European Review for Medical and Pharmacological Sciences 2018; 22: 8353-8366

The role of let-7 and HMGA2 in the occurrence and development of lung cancer: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: To evaluate the prognostic role of microRNA let-7 in lung cancer and the relationship between the expression of HMGA2 and clinical significance of lung cancer by meta-analysis.

MATERIALS AND METHODS: The studies on the correlation between the low expression of let-7 and the prognosis of lung cancer, and between the expression of HMGA2 and the occurrence and development of NSCLC were identified by searching PubMed, Web of the Science, Medline, Cochrane Library, Google Scholar, CNKI, CBM, and VIP databases. The StataSE12.0 software was used for meta-analysis.

RESULTS: A total of 10 studies correlating the low expression of let-7 with the lung cancer prognosis were analyzed. The results suggest that the low expression of let-7 indicates a poor overall survival rate, with a hazard ratio value of 1.55 (95%CI:1.16-2.09, $p<0.05$). Furthermore, nine case-control studies of HMGA2 expression in NSCLC tissues were evaluated. The results showed that the expression of HMGA2 in lung cancer is significantly higher than in normal paraneoplastic tissues. High expression of HMAG2 has been observed in patients with late TNM stages and lymph node metastasis.

CONCLUSIONS: Low expression of let-7 is closely related to the poor prognosis of lung cancer patients. The higher expression of HMGA2 in lung tissues correlates positively with the occurrence and invasiveness of lung cancer. Among malignant tumors, lung cancer is the leading cause of mortality. Early diagnosis and accurate prognosis are the keys to improving the survival rate of patients with this disease.

Key Words

Lung carcinoma, Let-7, Prognosis, High mobility group A2 (HMGA2), Meta-analysis.

Introduction

Several studies[1-3] demonstrated that the levels of various microRNAs (miRNA) and high mobility group A2 (HMGA2) were closely related to the occurrence and development of multiple tumors. Studies[4] showed that the low expression of miRNA let-7 is associated with clinical outcome of postoperative patients with lung cancer, suggesting a poor prognosis. Subsequently, a number of researchers[1,5] analyzed the association between the low expression of let-7 and the prognosis of lung cancer, leading to mixed results. The expression level of HMGA2 in non-small cell lung cancer (NSCLC) tissues was higher than that in the normal lung tissues, but discriminatory in NSCLC tissues with different clinical and pathological characteristics. The current results were not the same[6,7]. Furthermore, no meta-analysis of relevant findings was ever performed. We comprehensively retrieved the studies on let-7 and lung cancer prognosis (study 1) and those on HMGA2 and NSCLC (study 2). Our focus was to evaluate the relationship between the low expression of let-7 and poor prognosis of lung cancer, as well as the connection between HMGA2 and different clinical or pathological characteristics of the NSCLC patients.

Materials and Methods

Study Selection

The articles were retrieved from PubMed, Web of Science, Medline, Cochrane Library, Google Scholar, CNKI, CBM, Wan Fang and VIP databases by searching all publications from the earliest entries to December 2015. The languages were restricted to Chinese and English. The studies were chosen based on the following keywords: Study 1 - NSCLC, SCLC, lung cancer, let-7, microRNA, prognosis; Study 2 - lung adenocarcinoma, lung squamous cell carcinomas, HMGA2, HMGI-C. For each and every identified report, more studies were chosen from the cited references, as well as from the suggested 'Related Articles' in PubMed. The database entries were searched independently by two researchers and later cross-checked.

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Inclusion Criteria

The following three criteria formed the basis for inclusion of the published articles: 1) the reports have to focus on patients with lung cancer; 2) the articles should reveal the relationship between the expression levels of let-7 and the survival outcome with a follow-up time of more than 1 year, and 3) the information on the correlative data should be provided.

The following three criteria were used to select the published articles for study 2: 1) the articles have to be case-control studies on the expression of HMGA2 in lung cancer tissues and adjacent normal tissues in patients not treated with radiotherapy or chemotherapy; 2) the articles have to provide numeric information on the level of HMGA2 expression, and 3) the detection of HMGA2 should be performed by immunohistochemistry (SP).

Exclusion Criteria

The following articles were excluded from study 1: 1) articles published as letters, reviews and annals; 2) laboratory and fundamental investigation; 3) articles lacking the raw data information, including hazard ratio (HR), 95% confidence interval (CI), *p*-values and graphics, and 4) articles with repeated publication/analysis of the same data. The following articles were excluded from study 2: 1) articles lacking the raw data information; 2) laboratory and fundamental investigation; 3) repeated publications involving the same data; 4) articles where the test specimens of HMGA2 were originating from serum, and 5) articles where paracancerous normal tissues were not used as control groups.

Quality Assessment

The articles included in Study 1 were systematically evaluated using the MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines[8]. The following information was extracted: 1) the names of first authors and the year of publication; 2) the study population, country of origin, study design, staging and histological types of tumors; 3) the method of detecting let-7 and the cut-off values; 4) the period of follow-up, and 5) the HRs of overall survival rate, recurrence-free survival rate or tumor-related survival rate risk ratios, and confidence intervals. Studies lacking any of this data were excluded to ensure the quality of meta-analysis.

The articles included in Study 2 were systematically evaluated according to the case-control study guidelines by Lichtenstein[9]. The following five aspects were evaluated: 1) scientific rigor and the rationale of experiments; 2) the inclusion criteria and the basic characteristics of subjects are clearly defined; 3) intervention factors and methods are accurate; 4) statistical method is appropriate, and 5) any potential is analyzed and discussed. The quality of publications was evaluated by two independent researchers, and any differences were agreed upon through discussion.

Data Extraction

The relevant data were extracted from each study, according to the selection criteria and quality assessment. Names of the first author, years of publication, countries of origin of research, total numbers of cases (N), follow-up periods, methods of detecting let-7, types of let-7 family, survival analysis data, HRs of let-7 for prognosis and 95% CIs were collected for study 1 (Table I). The first author's names, years of publication, total numbers of cases (N), the cases and positive rates of HMGA2 positive expression were collected for study 2 (Tables II-IV). The data extractions were completed independently by two researchers, cross-checked and mutually agreed upon.

