

Association between an elevated level of HMGB1 and non-small-cell lung cancer: a meta-analysis and literature review

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Background: HMGB1 has been overexpressed in the tissues or serum of patients with non-small-cell lung cancer (NSCLC) in several studies. However, the results remain inconsistent.

Objective: The aim of this study was to perform a meta-analysis to investigate the relationship between elevated level of HMGB1 and NSCLC.

Methods: Associated studies were included, and the pooled risk difference and mean difference (MD) together with 95% confidence interval (CI) were calculated.

Results: A total of ten relevant studies on HMGB1 expression were included in this meta-analysis. The pooled results suggested that the expression of HMGB1 in NSCLC tissues was notably higher than those in corresponding nontumor normal tissues by using immunohistochemistry (risk difference = 0.38, 95% CI: 0.28–0.48, $Z=7.67$, $P<0.00001$, $P=0\%$), Western blot (MD = 0.27, 95% CI: 0.06–0.47, $Z=2.57$, $P<0.01$), or real-time polymerase chain reaction (MD = 15.15, 95% CI: 14.8–15.5, $Z=2.08$, $P=0.04$). Serum HMGB1 levels were similarly significantly higher in patients with NSCLC than those in healthy controls. The pooled MDs of HMGB1 in patients with NSCLC compared with healthy controls were 17.54 with 95% CI: 10.99–24.09, $Z=5.25$, $P<0.00001$. Two of the included studies were fully reviewed without performing meta-analysis due to the different detection methods used. The protein level of HMGB1 in patients with NSCLC of tumor, nodes, and metastasis (TNM) stages III–IV was higher than that of TNM stages I–II ($P<0.047$ and $P<0.001$, respectively).

Conclusion: The expression levels of HMGB1 in both tissues and serum of patients with NSCLC were statistically higher than those of normal lung samples, which indicated that elevated levels of HMGB1 can reveal changes that correlated with disease progression, or even the risk of NSCLC disease progression. The elevated level of HMGB1 could also be considered as a potential biomarker for the diagnosis of patients with NSCLC.

Keywords: HMGB1, non-small-cell lung cancer, meta-analysis

Introduction

Lung cancer is one of the most serious malignant tumors, and ~80%–85% of lung cancer is non-small-cell lung cancer (NSCLC).¹ During the past few years, there have been big breakthroughs in many aspects of the diagnosis and treatment of NSCLC. However, the knowledge of pathogenesis in NSCLC is still limited, and effective indicators for early diagnosis of NSCLC are lacking. It is universally considered that early diagnosis is a crucial means to decrease the mortality of NSCLC. Therefore, looking for perfect biomarkers for early diagnosis and prevention of lung cancer is of important clinical value. Overexpression of RAGE in the lung

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epithelium inferred that HMGB1 may play an important role in the development of lung cancer.^{2–5} Furthermore, the levels of HMGB1 expression are strongly correlated with tumor progression.⁶ However, until now studies have shown inconsistent results regarding the levels of HMGB1 expression in patients with NSCLC.

HMGB1 is a highly conserved nuclear protein that plays a pivotal role in chromatin organization and transcriptional regulation.^{7,8} Previously, we reported that HMGB1 can act as an inflammatory mediator and accelerate acute allograft rejection by interleukin-17⁺ $\gamma\delta$ T-cell response.⁹ Currently, increasing number of studies suggest that HMGB1 can also act as an extracellular signaling molecule during tumor progression.¹⁰ Elevated level of HMGB1 has been associated with unlimited replicative potential, evasion of programmed cell death, the ability to develop blood vessels, tissue invasion, and metastasis.^{11,12} During the past 10 years, various case-control studies were performed to investigate the expression of HMGB1 in patients with NSCLC that suggested that HMGB1 plays a pivotal role in diagnosis and prognosis of NSCLC.^{13–19} However, these studies reported conflicting results owing to different detection methods, small sample size, and low statistical power. For example, Shen et al¹⁸ reported that the level of HMGB1 is down-regulated in NSCLC tissues, while other studies indicated that there is a higher level of HMGB1 in NSCLC tissues compared with normal controls.^{14,16} Thus, whether HMGB1 was overexpressed or not remains unclear in patients with NSCLC, and the clinical diagnosis and prognosis value of HMGB1 need to be investigated further.

