Prognostic and clinicopathological value of Ki-67 expression in patients with nasopharyngeal carcinoma: a meta-analysis

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Abstract

Background: This meta-analysis aimed to identify the prognostic role of Ki-67 in patients with nasopharyngeal carcinoma (NPC).

Methods: Relevant studies were retrieved in the PubMed, Embase, Web of Science, and Cochrane Library databases up to November 2019. The pooled hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to estimate the association between Ki-67 expression and survival outcomes. Combined odds ratios (ORs) and 95% CIs were measured as effect size on the association between Ki-67 expression and clinical factors.

Results: A total of eight studies involving 936 patients with NPC were included in this meta-analysis. The pooled HR indicated that Ki-67 expression was significantly associated with poor overall survival (HR = 2.86, 95% CI = 1.91–4.27, $p < 0.001$), progression-free survival (HR = 1.78, 95% CI = 1.15–2.74, $p = 0.009$), and distant metastasis-free survival (HR = 1.65, 95% CI = 1.15–2.36, $p = 0.007$). However, there was no significant correlation between Ki-67 expression and local recurrence-free survival (HR = 1.07, 95% CI = 0.54–2.14, $p = 0.843$). Ki-67 overexpression was associated with higher T stage (OR = 1.48, 95% CI = 1.00–2.20, $p = 0.052$), and the relationship between Ki-67 expression and advanced stage was nearly significant (OR = 2.25, 95% CI = 0.99–5.14, $p = 0.054$). However, high Ki-67 expression was not significantly correlated with sex, age, N stage, or histological type.

Conclusion: This meta-analysis demonstrated that Ki-67 overexpression was a significant marker for poor prognosis in patients with NPC. Ki-67 should be recommended as a useful index for prognostication in patients with NPC.

Keywords: Ki-67, management, meta-analysis, nasopharyngeal carcinoma, prognosis

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Introduction

Nasopharyngeal carcinoma (NPC) has distinct characteristics from other head and neck cancers and accounts for only 0.7% of all cancer cases diagnosed in 2018 globally.[1,2] More than 70% of new NPC cases were reported in East and Southeast Asia.[1] There were approximately 42,100 new cases of NPC in China in 2013, accounting for 1.14% of all new cancer cases in China.[3] The primary treatment for early-stage NPC is intensity-modulated radiotherapy, alone or in combination with chemotherapy.[4,5]

However, approximately 8–10% of these patients have recurrent or distant metastasis, and the prognosis is poor.[6] To date, various biological markers, including Epstein-Barr virus (EBV) infection,[7] C-reactive protein level,[8] and neutrophil-to-lymphocyte ratio (NLR),[9] have been reported to be associated with the prognosis of NPC. However, the prognostic efficacy and accuracy are still unsatisfactory; therefore, the identification of effective and prognostic markers is important for the optimization of treatment strategies.

Ki-67 is a nuclear marker expressed in actively proliferating cells.[10] Ki-67 exists in almost all phases of the cell cycle, including G1, S, G2, and M stages, except for the G0 stage.[11] The expression level of Ki-67 detected by immunohistochemical (IHC) staining is usually considered as an index that reflects the activity of cell proliferation.[12] Many studies have also reported the prognostic value of Ki-67 in a variety of solid tumors, such as non-small-cell lung cancer,[13] colorectal cancer,[14] bladder cancer,[15] and renal cell carcinoma.[11] Previous studies also indicated an association between Ki-67 expression and prognosis of patients with NPC, but the results were conflicting.[16–23] Some studies showed the significant predictive role of Ki-67 for worse prognosis,[16,18] while other studies presented high Ki-67 expression as an indicator of favorable prognosis.[23] Therefore, this meta-analysis aimed to more accurately identify the prognostic and clinicopathological significance of Ki-67 in patients with NPC.

Materials and methods

Search strategy
This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[24] Ethical approval and patient consent were not required because the data were extracted from previously published studies. The PubMed, Embase, Web of Science, and Cochrane Library databases were searched up to November 2019. The keywords and MeSH terms were as follows: (Ki67 or Ki-67 or MIB-1 or MIB1) and (nasopharyngeal carcinoma or NPC or nasopharyngeal cancer or nasopharyngeal neoplasm or nasopharyngeal or carcinoma of the nasopharynx). The search details in PubMed are shown in Supplemental File S1. The references of relevant studies were screened for potential inclusions.

Inclusion and exclusion criteria
Studies meeting the following criteria were included: (a) the diagnosis of NPC was histopathologically confirmed; (b) the Ki-67 expression in tissues was detected by IHC analysis; (c) studies reported at least one survival outcome, including overall survival (OS), progression-free survival (PFS), distant metastasis-free survival (DMFS), and local recurrence-free survival (LRFS) with hazard ratio (HR) with 95% confidence interval (CI); (d) studies were published in English. The exclusion criteria were: (a) reviews, conference abstracts, letters, and case reports; (b) duplicate studies; and (c) studies that did not provide necessary data.

