ORIGINAL RESEARCH

Prognostic value of NEK2 overexpression in digestive system cancers: a meta-analysis and systematic review

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Background and objective: Many studies have reported that NEK2 is overexpressed in digestive system cancers (DSCs) and is also correlated with patient survival. We performed a meta-analysis to comprehensively evaluate the prognostic role of NEK2 expression in DSCs.

Materials and methods: A comprehensive literature search was performed using PubMed, EMBASE, and Web of Science. Synthesized hazard ratios (HRs) and odds ratios (ORs) with 95% confidence intervals (CIs) were used to evaluate the influence of NEK2 overexpression on the prognosis and clinicopathological features of patients with DSCs.

Results: A total of 13 studies involving 1,917 patients was included. Overall, patients with high NEK2 expression had poorer overall survival (HR =1.45; 95% CI: 1.15–1.83; P=0.002) and disease-free survival/recurrence-free survival (HR =2.28; 95% CI: 1.54–3.37; P<0.0001). Furthermore, subgroup analysis also suggested that elevated NEK2 expression was associated with poorer overall survival in patients with hepatocellular carcinoma (HR =1.45; 95% CI: 1.05–2.00; P=0.02) and colorectal cancer (HR =2.03; 95% CI: 1.16–3.54; P=0.01). Additionally, NEK2 overexpression was also associated with pretreatment serum AFP level (OR =1.79; 95% CI: 1.23–2.61; P<0.01) and portal vein thrombosis (OR =2.74; 95% CI: 1.22–6.17; P=0.01) in hepatocellular carcinoma.

Conclusion: NEK2 might act as a useful prognostic predictor and a potential therapeutic target in DSCs. However, multicenter homogeneous studies with larger sample sizes are needed to further confirm our findings owing to some limitations in our meta-analysis.

Keywords: NEK2, digestive system cancer, prognostic, meta-analysis

Introduction

Digestive system cancers (DSCs) represent considerable threats to human life and health.[1] Despite decreasing prevalence of cancer-related mortality during the past 2 decades, the incidence rates of DSCs, including cancers of the esophagus, pancreas, liver, and intestine, continue to increase.[2] Moreover, hepatocellular carcinoma (HCC) and colorectal cancer (CRC) remain the major medical problems and cause high mortality and heavy economic burdens.[3–5] Although diagnostic and therapeutic strategies for DSCs have been greatly improved, the prognosis of patients is still unsatisfactory. Clinicopathological characteristics have been widely used as prognostic factors in clinical practice, such as tumor differentiation, size, and number. However, the prognosis of patients with DSCs who have similar clinicopathological characteristics sometimes does not appear to be consistent. Hence, finding additional molecular markers with substantial prognostic value is urgently needed.

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NEK2 belongs to the serine/threonine kinase family and is important for the regulation of centrosome cell cycle, and mitosis.[6,7] In mitosis, the activation of Nek2 may lead to the phosphorylation of C-Nap1, rootletin, and β-catenin, which could promote centrosome separation by dissociating these proteins from centrosomes.[8–12] The increase in NEK2 expression may disturb the management of the mitotic checkpoint, subsequently contributing to the formation of centrosomal abnormalities and monopolar spindles.[7,13,14] Furthermore, uncontrolled NEK2 activity was involved in rearrangements and abnormal amplification of chromosomes, which leads to chromosome instability (CIN).[7,14–17] Overall, the biological functions of NEK2 mentioned indicate that the overexpression and aberrant activity of NEK2 might play a key role in tumorigenesis. Recently, several studies reported that NEK2 is overexpressed in various types of cancers, such as CRC breast cancer, pancreatic cancer, and lung adenocarcinoma.[18–24] In addition, the expression of NEK2 is closely associated with the prognosis and clinicopathological characteristics of CRC,[25,26] pancreatic ductal adenocarcinoma (PDAC),[19] and HCC.[27] However, there were inconsistencies regarding the prognostic role of NEK2 in DSCs,[19,28,29] which might be partly attributed to the small sample size of any single study exploring the prognostic significance of NEK2. Therefore, we performed a systematic review and meta-analysis to comprehensively evaluate the prognostic value of NEK2 in DSCs by combining the data of multiple relevant studies.

Materials and methods

To maximize clarity and transparency, this meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement issued in 2009.[30]

Literature search strategy and selection criteria

We comprehensively searched relevant studies assessing the relationship between NEK2 and the prognosis of patients with DSCs in PubMed, EMBASE, and Web of Science. The last search was performed in March 27, 2018. The search terms included: "NEK2 or NIMA related kinase 2" and "cancer or tumor or malignancy or carcinoma or neoplasm."

Studies were included if they met the following eligibility criteria: 1) the associations between NEK2 expression and the prognosis or the clinicopathological characteristics of patients with DSCs were reported and 2) the studies were published in English. On the contrary, the studies would be excluded if they met any of the exclusion criteria: 1) reviews, letters, comments, case reports, animal studies, noncomparative studies, and meeting abstracts; 2) articles with insufficient clinical data; and 3) duplicated articles.

