

# Prognostic and clinicopathological significance of kinesin family member C1 in various cancers

## A meta-analysis

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### Abstract

**Background:** Kinesin family member C1 (KIFC1), a C-type kinesin motor protein, plays important roles in centrosome assembly and intracellular transport. Numerous studies have focused on the prognostic value of KIFC1 in malignant tumors and the relationship between KIFC1 expression and clinicopathological traits of cancer patients, but the studies remain controversial. And no meta-analysis has yet shown the association between KIFC1 and various cancers.

**Methods:** Systematic retrieval was carried out within several databases, including PubMed, Embase, Web of Science, Wanfang and China National Knowledge Infrastructure (CNKI). In addition, hazard ratios (HR) and relative risks (RR) with 95% confidence intervals (CIs) were calculated to examine the risk or hazard correlation by Stata SE15.1.

**Results:** Eleven studies with the overall 2424 participants were included in this research. High KIFC1 expression was remarkably correlated with worse OS (HR=1.33, 95% CI=1.07–1.60) and poorer relapse-free survival (HR=2.28, 95% CI=1.75–2.80). In subgroup analysis, high KIFC1 expression was a negative predictor for OS in patients with ovarian cancer ( $P < .001$ ), breast cancer ( $P < .001$ ), hepatocellular carcinoma ( $P < .001$ ), and non-small cell lung cancer ( $P < .001$ ), but not for esophageal squamous cell carcinoma ( $P = .246$ ). Moreover, high levels of KIFC1 were related with positive lymph node metastasis (RR=1.23, 95% CI=1.01–1.50,  $P = .041$ ) and advanced tumor node metastasis (TNM) stage (RR=1.55, 95% CI=1.27–1.89,  $P < .001$ ).

**Conclusions:** KIFC1 overexpression indicates poor prognosis and more serious clinicopathological characteristics in kinds of malignancies. Thus, we conclude that KIFC1 could be a target for clinical diagnosis and treatment of various cancers.

**Abbreviations:** CI = confidence interval, HR = hazard ratio, KIFC1 = kinesin family member C1, OS = overall survival, RFS = relapse-free survival, RR = relative risk.

**Keywords:** cancers, KIFC1, meta-analysis, prognosis

## 1. Introduction

Cancer is a leading cause of death worldwide and a major problem affecting public health.<sup>[1]</sup> In spite of the great progress of diagnostic methods and treatments, accurate cancer prognosis

remains challenging.<sup>[2]</sup> The possible causes are the recurrence of cancers and the difficulty of early diagnosis. Effective biomarkers are powerful helpers in predicting cancer prognosis and monitoring cancer development. Therefore, clinicians and researchers are devoting great efforts to finding optimal prognostic biomarkers for cancer.

Kinesin family member C1 (KIFC1), namely HSET, is a minus end-directed motor protein<sup>[3]</sup> and a member of the kinesin-14 family.<sup>[4]</sup> It facilitates the crosslinking and sliding of microtubules, spindle pole focusing and vesicle transport.<sup>[5,6]</sup> KIFC1 also plays a vital role in centrosome clustering in cancer cells.<sup>[7]</sup> Centrosome amplification is a hallmark of cancers and contributes to genomic instability.<sup>[8]</sup> However, the extra centrosomes could lead to missegregation and aneuploidy eventually leading to cell death. KIFC1 may rescue cancer cells via centrosome clustering to limit negative effects of multipolar mitosis, which supports their survival.<sup>[9]</sup> By contrast, KIFC1 is nonessential for bipolar spindle assembly in normal somatic cells.<sup>[10]</sup> It has been testified that KIFC1 expression is upregulated in various human cancers, such as ovarian cancer, lung cancer, breast cancer, and hepatocellular carcinoma.<sup>[10–13]</sup> Furthermore, High KIFC1 expression induces resistance to docetaxel-mediated apoptosis in breast cancer cells<sup>[14]</sup> and its expression levels predict the risk of brain metastasis in lung cancer.<sup>[15]</sup> It is speculated that KIFC1 may play a vital role in the occurrence and development of various cancers. And further research on KIFC1 will provide new ideas for molecular therapy and targeted therapy of cancers.

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However, the present researches remain disputed and there is no correlated meta-analysis to evaluate the diagnostic accuracy of preoperative KIFC1 in malignancies. In this research, we systematically collected published evidences to reveal the relationship between KIFC1 expression and overall survival (OS), relapse-free survival (RFS) and clinicopathological characteristics of cancer patients. Afterwards, we could possibly identify a new biomarker for cancer prognosis and provide a reference for clinical diagnosis and risk assessment.

## 2. Methods

### 2.1. Literature retrieval strategy

A systematically comprehensive search was performed in different databases, including PubMed, Embase, Web of Science, Wanfang, and CNKI. The retrieval keywords were as follows: (“KIFC1” OR “HSET” OR “kinesin family member C1”) AND (“cancer” OR “tumor” OR “neoplasm” OR “carcinoma” OR “malignancy”) AND “prognosis.” In addition, manual examination was also performed in references from the retrieved literatures to further identify potentially relevant studies.