Data extraction and quality assessment
Two independent investigators (Z.S. and W.J.) reviewed the eligible studies and extracted basic information; any disagreements were settled by discussion. The following data were extracted: first author, publication year, country/region, sample size, sex, age, study duration, detection method, follow-up, disease stage, study type, and HRs and 95% CIs of OS, PFS, DMFS, and LRFS. If HRs and 95% CIs were not reported directly, they were calculated using Parmar's method from survival curves.[25] The quality of the included studies was evaluated using the Newcastle-Ottawa Scale (NOS) for cohort studies.[26] NOS score ranges from 0 to 9 and estimates studies from three aspects: selection, comparability, and outcome. Studies with scores ≥ 6 were regarded as high-quality studies.

Statistical analysis
All data analyses were conducted using Stata SE12.0 (Stata Corp., College Station, TX, USA). The pooled HRs and 95% CIs were calculated to quantify the correlation between Ki-67 expression and survival outcomes. Combined odds ratios (ORs) and 95% CIs were measured as effect size on the association between Ki-67 expression and clinical factors in NPC. The heterogeneity among studies was quantified using Cochran's Q statistic and I^2 statistic. In the presence of significant heterogeneity ($I^2 > 50\%$ or $p < 0.10$), the random-effects model was applied; otherwise, a fixed-effects model was used. Sensitivity analysis was performed to assess the stability of the results. Begg's test was used to assess potential publication bias. A p-value < 0.05 was considered statistically significant.

Results

Search results and study characteristics
A flow chart of the article retrieval process is shown in Figure 1. A total of 439 records were identified through an initial search. After duplicate records were removed, 247 studies were screened by title and abstract. Subsequently, 210 studies were excluded, and 37 full-text articles
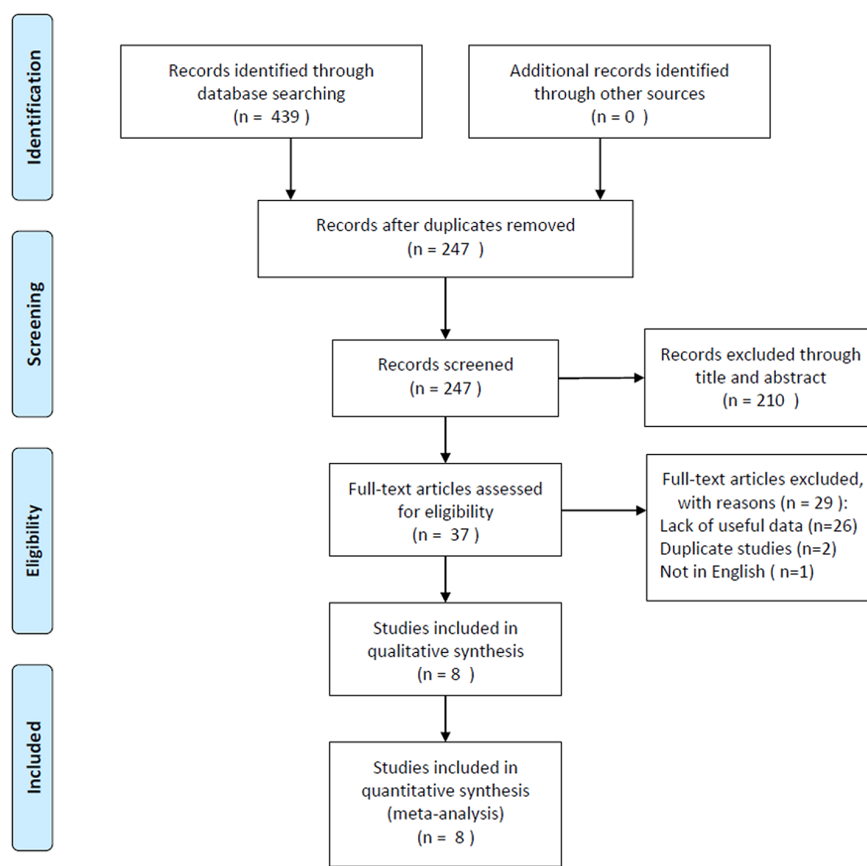
Figure 1. Flow diagram of the study selection process.

were evaluated for eligibility. Then, 29 studies were excluded for different reasons: 26 studies lacked necessary data, two studies used overlapped patients, and one study was not published in English. Finally, eight studies[16–23] were included in this meta-analysis. The detailed characteristics of the included studies are shown in Table 1. Seven studies were conducted in China[16–18,20–23] and one was performed in Taiwan.[19] The sample sizes ranged from 45 to 334, and the total number was 936. All eight studies used IHC detection methods, seven studies had a retrospective design,[16–22] and one study had a prospective design.[23] The cutoff values for Ki-67 ranged from 10% to 77.5%. Three studies reported the histological types of NPC. The NOS scores ranged from 6 to 8, with a median value of 7.[16,18,19]

