Prognostic and clinicopathological significance of nm23-H1 expression in non-small cell lung cancer
A meta-analysis

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Abstract
Background: The relationship between the expression of nm23-H1 and the invasion and prognosis of non-small cell lung cancer (NSCLC) is still controversial. Therefore, we conducted a meta-analysis to determine the prognostic value of nm23-H1 in patients with NSCLC. And to explore the relationship between the expression of nm23-H1 and clinicopathological features in patients with NSCLC.

Methods: Literature search in PubMed, EMBASE, Cochrane Library, CNKI, and WanFang database was performed up to June 14, 2021. Studies on the expression and clinical significance of nm23-H1 in NSCLC were included. According to the inclusion and exclusion criteria, 2 researchers independently screened the literatures, extracted the data, and evaluated the quality. Meta-analysis was performed using RevMan 5.4 software (Nordic Cochran Centre, Copenhagen, Denmark).

Results: Twenty-five studies met our inclusion criteria and were finally included for the analysis, involving 2198 participants. Our meta-analysis revealed that nm23-H1 expression was associated with tumor differentiation (OR = 0.54, 95% CI: 0.42–0.70, P < .00001), TNM stage (OR = 1.70, 95% CI: 1.23–2.34, P = .001), and lymph node status (OR = 0.26, 95% CI, 0.17–0.39, P < .00001), but have no associate with sex, age, pathological type, and T stages. Additionally, low nm23-H1 expression reduced the 3-year survival rate (OR = 2.74, 95% CI: 1.54–4.86, P = .0006) and 5-year survival rate (OR = 2.78, 95% CI: 1.36–5.69, P = .005).

Conclusion: Nm23-H1 can be used as a biomarker to predict tumor invasiveness and evaluate the prognosis of patients with NSCLC.

Abbreviations: IHC = immunohistochemistry, NOS = Newcastle–Ottawa quality assessment scale, NSCLC = non-small cell lung cancer, OS = overall survival, RT-PCR = reverse transcription-polymerase chain reaction.

Keywords: meta-analysis, nm23-H1, non-small cell lung cancer, prognosis

1. Introduction

Lung cancer is one of the most common malignant tumors in the world. In histopathology, lung cancer can be divided into small cell lung cancer and non-small cell lung cancer (NSCLC). NSCLC is the most common type of lung cancer, accounting for about 80%–85% of the total number of lung cancer patients.[1] As the early clinical symptoms of lung cancer are not obvious and the disease progresses rapidly, most of the patients are in the middle and late stage. Although great progress has been made in the treatment of NSCLC, the prognosis of patients is still poor, with a 5-year survival rate of only 15%.[2] Therefore, there is an urgent need to find reliable markers to predict the prognosis of NSCLC, so as to provide a basis for reasonable selection of individualized treatment. As the first metastasis suppressor protein of the 10 members of nm23 family, nm23-H1 has been found to be associated with the development and progression of various cancers.[3] Many clinical studies have revealed that reduced nm23-H1 expression is correlated with the prognosis and the metastatic potential of a variety of malignant tumors such as small cell lung cancer: A meta-analysis. Medicine 2022;101:39(e30815).
breast carcinoma, colon cancer, and liver cancer. Clinical studies on nm23-H1 expression in NSCLC have demonstrated conflicting results, however. Therefore, to clarify this question and explore its prognostic value, we performed this systematic review of the literature with meta-analysis.

2. Materials and Methods

2.1. Publication search

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The systematic literature search was performed through PubMed, EMBASE, Cochrane Library, CNKI, and WanFang database, covering all articles published up to June 2021. The following keywords were used to search articles: carcinoma, non-small-cell lung, non-small cell lung cancer, and nm23. References of the retrieved publications were also screened. The language was English or Chinese. Only published studies with full-text articles were included. When overlapping articles were found, we only included the publications that reported the most extensive information.

