

NIMA-related kinase 2 overexpression is associated with poor survival in cancer patients: a systematic review and meta-analysis

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Objective: NIMA-related kinase 2 (NEK2) has been reported to be overexpressed in various types of cancer and correlated with poor prognosis. The role(s) of NEK2 in cancer, however, is still uncertain. The aim of this study was to evaluate the prognostic value of NEK2 in human tumors.

Methods: A comprehensive literature search was performed for PubMed, Embase, Web of Science, and CNKI databases, and eligible studies were included based on the inclusion and exclusion criteria. A meta-analysis of the included studies was then carried out.

Results: Fifteen studies with 3,280 cancer patients were included in the present meta-analysis. All publications were of moderate to high quality, and had no significant heterogeneity ($I^2=46\%$, $P=0.03$) or publication bias was discovered. The results showed that a high NEK2 level was associated with shorter overall survival (OS) in patients with various types of cancers (pooled HR=1.72, 95% CI 1.49–2.00, $P<0.00001$). However, the disease-free survival (DFS) had no significant association with NEK2 level (HR=1.13, 95% CI: 0.29–4.38, $P=0.85$). In the subgroup analyses, high NEK2 level was correlated with an increased risk of poor OS in patients with hepatocellular carcinoma (HR=1.62, 95% CI: 1.25–2.10, $P=0.02$) and lung cancer (HR=2.18, 95% CI: 1.40–3.38, $P=0.0005$). However, other factors, including sample size, follow-up period, HR estimation method, and country, also affect the association between NEK2 expression and OS. Analysis of clinicopathological parameters further showed that increased NEK2 level was correlated with younger age, male gender, better tumor differentiation, and lower number of tumor nodules.

Conclusion: The results of this study indicated that increased expression of NEK2 was associated with unfavorable survival of cancer patients and that NEK2 could be used as a prognostic predictor for cancers.

Keywords: NEK2, prognosis, cancer, diagnosis, meta-analysis, clinical characteristics

Introduction

Cancer is one of the main causes of death and is a challenge to healthcare systems around the world.¹ Epidemiological studies show that 14.1 million new cancer cases and 8.2 million cancer-related deaths occur annually worldwide, and these numbers are on the rise.^{2,3} Early diagnosis and prognosis prediction are helpful for choosing treatments for cancer patients, but traditional detection methods such as imaging techniques and biopsy have their limitations.^{4,5} Therefore, it is necessary to identify new biomarkers for early diagnosis and for predicting patients' prognosis to improve the efficacy of cancer treatment.

NIMA-related kinase 2 (NEK2), which is a member of the cell cycle-related kinase (CCRK) family of proteins, is a serine/threonine kinase located in the centrosome.⁶

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In recent years, determining the role(s) of NEK2 in tumor pathogenesis and progression has become a hotspot of research.^{7,8} Elevation in NEK2 level contributes to the formation of centrosomal abnormalities and monopolar spindles and promotes aneuploidy by disrupting the control of mitotic checkpoints.^{9,10} An increasing number of studies have reported that expression of NEK2 is increased in cancer and that up-regulation of NEK2 is associated with tumor progression and poor prognosis in various types of cancer, including breast cancer,^{11,12} colorectal cancer,^{13,14} cervical cancer,¹⁵ and cholangiocarcinoma.¹⁶ Notably, the number of studies on NEK2 is still small and the role, or roles, of NEK2 in cancer remains unclear. Overall, the reported results are inconclusive, and no consensus has been reached. Thus, we performed this meta-analysis to summarize the existing data and evaluate the prognostic value of NEK2 in cancer patients.

Methods

Literature search strategy

A comprehensive literature search of online databases, including PubMed, Web of Science, Embase, and CNKI, was carried out to retrieve studies evaluating the association between NEK2 expression and clinical outcome in any type of tumor up to August 2017. The keywords for the literature search included: “NIMA-related kinase 2”, “NEK2”, “cancer”, “tumor”, “carcinoma”, “neoplasm”, “survival”, or “prognosis”. The references of eligible literature were also manually screened to further retrieve potentially eligible publications. Conflicts were solved through group discussion.

Inclusion and exclusion criteria

To be eligible for inclusion, a study had to meet the following criteria: 1) the association of NEK2 level with the clinicopathological features or prognosis of cancer patients was described; 2) patients were categorized into two groups based on high and low expression levels of NEK2; and 3) the study provided the data for estimating the HRs and 95% CIs of survival outcomes. The exclusion criteria included: 1) studies that did not provide the correlation between NEK2 level and the clinicopathological features or prognosis of cancer patients; 2) duplicated publications; and 3) letters, reviews, case reports, and expert opinions.

Data extraction and quality assessment

Two investigators independently evaluated the included studies for the number of patients, name of the first author, year of publication, cancer type, TNM stage, follow-up period,

outcome measures, methods for measuring NEK2 expression, HR and its 95% CI, and clinicopathological parameters from each study. The quality of included studies was assessed with the Newcastle–Ottawa Scale (NOS), which is composed of three domains: selection, comparability, and exposure. The NOS is a semi-quantitative scale, from which a score of 0–9 was assigned to each study. A total score of ≤ 3 was considered poor quality, 4–6 was considered moderate quality, and 7–9 was deemed high quality.