Association between Ki-67 expression and OS, PFS, DMFS, and LRFS

Six studies reported the prognostic value of Ki-67 in OS.[16,18,20–23] As shown in Figure 2 and Table 2,

a fixed-effects model was used because of nonsignificant heterogeneity ($I^2 = 0$, $p = 0.462$). The pooled data were as follows: HR = 2.86, 95% CI = 1.91–4.27, $p < 0.001$, indicating that high Ki-67 expression predicted poor OS. Similarly, the combined HRs and 95% CIs from six studies,[16–19,22,23] and three studies,[18,19,23] showed that Ki-67 overexpression was also correlated with worse PFS (HR = 1.78, 95% CI = 1.15–2.74, $p = 0.009$; $I^2 = 52\%$, $p = 0.064$) and unfavorable DMFS (HR = 1.65, 95% CI = 1.15–2.36, $p = 0.007$; $I^2 = 23.4\%$, $p = 0.271$) (Figure 2, Table 2). However, no significant correlation was found between high Ki-67 expression and LRFS (HR = 1.07, 95% CI = 0.54–2.14, $p = 0.843$; $I^2 = 52.1\%$, $p = 0.124$) based on the data of three studies.[18,19,23]

Correlation between Ki-67 expression and clinicopathological factors

We investigated the relationship between Ki-67 expression and various clinicopathological

Table 1. Characteristics of the included studies.

Author	Country/region	No. of patients	Gender (M/F)	Age (years) Median (range)	Stage	Duration	Follow-up (month) Median (range)	Study design	NOS score	Survival analysis	Resource of HR and 95% CI	Cut-off value for Ki-67	Histological type	WHO subtype
Zhao et al.[16]	China	45	31/14	47 (27–79)	I–IV	2013–2015	41 (15–56)	Retrospective	7	OS, PFS	Reported	77.5%	Non-keratinizing undifferentiated: 45	WHO III
Zhao et al.[17]	China	108	75/33	47 (17–82)	III–IVa	2008–2012	51.5 (2–91)	Retrospective	7	PFS	Reported	30%	NA	NA
Lu et al.[18]	China	334	244/90	48 (17–72)	I–IV	2011–2014	48.7	Retrospective	7	OS, PFS, DMFS, LRFS	Calculated	25%	Non-keratinizing carcinoma Differentiated: 17 Undifferentiated: 317	WHO II and WHO III
Chang et al.[19]	Taiwan	124	95/29	48.6 (20–83)	I–IV	1993–2002	71 (1–141)	Retrospective	8	PFS, DMFS, LRFS	Calculated	H-score ≥median	Keratinizing: 5 Non-keratinizing: 42 Undifferentiated: 77	WHO I, WHOII and WHO III
Zhang et al.[20]	China	59	43/16	48.4 (15–80)	I–IV	2000–2008	68 (5–84)	Retrospective	7	OS	Calculated	25%	NA	NA
You et al.[21]	China	118	76/42	NA	I–IV	NA	NA	Retrospective	6	OS	Reported	50%	NA	NA
Guan et al.[22]	China	58	42/16	45 (24–74)	I–IV	2001–2011	96	Retrospective	7	OS, PFS	Reported	10%	NA	NA
Hui et al.[23]	China	90	74/16	47 (29–75)	I–IV	1998–1999	NA	Prospective	8	OS, PFS, DMFS, LRFS	Reported	26.1%	NA	NA

