

Low expression of nm23-H1 associates with poor survival of nasopharyngeal carcinoma patients

A prisma-compliant meta-analysis

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Abstract

Background: Developing a new reliable prognostic marker to predict the prognosis and supply better and more suitable therapy for patients with nasopharyngeal carcinoma (NPC) is urgent. Therefore, we performed this systematic review of the literature with meta-analysis to clarify and explore the associate expression of nm23-H1 with prognosis of NPC patients.

Methods: Literature research in Cochrane Library, PubMed, and EMBASE was performed up to July 2016. Eligible case-control studies of associate expression of nm23-H1 with prognosis of NPC patients were included.

Results: Nine studies met our inclusion criteria and were finally included for the analysis, involving 861 participants. Our meta-analysis revealed that the low expression of nm23-H1 in NPC was: RR=2.13, 95% CI 1.15–3.95 and R=2.56, 95% CI 2.03–3.22; and poorer overall survival (OS) rate was 3-year OS rate: RR: 0.55; 95% CI: 0.45–0.67 and 5-year OS rate: RR: 0.60; 95% CI: 0.52–0.69. Furthermore, the statistical significance was constant irrespective of different NPC subtypes.

Conclusion: The low expression of nm23-H1 is associated with poorer prognosis in patients with NPC, suggesting that it is a prognostic factor and potential biomarker for survival in NPC.

Abbreviations: CI = confidence interval, HNSCC = head and neck squamous cell carcinoma, NKC = nonkeratinizing carcinomas, NOS = Newcastle–Ottawa Scale, NPC = nasopharyngeal carcinoma, OS = overall survival, RR = relative risk, SCC = squamous carcinoma, UC = undifferentiated carcinoma.

Keywords: meta-analysis, nasopharyngeal carcinoma, nm23-H1

1. Introduction

Nasopharyngeal carcinoma (NPC) is an endemic malignancy in southern China, Hong Kong, Taiwan and Singapore where there is a strong genetic predisposition.^[1,2] The mainstay of treatment

for NPC is either radiotherapy or combined chemoradiotherapy, which demonstrates a cure rate of over 90% in early-stage patients.^[3] However, the 5-year survival rate is only 40% to 50% even with the advanced radiotherapy technique and combined chemotherapy.^[4,5] Besides, patients at the same status, for instance tumor differentiation, lymph node metastases, and TNM stage, may have diverse clinical outcomes. Therefore, we need to develop a new reliable prognostic marker to predict the prognosis and supply better and more suitable therapy for patients with NPC.

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.^[6–8] Recently, a research by Wang et al^[9] confirmed the low expression of nm23-H1 in head and neck squamous cell carcinoma (HNSCC) to be correlated with poor patients' prognosis. In addition, nm23-H1 also plays a critical role in prognosis of patients with NPC, and the in vitro experiment found nm23-H1 expression correlated with the cellular and tumor radioresponse.^[10] However, clinical studies on nm23-H1 expression in NPC did not draw a consistent conclusion. Most researches suggested that the low expression of nm23-H1 was associated with poorer survival in patients with NPC, while certain studies^[11,12] showed no significant difference. Furthermore, none of these reports have been confirmed by systematic reviews with meta-analysis. Therefore, to clarify this question and explore its prognostic value, we performed this systematic review of the literature with meta-analysis.

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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, and Cochran Library, covering all articles published up to July 2016. The following keywords were used to retrieve articles: nasopharyngeal carcinoma, nasopharyngeal neoplasms, 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

In our meta-analysis, the inclusion criteria for the studies were as follows: evaluating the association between nm23-H1 expression and prognosis of patients with NPC; and reporting endpoints including tumor local recurrence, distant metastasis, or overall survival (OS) displaying outcomes in the form of relative risk (RR) with 95% confidence interval (CI).

2.3. Evaluation of study quality

The levels of evidence were estimated for all included studies with the Oxford Centre for Evidence-Based Medicine criteria, and the methodological quality evaluation of the studies was conducted using the Newcastle–Ottawa Scale for the cohort study. The specific quality assessment of prognosis studies was estimated according to the approach of Hayden et al.^[13] The assessments were processed independently by 2 reviewers (CY and LX) and the final decision was achieved by consensus.