2.2. Study selection and inclusion criteria

2.2.1. Criteria for including studies. The expression of nm23-H1 in NSCLC was detected by immunohistochemistry (IHC); provide clinicopathological parameters or prognostic data, such as 3-year, 5-year overall survival (OS), etc.; literature is published in Chinese or English; and literature is original research.

2.2.2. Criteria for excluding studies. Review, case report, and repeat studies; literature with incomplete data and no access to original data; number of cases <30; study follow-up time for survival analysis <3 years; literature of reverse transcription-polymerase chain reaction and Western-blot detection.

2.3. Assessment of included studies

The Newcastle–Ottawa quality assessment scale of case control studies (NOS) was adopted to assess the quality of included studies, which has 3 categories (selection, comparability, and exposure) and 8 items. The quality assessment values ranged from 0 to 9 stars. Studies scored >5 stars were included for our analysis (Table 1).

Table 1

| Category            | Entries | Study |
|---------------------|---------|-------|
| Is the definition adequate | ☆☆☆☆☆☆☆☆☆☆ | ☆☆☆☆☆☆☆☆☆☆ |
| Section: Representativeness of the cases | ☆☆☆☆☆☆☆☆☆☆ | ☆☆☆☆☆☆☆☆☆☆ |
| Selection of controls | ☆☆☆☆☆☆☆☆☆☆ | ☆☆☆☆☆☆☆☆☆☆ |
| Definition of controls | ☆☆☆☆☆☆☆☆☆☆ | ☆☆☆☆☆☆☆☆☆☆ |
| Comparability: Comparability of cases and controls on the basis of the design and analysis | ☆☆☆☆☆☆☆☆☆☆ | ☆☆☆☆☆☆☆☆☆☆ |
| Ascertainment of exposure | ☆☆☆☆☆☆☆☆☆☆ | ☆☆☆☆☆☆☆☆☆☆ |
| Exposure: Same method of ascertainment for cases and controls | ☆☆☆☆☆☆☆☆☆☆ | ☆☆☆☆☆☆☆☆☆☆ |
| Non-response rate | ☆☆☆☆☆☆☆☆☆☆ | ☆☆☆☆☆☆☆☆☆☆ |
| Total scores | 8 6 8 6 6 7 7 8 7 8 6 7 7 7 8 7 8 7 8 7 7 7 |

Notes: In the selection category (adequate definition of the cases, representativeness of the cases, selection of controls, definition of controls) and exposure category (ascertainment of exposure, same method of ascertainment for cases and controls, non-response rate), a quality research item received 1 star, and a comparable category (comparability of cases and controls on the basis of the design or analysis) could receive at most 2 stars. HB Wang; CG Fan; SH Ma; WH Wang; LI Sun; Tao Wang; Rui Kang; YH Song; ZH Jiang; YF Zhang; LF Kong; XM Li; QY Chen; FY Du; YW Zhang; BL Li; XY Xue; CF Luz; Goncharuk VN; Gazzeri S; QL Liu; Lai WW; Wang Z; We M; Xie Y. NOS = Newcastle–Ottawa quality assessment scale.

2.4. Data extraction

Records retrieved from the initial search were independently scanned by 2 authors to exclude clearly irrelevant studies. Then, the full text articles were independently reviewed by 2 authors to see if they met the inclusion criteria. In case of disagreement, the decision is made through discussion or by referring to the opinion of the third researcher. All of the data were extracted independently by 2 authors. The primary data were clinicopathological indicators and OS. Additional data included first author, year of publication, number of patients, duration of follow-up, sample source, test method, clinical stage, histological type, and nm23-H1 positive criteria. The corresponding author of some study was contacted to provide information on missing or incomplete data if the report is unclear or information is lacking.

