REVIEW

Clinicopathological Significance of MTA 1 Expression in Patients with Non-Small Cell Lung Cancer: A Meta-Analysis

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Abstract

Background: Metastasis associated gene 1(MTA1) is one of the most deregulated molecules in human cancer and leads to cancer progression and metastasis. We performed a meta-analysis to determine the correlations between MTA1 expression and the clinicopathological characteristics of non-small cell lung cancer (NSCLC). **Methods:** We searched PubMed, Springer, Science Direct, Google Scholar and China National Knowledge Infrastructure (CNKI) for relevant articles. For statistical analyses, we used R3.1.1 software. The fixed or random effects model was employed based on the results of the statistical test for homogeneity. **Results:** Seven studies involving 660 NSCLC patients were included. The proportion of MTA1 overexpression with 95% confidence interval (95% CI) was 0.53(95%CI: 0.43-0.62) in NSCLC patients; 0.47(95%CI: 0.40-0.55) in age <60 years and 0.52(95%CI: 0.34-0.70) in age ≥60 years; 0.5(95%CI: 0.41-0.62) in males and 0.51(95%CI: 0.39-0.62) in females; 0.59(95%CI: 0.48-0.69) in squamous cell carcinoma (SC**)** and 0.57(95%CI: 0.46-0.67) in adenocarcinoma (AC); 0.39(95%CI: 0.23-0.56) in well-differentiated tumors, 0.44(95%CI: 0.37-0.51) in moderately differentiated tumors and 0.55(95%CI: 0.37-0.51) in poorly differentiated tumors; 0.48(95%CI: 0.36-0.60) in clinical grade (III-IV) NSCLC and 0.75 (95%CI: 0.69-0.81) in clinical grade (I-II) NSCLC; 0.58(95%CI: 0.45-0.71) in T Stage (T1/T2) NSCLC; 0.68(95%CI: 0.49-0.82) in NSCLC patients with lymph node positivity and 0.51(95%CI: 0.43-0.58) in NSCLC patients with lymph node negativity. **Conclusions:** These results indicated that MTA1 might be a valuable biomarker in the diagnosis of NSCLC. MTA1 overexpression was significantly associated with age ≥60 years, gender, histopathological type, clinical grade (I-II), T stage (T1/T2) and lymph node positivity in NSCLC patients.

Keywords: MTA1- NSCLC- meta-analysis

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Introduction

leading cause of cancer-related death in both men and women worldwide. In 2016, an estimated 158,080 deaths are predicted, about a quarter of all cancer deaths are lung cancer (American Cancer Society (Internet), 2016). There are several types of lung cancer, and non-small cell lung cancer (NSCLC) is by far the most common type, which accounts for approximately 85% (Ettinger et al., 2012). Appropriate treatment for NSCLC depends on the stage of cancer and specific molecular characteristics of cancer cells (Edge et al., 2010). Consequently, understanding the mechanism of initiation and progression, as well as identifying a promising molecular marker in NSCLC, are urgently needed.

MTA1, a component of the nucleosome remodeling and deacetylation (NuRD) complex, is involved in ATP-dependent chromatin remodeling and histone deacetylase activity, and plays an important role in gene specific transcriptional regulation (Xue et al., 1998; Li et al., 2012). Accumulating evidence suggests that MTA1 is closely related to tumorigenesis, invasion, angiogenesis and metastasis (Toh et al., 1999; Toh, 2009; Li et al., 2013; Kai et al., 2011; Toh, 2014). In recent years, numerous studies have shown a relationship between different clinical parameters and a high level of MTA1 expression in a variety of malignant tumors (Li et al., 2012; Kang et al., 2014; Fan et al., 2016; Dhar et al., 2016; Andisheh-Tadbir et al., 2016; Deng et al., 2015; Wang et al., 2014; Yuan et al., 2014; Marzook et al., 2014; Andishehtadbir et al., 2014; Miyashita et al., 2014; Liu et al., 2013), but the number of cases was low. Therefore, in order to clarify the value of MTA1 expression in NSCLC requires the combined analysis of published data. Furthermore, it is beneficial to determine the role of MTA1 in the development of NSCLC.