### 2.2. Selection criteria

Eligible materials were collected into this meta-analysis based on the following criteria:

- (1) KIFC1 expression was detected in cancers;
- (2) illuminated the relationship between the level of KIFC1 and OS or RFS; and
- (3) hazard ratios (HR) and 95% confidence intervals (CI) can be accessed directly or estimated.

Exclusion criteria were:

- (1) non-English publication;
- (2) studies with insufficient data;
- (3) case reports, letters, reviews, and expert opinions.

### 2.3. Data extraction and quality assessment

The extracted data and information were following: the first author's name, year of publication, country, cancer type, number of patients, gender, method of assessing KIFC1 expression, cut-off value, follow-up times (months), outcome measures, analysis type, clinicopathological characteristics, HRs with 95% CI, prognostic value (OS, RFS), and *P*-values. For studies that only provide the survival curve in figures, the approximated survival data were extracted by Engauge Digitizer.

### 2.4. Statistical analysis

All related statistical analyses were carried out using Stata SE15.1. The HR with 95% CI for OS and RFS were computed, as well as the relative risks (RRs) for clinical pathology parameters. Chi-squared tests and  $I^2$  statistics were used to assess heterogeneity among studies.  $I^2 > 50\%$  and  $P_{\text{heterogeneity}} \leq .10$  were used as criteria for statistically significant heterogeneity. Studies with markedly heterogeneity adopted the random-effect model. Otherwise ( $I^2 \leq 50\%$ ,  $P_{\text{heterogeneity}} > .10$ ), a fixed-effects model was used. In addition, the publication bias was assessed with a funnel plot and the Egger test, in which case  $P < .05$  was recognized as statistically significant.

## 3. Results

### 3.1. Characteristics of the included studies

The above-described keyword search in the PubMed, Web of Science, Embase, Wanfang, and CNKI databases yielded 389 potentially relevant studies. After screening the titles and abstracts, 378 studies were excluded, and 11 studies<sup>[7,11–13,16–22]</sup> were included in this meta-analysis, encompassing a total of 2424 patients (Fig. 1). Table 1 lists the main information of the 11 eligible studies. All included studies were published between 2014 and March 2018, and the sample sizes ranged from 48 to 737. Four researches were from China, 3 from Japan, 3 from the USA and 1 from Italy. A variety of cancers were investigated, including hepatocellular carcinoma, esophageal squamous cell carcinoma, renal cell carcinoma, non-small cell lung cancer, ovarian cancer, triple-negative breast cancer, gastric cancer, and prostate cancer. The cut-off values used in these studies were not uniform. Four studies had a KIFC1 cut-off value of immunostaining  $>10\%$ , 1 study applied 1 standard deviation above the mean, and 2 studies used staining indices greater than 8 and 2, respectively. The remaining 4 studies obtained data from datasets, each with different cut-off values, which were provided in Table 1. Among the 11 studies, 8 were available to appraise HR of OS for various cancers, and 3 of these directly reported HRs with the corresponding 95% CIs, while 5 studies only provided Kaplan–Meier curves.