Data extraction

Data were independently extracted by 2 investigators. The senior investigator resolved incompatibilities between the reviewers in data extraction. The basic information extracted from the literature included the name of first author, publication year, country, cancer type, the number of subjects, gender, tumor stage, detection methods, cutoff scores for NEK2 overexpression, and follow-up. The endpoints of interest included overall survival (OS), disease-free survival (DFS), recurrence-free survival (RFS), and clinicopathologic characteristics.

Quality assessment and statistical analysis

The quality of eligible articles was assessed using the Newcastle–Ottawa scale (NOS),[31] which consists of 3 aspects: selection, comparability, and outcome. The score of NOS ranged from 0 to 9, and articles with scores >6 were considered as high quality.

Cochrane Collaboration's Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) was used to synthesize all the data, and Stata version 12.0 (StataCorp LP, College Station, TX, USA) was employed to perform sensitive analysis, meta-regression analysis, and publication bias assessment. Synthesized hazard ratios (HRs) with 95% confidence intervals (CIs) were used to describe the prognostic value of NEK2 on survival outcomes in DSCs, and odds ratios (ORs) with 95% CIs were used to evaluate the relationship between the clinicopathologic characteristics and NEK2 expression. Heterogeneity among the published articles was assessed by Cochran's Q and Higgins I^2 statistics. The combination of $P<0.05$ and $I^2>50\%$ indicates significant heterogeneity, in which situation data were pooled using a random-effects model. Otherwise, a fixed-effects model was applied to pool the data. In order to minimize the influence of confounding factors and to explore potential source of heterogeneity, subgroup analysis was performed according to country, cancer type, sample size, and detection method. Sensitivity analysis was performed by omitting each individual article step-by-step to test the stability of the meta-analysis results. Furthermore, meta-regression analysis was also used to investigate potential source of heterogeneity. Publication bias was assessed by Begg's funnel plots[32] and Egger's test.[33] Symmetrical plots and P-value >0.05 indicate that there is no significant publication bias across the included studies.

Table 1 Basic characteristics of eligible articles

Study	Country	Cancer type	Case number	Age (years)	Sex (M/F)	Cancer stage or grade	Detection level	Cutoff scores (high/low)	Follow-up (months)	Survival analysis
Fu et al,[28] 2017	People's Republic of China	HCC	310	NR	252/49	Edmondson grade: I–III	Protein	Scores >6, 154/156	NR	OS
Fu et al,[27] 2017	People's Republic of China	HCC	100	NR	NR	NR	Protein	NR, 69/31	NR	OS, DFS
Lai et al,[35] 2017	People's Republic of China	HCC	52	NR	NR	Edmondson grade: I–IV	Protein	NR, 30/22	NR	NR
Li et al,[36] 2017	People's Republic of China	HCC	359	NR	NR	Edmondson grade: II–IV	RNA	NR, 60/293	NR	OS
Lin et al,[37] 2016	People's Republic of China	HCC	104	NR	32/12	TNM stage: I–III	Protein	++/+++[b]	NR	OS, RFS
Lu et al,[42] 2015	People's Republic of China	CRC	60	NR	32/28	TNM stage: I–IV	Protein	Scores >3,[a] 55/44	NR	OS
Neal et al,[26] 2014	United Kingdom	CRC	103	NR	57/46	AJCC stage: I–IV	Protein	>10%, 89/14	NR	OS, DFS, CSS
Takahashi et al,[25] 2014	Japan	CRC	180	NR	104/76	AJCC stage: 0–IV	RNA	NR, 90/9	35.16	OS
Wen et al,[38] 2016	People's Republic of China	HCC	64	NR	52/12	NR	Protein	NR	NR	NR
Wu et al,[39] 2017	People's Republic of China	HCC	154	NR	76/78	TNM stage: I–III	RNA	NR	NR	NR
Wubetu et al,[29] 2016	Japan	HCC	50	NR	34/16	TNM stage: I–IV	Protein	Scores >3,[a] 25/25	NR	OS, RFS
Zhang et al,[40] 2016	People's Republic of China	HCC	40	48.5	32/8	TNM stage: I–IV	Protein	NR, 25/15	NR	NR
Zhen et al,[19] 2014	People's Republic of China	PDAC	136	NR	72/64	TNM stage: I–IV	Protein	Scores >3,[a] 74/62	NR	OS

Notes: [a]Different scores with combination of percentage of positives cells and intensity; [b]the proportion of the staining tumor cells by optical analysis of the immunohistochemistry.
Abbreviations: CRC, colorectal cancer; HCC, hepatocellular carcinoma; PDAC, pancreatic ductal adenocarcinoma; DFS, disease-free survival; NR, not reported; OS, overall survival; RFS, recurrence-free survival.