Statistical Analysis

StataSE12.0 software was used for statistical analysis. In this meta-analysis, we used a random effects model or a fixed effects model, depending on the heterogeneity between the studies. Q test was used to test heterogeneity (p-values ≤ 0.05 were considered statistically significant) and I^2 statistics (the values of 25, 50, and 75% were considered representative of low, medium and high heterogeneity, respectively). The random effects model was used when there was statistically significant heterogeneity ($p>0.05$, $I^2<50\%$) and clinical heterogeneity (the results were opposite between the studies); otherwise, the fixed effects model was used. Publication bias was seen when funnel plots showed asymmetry or were incomplete. Student's two-sided test was used for analyses, and p-values <0.05 were considered statistically significant. The effects of HR and 95% CI were evaluated for the let-7 expression level and prognosis of lung cancer, and HR>1 was regarded to be associated with poorer prognosis. The HR and 95% CI values that were not directly provided in some studies were extracted from the survival curves by the Engauge Digitizer 4.1 software. The effects of odds ratio (OR) and 95% CI were evaluated for the relationship between the expression of HMGA2 and clinical significance of NSCLC.

Table I. General characteristics of selected studies about the relationship between the low expression of let-7 with prognosis of lung cancer.

First author	Publication dates (year)	Country	Let-7	No.	Follow-up years	Gene expression analysis	Survival analysis	Cut-off	Hazard ratio (HR)
Xia et al[23]	2010	China	let-7	31	>3	qRT-PCR	Kaplan-Meier analysis	0.5	NR
Landi et al[24]	2010	USA	Let-7e	290	>5	qRT-PCR	Kaplan-Meier analysis	median	Reported
Zhao et al1[2]	2014	China	let-7c	94	>6	qRT-PCR	Kaplan-Meier analysis	median	Reported
Zhang et al[25]	2012	China	Let-7e	51	>2	qRT-PCR	Kaplan-Meier analysis	median	Reported
Takamizawa et al[4]	2004	Japan	let-7	143	>5	qRT-PCR	Kaplan-Meier analysis	Hierarchical clustering	Reported
Inamura et al[5]	2007	Japan	let-7	66	>5	qRT-PCR	Kaplan-Meier analysis	Hierarchical clustering	NR
Yanaihara et al[26]	2006	USA	let-7a-2	52	>1	qRT-PCR	Kaplan-Meier analysis	mean	Reported
Voortman et al[11]	2010	USA	let-7a	638	>8	qRT-PCR	Multivariate Cox analysis	median	Reported
Jusufovic et al[27]	2012	Italy	Let-7b	327	>1	qRT-PCR	Kaplan-Meier analysis	median	Reported
Capodanno et al[28]	2013	Italy	Let-7g	55	>5	qRT-PCR	Kaplan-Meier analysis	median	NR

Table II. The expression levels of HMGA2 in lung cancer tissues and normal adjacent tissues.

First author	Publication dates (year)	Cancer		Control	
		No.	HMGA2(+)	No.	HMGA2(+)
Lan et al[29]	2008	38	15	38	0
Yan et a[16]	2011	68	43	20	0
Liu et al[30]	2011	64	51	18	5
Yang et al[7]	2015	138	82	138	41
Xiao et al[31]	2013	40	22	15	3
Meyer et al[32]	2007	18	6	18	0

Table III. The expression levels of HMGA2 in lung cancer tissues of patients of different gender, smoking history, tumors size and stage.

First author	Publication dates (year)	Gender				Smoking history				Tumors size(T)				Stage			
		Male		Female		Y		N		T≤3cm		T >3cm		I+II		III+IV	
		+	–	+	–	+	–	+	–	+	–	+	–	+	–	+	–
Wu et al[33]	2008	31	12	15	1	–	–	–	–	–	–	–	–	30	11	16	2
Lan et al[29]	2008	–	–	–	–	–	–	–	–	4	4	11	19	6	14	9	9
Yan et al[6]	2011	20	33	7	8	29	15	14	10	14	17	29	8	21	35	6	6
Liu et al[30]	2011	31	6	20	7	14	5	37	8	12	6	38	8	20	19	24	1
Yang et al[7]	2015	60	36	22	20	43	41	39	15	38	22	44	34	39	41	43	15
Xiao et al[31]	2013	12	8	9	11	–	–	–	–	12	6	38	8	4	9	24	3
Meyer et al[32]	2007	4	9	2	3	–	–	–	–	–	–	–	–	1	7	5	5

Table IV. The expression levels of HMGA2 in lung cancer tissues of patients of different node metastasis pathologic type and differentiation degree.

First author	Publication dates (year)	Node metastasis				Pathologic type				Differentiation degree			
		Y		N		Squamous cell carcinoma		Adeno-carcinoma		Middle-high		Low	
		+	–	+	–	+	–	+	–	+	–	+	–
Wu et al[33]	2008	13	9	33	4	19	8	23	5	–	–	–	–
Lan et al[29]	2008	4	17	11	6	–	–	–	–	10	16	5	7
Yan et al[6]	2011	15	28	12	13	11	24	16	17	21	22	6	19
Liu et al[30]	2011	12	17	33	2	23	5	28	8	–	–	–	–
Yang et al[7]	2015	39	41	43	15	52	38	30	18	48	44	34	12
Xiao et al[31]	2013	11	9	8	12	8	9	12	11	10	15	11	4
Meyer et al[32]	2007	–	–	–	–	4	7	2	7	–	–	–	–
Eide et al34	2015	–	–	–	–	34	4	41	47	–	–	–	–
Sarhadi et al[35]	2006	–	–	–	–	60	2	41	10	–	–	–	–

Results

General Characteristics

A total of 447 published articles were retrieved for Study 1 by screening PubMed, Web of Science, Medline, Cochrane Library, Google Scholar, CNKI, CBM, Wan Fang and VIP database. By browsing and skimming through the topics and abstracts, we excluded 405 articles that were not in line with the Study 1. The remaining 42 articles were reviewed and evaluated. Finally, a total of 10 articles met the inclusion criteria and were included in Study 1. There were 1799 patients who all suffered from NSCLC. In order to evaluate the