Therefore, to reveal the relationship between HMGB1 expression and NSCLC, we performed a meta-analysis and literature review to evaluate the expression of HMGB1 in patients with NSCLC, and we found that high expression of HMGB1 was associated with NSCLC. The abovementioned evidence suggested that high serum or tissue HMGB1 expression may play an important role in the development and progression of NSCLC.

Methods

Search strategy and selection criteria

A bibliographic search was conducted on PubMed, VIP Database for Chinese Technical Periodicals and Embase,

Wanfang Data Knowledge Service Platform, and China National Knowledge Infrastructure (up to December 2015) by two investigators (Quansong Xia and Juan Xu) by using the following terms: high-mobility group box 1 (HMGB1) and NSCLC. Manual searches of reference lists from potentially relevant researches were also performed to identify any additional articles that may have been missed using the computer-assisted strategy. No limits were set in terms of language used or study design. The data from the full published article instead of any meeting or abstract were taken. Studies included in this meta-analysis must be focusing on: 1) the expression of HMGB1 in patients with NSCLC was compared with normal controls and usable data can be extracted and 2) the use of real-time polymerase chain reaction (RT-PCR), Western blot, and immunohistochemistry for the detection of tissue HMGB1 expression. Enzyme-linked immunosorbent assay (ELISA) was used for serum HMGB1 detection. All studies were double checked with inclusion and exclusion criteria independently by two investigators (Quansong Xia and Juan Xu).

Data extraction

The first author, published year, country, journal, language, sample size of NSCLC, detection methods, tissue types, and confirmation of diagnosis were extracted from each included studies.^{13–24} These processes were performed independently by two investigators (Quansong Xia and Juan Xu), and a consensus was reached.

Statistical analysis

The pooled mean difference (MD) and risk difference (RD) together with 95% confidence intervals (CI) were calculated. Then, χ^2 -based Q statistics and I^2 metrics were used to assess the heterogeneity between studies. When $I^2 < 50\%$, a fixed effect model was used to calculate pooled MD or RD, otherwise a random effect model was used. HMGB1 protein or gene expression between NSCLC and normal tissue was compared by the meta-analysis. Two studies investigated the HMGB1 expression levels in different tumor, nodes, and metastasis (TNM) stages of NSCLC, and they are listed in Table 1. All the statistical analyses were performed by using Review manager software (v.5.2, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark,

Table 1 Expression of HMGB1 in TNM patients with NSCLC

Study	Sample size	Stages I–II	Stages III–IV	P-value	Detection methods
Wang et al ¹⁴	30	0.62±0.28	0.85±0.32	0.047	Western blot
Shang et al ¹⁶	145	52.9±23.8	102.1±29.4	<0.001	ELISA

Abbreviations: ELISA, enzyme-linked immunosorbent assay; HMGB1, high-mobility group box 1; NSCLC, non-small-cell lung cancer; TNM, tumor, nodes, and metastasis.

<http://tech.cochrane.org>) and STATA (v.12.0, StataCorp LP, College Station, TX, USA).

Results

A database, including first author, published year, country, language, sample size, methods, and tissue types, was established according to the extracted information from ten studies that met the inclusion criteria (Table 2). The original study yielded a total of 125 articles related to the searched keywords. Figure 1 summarizes the selection process of this study. By screening the title, keywords, and abstracts, 110 of these articles were excluded. Full-text articles from 15 articles were reviewed, and an additional five articles were excluded (four were excluded for not presenting the usable data and one due to the same article with different languages), leaving ten studies for further review.