Statistical methods

The meta-analysis was performed with RevMan 5.3 software. The HR with corresponding 95% CI was used to estimate the strength of the relationship between NEK2 expression and prognosis of patients. Heterogeneity among studies was quantified using the chi-squared test and I^2 statistics. A chi-squared test with $P < 0.05$ or $I^2 > 50\%$ indicated significant heterogeneity across the studies. If the heterogeneity was not significant, a fixed effects model was used to investigate the pooled HRs. A random effects model was used to summarize the statistical synthesis if among-study heterogeneity was substantial. Sensitivity analysis was also carried out to assess the stability of the results. Publication bias was estimated qualitatively using funnel plots with the standard error.

Results

Study characteristics

The initial literature search retrieved 322 relevant studies. According to the inclusion and exclusion criteria, 14 eligible studies with 3,280 enrolled patients were included in the present meta-analysis (Figure 1). The characteristics of the included studies are summarized in Table 1. All studies were published in the past 4 years, suggesting that the value of NEK2 in predicting prognosis is a novel field of research. Regarding the type of cancer, four studies investigated hepatocellular carcinoma (HCC),^{18,20,26,28} three studies were focused on colorectal cancer,^{23,25,29} two studies were focused on non-small cell lung cancer,^{22,24} and one each evaluated prostate cancer,¹⁷ pancreatic ductal adenocarcinoma,¹⁹ malignant glioma,²¹ lung cancer,²⁷ multiple myeloma,³⁰ and breast cancer.³¹ The maximum and minimum sample sizes of the included studies were 594 and 50, respectively. The follow-up time ranged from 40 to 240 months. All included studies were carried out in four countries (PR China, Japan, the UK, and the USA) and published prior to August 2017. The NOS method was applied to evaluate the quality of each study, and the mean score of the included studies was 8.6 (range 6–9).

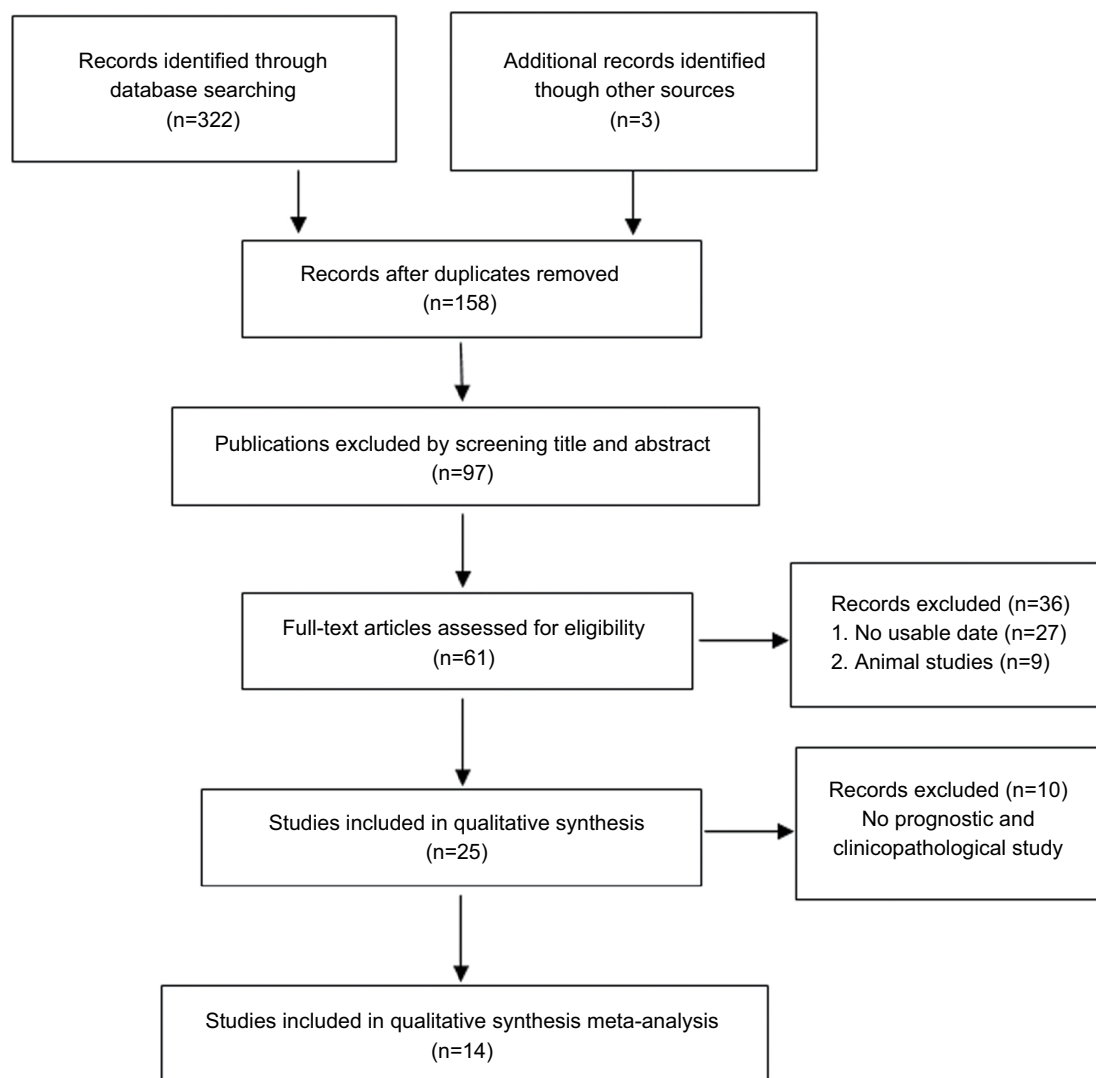


Figure 1 Flow diagram of literature search and selection.