### 3.2. Correlation between KIFC1 expression levels and OS

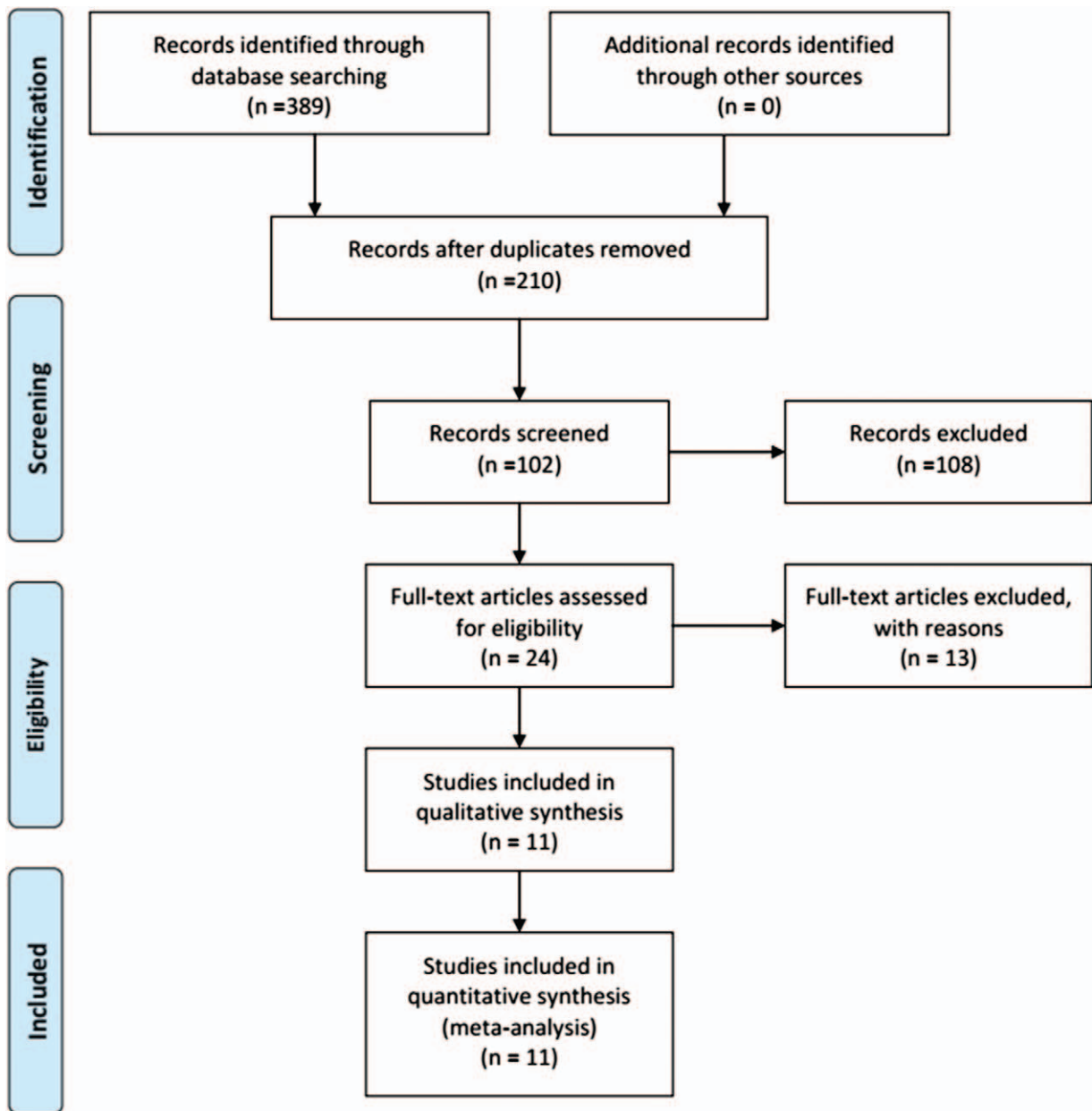
There were 8 studies including 2105 patients showed HRs for OS in this meta-analysis. A random-effect model was adopted in the analysis of data between KIFC1 expression level and OS with significant heterogeneity ( $I^2 = 57.1\%$ ,  $P_{\text{heterogeneity}} = .004$ ). The outcome indicated that a shorter OS in the patients with high expression of KIFC1 than in the low KIFC1 expression (HR = 1.33, 95% CI = 1.07–1.60,  $P < .001$ ; Fig. 2). Subgroup analyses classified by cancer type and analysis type were processed to further investigate the correlation between high KIFC1 expression and OS. A significant association between KIFC1 expression and OS remained in hepatocellular carcinoma ( $P < .001$ ), ovarian cancer ( $P < .001$ ), breast cancer ( $P < .001$ ), non-small cell lung cancer ( $P < .001$ ), but not in esophageal squamous cell carcinoma ( $P = .246$ ) (Table 2). In terms of analysis type, significant correlation was found in univariate analysis (HR = 1.39, 95% CI = 1.10–1.68), but not in multivariate analysis (HR = 0.96, 95% CI = 0.40–1.53; Fig. 2).

### 3.3. Correlation between KIFC1 expression level and RFS

The HRs for RFS from 3 studies involving 1162 patients was available. A fixed-effect model was used on account of no significant heterogeneity ( $I^2 = 0.0\%$ ,  $P_{\text{heterogeneity}} = .898$ ). The pooled HR for RFS was 2.28 (95% CI = 1.75–2.80,  $P < .001$ ), which indicated a significant association between high KIFC1 levels and poorer RFS, as shown in Figure 3. A subgroup analysis based on the analysis model revealed that increased expression of KIFC1 was a negative predictor for RFS in both univariate and multivariate analysis.

### 3.4. Correlation between KIFC1 expression levels and clinicopathological characteristics

Associations between high expression of KIFC1 and clinicopathological characteristics were summarized as pooled RRs with



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Figure 1. Flow chart of the literature retrieval and selection process.

95% CIs, as shown in Table 3. The results suggested that elevated KIFC1 expression levels were associated with advanced TNM stage (RR=1.55, 95% CI=1.27–1.89,  $P < .001$ ) and positive lymph node metastasis (RR=1.23, 95% CI=1.01–1.50,  $P = .041$ ). Whereas, insignificant association was discovered between high expression of KIFC1 and gender (RR=1.03, 95% CI=0.92–1.15,  $P = .631$ ), age (RR=1.01, 95% CI=0.84–1.22,  $P = .883$ ), depth of invasion (RR=1.34, 95% CI=0.96–1.86,  $P = .087$ ), or tumor diameter (RR=0.64, 95% CI=0.39–1.03,  $P = .066$ ). Currently, knowledge about the relation between high KIFC1 expression and other clinicopathological characteristics is still limited.