The pooled results indicated that the levels of HMGB1 in NSCLC tissues were notably higher than those in corresponding nontumor normal tissues by using immunohistochemistry (RD=0.38, 95% CI: 0.28–0.48, $Z=7.67$, $P<0.00001$, $I^2=0\%$; Figure 2A), Western blot (MD=0.27, 95% CI: 0.06–0.47, $Z=2.57$, $P<0.01$; Figure 2B). Serum HMGB1 levels were similarly significantly higher in patients with NSCLC than those in healthy controls. The pooled MDs of HMGB1 in patients with NSCLC compared with healthy controls were 17.54 with 95% CI: 10.99–24.09, $Z=5.25$, $P<0.00001$ (Figure 3A). By using RT-PCR, the pooled MDs of HMGB1 in patients with NSCLC compared with healthy controls were 15.15 with 95% CI: 14.8–15.5, $Z=2.08$, $P=0.04$ (Figure 3B).

Two of the included studies were carefully reviewed without conducting a meta-analysis due to the different detection methods used. The protein level of HMGB1 in patients with NSCLC of TNM stages III–IV was higher than TNM stages I–II (two studies showed $P<0.047$ and $P<0.001$, respectively; Table 1).

A sensitivity analysis was performed to assess the result stability by removing one study at a time. The pooled MD or RD of HMGB1 in patients with NSCLC compared with normal controls by RT-PCR, Western blot, ELISA, and immunohistochemistry was not significantly changed, suggesting the stability of our results. The funnel plots were substantially symmetric (Figure 4), indicating that no publication biases exist in the meta-analysis of HMGB1 expression. Finally, we performed Egger's test to calculate the publication bias by using STATA software. No publication bias was detected in the Egger's test that performed to provide statistical evidence for funnel plot symmetry ($P=0.188$ for immunohistochemistry, $P=0.097$ for Western blot, $P=0.854$ for ELISA, and $P=0.317$ for RT-PCR).

Discussion

Cancer development is a complicated dynamic process. Accumulated evidences indicate that HMGB1 is associated with cancer development.²⁵ Nevertheless, the clinical value of HMGB1 in the diagnosis and prognosis of NSCLC is not fully understood at present. In this study, we performed a meta-analysis and indicated that the levels of HMGB1 in NSCLC tissues were notably higher than those in corresponding nontumor normal tissues by using immunohistochemistry, RT-PCR, and Western blot. Moreover, the serum HMGB1 levels were similarly significantly higher in patients with NSCLC than those with normal controls, suggesting that overexpression of HMGB1 can be regarded as an important molecular marker for NSCLC diagnosis. In addition, after a literature review of two included studies, it was found that the protein level of HMGB1 in patients with NSCLC of TNM stages III–IV was higher than TNM stages I–II, suggesting that HMGB1 plays a pivotal role in the progression of NSCLC.

Table 2 Main characteristics of included studies

Study	Year	Country	Language	NSCLC sample size	Method	Tissue/serum
Shang et al ¹⁶	2009	People's Republic of China	English	145	ELISA	Serum
Naumnik et al ¹⁷	2009	Poland	English	40	ELISA	Serum
Shen et al ¹⁸	2009	People's Republic of China	English	63	PCR/Western blot	Tissue
Su et al ²³	2012	People's Republic of China	Chinese	69	Immunohistochemistry	Tissue
Zhang et al ¹⁵	2013	People's Republic of China	English	106	Immunohistochemistry	Tissue
Yang and Yang ²²	2013	People's Republic of China	Chinese	64	Immunohistochemistry	Tissue
Wang et al ¹⁴	2014	People's Republic of China	English	30	Immunohistochemistry/PCR/Western blot	Tissue
Yan et al ²⁴	2014	People's Republic of China	Chinese	30	PCR/Western blot	Tissue
Zhengsen et al ²⁰	2014	People's Republic of China	Chinese	30	ELISA	Serum
Jakubowska et al ¹³	2015	Poland	English	45	ELISA	Serum

Abbreviations: ELISA, enzyme-linked immunosorbent assay; NSCLC, non-small-cell lung cancer; PCR, polymerase chain reaction.

