

# Expression of tripartite motif-containing 44 and its prognostic and clinicopathological value in human malignancies—a meta-analysis

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## Research article

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# Abstract

**Background:** Previous researches have reported that tripartite motif-containing 44 (TRIM44) is related to the prognosis of multiple human tumors. This study was designed to systematically assess the prognostic value of TRIM44 in human malignancies and to describe its possible mechanisms of oncogenesis. **Methods:** The available databases worldwide were searched for eligible studies that evaluated the clinicopathological and prognostic roles of TRIM44 in patients with malignancies. The hazard ratio (HR) and combined odds ratios (ORs) were combined to assess the predictive role of TRIM44 using Stata/SE 14.1 software. **Results:** A total of 1,740 patients from thirteen original studies were finally included in this study. The results of the combined analysis showed that over-expression of TRIM44 was significantly correlated with shorter overall survival (OS) in cancer patients (HR = 2.16, 95% CI: 1.65–2.83) as well as worse disease-free survival (DFS) (HR= 2.13 (95% CI 1.45–3.11)). Additionally, the combined ORs indicated that elevated TRIM44 expression was significantly associated with lymph node metastasis (OR=2.69, 95% CI: 1.71–4.24), distant metastasis (OR=10.35, 95% CI: 1.01-106.24), poor tumor differentiation (OR=1.78, 95% CI: 1.03–3.09), increased depth of tumor invasion (OR=2.72, 95% CI: 1.73–4.30), advanced clinical stage (OR=2.75, 95% CI: 2.04-3.71), and recurrence (OR=2.30, 95% CI: 1.34–3.95). Analysis of expression using Gene Expression Profiling Interactive Analysis (GEPIA) indicated that the expression of TRIM44 was higher in most tumor tissues than in the corresponding normal tissues. Survival analysis indicated high levels of TRIM44 mRNA were associated with unfavorable OS and DFS in various malignancies. **Conclusions:** TRIM44 may serve as a valuable prognostic biomarker and a potential therapeutic target for patients with malignancies.

## Background

Malignant cancers are one of the main causes of disease-related death in the world. Advances in detection techniques have resulted in discovery of early cancer and progress of perioperative treatment has reduced the mortality in patients with malignancies. However, after standard treatment, advanced malignancies still show poor survival rates due to consequent recurrence or metastasis. Due to the ongoing intensive tumor research, the mechanisms of tumor occurrence and progression have gradually been understood and an increasing number of therapeutic targets has been identified.

The field is moving toward targeted therapy as a primary form of tumor therapy. Therefore, major efforts have been made to identify molecular markers that predict the prognosis. More importantly, these markers can often be used as therapeutic targets, and then the corresponding targeted drug design can be carried out. Compared with gene therapy, the current targeted drug design for functional proteins may be more conducive to bringing new progress in tumor therapy.

Recent studies have shown that some tripartite motif (TRIM) proteins are involved in tumorigenesis and progression and they function as a protein regulator, and they are an important intersection in the gene pathway [1]. Tripartite motif-containing 44 (TRIM44), which is localized to the cytoplasmic compartment of cells, was reported to contribute to diverse pathological conditions, such as cancer, growth

disorders, and neurodegeneration [2-7]. TRIM44 protein has a zinc-finger domain, which plays the role of ubiquitin-specific proteases (USPs). Thus, it has been defined as the “USP-like” TRIM [7]. The ubiquitin–proteasome system plays an important role in the regulation of cell function and is the intersection of multiple regulatory pathways [8]. TRIM44 is an atypical TRIM-family protein that lacks the RING-finger domain but contains a zinc-finger domain that is often found in ubiquitin-specific proteases [9].

Some studies have suggested that TRIM44 plays a cancer-promoting role in oncogenesis and tumor progression, and increased TRIM44 expression was detected in cancer tissues and it was associated with poor prognosis and advanced clinicopathological parameters [10-12]. Importantly, recent studies have revealed that high levels of TRIM44 induce the epithelial-to-mesenchymal transition (EMT) in cancer cells and that TRIM44 promotes tumor initiation and progression by activating the PI3K/AKT/mTOR pathway [11,13]. Another report indicated that TRIM44 could activate the NF- $\kappa$ B pathway to promote lung cancer cell migration and invasion [14].

