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ORIGINAL ARTICLE

Clinicopathological Significance of Micropapillary Pattern in Lung Adenocarcinoma

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Abstract The aim of this study was to elucidate the clinicopathological characteristics of the micropapillary (MP) subtype and its correlation with survival in lung adenocarcinoma. We investigated the clinicopathological characteristics, including the incidence, sex, smoking history, tumor size, lymph node metastasis, lymphovascular invasion, distant metastasis, genetic alteration, and prognosis in lung adenocarcinoma with the MP pattern through a meta-analysis. From 48 eligible studies, 19,502 lung adenocarcinomas were included. The incidence rate of the MP pattern was 0.101 [95% confidence interval (CI) 0.075–0.136]. There was no significant difference between stage I and III tumors. Lung adenocarcinoma with the MP pattern showed higher rates of lymphatic invasion (0.526, 95% CI 0.403–0.645). MP pattern was found in 0.150 (95% CI 0.008–0.790) of lung adenocarcinoma with distant metastasis. In lung adenocarcinoma with the MP pattern, the estimated rates of *ALK*, *EGFR*, and *KRAS* mutations were 0.102 (95% CI 0.027–0.322), 0.620 (95% CI 0.444–0.769), and 0.118 (95% CI 0.027–0.393), respectively. The MP pattern of lung adenocarcinoma was significantly correlated with worse overall and disease-free survival rates (hazard ratio 1.704, 95% CI 1.216–2.387, and 2.082, 95% CI 1.541–2.813, respectively). Taken together, identification of the MP pattern in lung adenocarcinoma is useful for prediction of clinicopathological characteristics and prognosis of patients.

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Keywords Lung adenocarcinoma · Micropapillary pattern · Clinicopathological characteristics · Meta-analysis

Abbreviations

MP	Micropapillary
ALK	*anaplastic lymphoma kinase*
HR	Hazard ratio
CI	Confidence interval

Introduction

Lung adenocarcinomas usually contain various histopathological subtypes, such as lepidic, acinar, papillary, solid, and micropapillary (MP) [1, 2]. Tumor heterogeneity can be a major concern for the application of personalized medicine and development of targeted therapy [3]. Previous studies have reported that solid and MP predominant subtypes were significantly correlated with a worse prognosis in lung adenocarcinoma [4–6]. These histopathological subtypes are classified as high grade among three grades [4–6]. In lung adenocarcinoma, a major histopathological subtype is defined by greater than 5% increment. In terms of histology, the MP pattern of lung adenocarcinoma has tumor cells that lack a fibrovascular core, which is detached or connected from the alveolar wall [7–9]. Lung adenocarcinoma with the MP pattern is associated with non-smokers, intralobar satellites, mediastinal lymph nodes, and poor survival [10–13]. The clinicopathological characteristics of lung adenocarcinoma with the MP pattern may differ from those of other histopathological subtypes [14]; however, conclusive information is not available. We investigated the clinicopathological characteristics of

lung adenocarcinoma with the MP pattern through a meta-analysis. In addition, the correlation between MP pattern in lung adenocarcinoma and prognosis was evaluated.

Materials and Methods

Published Studies Search and Selection Criteria

Relevant articles were obtained by searching the PubMed and MEDLINE databases through September 30, 2016. These databases were searched using the following key words: "lung cancer or non-small cell lung cancer" and "micropapillary". The titles and abstracts of all searched articles were screened for exclusion. Review articles were also screened to find additional eligible studies. Articles were included if the study was performed in human lung cancer and if there was information about the clinicopathological characteristics of lung adenocarcinoma with the MP pattern. Articles were excluded if they were case reports or non-original articles, or if the article was not written in English.

Data Extraction

Data from all eligible studies were extracted independently by two researchers. The data extracted from each of the eligible studies [4–7, 11, 13–56] included: the first author's name, year of publication, study location, number of patients analyzed, and information for patient's age and sex, tumor size, lymphovascular invasion, lymph node metastasis, distant metastasis, mutations of *anaplastic lymphoma kinase* (*ALK*), *EGFR*, and *KRAS*, and survival rate.