effect of the let-7 expression level on the clinical outcome of the patients, the expression level of let-7 was classified into two categories, and the survival analysis was performed using either regression models or Kaplan-Meier curves. The cut-off points were selected differently in different articles: median points were selected in 6 articles, average value in 1 article, clustering analysis was performed in 2 articles and another indicator was used in 1 article. The prognosis of lung cancer might be influenced by a variety of clinical or pathological factors. Six of the included articles analyzed these factors by regression model and corrected the conclusions accordingly. Age, gender, TNM staging and pathological typing were the most common correction indices. Voortman et al[11] showed that chemotherapy did not affect the prognosis outcome. The remaining 4 articles analyzed multiple factors and found that the low and high expression of let-7 in lung cancer patients was linked to only a few individual clinical features. After a thorough analysis, the effects of various clinical or pathological factors on the prognosis were excluded. A total of 137 published articles were retrieved for Study 2 through the screening of PubMed, Web of Science, Medline, Cochrane Library, Google Scholar, CNKI, CBM, Wan Fang and VIP database. Initial screening eliminated 120 articles that were not in line with the study and the remaining 17 articles were reviewed and evaluated. Nine articles that met the inclusion criteria were retained for full analysis. All 9 articles were of high quality. Six articles provided original data for 366 cases of lung cancer tissues and 247 cases of adjacent normal tissues. Six articles analyzed the expression level of HMGA2 in lung cancer tissues of male and female; 3 articles analyzed data for smokers and non-smoker; 5 articles reported the tumor size (3 cm was the lower limit); 7 articles reported the staging of lung cancer; 6 articles reported the data for lung cancer with and without lymph node metastases; 8 articles reported data for lung squamous cell carcinomas and adenocarcinomas; 4 articles reported the degree of tumor differentiation (Tables II-IV).

Low Expression of Let-7 Predicts Poor Prognosis in Lung Cancer Patients

The analysis of data with StataSE12.0 statistical software revealed a statistical heterogeneity (p=0.000, I^2=78.2%) between the studies. Therefore, the random effect model was used for this meta-analysis. The low expression of let-7 was associated with worse overall survival (HR=1.55, 95% CI 1.16-2.09, p<0.05). The combined HR value was significantly more statistically effective than the single HR value (Figure 3).

Expression Level of HMGA2 in Lung Cancer Tissues and Adjacent Normal Tissues

Six articles were included in the study of the HMGA2 expression level in lung cancer tissues and adjacent normal tissues. The articles provided data for 219 HMGA2 positive cases in the lung cancer group, and 49 HMGA2 positive cases in normal tissue group. There was statistical heterogeneity between the studies (p=0.052, I^2=54.4%), but the research findings were pointing in the same direction. Therefore, the fixed effect model was used for this meta-analysis. The positive rate of HMGA2 expression was 59.84% (219/366) in the lung cancer tissues, while 19.84% (49/247) in the adjacent normal tissues. There was a significant difference in the expression level of HMGA2 between the lung cancer and adjacent normal tissues (OR=5.92, 95% CI: 3.96-8.85, p=0.000) (Figure 4).

Expression Level of HMGA2 in Lung Cancer Tissues of Men and Women

Six articles were included in the study of the HMGA2 expression level in the lung cancer tissues of men and women, including 158 HMGA2 positive cases in male lung cancer group, and 75 HMGA2 positive cases in female lung cancer group. There was no statistical heterogeneity among the studies (p=0.339, I^2=11.9%). Therefore, the fixed effect model was used for meta-analysis. The positive rate of HMGA2 expression was 60.31% (158/262) in male lung cancer tissues, the positive rate of HMGA2 expression was 60.00% (75/125) in female lung cancer tissues. There was no statistically significant difference in HMGA2 expression levels between male and female lung cancer tissues (OR=1.12, 95% CI: 0.71-1.78, p>0.05) (Figure 5).

Expression Level of HMGA2 in Smoking and Non-Smoking Lung Cancer Patients

Three articles were included in the study of the HMGA2 expression level in the lung cancer tissues of smokers and non-smokers, covering 86 HMGA2 positive cases in the smokers lung cancer group, and 90 HMGA2 positive cases in the non-smokers lung cancer group. There was no statistical heterogeneity between the studies (p=0.159, I^2=45.5%). Therefore, the fixed effect model was used for this meta-analysis.

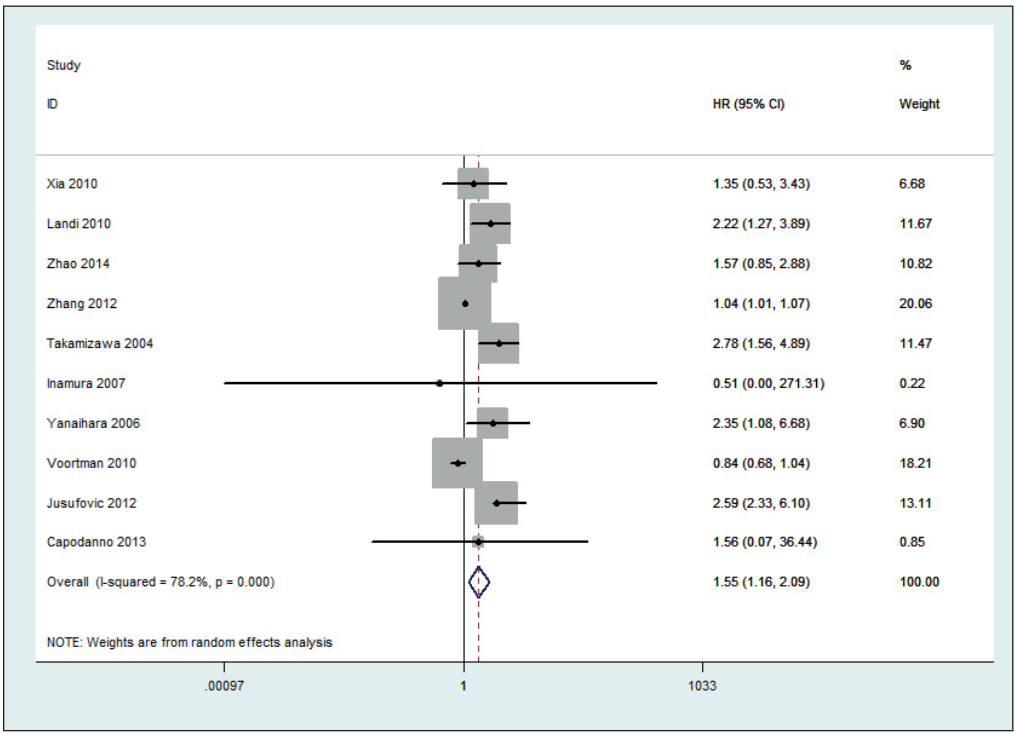

Figure 1. Meta-analysis on the relationship between low expression of let-7 with prognosis of lung cancer.