Association between NEK2 and overall survival (OS)

Fourteen included studies assessed the HRs for poor OS. As shown in Figure 2, no obvious heterogeneity among these studies was found ($I^2=46\%$, $P=0.03$). Thus, a fixed effects model was employed to evaluate the pooled association between NEK2 expression and OS of different types of malignancies. The HR of the high NEK2 level group vs the low NEK2 expression group was 1.72 (95% CI: 1.49–2.00, $P<0.00001$), suggesting that up-regulated NEK2 expression was correlated with inferior OS in cancer patients (Figure 2).

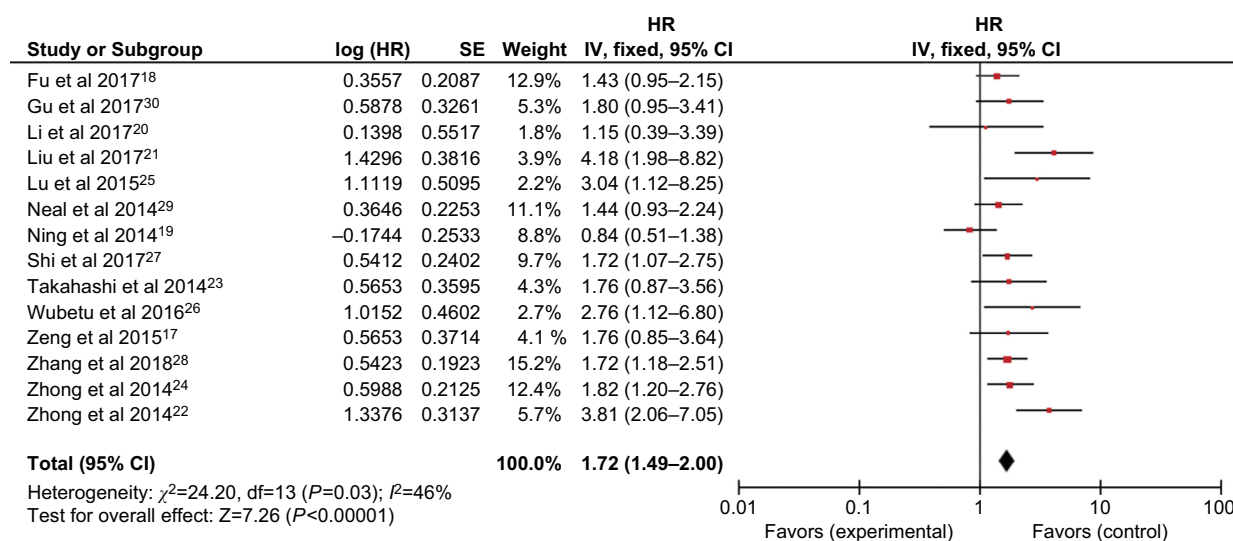
Subsequent stratified analyses were performed according to cancer type, sample size, follow-up period, HR estimation method, and country (Figures 3 and 4 and Table 2). Increased NEK2 expression was associated with poor OS in patients

with HCC (HR=1.62, 95% CI: 1.25–2.10, $P=0.0002$) or lung cancer (HR=2.18, 95% CI: 1.40–3.38, $P=0.0005$) (Figure 3). In the analysis stratified by sample size, NEK2 expression was found to be significantly correlated with patient survival in studies with a sample size <300 (HR=1.88, 95% CI: 1.43–2.46, $P<0.00001$) or more than 300 (HR=1.59, 95% CI: 1.20–2.10, $P=0.001$) (Figure 4A). There was a significant correlation between NEK2 expression level and patient survival in studies with follow-up time ≤ 100 months (HR=1.68, 95% CI: 1.09–2.59, $P=0.02$) or >100 months (HR=1.95, 95% CI: 1.56–2.44, $P<0.00001$) (Figure 4B). Regarding the location of the study, the stratified analysis revealed a significant association between NEK2 level and OS in both Asian countries (HR=1.86, 95% CI: 1.45–2.38, $P<0.0001$) and other countries (HR=1.55, 95%

