Original Article

MTA1 is an indicator of prognosis in Chinese patients with lung adenocarcinoma

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Background: The predictive role of metastatic tumor antigen 1 (MTA1) expression in lung cancer (LC) is still uncertain. This meta-analysis was performed to clarify the relationship of MTA1 protein expression with the prognosis of LC.

Methods: The PubMed and CNKI databases were searched for clinical studies demonstrating the expression of MTA1 in LC for further review.

Results: A total of ten studies comprising 982 patients were included in the meta-analysis according to the predefined selection criteria. Our results indicated that MTA1 overexpression had a significant impact on progression-free survival (PFS) (HR 2.16; 95% CI, 1.62–2.89) and OS (HR 2.38; 95% CI, 1.78–3.19). Heterogeneity was observed (I^2=34.6%). When the analyses were restricted to adenocarcinoma cases, high expression of MTA1 also predicted poor prognosis (HR 2.14; 95% CI, 1.48–3.08). However, no statistically significant heterogeneity was observed among the studies (I^2=4.1%).

Conclusions: A high level of MTA1 expression predicts poor survival in Chinese patients with lung adenocarcinoma.

Keywords: Metastatic tumor antigen 1 (MTA1); prognosis; lung cancer (LC); adenocarcinoma; meta-analysis

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Introduction

Lung cancer (LC) is one of the most common human malignant diseases and the leading cause of cancer-related death globally (1). A further understanding of the mechanisms underlying the pathogenesis and progression of LC would promote the development of novel prognostic markers and therapeutic targets. The selection of appropriate treatment for each individual patient is determined by several factors, including the assessment of prognosis. Epithelial-to-mesenchymal transition (EMT) is a key step in the progression of tumor cell metastasis. Various types of metastasis-associated cancer genes and proteins have been investigated extensively. Metastatic tumor antigen 1 (MTA1), a core component of the nucleosome remodeling and deacetylase (NuRD) complex, appears to correlate with human cancer progression and metastasis (2,3). High levels of MTA1 expression have been shown to be involved in migration, invasion, metastasis, early recurrence, and poor prognosis, suggesting that MTA1 is a molecular target for future anticancer therapeutics. Therefore, MTA1 may be a new indicator of cancer prognosis. A previous meta-analysis published in 2014 found that overexpression of MTA1 in non-small cell lung cancer (NSCLC) patients might be a poor prognostic factor for survival (4). Only 4 studies were included in this meta-analysis (5-8). However, the fact that the significant associations were based on a limited number of studies may reduce the statistical power.

Table 1 Characteristic of the studies for meta-analysis for MTA1 on NSCLCs

First author	Country	No. of patients	Age (y)	Histology	SCC	ADC	Stage	Methods	Follow-up time (mo)
Chen, 2014	China	52	16–80 (56.9±10.7)	SCLC	0	0	I-III	IHC	26–64
Li, 2011	China	102	34–81	NSCLC	44.1%	55.9%	I	IHC	16–110
Li, 2016	China	125	NA	NSCLC	0	100%	I-III	IHC	16–90
Liu, 2018	China	208	31–81	NSCLC	0	100%	I-III	IHC	52 (average)
Ma, 2017	China	56	32–79	NSCLC	58.9%	39.2%	I-IV	IHC	NA
Yu, 2011	China	60	42–74	NSCLC	37%	63%	I	IHC	12–64
Zhang, 2007	China	101	18–72 (54±19)	NSCLC	58.4%	41.6%	I-IV	IHC	1–101
Zhang, 2010	China	60	42–74	NSCLC	36.7%	63.3%	I	IHC	26–64
Zhou, 2015	China	118	NA	LC	35%	46%	I-III	IHC	NA
Zhu, 2010	China	100	NA	NSCLC	44%	38%	I-IV	IHC	1.4–59.3

NSCLC, non-small cell lung cancer; SCC, squamous cell carcinoma; ADC, adenocarcinoma; NA, not available.