Statistical Analyses

To perform the meta-analysis, all data were analyzed using the Comprehensive Meta-Analysis software package (Biostat, Englewood, NJ, USA). The incidence rate and various clinicopathological characteristics of the MP pattern in lung adenocarcinoma were investigated, and meta-analysis was performed using fixed-effect and random-effect models. Because eligible studies used various diagnostic criteria and populations, the application of the random-effect model rather than fixed-effect model was more suitable. The terminologies for MP pattern, including MP predominant or MP component, were allowed in the original articles. Heterogeneity between the studies was checked by the Q and I^2 statistics and expressed as *P*-values. Additionally, sensitivity analysis was conducted to assess the heterogeneity of eligible studies and the impact of each study on the combined effect. For quantitative aggregation of survival results, the correlation between the MP pattern and survival was analyzed according to the hazard ratio (HR) using one of three methods. In studies not quoting the HR or its confidence interval (CI), these variables were calculated from the presented data using the HR point estimate, log-rank statistic or its *P*-value, and the O-E statistic (difference between the number of observed and expected events) or its variance. If those data were unavailable, HR was estimated using the total number of events, number of patients at risk in each group, and the log-rank statistic or its *P*-value. Finally, if the only useful data were in the form of graphical representations of survival distributions, survival rates were extracted at specified times to reconstruct the HR estimate and its variance under the assumption that patients were censored at a constant rate during the time intervals [56]. The published survival curves were read independently by two researchers in order to reduce variability. The HRs were then combined into an overall HR using Peto's method [57]. In addition, we performed a subgroup analysis and meta-regression test for MP predominant and MP component subgroups. For the assessment of publication bias, Begg's funnel plot and Egger's test were used. If significant publication bias was found, the fail-safe N and trim-fill tests were additionally conducted to confirm the degree of publication bias. The results were considered statistically significant at $P < 0.05$.

Results

Selection and Characteristics of the Studies

Two hundred fifty relevant reports were identified in the database search for this meta-analysis. Among them, 124 studies were excluded because of insufficient or lack of information on the correlation between clinicopathological findings and the MP pattern of lung adenocarcinoma. Two reports were excluded owing to duplication of patients. In addition, other reports were excluded because they involved other diseases (n = 26), non-English (n = 13), use of animals or cell lines (n = 1), or were non-original articles (n = 36). Finally, 48 eligible studies were included in this meta-analysis (Fig. 1 and Table 1). The present meta-analysis included 19,502 lung adenocarcinomas.

Meta-Analysis

The estimated incidence rate of the MP pattern in lung adenocarcinomas was 0.101 (95% CI 0.075–0.136) (Table 2). The estimated rate of MP predominant subtype in lung adenocarcinoma was 0.060 (95% CI 0.045–0.080). However, lung adenocarcinoma with MP component was 0.229 (95% CI 0.149–0.334). In eligible