Table I Characteristics of the included studies

Study (first author)	Year	Country	Cancer type	No. of cases	Gender (M/F)	Follow-up (months)	Detection method	Outcome measurements	HR (95% CI)	NOS
Zeng et al ¹⁷	2015	PR China	PCa	180	NR/NR	140	qRT-PCR	OS	1.76 (0.85–3.64)	7
Fu et al ¹⁸	2017	PR China	HCC	310	252/59	40	IHC	OS	1.44 (0.96–2.17)	8
Ning et al ¹⁹	2014	PR China	PDA	136	72/64	100	qRT-PCR	OS	0.84 (0.56–1.38)	8
Li et al ²⁰	2017	PR China	HCC	63	52/11	116	qRT-PCR	OS	1.15 (0.39–3.35)	8
Liu et al ²¹	2017	PR China	MG	105	47/52	200	IHC	OS	4.177 (1.97–8.82)	9
Zhong et al ²²	2014	PR China	NSCLC	270	192/78	60	IHC	OS	3.810 (2.06–7.036)	8
Takahashi et al ²³	2014	Japan	CRC	180	104/76	180	qRT-PCR	OS	1.76 (0.87–3.59)	7
Zhong et al ²⁴	2014	PR China	NSCLC	270	192/78	10	IHC	OS	1.85 (1.20–2.83)	8
Lu et al ²⁵	2015	PR China	CC	60	32/28	100	IHC	OS	3.04 (1.12–8.29)	7
Wubetu et al ²⁶	2016	Japan	HCC	50	16/34	180	qRT-PCR	OS	2.76 (1.12–8.29)	8
Shi et al ²⁷	2017	PR China	LC	349	159/190	240	qRT-PCR	OS/DFS	1.749 (1.140–2.681)/ 1.738 (1.161–2.601)	9
Zhang et al ²⁸	2018	PR China	HCC	259	230/29	100	qRT-PCR	OS	1.72 (1.18–2.53)	8
Neal et al ²⁹	2014	UK	CC	103	57/46	NR	IHC	OS/DFS	1.654 (0.926–2.956)/ 2.393 (1.096–5.227)	8
Gu et al ³⁰	2017	USA	MM	351	NR/NR	80	qRT-PCR	OS	1.80 (0.95–3.42)	6
Marina and Saavedra ³¹	2014	USA	BC	594	NR/NR	133	qRT-PCR	DFS	0.6 (0.5–0.9)	6

Abbreviations: BC, breast cancer; CC, colon cancer; CRC, colorectal cancer; DFS, disease-free survival; F, female; HCC, hepatocellular carcinoma; IHC, immunohistochemistry; LC, lung cancer; M, male; MG, malignant glioma; MM, multiple myeloma; NOS, Newcastle-Ottawa Scale; NR, not reported; NSCLC, non-small cell lung cancer; OS, overall survival; PDA, pancreatic ductal adenocarcinoma; PCa, prostate cancer.

**Figure 2** Forest plot of HRs for the association between high NIMA-related kinase 2 (NEK2) expression and overall survival in cancer patients.

CI: 1.08–2.23, $P=0.02$) (Figure 4C). In addition, the association was significant in studies with both direct (HR=2.01, 95% CI: 1.18–3.43, $P=0.01$) and indirect (HR=1.75, 95% CI: 1.37–2.23, $P<0.00001$) HR estimation methods (Figure 4D). Altogether, the subgroup analyses indicated that sample size, follow-up period, country, and HR estimation method did not have any significant influence on the correlation between NEK2 level and patient OS, suggesting that the association

is stable and therefore highlighting the value of NEK2 as a prognostic biomarker for cancer patients.

Association between NEK2 and disease-free survival (DFS)

As shown in Figure 5, two studies with 697 patients investigated the role of NEK2 expression in DFS. However, the pooled analysis failed to show a significant correlation