2.4. Data extraction

Articles were independently reviewed by 2 investigators (CY and LX) for data extraction. Any discrepancy was discussed further to reach a consensus. The data were independently extracted from eligible studies by 2 investigators (CY and LX). The primary data were survival outcomes of OS. The additional data obtained from the studies included first author, publication year, number of patients, patients' mean age, median follow-up time, TNM stage, histological classification, sampling time, sampling site, and test method.

2.5. Statistical analysis

In order to pool the various outcomes included studies, firstly, heterogeneity was assessed using the Q and I^2 statistics. Significant heterogeneity was defined as Q statistic P value $<.10$ or I^2 value $>50\%$. A fixed-effect model was used if there was no evidence of heterogeneity, otherwise, a random-effect model was performed. Results were reported as pooled as RR and their 95% CI and presented by forest plots, and the P value less than $.05$ was considered significant. Publication bias was evaluated through funnel plots. All analyses were performed using STATA 13.0 (Stata Corporation, College Station, TX) and Review Manager (version 5.3, the Cochran collaboration), using 2-sided P values.

3. Results

3.1. Study characteristics

The detailed information of included studies is summarized in Table 1. Nine studies^[11,12,14–20] met our inclusion criteria and were finally included for the analysis, involving 3 different subtypes (squamous carcinoma (SCC), nonkeratinizing carcinomas (NKC), and undifferentiated carcinoma). A total of 861 participants were analyzed for the association between nm23-H1 expression and disease prognosis, of which 416 (53.54%) and 861 (100.00%) ones were respectively included into 3-year OS and 5-year OS analyses.

According to the guidelines for assessing quality in prognostic studies, the evaluation results of each item with potential bias are in Table 2. The key baseline characteristics of patients were adequately presented and the adopted statistical analyses were appropriate in all included studies.

3.2. Tumor local recurrence and distant metastasis

A total of 4 studies reported the relationship between nm23-H1 expression and tumor recurrence, and 6 reflected distant metastasis of NPC. Notably, our meta-analysis revealed that the low expression of nm23-H1 in NPC was significantly associated with a high local recurrence and distant metastasis (RR=2.13, 95% CI 1.15–3.95, Fig. 1; RR=2.56, 95% CI 2.03–3.22, Fig. 2).

3.3. Survival outcome

In all, 9 studies included data on OS in 3 types of cancer. Homogeneity tests showed evidence of nonsignificant heterogeneity among studies in all the OS analyses. The low expression of

Table 1

Characteristics of published studies included in this meta-analysis.

Study	Year	No. of patients	Median age, years	Median follow-up time, months	Sampling site	Sampling time	Method	Stage	WHO histologic classification	Survival outcomes
Cao et al ^[14]	2012	127	45	60	Tissue	Pre	IHC	III–IVa	NPC	5-year OS
Guo et al ^[15]	1998	153	NR	60	Tissue	Pre	IHC	I–IV	NKC	3-year OS; 5-year OS
He and Zhang ^[16]	2006	80	49	NR	Tissue	Pre	IHC	NA	NKC	5-year OS
Jiang et al ^[17]	2006	108	48.2	NR	Tissue	Pre	IHC	I–IV	SCC	3-year OS; 5-year OS
Kim et al ^[11]	2011	38	48	30	Tissue	Pre	IHC	I–IV	SCC; UC	5-year OS
Li et al ^[18]	2012	93	NR	48	Tissue	Pre	IHC	I–IV	NKC	3-year OS; 5-year OS
Wang et al ^[19]	2006	62	48	NR	Tissue	Pre	IHC	I–IV	SCC; UC	3-year OS; 5-year OS
Zhang et al ^[20]	2001	75	46	NR	Tissue	Pre	IHC	NA	SCC; UC	5-year OS
Zhou et al ^[12]	1998	125	43	NR	Tissue	Pre	IHC	NA	SCC; NKC	5-year OS

IHC=immunohistochemistry, NKC=nonkeratinizing carcinomas, NPC=nasopharyngeal carcinoma, NR=not reference, OS=overall survival, SCC=squamous carcinoma, UC=undifferentiated Carcinoma.

Table 2

Quality assessment of the studies included in the meta-analysis.