2.5. Statistical analysis

The software RevMan 5.4 (Nordic Cochrane Centre, Copenhagen, Denmark) was applied to analyze the data. Results were showed with odds ratios (OR) and 95% confidence intervals (95% CI) and meta-analysis forest map was drawn. Fixed-effects model was adopted when there was no evidence of significant heterogeneity (P > .1 and I² < 50%); otherwise, random-effects model was used. Sensitivity analysis was used to test the stability of the results and funnel plots were used to evaluate publication bias. If possible, heterogeneity was explored and subgroup analyses were performed. All P values were 2-sided, and P < .05 was considered significant.

3. Results

3.1. Literature search and study characteristics

The literature searches revealed 508 studies, of which 176 studies were excluded owing to duplication. After reading the titles, abstracts, and full-length texts, 307 studies were excluded. Finally, 25 studies were included in the quantitative analysis (Fig. 1). A total of 2198 patients with NSCLC were enrolled. Study quality was assessed using the NOS. The scores ranged from 6 to 8 (the average was 6.96), with higher numbers indicating better methods. Key baseline characteristics of patients were adequately described in all of the included studies (Table 2).
3.2. Nm23-h1 expression and sex
A total of 10 studies were included,[6,10,12,14,16–19,23,31] including 721 male patients, 446 patients with positive nm23-H1 expression, and 61.9% positive nm23-H1 expression rate. Among 323 female patients, 194 had positive expression of nm23-H1, and the positive expression rate of nm23-H1 was 60.1%. Meta-analysis results showed that $P = .40$, $I^2 = 4\%$, fixed effect model was used. OR = 1.12, 95% CI: 0.85–1.48, $P = .41$, prisms across the invalid line. It is not considered that there is a difference in the positive expression rate of nm23-H1 among patients with different genders (Fig. 2).

3.3. Nm23-h1 expression and age
The association between nm23-H1 and age was reported in 3 studies,[19,23,31] including 107 patients ≤60 years old and 112 patients >60 years old. Without heterogeneity ($P = .51, I^2 = 0\%$), a fixed-effects model showed that the positive expression rate of nm23-H1 could not be considered to be different among patients of different ages (OR = 1.18, 95% CI: 0.69–2.03, $P = .54$) (Fig. 3).

3.4. Nm23-H1 expression and t stage
A total of 3 studies were included, including 47 patients with T1 stage and 106 patients with T2–T4 stage.[6,12,18] Without heterogeneity ($P = .24, I^2 = 30\%$), a fixed-effects model showed that there was no difference in the positive expression rate of nm23-H1 between T1 and T2–T4 (OR = 0.82, 95% CI: 0.36–1.85, $P = .63$) (Fig. 4).

3.5. Nm23-H1 expression and histological type
The association between nm23-H1 and histological type was reported in 17 studies.[5,8,10–14,17–20,22,23,26,27,29,30] Of the 700 squamous cell carcinoma patients, 378 had positive expression of nm23-H1 and the positive expression rate of nm23-H1 was 54%. Among the 577 adenocarcinoma patients, 334 had positive expression of nm23-H1 and the positive expression rate of nm23-H1 was 57.9%. Without heterogeneity ($P = .16$, $I^2 = 25\%$), a fixed effect model showed that there was no difference in the positive expression rate of nm23-H1 between squamous cell carcinoma and adenocarcinoma (OR = 0.85, 95% CI: 0.68–1.08, $P = .18$) (Fig. 5).

3.6. Nm23-H1 expression and tissue differentiation
The association between nm23-H1 and tissue differentiation was reported in 15 studies,[6,12–14,17–19,21–23,25,26,28,29,31] including 357 patients with poor differentiation, 161 patients with positive expression of nm23-H1, and 45.1% positive expression rate of nm23-H1. A total of 1067 patients with moderate and well differentiation, 640 patients with positive expression of nm23-H1, the positive expression rate of nm23-H1 was 60.0%. Without heterogeneity ($P = .15$, $I^2 = 28\%$), a fixed effect model showed that the positive expression rate of nm23-H1 in the moderate and well differentiation group was higher than that in the poor differentiation group (OR = 0.54, 95% CI: 0.42–0.70, $P < .00001$) (Fig. 6).