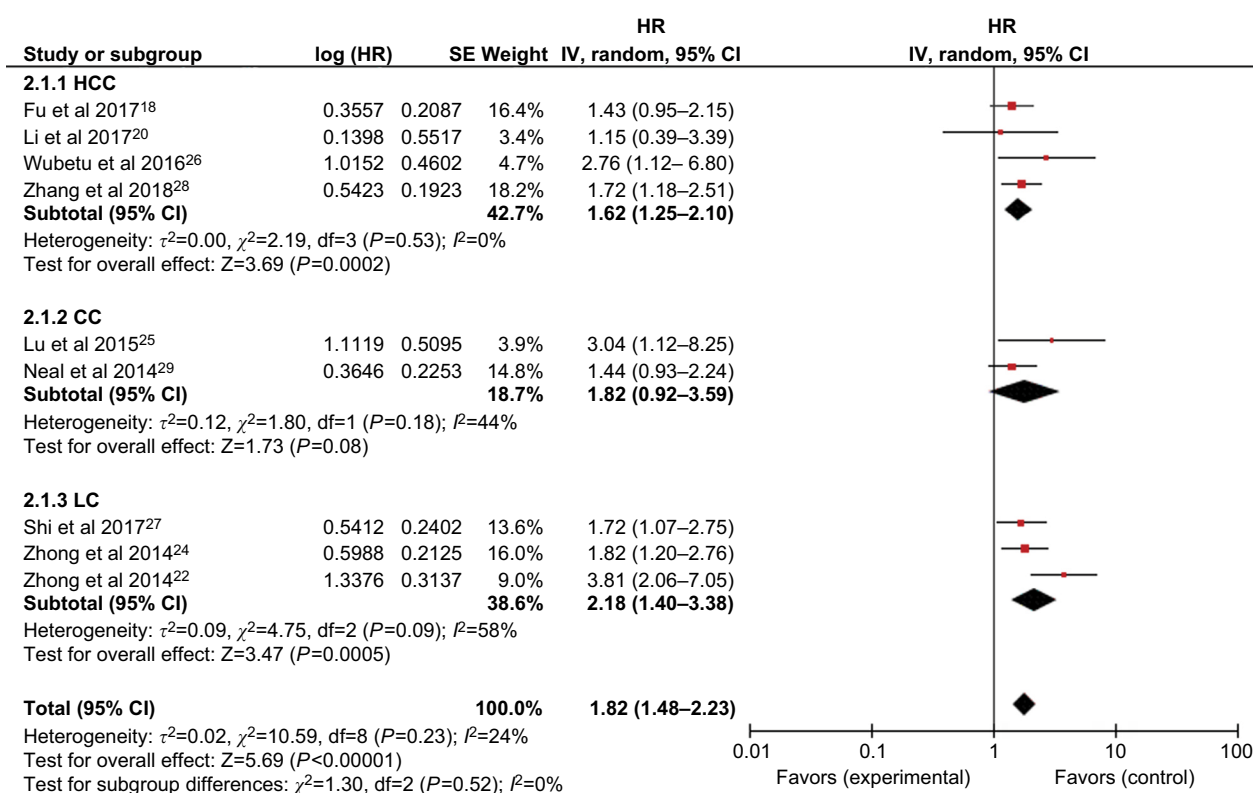


Figure 3 Forest plot of HRs for the association between high NEK2 expression and overall survival stratified by cancer type.

Table 2 Subgroup analysis of the pooled HRs for OS

Categories	Studies (n)	No. of patients	Fixed effects model		Heterogeneity	
			HR (95% CI) for OS	P-value	I^2 (%)	P-value
OS	14	2,335	1.72 (1.49–2.00)	<0.00001	46	0.03
DFS	2	697	1.13 (0.29–4.38)	<0.00001	91	0.0007
Cancer type						
HCC	4	682	1.62 (1.25–2.10)	0.02	1	0.37
CC	2	163	1.82 (0.92–3.59)	0.08	44	0.18
LC	3	889	2.18 (1.40–3.38)	0.0005	58	0.09
Sample size						
≤300	11	1,325	1.88 (1.43–2.46)	<0.00001	57	0.010
>300	3	1,010	1.59 (1.20–2.10)	0.001	0	0.78
Follow-up						
≤100 months	5	1,342	1.68 (1.09–2.59)	0.02	73	0.005
>100 months	8	1,077	1.95 (1.56–2.44)	<0.00001	1	0.42
HR estimation method						
Indirect	11	2,129	1.75 (1.37–2.23)	<0.00001	45	0.05
Direct	3	557	2.01 (1.18–3.42)	0.01	66	0.05
Country						
Asian	12	2,232	1.86 (1.45–2.38)	<0.0001	53	0.02
Other	2	451	1.55 (1.08–2.23)	0.02	0	0.57

Abbreviations: CC, colon cancer; DFS, disease-free survival; HCC, hepatocellular carcinoma; LC, lung cancer; OS, overall survival.

