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Lepidic component identifies a subgroup of lung adenocarcinoma with a distinctive prognosis: a multicenter propensity-matched analysis

Erjia Zhu*, Chenyang Dai*, Huikang Xie, Hang Su, Xuefei Hu, Ming Li, Junqiang Fan, Jinshi Liu, Quan Zhu, Lei Zhang, Honggang Ke and Chang Chen, on behalf of the Surgical Thoracic Alliance of Rising Star (STAR) Collaborative Group

Abstract

Background: Our aim was to investigate the prognostic impact of the lepidic component on T stage in patients with lung adenocarcinoma (LUAD).

Methods: A retrospective data set including 863 cases of LUAD with lepidic component and 856 cases without lepidic component was used to identify matched lepidic-positive and lepidic-negative cohorts ($n = 376$ patients per group) using a propensity-score matching. Primary outcome variables included recurrence-free survival (RFS) and overall survival (OS). Prognostic factors were assessed by Cox regression analysis and Kaplan–Meier estimates.

Results: Multivariate analysis revealed that lepidic component presence was an independent prognostic factor for prolonged RFS ($p < 0.001$) and OS ($p < 0.001$). Furthermore, lepidic ratio (LR) >25% or ⩽25% were confirmed to be independent prolonged survival predictors. No survival differences were observed between patients with LUAD with LR >25% or ⩽25% (RFS $p = 0.333$; OS $p = 0.078$). The 5-year OS rates of patients with LUAD with a lepidic component were 90% regardless of the T stage, and these survival rates were significantly better than those of patients with LUAD without a lepidic component in the corresponding T stage. Multivariate analysis confirmed that T stage was associated with survival only in patients with LUAD without a lepidic component.

Conclusions: Lepidic component presence identifies a LUAD subgroup with an excellent prognosis independent of the LR, pathological T classification. Considering the lepidic component presence may improve prognostic predictions for patients with LUAD.

Keywords: ground-glass opacity, lepidic component, lung adenocarcinoma, T classification

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Correspondence to:
Chang Chen
Department of Thoracic Surgery, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Zhengmin Road 507, Shanghai 200443, China
chenthoracic@163.com

Erjia Zhu
Chenyang Dai
Hang Su
Xuefei Hu
Department of Thoracic Surgery, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, People's Republic of China

Huikang Xie
Department of Pathology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, People's Republic of China

Ming Li
Department of Thoracic Surgery, Jiangsu Cancer Hospital, Nanjing, People's Republic of China

Junqiang Fan
Department of Thoracic Surgery, The Second Affiliated Hospital of Zhejiang University School of Medicine, Zhejiang University School of Medicine, Hangzhou, People's Republic of China

Jinshi Liu
Department of Thoracic Surgery, The Second Affiliated Hospital of Zhejiang University School of Medicine, Zhejiang Cancer Hospital, Hangzhou, People's Republic of China

Quan Zhu
Department of Thoracic Surgery, Jiangsu Province Hospital, Nanjing, People's Republic of China

Lei Zhang
Department of Thoracic Surgery, The First People's Hospital of Changzhou, Changzhou, People's Republic of China

Introduction

With the application of computed tomography (CT), a large number of lung adenocarcinomas (LUADs) manifesting as part-solid nodules are detected. Ground-glass opacity (GGO) on CT images and the corresponding lepidic growth pattern observed by microscopy are considered non-invasive components.[1,2] Many studies have revealed that invasive size (tumor size excluding the GGO or lepidic component) is a better predictor of survival than total tumor size.[3–8] Thus, the eighth edition of Lung Cancer Stage Classification recommends invasive size be used as a T descriptor, regardless of the extent and size of the GGO or lepidic component.[1,9]

However, a few studies have found that the presence of GGO may affect the prognostic significance of clinical T stage in patients with LUAD. Ye *et al.* reported excellent prognoses for patients with part-solid LUAD and demonstrated that clinical T stage could not predict patient prognosis.[10]

Honggang Ke
Department of Thoracic Surgery, Affiliated Hospital of Nantong University, Nantong University, Nantong, People's Republic of China

*Erjia Zhu and Chenyang Dai are joint first authors.

Furthermore, Hattori *et al.* found similar results and proposed that part-solid LUAD should be categorized as clinical 'T1a' regardless of invasive size.[11,12] In contrast, two studies found that part-solid LUAD and pure-solid LUAD within the same T stage had similar survival rates after multivariate adjustment or propensity-score matching.[13,14] Thus, the influence of GGO on clinical T stage is still unclear.

For pathological staging, invasive size was estimated according to an alternative method proposed by the 2015 World Health Organization classification criteria, which multiplies the percentage of the invasive component by the overall tumor size; in contrast, clinical staging directly measures the maximum diameter. In addition, there are limited studies focusing on the prognostic influence of lepidic components on pathological T stage. Whether a lepidic component has a similar impact on pathological T stage is unknown. To investigate this issue, we aimed to reveal the prognostic value of lepidic components in a Chinese population-based multicenter cohort of patients with LUAD.