3.7. Nm23-H1 expression and TNM stage
The association between nm23-H1 and TNM stage was reported in 11 studies,[6,12–14,19,21–23,26,27,29] including 107 patients with I–II stage, 106 patients with III stage, and 106 patients with IV stage. Without heterogeneity ($P = .24$, $I^2 = 30\%$), a fixed effects model showed that there was no difference in the positive expression rate of nm23-H1 between I–II and III (OR = 0.82, 95% CI: 0.36–1.85, $P = .63$) (Fig. 4).
### Table 2

Basic characteristics of included literature.

| Study      | n     | Sex (M/F) | Age      | Follow time (mo) | Sample source     | Detection methods | Source of antibody | Clinical stage | Tumor type | Nm23-H1 positive criteria | NOS score |
|------------|-------|-----------|----------|------------------|-------------------|-------------------|-------------------|----------------|------------|--------------------------|-----------|
| HB Wang[10] | 50    | 26/24     | 63.7     | NA               | Paraffin specimens | IHC               | NA                | I–II           | NSCLC A    | Brown                    | 8         |
| CG Pan[11]  | 90    | 48/42     | 54.3     | 60               | Paraffin specimens | IHC               | NA                | I–II           | NSCLC B    | >10%                     | 6         |
| SH Ma[12]   | 31    | 17/14     | 56.4     | NA               | Paraffin specimens | IHC               | NA                | I–IV           | NSCLC A    | >2                      | 8         |
| WH Wang[3]  | 65    | 50/15     | 46       | NA               | Paraffin specimens | IHC               | Zymed             | I–IV           | NSCLC B    | >25%                     | 6         |
| Li Sun[4]   | 90    | 67/23     | 54       | 36               | Paraffin specimens | IHC               | Zymed             | I–IV           | NSCLC B    | >30%                     | 6         |
| Tao Wang[5] | 34    | 24/10     | NA       | NA               | Paraffin specimens | IHC               | Wuhan Doctoral Ethics | I–IV           | NSCLC A    | 0                       | 6         |
| Ru Kang[6]  | 58    | 37/21     | NA       | NA               | Paraffin specimens | IHC               | Zymed             | NA             | NSCLC A    | 0                       | 7         |
| YH Song[7]  | 84    | 56/28     | 53       | 36               | Paraffin specimens | IHC               | Fuzhou Wallace new | I–III          | NSCLC A    | >2                      | 7         |
| Jiang[8]    | 60    | 39/21     | 52.5     | NA               | Paraffin specimens | IHC               | Nakasi Jinqiao, Beijing | I–III          | NSCLC B    | >10%                     | 8         |
| YF Zhang[9] | 52    | 38/14     | 52       | NA               | Paraffin specimens | IHC               | Nakasi Jinqiao, Beijing | I–IV           | NSCLC A    | ≥2                      | 7         |
| LF Kong[10] | 84    | 72/12     | 56.7     | NA               | Paraffin specimens | IHC               | Santa Cruz        | NA             | NSCLC B    | >25%                     | 6         |
| XM Li[11]   | 42    | 29/13     | 63.5     | NA               | Paraffin specimens | IHC               | Fuzhou Wallace new | I–IV           | NSCLC B    | >5%                      | 7         |
| GY Chen[12] | 65    | 50/15     | 46       | NA               | Paraffin specimens | IHC               | Zymed             | NA             | NSCLC B    | >25%                     | 7         |
| YM Du[13]   | 123   | 88/35     | 58.5     | NA               | Paraffin specimens | IHC               | NA                | I–IV           | NSCLC B    | >30%                     | 6         |
| YW Zhang[14]| 112   | 68/44     | 61.2     | Unclear          | NA               | IHC               | NA                | I–III          | NSCLC B    | >20%                     | 7         |
| Bo Liu[15]  | 108   | 83/25     | 50.1     | 40.8             | Paraffin specimens | IHC               | Fuzhou Wallace new | NA             | NSCLC A    | ≥2                      | 7         |
| XY Xue[16]  | 97    | 66/31     | 57.7     | NA               | Paraffin specimens | IHC               | Epitomics          | NA             | NSCLC B    | ≥25%                     | 7         |
| CF Lu[17]   | 40    | NA        | NA       | NA               | Paraffin specimens | IHC               | Santa Cruz        | I–IV           | NSCLC A    | Brown                    | 7         |
| Goncharuk VN[18] | 104 | 77/27     | 65       | 52               | Paraffin specimens | IHC               | Santa Cruz        | I–IV           | NSCLC A    | ≥2                      | 8         |
| Gazzotti S[19] | 62   | NA        | NA       | Unclear          | Paraffin specimens | IHC               | PA, US            | I–IV           | NSCLC A    | ≥2                      | 8         |
| Liu[20]     | 452   | 312/140   | NA       | >60              | Paraffin specimens | IHC               | Laboratory, UK    | I              | NSCLC A    | ≥20%                     | 8         |
| Lai WW[21]  | 38    | 25/7      | 61.5     | 35               | Paraffin specimens | IHC               | Oncogene Science, US | I              | NSCLC B    | >10%                     | 7         |
| Wang Z[22]  | 147   | 103/44    | 55.1     | 36–60            | Paraffin specimens | IHC               | Santa Cruz        | I–IV           | NSCLC B    | >10%                     | 7         |
| Wei M[23]   | 60    | 40/20     | 59       | 60               | Paraffin specimens | IHC               | Nakasi Jinqiao, Beijing | NA             | NSCLC A    | ≥2                      | 7         |
| Xie Y[24]   | 50    | 47/3      | NA       | 61               | Paraffin specimens | IHC               | Nakasi Jinqiao, Beijing | I–III          | NSCLC B    | Brown                    | 7         |