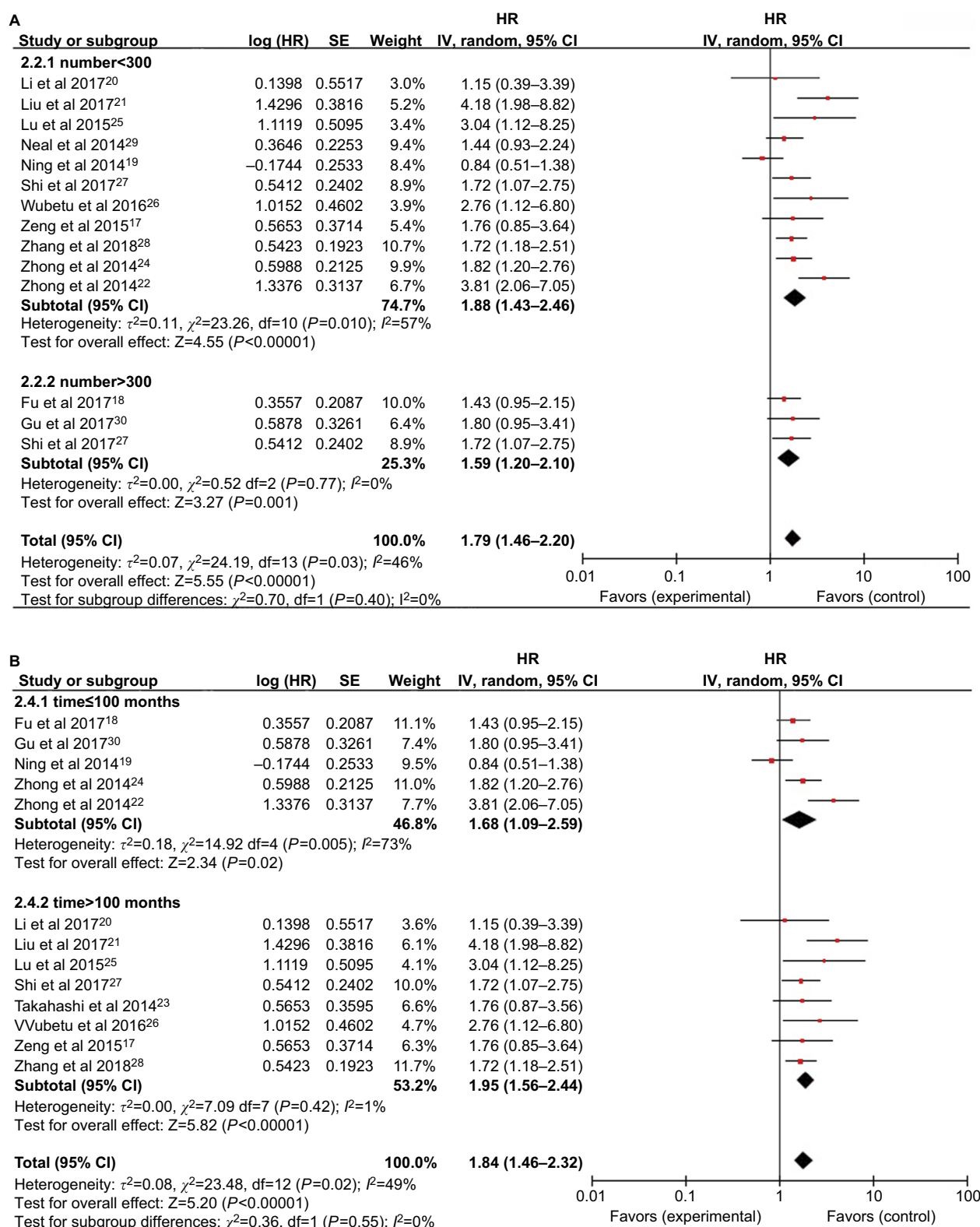


Figure 4 (Continued)

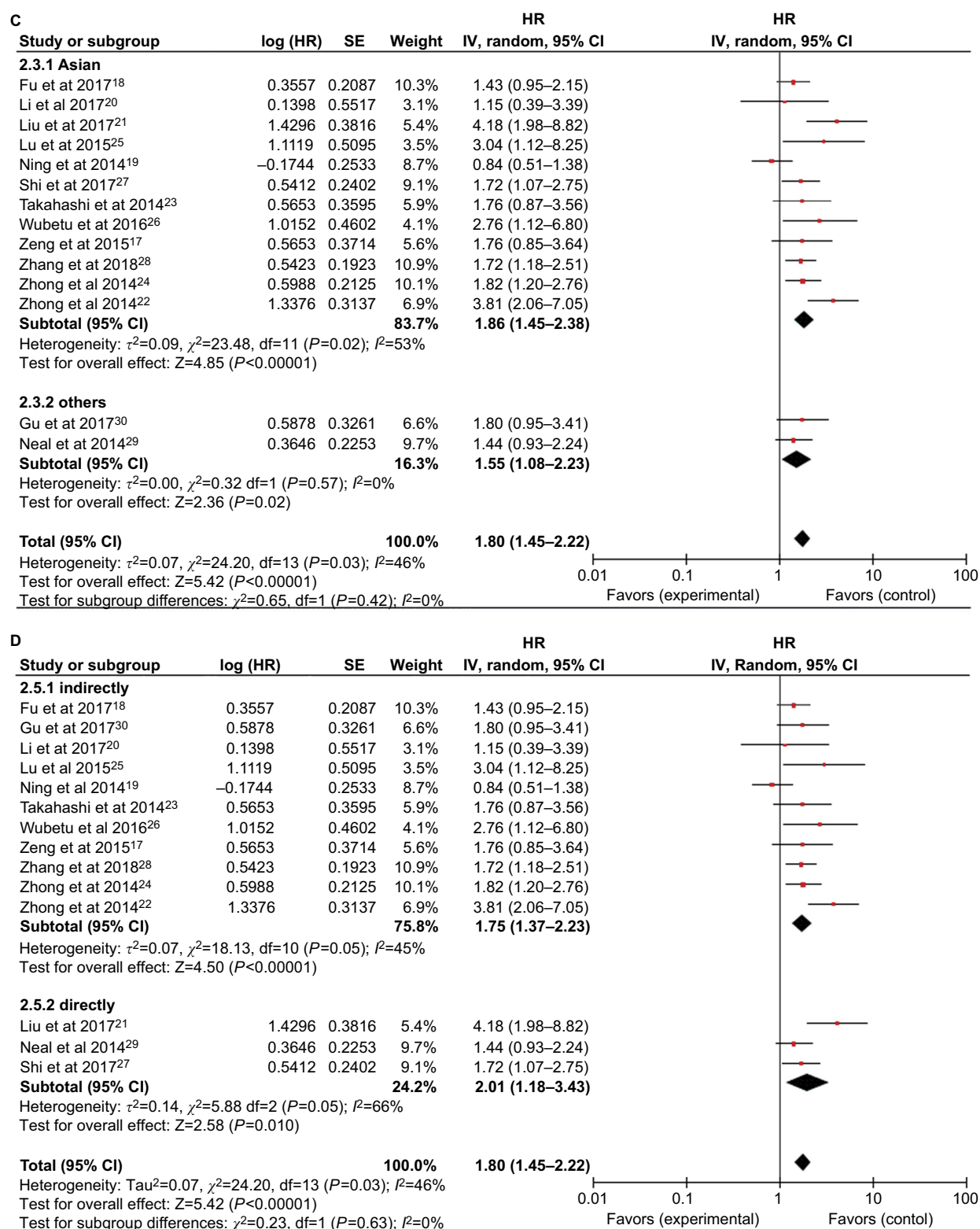


Figure 4 Forest plot of the subgroup analyses evaluating HRs of NEK2 for overall survival by the factors of (A) sample size, (B) follow-up months, (C) region, and (D) HR estimation method.

Abbreviations: CC, colon cancer; HCC, hepatocellular carcinoma; LC, lung cancer; NEK2, NIMA-related kinase 2.

between NEK2 level and DFS of patients (HR=1.13, 95% CI: 0.29–4.38, $P=0.85$) (Figure 5).