Materials and methods

Patient cohort

This retrospective study was approved by the Institutional Review Boards of Shanghai Pulmonary Hospital, Zhejiang Cancer Hospital, Jiangsu Cancer Hospital, Jiangsu Province Hospital, The Second Affiliated Hospital of Zhejiang University School of Medicine, the Affiliated Hospital of Nantong University and The First People's Hospital of Changzhou on behalf of our collaborative group, the Surgical Thoracic Alliance of Rising Star (STAR). All patients diagnosed with solitary LUAD who had undergone surgical resection at one of the seven institutions included in STAR between January 2009 and December 2012 were reviewed. Patients with surgically resected p-stage T1a–T2a N0M0 LUAD based on the eighth edition of Lung Cancer Stage Classification were included. The T category was determined by invasive size. The exclusion criteria were as follows: (a) receipt of induction therapy; (b) lung cancer within the past 2 years; (c) positive surgical margins; (d) concurrent disease progression; and (e) adenocarcinoma *in situ*, minimally invasive adenocarcinoma; invasive mucinous adenocarcinoma, or colloid-predominant adenocarcinoma. Clinical and follow-up information were obtained by reviewing electronic medical records.

Histological evaluation

Standardized training of pathologists from each institution was performed to reduce the interobserver inconsistency before beginning of the study. All available hematoxylin and eosin-stained tumor slides were reviewed by two senior pathologists at each institution who were blinded to the patient's survival and clinical data. Any discrepancies between the pathologists were resolved *via* consensus by concurrent diagnosis using a multiple-headed microscope. The percentages of lepidic, acinar, papillary, solid and micropapillary patterns were recorded in 5% increments. Tumors were classified into lepidic-predominant adenocarcinoma, acinar-predominant adenocarcinoma, papillary-predominant adenocarcinoma, micropapillary-predominant adenocarcinoma, and solid-predominant adenocarcinoma according to the 2015 World Health Organization (WHO) classification criteria. LUAD with a lepidic component was defined as non-mucinous lung adenocarcinoma with a lepidic component $\geqslant 5\%$. The lepidic ratio (LR) was defined as the proportion of lepidic components.

Pathologic assessment of invasive size

Invasive size was defined as the size of invasive components, excluding lepidic components. In some cases with a single, invasive focus, invasive size was directly measured with a ruler. However, a large proportion of cases had multiple invasive foci or invasive areas on multiple slides. The 2015 WHO classification system proposed an alternative method to estimate invasive size by multiplying the percentage of invasive component by the overall tumor diameter. Invasive size was estimated using the following equation: invasive size = total size × percentage of invasive components / 100.[15]

Follow-up strategy

Physical examination, internal history review, chest CT scans with or without contrast, ultrasonography of the abdominal/cervical/supraclavicular regions, bone scans and magnetic resonance imaging of the brain were performed every 4–6 months for the first 2 years after surgery, every 6–12 months for 2–5 years after surgery, and every 12 months for subsequent years. Overall survival (OS) was defined as the period from the date of surgery to

the date of death or last survival follow up. Recurrence-free survival (RFS) was defined as the period from the date of surgery to the day of first relapse or last follow up.

Statistical analysis

A chi-square test was used to compare categorical variables. To investigate the prognostic implication of lepidic component, propensity-score matching was conducted on the basis of inverse probability weighting. Inverse probability weighting was calculated using a logistic regression with age, sex, smoking status, surgical mode, and T category and pathological components as inputs with a 0.001 caliper size. A Cox proportional hazards model was used to identify prognostic factors. The Kaplan–Meier method was used to evaluate OS and RFS. We used the log-rank test to compare the survival of different groups. A two-sided p value less than 0.05 was considered statistically significant. All analyses were conducted with Statistical Package software for Social Sciences 23.0 (IBM, Chicago, IL, US), and survival curves were drawn with R software.

Results

Clinicopathologic characteristics based on the presence of lepidic components

Patient characteristics before propensity-score matching are summarized in Supplementary Table 1. Of the 1719 patients with T1a–T2a N0M0 LUAD, 863 (50%) had a lepidic component. Nearly half (47%) of the LUAD patients with a lepidic component had an LR $\leqslant$ 25%. The presence of a lepidic component was associated with female sex ($p < 0.001$), a nonsmoking status ($p < 0.001$), a relatively low T stage ($p < 0.001$), the absence of a solid component ($p < 0.001$) and a micropapillary component ($p < 0.001$). After propensity-score matching, patient age, sex, smoking status, T category and pathological components, and surgical mode were equivalent between the matched groups (Table 1). The median follow-up period was 1820 days for RFS and 1950 days for OS.

Prognostic impact of lepidic components on patients with LUAD

Patients with LUAD with a lepidic component had significantly better survival than those with LUAD without a lepidic component [RFS $p < 0.001$, Figure 1(a); OS $p < 0.001$, Figure 1(b)]. Multivariate analysis confirmed that the presence of a lepidic component was an independent prognostic factor for prolonged RFS [hazard ratio (HR) 0.38; 95% confidence interval (CI) 0.27–0.54; $p < 0.001$] and OS (HR 0.34; 95% CI 0.22–0.51; $p < 0.001$). For the other variables, sex, T stage, and solid and micropapillary components were found to be independent prognostic factors for RFS and OS (Table 2). Results before propensity-score matching is shown in Supplementary Figure 1 and Supplementary Table 2.