When significant publication bias exists, the trim and fill method was used to estimate the influence of publication bias on the stability of meta-analysis results.[34]

Results

Search results and study characteristics

The main characteristics of the eligible, included studies are presented in Table 1. Overall, the initial search yielded 622 publications by retrieving PubMed, EMBASE, and Web of Science entries. After excluding 59 duplicate articles, 563 articles remained for screening of the title and abstract, after which process 517 articles were excluded for being reviews and comments (n=26) and irrelevant studies (n=491). Next, 46 articles were left for full-text screening and, consequently, 33 articles were excluded for being non-DSCs (n=4), conference abstracts (n=13), and lacking extractable data (n=16). Eventually, 13 articles involving 1,917 patients were included in this meta-analysis.[25–29,35–42] The details of the study search and selection processes are shown in Figure 1.

All of the eligible studies were published in the most recent 5 years (2014–2017). A total of 10 studies were investigated involving the Chinese population, 2 included Japanese individuals, and 1 represented a British study. A total of 9 studies analyzed the relationship between NEK2 and HCC, 3 studies reported the role of NEK2 in CRC, and 1 study referred to PDAC. The expression of NEK2 at the protein level was detected by immunohistochemistry (IHC) in 7 studies, and 2 studies utilized reverse transcription
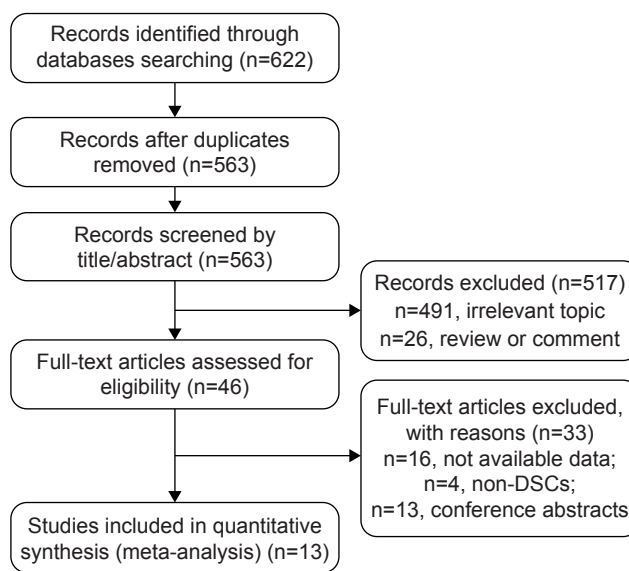

Figure 1 Flow chart representing the article selection process.
Abbreviation: DSC, digestive system cancer.

Table 2 The NOS quality evaluation of the included articles

Study ID	Selection				Comparability	Outcome			Total
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Fu et al,[28] 2017	★	★	★	★	★☆	☆	★	★	7
Fu et al,[27] 2017	☆	★	★	★	★☆	★	★	★	7
Lai et al,[35] 2017	★	☆	★	★	★☆	★	★	☆	6
Li et al,[36] 2017	★	★	☆	★	★☆	★	★	☆	7
Lin et al,[37] 2016	★	★	☆	★	★☆	★	★	☆	7
Lu et al,[42] 2015	★	★	☆	★	★☆	★	★	★	6
Neal et al,[26] 2014	★	★	★	★	★☆	★	★	★	7
Takahashi et al,[25] 2014	★	★	★	★	★☆	★	★	★	7
Wen et al,[38] 2016	★	☆	★	★	★☆	★	★	★	7
Wu et al,[39] 2017	☆	★	★	★	★☆	★	☆	★	6
Wubetu et al,[29] 2016	★	☆	★	★	★☆	★	★	★	7
Zhang et al,[40] 2016	☆	★	★	★	★☆	★	★	☆	6
Zhen et al,[19] 2014	☆	☆	★	★	★☆	★	★	★	6

Notes: ★ one score; ☆ no score.
Abbreviation: NOS, Newcastle–Ottawa Scale.

Study or subgroup	Log (HR)	SE	Weight (%)	HR IV, random, 95% CI
Fu et al,[28] 2017	−0.4137	0.4294	5.2	0.66 (0.28, 1.53)
Fu et al,[27] 2017	1.1256	0.4125	5.6	3.08 (1.37, 6.92)
Li et al,[36] 2017	0.207	0.0847	19.3	1.23 (1.04, 1.45)
Lin et al,[37] 2016	0.6851	0.3208	7.9	1.98 (1.06, 3.72)
Lu et al,[42] 2015	1.4839	0.4137	5.5	4.41 (1.96, 9.92)
Neal et al,[26] 2014	0.5032	0.296	8.7	1.65 (0.93, 2.95)
Takahashi et al,[25] 2014	0.4055	0.2018	12.8	1.50 (1.01, 2.23)
Wu et al,[39] 2017	0.4637	0.211	12.3	1.59 (1.05, 2.40)
Wubetu et al,[29] 2016	−0.1165	0.9679	1.3	0.89 (0.13, 5.93)
Zhen et al,[19] 2014	0.0619	0.028	21.4	1.06 (1.01, 1.12)
Total (95% CI)			**100**	**1.46 (1.17, 1.83)**

Heterogeneity: $\tau^2=0.06$; $\chi^2=32.74$, $df=9$ ($P=0.0001$); $I^2=73\%$
Test for overall effect: $Z=3.38$ ($P=0.0007$)