Correlation between NEK2 expression and clinicopathological parameters

To examine whether the NEK2 level had an association with the clinicopathological parameters of patients, we pooled the clinicopathological data to conduct a meta-analysis. As shown in Table 3, increased NEK2 expression was negatively associated with age (OR=0.45, 95% CI: 0.11–1.84, $P<0.00001$), but positively correlated with male gender (OR=3.02, 95% CI: 1.30–7.02, $P=0.01$), better tumor differentiation (OR=4.23, 95% CI: 1.30–13.77, $P<0.00001$), and lower tumor nodule number (OR=5.88, 95% CI: 2.19–5.80, $P=0.0004$). However, NEK2 expression was not correlated with other clinicopathological features, including disease stage and tumor size (Table 3).

Sensitivity analysis

A sensitivity analysis was then performed by removing each study in turn from the pooled analysis for the association between NEK2 level and OS. This analysis enabled us to examine the impact of the removed study on the overall HRs. The results revealed that removing any of the included studies had no significant influence on the final results, which suggested the robustness of the association (Table 4).

Publication bias

No significant publication bias was discovered in the included studies from the funnel plots (Figure 6).

Discussion

NEK2 belongs to the CCRK family of cell cycle-regulating proteins and it is a serine/threonine kinase located in the centrosome.^{32–34} Previous studies have demonstrated that elevation in NEK2 contributes to the regulation of centrosome separation and spindle formation, and to ensuring that the chromosome structure is more stable and complete.^{35,36} In cancer-related studies, NEK2 was found to be up-regulated in various types of cancer tissues and cell lines, suggesting the involvement of NEK2 in tumorigenesis. NEK2 has also been shown to be involved in abnormal cell differentiation, tumor proliferation, drug resistance, and poor prognosis in several kinds of tumors.^{37–39}

A lot of effort has been made to understand the functional role of NEK2 in cancer. Zhang et al found that NEK2 significantly enhanced the invasive ability of HCC cells, and epithelial–mesenchymal transition played a pivotal role in the NEK2-mediated promotion of HCC cell invasion.²⁸ Zhang et al demonstrated that NEK2 may regulate proliferation, apoptosis, and other biological behaviors of HepG2 cells via the mitogen-activated protein kinase signaling pathway.⁴⁰ Tsunoda et al showed that interfering with or silencing

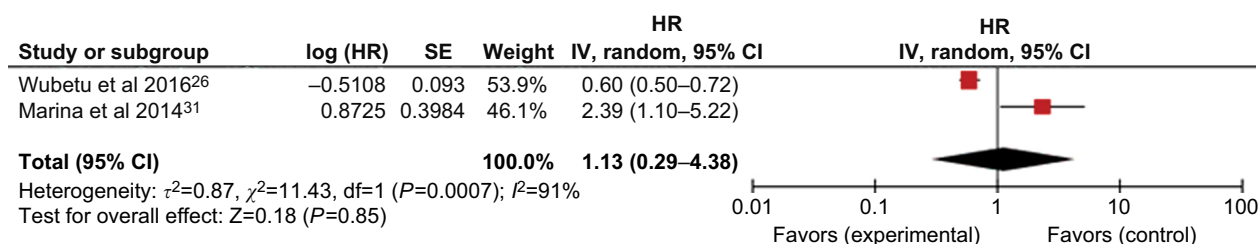


Figure 5 Forest plot of HRs for the association between high NIMA-related kinase 2 (NEK2) expression and disease-free survival in cancer patients by different cancer types.

Table 3 Association between NEK2 expression and clinicopathological features

Clinicopathological parameters	Studies (n)	Patients (n)	OR (95% CI)	P-value	Heterogeneity	
					I^2 (%)	P-value
Age (≥ 65 vs <65 years)	3	403	0.45 (0.11–1.84)	<0.00001	96	0.27
Gender (male vs female)	12	2,150	3.02 (1.30–7.02)	0.01	97	<0.00001
Clinical stage (I–II vs III–IV)	6	1,086	2.50 (0.78–8.03)	0.13	97	<0.00001
Tumor differentiation (well/moderate vs poor)	5	625	4.23 (1.30–13.77)	<0.00001	95	<0.00001
Tumor nodule number (solitary vs multiple)	4	682	5.88 (2.19–5.80)	0.0004	93	<0.00001
Tumor size (≥ 5 vs <5 cm)	3	602	1.07 (0.16–7.31)	0.95	98	<0.00001
Venous invasion (present vs absent)	3	667	6.55 (0.86–49.59)	0.07	98	<0.00001

Abbreviation: NEK2, NIMA-related kinase 2.

NEK2 expression could inhibit the invasive capacity of breast cancer cells.⁴¹ Two groups reported that elevation in NEK2 contributed to the activation of the PI3K/AKT signaling pathway, a potent and critical oncogenic pathway for a variety of malignancies.^{41,42} Li et al reported that overexpression of NEK2 resulted in high expression of phospho-AKT and matrix metalloproteinase-2 proteins in HCC, which are key factors in HCC invasion and metastasis.⁴³ These results suggest that targeting NEK2 may be beneficial in the treatment of human cancers. However, the role of NEK2 in other

non-studied types of cancer needs to be further investigated to fully understand the functions of NEK2 in cancer.