### 3.5. Publication bias and sensitivity analysis

The funnel plot for publication bias showed symmetry (Fig. 4). And no publication bias was detected by the Begg test ( $P = .827$ ) and Egger test ( $P = .310$ ) for OS, respectively. Additionally, the sensitivity analysis results showed that omitting single 1 study had no significant influence on pooled HRs, confirming the robustness of the result (Fig. 5).

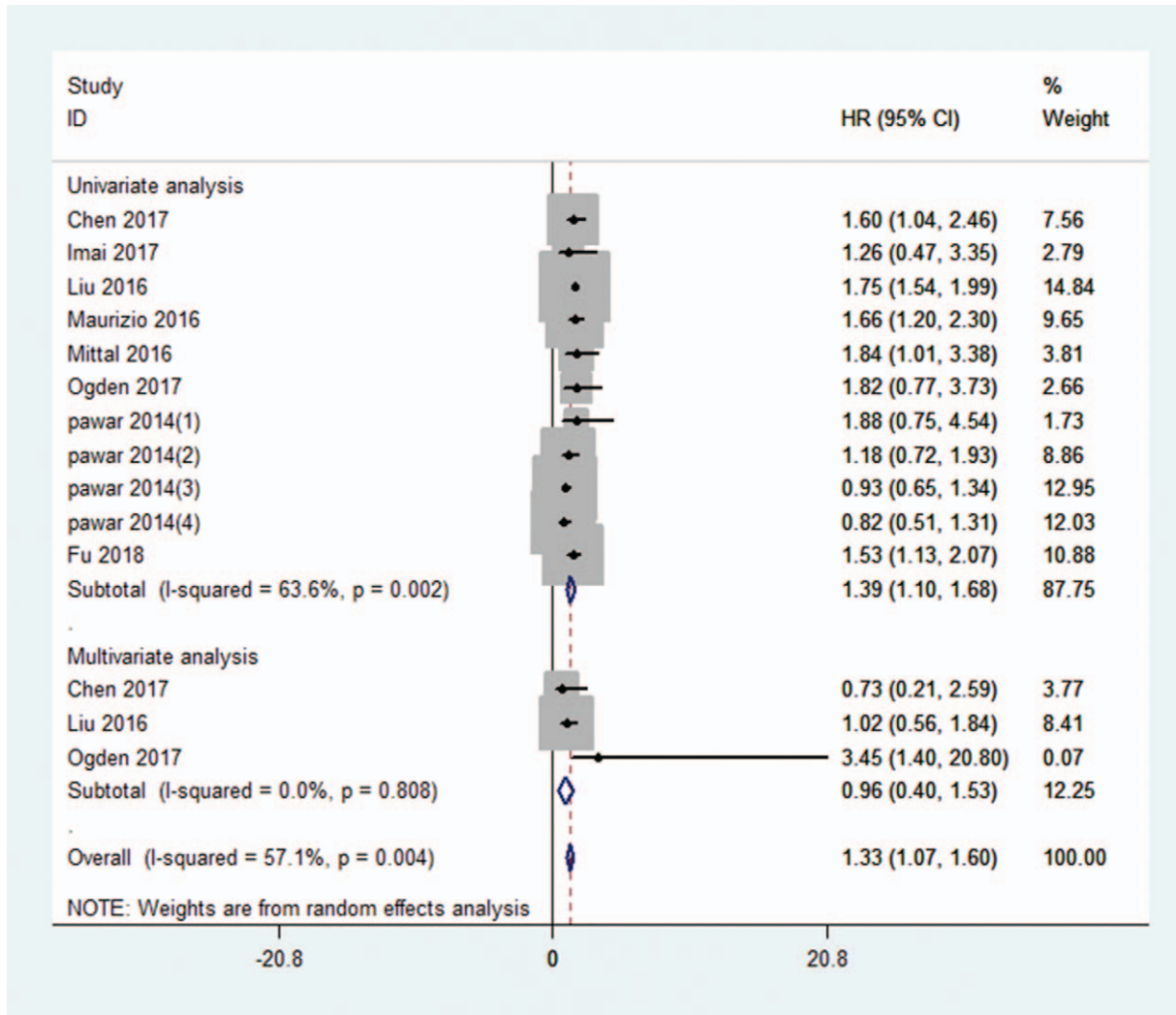
## 4. Discussion

In spite of its high incidence, cancer is usually discovered comparatively late, even though it is much easier to treat if