Study	Quality evaluation of prognosis study						Study quality	Level of evidence
	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Confounding measurement and account	Analysis		
Cao et al ^[14]	Yes	Yes	Yes	Partly	Partly	Yes	6	1b
Guo et al ^[15]	Yes	Yes	Yes	Yes	Partly	Yes	7	1b
He and Zhang ^[16]	Yes	Yes	Yes	Partly	Partly	Yes	7	1b
Jiang et al ^[17]	Yes	Yes	Yes	Yes	Partly	Yes	6	1b
Kim et al ^[11]	Yes	Yes	Yes	Partly	Partly	Yes	7	1b
Li et al ^[18]	Yes	Yes	Yes	Yes	Partly	Yes	6	1b
Wang et al ^[19]	Yes	Yes	Yes	Yes	Partly	Yes	6	1b
Zhang et al ^[20]	Yes	Yes	Yes	Partly	Partly	Yes	7	1b
Zhou et al ^[12]	Yes	Yes	Yes	Partly	Partly	Yes	6	1b

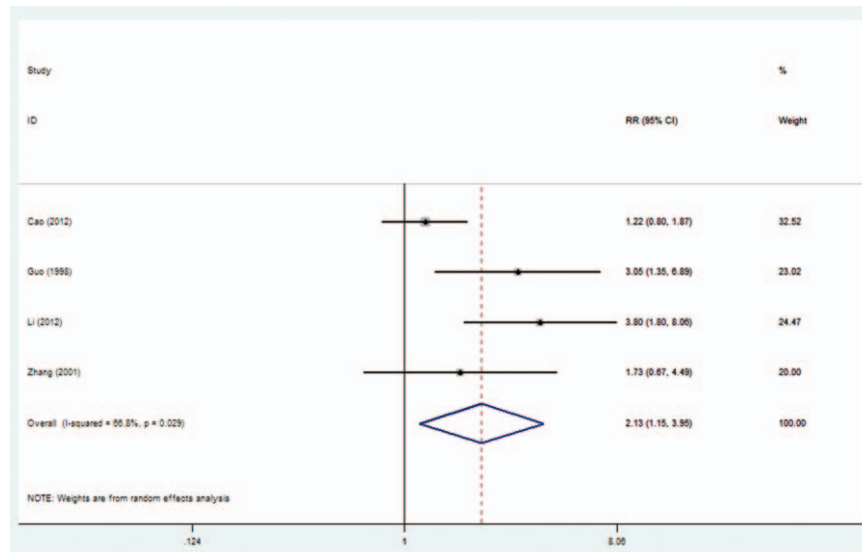


Figure 1. Forest plot evaluating the association of nm23-H1 expression and local recurrence in NPC patients. NPC = nasopharyngeal carcinoma.

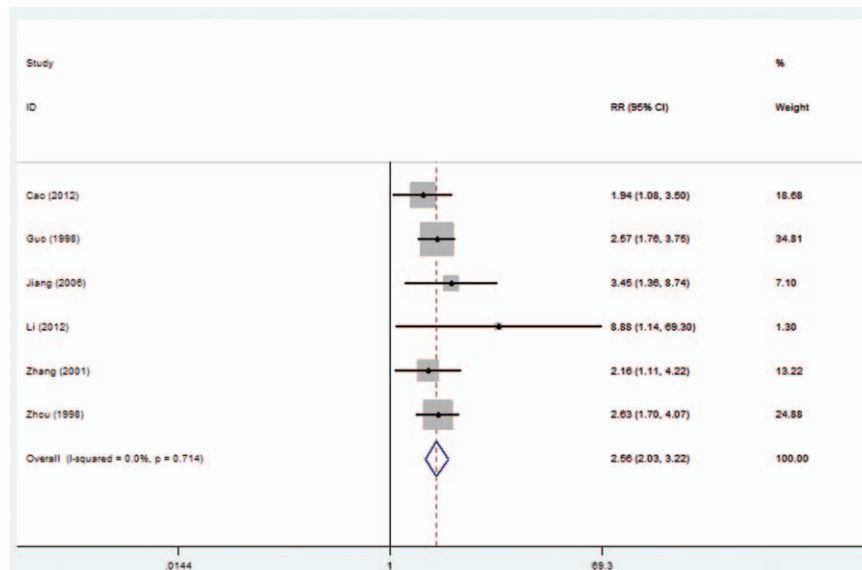


Figure 2. Forest plot evaluating the association of nm23-H1 expression and distant metastasis in NPC patients. NPC = nasopharyngeal carcinoma.