CI, confidence interval; DMFS, distant metastasis-free survival; F, female; HR, hazard ratio; IHC, immunohistochemistry; LRFS, local recurrence-free survival; M, male; NA, not available; NOS, Newcastle Ottawa Scale; OS, overall survival; PFS, progression-free survival.
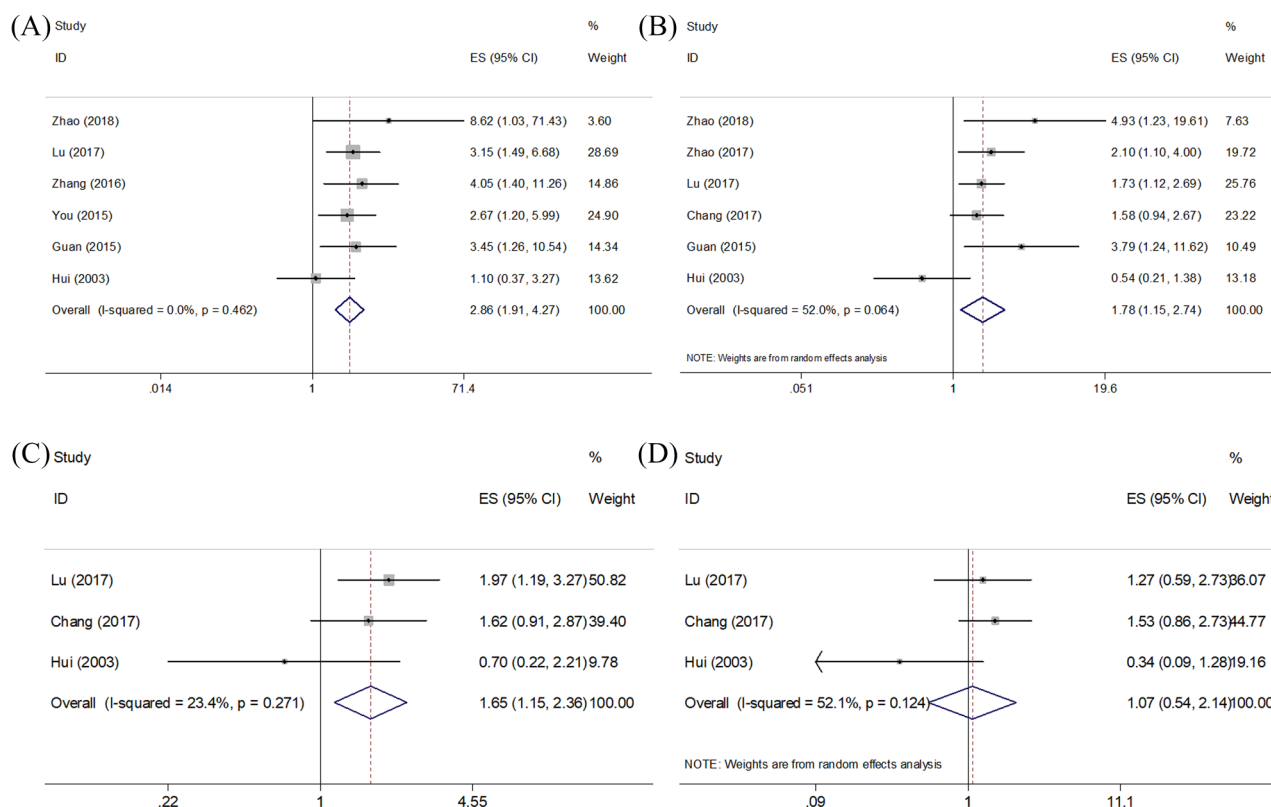
Figure 2. Forest plot of OS, PFS, DMFS, and LRFS. Note. (A) Meta-analysis of Ki-67 expression and OS. (B) Meta-analysis of Ki-67 expression and PFS. (C) Meta-analysis of Ki-67 expression and DMFS. (D) Meta-analysis of Ki-67 expression and LRFS. DMFS, distant metastasis-free survival; LRFS, local recurrence-free survival; OS, overall survival; PFS, progression-free survival.

Table 2. Meta-analysis of pooled HRs and 95% CIs for the association between Ki-67 and OS, PFS, DMFS, and LRFS in NPC patients.

Outcome	No. of studies	HR (95% CI)	p	Heterogeneity		Effects model
				I^2 (%)	Ph	
OS	6	2.86 (1.91–4.27)	<0.001	0	0.462	Fixed
PFS	6	1.78 (1.15–2.74)	0.009	52	0.064	Random
DMFS	3	1.65 (1.15–2.36)	0.007	23.4	0.271	Fixed
LRFS	3	1.07 (0.54–2.14)	0.843	52.1	0.124	Random

CI, confidence interval; DMFS, distant metastasis-free survival; HR, hazard ratio; LRFS, local recurrence-free survival; NPC, nasopharyngeal carcinoma; OS, overall survival; PFS, progression-free survival.

characteristics, including sex, age, clinical stage, T stage, N stage, and histological type. As shown in Figure 3 and Table 3, the merged results demonstrated that Ki-67 overexpression was associated with higher T stage (OR = 1.48, 95% CI = 1.00–2.20, p = 0.052). In addition, the association between Ki-67 expression and advanced stage was nearly significant (OR = 2.25, 95% CI = 0.99–5.14, p = 0.054). However, high Ki-67 expression is not significantly correlated with sex (OR = 1.01, 95% CI = 0.71 to −1.44, p = 0.963), age (OR = 1.10, 95% CI = 0.68–1.77, p = 0.699), N stage (OR = 1.73, 95% CI = 0.71–4.24, p = 0.231), or histological type (OR = 0.74, 95% CI = 0.40–1.32, p = 0.295).