HR IV, random, 95% CI

0.1 0.2 0.5 1 2 5 10
Favors (low NEK2)   Favors (high NEK2)

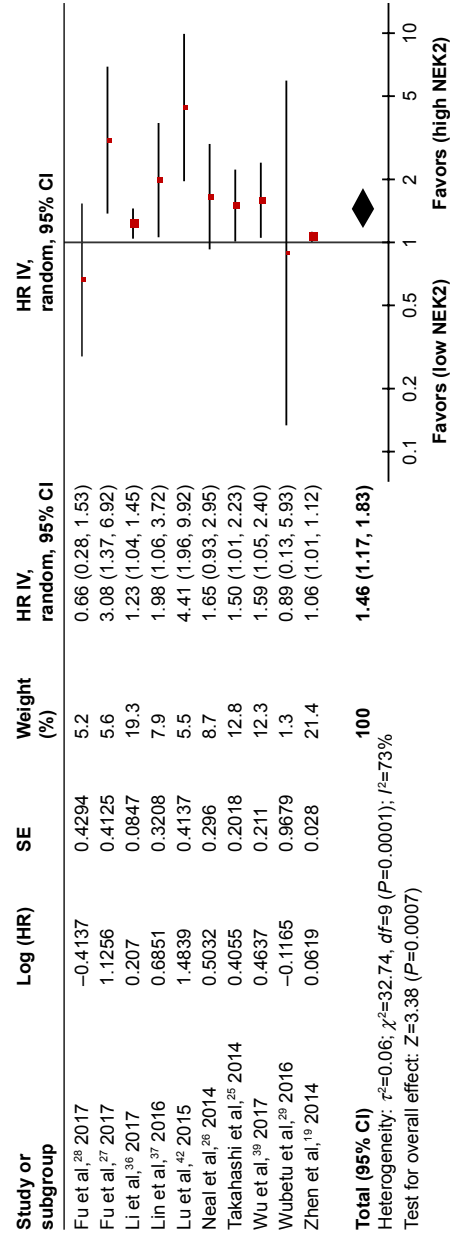**Figure 2** Pooled results for the relationship between NEK2 and OS in patients with DSCs.
Note: Only 10 of the 13 studies investigated OS.
Abbreviations: OS, overall survival; DSC, digestive system cancer; SE, standard error.
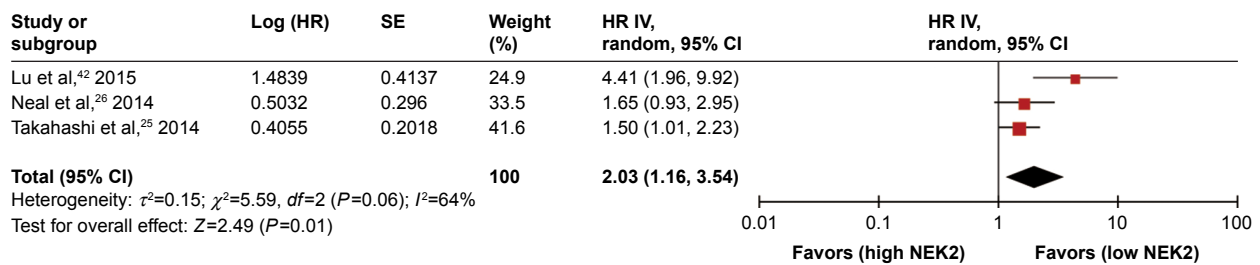
Study or subgroup	Log (HR)	SE	Weight (%)	HR IV, random, 95% CI	HR IV, random, 95% CI
Lu et al,[42] 2015	1.4839	0.4137	24.9	4.41 (1.96, 9.92)	
Neal et al,[26] 2014	0.5032	0.296	33.5	1.65 (0.93, 2.95)	
Takahashi et al,[25] 2014	0.4055	0.2018	41.6	1.50 (1.01, 2.23)	
Total (95% CI)			**100**	**2.03 (1.16, 3.54)**	

Heterogeneity: τ^2=0.15; χ^2=5.59, df=2 (P=0.06); I^2=64%
Test for overall effect: Z=2.49 (P=0.01)

0.01   0.1   1   10   100

Favors (high NEK2)   **Favors (low NEK2)**

Figure 3 Pooled results for the relationship between NEK2 and OS in CRC patients.
Abbreviations: OS, overall survival; CRC, colorectal cancer; SE, standard error.

polymerase chain reaction (RT-qPCR) to describe the expression of NEK2 at the RNA level, and 1 study used TCGA RNASeqV2 database. In addition, the prognostic value of NEK2 in OS was investigated in 10 studies involving 1,556 patients, and associations between NEK2 expression and DFS/RFS were described in 4 studies with 357 patients. Upon quality assessment of the included studies, all of the eligible studies were found to be of high quality and were scored as 6 or more based on NOS values (Table 2).