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Materials and Methods

Search strategy

An internet literature search of databases including PubMed, Springer, Science Direct, Google Scholar, Chinese National Knowledge Infrastructure (CNKI) was carried out. Articles were searched using the following keywords: "MTA1" OR "metastasis-associated protein-1", "non-small cell lung cancer" OR "NSCLC".

Inclusion and exclusion criteria

The following criteria were used for literature selection: (1) articles must describe the role of MTA1 expression in NSCLC tissues; (2) IHC must be the only method used to measure MTA1 expression in NSCLC tissues; (3) articles should provide clinical data on cancer patients who were not subjected to chemotherapy or radiotherapy prior to the investigation; and (4) full texts must be available.

The exclusion criteria were as follows: (1) MTA1 expression was determined in cell lines or animals, or in the blood of patients; (2) duplicate publications, reviews or articles with insufficient information; and (3) articles published in a book or conference proceedings.

Data extraction

The following information was extracted from each study: first author, publication year, geographical location, age distribution of the patients, sample size, protein detection methods, the number of cases with abnormal MTA1 level and the data regarding age (<60 and ≥60 years), gender (male and female), histopathological type (SC and AC), histological differentiation (well, moderate and poor), clinical grade (I-II and III-IV), T stage (T1/T2) and lymph node status (positivity and negativity). Two reviewers independently collected the data, and discordant results were resolved by consensus after discussion.

Statistical analysis. Statistical analysis was performed using R3.1.1 software (Wolfgang Viechtbauer, 2015 http://www.metafor-project.org). Heterogeneity was determined using the I2 statistic, which describes the percentage of total variation across the studies resulting from heterogeneity (Higgins and Thompson, 2002). The I2 statistic used 25%, 50%, and 75% as the boundary values to evaluate literature heterogeneity as low, moderate, and high, respectively. If the heterogeneity was moderate or high, a random effects model was chosen; otherwise, a fixed effects model was selected (Higgins et al., 2003; DerSimonian et al.,2007). Publication bias was described using a funnel plot. The qualitative data extracted from the included studies were analyzed in subgroups to reduce the heterogeneity, as follows: (1) aberrant MTA1 expression in NSCLC patients; (2) MTA1 overexpression in NSCLC patients aged <60 and ≥60 years; (3) MTA1 overexpression in relation to gender of NSCLC patients; (4) MTA1 overexpression in relation to histopathological type (SC and AC); (5) MTA1 overexpression in relation to histological differentiation (well, moderate and poor) in NSCLC patients; (6) MTA1 overexpression in NSCLC stage T1/T2 patients; (7) MTA1 overexpression in relation to NSCLC clinical grade (TNM stage); and (8) MTA1 overexpression in relation to lymph node status in NSCLC patients.

Results

Analysis of the included literature

Based on the inclusion and exclusion criteria, a total of seven studies were included, and the data from these studies were extracted (Zhang et al., 2007; Zhu et al., 2010; Yu et al., 2011; Xu et al., 2011; Li et al., 2011; Xia et al., 2013; Li et al., 2016) (Figure 1).

Coincidently, all the studies were conducted in the Chinese population. No studies on other ethnicities such as Caucasian were included as no relevant reports were identified in the databases searched. The characteristics of the seven included studies are listed in Table 1. It should be noted that the information on survival time was not available due to a lack of relevant data in the primary papers. Therefore, the prognosis of patients could not be assessed in the present meta-analysis. The quality assessment indicated that the quality of the included studies was intermediate. Meta-analysis of associations between MTA1 expression and clinic-pathlogical factors in NCLSC are listed in Table 2.

Quantitative analysis of aberrant MTA1 expression in NSCLC

Seven studies involving 660 NSCLC patients were included in the analysis, and 350 cases showed aberrant MTA1 expression. The overall proportion of MTA1 overexpression in these patients was 0.53 (95% CI: 0.43-0.62). As the heterogeneity test showed high heterogeneity (I^2 = 84.6%, P< 0.0001), the random effects model was selected.