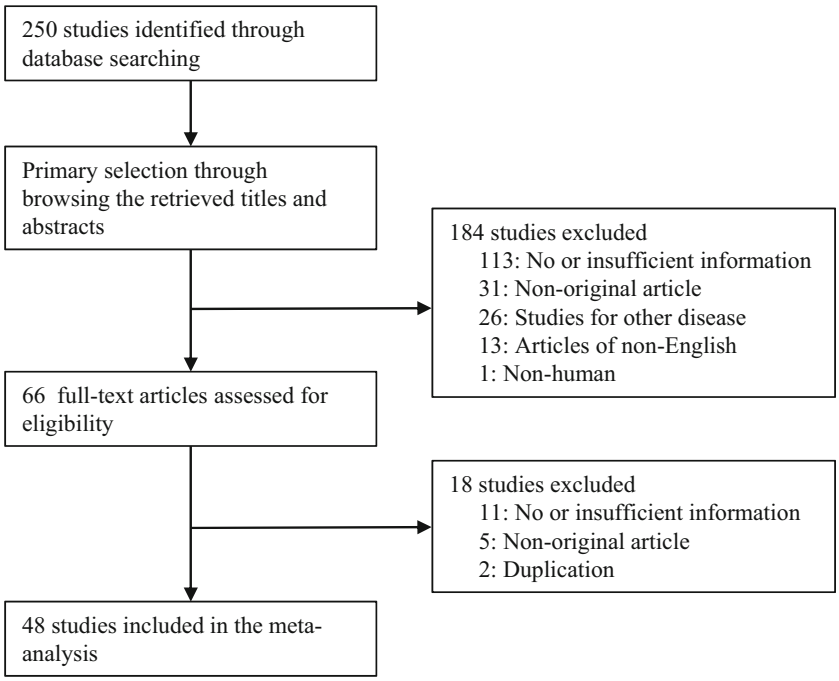

Fig. 1 Flow chart of study search and selection methods

studies, the incidence rates of MP predominant and MP component ranged from 0.87–27.49% and 3.40–66.67%, respectively. A history of smoking was identified in 46.1% (95% CI 36.3–56.3%) of patients with lung adenocarcinomas with the MP pattern (Table 3). Lymph node metastasis was found in 45.6% (95% CI 34.6–57.1%). In addition, venous and lymphatic invasions were detected in 39.0% (95% CI 19.2–63.2%) and 52.6% (95% CI 40.3–64.5%) of cases, respectively. Among lung adenocarcinomas with the MP pattern, distant metastasis was found in 15.0% (95% CI 0.8–79.0%). Next, subgroup analysis, based on MP predominant or MP component, was performed. In addition, to confirm the difference between the two subgroups, a meta-regression test was conducted. The incidence rates for various parameters, including male gender, a history of smoking, lymph node metastasis, venous invasion, and lymphatic invasion, were higher in the MP predominant subgroup than in the MP component subgroup. However, in meta-regression test, the rates of a history of smoking and venous invasion were significantly higher in MP predominant subgroup than in MP component subgroup (P = 0.028 and P = 0.041, respectively). Comparisons for tumor size (>3 cm) and distant metastasis could not be performed owing to insufficient information.

Next, genetic alterations in lung adenocarcinoma with the MP pattern were investigated. The rate of *ALK* mutation was 0.102 (95% CI 0.027–0.322) (Table 4). In lung adenocarcinoma with the MP predominant and MP component types, the rates of *ALK* mutation were 0.141 (95% CI 0.025–0.513) and 0.053 (95% CI 0.011–0.229), respectively. The *EGFR* mutation was found in 62.0% (95% CI 44.4–76.9%). The rates of *EGFR* mutation in Asian and non-Asian patients were 0.699 (95% CI 0.526–0.829) and 0.343 (95% CI 0.210–0.505), respectively. The rate of *KRAS* mutation was 0.118 (95% CI 0.027–0.393). The rates of *KRAS* mutation in Asian and non-Asian patients were 0.039 (95% CI 0.005–0.228) and 0.216 (95% CI 0.043–0.627), respectively.

The presence of the MP pattern in lung adenocarcinomas was significantly correlated with poorer overall survival rates (HR 1.704, 95% CI 1.216–2.387) and disease-free survival rates (HR 2.082, 95% CI 1.541–2.813) (Fig. 2). However, in stage I lung adenocarcinoma, there was no significant correlation between the MP pattern and worse overall or disease-free survival rates (HR 1.435, 95% CI 0.578–3.563 and HR 1.617, 95% CI 0.719–3.636, respectively).

Discussion

Various histopathological patterns of lung adenocarcinoma have been described, and those with clinicopathological significance have been investigated. Some authors reported that the MP pattern was correlated with a worse prognosis, even if this pattern was not predominant [29, 33, 52]. However, there are limitations in the interpretation of clinicopathological significance and prognosis of the MP pattern from each eligible study, because of the small number of patients and varied criteria used for the MP pattern. Therefore, a meta-analysis is useful for