**Table 1**  
**Characteristics of enrolled studies in the meta-analysis.**

Study	Year	Country	Cancer type	Number	Gender (male/female)	Test method	Tumor stage (I/II/III/IV)	Cut-off value	Follow-up, mo	Outcome measures	Analysis type
Maurizio <sup>[7]</sup>	2016	Italy	BC	737	NR	Dataset	NR	NR	>60	OS, RFS	M and U
Pawar <sup>[11]</sup>	2014	USA	EOC	443	NR	Dataset	NR	Average KIFC1 expression	>60	OS	U
Liu <sup>[12]</sup>	2016	China	NSCLC	90	49/41	Tissue	57/33 (I-II/III-IV)	Staining index* ≥8	>60	OS	M and U
Fu <sup>[13]</sup>	2018	China	HCC	91	76/15	Tissue	69/22 (I-II/III-IV)	Staining index* ≥2	>60	OS, RFS	M and U
Chen <sup>[16]</sup>	2017	China	HCC	295	198/97	Dataset	143/70/78/4	Above Median	>60	OS	M and U
Imai <sup>[17]</sup>	2017	Japan	ESCC	132	117/15	Tissue	60/71 (II-IV)	Immunostaining	>80	OS	M and U
								>10%			
Li <sup>[18]</sup>	2018	China	RCC	48	33/15	Tissue	10/38 (I-II/III-IV)	Immunostaining	60	OS, DFS	U
								>10%			
Mittal <sup>[19]</sup>	2016	USA	SOC	154	NR	Dataset	9/9/126/10	NR	60	OS	M and U
Ouel <sup>[20]</sup>	2016	Japan	GC	114	69/45	Tissue	53/61 (II-IV)	Immunostaining	NR	NR	M and U
								>10%			
Sekino <sup>[21]</sup>	2017	Japan	PCA	157	NR	Tissue	NR	Immunostaining	>60	RFS	M and U
								>10%			
Ogden <sup>[22]</sup>	2017	USA	TNBC	163	NR	IHC+TMA	109/52 (I-II/III-IV)	1 standard deviation above the mean	>60	OS, nob	M and U

BC=breast cancer, DFS=disease-free survival, EOC=epithelial ovarian cancer, ESCC=esophageal squamous cell carcinoma, GC=gastric cancer, HCC=hepatocellular carcinoma, IHC=immunohistochemistry, M=multivariate, NR=not reported, NSCLC=non-small cell lung cancer, OS=overall survival, PCA=prostate cancer, PFS=progression-free survival, RCC=renal cell carcinoma, RFS=relapse-free survival, SOC=serous ovarian adenocarcinoma, TMA=tissue microarray, TNBC=triple-negative breast cancer, U=univariate.  
 \* Staining index=staining intensity × proportion of immune-positive cells.



**Figure 2.** Forest plot of the pooled HRs for OS in cancer patients. Eight studies were included and the random-effect model was adopted. The pooled HR was 1.33 (95% CI=1.07–1.60, P<.001). CI=confidence interval, HR=hazard ratio, OS=overall survival.



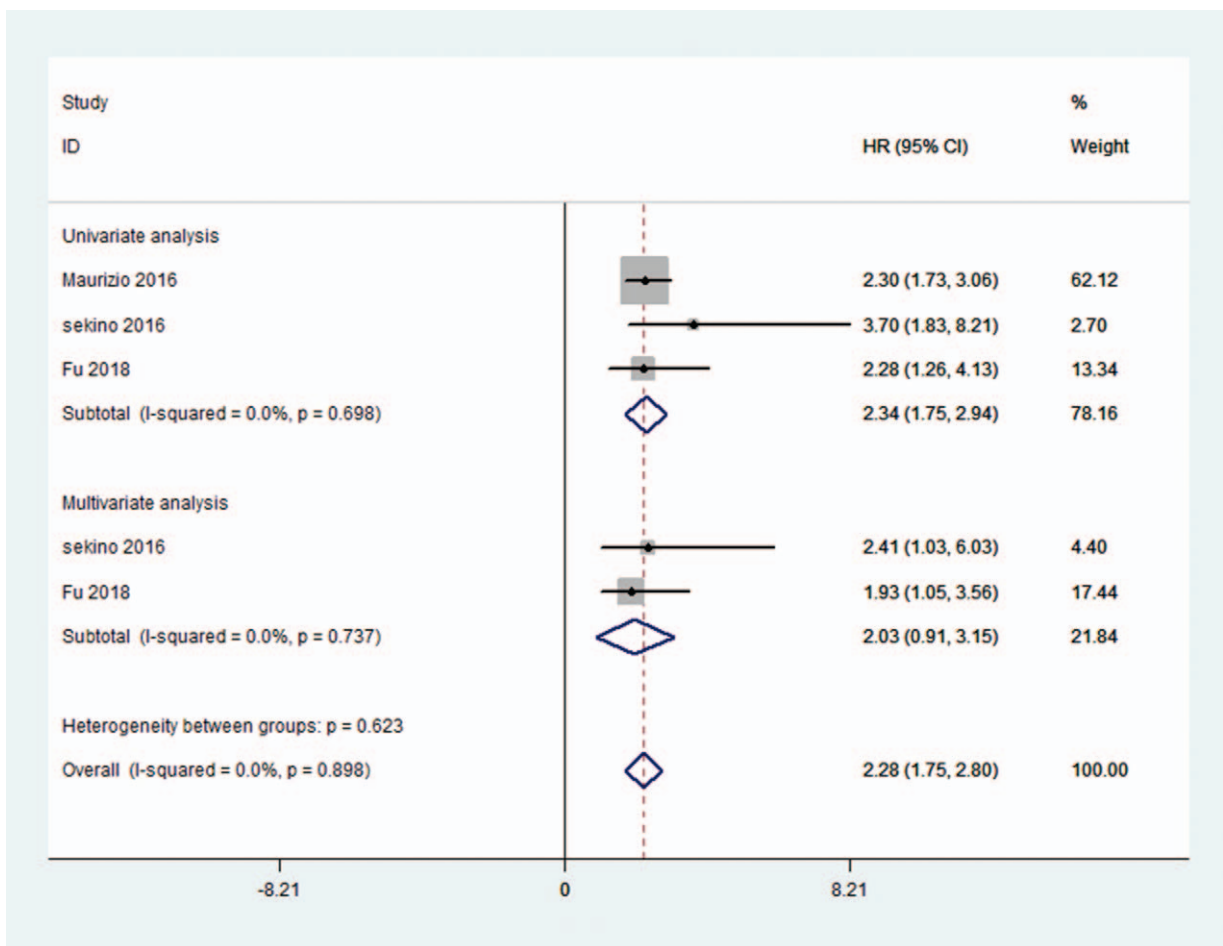
**Table 2**  
The subgroup analysis of HRs for overall survival.