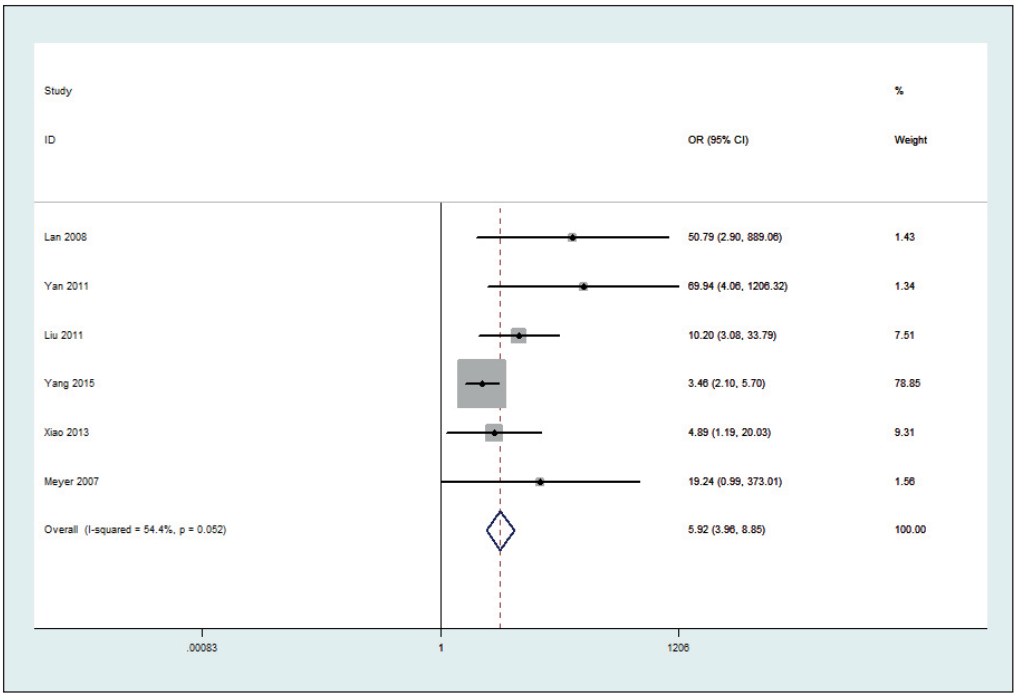

Figure 2. Meta-analysis on the expression levels of HMGA2 in lung cancer tissues and normal adjacent tissues.

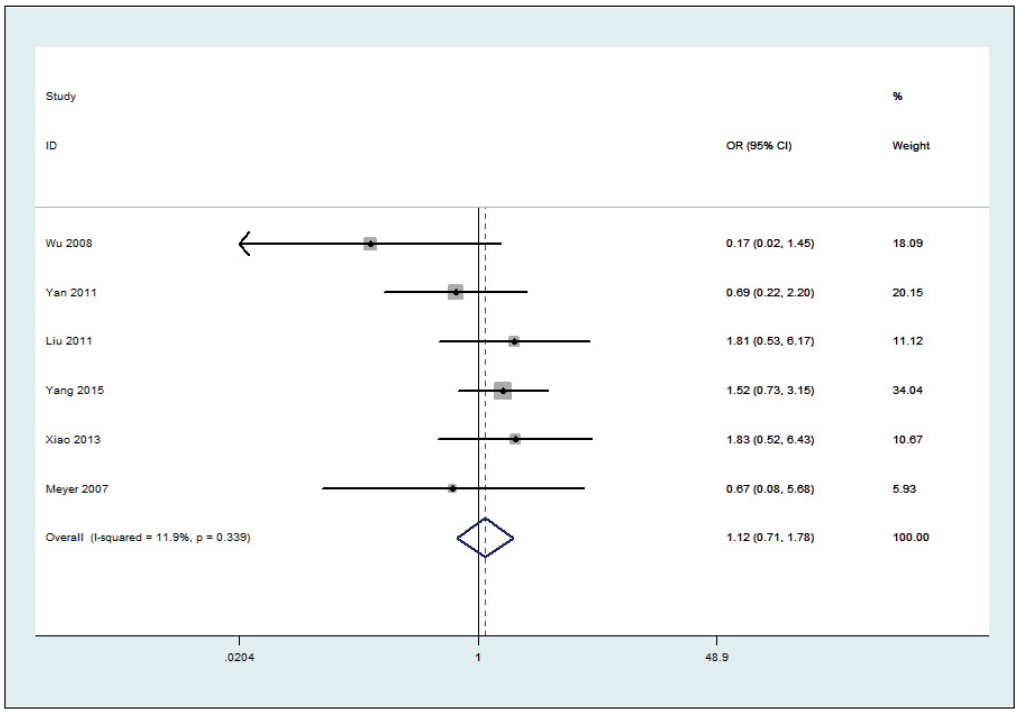

Figure 3. Meta-analysis on the expression levels of HMGA2 in lung cancer tissues of male and female patients with lung cancer.

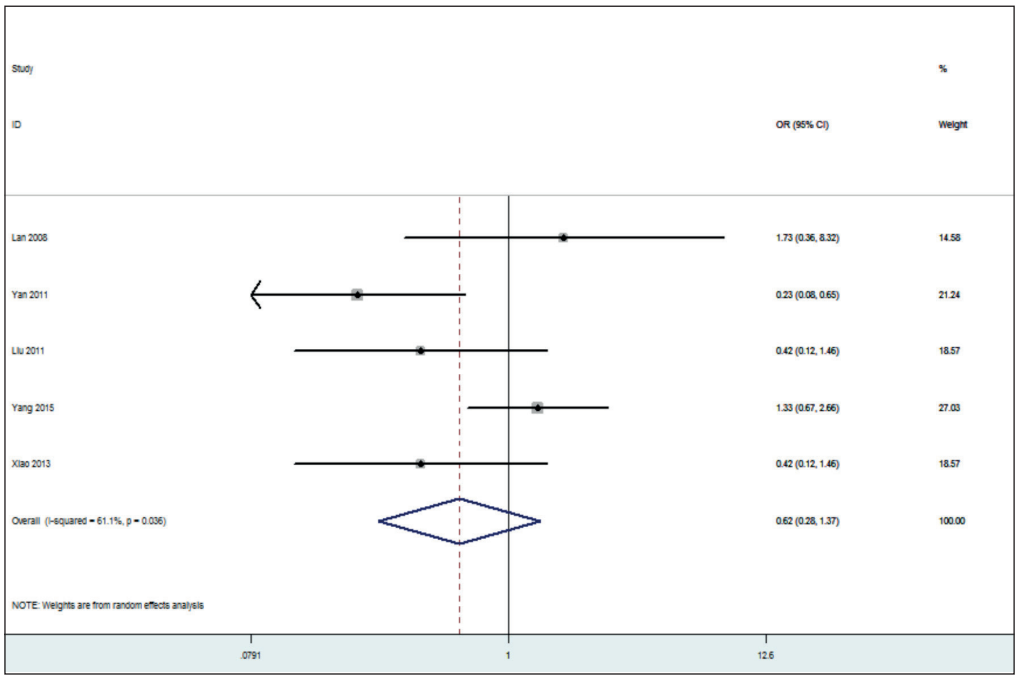

Figure 4. Meta-analysis on the expression levels of HMGA2 in lung cancer tissues of patients who smoke or not.