Table 1 Main characteristics of eligible studies

Author, Year	Location	Subgroup	Classi- fication	Criteria	Number of patients Total	Pathologic stage MP	I	II	III	IV
Bao 2014	China	I	MP_PD	5%	315	24				
Cai 2016	China	I-IV	MP_PD	5%	211	58				
Cha 2014	Korea	ND	MP_PD	30%	511	27				
Furukawa 2016	Japan	I-IV	MPC	ND	166	28	13	7	4	4
		IA	MPC	ND	76	11				
Gu 2013	China	I-III	MP_PD	5%	292	30	12	4	14	
Hirano 2014	Japan	IA	MPC	5%	218	18				
Hung 2016	Taiwan	I-IV	MP_PD	5%	748	105				
Kadota 2013	USA	I	MP_PD	5%	452	14				
Kamiya 2008	Japan	I-III	MPC	1%	383	184				
		IA	MPC	1%	197	78				
Kawakami 2007	Japan	IA	MPC	10%	120	80				
Kawakami 2009	Japan	I	MPC	10%	146	88	70	5	13	
Koga 2013	Japan	I	MPC	10%	120	73				
Lee 2015	Korea	I-III	MP_PD	5%	525	114				
Li 2013	China	I-IV	MP_PD	5%	230	13				
Lu 2016	China	I-IV	MP_PD	5%	269	3				
Luo 2016	China	IB	MP_PD	5%	928	12				
Maeda 2009	Japan	ND	MPC	5%	122	15				
		I	MPC	5%	49	10				
Mäkinen 2015	Finland	I-IV	MP_PD	5%	112	7				
Miyoshi 2003	Japan	ND	MPC	1%	344	139				
		I	MPC	1%	154	45				
Ninomiya 2009	Japan	I-IV	MPC	5%	107	61				
Nishino 2012	USA	ND	MP_PD	10%	226	28				
Nitadori 2013	USA	ND	MPC	5%	734	43				
Ohe 2012	Japan	I-IV	MPC	1%	559	19				
		I								
Onozato 2013	USA	I-II	MP_PD	5%	261	14				
Roh 2004	Korea	I	MPC	1%	35	16				
Russell 2013	Australia	III	MP_PD	5%	69	13				
Russell 2011	Australia	I-III	MP_PD	5%	210	14	7	1	6	
Song 2013	China	I-III	MPC	5%	161	23				
Sumiyoshi 2013	Japan	ND	MP_PD	440	19					
		ND	MPC	5%	333	93				
Sun 2014	China	IB	MP_PD	5%	136	22				
Tsutsumide 2007	USA	I-III	MPC	1%	185	21	7	6	8	
Wang 2015	China	IA	MP_PD	5%	247	14				
Warth 2014	Germany	ND	MPC	5%	425	25				
Warth 2012	Germany	I-IV	MP_PD	5%	487	33	8	3	21	1
Yanagawa 2016	Japan	I-III	MP_PD	5%	531	11	2	3	6	
Yang F 2014	China	I	MP_PD	5%	177	19				
Yang X 2014	China	I	MPC	30%	211	14				
Ye 2014	China	IA	MP_PD	5%	651	17				
Yeh 2012	Taiwan	I	MP_PD	5%	212	5				
		I	MPC	NA	212	67				
Yoshiya 2016	Japan	IA	MP_PD	5%	153	2				
Yoshizawa 2011	USA	I	MP_PD	5%	514	12				
Yu Y 2016 (a)	China	IB	MP_PD	5%	104	20				
Yu Y 2016 (b)	China	I-III	MP_PD	5%	2299	170				
Zhang J 2011	China	I-IV	MPC	1%	886	246	57	48	112	29
Zhang Y 2014 (a)	China	I-III		ND	1302	121	46		75*	
		I-III	MP_PD	5%		21	7		14*	
		I-III	MPC	ND		100	39		61*	
Zhang Y 2014 (b)	China	I	MP_PD	5%	344	3				
Zhao 2016	China	I-IV	MP_PD	5%	1244	68				
Zhao 2015	China	I	MP_PD	5%	226	8				

ND no description, *MP* micropapillary, *PD* predominant, *MPC* micropapillary component

*included stage II and III

understanding of the impact of the MP pattern in lung adenocarcinoma. The present study is the first meta-analysis of the clinicopathological significance and prognostic role of the presence of the MP pattern in lung adenocarcinoma.