Cancer type	Studies (n)	Number of patients (n)	HR, 95% CI	P	I <sup>2</sup> (%)	P <sub>heterogeneity</sub>	Model
Hepatocellular carcinoma	2	386	1.55, 1.16–1.94	<.001	0.0	.875	Fixed
Ovarian cancer	2	597	0.98, 0.75–1.21	<.001	0.1	.405	Fixed
Breast cancer	2	900	1.68, 1.16–2.19	<.001	0.0	.843	Fixed
Non-small cell lung cancer	1	90	1.75, 1.54–1.99	<.001	NA	NA	Fixed
Esophageal squamous cell carcinoma	1	132	1.26, 0.47–3.35	.246	NA	NA	Fixed

CI=confidence interval, HR=hazard ratio, NA=not available.

diagnosed at early stages. Thus, finding optimal biomarkers with high prognostic value would greatly aid cancer therapy. KIFC1 is a C-type kinesin motor protein that is encoded by the *KIFC1* gene located on chromosome 6 in humans.<sup>[4]</sup> It not only assists the motility of microtubules, but is also considered a promising chemotherapy target due to its multi-centrosome clustering activity in multi-centrosome cancer cells.<sup>[9]</sup> KIFC1 is absent or shows low-level expression in normal tissues but is overexpressed in cancer cells.<sup>[10,11]</sup> Several studies have shown that KIFC1 knockdown significantly inhibits cancer cell proliferation,<sup>[18]</sup> sphere formation,<sup>[17,20,21]</sup> and cell migration and invasion,<sup>[13,18]</sup> as well as causes G2/M cell cycle arrest.<sup>[12,18]</sup> Moreover,

depletion of KIFC1 produces multiple microtubule organizing centers (MTOCs) and delays early mitosis, while KIFC1 silencing suppresses cell proliferation and delays cyclin A degradation in the human primary fibroblast cell line IMR-90, suggesting that it plays an essential role in bipolar MTOC formation and maintaining chromosomal stability during mitosis.<sup>[23]</sup> Thus, it is possible that KIFC1 serves as an oncogene in human tumorigenesis. On the other hand, KIFC1 can increase the probability of genetic instability to enhance the degree of tumor malignancy in breast cancer<sup>[10]</sup> and ovarian cancer.<sup>[11]</sup> Consequently, extensive attention has been paid to the potential prognostic value of KIFC1 expression. However, the present



**Figure 3.** Forest plot of the pooled HRs for RFS in cancer patients. Three studies were available and the fixed-effect model was used. The pooled HR was 2.28 (95% CI=1.75–2.80, P<.001). CI=confidence interval, HR=hazard ratio, RFS=relapse-free survival.