Notes: IHC Score = A/B (positively stained nm23-H1, mainly located in the plasma membrane and cytoplasm, exhibiting a yellowish or brown color). Under a high-magnification field, each slide of the specimen was examined individually by 3 pathologists and graded according to varying staining states in the plasma membrane and the cytoplasm. Unstained, weakly stained, moderately stained, and deeply stained specimens were given 0, 1, 2, and 3 points, respectively, designated as score A. Ratios of stained cell numbers to unstained cell numbers: when <5%, between 6% and 25%, between 26% and 50%, or >51% received 0, 1, 2, or 3 points, respectively, designated as score B.

IHC = immunohistochemistry; NSCLC = non-small cell lung cancer; NOS = Newcastle–Ottawa quality assessment scale.

*A total of 104 cases, 62 cases of NSCLC.

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**Figure 2.** nm23-H1 expression and sex.

**Figure 3.** nm23-H1 expression and age.
502 cases of patients, 307 cases of patients with positive expression, and nm23-H1 positive expression rate of 61.2%. III–IV stage, 310 cases of patients, 159 cases of patients with positive expression of nm23-H1 positive expression rate of 51.3%. Without heterogeneity ($P = .25$, $I^2 = 20\%$), a fixed-effect model was used, and the results of our meta-analysis showed statistically significant differences ($OR = 1.70$, 95% CI: 1.23–2.34, $P = .001$). Nm23-H1 in I–II stage patients with positive expression rate is higher than III–IV stage patients (Fig. 7).
3.8. nm23-H1 expression and lymph node metastasis

The association between nm23-H1 and lymph node metastasis was reported in 21 studies,[5,8,10–23,25–27,29,31] including 745 patients in the lymph node metastasis group, 286 had positive nm23-H1 expression, and the positive nm23-H1 expression rate was 38.4%. Among 788 patients in the non-lymph node metastatic group, 532 patients had positive expression of nm23-H1, and the positive expression rate of nm23-H1 was 67.5%. With significant heterogeneity ($P < .00001$, $I^2 = 67\%$), a random-effects model showed that the positive expression rate of nm23-H1 in non-lymph node metastasis group was higher than that in lymph node metastasis group (OR = 0.26, 95% CI: 0.17–0.39, $P < .00001$) (Fig. 8).