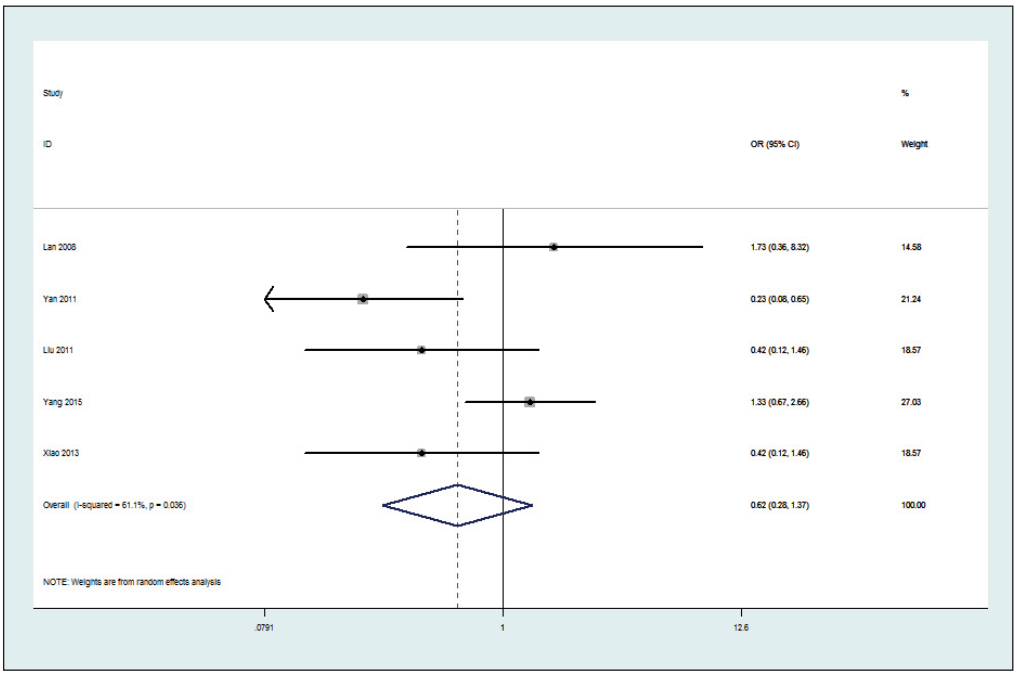

Figure 5. Meta-analysis on the expression levels of HMGA2 in lung cancer tissues of patients who had different tumors size.

The positive rate of HMGA2 expression in the lung cancer tissues of smokers was 58.50% (86/147), the positive rate of HMGA2 expression in the lung cancer tissues of no-smokers was 73.17% (90/123). The result showed no statistically significant difference in the HMGA2 expression level between lung cancer tissues of smokers and non-smokers (OR=0.61, 95% CI: 0.36-1.04, $p>0.05$) (Figure 6).

Expression Level of HMGA2 in Lung Cancer Tissues from Tumors of Different Size

Five articles were included in the study of HMGA2 expression in the lung cancer tissues of the tumors that differ in size, including 80 HMGA2 positive cases in the lung cancer group with tumor diameter ≤ 3 cm, and 160 HMGA2 positive cases in the lung cancer group with tumor diameter > 3 cm. There was statistical heterogeneity between the studies ($p=0.036$, $I^2=61.1\%$), as the results of these studies were different from each other. Therefore, the random effect model was used for this meta-analysis. The positive rate of the HMGA2 expression in the former was 59.26% (80/135), while in the latter was 67.51% (160/237). The results showed that there was no statistically significant difference in the expression of HMGA2 between the lung cancer tissues obtained from tumors of different sizes (OR=0.62, 95% CI: 0.28-1.37, $p>0.05$) (Figure 7).

Expression Level of HMGA2 in Lung Cancer Tissues at Different Stages of Disease

Seven articles were included in the study of HMGA2 expression in the lung cancer patients with different staging, including 121 cases of HMGA2 positive tissues from the stage I+II lung cancer patients, and 127 cases of HMGA2 positive tissues from the stage III+IV lung cancer patients. There was no statistical heterogeneity between the studies ($p=0.171$, $I^2=33.7\%$). Therefore, the fixed effect model was used for this meta-analysis. The positive rate of HMGA2 in the lung cancer patients at the stage I+II was 47.08% (121/257), and in the patients at the stage III+IV was 75.60% (127/168). There was a significant difference in the expression level of HMGA2 between the stages I+II and III+IV in the lung cancer patients (OR=0.26, 95% CI: 0.16-0.41, $p<0.05$) (Figure 8).

Expression Level of HMGA2 in the Lung Cancer Tissues With or Without Lymph Node Metastasis

Six articles were included in the study of HMGA2 expression in the lung cancer patients with or without lymph node metastasis, including 94 HMGA2 positive cases in lung cancer tissues without lymph node metastasis, and 140 HMGA2 positive cases in lung cancer tissues with lymph node metastasis.