Quantitative analysis of MTA1 overexpression in relation to age of NSCLC patients

Four studies involving 156 NSCLC patients aged <60 years were included in the analysis, and 73 cases showed MTA1 overexpression. The overall proportion of MTA1 overexpression in these patients was 0.47 (95% CI: 0.40-0.55). As the heterogeneity test showed no heterogeneity (I^2 = 0%, P = 0.5136), the fixed effects model was used. Four studies involving 207 NSCLC patients aged ≥60 years were included in the analysis, and 108 cases showed MTA1 overexpression, with an overall proportion of 0.52 (95% CI: 0.34-0.70). The heterogeneity test showed high heterogeneity (I^2 = 84.9%, P = 0.0002), and the random effects model was thus selected.

Quantitative analysis of MTA1 overexpression in male and female NSCLC patients

Seven studies involving 367 male NSCLC patients were included in the analysis, and 191 cases showed MTA1 overexpression. The overall proportion of MTA1 overexpression in these patients was 0.52 (95% CI: 0.41-0.62). As the heterogeneity test showed high heterogeneity (I^2 =71.8%, P = 0.0016), the random effects model was selected. Seven studies involving 274 female NSCLC patients were included in the analysis, and 140 cases showed MTA1 overexpression, with an overall proportion

Table 1. Characteristics of the Seven Eligible Studies

Authors (year of publication)	Country	No. of patients	Age (year)	Detection method
Zhang et al., (2007)	China	101	18-72	IHC
Zhu et al., (2010)	China	100	50 (mean)	IHC
Yu et al., (2011)	China	60	42-74	IHC
Xu et al., (2011)	China	96	26-79	IHC
Li et al., (2012)	China	102	34-81	IHC
Xia et al., (2013)	China	75	60 (mean)	IHC
Li et al., (2016)	China	126	60 (mean)	IHC

of 0.51 (95% CI: 0.39-0.62). As the heterogeneity test showed high heterogeneity (I^2 = 70.59%, P = 0.0024), the random effects model was selected.

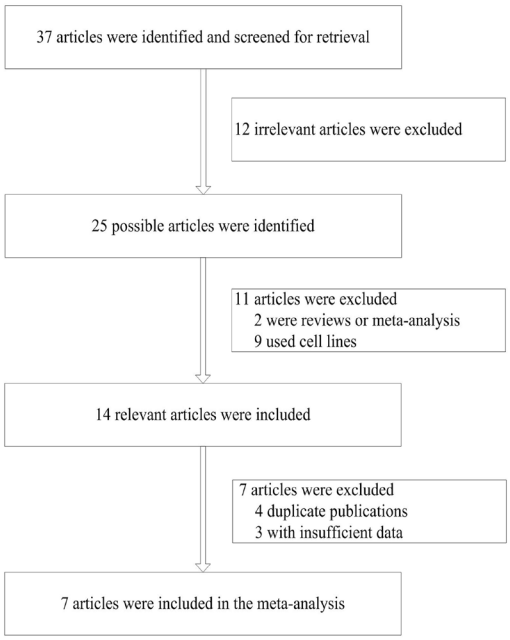

Figure 1. Flow Chart for the Selection of Literature

Quantitative analysis of MTA1 overexpression in relation to histopathological type in NSCLC

Six studies involving 246 NSCLC patients with squamous cell carcinoma (SC) were included in the analysis, and 145 cases showed MTA1 overexpression. The overall proportion of MTA1 overexpression in these patients was 0.59 (95% CI: 0.48-0.69). As the heterogeneity test showed high heterogeneity (I^2 = 64.4%, P = 0.0152), the random effects model was selected. Seven studies involving 274 NSCLC patients with adenocarcinoma (AC) were included in the analysis, and 140 cases showed MTA1 overexpression. The overall proportion of MTA1 overexpression in these patients was 0.57 (95% CI: 0.46-0.67). As the heterogeneity test showed high heterogeneity (I^2 = 74.8%, P = 0.0006), the random effects model was selected.