Lepidic component indicated significantly prolonged survival independent of the LR

The log-rank test revealed that the presence of a lepidic component with an LR $>$ 25% or an LR $\leqslant$ 25% was associated with better 5-year RFS [LR $>$ 25%, $p < 0.001$; LR $\leqslant$ 25%, $p = 0.001$; Figure 1(c)] and OS [LR $>$ 25%: $p < 0.001$; LR $\leqslant$ 25%: $p = 0.002$; Figure 1(d)] than the absence of lepidic components. No survival difference was observed among patients with LUAD with an LR $>$ 25% or an LR $\leqslant$ 25% [RFS $p = 0.333$, Figure 1(c); OS $p = 0.078$, Figure 1(c)]. Multivariate analysis confirmed that the presence of a lepidic component with an LR $>$ 25% or an LR $\leqslant$ 25% were all independent prognostic factors for prolonged RFS (LR $>$ 25%: HR 0.38; 95% CI 0.19–0.75; $p = 0.006$; LR $\leqslant$ 25%: HR 0.38; 95% CI 0.26–0.56; $p < 0.001$) and OS (LR $>$ 25%: HR 0.27; 95% CI 0.11–0.67; $p = 0.005$; LR $\leqslant$ 25%: HR 0.35; 95% CI 0.23–0.55; $p < 0.001$; Table 2). Results before propensity-score matching is shown in Supplementary Figure 2 and Supplementary Table 2.

Prognostic impact of lepidic components on pathological T classification

T classification clearly delineated differences in 5-year RFS (91.4% in T1a, 83.0% in T1b, 75.9% in T1c, and 49.3% in T2a; $p < 0.001$) and OS (95.6% in T1a, 88.1% in T1b, 83.3% in T1c, and 65.2% in T2a; $p < 0.001$). In each T stage except for T1a, the presence of a lepidic component indicated significantly prolonged 5-year RFS [T1a: LR $>$ 25%, $p = 0.894$; LR $\leqslant$ 25%, $p = 0.283$, Figure 2(a); T1b: LR $>$ 25%, $p = 0.255$; LR $\leqslant$ 25%, $p = 0.015$, Figure 2(c); T1c: LR $>$ 25%, $p = 0.138$; LR $\leqslant$ 25%, $p = 0.001$, Figure 2(e); T2a: LR $>$ 25%, $p = 0.002$; LR $\leqslant$ 25%, $p = 0.006$, Figure 2(g)] and OS [T1a: LR $>$ 25%, $p = 0.682$; LR $\leqslant$ 25%, $p = 0.702$, Figure 2(b); T1b: LR $>$ 25%, $p = 0.120$;

Table 1. Clinicopathologic characteristics after propensity score matching based on presence of lepidic component.

Characteristics	Lepidic (+)	Lepidic (–)	Adjusted *p*
	n = 376	*n* = 376	
Age			0.952
⩽65	277 (74)	278 (74)	
>65	99 (26)	98 (26)	
Sex			0.672
Male	159 (42)	163 (43)	
Female	217 (58)	213 (57)	
Smoking			0.999
Yes	80 (21)	80 (21)	
No	296 (79)	296 (79)	
T stage			0.852
T1a	39 (10)	40 (11)	
T1b	208 (55)	211 (56)	
T1c	76 (20)	69 (18)	
T2a	53 (14)	56 (15)	
Pathological subtype			/
Lepidic	33 (9)	0 (0)	
Acinar	206 (55)	224 (60)	
Papillary	121 (32)	115 (31)	
Solid	10 (3)	18 (4)	
Micropapillary	6 (1)	19 (5)	
Lepidic ratio			/
>25%	82 (22)		
⩽25%	294 (78)		
Acinar			0.951
Present	305 (81)	303 (81)	
Absent	71 (19)	73 (19)	
Papillary			0.876
Present	247 (66)	250 (66)	
Absent	129 (34)	126 (34)	
Solid			0.595
Present	32 (9)	28 (7)	
Absent	344 (91)	348 (93)	
Micropapillary			0.730
Present	153 (41)	158 (42)	
Absent	223 (59)	218 (58)	
Surgery			0.564
Lobectomy	343 (91)	347 (92)	
Limited resection	33 (9)	29 (7)	