Table 2 Meta-analysis for the rate of lung adenocarcinoma with micropapillary pattern

	Number of subset	Fixed effect [95% CI]	Heterogeneity test [*P*-value]	Random effect [95% CI]	Egger's Test
Overall	49	0.153 [0.147, 0.160]	< 0.001	0.101 [0.075, 0.136]	0.012
MP predominant	30	0.088 [0.083, 0.094]	< 0.001	0.060 [0.045, 0.080]	0.007
MP component	18	0.287 [0.272, 0.303]	< 0.001	0.229 [0.149, 0.334]	0.183
Tumor stage					
Stage I	24	0.201 [0.186, 0.217]	< 0.001	0.112 [0.064, 0.189]	0.001
IA	5	0.057 [0.044, 0.072]	< 0.001	0.053 [0.026, 0.104]	0.777
IB	3	0.095 [0.073, 0.122]	< 0.001	0.078 [0.015, 0.318]	0.241
Stage III	1	0.188 [0.113, 0.298]	1.000	0.188 [0.113, 0.298]	-

CI Confidence interval, *MP* micropapillary

According to the new IASLC/ATS/ERS classification system, lung adenocarcinoma is classified into five major histopathological subtype patterns: lepidic, acinar, papillary, solid, and MP [2]. Since the introduction of this classification, many studies have investigated the clinicopathological significance of the predominant architectural subtype as a prognostic factor. In classifying invasive lung adenocarcinomas, a predominant subtype is defined as a major histopathological pattern greater than 5% increments. In previous studies, lung adenocarcinomas of solid and/or MP predominant subtypes were significantly correlated with a worse prognosis than other predominant subtypes [4–6, 43, 58]. Similarly, our study also showed that the presence of the MP pattern was significantly correlated with worse overall and disease-free survival rates. Therefore, the careful detection of not only major histopathological subtypes but also minor morphologic patterns may be important in pathologic examination.

The clinicopathological characteristics of lung adenocarcinoma with the MP pattern are not fully understood. Many lung adenocarcinomas show mixed-subtype patterns with two or

Table 3 Meta-analysis for clinicopathological parameters of lung adenocarcinoma with micropapillary pattern

	Number of subset	Fixed effect [95% CI]	Heterogeneity test [*P*-value]	Random effect [95% CI]	Egger's Test
Gender (Male)	16	0.497 [0.464, 0.530]	0.522	0.497 [0.464, 0.530]	0.181
MP predominant	5	0.526 [0.389, 0.660]	0.873	0.526 [0.389, 0.660]	0.072
MP component	10	0.505 [0.468, 0.542]	0.291	0.508 [0.463, 0.552]	0.331
Smoking	10	0.396 [0.358, 0.436]	< 0.001	0.461 [0.363, 0.563]	0.106
MP predominant	4	0.661 [0.500, 0.792]	0.317	0.666 [0.489, 0.806]	0.334
MP component	5	0.401 [0.358, 0.447]	0.004	0.424 [0.319, 0.537]	0.722
Tumor size (> 3 cm)	6	0.474 [0.437, 0.512]	< 0.001	0.439 [0.319, 0.567]	0.522
MP component	5	0.501 [0.460, 0.542]	< 0.001	0.463 [0.326, 0.606]	0.603
LN metastasis	16	0.511 [0.477, 0.545]	< 0.001	0.456 [0.346, 0.571]	0.194
MP predominant	7	0.506 [0.431, 0.582]	0.030	0.507 [0.383, 0.631]	0.952
MP component	8	0.503 [0.460, 0.545]	< 0.001	0.403 [0.233, 0.600]	0.187
Venous invasion	7	0.437 [0.393, 0.481]	< 0.001	0.418 [0.44, 0.616]	0.759
MP predominant	1	0.929 [0.630, 0.990]	1.000	0.929 [0.630, 0.990]	-
MP component	6	0.431 [0.388, 0.475]	< 0.001	0.355 [0.197, 0.553]	0.462
Lymphatic invasion	7	0.541 [0.497, 0.584]	< 0.001	0.526 [0.403, 0.645]	0.756
MP predominant	1	0.857 [0.573, 0.964]	1.000	0.857 [0.573, 0.964]	-
MP component	6	0.536 [0.491, 0.579]	< 0.001	0.494 [0.374, 0.615]	0.340
Lymphovascular invasion	4	0.312 [0.239, 0.395]	< 0.001	0.476 [0.173, 0.798]	0.405
MP predominant	1	0.727 [0.414, 0.910]	1.000	0.727 [0.414, 0.910]	-
MP component	2	0.368 [0.149, 0.660]	0.001	0.515 [0.018, 0.984]	-
Distant metastasis	2	0.391 [0.305, 0.485]	0.002	0.150 [0.008, 0.790]	-
MP predominant	2	0.391 [0.305, 0.485]	0.002	0.150 [0.008, 0.790]	-