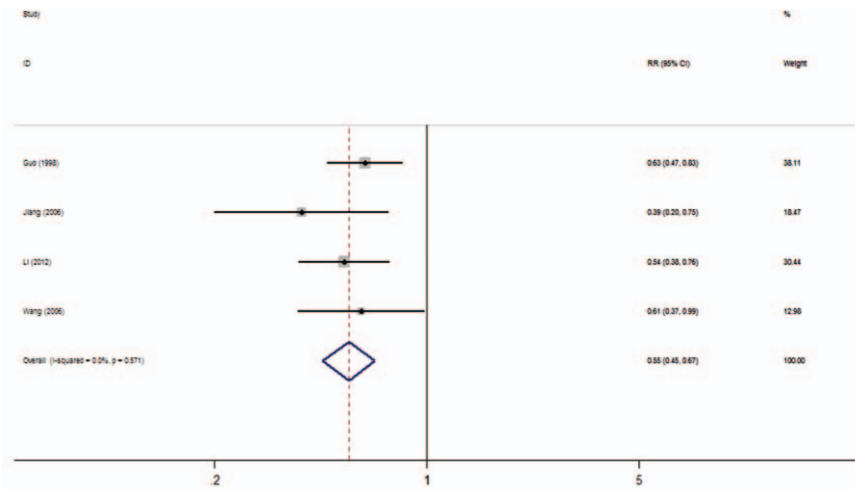


Figure 3. Forest plot evaluating the association of nm23-H1 expression and 3-year OS rate in NPC patients. NPC = nasopharyngeal carcinoma, OS = overall survival.

nm23-H1 was significantly associated with a poorer OS in patients with NPC (3-year OS rate: RR: 0.55; 95% CI: 0.45–0.67, Fig. 3 and 5-year OS rate: RR: 0.60; 95% CI: 0.52–0.69, Fig. 4). Furthermore, the statistical significance was constant irrespective of different NPC subtypes containing NKC (3-year OS rate: RR: 0.25, 95% CI: 0.14–0.44 and 5-year OS rate: RR: 0.23, 95% CI: 0.14–0.38) and SCC (3-year OS rate: RR: 0.26, 95% CI: 0.11–0.63 and 5-year OS rate: RR: 0.26, 95% CI: 0.11–0.63).

3.4. Sensitivity analysis

Sensitivity analysis was performed to estimate individual study’s influence on the pooled RR, and the result of sensitivity analysis showed no other single study influenced the summary RR qualitatively, suggesting stability of the meta-analyses.

3.5. Heterogeneity and publication bias

There was no evidence of heterogeneity in all survival outcomes in the χ^2 and I^2 tests, and a fixed effect model was carried out. The funnel plot was performed to assess the publication bias in all the included studies for evaluation of the OS. As shown in Fig. 5, the funnel plot did not reveal any evidence of significant asymmetry.

4. Discussion

There has been a growing interest in evaluating prognostic markers for patients diagnosed with NPC, which might help conduct clinical therapies with regard to outcomes. In the present meta-analysis, 9 eligible studies including 861 cases were analyzed. The results indicated that the low expression of nm23-H1 was significantly associated with a poorer 3-year and 5-year OS rate and higher local recurrence and distant metastasis