However, to date, no specific meta-analysis has been performed to evaluate the association between TRIM44 expression and clinical outcomes in diverse malignancies. Therefore, we conducted this study to provide a systematic evaluation of the predictive value of TRIM44 and to explore its feasibility as a new therapeutic target.

## Methods

### Search strategy

A comprehensive search strategy was conducted in the following databases: Web of Science, PubMed, CNKI, Wanfang, EMBASE, Google Scholar, and other available databases. The search deadline was November 2, 2019. The following keywords were adopted according to the retrieval strategy: “Tripartite motif-containing 44” “TRIM44” OR “cancer” OR “tumor” OR “carcinoma” OR “malignancy.”

### Inclusion and exclusion criteria

Inclusion criteria were as follows: 1) The expression of TRIM44 protein was measured in tissue samples from primary solid cancers; 2) All patients included in the original studies were divided into two groups according to the high and low levels of TRIM44 protein expression; 3) the hazard ratio (HR) of survival outcomes or clinicopathological data based on the high and low levels of TRIM44 protein expression were reported; 4) The survival curve presented or sufficient data were available for calculating the HR with 95% CI.

Exclusion criteria were as follows: not original studies, studies without a control group, articles that only explored the molecular functions of TRIM44, and studies that included less than 50 cases.

### Data extraction

For each study, the following general information was independently collected by two investigators : author's name, number of patients, cancer type, high expression rate, end-points (analysis type), evaluation standard of TRIM44 overexpression, follow-up time, detection method, and outcome measures.

Additionally, information on the clinicopathological parameters related to tumor progression was collected. For survival data extraction, the HRs and 95% CIs were directly used from the multivariate survival analysis or the univariate analysis second priority; otherwise, they were retrieved using the Engauge Digitizer version 4.1 if a study only provided Kaplan-Meier curves.

### **Quality assessment**

Newcastle-Ottawa quality assessment scale (NOS) was adopted to evaluate the quality of enrolled studies. NOS scores greater than 6 were considered to indicate high-quality studies.

### **Public data and tools**

In this study, the Gene Expression Profiling Interactive Analysis (GEPIA) database was used to show the expression level of TRIM44 in other types of human cancer and to further validate its prognostic value for overall survival (OS)/disease-free survival (DFS) in the TCGA dataset. Patients with cancers were divided into a high or low TRIM44 group according to the expression above or below the median expression level. A box plot was used to represent the RNA expression level in different tumors, and Kaplan–Meier plots for survival analysis were utilized to show the long-term prognosis of tumor patients.

### **Statistical analysis**

STATA/SE 14.1 was used to analyze the relationship between TRIM44 expression and OS/DFS and to assess the clinicopathological significance of TRIM44 expression in human cancers.  $I^2$  statistics and chi-square Q test were adopted to estimate the heterogeneity among enrolled studies.  $I^2 \geq 50\%$  or a  $P$ -value  $< 0.10$  statistically defined a significant difference. Then, the random effects model was adopted to conduct the meta-analysis with significant heterogeneity, while the fixed effects model was used with no heterogeneity. The funnel plot and Begg's/Egger's test were applied to assess publication bias, and sensitivity analysis was adopted to test the stability of the analysis results.  $p < 0.05$  was used to indicate significant effects.