3.9. nm23-H1 expression and 3-year OS

Three studies reported the relationship between nm23-H1 expression and 3-year OS,[14,28,29] including 125 cases nm23-H1 positive expression group, 78 cases survived at 3 years, and the 3-year OS rate was 62.4%. In the nm23-H1 negative expression group, there were 103 cases, 44 cases survived at 3 years, and the 3-year OS rate was 42.7%. Without heterogeneity ($P = .53$, $I^2 = 0\%$), a fixed-effect model was used. The results of our meta-analysis showed a significant difference (OR = 2.74, 95% CI: 1.54–4.86, $P = .0006$). It can be concluded that the 3-year OS of the positive nm23-H1 expression group was higher than that of the negative expression group (Fig. 9).

3.10. nm23-H1 expression and 5-year OS

Four studies reported the relationship between nm23-H1 expression and 5-year OS,[6,24,27,30] including 484 cases nm23-H1 positive expression group, 347 cases survived at 5 years, and the 5-year OS rate was 71.7%. In the nm23-H1 negative expression group, there were 240 cases, 122 cases survived at 5 years, and the 5-year OS rate was 50.8%. With positive expression group, 78 cases survived at 3 years, and the 3-year OS rate was 62.4%. In the nm23-H1 negative expression group, there were 103 cases, 44 cases survived at 3 years, and the 3-year OS rate was 42.7%. Without heterogeneity ($P = .53$, $I^2 = 0\%$), a fixed-effect model was used. The results of our meta-analysis showed a significant difference (OR = 2.74, 95% CI: 1.54–4.86, $P = .0006$). It can be concluded that the 3-year OS of the positive nm23-H1 expression group was higher than that of the negative expression group (Fig. 9).

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significant heterogeneity \((P = .03, I^2 = 68\%)\), a random-effect model was used. The results of our meta-analysis showed a significant difference \((OR = 2.78, 95\% CI: 1.36–5.69, P = .005)\). It can be concluded that the 5-year OS of the positive nm23-H1 expression group was higher than that of the negative expression group (Fig.10).

### 3.11. Subgroup results

We found that there was significant heterogeneity in the expression of nm23-H1 in lymph node metastasis group and 5-year OS group \((P < .00001, I^2 = 67\%; P = .03, I^2 = 68\%)\). In subgroup analysis, studies were analyzed by race, antibody source, and IHC scoring method. The results showed that race, antibody source, and IHC scoring method could not fully explain the source of heterogeneity (Table 3, 4).

### 3.12. Sensitivity analysis and publication bias

Sensitivity analyses, in which 1 study is removed at a time, were performed for each meta-analysis to evaluate the stability of the results. These analyses showed that the corresponding OR value was not significantly altered and suggested that our results are stable. In addition, in the overall topic of the relationship between nm23-H1 expression and 5-year OS, we found that Wei study was the main source of heterogeneity. The heterogeneity was significantly reduced when this study was excluded \((P = .21, I^2 = 36\%)\). Finally, funnel plots were used to judge the deviation degree of literature publication, and funnel plots did not show any obvious evidence of asymmetry (Fig. 11).