CI Confidence interval, *LN* lymph node

Table 4 Meta-analysis for genetic mutations of lung adenocarcinoma with micropapillary pattern

	Number of subset	Fixed effect [95% CI]	Heterogeneity test [*P*-value]	Random effect [95% CI]	Egger's Test
ALK mutation	5	0.141 [0.096, 0.201]	< 0.001	0.102 [0.027, 0.322]	0.721
MP predominant	3	0.151 [0.102, 0.217]	< 0.001	0.141 [0.025, 0.513]	0.991
Asian	2	0.074 [0.044, 0.123]	0.584	0.074 [0.044, 0.123]	-
Non-Asian	1	0.429 [0.262, 0.613]	1.000	0.429 [0.262, 0.613]	-
MP component	2	0.053 [0.011, 0.229]	0.358	0.053 [0.011, 0.229]	-
Asian	1	0.091 [0.013, 0.439]	1.000	0.091 [0.013, 0.439]	-
Non-Asian	1	0.019 [0.001, 0.244]	1.000	0.019 [0.001, 0.244]	-
EGFR mutation	9	0.629 [0.556, 0.698]	< 0.001	0.620 [0.444, 0.769]	0.860
MP predominant	5	0.708 [0.595, 0.800]	0.001	0.710 [0.428, 0.889]	0.981
Asian	4	0.772 [0.660, 0.856]	0.006	0.782 [0.502, 0.927]	0.917
Non-Asian	1	0.385 [0.170, 0.656]	1.000	0.385 [0.170, 0.656]	-
MP component	4	0.578 [0.482, 0.669]	0.002	0.520 [0.298, 0.735]	0.417
Asian	3	0.647 [0.542, 0.739]	0.039	0.600 [0.372, 0.792]	0.558
Non-Asian	1	0.320 [0.169, 0.522]	1.000	0.320 [0.169, 0.522]	-
KRAS mutation	4	0.243 [0.136, 0.394]	0.054	0.118 [0.027, 0.393]	0.004
MP predominant	2	0.059 [0.012, 0.248]	0.648	0.059 [0.012, 0.248]	-
Asian	1	0.036 [0.002, 0.384]	1.000	0.036 [0.002, 0.384]	-
Non-Asian	1	0.077 [0.011, 0.391]	1.000	0.077 [0.011, 0.391]	-
MP component	2	0.316 [0.174, 0.503]	0.089	0.185 [0.020, 0.715]	-
Asian	1	0.042 [0.003, 0.425]	1.000	0.042 [0.003, 0.425]	-
Non-Asian	1	0.360 [0.199, 0.560]	1.000	0.360 [0.199, 0.560]	-

CI Confidence interval, *MP* micropapillary

more different architectural subtypes. The estimated rate of lung adenocarcinoma with the MP component subtype, but not MP predominant subtype, was 22.9% (95% CI 14.9–33.4%). On the other hand, the estimated rate of lung adenocarcinoma with MP predominant subtype was 6.0% (95% CI 4.5–8.0%). In meta-regression test, the rates of smoking history and venous invasion were significantly higher in MP predominant subgroup than in MP component subgroup. In addition, the rate of venous invasion was significantly higher in lung adenocarcinoma with MP pattern than in those without MP pattern (0.418, 95% CI 0.244–0.616 vs. 0.143, 95% CI 0.082–0.237, $P = 0.004$ in meta-regression test). However, there were no significant differences in other clinicopathological parameters, such as lymph node metastasis and lymphatic invasion, between lung adenocarcinoma with MP pattern and without MP pattern. In the previous study, the tumor size of lung adenocarcinoma with MP pattern was larger than that that of tumor with other patterns [43]. In our study, in lung adenocarcinoma with MP pattern, the rate of tumor size >3 cm was 45.3%. However, distant metastasis was found in 15.0% of lung adenocarcinoma with MP predominant subtype. These results indicated a clinical aggressiveness of lung adenocarcinoma with the MP pattern, similar to a previous report [14]. Taken together, in daily practice, the presence of the MP pattern in lung adenocarcinoma could be an indication to clinicians of possible metastasis. Because various histopathological patterns are mixed in lung adenocarcinoma, the impact of the proportion of a specific pattern on clinicopathological significance cannot be easily elucidated. When the MP pattern in small biopsied specimens is over the 5% increment, the use of the terminology "predominant" can be limited. To evaluate the clinicopathological significance of the MP pattern, histologic examination of the entire tumor should be performed before using conclusive terminology, such as "predominant".