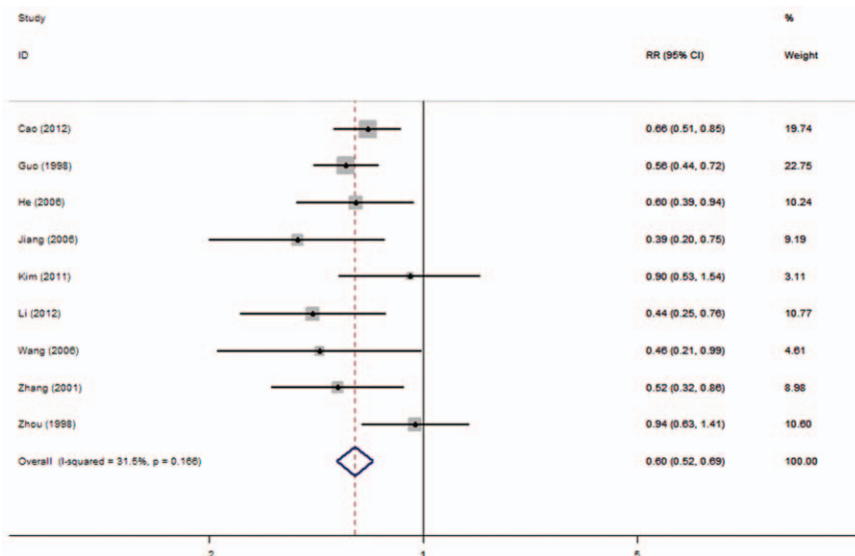


Figure 4. Forest plot evaluating the association of nm23-H1 expression and 5-year OS rate in NPC patients. NPC = nasopharyngeal carcinoma, OS = overall survival.

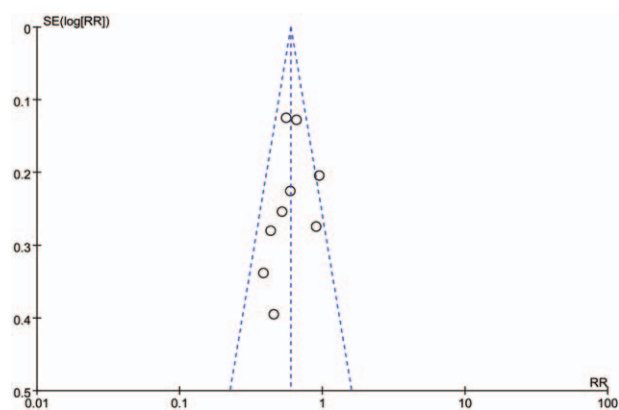


Figure 5. The funnel plot of publication bias.

in patients with NPC. Furthermore, the statistical significance was constant irrespective of different NPC subtypes containing NKC and SCC.

The reason that the low expression of nm23-H1 is potent to be the prognostic marker might be due to its implication in NPC treatment failure by disturbing the normal patterns of the nasopharyngeal cells. The overexpression of nm23-H1 correlated with the cellular and tumor radioresponse, and the mechanisms is the nm23-H1 protein involved in the regulation of intracellular functions, including stress responses, cell proliferation, and DNA repair. The overexpression of nm23-H1 also correlated with favorable response to chemotherapy in various cancers,^[21–23] and the low expression of nm23-H1 attenuated the chemosensitivity of cancer cells to cisplatin, which was associated with reduced cisplatin-induced S-phase accumulation.^[9]

Furthermore, downregulated nm23-H1 plays a role in tumor metastasis. Hartsough's study has revealed that the expression level of nm23-H1 is negatively correlated with the metastatic potential of certain human tumors.^[24] Nm23-H1 strongly inhibited the metastasis in nude mice and inhibited the epidermal growth factor-induced cell migration in vitro, which may relate to the regulation of the myosin light-chain phosphorylation.^[25] Decreased nm23-H1 expression by small interfering RNA significantly increased in vitro invasive ability of NPC cell line. The results further supported that nm23-H1 behaves as a metastasis suppressor in human NPC. It is worth noting that the above conclusions are controversial for certain tumors. The overexpression of nm23-H1 might even facilitate disease progression and poor prognosis in colonic neoplasms, gastric carcinoma, T-cell lymphoma, etc.^[26–29]

However, the limitations of this study cannot be ignored. Firstly, variation in definitions of clinical outcomes, measurements, and experimental procedures might contribute to between-study heterogeneity. Secondly, the 9 trials included in the meta-analysis were mainly concentrated in the Asian population, and this may be related to the high incidence of NPC in southern China, Hong Kong, Taiwan, and Singapore. Thirdly, there was limited information regarding some patients, and the total sample sizes were small.

In summary, the low expression of nm23-H1 is associated with poorer prognosis patients with various subtypes of NPC, suggesting that it is a prognostic factor and a potential biomarker for survival in NPC.

4.1. Ethical review

Ethical approval was not necessary, because this article is a meta-analysis and it does not involve the participation of ethics committee.

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