Quantitative analysis of MTA1 overexpression in relation to histological differentiation in NSCLC

Five studies involving 126 NSCLC patients with well differentiated tumors were included in the analysis, and 49 cases showed MTA1 overexpression. The overall proportion of MTA1 overexpression in these patients was 0.39 (95% CI: 0.23-0.56). As the heterogeneity test showed high heterogeneity (I^2 = 70.7%, P = 0.0085), the random effects model was selected. Five studies involving 185 NSCLC patients with moderately differentiated tumors were included in the analysis, and 81 cases showed MTA1 overexpression, with an overall proportion of 0.44 (95% CI: 0.37-0.51). As the heterogeneity test showed moderate heterogeneity (I^2 = 49.1%, P = 0.0967), the fixed effects model was selected. Five studies involving 150 NSCLC patients with poorly differentiated tumors were included in the analysis, and 83 cases showed MTA1 overexpression. The overall proportion of MTA1 overexpression in these patients was 0.55 (95% CI: 0.37-0.51). As the heterogeneity test showed moderate heterogeneity (I^2 = 36.2%, P = 0.1797), the fixed effects model was selected.

Table 2. Meta-Analysis of Associations between MTA1 Expression and Clinic-Pathlogical Factors in NCLSC

Categories	subgroups	events	total	proportion	95%CI	I-squared	P
ALL		345	660	0.53	0.43, 0.62	0.85	<0.0001
Age	<60years	57	156	0.47	0.40, 0.55	0	0.5136
	≥60 years	100	207	0.52	0.34, 0.70	0.85	0.0002
Gender	Male	193	367	0.52	0.41, 0.62	0.72	0.0016
	Female	135	247	0.51	0.39, 0.62	0.71	0.0024
Histopathological type	SC	204	385	0.57	0.46, 0.67	0.75	0.0006
	AC	144	246	0.59	0.48, 0.69	0.64	0.0152
Histological differentiation	Well	50	126	0.39	0.23, 0.56	0.71	0.0085
	Moderate	81	185	0.44	0.37, 0.51	0.49	0.0967
	Poor	82	150	0.55	0.46, 0.63	0.36	0.1797
Clinical grade	I-II	89	182	0.48	0.36, 0.60	0.62	0.0464
	III-IV	144	190	0.75	0.69, 0.81	0	0.459
T stage	T1/T2	168	299	0.58	0.45, 0.71	0.81	0.0012
lymph node status	Positivity	192	320	0.68	0.49, 0.82	0.89	<0.0001
	Negativity	90	178	0.51	0.43, 0.58	0.19	0.2947

Quantitative analysis of MTA1 overexpression in relation to clinical grade (TNM stage) of NSCLC

Four studies involving 182 patients with clinical grade I-II NSCLC were included in the analysis, and 87 cases showed MTA1 overexpression. The overall proportion of MTA1 overexpression in these patients was 0.48 (95% CI: 0.36-0.60). As the heterogeneity test showed high heterogeneity ($I^2 = 62.4\%$, $P = 0.0464$), the random effects model was selected. Four studies involving 190 patients with clinical grade III-IV NSCLC were included in the analysis, and 143 cases showed MTA1 overexpression. The overall proportion of MTA1 overexpression in these patients was 0.75 (95% CI: 0.69-0.81). As the heterogeneity test showed no heterogeneity ($I^2 = 0\%$, $P = 0.459$), the fixed effects model was selected.

Quantitative analysis of MTA1 overexpression in stage T1/T2 NSCLC

Four studies involving 299 patients with stage T1/T2 NSCLC were included in the analysis, and 173 cases