Sensitivity analyses

To evaluate the stability of the results, a sensitivity analysis by sequential deletion of each single
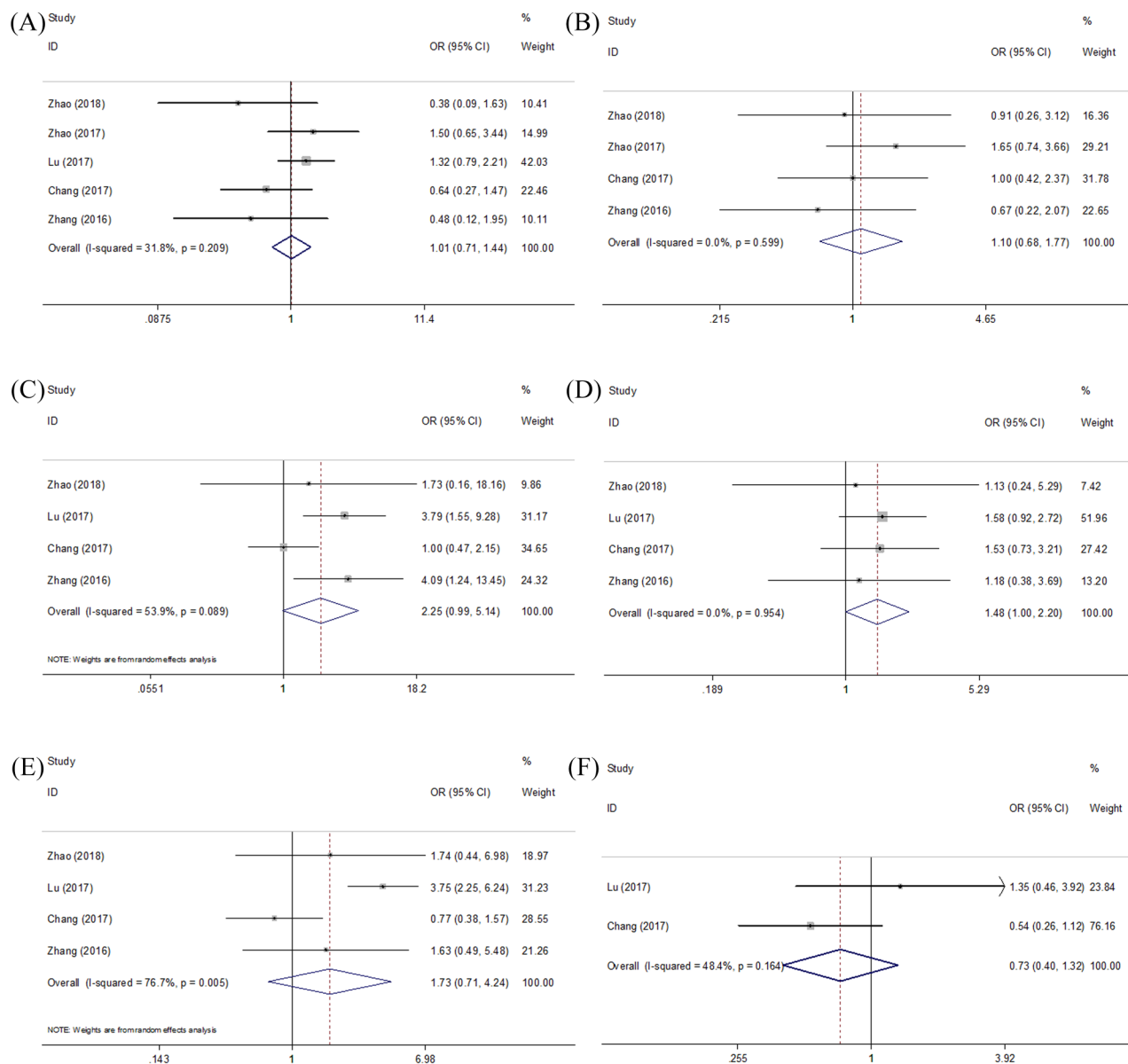
Figure 3. Meta-analysis of Ki-67 expression and clinical factors: (A) gender, (B) age, (C) clinical stage, (D) T stage, (E) N stage, and (F) histological type.

study was conducted. As shown in Figure 4, the results showed that no separate study significantly affected the total HRs, which suggested that this meta-analysis presented reliable results.

Publication bias

Publication bias was evaluated using Begg's test. As shown in Figure 5, the funnel plot did not indicate any evidence of publication bias for OS ($p = 0.707$), PFS ($p = 0.260$), DMFS ($p = 0.296$), and LRFS ($p = 0.296$).

Discussion

NPC is a rare cancer type, and the prognosis of advanced stage of disease is unsatisfactory.[27] In the current study, we performed a meta-analysis to identify the prognostic value of Ki-67 expression in patients with NPC. We found that the Ki-67 index showed significant prognostic efficiency in different survival endpoints, including OS, PFS, and DMFS, suggesting that Ki-67 could be validated as a useful index in the prognostication of patients with NPC. In addition, the pooled data also indicated an

Table 3. Meta-analysis of the association between high Ki-67 expression and clinicopathological features of NPC.