### 4. Discussion

Cancer is one of the major threats to human health. Lung cancer is the leading cause of death of cancer, of which NSCLC accounts for 80%–85% of all lung cancer.\[1\] In recent years, although major breakthroughs have been made in the treatment of lung cancer, the prognosis of NSCLC patients is still very poor, with a 5-year survival rate of only 15%.\[2\] Therefore, it is particularly important to find a biomarker that can be used to evaluate the prognosis of NSCLC, which will help to develop a better treatment strategy for high-risk patients at an early stage.
Nm23-H1 is a metastasis-suppressant gene whose inactivation can affect microtubule polymerization, leading to chromosomal aberrations and aneuploidy formation, thereby promoting tumor metastasis.\(^{[32]}\) Nm23-H1 can inhibit tumor metastasis and tumor progression in a variety of human tumors, but its role in NSCLC remains controversial. Some studies have reported that the expression of nm23-H1 in NSCLC is related to tumor progression, is an indicator of tumor development, and is positively correlated with the prognosis of patients.\(^{[13,14]}\) However, Engel et al.\(^{[7]}\) believed that the expression of nm23-H1 was negatively correlated with the prognosis of patients. Lai et al.\(^{[28]}\) study found that the expression of nm23-H1 is closely related to the invasive metastatic ability of lung cancer cells. The result of Gazzeri research is the opposite.\(^{[8]}\) Therefore, to clarify this question and explore its prognostic value, we performed this systematic review of the literature with meta-analysis.

Our meta-analysis showed that the positive expression rate of nm23-H1 in middle and high differentiation group was higher than that in poor differentiated group, the positive expression rate of nm23-H1 in stage I–II was higher than that in stage III–IV, the positive expression rate of nm23-H1 in non-lymph node metastasis group was higher than that in lymph node metastasis group, and the low expression of nm23-H1 was significantly correlated with poor 3- and 5-year survival rate. These results suggest that negative expression of Nm23-H1 is a poor prognostic factor for NSCLC, and the expression of Nm23-H1 is correlated with the progression of NSCLC. However, there was no statistically significant difference in nm23-H1 positive expression rates among different gender, age, pathological type, and T stage.

A total of 25 trials were included in this meta-analysis, and all of them were of high quality with NOS scores above 5. Heterogeneity assessment showed that the heterogeneity among the outcome indicators was small, with obvious heterogeneity only among the lymph node metastasis group and 5-year survival rate. Subgroup analysis and sensitivity analysis revealed that the study of Wei was a major source of heterogeneity in the 5-year survival study. Careful analysis speculated that the possible reasons were related to the higher nm23-H1 positive criteria and fewer included cases compared with the other 3 studies. When this study was excluded, the heterogeneity was significantly reduced (\(P = .21, I^2 = 36\%\)). The results of sensitivity analysis showed that the results of each meta-analysis were stable, and the publication bias of funnel diagram was small.

Although the present study showed that the expression of nm23-H1 was closely related to the progression and prognosis of NSCLC, it also had its own limitations. The analysis was as follows: a total of 2198 patients with NSCLC were included in 25 studies, but not every meta-analysis had a large enough sample size. For some results (e.g., T-stage, 3-year OS), the sample size is relatively small. Therefore, more clinical studies are needed to confirm our conclusions in the future. In this study, the expression of nm23-H1 is based on IHC staining data. Therefore, the selection of the first antibody and the dilution used may lead to inconsistency in nm23-H1 detection. Different criteria for nm23-H1 positivity included in the study led to heterogeneity among studies.

In summary, despite the above deficiencies, this study showed that the expression of nm23-H1 was associated with tissue differentiation, TNM stage and lymph node metastasis of NSCLC through meta-analysis, and the 3- and 5-year survival rates of patients with negative expression of nm23-H1 were poor. It is suggested that nm23-H1 can be used as a biomarker to predict tumor invasiveness and evaluate the prognosis of patients with NSCLC.

**Author contributions**

**Conceptualization:** Cheng Tian, Dailong Li, Xinhua Xu, Yaqi Pang, Yuke Wang.

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**Investigation:** Dailong Li.

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**Software:** Cheng Tian, Dailong Li, Wanqiang Li, Yaqi Pang.

**Visualization:** Dailong Li.

**Writing – original draft:** Dailong Li.

**Writing – review & editing:** Dailong Li, Wanqiang Li, Yuke Wang.
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