Prognostic role of NEK2 in digestive system tumors with regard to OS

A total of 10 studies involving 1,556 patients described the relationship between NEK2 and OS.[26,35,36,38–41,43,44,46] Since significant heterogeneity among the studies was found (I^2=73%, P<0.01), the randomized effects model was used to calculate the pooled HR and 95% CI. Elevated expression of NEK2 was significantly correlated with worse OS (HR =1.45 95% CI: 1.15–1.83; P=0.002, Figure 2). Additionally, subgroup analysis was conducted based on cancer type, country, sample size, and detection level. We found that high expression of NEK2 could act as an independent prognostic factor in CRC (HR =2.03; 95% CI: 1.16–3.54; P=0.01, Figure 3) and HCC (HR =1.45; 95% CI: 1.05–2.00; P=0.02, Figure 4). Furthermore, for the subgroup of country, it was observed that NEK2 was closely

correlated with poorer OS in Chinese populations (HR =1.46; 95% CI: 1.13–1.90; P<0.01). Similarly, NEK2 was significantly associated with worse OS in large sample sizes (n>150: HR =1.30; 95% CI: 1.05–1.61; P=0.02) and in small sample size groups (n≤150: HR =1.90; 95% CI: 1.12–3.21; P=0.02). For the subgroup involving detection level, we found that patients with high NEK2 RNA and protein expression both had a worse OS (RNA: HR =1.30; 95% CI: 1.13–1.50; P<0.01; protein: HR =1.65; 95% CI: 1.03–2.63; P=0.04). All results of subgroup analysis are shown in Table 3.

Prognostic role of NEK2 in digestive system tumors in DFS/RFS

Considering the similarity between DFS and RFS, we merged these data to evaluate the prognostic value of NEK2. Due to the absence of heterogeneity among articles (I^2=0%, P=0.54), a fixed-effects model was used to pool the HR values. The results indicated that overexpression of NEK2 was related to significantly worse DFS/RFS (HR =2.28; 95% CI: 1.54–3.37; P<0.0001) (Figure 5).

Relationship of NEK2 with clinicopathological characteristics of DSCs

Owing to the differences in clinicopathological features of various cancers, the association of high NEK2 expression
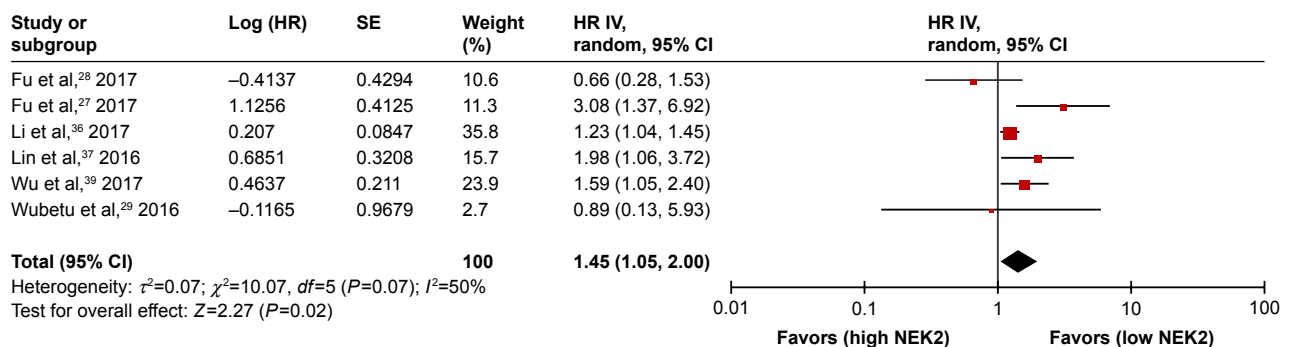
Study or subgroup	Log (HR)	SE	Weight (%)	HR IV, random, 95% CI	HR IV, random, 95% CI
Fu et al,[28] 2017	−0.4137	0.4294	10.6	0.66 (0.28, 1.53)	
Fu et al,[27] 2017	1.1256	0.4125	11.3	3.08 (1.37, 6.92)	
Li et al,[36] 2017	0.207	0.0847	35.8	1.23 (1.04, 1.45)	
Lin et al,[37] 2016	0.6851	0.3208	15.7	1.98 (1.06, 3.72)	
Wu et al,[39] 2017	0.4637	0.211	23.9	1.59 (1.05, 2.40)	
Wubetu et al,[29] 2016	−0.1165	0.9679	2.7	0.89 (0.13, 5.93)	
Total (95% CI)			**100**	**1.45 (1.05, 2.00)**	

Heterogeneity: τ^2=0.07; χ^2=10.07, df=5 (P=0.07); I^2=50%
Test for overall effect: Z=2.27 (P=0.02)

0.01   0.1   1   10   100

Favors (high NEK2)   **Favors (low NEK2)**

Figure 4 Pooled results for the relationship between NEK2 and OS in liver cancer patients.
Note: Only 6 of included studies investigated OS in liver cancer.
Abbreviations: OS, overall survival; SE, standard error.