Variables	No. of studies	OR (95% CI)	p	Heterogeneity		Effects model
				I^2 (%)	Ph	
Gender (male *versus* female)	5	1.01 (0.71–1.44)	0.963	31.8	0.209	Fixed
Age (years) (≥45 *versus* <45)	4	1.10 (0.68–1.77)	0.699	0	0.599	Fixed
Clinical stage (III+IV *versus* I+II)	4	2.25 (0.99–5.14)	0.054	53.9	0.089	Random
T stage (T3+T4 *versus* T1+T2)	4	1.48 (1.00–2.20)	0.052	0	0.954	Fixed
N stage (N2+N3 *versus* N0+N1)	4	1.73 (0.71–4.24)	0.231	76.7	0.005	Random
Histological type (undifferentiated *versus* keratinizing/non-keratinizing)	2	0.74 (0.40–1.32)	0.295	48.4	0.164	Fixed

CI, confidence interval; NPC, nasopharyngeal carcinoma; OR, odds ratio.
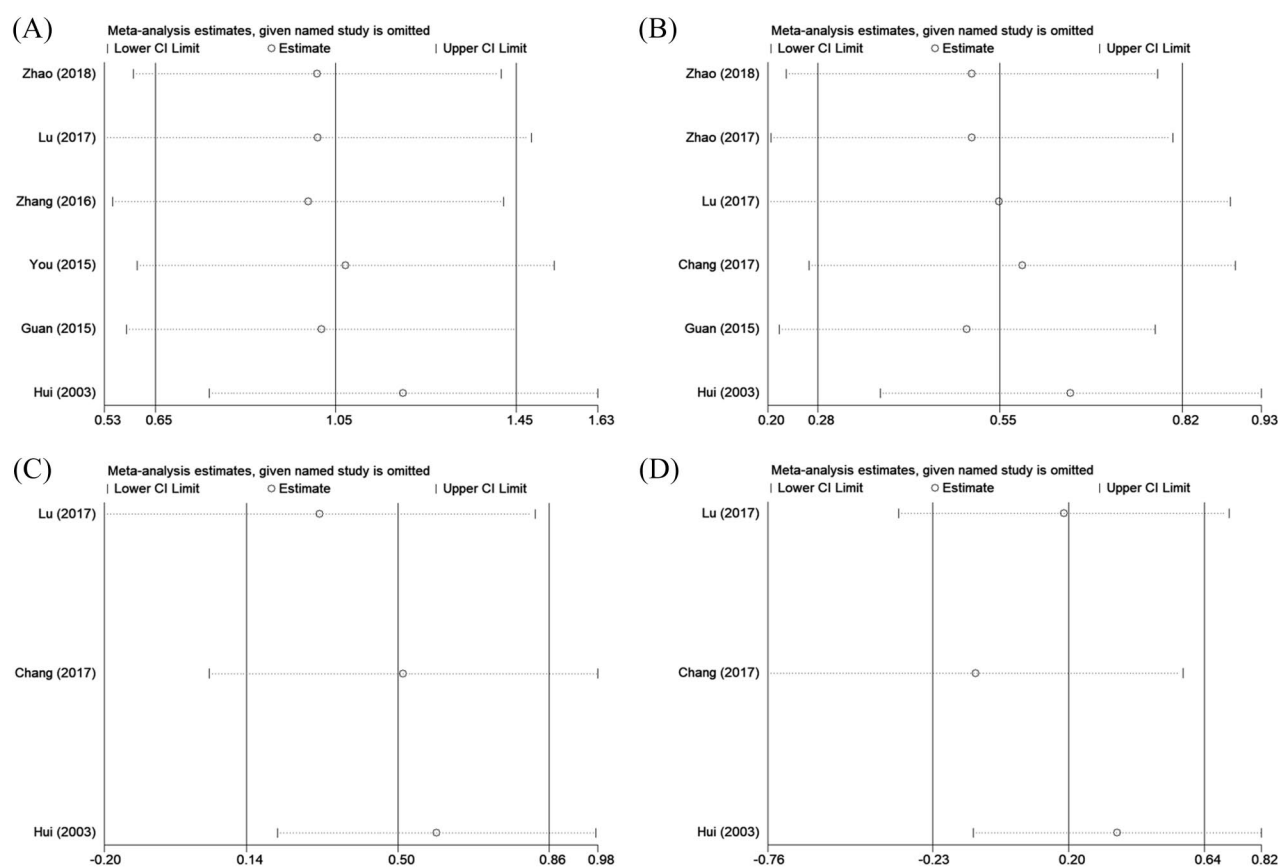
Figure 4. Sensitivity analysis for (A) OS, (B) PFS, (C) DMFS, and (D) LRFS.
DMFS, distant metastasis-free survival; LRFS, local recurrence-free survival; OS, overall survival; PFS, progression-free survival.