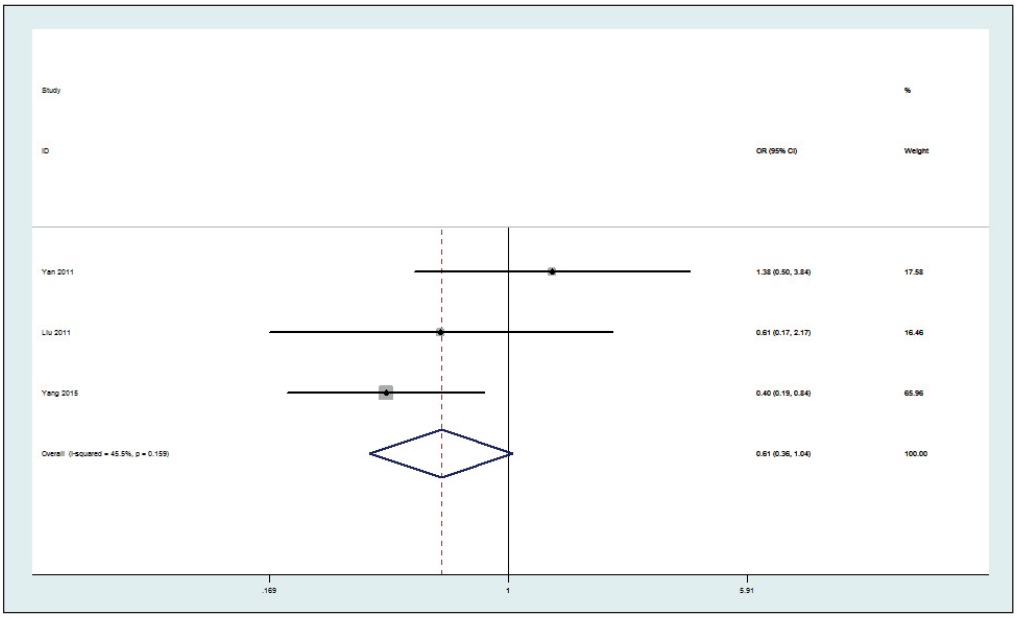

Figure 6. Meta-analysis on the expression levels of HMGA2 in lung cancer tissues of patients who had I + II and III+IV lung cancer.

There was statistical heterogeneity between the studies (p=0.004, I^2=70.7%), and the results of each study were inconsistent. Therefore, a random effect model was used for this meta-analysis. The positive rate of HMGA2 expression in the lung cancer tissues without lymph node metastasis was 43.72% (94/215); the positive rate of HMGA2 expression in the lung cancer tissues with lymph node metastasis was 72.92% (140/192). There was a significant difference in the expression level of HMGA2 between tumors with and without lymph node metastasis in lung cancer (OR=0.29, 95% CI: 0.12-0.71, p<0.05) (Figure 9).

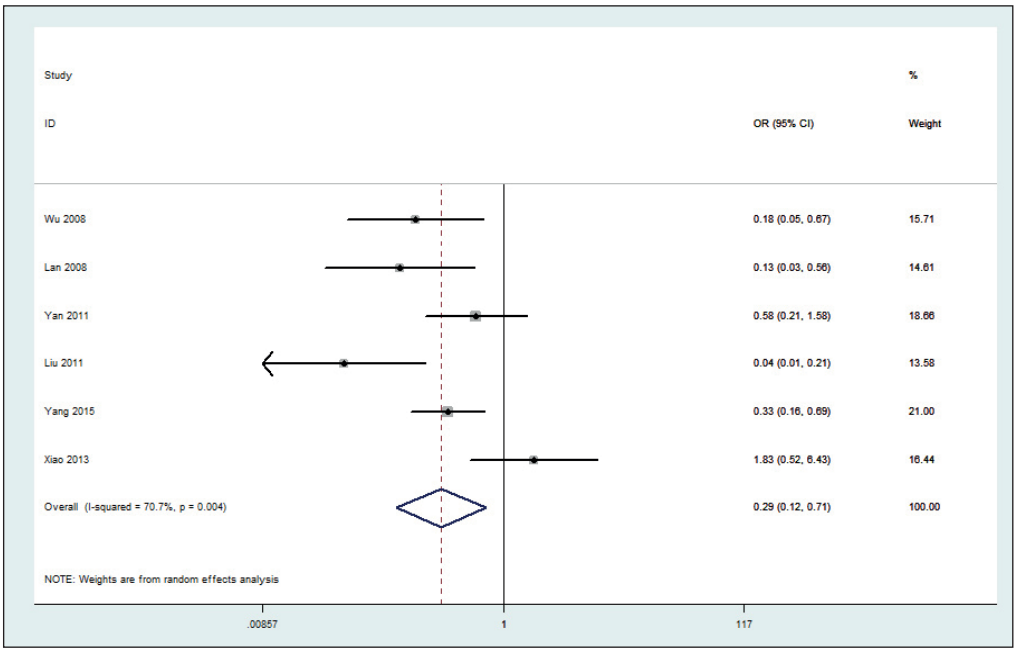

Figure 7. Meta-analysis on the expression levels of HMGA2 in lung cancer tissues of patients whether me-tastasis of lymph node or not.

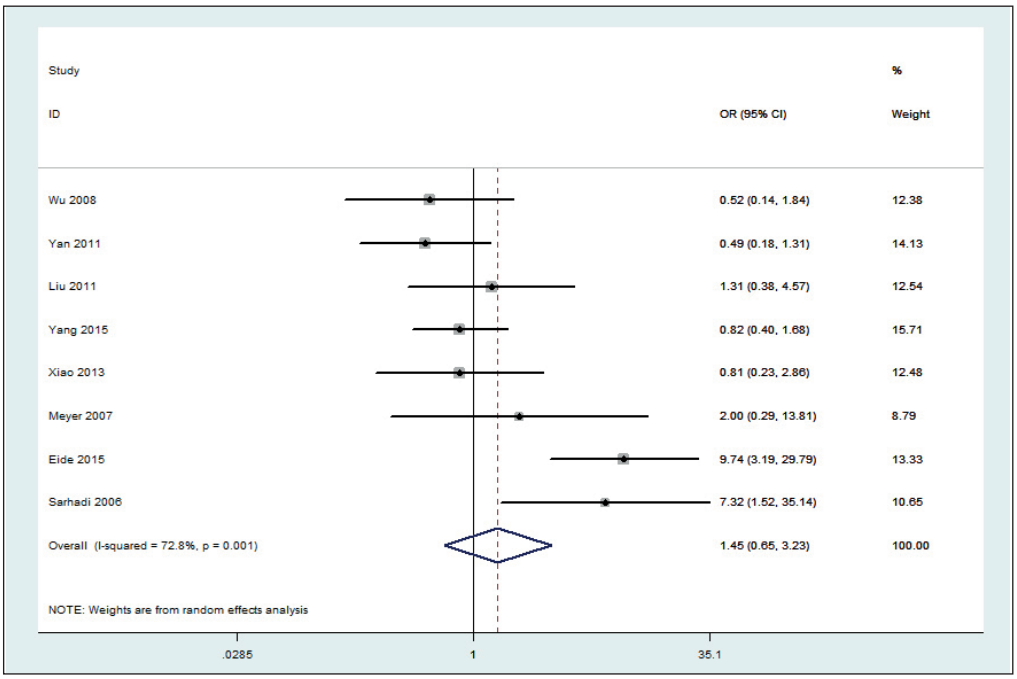

Figure 8. Meta-analysis on the expression levels of HMGA2 in lung squamous carcinoma and lung adeno-carcinoma tissues of lung cancer patients.