Table 3 Results of subgroup analysis of synthesized HRs of OS of patients with NEK2

Subgroup analysis	Number of studies	Number of patients	Pooled HR (95% CI)	P-value	Heterogeneity		
					I² (%)	P-value	Model
Tumor type							
HCC	6	1,233	1.45 [1.05, 2.00]	0.02	50	0.07	Fixed model
CRC	3	343	2.03 [1.16, 3.54]	0.01	64	0.06	Randomized model
PDAC	1	136	1.06 [1.00, 1.12]	0.05	–	–	–
Country							
People's Republic of China	7	1,379	1.46 [1.13, 1.90]	<0.01	79	<0.01	Randomized model
United Kingdom	1	103	1.65 [0.93, 2.95]	0.09	–	–	–
Japan	2	230	1.47 [1.00, 2.16]	0.05	0	0.60	Fixed model
Sample size							
>150	4	1,003	1.30 [1.05, 1.61]	0.02	30	0.32	Fixed model
≤150	6	709	1.90 [1.12, 3.21]	0.02	79	<0.01	Randomized model
Detection level							
Protein	7	863	1.65 [1.03, 2.63]	0.04	76	<0.01	Randomized model
RNA	3	693	1.30 [1.13, 1.50]	<0.01	0	0.40	Fixed model

Abbreviations: OS, overall survival; HCC, hepatocellular carcinoma; CRC, colorectal cancer; PDAC, pancreatic ductal adenocarcinoma.

with clinicopathological characteristics was investigated according to cancer type. As presented in Table 4, NEK2 levels exhibited no obvious correlation with tumor size, differentiation, HBsAg status, hepatic cirrhosis, tumor number and differentiation in HCC, and lymph node metastasis in CRC. However, it was observed that high expression of NEK2 was significantly associated with positive AFP (6 studies, n=616, + vs −, OR =1.79; 95% CI: 1.23–2.61; P<0.01) and the occurrence of portal vein thrombosis (3 studies, n=206, + vs −, OR =2.74; 95% CI: 1.22–6.17; P=0.01).

Sensitivity analysis and meta-regression analysis

Sensitivity analysis was performed to test the robustness of the synthesized results of the effect of NEK2 on OS in DSCs by omitting single studies, stepwise. We found that the pooled HR for OS was not altered significantly when excluding any individual study, suggesting that our synthesized results of the effect of NEK2 on OS were rigorous

(Figure 6). The robustness of the synthesized result for DFS/RFS was not evaluated by sensitivity analysis because of limited numbers of relevant studies.

Considering the significant heterogeneity for the pooled HR data for OS, meta-regression analysis was further conducted to identify the source of heterogeneity, based on the cancer type, country, sample size, and detection level. However, similar to the results of our subgroup analysis, the outcomes of meta-regression analysis indicated that these factors might not account for the heterogeneity either (Table 5).

Publication bias

We used Egger's and Begg's tests to evaluate publication bias in the meta-analysis of the influence of NEK2 on OS in DSCs. It was found that Begg's test had a value of 0.79, Egger's test had a value of 0.93, and the funnel plot was symmetrical, indicating that there was no significant publication bias (Figure 7). Publication bias was not assessed in the
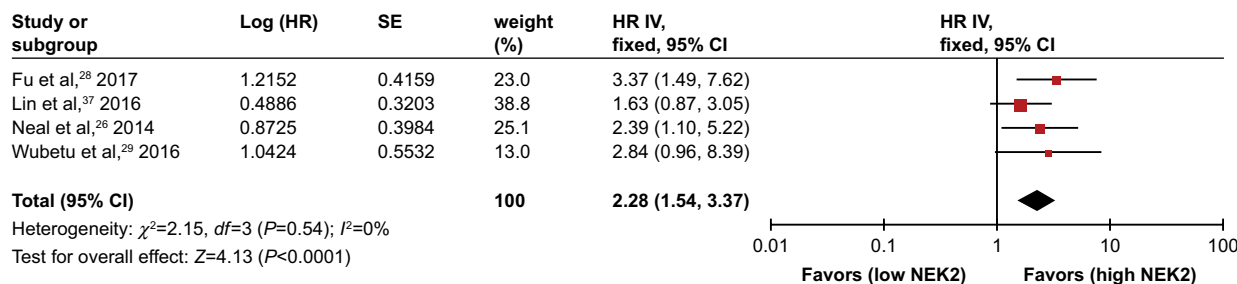
Study or subgroup	Log (HR)	SE	weight (%)	HR IV, fixed, 95% CI	HR IV, fixed, 95% CI
Fu et al,[28] 2017	1.2152	0.4159	23.0	3.37 (1.49, 7.62)	
Lin et al,[37] 2016	0.4886	0.3203	38.8	1.63 (0.87, 3.05)	
Neal et al,[26] 2014	0.8725	0.3984	25.1	2.39 (1.10, 5.22)	
Wubetu et al,[29] 2016	1.0424	0.5532	13.0	2.84 (0.96, 8.39)	
Total (95% CI)			100	**2.28 (1.54, 3.37)**	

Heterogeneity: χ^2=2.15, df=3 (P=0.54); I²=0%
Test for overall effect: Z=4.13 (P<0.0001)

0.01   0.1   1   10   100
Favors (low NEK2)   Favors (high NEK2)

Figure 5 Pooled results for the relationship between NEK2 and DFS/RFS in patients with DSCs.
Notes: Only 4 of the 13 studies investigated DFS/RFS.
Abbreviations: DFS/RFS, disease-free survival/recurrence-free survival; DSC, digestive system cancer.