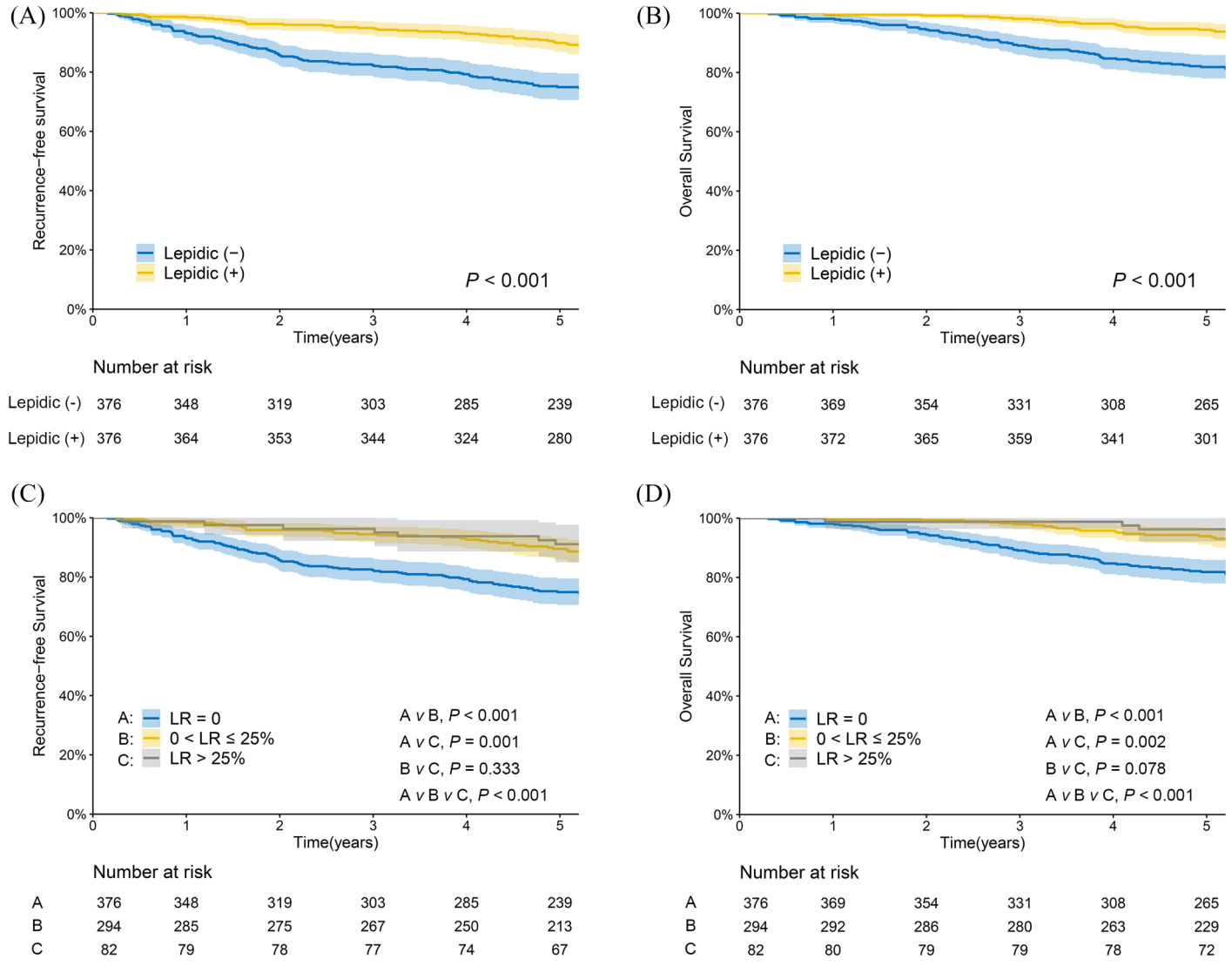

Figure 1. Comparison of survival of patients with lung adenocarcinoma based on presence of lepidic component and LR.
Lepidic (+), lung adenocarcinoma with lepidic component; lepidic (–), lung adenocarcinoma without lepidic component; LR, lepidic ratio.

LR ⩽25%, $p = 0.016$, Figure 2(d); T1c: LR >25%, $p = 0.090$; LR ⩽25%, $p = 0.002$, Figure 2(f); T2a: LR >25%, $p = 0.021$; LR ⩽25%, $p = 0.006$, Figure 2(h)] independent of LR in patients with LUAD. No survival difference was observed between LR >25% and LR ⩽25% in each T stage (RFS: T1a, $p = 0.388$; T1b, $p = 0.872$; T1c, $p = 0.748$; T2a, $p = 0.066$; and OS: T1a, $p = 0.947$; T1b, $p = 0.713$; T1c, $p = 0.756$; T2a, $p = 0.336$).

Distinctive prognosis of patients with LUAD with a lepidic component

Because of the excellent survival of LUAD with lepidic component, we performed a survival analysis to investigate potential prognostic factors. Surprisingly, T stage was not associated with survival in patients with LUAD with lepidic component [Figure 3(a–b)]. A further multivariate analysis confirmed the results. T stage was an independent prognostic factor of relatively poor survival only in LUAD without a lepidic component (Table 3). Results before propensity-score matching was shown in Supplementary Table 3.

Thus, LUAD with lepidic component was considered as one subgroup in further analysis. LUAD with a lepidic component had comparable or better RFS [T1a without lepidic, $p = 0.460$; T1b without lepidic, $p = 0.021$; T1c without lepidic, $p < 0.001$; T2a without lepidic, $p < 0.001$; Figure 3(c)], and OS [T1a without lepidic,

Table 2. Cox regression analysis for recurrence-free survival and overall survival after propensity score matching.

