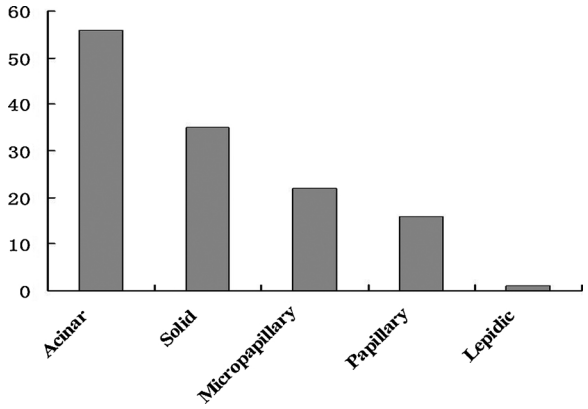

Fig. 2. The distribution of cribriform pattern in each predominant subtype.

3.3. Association between cribriform pattern and clinicopathological factors

Cribriform pattern (≥5%) was significantly associated with lymph/vascular invasion ($P < 0.001$), nodal positivity ($P = 0.003$), higher T stage ($P = 0.005$) and higher TNM stage ($P = 0.001$). No other clinicopathological factors including age, sex or smoking history, were significantly associated with cribriform pattern. Cribriform predominant subtype was significantly associated with nodal positivity ($P = 0.002$), higher TNM stage ($P = 0.021$), and smoking history ($P =$

Table 2
Clinicopathological characteristics of patients with cribriform pattern.

Parameter	Total	patients with cribriform pattern		*p* Value	patients with cribriform predominant pattern		*p* Value
	395	130	(32.9)		32	(8.1)	
Age							
≤59	206	68	(33.0)	0.526	18	(8.7)	0.475
>59	189	62	(32.8)		14	(7.4)	
Sex							
Male	203	70	(34.5)	0.282	14	(6.9)	0.720
Female	192	60	(31.3)		18	(9.4)	
pT							
1	201	50	(24.9)	0.005	13	(6.5)	0.379
2	167	71	(42.5)		17	(10.2)	
3	24	8	(33.3)		2	(8.3)	
4	3	1	(33.3)		0	0.0	
pN							
0	224	58	(25.9)	0.003	10	(4.5)	0.002
1	49	20	(40.8)		7	(14.3)	
2	122	52	(42.6)		15	(12.3)	
3	–	–	–		–	–	
pStage							
I	206	51	(24.8)	0.001	10	(4.9)	0.021
II	63	25	(39.7)		6	(9.5)	
III	126	54	(42.9)		16	(12.6)	
Smoking							
Nonsmoker	236	82	(34.7)	0.202	26	(11.0)	0.005
Current/exsmoker	159	48	(30.2)		6	(3.8)	
Lymph/vascular invasion							
No	211	52	(24.6)	< 0.001	12	(5.7)	0.152
Yes	184	78	(42.4)		20	(10.9)	

0.005) (Table 2).

3.4. Association between cribriform pattern and gene mutations

Of the 395 cases, 131 were available for molecular data assessment of *EGFR* and *KRAS* mutations or *ALK* rearrangements. Of these 131 cases, 66 (50%) had *EGFR* mutations, 10 (8%) had *KRAS* mutations and 15 (11%) had *ALK* rearrangements. Of cases positive for genetic mutations, 31 (47%) with *EGFR* mutations, 5 (50%) with *KRAS* mutations, and 8 (53%) with *ALK* rearrangements were present with cribriform pattern, respectively. Of the 32 cases with cribriform predominant subtypes, 8 (25%) had *EGFR* mutations, 5 (16%) had *KRAS* mutations and 4 (13%) had *ALK* rearrangements. Cribriform pattern (minor or predominant) was not significantly associated with *EGFR*, *KRAS* mutations or *ALK* rearrangements.

3.5. Association between cribriform pattern and prognosis

Comparisons of DFS or OS between two categories in univariate analysis are listed in Table 1. Among clinicopathological factors, male sex ($P = 0.009$), higher T stage ($P < 0.001$), nodal positivity ($P < 0.001$), higher TNM stage ($P < 0.001$) and lymph/vascular invasion ($P = 0.001$) were negative prognostic factors by univariate analysis. Smoking history was significantly associated with worse OS ($P = 0.027$) but not DFS ($P = 0.072$).