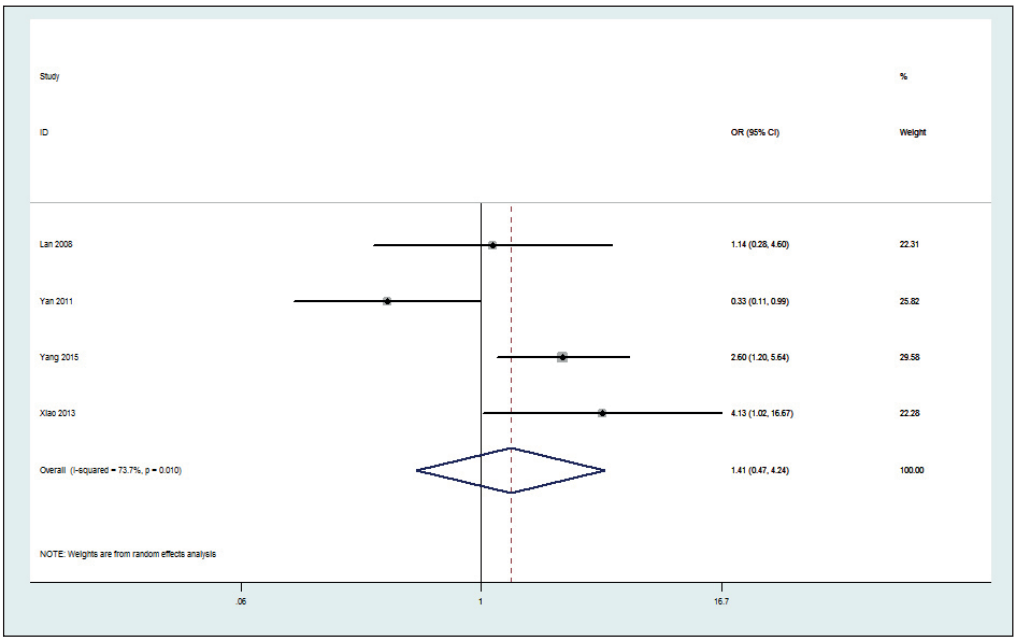

Figure 9. Meta-analysis on the expression levels of HMGA2 in the differentiation of low and middle+high lung cancer tissues of lung cancer patients.

Expression Level of HMGA2 i n Lung Squamous Cell Carcinomas and Adenocarcinomas

Eight articles were included in the study of HMGA2 expression in the lung cancer patients with lung squamous cell carcinomas and adenocarcinomas, including 211 HMGA2 positive cases in the lung squamous cell carcinoma group, and 193 HMGA2 positive cases in the lung adenocarcinoma group. There was statistical heterogeneity between the studies (p=0.001, I^2=72.8%), and the results of each study were inconsistent. Therefore, a random effects model was used for this meta-analysis. The positive rate of HMGA2 in the lung squamous cell carcinoma patients was 68.06% (211/310); the positive rate of HMGA2 in the lung adenocarcinoma patients was 60.69% (193/318). There was no significant difference in the positive expression rate of HMGA2 between lung squamous cell carcinomas and adenocarcinomas (OR=1.45, 95% CI: 0.65-3.23, p>0.05) (Figure 10).

Expression Level of HMGA2 in Lung Cancer Tissues With Different Degree of Differentiation

Four articles were included in the study on a different degree of differentiation, including 56 HMGA2 positive cases in tumors with poor differentiation, and 89 HMGA2 positive cases in well-differentiated tumors. There was statistical heterogeneity between the studies (p=0.01, I^2=73.7%); the results of each study were inconsistent. Therefore, a random effect model was used for this meta-analysis. The positive rate of the HMGA2 expression in lung cancer patients with poor tumor differentiation was 57.14% (56/98), the positive rate of the HMGA2 expression in the well-differentiated lung cancer tissues was 47.85% (89/186). There was no significant difference in the positive expression rate of HMGA2 between poor and well-differentiated tumors (OR=1.41, 95% CI: 0.47-4.24, p>0.05) (Figure 11).

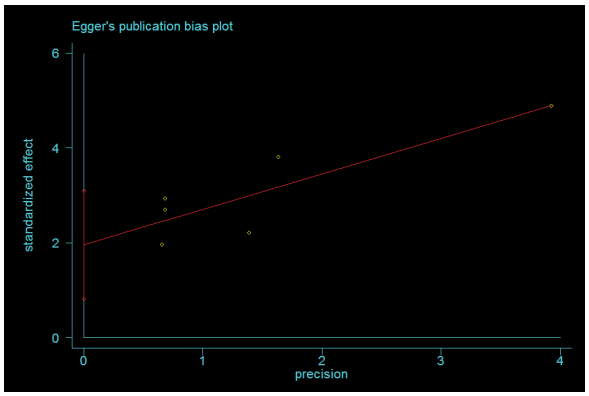

Figure 11. Egger's publication bias plot on the expression levels of HMGA2 in lung cancer tissues and normal adjacent tissues.

Publication Bias

The funnel plot, Begg and Egger's regressions were used to assess publication bias. In the study of the HMGA2 expression in lung cancer tissues and adjacent normal tissues, the results of Begg and Egger regressions were inconsistent, with Begg regression test showing Pr > IzI = 0.452, and Egger regression test showing p = 0.009 (Figure 10, 11). The trim and fill method that yields an effect adjusted for funnel plot asymmetry showed that the result does not reverse, suggesting that they were relatively stable (Figure 12).

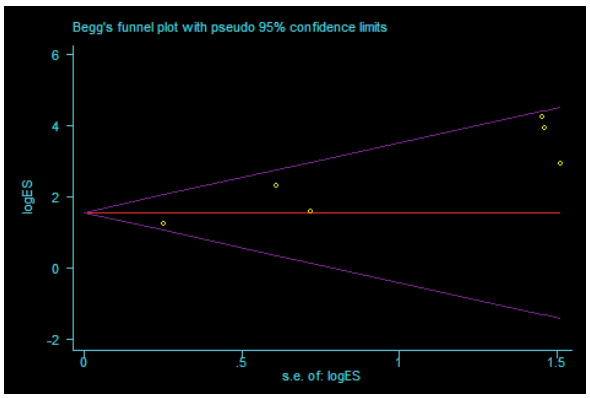

Figure 10. Begg's funnel plot on the expression levels of HMGA2 in lung cancer tissues and normal adjacent tissues.