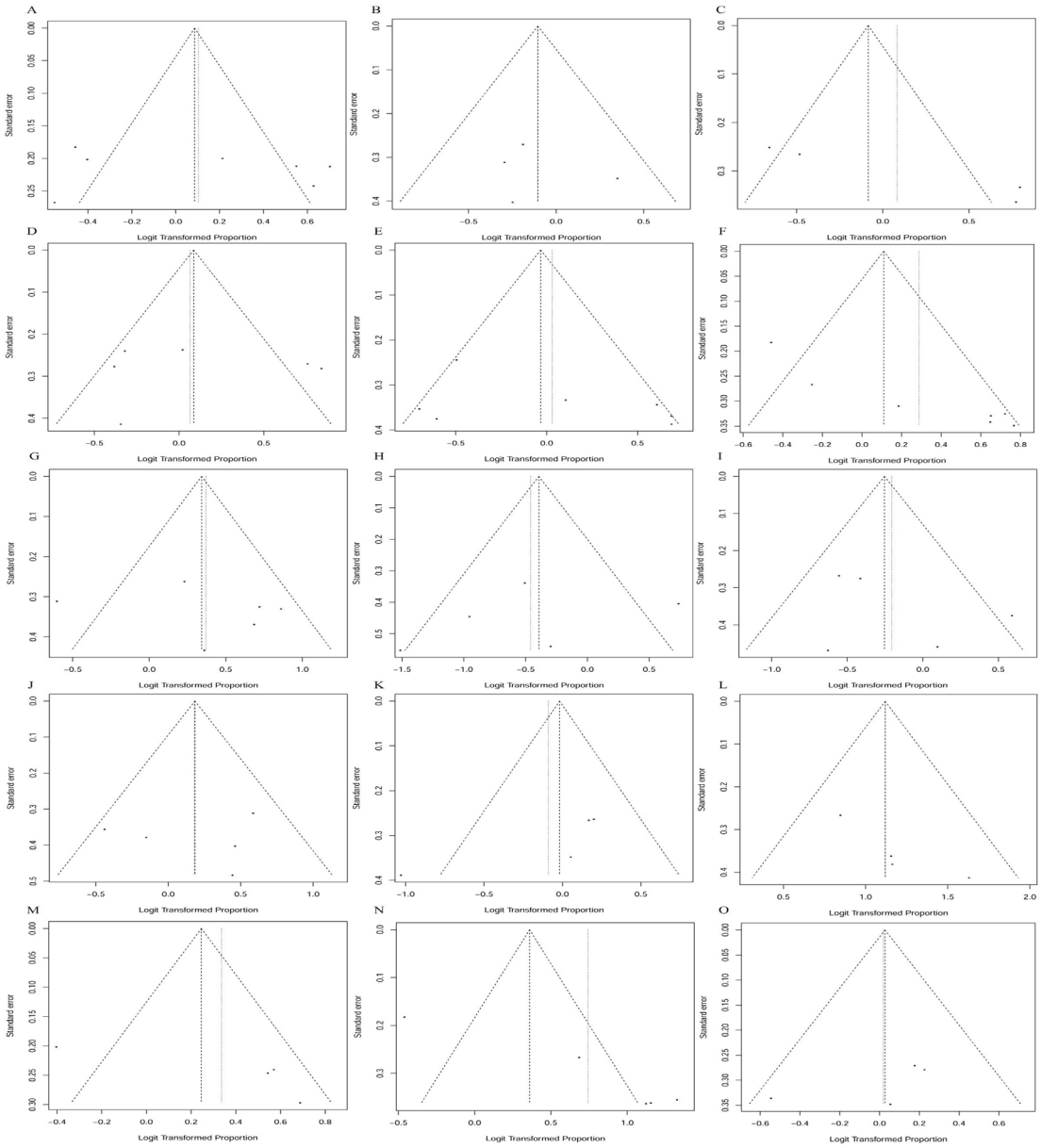

Figure 2. Funnel Plot Showing Publication Bias. The Logit transformed effect is shown on the horizontal axis, and the standard error of effect is shown on the longitudinal axis. A, Publication bias of aberrant MTA1 expression in NSCLC patients; B, Publication bias of MTA1 overexpression in NSCLC patients aged <60 years; C, Publication bias of MTA1 overexpression in NSCLC patients aged ≥60 years; D, Publication bias of MTA1 overexpression in male NSCLC patients; E, Publication bias of MTA1 overexpression in female NSCLC patients; F, Publication bias of MTA1 overexpression in NSCLC patients with SC; G, Publication bias of MTA1 overexpression in NSCLC patients with AC; H, Publication bias of MTA1 overexpression in NSCLC patients with well differentiated tumors; I, Publication bias of MTA1 overexpression in NSCLC patients with moderately differentiated tumors; J, Publication bias of MTA1 overexpression in NSCLC patients with poorly differentiated tumors; K, Publication bias of MTA1 overexpression in patients with NSCLC clinical grade I-II; L, Publication bias of MTA1 overexpression in patients with NSCLC clinical grade III-IV; M, Publication bias of MTA1 overexpression in patients with NSCLC stage T1/T2; N, Publication bias of MTA1 overexpression in NSCLC patients with lymph node positivity; O, Publication bias of MTA1 overexpression in NSCLC patients with lymph node negativity.