This meta-analysis is the first systematic review to comprehensively investigate the relationship between NEK2 expression and the OS of patients with different types of cancers. Survival data of 3,280 patients from 15 included studies were systematically analyzed. The pooled HRs suggested the value of NEK2 in predicting the OS in cancer patients. Regarding tumors originating from different tissues, high NEK2 expression was relevant to poor OS in HCC and lung cancer. Further subgroup analyses for sample size, follow-up time, HR estimation method, and country showed that the significance of NEK2 in OS was not affected by these factors. The meta-analysis for the association between increased NEK2 expression and clinicopathological parameters was also analyzed in this study. Our results showed that increased NEK2 expression was significantly associated with younger age, male gender, better tumor differentiation, and solitary tumor nodule. Overall, this study highlighted the potential of NEK2 as a prognostic biomarker for cancer patients.

However, this meta-analysis had some deficiencies and limitations. First, the total sample size was relatively small, and most of the patients included in the meta-analysis were from PR China, raising concerns when applying the results of this study to different ethnicities and regions. Therefore, more large-scale studies are warranted to further verify the prognostic value of NEK2 in different ethnicities and regions. Second, some

Table 4 Sensitivity analysis

Study (first author)	HR (95% CI)	P-value of heterogeneity	I ²
Neal et al ²⁹	1.76 (1.51–2.06)	<0.00001	49
Li et al ²⁰	1.74 (1.50–2.01)	<0.00001	49
Wubetu et al ²⁶	1.70 (1.47–1.97)	<0.00001	48
Liu et al ²¹	1.66 (1.43–1.93)	<0.00001	35
Lu et al ²⁵	1.70 (1.47–1.97)	<0.00001	48
Fu et al ¹⁸	1.77 (1.51–2.07)	<0.00001	48
Zhong et al ²²	1.71 (1.46–2.00)	<0.00001	50
Zhong et al ²⁴	1.64 (1.41–1.91)	<0.00001	31
Zeng et al ¹⁷	1.72 (1.48–2.00)	<0.00001	50
Zhang et al ²⁸	1.72 (1.47–2.02)	<0.00001	50
Shi et al ²⁷	1.72 (1.48–2.01)	<0.00001	50
Takahashi et al ²³	1.72 (1.48–2.00)	<0.00001	50
Ning et al ¹⁹	1.85 (1.58–2.15)	<0.00001	22
Gu et al ³⁰	1.72 (1.48–2.00)	<0.00001	50

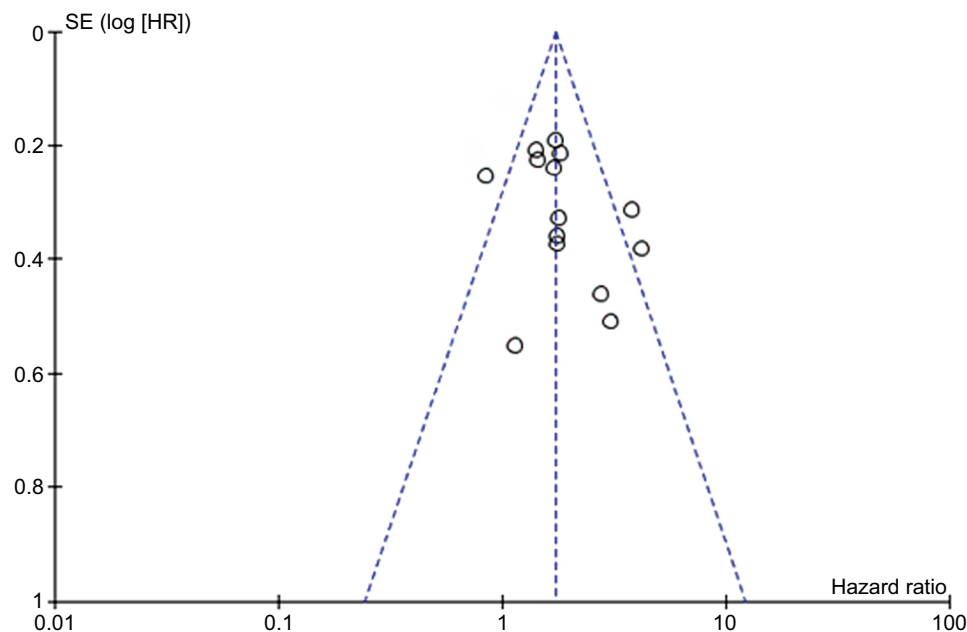


Figure 6 Funnel plot analysis for the potential publication bias among included studies.

included studies did not offer HRs directly, and we calculated the HRs using the Kaplan–Meier curves from these studies. This may compromise the validity of the conclusions. Third, publication bias may exist, as studies with small sample size or negative results are less likely to be reported, despite the fact that no significant publication bias was observed for the included studies upon sensitivity and funnel plot analyses. Therefore, larger, multicenter, and higher-quality studies with unified criteria for determining NEK2 expression are necessary to validate the conclusions of this study.

Conclusion

In summary, our meta-analysis has demonstrated that high NEK2 levels in different types of solid tumors are significantly associated with poor prognosis. Accordingly, NEK2 has potential value as a prognostic biomarker for tumors. Nevertheless, this conclusion needs to be confirmed by larger-scale prospective studies in the future.

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Disclosure

The authors report no conflicts of interest in this work.

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