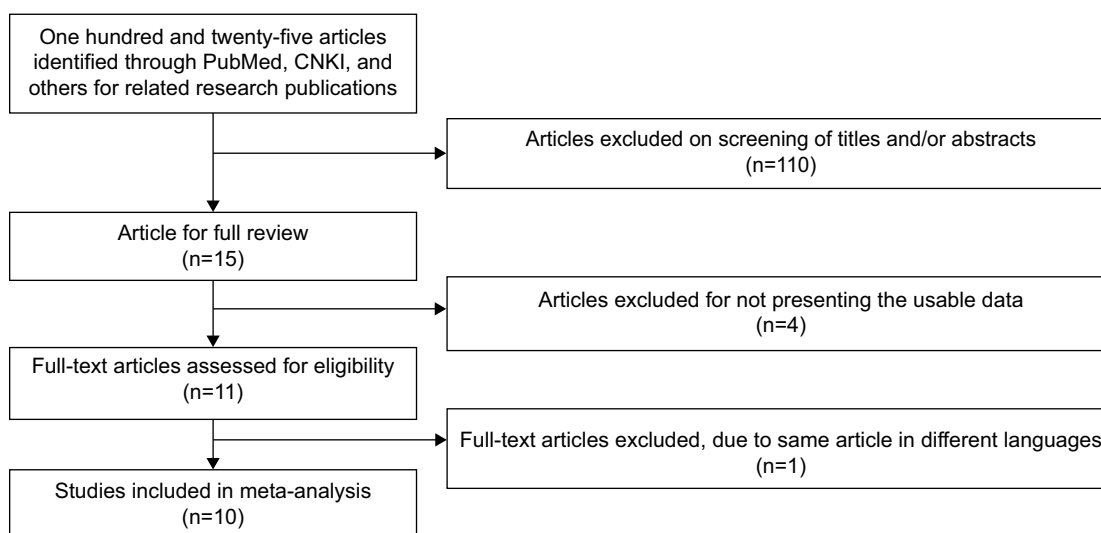


Figure 1 Flow diagram of the search and selection process of this study.

Abbreviation: CNKI, China National Knowledge Infrastructure.

As a late-acting proinflammatory cytokine, HMGB1 plays an important role in many crucial pathological processes including inflammation, cell migration, and tissue regeneration.^{26–28} Furthermore, HMGB1 may be actively involved in the development and evolution of malignant processes by promoting cell proliferation and migration, modulating the adhesive properties,²⁹ and stimulating tumor neoangiogenesis.^{30,31} Currently, some reports even suggest

that downregulation of HMGB1 may affect the progression of NSCLC,^{32,33} and interference with HMGB1 expression may increase the sensitivity to chemotherapy drugs by inhibiting HMGB1-mediated cell autophagy or cell apoptosis.^{34,35} In this regard, the rising degree of HMGB1 serum and tissue level can amplify the progression of lung cancer and may be closely associated with the severity of NSCLC and its development.