In addition, various clinicopathological parameters may influence the prognosis and decision of therapeutic modalities regardless of the proportion of the MP pattern [43]. In eligible studies, the criteria for MP predominant varied from 1% to 10%. Recently, it has been reported that the ratio of the MP pattern in lung adenocarcinoma was correlated with tumor stage and lymph node metastasis [7]. However, when a tumor contains heterogeneous histopathological patterns, the interpretation of histopathological subtype can be difficult. The detection of high-grade histopathological patterns, such as solid or MP patterns, can be useful in intraoperative frozen pathologic examination.

Recently, various targeted therapies for biological markers have been applied to lung adenocarcinomas. However, the correlation between the MP pattern and genetic mutations, including *EGFR, ALK,* and *KRAS* mutations, is not fully elucidated in

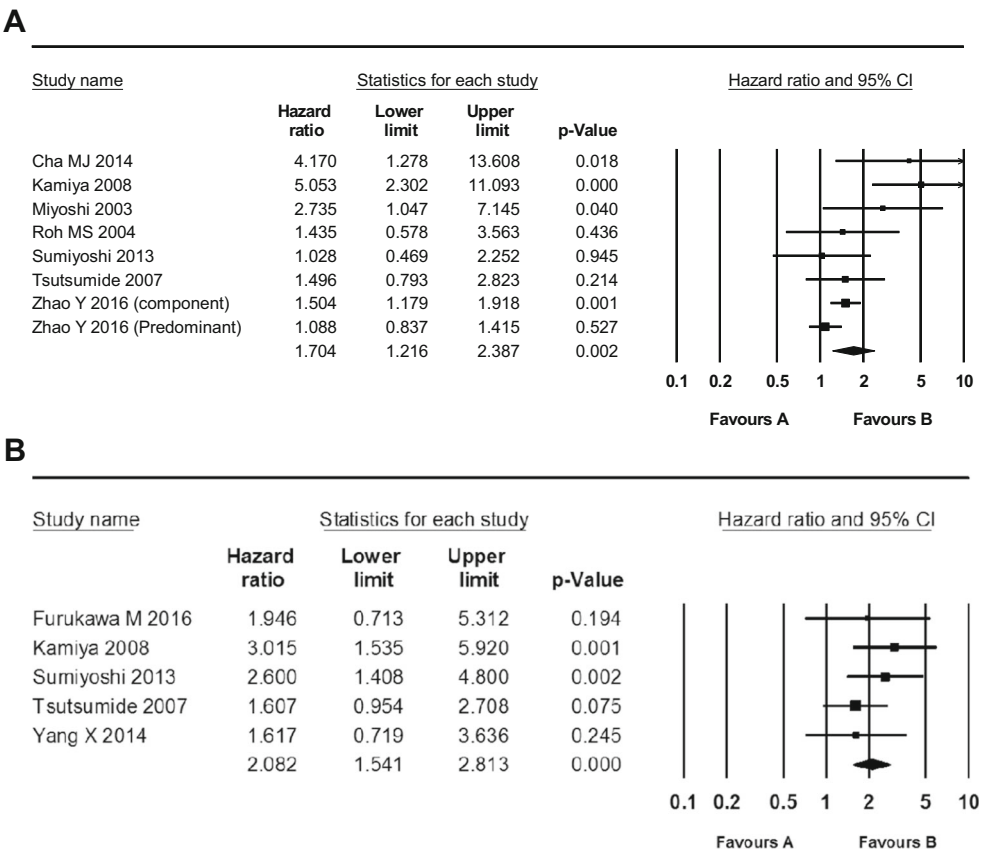

Fig. 2 Forest plots for the correlations between the micropapillary pattern and survival rate. (**a**) Overall survival and (**b**) disease-free survival