Variables	Recurrence-free survival					Overall survival				
	Univariate	Multivariate model 1		Multivariate model 2		Univariate	Multivariate model 1		Multivariate model 2	
	p	HR (95% CI)	*p*	HR (95% CI)	*p*	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Sex (female)	**0.015**	0.70 (0.50–0.98)	**0.039**	0.70 (0.50–0.98)	**0.040**	**0.002**	0.60 (0.40–0.88)	**0.009**	0.59 (0.40–0.88)	**0.008**
Age (>65)	0.239					**0.004**	1.41 (0.95–2.10)	0.090	1.41 (0.95–2.11)	0.089
Smoking (yes)	0.935					0.294				
T stage	<**0.001**		<**0.001**		<**0.001**	<**0.001**		<**0.001**		<**0.001**
T1a	ref	ref		ref		ref	ref		ref	
T1b	0.755	1.23 (0.63–2.42)	0.546	1.23 (0.77–1.87)	0.550	0.289	1.77 (0.70–4.50)	0.230	1.72 (0.68–4.39)	0.255
T1c	**0.029**	2.56 (1.26–5.24)	**0.010**	2.56 (1.25–5.25)	**0.010**	**0.007**	4.10 (1.57–10.74)	**0.004**	3.99 (1.52–10.51)	**0.005**
T2a	**0.001**	3.31 (1.65–6.64)	**0.001**	3.31 (1.64–6.66)	**0.001**	**0.001**	4.47 (1.74–11.51)	**0.002**	4.37 (1.69–11.29)	**0.002**
Surgery (lobectomy)	0.436					0.764				
Pathological subtype	0.059	[a]		[a]		**0.015**	[a]		[a]	
Lepidic	ref	[a]		[a]		ref	[a]		[a]	
Acinar	0.213	[a]		[a]		0.266	[a]		[a]	
Papillary	0.455	[a]		[a]		0.423	[a]		[a]	
Solid	0.023	[a]		[a]		**0.020**	[a]		[a]	
Micropapillary	0.154	[a]		[a]		**0.045**	[a]		[a]	
Acinar (presence)	0.813					0.634				
Papillary (presence)	**0.018**	0.71 (0.50–1.01)	0.059	0.72 (0.50–1.01)	0.059	**0.027**	0.71 (0.48–1.05)	0.086	0.71 (0.48–1.05)	0.088
Solid (presence)	**0.040**	1.86 (1.08–3.18)	**0.024**	1.86 (1.08–3.19)	**0.025**	**0.002**	2.20 (1.25–3.86)	**0.006**	2.16 (1.23–3.81)	**0.008**
Micropapillary (presence)	**0.001**	2.07 (1.47–2.93)	<**0.001**	2.07 (1.47–2.93)	<**0.001**	**0.016**	1.99 (1.35–2.95)	**0.001**	1.98 (1.34–2.94)	**0.001**
Lepidic (presence)	<**0.001**	0.38 (0.27–0.54)	<**0.001**			<**0.001**	0.34 (0.22–0.51)	<**0.001**		
Lepidic ratio	<**0.001**				<**0.001**	<**0.001**				<**0.001**
0%	ref			ref		ref			ref	
⩽25%	<**0.001**			0.38 (0.26–0.56)	<**0.001**	<**0.001**			0.35 (0.23–0.55)	<**0.001**
>25%	**0.003**			0.38 (0.19–0.75)	**0.006**	**0.002**			0.27 (0.11–0.67)	**0.005**

Multivariable model 1 includes the lepidic (presence) instead of the lepidic ratio. Multivariable model 2 includes the lepidic ratio instead of the lepidic (presence).
[a]Pathological subtypes were not included in multivariate analysis because of the association with presence of each component in adenocarcinomas.
Bold numerals indicate statistical significance.
CI, confidence interval; HR, hazard ratio; ref, reference value.