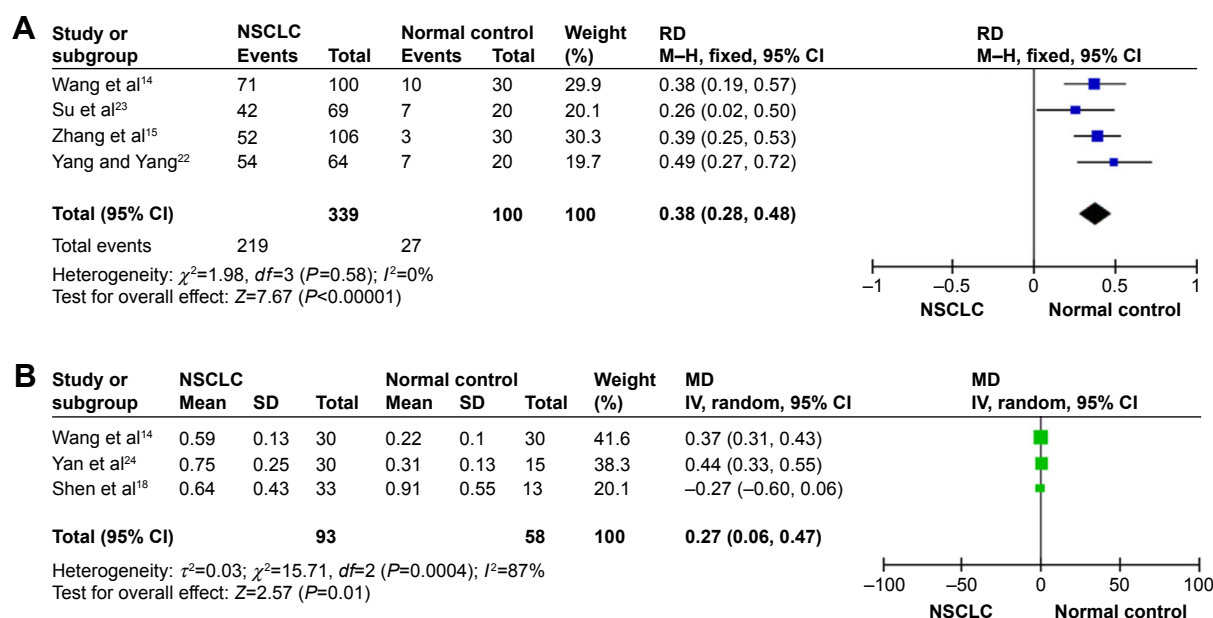


Figure 2 Forest plots for HMGB1 in tissue with NSCLC and normal controls detected by immunohistochemistry (A) and Western blot (B).

Abbreviations: CI, confidence interval; HMGB1, high-mobility group box 1; IV, inverse variance; MD, mean difference; M-H, Mantel-Haenszel; NSCLC, non-small-cell lung cancer; RD, risk difference; SD, standard deviation.