association between Ki-67 expression and higher T stage in NPC. Taken together, this is the first study to demonstrate the positive correlation between high Ki-67 expression and worse survival outcomes using the meta-analytic approach.
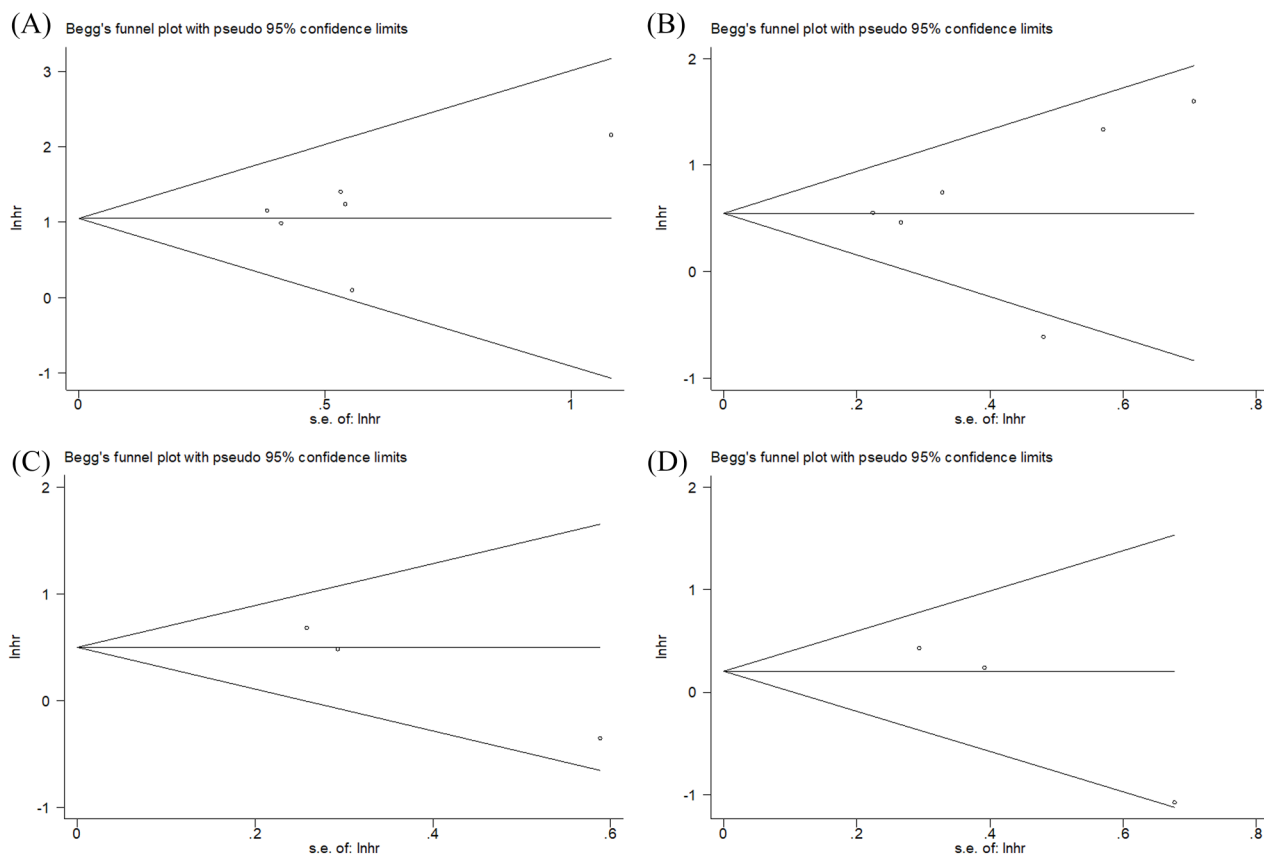
Figure 5. Funnel plots for publication bias of (A) OS, (B) PFS, (C) DMFS, and (D) LRFS.
DMFS, distant metastasis-free survival; LRFS, local recurrence-free survival; OS, overall survival; PFS, progression-free survival.