Presence of cribriform pattern (≥5%) was significantly associated with worse DFS (mean DFS: 46.1 months, $P = 0.002$) and OS (mean OS: 65.9 months, $P = 0.026$). When we stratified tumors by percentage of cribriform pattern similar to the methods in Kadota et al. [10], mean DFS and OS were 58.1 months and 72.9 months respectively for 0% cribriform pattern ($n = 265$), 56.7 and 71.9 for 5% ($n = 33$), 33.1 and 56.0 for 10% (n = 26), 44.3 and 65.9 for >10% ($n = 75$). Then, we used a 10% cut-off value to divide tumors into two groups. The mean DFS and OS of patients with ≥10% cribriform pattern were significantly lower than those of patients with <10% cribriform pattern (mean DFS: 42.6 months versus 57.9 months, $P < 0.001$; mean OS: 64.1 months versus 72.6 months, $P = 0.012$) (Table 3) (Fig. 3).

When tumors were classified into five predominant subtypes, patients with lepidic predominant subtypes had the most favorable prognosis, followed by acinar and papillary, whereas patients with solid or micropapillary predominant subtypes had the worst prognosis. When we reclassified cribriform patterns as an independent predominant subtype, patients with cribriform predominant subtypes had worse survival (mean DFS: 42.8 months; mean OS: 66.8 months) compared to those with acinar or papillary predominant subtypes, whose survival was closer to that of patients with solid or micropapillary predominant subtypes (Table 3) (Fig. 3).

In this study, 337 tumors presented with two or more subtypes each. Besides predominant subtypes, we also investigated prognostic impact of minor components including solid, micopapillary and cribriform patterns, which were divided into eight groups listed in Table 3. We found patients with any one or two of the three minor components had worse DFS and OS than those with none of them, but had better DFS and OS than those with all of them. Patients with all of the minor components exhibited worst DFS but not OS. However, we didn't observe significant difference for either DFS or OS between patients with one of the three patterns and those with two of them (Fig. 3).

In multivariate analyses, sex ($P = 0.012$), stage ($P < 0.001$), lymph/vascular invasion ($P = 0.001$), cribriform pattern (≥10%, $P = 0.009$) and cribriform predominant subtype ($P = 0.001$) were independent predictors for DFS. Stage ($P < 0.001$), lymph/vascular invasion ($P = 0.001$), cribriform pattern (≥10%, $P = 0.001$) were independent predictors for OS. Cribriform predominant subtype was not an independent predictor for OS with only minor significance ($P = 0.066$) (Table 4).

To extend our comparisons to previous studies, we also performed analyses in stage I subgroup. Clinicopathological characteristics of patients with cribriform pattern in stage I subgroup are summarized in Supplementary Table 1. In this cohort (n = 206), 51 (24.8%) patients were present with cribriform pattern, 10 (4.9%) of whom were present with cribriform predominant subtypes. Cribriform pattern (≥5%) was significantly associated with lymph/vascular invasion ($P = 0.001$) and higher T stage ($P = 0.004$). Survival data in stage I subgroup has been listed in Supplementary Table 2. No significant difference was found between cribriform pattern (≥10%) and DFS or OS. However, patients with cribriform predominant subtypes exhibited worse survival (mean DFS: 49.5 months; mean OS: 70.0 months) compared to those with acinar or papillary predominant subtypes, whose survival was closer to that of patients with solid or micropapillary predominant subtypes. In multivariate analyses, tumor size ($P = 0.041$) and lymph/vascular invasion ($P = 0.035$) were independent predictors for DFS, but impact of cribriform predominant subtype on DFS reached only borderline significance ($P = 0.070$). and none of the factors were independent predictors for OS (Supplementary Table 3).

Table 3
Prognostic impact of cribriform pattern, predominant patterns and minor pattern groups.