The role of MTA1 expression in lung cancer patients remains uncertain. Therefore, to derive a more precise evaluation of the association, we performed this meta-analysis.

Methods

Publication search

The PubMed and CNKI databases were searched for clinical studies demonstrating the expression of MTA1 in LC for further review using the keywords "MTA1", "lung cancer", and "lung carcinoma". An early date limit of August 31, 2019, was used. Additional publications were identified from review articles and from the references cited in the previously found articles. Studies included in the meta-analysis were in any language, studied human subjects, and were primary studies. Only published full-text articles were reviewed and assessed for relevant content. When several papers from the same study had been published, only the most complete or most recent paper was used.

Data extraction and statistical analysis

Study characteristics, such as first authors, year of publication, region/country, number of cases, and the cut-off values of MTA1, were noted. The hazard ratio (HR) was used as the outcome measure for time-to-event data. When HRs were not captured in a study, they were calculated according to the data extracted from the Kaplan-Meier curves (9). To account for the heterogeneity, a random effects model was used to pool the data because of the wide confidence intervals (CIs). Cochran's Q statistic was used to assess heterogeneity. Funnel plots and Egger's linear regression test were used to inspect potential publication bias. Subgroup analyses were performed to eliminate heterogeneity by using the following criteria: (I) NSCLC; (II) stage I; (III) adenocarcinoma; and (IV) squamous cell carcinoma rate >50%. Stata 10.0 was used to perform statistical analysis.

Results

Study characteristics

Our search strategy identified a total of 251 articles. After reading the titles and abstracts, 27 articles were selected for full reading. Finally, ten studies published between 2007 and 2018 comprising 982 patients were included in the study (5-8,10-15). The characteristics of the studies are shown in *Table 1*. In the 10 studies, the sample sizes ranged from 52 to 208. Four studies provided progression-free survival (PFS) outcome data (5,12,13,15). Immunohistochemistry (IHC) was used to confirm the expression of MTA1. Different expression values of MTA1 were used as cut-off points. Few of MTA1 expression was positive in adjacent nonneoplastic lung tissues (OR 18.24; 95% CI, 8.86–2.37.54, compared with tumoral tissues).

Meta-analysis results

The outcome of meta-analysis is shown in *Figure 1*. The protein expression levels of MTA1 were significantly associated with the PFS (HR 2.16; 95% CI, 1.62–2.89) and OS (HR 2.38; 95% CI, 1.78–3.19, *Figure 2*). Heterogeneity