Ki-67 is present in the active phases of the cell cycle, including G1, S, and G2 phases but is not expressed in quiescent or G0 phases.[28] The role of Ki-67 in the cell cycle makes it an optimal marker in the evaluation of the proportion of proliferative cells.[12] In patients with cancer, the Ki-67 level determined by IHC analysis is indicative of survival outcomes. Recent studies have also reported the prognostic value of Ki-67 expression in different types of cancer. A meta-analysis including 21 studies showed that high Ki-67 expression in localized prostate cancer was predictive of poor disease-specific survival, biochemical failure-free survival, DFS, and OS.[29] Liu *et al.* reported that Ki-67 overexpression was correlated with poor prognosis in patients with gastric cancer.[30] Furthermore, their study also found that Ki-67 positivity was associated with age, lymph node metastasis, and tumor size in patients with gastric cancer.[30] Another recent study also revealed the significant relationship between Ki-67 expression and poor OS in patients with ovarian cancer.[31] The previous findings of the positive correlations

of Ki-67 expression and poor prognosis in various cancers are in accordance with the present study. However, we did not identify an association between high Ki-67 expression and any clinicopathological features in NPC. However, the data of clinical stage ($p = 0.054$) and T stage ($p = 0.052$) (Table 3) are extremely close to statistical significance. The negative association may be the result of a limited sample size. Notably, the included studies recruited patients with stage I–IV (seven studies) and stage III–IVa (one study) diseases.[16–23] In the survival analysis in each study, the investigators analyzed the prognostic value of Ki-67 and the whole group of patients (stage I–IV or stage III–IVa) but not patients with stage I–II and III–IV diseases. Therefore, the possible difference in the prognostic role of Ki-67 in different disease stages (early *versus* advanced) could not be determined based on the current evidence. Thus, we suggest that the potential distinct prognostic efficiency of Ki-67 in NPC at different disease stages (early *versus* advanced) should be explored in further studies.

EBV infection is a risk factor for NPC, and the non-keratinizing subtype of NPC is associated predominantly with EBV infection.[1] In the present meta-analysis, the data were insufficient to explore the association between EBV positivity and Ki-67 expression. A previous study involving 19 patients showed that EBV positivity was correlated with highly Ki-67 expression ($p = 0.0174$) in NPC.[32] Another study suggested that the f variant of EBV was correlated with high Ki-67 expression in NPC and therefore indicated the possible role of EBV in nasopharyngeal carcinogenesis.[33] This evidence indicates the potential relationship between EBV and proliferation of NPC, which could be measured quantitatively by Ki-67 expression. In the present meta-analysis, the data were insufficient to explore the association between EBV positivity and Ki-67 expression. We suggest that the association between EBV positivity and Ki-67 expression should be explored in large-scale studies.

A variety of prognostic factors for NPC have been explored recently, including programmed cell death ligand-1,[34] EBV DNA levels,[35] micro-RNAs,[36] NLR,[9] and platelet-to-lymphocyte ratio.[37] These prognostic indicators showed significant prognostic value in NPC and are associated with the tumor microenvironment, immune responses, and EBV positivity. Compared with these markers, Ki-67 is an index of proliferation and usually measured in pathological tests. Other markers of cell proliferation, including the MCM family, cyclin D1, Bcl-2, CDK family, and p16IN4Ka have also been investigated as prognostic markers in NPC in previous studies.[38,39] However, due to insufficient data in the current meta-analysis, direct comparisons between other proliferative markers and Ki-67 could not be performed. We suggest that the distinction between other cell proliferation indexes and Ki-67 in NPC should be explored. Ki-67 is widely available in clinical practice and could provide implications for survival outcomes in the management of patients, as suggested by the current meta-analysis.

The current meta-analysis had several limitations. First, the total sample size was small. Although eight studies were included in the meta-analysis, the total sample size was 936, which may be due to the rarity of NPC. Second, all studies were from China and Taiwan, which restricted the applicability of the results to other regions worldwide. Third, all studies used IHC analysis to detect Ki-67 expression, whereas the criteria to determine high or low Ki-67 expression were different in the included studies. The various cutoff values may contribute to heterogeneity. Fourth, as EBV is associated with nasopharyngeal carcinogenesis, the impact of EBV on Ki-67 expression needs to be investigated. In the current meta-analysis, due to insufficient data, the relationship between EBV infection and Ki-67 expression could not be analyzed. Although previous studies reported the potential association between EBV infection and Ki-67 expression in NPC,[32,33] the detailed mechanisms underlying the crosstalk between EBV infection and Ki-67 expression remain to be elucidated in further investigations.

Therefore, this meta-analysis demonstrated that Ki-67 overexpression was a significant marker for poor prognosis in patients with NPC. Ki-67 should be recommended as a useful index in the prognostication of patients with NPC after treatment. However, due to some limitations, more large-scale, multicenter prospective studies are still needed to verify our results.

Author contributions
Z.S., W.J., X.C., and M.X. conceived and designed the study. Z.S., W.J., X.W., and D.Z. performed the analysis, prepared the figures and tables and wrote the main manuscript. All of the authors reviewed the manuscript. All authors read and approved the final manuscript.

Availability of data and materials
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest statement
The authors declare that there is no conflict of interest.

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Supplemental material
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