showed MTA1 overexpression. The overall proportion of MTA1 overexpression in these patients was 0.58 (95% CI: 0.45-0.71. As the heterogeneity test showed high heterogeneity (I^2 = 81%, P = 0.0012), the random effects model was selected.

Quantitative analysis of MTA1 overexpression in relation to lymph node status in NSCLC

Five studies involving 320 NSCLC patients with lymph node positivity were included in the analysis, and 218 cases showed MTA1 overexpression. The overall proportion of MTA1 overexpression in these patients was 0.68 (95% CI: 0.49-0.82). As the heterogeneity test showed high heterogeneity (I^2 = 89.5%, P<0.0001), the random effects model was selected. Four studies involving 178 NSCLC patients with lymph node negativity were included in the analysis, and 89 cases showed MTA1 overexpression. The overall proportion of MTA1 overexpression in these patients was 0.51 (95% CI: 0.43-0.58). As the heterogeneity test showed low heterogeneity (I^2 = 19.1%, P = 0.2947), the fixed effects model was selected.

Publication bias

As publication bias could not be avoided, we used a funnel plot to assess this bias. With the exception of aberrant MTA1 expression in NSCLC patients, MTA1 overexpression in relation to age (<60 and ≥60 years), gender (male and female), histopathological type (SC and AC), histological differentiation (well, moderate and poor), clinical grade (I-II and III-IV), T stage (T1/T2), and lymph node status (positivity and negativity) showed publication bias based on the funnel plot (Figure 2).

Discussion

This meta-analysis was a systematic evaluation of the associations between MTA1 expression and the clinicopathological characteristics of NSCLC. Our pooled results from seven studies involving 660 patients provide evidence of a significant correlation between MTA1 expression and age, gender, histological type, histological differentiation, clinical grade, T stage and lymph node metastasis in NSCLC.

MTA1, a major member of the MTA family, is one of the most deregulated molecules in human cancer and leads to cancer progression and metastasis (Kumar, 2014). MTA1 was initially identified in rat metastatic mammary tumors (Toh et al., 1994). Elevated expression of MTA1 and its clinicopathologic and biologic relevance have subsequently been reported in various cancers including prostate cancer (Dhar et al., 2016; Dhar et al., 2015), hepatocellular carcinoma (Deng et al., 2015), ovarian cancer (Prisco et al., 2012), cervical cancer (Liu et al., 2013), nasopharyngeal carcinoma (Yuan et al., 2014), and colorectal carcinoma (Fan et al., 2016; Zhu et al., 2012), particularly in NSCLC (Zhang et al., 2007; Zhu et al., 2010; Yu et al., 2011; Xu et al., 2011; Li et al., 2011; Xia et al., 2013; Li et al., 2016). With accumulated researches, MTA1 has been found to have numerous important molecular mechanisms in malignancies. Eukaryotic initiation factor 5A2 (EIF5A2), a putative oncogene, regulated MTA1 through c-myc, consequently, induced epithelial-mesenchymal transition (EMT) and promoted cell invasion/metastasis (Zhu et al., 2012). MTA1 upregulated the expression of epithelial cell adhesion molecule (EpCAM) to mediated invasion and migration (Zhou et al., 2015). MTA1 dysregulation activated ERβ to promote salivary gland cancer aggressive phenotypes (Ohshiro and Kumar, 2015). In addition, MTA1 is connected to certain signal pathways. For example, it stimulated the canonical Wnt (Wingless) signaling via inhibiting SIX3 (the SIX homeobox 3) and GSK3-β (glycogen synthase kinase-3 beta) that were two known regulators of Wnt pathway (Kumar et al., 2010; Kumar et al., 2010). Moreover, MTA1 overexpression promoted EMT via the Wnt1/β-catenin (Lin et al., 2014). MTA1 was also involved in TGF-β (transforming growth factor-β) signaling by regulating SMAD7 (mothers against decapentaplegic homolog 7) (Salot and Gude, 2013). And the expression of Period 2, a clock gene, is an important role in tumor suppression and could inhibit MTA1 expression to restrain tumor development (Wang et al., 2016) Besides, miR-421 directly inhibited MTA1 expression so as to suppress breast cancer metastasis (Pan et al., 2016). Furthermore, it was recently reported that MTA1 had the closest relationship with the key molecules which play a vital role in carcinogenesis, such as AKT1 (v-akt murine thymoma viral oncogene homologue 1), SPARC4(Secreted protein acidic and rich in cysteine 4), EP300 (p300 lysine acetyltransferase), CREBBP (CREB-binding protein), CAD (Cath.a-differentiated) and RHOA(Li et al., 2016). These theories supported tumor growth, migration and invasion associated with elevated MTA1 expression in differently exploratory directions.