Table 4 Meta-analysis results of the associations of NEK2 with clinicopathological parameters

Clinicopathological parameter	Number of studies	OR (95% CI)	P-value	Heterogeneity test	
				I²	P-value
HCC					
Tumor size (≥5 vs <5 cm)	6	1.72 [0.86, 3.45]	0.70	41	0.16
Differentiation (well/moderate vs poor)	5	0.83 [0.39, 1.73]	0.61	65	0.02
HBsAg (+ vs −)	4	0.91 [0.58, 1.45]	0.70	41	0.16
Liver cirrhosis (+ vs −)	4	0.90 [0.63, 1.29]	0.56	0.0	0.87
Tumor number (multiple vs single)	4	1.14 [0.72, 1.80]	0.57	0.0	0.68
AFP (+ vs −)	6	1.79 [1.23, 2.61]	<0.01	7.4	0.37
Portal vein thrombosis (+ vs −)	3	2.74 [1.22, 6.17]	0.01	40	0.19
CRC					
Tumor differentiation (moderate–well vs poor)	3	0.51 [0.24, 1.08]	0.08	10	0.33
Lymph node metastasis (+ vs −)	3	1.74 [0.28, 10.69]	0.55	87	<0.01

Abbreviations: AFP, alpha fetoprotein; HCC, hepatocellular carcinoma; CRC, colorectal cancer.

meta-analysis of the influence of NEK2 on DFS/RFS owing to the limited number of relevant studies.

Discussion

It is believed that abnormal cell cycle regulation is important for the occurrence and development of cancers, and NEK2 might play a crucial role in regulating cell cycle via promoting the separation of centrosome in the process of cell division and orchestrating the composition and function of centrosomes.[13,43,44] Furthermore, several studies reported that NEK2 is overexpressed in various cancers and was related to unfavorable prognosis and clinicopathological characteristics,[18–24] indicating the involvement of NEK2 in tumorigenesis. However, the conclusions were inconsistent with respect to the prognostic role of NEK2 in DSCs. Therefore, the current meta-analysis was performed to comprehensively evaluate the influence of NEK2 overexpression

on the prognosis and clinicopathological characteristics of patients with DSCs.

In the present study, we comprehensively analyzed the survival data of 1,917 patients from 13 studies and found that overexpression of NEK2 was significantly correlated with worse OS and DFS in patients with DSCs. Considering that some confounding factors might affect the reliability of our synthesized results, subgroup analysis and meta-regression were conducted according to several potential confounding factors, such as cancer type, country, sample size, and detection level. From the results, we observed that CRC and HCC patients with elevated NEK2 expression had a poorer survival prognosis. Moreover, with different sample sizes and detection levels, the overexpression of NEK2 consistently acted as an indicator of worse OS in patients with DSCs. Additionally, we also investigated the relationship between NEK2 expression and clinicopathological characteristics in patients with DSCs. Our results indicated that high expression of NEK2 was significantly associated with serum positive AFP levels and portal vein thrombosis in HCC, which might partly explain the role of NEK2 overexpression as an indicator of poorer OS in HCC.
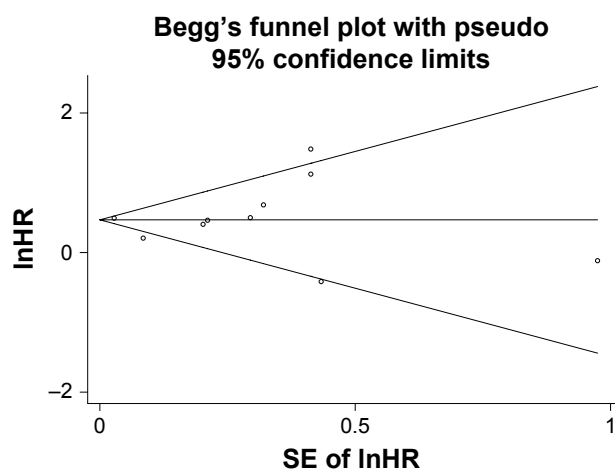

Figure 6 Sensitive analysis of the influence of individual studies on the pooled HR of OS.
Abbreviation: SE, standard error.

Table 5 The influence of study characteristics on heterogeneity assessed by meta-regression

Study characteristic	P-value	Regression coefficient	95% CI
Cancer type (HCC vs CRC vs PDAC)	0.601	1.09	(0.74–1.62)
Country (People's Republic of China vs Japan vs United Kingdom)	0.89	0.97	(0.59–1.59)
Sample size (>150 vs ≤150)	0.09	1.43	(0.93–2.20)
Detection level (protein vs RNA)	0.24	0.79	(0.51–1.22)

Abbreviations: HCC, hepatocellular carcinoma; CRC, colorectal cancer; PDAC, pancreatic ductal adenocarcinoma.