	N	DFS, mo Mean (SE)	*p* Value	OS, mo Mean (SE)	*p* Value
Cribriform pattern					
Absent[a]	265	58.1(2.3)	0.002	72.9(1.9)	0.026
Present[b]	130	46.1(3.3)		65.9(2.9)	
<10%	294	57.9(2.2)	< 0.001	72.6(1.8)	0.012
≥10%	101	42.6(3.7)		64.1(3.4)	
Predominant subtypes without cribriform					
Lepidic	21	78.1(1.9)	< 0.001	79.3(2.1)	< 0.001
Acinar	145	57.4(3.1)		74.3(2.4)	
Papillary	63	58.2(4.6)		74.5(3.5)	
Solid	104	48.1(3.8)		64.1(3.5)	
Micropapillary	62	41.8(4.5)		61.8(4.3)	
Predominant subtypes with cribriform					
Lepidic	21	78.1(1.9)	< 0.001	79.3(2.1)	< 0.001
Acinar	113	60.7(3.5)		76.8(2.6)	
Papillary	63	58.2(4.6)		74.5(3.5)	
Solid	105	47.9(3.7)		64.4(3.5)	
Micropapillary	61	42.2(4.6)		59.6(4.1)	
Cribriform	32	42.8(6.1)		66.8(5.9)	
Minor high grade subtype groups					
M-S-C-[c]	14	76.2(3.2)	< 0.001	80.6(1.8)	0.003
M-S-C+	9	58.0(10.1)		58.0(10.1)	
M + S-C-	28	53.7(4.3)		69.8(3.5)	
M-S + C+	6	45.0(6.6)		57.1(6.2)	
M + S + C-	63	49.3(4.6)		68.8(3.9)	
M + S-C+	36	49.5(6.1)		76.0(4.5)	
M-S + C-	62	52.6(4.7)		67.3(4.2)	
M + S + C+	16	40.9(4.8)		61.5(4.4)	

[a] Cribriform pattern not observed or less than 5%.
[b] Cribriform pattern no less than 5%.
[c] Minor subtype group: M = micropapillary; S = solid; C = cribriform. "- ": Absent for this pattern in one case; "+": Present for this pattern in one case but not predominant.

4. Discussion

In the present study, we demonstrated that cribriform pattern with any percentage (≥5%) highly correlated with lymph/vascular invasion, lymph node metastasis, and advanced TNM stage. Furthermore, cribriform predominant subtype was also significantly associated with smoking history. For survival analysis, we found patients with ≥10% cribriform pattern had worse prognosis. In multivariate survival analyses, we found cribriform predominant subtype or ≥10% cribriform pattern together with sex, stage and lymph/vascular invasion were