In our meta-analysis, seven studies were included, we found a high proportion of MTA1 abnormalities in all NSCLC patients. Interestingly, our study found that MTA1 overexpression is associated with age (≥60 years), gender (male and female), histopathological type (SC and AC). However, a previous meta-analysis of the prognostic significance of MTA1 expression in solid tumor prognosis demonstrated that no association existed between MTA1 and age, sex, tumor differentiation (Luo et al., 2014). These divergences prompted that further more studies are needed to shed more light on the potential causes. Besides, MTA1 overexpression is associated with well differentiated tumors, whereas no statistical difference is found for moderately or poorly differentiated tumors. This is inconsistent with two studies which demonstrated that MTA1 expression was significantly associated with histological differentiation (Zhang et al., 2007; Xu et al., 2011). Moreover, MTA1 overexpression is associated with clinical grade I-II. Although up-regulation of MTA1 was seen in NSCLC patients with advanced clinical stage (Zhu et al., 2010; Yu et al., 2011; Xu et al., 2011), it was not statistically significant in our results. In addition, analyses of the pooled data showed that MTA1 overexpression is significantly correlated with T stage (T1/T2) and lymph node positivity in NSCLC patients. These results suggest that MTA1 may play a valuable role in the genesis and evolution of NSCLC, particularly invasion and metastasis.

Heterogeneity is a potential problem in explaining the results of any meta-analysis. Our systematic review robustly confirmed the importance of MTA1 in NSCLC, but had several limitations. First, some sub-analysis results were less powerful because the combined MTA1 of some subgroups was calculated on the basis of 4–5 studies with a relatively small sample size. Second, although we conducted a full-text search in PubMed, Springer, Science Direct, and Google Scholar, all the studies included were written in Chinese, thus we also searched CNKI. Hence, publication language included English or Chinese, which may have led to selection bias. Third, unpublished data and ongoing studies were not included, which may also have contributed to publication bias. Fourth, in several of the studies included, there was an absence of original data, and the expression of MTA1 in NSCLC could not be analyzed statistically.

Due to a low sample size and the absence of relevant data, we were unable to demonstrate associations between other clinicopathological parameters including smoking status, tumor size, T stage (T3/T4) and other factors. Therefore, further high-quality research and larger sample sizes are needed to obtain more reliable results.

In conclusion, the results of our meta-analysis are encouraging, although future studies are warranted to assess the value of MTA1 in the clinicopathological screening of NSCLC before its clinical application. Increased expression levels of MTA1 were significantly associated with age ≥60 years, gender, histopathological type (SC and AC), clinical grade (I-II), T stage (T1/T2) and lymph node positivity in NSCLC patients. The identification of MTA1 is a promising molecular marker in NSCLC.

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