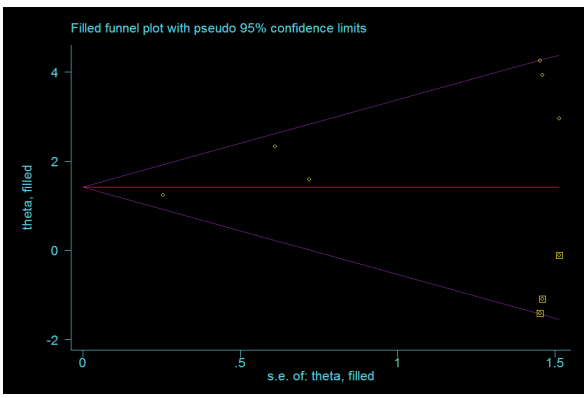

Figure 12. Filled funnel plot on the expression levels of HMGA2 in lung cancer tissues and normal adjacent tissues.

Discussion

The connection between aberrant expression of miRNAs and prognosis for pulmonary cancer, especially NSCLC, has been evaluated in many meta-analysis studies. According to Xia et al[8], the low expression of miRNA let-7 is closely related to the prognosis of aberrant cancers. Moreover, seven of the studies prove that the low expression of let-7 often indicates poor prognosis of pulmonary cancer. In our work, more publications samples were included. We proved that the low expression of let-7 is statistically correlated with some clinical outcomes. The HR of low let-7 expression in pulmonary cancers was 1.55, which indicates that low let-7 expression is associated with poor prognosis in pulmonary tumors. However, whether the low expression of let-7 could be an independent factor of adverse outcomes for patients with lung cancer is still debatable. According to Zhao et al[12], the low let-7 expression is connected with metastasis, vascular invasiveness and advanced stages of lung cancer, but it is not an independent factor of adverse outcomes for lung cancer patients. However, in another research by Takamizawa et al[4], it was proven that the low let-7 expression can be an independent factor of adverse outcomes for lung cancer patients. More rigorous research data are needed to solve this controversy. HMGA2, as a kind of non-histone chromosome gene, is mainly involved in gene transcription and regulation of proliferation and differentiation, to ensure the independent growth and migration of cancer cells. Studies[13-14] have proved that let-7 can specifically inhibit HMGA2 proto-oncogene. An effective dose of let-7 that could reduce HMGA2 expression was introduced into the tumor cells. The results couldn't lead to the change in the RAS dose, thus indicating that the effect of let-7 on targeting HMGA2 is superior to RAS. In addition, let-7 can also function as a tumor suppressor gene by negatively regulating certain oncogenes (C-MYC, MP-1, CRD-BP) and cell cycle regulators (CDK6, Cyclin D2, and so on)[15,16]. The under-expression of let-7 in NSCLC tissues leads to the abnormal expression of the above-mentioned oncogenes and cell cycle abnormalities, resulting in the proliferation of tumor cells, and ultimately affects the prognosis of lung cancer. HMGA2 consists of three basic DNA-binding domains, the AT-hooks, which facilitate its binding to adenine-thymine (AT)-rich regions of nuclear DNA. As a result of binding, the structure of DNA is altered and the assembly of protein complexes is promoted, leading to the changes in the regulation of cell growth, proliferation, apoptosis and other biological processes. HMGA2 can lead to the formation of malignant tumors by promoting epithelial-mesenchymal transformation (EMT), destructing DNA repair system, upregulating transcriptional cyclin A and other mechanisms. Previous studies[17-19] showed that HMGA2 protein is involved in the development of a variety of human tumors, such as colon cancer, prostate cancer, breast cancer and so on. Some studies[2,3,19,20] showed that HMGA2 is highly expressed in metastatic lung adenocarcinoma tissues and promotes progression and metastasis of cancer as a kind of competitive endogenous RNA (ceRNA) of microRNA let-7 family. In addition, the overexpression of HMGA2 up-regulates the expression of transforming growth factor-beta (TGF-β) co-receptor named Tgfbr3, thereby activating the TGF-β signaling pathway. Thus, high expression of HMGA2 serves to promote cancer progression at the level of the protein-coding gene as well as non-coding RNA[20]. The expression of HMGA2 is regulated by a variety of molecules, such as thyroid transcription factor-1 (TTF-1) in lung cancer tissues, although TTF-1 is not expressed in poorly differentiated lung cancers. Studies[21,22] demonstrated that TTF-1 could induce the expression of miR-33a by direct or indirect means, thereby affecting the deletion of mRNA, and thus inhibiting the expression of HMGA2. The absence of TTF-1 could cause the overexpression of HMGA2. Our work shows that the positive rate of the HMGA2 expression in NSCLC tissues and adjacent normal tissues was statistically significant, suggesting that the high expression of HMGA2 is associated with the occurrence of NSCLC. High expression of HMGA2 is closely related to the late TNM staging and lymph node metastasis of lung cancer. Meta-analysis performed in this work has a number of limitations: 1) heterogeneity between the studies caused by the differences in clinical characteristics of patients (age, gender, tumor stage, pathological type, ethnicity, etc.), methods of data analysis, technical platform used, sensitivity and specificity, cut-off values, etc. were impossible to eliminate; 2) we intended to evaluate the connections between gender, differentiation and HMGA2 expression, but the number of articles included in the analysis was limited, which might affect the validity of the findings; 3) there was publication bias between the studies that might affect the final outcomes. The most likely cause of publication bias was that positive results attracted

more attention, and negative results were rarely published or cited and could easily be missed. In the future publications, the experimental design should be described in detail, including the characteristics of subjects, diagnostic criteria, etc. In addition, increasing the sample size and strengthening the control of bias can make up for the shortage.

Conclusions

We observed that the low expression of microRNA let-7 was closely related to the poor prognosis of lung cancer. Thus, let-7 may become a new tumor marker for evaluating the prognosis of lung cancer patients. The higher positive expression rate of HMGA2 in lung tissues is positively correlated with the occurrence and invasiveness of lung cancer. Hence, HMGA2 may be a tumor marker for early diagnosis of lung cancer, providing a new method to establish the biological behavior and prognosis of lung cancer and opening a new way for biological treatment of lung cancer.

Acknowledgments

This study was supported by Guidance Fund for the Development of Medical and Health Industry in Jilin Province (No. 201603034YY), Special Fund for Industrial Innovation in Jilin Province (No. 2016C043-3), and Health Technology Innovation Project in Jilin province (No. 2016J058).

Authors contribution

XL, XD, SC and YW surveyed the literature and analyzed the reports; XL prepared the first draft; XD, SC and YW proofread the manuscript drafts; KW conceptualized the study, secured funding, provided resources, finalized manuscript and approved its submission.

Conflict of Interests

The authors declare that they have no conflict of interest.

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