**Table 3**  
**Meta-analysis of the correlation between overexpressed KIFC1 and clinicopathological characteristics.**

Categories	Studies (n)	Number of patients (n)	P	RR, 95% CI	Heterogeneity $I^2$ (%), $P_h$	Model
Gender	5	475	.631	1.03, 0.92–1.15	35.7, .183	Fixed
Age	6	632	.883	1.01, 0.84–1.22	0.0, .722	Fixed
Lymph node metastasis	5	541	.041	1.23, 1.01–1.50	26.8, .243	Fixed
TNM stage	5	680	<.001	1.55, 1.27–1.89	28.0, .235	Fixed
Depth of invasion	4	451	.087	1.34, 0.96–1.86	61.7, .050	Random
Tumor diameter	3	229	.066	0.64, 0.39–1.03	85.6, .001	Random

CI=confidence interval, KIFC1=kinesin family member C1, RR=relative risk.

studies remain controversial and no meta-analysis has been conducted to evaluate the prognostic role of high KIFC1 expression in human malignancies. Therefore, the first meta-analysis was completed by us to assess whether KIFC1 expression influenced cancer prognosis.

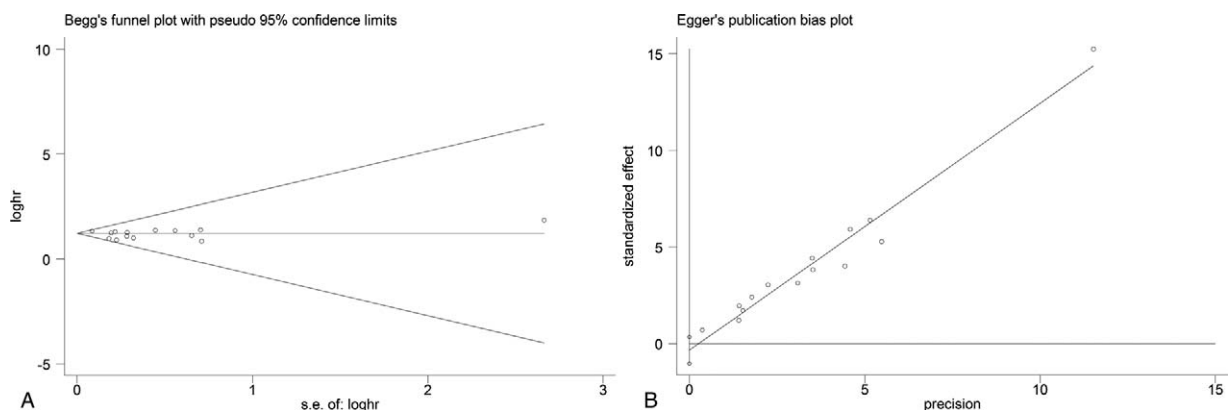
The pooled results of this meta-analysis showed that KIFC1 overexpression was significantly correlated with worse OS in univariate analysis and poorer RFS in both univariate and multivariate analysis. This implied that KIFC1 is a potential prognostic biomarker of multiple cancers. However, multivariate analysis showed no significant correlation between high KIFC1 expression levels and OS. The potential reason could be the small sample size. Only 3 studies reported multivariate analysis in hepatocellular carcinoma, non-small cell lung cancer, and breast cancer, respectively. Second, the complex mechanism by which KIFC1 acts may lead to tumor type-specific roles of this molecule. In terms of cancer type, high KIFC1 expression predicted poorer OS in patients with hepatocellular carcinoma, ovarian cancer, breast cancer, and non-small cell lung cancer, but not esophageal squamous cell carcinoma. The studies included in this meta-analysis did not cover all types of cancer and the subgroup analysis was only data obtained from 1 or 2 studies. Therefore, further studies are needed to explore the prognostic significance of KIFC1 in other cancer types.

In terms of clinicopathological characteristics, high levels of KIFC1 were related with advanced TNM stage (RR=1.55, 95% CI=1.27–1.89,  $P<.001$ ) and positive lymph node metastasis (RR=1.23, 95% CI=1.01–1.50,  $P=.041$ ). This indicated that KIFC1 could promote tumor progression, deepen tumor malignancy and enhance the mobility of cancer cells. Hence,

high KIFC1 expression reduced the survival of the patients compared to the low expression group. However, gender, age, depth of invasion, and tumor diameter were not significantly related to high KIFC1 expression

As far as we know, this is the first meta-analysis to systematically review the prognostic value of KIFC1 in various cancers. However, several limitations still existed. First of all, only 11 studies including 2424 patients could be included in this meta-analysis. Hence, the sample size was not big enough, which may lead to bias. Second, the technique for detecting KIFC1 expression and the definition of cut-off value was not uniform in the studies, and these differences could contribute to heterogeneity. Third, any types of cancer were not included. Additional studies are therefore still required to assess the prognostic value of KIFC1 in other types of malignant tumors. Furthermore, most studies were based on Asian patients, and are, therefore, not representative of the entire world population. Finally, some survival data were extracted from survival curves rather than direct data, which may have led to errors.