lung adenocarcinoma. Understanding these genetic alterations in lung adenocarcinoma with MP pattern may be important for the application of molecular analysis and prediction of therapeutic effect. For example, in lung adenocarcinoma, the *EGFR* mutation is more frequently found in the MP pattern than in the solid pattern [39]. In the previous study, the *EGFR* mutation was found in 91.4% of lung adenocarcinoma with the MP pattern [7]. In our results, the rates of *EGFR* mutations were 71.0% (95% CI 42.8–88.9%) and 52.0% (95% CI 29.8–73.5%) in cases with MP predominant and MP component, respectively. In addition, *ALK*, *KRAS* and *BRAF* mutations are more frequent in lung adenocarcinomas with MP pattern than in those with other patterns [14, 59]. In the current study, the rates of *ALK*, *EGFR*, and *KRAS* mutations were 10.2%, 62.0%, and 11.8%, respectively. The rates of *EGFR* mutation in Asian and non-Asian patients were 0.699 (95% CI 0.526–0.829) and 0.343 (95% CI 0.210–0.505), respectively. These rates of Asian and non-Asian patients were respectively higher than the known rates [1]. However, there was no significant difference of the rates of *KRAS* mutation between cases with MP pattern and overall cases. Therefore, the defining histopathological subtype might be useful for application and prediction of therapeutic effect of adjuvant therapeutic modalities [48, 60]. To obtain the conclusive information, further cumulative studies will be needed.

As described above, targeted therapy might be critical in patients with inoperable advanced stage lung adenocarcinoma. Histopathologic information obtained from only small biopsied specimens may be limited in usefulness for determining the therapeutic modalities. However, the detection of histopathological pattern can be useful for interpretation of molecular characteristics of tumor. Furthermore, when the tissue samples are insufficient for molecular tests to detect genetic alterations in small biopsied specimens, proper molecular analysis based on histology with various analyses should be recommended for patients with advanced disease. In the current meta-analysis, subgroup analysis between MP predominant and MP component was performed. The rates of *ALK* and *EGFR* mutations were higher in MP predominant cases than in cases with MP component. The rate of *KRAS* mutations in cases with MP predominant was lower than that in cases with MP component.

There are some limitations in the current meta-analysis. First, the evaluation criteria for included MP pattern varied between eligible studies. In the eligible studies, the ranges of incidence rates of MP predominant and MP component were varied as 0.87–27.49% and 3.40–66.67%, respectively. The incidence rate of lung adenocarcinoma with MP component was 22.9% (Table 2). Because the detailed incidence rates of MP pattern are variable owing to varied criteria, more detailed information should be obtained from large prospective studies. Second, subgroup analysis based on tumor stage could be

not performed owing to insufficient information. Third, because lung adenocarcinoma can be admixed with various histopathological patterns, subgroup analysis from types of obtained specimen is useful for application in daily practice. Fourth, from Hung's report, lung adenocarcinoma with MP predominant showed higher rates of distant metastasis to brain (25.5% vs. 8.4%), contralateral lung (21.9% vs. 10.9%), and bone (16.2% vs. 8.3%) than those without MP predominant. However, the present study could not deal the detailed analysis for obtained specimen and the sites of distant metastasis.

In conclusion, our results showed that the MP pattern of lung adenocarcinoma was significantly correlated with a higher tumor stage, distant metastasis, and a worse prognosis. In addition, higher rates of *ALK* and *EGFR* mutations were found in lung adenocarcinoma with the MP pattern. However, detailed guidelines for interpretation of the MP pattern in lung adenocarcinoma will be required according to the obtained specimen.

Compliance with Ethical Standards

Funding None.

Conflict of Interest The authors declare that they have no conflict of interest.

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