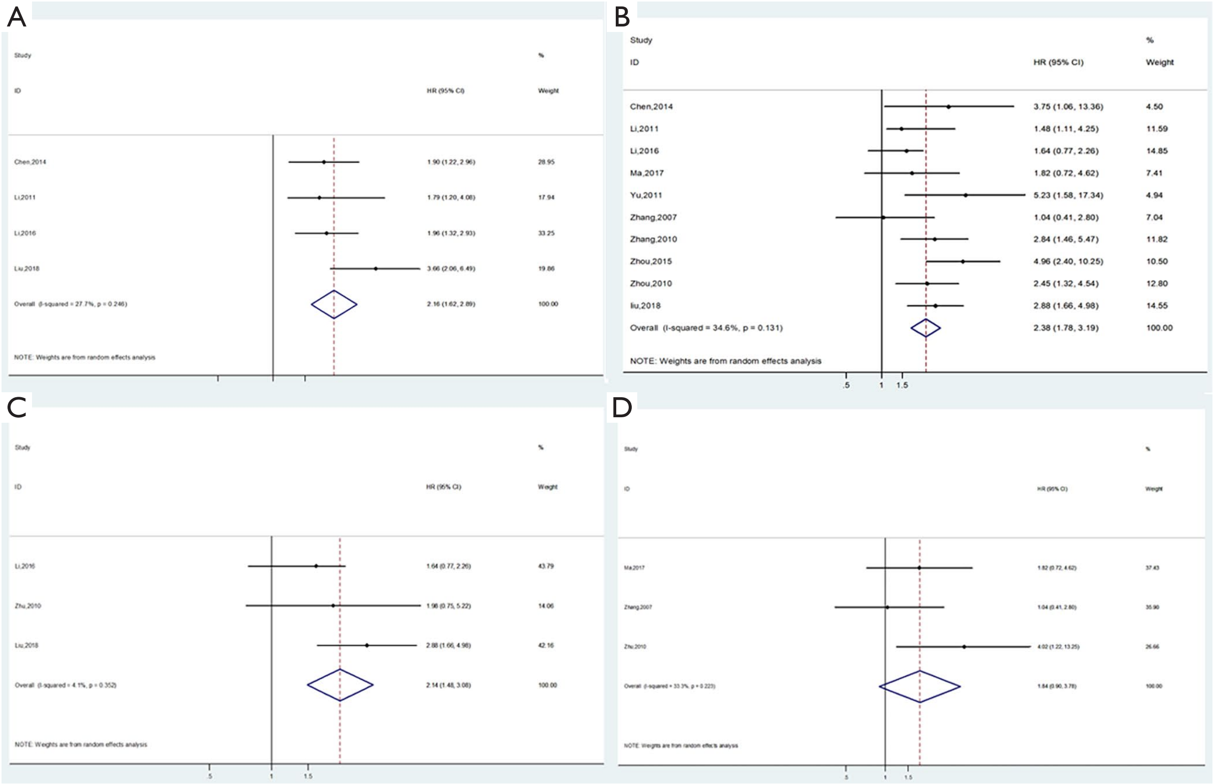

Figure 1 Forest plot. (A) PFS; (B) OS; (C) adenocarcinoma; (D) squamous cell carcinoma. PFS, progression-free survival; OS, overall survival.

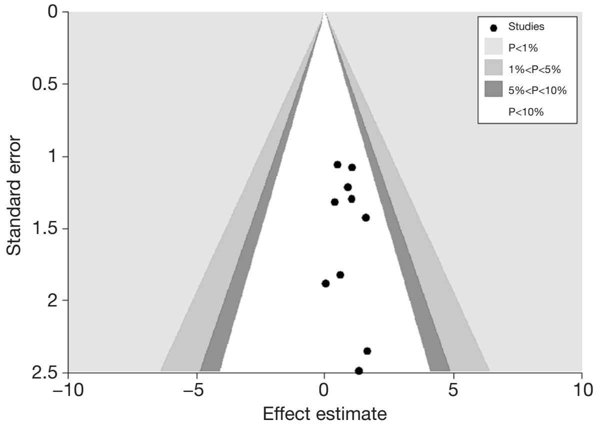

Figure 2 Funnel plot for publication bias.

was observed (I^2=34.6%). The subgroup analysis was performed according to the protocol described in the methods section, and the outcome is shown in *Table 2*. When the analyses were restricted to adenocarcinoma cases, high expression of MTA1 also predicted poor prognosis (HR 2.14; 95% CI, 1.48–3.08). No significant heterogeneity was observed among the studies (I^2=4.1%).

Publication bias

Publication bias was assessed using a funnel plot and Egger's test. No obvious publication bias was observed (Egger's test, P=0.421, *Figure 3*).

Discussion

Exploring the association between novel biomarkers and the prognosis of LC is important for improving the clinical prognosis of LC. MTA1 is known to increase the migration, invasion and metastasis of cancer cells (16,17). However, the mechanism by which MTA1 affects tumor growth and metastasis remains unclear. MTA1 might promote tumor growth and metastasis via the AKT/GSK3β/β-catenin signaling pathway (10). MTA1 has been reported to mediate PTEN acetylation and indirectly activate AKT (18).