This meta-analysis confirms the prognostic role of KIFC1 in various malignancies. In addition, a number of studies suggest that KIFC1 might be a novel therapeutic target. Recently, the 3 small-molecule KIFC1 inhibitors AZ82, CW069, and PJ34, have been identified.<sup>[24–26]</sup> The ATP hydrolysis sites and microtubule-binding site in the motor domain of KIFC1 are common inhibitory sites.<sup>[19,27]</sup> Inhibition of KIFC1 expression induces multipolar spindle formation, and ultimately decreases cancer cells proliferation.<sup>[28]</sup> Therefore, KIFC1 may be an effective chemotherapy target in centrosome-amplified cancers.



**Figure 4.** Begg funnel plot (A) and Egger test (B) for publication bias of the correlation between KIFC1 expression and OS. The  $P$ -value of Begg test was .827 and .310 for Egger test. OS=overall survival.

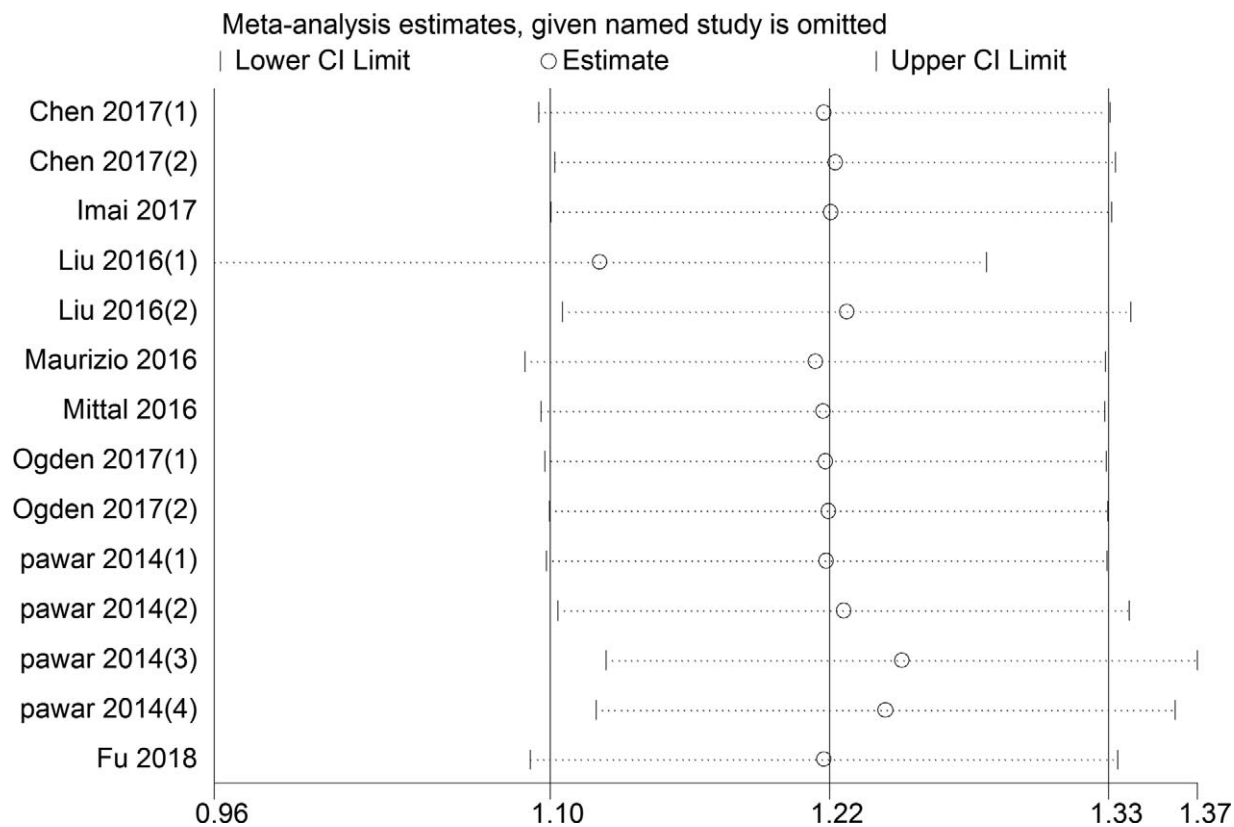


Figure 5. Sensitivity analysis for OS. OS=overall survival.

## 5. Conclusion

In conclusion, increased KIFC1 expression is significantly associated with worse OS, RFS, positive lymph node metastasis, and advanced TNM stage in malignant tumors. KIFC1 can, therefore, be considered a prognostic biomarker for patients with various cancers.

## Author contributions

**Conceptualization:** Zhenhong Zou.

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**Formal analysis:** Yuting Sun, Yi Zhang, Zhiquan Lang, Junfu Huang.

**Funding acquisition:** Zhenhong Zou.

**Resources:** Yuting Sun, Junfu Huang.

**Software:** Yuting Sun, Yi Zhang.

**Validation:** Zhenhong Zou.

**Writing – original draft:** Yuting Sun, Yi Zhang, Zhiquan Lang.

**Writing – review & editing:** Junfu Huang, Zhenhong Zou.

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