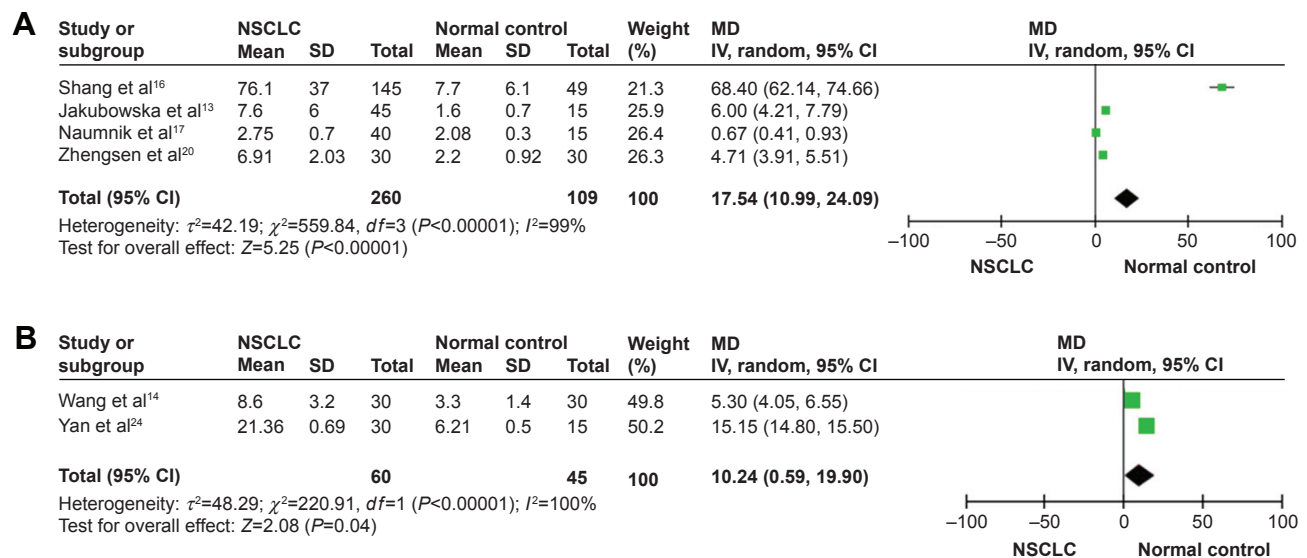


Figure 3 Forest plots for HMGB1 in serum with NSCLC and normal controls detected by ELISA (**A**) and for HMGB1 in tissue with NSCLC and normal controls detected by PCR (**B**).

Abbreviations: CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; HMGB1, high-mobility group box 1; IV, inverse variance; MD, mean difference; NSCLC, non-small-cell lung cancer; PCR, polymerase chain reaction; SD, standard deviation.

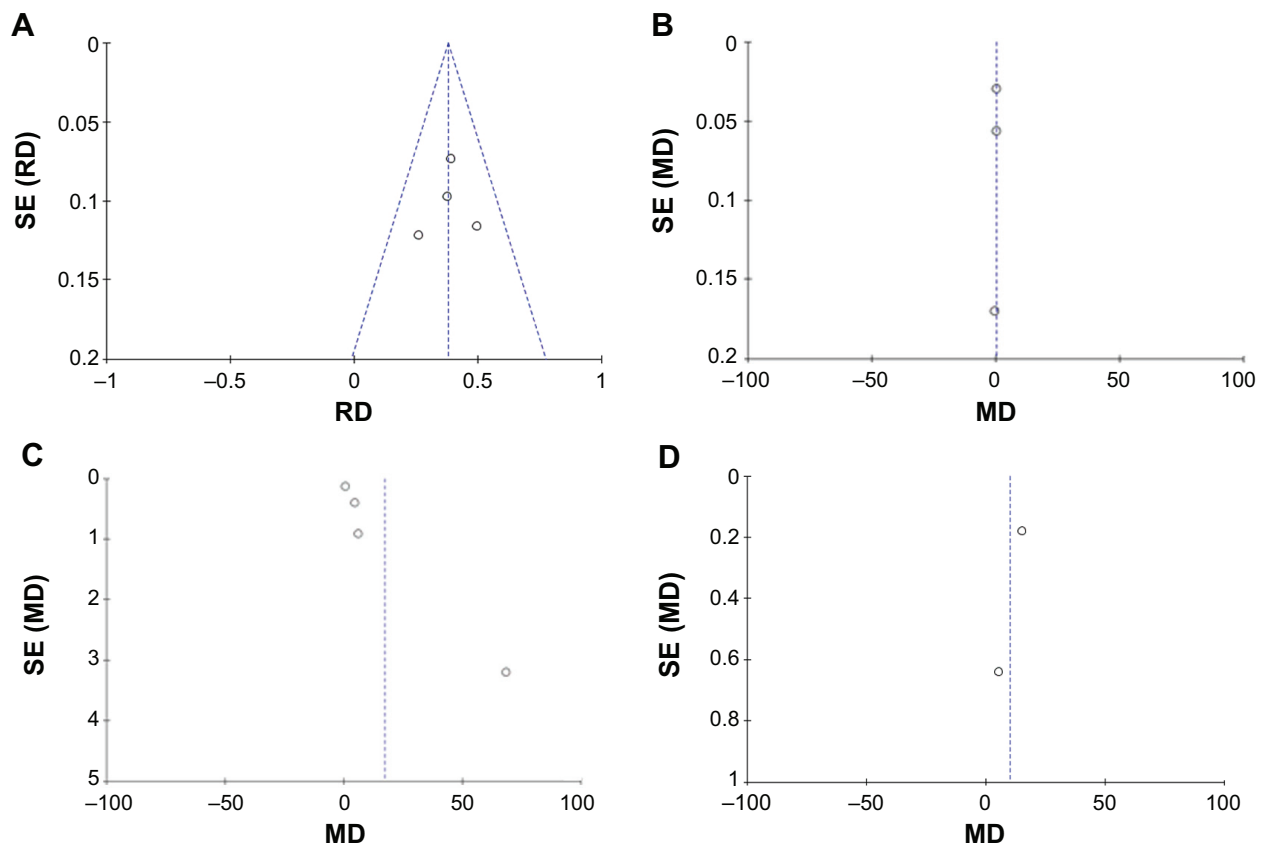


Figure 4 Funnel plots for publication bias.