Some studies indicated that MTA1 was a predictor for clinical outcome (5,8,14), but others did not replicate this association (6,10,13). At present, no consensus has been reached regarding whether MTA1 could be a predictive marker in patients with LC. To derive a more precise estimation of the prognostic role of MTA1 expression, we

Table 2 Subgroup analyses for OS according to study characteristics

Variables	HR	Heterogeneity	
	Random effects (95% CI)	I^2 (%)	P value Q test
Total	2.38 (1.78–3.19)	34.6	0.131
NSCLC	1.21 (1.62–2.80)	17.9	0.288
Stages I	2.48 (1.31–4.71)	48.1	0.146
Adenocarcinoma	2.14 (1.48–3.08)	4.1	0.352
Squamous cell carcinoma	1.84 (0.90–3.78)	33.3	0.223

NSCLC, non-small cell lung cancer; HR, hazard ratio; OS, overall survival; CI, confidence interval.

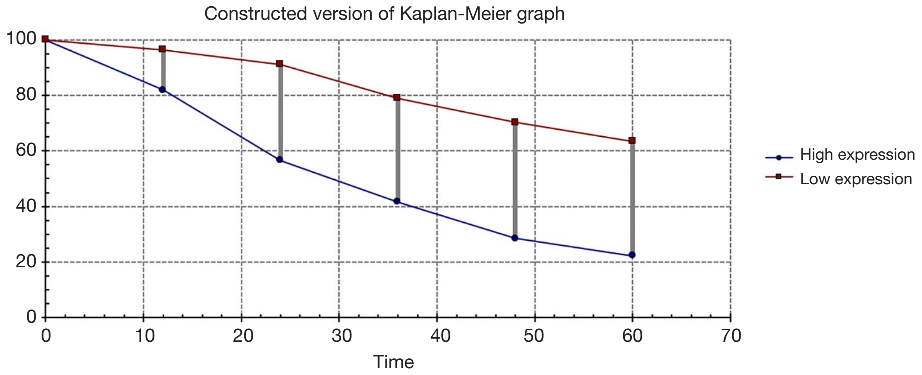

Figure 3 Kaplan-Meier survival curves for MTA1 expression LC patients according to MTA1 expression. LC, lung cancer; MTA1, metastatic tumor antigen 1.

performed an updated meta-analysis of all studies. Only one study provided the survival data of squamous cell carcinoma (7), so we used a squamous cell carcinoma rate of 50% as a cut-off value to complete the subgroup analyses. When we subgrouped the studies according to histology, we found that MTA1 was not a prognostic marker for squamous cell carcinoma. However, high expression of MTA1 was associated with an adverse outcome in patients with adenocarcinoma. There were only 3 studies based on adenocarcinoma that obtained positive results (7,13,15). All studies selected in this study were from China. The results were similar to previous studies and suggest that these studies were representative. Our results thus far suggest that MTA1 might be a potential target for anti-adenocarcinoma therapy. However, further research is needed to clarify the association.

The final results from a meta-analysis should be interpreted extremely carefully, particularly when the number of studies is small and the heterogeneity is large. The previously published meta-analysis had only four studies to evaluate the influence of the expression of MTA1 on the prognosis of NSCLC (4), and significant heterogeneity was observed (P=0.04). Subgroup analyses were performed to eliminate heterogeneity in our study. In adenocarcinoma cases, no statistically significant heterogeneity was observed, which might reveal that the clinical outcome of LC may differ by histology.

Some limitations of this study should be taken into consideration. First, among the studies included in this meta-analysis, all were conducted in China. Thus, data representing other ethnicities were not sufficient. Second, the inherent biases of patients may lead to spurious correlations. Third, the small sample size may lack sufficient power to identify real interactions. Fourth, subgroup analysis according to MTA1 IHC positivity was not conducted because of the different methods used to determine the staining intensity and proportion of positively stained cancer cells in the various studies. Finally, subgroup analyses based on age, sex, and other factors (such as smoking status consumption and diabetes) were not performed in this study because relevant data were not available in the primary articles.

In conclusion, a high level of MTA1 expression predicts poor survival in Chinese patients with lung adenocarcinoma.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2020.01.68). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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