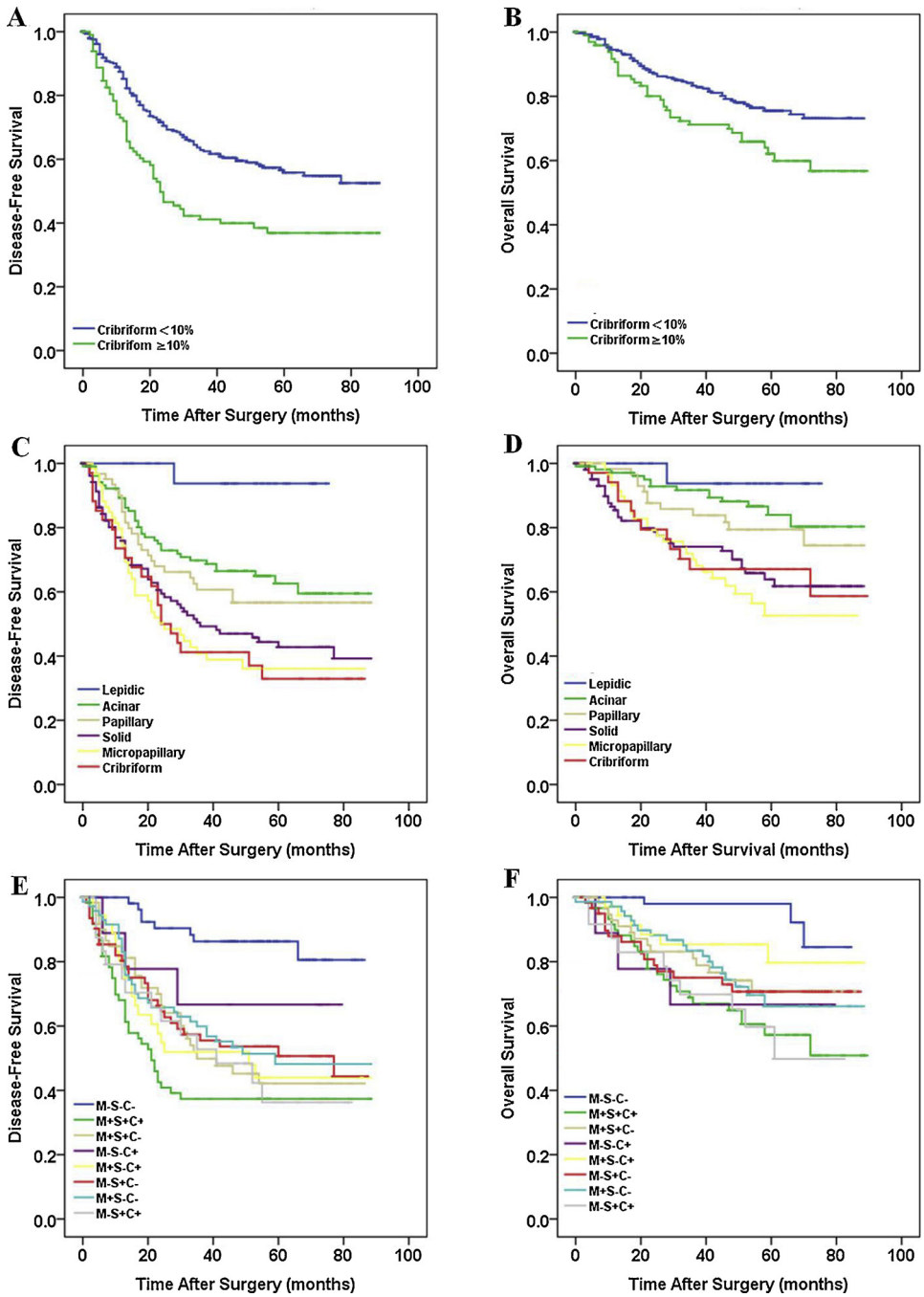

Fig. 3. Survival analysis associated with cribriform pattern. A and B, Disease-free and overall survival for cribriform pattern with 10% cut-off value. C and D, Disease-free and overall survival for predominant subtypes including cribriform predominant subtype.

independent predictors for DFS but not OS.

The prognostic value of cribriform pattern on survival has been investigated in several studies [10–13]. In an American cohort of stage I lung adenocarcinomas, patients with ≥10% cribriform pattern or cribriform predominant subtype had lower 5-year recurrence-free probability [10]. In a German cohort, cribriform predominant pattern was associated with the worst DFS and OS of all patterns [12]. Our present study included a large Chinese cohort which can well represent the features of Asia population. In our study, the prognostic impact of cribriform pattern was consistent with that observed in previous studies [10–13]. Cribriform pattern has been included in acinar pattern because of its glandular structure in the new WHO classification [3]. As the most common pattern, acinar predominant pattern has been confirmed to be a moderate grade pattern for risk of recurrence and/or OS [4]. However, our study, combined with previous studies found that cribriform pattern predicts a worse prognosis. We also found that presence of even minor percentages of cribriform pattern correlated with more aggressive behavior, presenting with lymph/vascular invasion, lymph node metastasis, and advanced TNM stage, suggesting cribriform pattern should be a high grade pattern independent of acinar pattern. It is important to record cribriform pattern in regular pathology reports, especially for patients with unresectable lung cancer whose pathologic information is solely dependent on small pieces of specimen from biopsies and not from a resected specimen. In addition, cribriform predominant subtype was found to be significantly associated with smoking history in our study. Maeshima et al. and Kadota et *al.* also found a correlation between cribriform pattern and smoking history, although the distribution of smoking status in our cohort was different

Table 4
Multivariate Cox proportional hazards model.