**Meta–analysis random–effects estimates
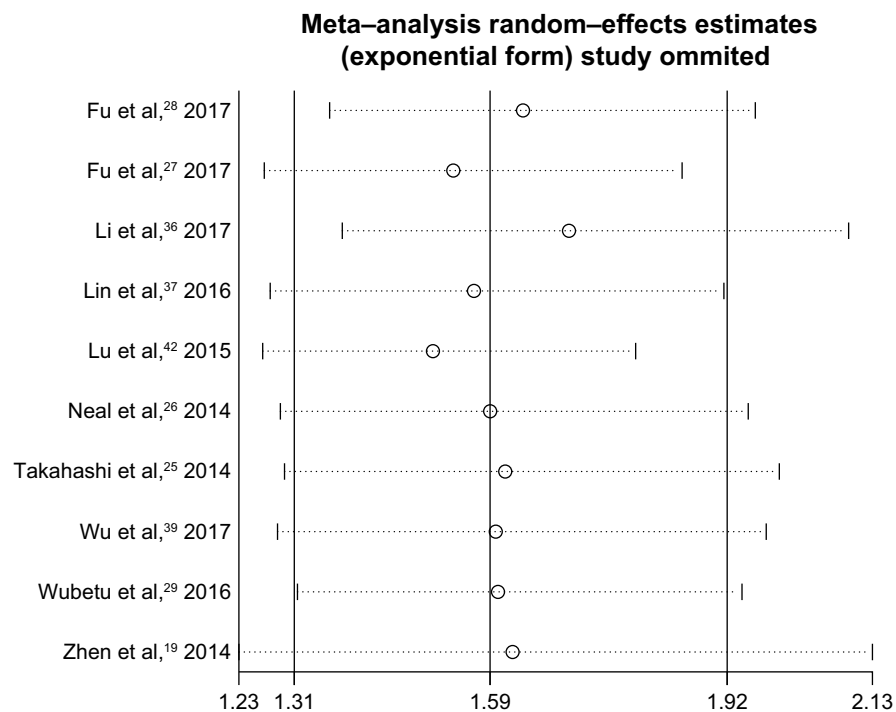(exponential form) study ommited**

Figure 7 Begg's funnel plot for potential publication bias involving eligible studies reporting OS.
Abbreviation: OS, overall survival.

To date, several mechanisms have been reported to be responsible for the oncogenic roles of NEK2, which might explain the inverse association between NEK2 expression and prognosis of patients with DSCs. Elevated expression of NEK2 and its homologs could lead to abnormal aggregation of centrosomes and splitting of chromatin, and finally dramatic mitotic progress, which may contribute to the aberrant proliferation of cells.[45,46] It has been reported that NEK2 overexpression could enhance tumor progression by involving the activation of the PI3K/AKT pathway.[16,46] For instance, Li et al[36] found that overexpression of NEK2 could promote the invasion and metastasis of HCC by activating AKT signaling and upregulating the expression of MMP-2. Additionally, NEK2 overexpression was also reported to abnormally activate the MAPK and Wnt/β-catenin pathways, which contributed to the proliferation, invasion, and migration of cancer cells.[26,37,40] More importantly, Lin et al[37] and Fu et al[27] found that deletion of NEK2 could significantly reduce stem-like properties, proliferation, colony formation, migration, and invasion in in vivo tumors formed by HCC cell lines, indicating that NEK2 has certain biological functions that driver genes specifically have. Therefore, we speculated that NEK2 might act as a driver gene and exhibit the potential to be a useful molecular target in HCC and in other digestive system tumors. Of course, more rigorous studies are required to determine whether NEK2 is a driver or passenger gene in digestive system tumors.

There were some limitations to our meta-analysis, which should be considered when interpreting our results. First, all the eligible studies were retrospectively designed, which inevitably had a bias risk and influenced the dependability of our synthesized results. Second, most of the studies were conducted in Asian populations, so our meta-analysis might not represent the worldwide population. Third, although our subgroup analysis and meta-regression indicated that cancer type, country, detection method, and cutoff value might not be responsible for the source of heterogeneity, the reliability of our pooled results were still challenged by significant heterogeneity. Thus, homogeneous studies are needed to further investigate the prognostic role of NEK2 in patients with DSCs. Fourth, only 4 eligible studies with small sample sizes provided data on DFS/RFS for our meta-analysis, which might be insufficient to draw a robust conclusion in this regard. Last but not least, in this meta-analysis, some survival data were manually extracted from Kaplan–Meier curves, which also caused unavoidable bias and heterogeneity.

Conclusion

In summary, this study demonstrated that NEK2 could act as a useful prognostic indicator and as a promising therapeutic target in DSCs. However, considering the limitations mentioned above, multicenter homogeneous studies with lager sample sizes are needed to further confirm our findings. Meanwhile, the relevant mechanisms underlying

the prognostic roles of NEK2 in digestive system tumors, including NEK2 interaction with other genes or molecules and tumor-associated signaling pathways, should also be further explored in the future.

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Disclosure

The authors report no conflicts of interest in this work.

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