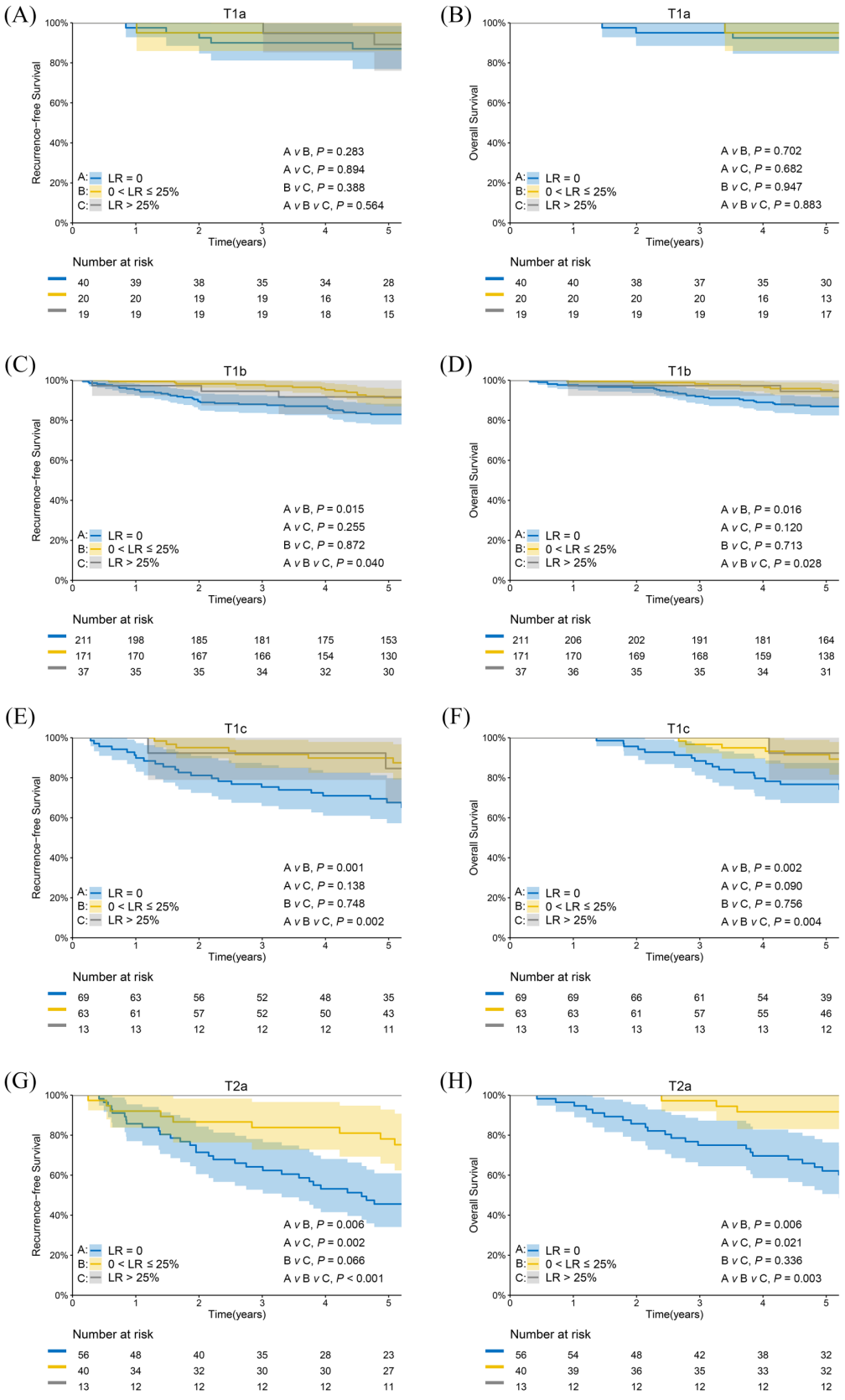

Figure 2. Survival outcomes regarding overall survival and recurrence-free survival based on the presence of lepidic components in each T stage.
LR, lepidic ratio.

Table 3. Cox regression model in lung adenocarcinoma with or without lepidic component after propensity score matching.

Variables	Recurrence-free survival			Overall survival		
	Univariate	Multivariate		Univariate	Multivariate	
	p	HR (95% CI)	*p*	*p*	HR (95% CI)	*p*
Lepidic (+)						
Sex (female)	0.953			**0.031**	0.55 (0.23–1.31)	0.176
Age (>65)	0.146			0.677		
Smoking (yes)	0.893			**0.042**	1.74 (0.71–4.28)	0.230
T stage	0.503			0.336		
T1a	ref			ref		
T1b	0.934			0.747		
T1c	0.648			0.288		
T2a	0.375			0.272		
Surgery (lobectomy)	0.469			0.992		
Pathological subtype	0.931			0.985		
Lepidic	ref			ref		
Acinar	0.726			0.732		
Papillary	0.826			0.981		
Solid	0.977			0.982		
Micropapillary	0.982			0.983		
Acinar (presence)	0.382			0.394		
Papillary (presence)	0.218			0.285		
Solid (presence)	0.295			0.126		
Micropapillary (presence)	**0.001**			**0.070**	2.06 (0.99–4.27)	0.052
Lepidic ratio (>25%)	0.780			0.337		
Lepidic (–)						
Sex (female)	**0.005**	0.63 (0.42–0.95)	**0.026**	**0.021**	0.67 (0.42–1.06)	0.090
Age (>65)	**0.013**	1.41 (0.92–2.15)	0.116	<**0.001**	1.83 (1.16–2.90)	**0.010**
Smoking (yes)	0.772			0.912		
T stage	<**0.001**		<**0.001**	<**0.001**		<**0.001**
T1a	ref	ref		ref	ref	
T1b	0.634	1.36 (0.57–3.24)	0.490	0.289	2.00 (0.61–6.61)	0.256
T1c	**0.017**	3.15 (1.27–7.79)	**0.013**	**0.011**	5.03 (1.48–17.09)	**0.010**
T2a	**0.001**	4.15 (1.72–10.00)	**0.002**	**0.002**	5.71 (1.72–19.03)	**0.005**

(Continued)

Table 3. (Continued)

Variables	Recurrence-free survival			Overall survival		
	Univariate	Multivariate		Univariate	Multivariate	
	p	HR (95% CI)	*p*	*p*	HR (95% CI)	*p*
Surgery (lobectomy)	0.793			0.531		
Pathological subtype	**0.040**	[a]		**0.013**	[a]	
Acinar	ref	[a]		ref	[a]	
Papillary	0.475	[a]		0.687	[a]	
Solid	0.011	[a]		0.008	[a]	
Micropapillary	0.541	[a]		0.077	[a]	
Acinar (presence)	0.759			0.279		
Papillary (presence)	**0.035**	0.75 (0.49–1.14)	0.174	**0.040**	0.73 (0.45–1.16)	0.183
Solid (presence)	**0.047**	1.54 (0.79–3.01)	0.204	**0.006**	1.99 (1.01–3.95)	**0.047**
Micropapillary (presence)	**0.089**	1.66 (1.10–2.52)	**0.017**	**0.073**	1.88 (1.18–3.01)	**0.008**

[a]Pathological subtypes were not included in multivariate analysis because of the association with presence of each components in adenocarcinoma.
Bold numerals indicate statistical significance.
CI, confidence interval; HR, hazard ratio; lepidic (+), lung adenocarcinoma with lepidic component; lepidic (–), lung adenocarcinoma without lepidic component; ref, reference value.

$p = 0.979$; T1b without lepidic, $p = 0.011$; T1c without lepidic, $p < 0.001$; T2a without lepidic, $p < 0.001$; Figure 3(d)] compared with LUAD without a lepidic component in each stage. Results before propensity-score matching is shown in Supplementary Figures 3 and 4.