	DFS			OS		
	HR	(95% CI)	*p* Value	HR	(95% CI)	*p* Value
Age	0.83	(0.62-1.12)	0.618	1.09	(0.73-1.64)	0.672
Sex	1.47	(1.09-1.99)	0.012	1.34	(0.75-2.41)	0.325
Smoking	0.96	(0.63-1.47)	0.961	0.84	(0.47-1.49)	0.544
Stage(I/II + III)	3.49	(2.49-4.89)	<0.001	5.77	(3.36-9.89)	<0.001
Lymph/vascular invasion	1.71	(1.25-2.34)	0.001	1.97	(1.30-2.99)	0.001
with cribriform(< 10% or ≥ 10%)	1.54	(1.11-2.14)	0.009	1.95	(1.28-2.99)	0.001
Age	0.91	(0.68-1.23)	0.552	1.11	(0.74-1.66)	0.630
Sex	1.24	(0.81-1.89)	0.323	1.37	(0.77-2.44)	0.279
Smoking	1.01	(0.66-1.56)	0.959	0.93	(0.53-1.63)	0.796
Stage(I/II + III)	3.29	(2.34-4.63)	<0.001	6.08	(3.54-10.4)	<0.001
Lymph/vascular invasion	1.72	(1.25-2.35)	0.001	1.38	(0.90-2.11)	1.380
with cribriform predominant	2.34	(1.43-3.84)	0.001	1.91	(0.96-3.79)	0.066

from theirs, which included almost Caucasian patients [10,17].

The five main predominant subtypes of lung invasive adenocarcinomas in the new WHO classification are highly associated with prognosis and genetic mutations [4–7]. Our study showed both DFS and OS were significantly different among these subtypes, similar to results reported in previous studies. Survival of patients with cribriform predominant subtypes is significantly lower than in acinar predominant subtypes, but closer to solid and micropapillary predominant, similar to previous study [10–13]. However, Lung cancer is more heterogeneous than other cancers. About eighty percent of lung adenocarcinomas include two or more subtypes in a single tumor [2,3]. Beyond those predominant subtypes, accumulating evidence has demonstrated that non-predominant pattern, especially solid or micropapillary pattern, is also more predictive for prognosis [18,19]. In our study, we defined these non-predominant high grade patterns as minor components with no less than 5%. To investigate their impact on survival, we divided them into different groups, and results revealed presence of any single minor component can predict prognosis very well, further suggesting cribriform pattern should be independently recognized.

Cribriform pattern has also been recognized in various organs as a positive or negative predictor for prognosis. In prostate cancer, cribriform pattern is a strong prognostic marker for distant metastasis and disease-specific death even in biopsy specimens [8]. Similarly, in colonic adenocarcinoma, cribriform pattern also predicts a negative outcome [20]. The prognostic significance of cribriform pattern in these organs is consistent with that in lung adenocarcinomas. In contrast, in breast cancer, cribriform pattern was reported to be highly associated with better prognosis [9]. A study by Lam AK et al. concluded cribriform-morular variant of papillary thyroid carcinoma had lower recurrence rates (8.5%) and patient mortality rates (2%) compared to conventional papillary thyroid carcinoma [21]. Thus, much evidence suggests cribriform pattern is not only a morphologic tumor growth pattern but also a prognostic factor.

The frequency of *EGFR* mutation is higher in Asian population than Caucasian population [22]. It has been reported that *ALK* rearrangements range from 2 to 7% among unselected Caucasian non-small cell lung cancer patients [23]. The frequency has been reported to be as high as 5–10% and is higher in the Asian population [22]. Fifty percent and 11% cases in our study were found to harbor *EGFR* mutations and *ALK* rearrangements, respectively. The frequencies were consistent with previous findings. However, we didn't observe any association between cribriform pattern and *EGFR* and *KRAS* mutations or *ALK* rearrangements, similar to previous studies [9,10]. Some studies reported cribriform pattern was highly associated with *ALK* rearrangements [24,25], however, only 4 of 32 patients with cribriform predominant tumors were found to harbor *ALK* rearrangements. The reason for these differential results remains under investigation. Limited availablility of molecular data may have introduced bias into our study.

The limitation of our study was that our study was performed on in a small cohort in a single centre in North China. In addition, the term "complex glandular patterns" was mentioned in Moreira et al. and Kuang et al. studies [11,13], suggesting not only cribriform pattern but also fused glands predict worse survival. Further study is needed to identify additional prognostic factors for stratifying acinar predominant pattern.

In conclusion, we demonstrated that cribriform pattern correlates with more aggressive behavior and worse prognosis. Our study supplies further evidence for cribriform pattern to be considered an independent subtype in lung adenocarcinoma in future classification.

Compliance with ethical standards

The study was performed according to the Declaration of Helsinki and ethics approval was not required due to the retrospective nature of the study. Informed consents were obtained from all participants.

Conflict of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.prp.2018.12.014.

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