Notes: HMGB1 in tissue with NSCLC and normal controls detected by immunohistochemistry (**A**) and Western blot (**B**). HMGB1 in serum with NSCLC and healthy controls detected by ELISA (**C**). HMGB1 in tissue with NSCLC and normal controls detected by RT-PCR (**D**).

Abbreviations: ELISA, enzyme-linked immunosorbent assay; HMGB1, high-mobility group box 1; MD, mean difference; NSCLC, non-small-cell lung cancer; RD, risk difference; RT-PCR, real-time polymerase chain reaction; SE, standard error.

To gather more evidence, a literature review about the association between HMGB1 expression and TNM stage was performed. Two studies reported that the protein levels of HMGB1 in patients with NSCLC were significantly different between TNM stages I–II and III–IV ($P < 0.01$ and $P < 0.0001$ respectively), and the elevated HMGB1 protein expression was detected in TNM stages III–IV of patients with NSCLC. This suggests that HMGB1 may play a pivotal role in the development and progression of NSCLC. In support of this, recent studies indicated that HMGB1 was co-localized with RAGE, which was closely associated with invasive and metastatic behavior, indicating their potential ability to promote cellular migration and cancer invasion.^{6,36} Furthermore, the interaction between HMGB1 and RAGE leads to activation of the NF- κ B, MAPK, and MMP-2/MMP-9 signaling pathways.^{12,37–39} What is important is that by blocking RAGE–HMGB1 complex in human and murine cancer cells, tumor growth and metastasis were suppressed.^{37,38} Based on the abovementioned evidence, it is suggested that HMGB1 is associated with the progression of NSCLC, besides acting as a diagnosis biomarker. However, due to the different detection methods used and lower statistical power, we did not calculate the pooled results, but we inferred that HMGB1 may act as an important mediator in the progression of NSCLC. Reports suggested that HMGB1 mainly elevated in patients with advanced NSCLC. Thus, the diagnosis value of HMGB1 is limited and HMGB1 may reveal changes in a biological pathway that correlated with disease progression, or even the risk of NSCLC progression.

On the other hand, some limitation in the current meta-analysis did exist that should be noted. First, although some reports had suggested that patients with higher level of HMGB1 expression had a poor clinical prognosis,^{6,40} Naumnik et al¹⁷ insisted that determination of HMGB1 concentrations has no clinical significance in the prognosis of survival time in patients with NSCLC. However, methodological assessment of these studies was not performed due to the different detection methods and lack of usable data, and more work needs to be performed in the future. Second, there is a potential publication bias in this study, since we did not take several unpublished articles and abstracts into account due to their unavailability. In addition, we picked up only eligible English or Chinese language studies in this meta-analysis, while other languages were excluded based on language criteria, which may also introduce bias and affect the findings in our study. A last potential limitation is that our meta-analysis is underpowered to acquire original data from the included studies. Despite all these mentioned limitations, to our knowledge, this is the first meta-analysis

on the association of serum and tissue HMGB1 levels with the development of NSCLC.

Conclusion

The expression levels of HMGB1 in both tissues and serum of patients with NSCLC were statistically higher than those of normal lung samples, which indicated that elevated levels of HMGB1 can reveal changes associated with disease progression, or even the risk of NSCLC disease progression. The early detection of HMGB1 may help clinicians to determine valuable therapeutic strategies for patients with NSCLC.

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Disclosure

The authors report no conflicts of interest in this work.

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