Discussion

The presence of GGO on CT images always indicates a long natural history and favorable oncologic outcome for early-stage LUAD. Many studies have indicated that the prognostic significance of GGO is associated with the consolidation/tumor ratio (CTR). The 5-year OS of LUAD with a CTR < 0.5 is higher than that of LUAD with a CTR > 0.5.[16,17] Whether a small amount of GGO predicts prolonged survival still needs to be investigated. Correspondingly, limited studies have focused on the prognostic impact of a small lepidic component. In our study, the presence of a lepidic component proportion $\leqslant 25\%$ was an independent prognostic factor for prolonged RFS (HR, 0.51; $p < 0.001$) and OS (HR, 0.36; $p < 0.001$), which was confirmed by multivariate Cox analysis. This result indicated that LUAD patients with even a small lepidic component have better survival than patients with LUAD without a lepidic component. The prognostic significance of the lepidic component was also proven in each T stage and pathological subtype. The lepidic component was a strong indicator of a relatively good prognosis, more than a noninvasive component of LUAD.

In 2011, the Japanese Clinical Oncology Group recommended the CTR as an important radiological indicator to guide surgical treatment. Tumors with a total size $\leqslant 2$ cm and a CTR $\leqslant 0.25$ were considered radiologically noninvasive LUAD. The CTR was associated with the prognosis of patients with LUAD.[18] However, a study performed by Hattori *et al.* suggested that the CTR was not associated with 5-year OS in patients with part-solid lung cancer ($0 < \text{CTR} < 0.5$: 98.4%; $0.5 < \text{CTR} < 1.0$: 95.0%; $p = 0.125$).[19] Ye *et al.* also found that the CTR with a cut-off value of 0.5 or 0.8 was not a prognostic factor for part-solid LUAD.[10] Theoretically, the prognostic influence of a lepidic component is equivalent to that of a GGO component. Our study revealed that the LR was not associated with the prognosis of LUAD with a lepidic component. No survival difference was observed

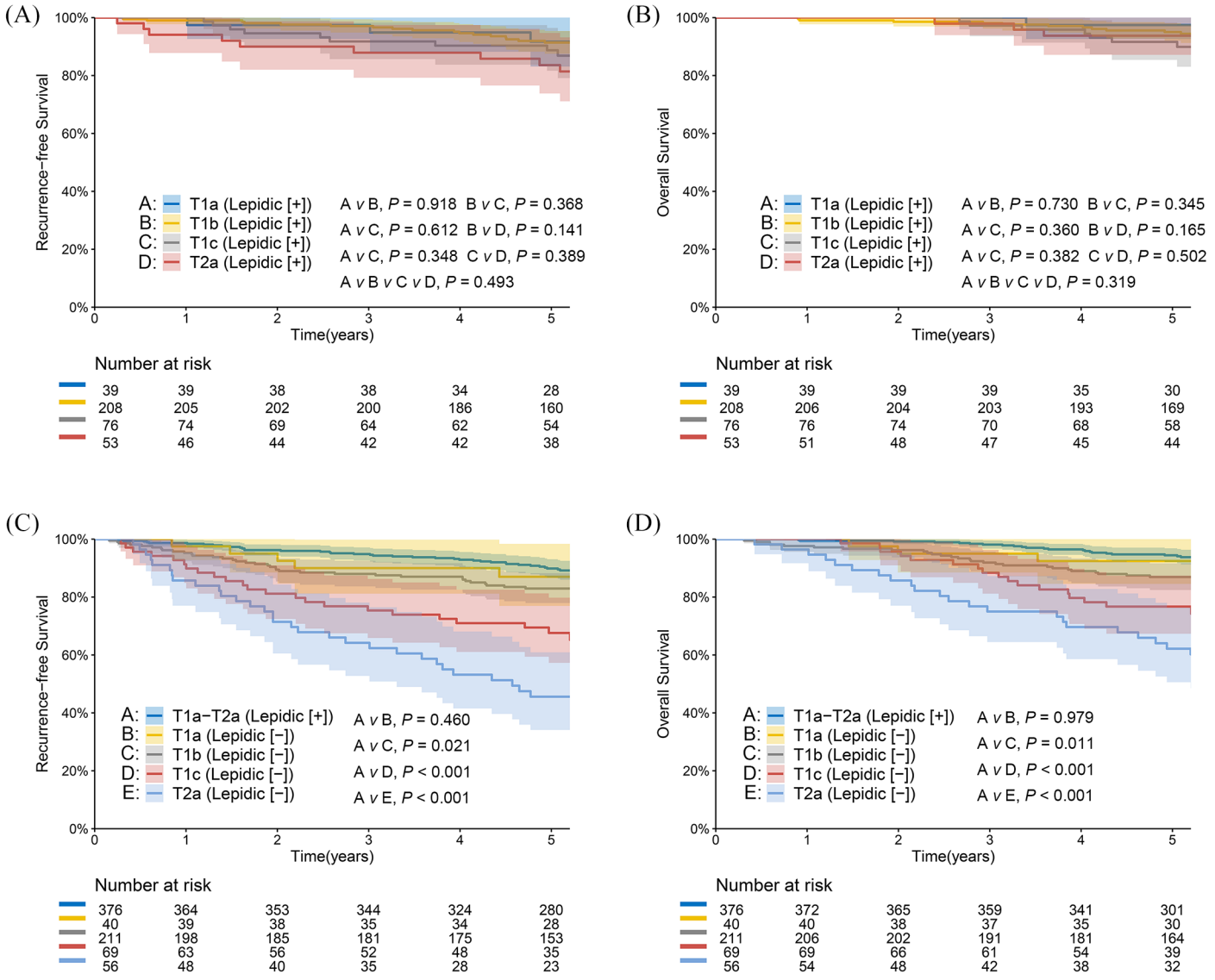

Figure 3. Comparison of survival based on the T stage in patients with lung adenocarcinoma with lepidic component (a–b). Comparison of survival based on T stage and when considering lung adenocarcinoma with lepidic component as one subgroup (c–d). Lepidic (+), lung adenocarcinoma with lepidic component; lepidic (–), lung adenocarcinoma without lepidic component.

among LUAD patients with different LRs. The 5-year OS rate of patients with LUAD with a lepidic component was 95.2%. When there was no lepidic component in LUAD, the 5-year OS rate decreased significantly to 75.2%. The presence of a lepidic component, not a specific LR, predicted significantly prolonged survival in LUAD. Our study also supported the conclusion that the CTR may not be a good prognostic marker in part-solid LUAD from the standpoint of pathology.

In 2017, the eighth edition of Lung Cancer Stage Classification recommended invasive size instead of total tumor size be used as a T descriptor. The GGO component is not taken into consideration in T classification. Part-solid LUAD and pure-solid LUAD with the same solid component size are classified within the same clinical T category. Yamanashi *et al.* found that the prognoses of part-solid and pure-solid LUAD in clinical T1a–c were similar after propensity-score matching. T stage determined by solid component size could stratify the prognosis of part-solid tumors.[13] However, many studies have indicated that the T stage of part-solid LUAD may not be simply determined by the solid component size. Hattori *et al.* revealed that survival was excellent at 90%

despite the revised T categories (5-year OS: T1a, 98.9%; T1b, 90.2%; T1c, 90.8%; T2, 90.0%) for part-solid LUAD.[11] Similarly, Ye *et al.* found that solid component size was not associated with the prognosis of patients with part-solid LUAD.[10] For pathological staging, our study suggested that patients with LUAD with a lepidic component had significantly better 5-year OS than patients with LUAD without a lepidic component after stratification by T classification (T1b: 94.9% *versus* 83.5%, $p < 0.001$; T1c: 93.8% *versus* 72.8%, $p < 0.001$; T2a: 93.0% *versus* 57.6%, $p < 0.001$). LUAD with a lepidic component staged in T1a–T2a had survival comparable with that of LUAD without a lepidic component staged in T1a. Furthermore, LUAD with a lepidic component staged in T1a–T2a had better survival than LUAD without a lepidic component staged in T1b, T1c, or T2a. Our study supported the conclusion of the study described above, specifically that part-solid LUAD and pure-solid LUAD with equal solid component sizes may not be classified into the same T stage from the standpoint of pathology.

GGO or the lepidic component may be a potential T stage migration factor. Recognition of the presence of a lepidic component would be simpler and more reproducible than measurement of the percentage of the lepidic component. Frozen-section diagnosis of lepidic components to guide surgical strategies seems possible because of the high specificity.[20,21] However, there are still insufficient data to utilize either GGO or the lepidic component as a T factor in clinical practice. First, there is still no globally accepted standard for GGO. Measurements of part-solid LUAD with the presence of scattered consolidations cannot be made uniform. The interobserver consistency for diagnosing the lepidic component is unsatisfying, as the kappa value is only 0.55 in typical cases and 0.08 in difficult cases.[22] Second, evaluation of a particular T factor must be subjected to confirmation in multiple patient subgroups, institutions, and regions, as was done for the stage classification system. All above conclusions need further prospective multicenter validation.

The limitations of this study are that the mean follow-up period was relatively short considering the favorable prognosis of LUAD with a lepidic component. Therefore, a cohort of patients with a longer follow-up period may be required to evaluate the prognostic effects of T stage and pathological subtype in the future. In addition, although a large cohort of cases was included, there were only a small number of solid- and micropapillary-predominant LUADs with a lepidic component. The excellent prognosis needs further evaluation. Moreover, despite standardized training of pathologists from all institutions before the beginning of the study, interobserver inconsistency may still cause unpredictable bias due to the multicenter study set-up.

In conclusion, the lepidic component identifies a subgroup of LUAD with a favorable prognosis regardless of the LR and T stage. Considering the presence of the lepidic component may improve prognostic predictions for patients with LUAD. Although our results need further validation, the forthcoming tumor-node-metastases staging system may take these findings into consideration.

Author contributions

Erjia Zhu conceived the idea; Erjia Zhu and Chenyang Dai conceived and designed the experiments; Erjia Zhu wrote the paper; Huikang Xie, Hang Su, Xuefei Hu, Ming Li, Junqiang Fan, Jinshi Liu, Quan Zhu, Honggang Ke, Lei Zhang, and Chang Chen provided all the data from seven institutions of our collaboration group. All authors approved the final version.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Ethics approval and consent to participate

This study has been authorized by ethic committee of seven institution from our collaboration

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ORCID iD

Chang Chen https://orcid.org/0000-0002-9981-3110

Supplemental material

Supplemental material for this article is available online.

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