## **Results**

### **Characteristics of eligible studies**

Study collection and screening process are shown in Figure 1. After further discussion and consideration of the selected articles, 13 cohort studies published between 2012 and 2019 were selected for further analysis[10,11,15-25]. In total, these 13 studies included 1,740 patients with a mean sample size of 133.8 and a range from 90 to 331. Ten studies presented data on the association between the TRIM44 protein

levels and OS, and six of the selected eligible studies presented data on the link between TRIM44 and DFS. In these studies, 13 different kinds of solid tumors were analyzed, including gastric cancer (GC), osteosarcoma, cervical cancer (CC), breast cancer (BC), hepatocellular carcinoma (HCC), endometrial carcinoma (EC), esophageal squamous cell carcinoma (ESCC), human esophageal cancer (HEC), melanoma, testicular germ cell tumor (TGCT), non-small cell lung cancer (NSCLC), intrahepatic cholangiocarcinoma (ICC), and epithelial ovarian cancer (EOC). All primary cancer tissues and adjacent non-tumor tissue samples were collected from patients in Japan and P.R. China. The expression of TRIM44 protein in tissue samples was measured by immunohistochemistry (IHC). All included articles were written in English, and they were of good quality. The basic characteristic information is presented in Table 1.

Categories	Studies(n)	Number of patients	HR (95% CI)	p-value	Heterogeneity		
					I <sup>2</sup> (%)	P-value	Model
OS	11	1547	2.16(1.65-2.83)	0.000	32.6	0.138	Fixed
Cutoff value							
Final staining scores <sup>1</sup> or <sup>3</sup> (≥ 4 or 5 vs. ≤4)	7	1118	2.03(1.42-2.19)	0.000	40.9	0.119	Fixed
Final staining scores <sup>1</sup> (≥ 3 vs. ≤3)	2	231	4.27(1.83-9.95)	0.001	0.0	0.604	Fixed
Others (High vs. Low)	2	198	2.10(1.44-3.06)	0.000	0.0	0.571	Fixed
Analysis type							
Multivariate	10	1404	2.20(1.66-2.93)	0.000	39.0	0.098	Fixed
Survival curves	1	143	8.66(1.10-68.22)	0.001	-	-	-
Sample size							
≥ 100	10	1336	2.29(1.68-3.12)	0.000	44.9	0.060	Fixed
< 100	1	68	2.82(1.04-9.13)	0.041	-	-	-

Table 1  
Characteristics of included studies.

## The correlation between increased TRIM44 expression and OS

Eleven studies involving 1,547 malignancy patients reported the HRs for OS. The pooled results for OS are displayed in Figure 2. High expression of TRIM44 protein in malignant tissues was found to be strongly associated with poor OS (HR=2.16, 95% CI: 1.65–2.83,  $p=0.000$ ), and the heterogeneity test revealed a mild heterogeneity ( $I^2=32.6\%$ ;  $P_h=0.138$ ). The over-expression of TRIM44 could serve as a poor prognostic factor in human malignancies. In addition, for OS, the pooled HR values  $>1$  were consistently calculated in the subgroup meta-analysis stratified by the analysis type, sample size, and cutoff value; thus, indicating a significant difference (Table 2).

Clinicopathological parameter	Studies(n)	OR (95% CI)	p-value	Heterogeneity		
				I <sup>2</sup> (%)	P-value	Model
Gender (male vs. female)	8	1.00 (0.78-1.29)	0.990	0.0	0.699	Fixed
Recurrence (+ vs. -)	3	2.30 (1.34-3.95)	0.002	14.2	0.312	Fixed
Tumor depth (T3-4 vs. T1-2)	4	2.72 (1.73-4.30)	0.000	0.0	0.488	Fixed
Lymph node metastasis (+ vs. -)	10	2.69 (1.71-4.24)	0.000	56.4	0.014	Random
Distant metastasis (+ vs. -)	3	10.35 (1.01-106.24)	0.049	90.0	0.000	Random
TNM stage (III-IV vs. I-II)	7	2.75 (2.04-3.71)	0.000	32.7	0.179	Fixed
Poorly/undifferentiated vs. well/moderately	6	1.78 (1.03-3.09)	0.000	62.8	0.020	Random
Vascular invasion (+ vs. -)	3	2.43 (0.85-6.94)	0.097	71.7	0.029	Random

Table 2  
Pooled HR for OS according to subgroup analysis

### The correlation between increased TRIM44 expression and DFS/ recurrence-free survival (RFS)

Six studies involving 1,018 cases investigated the association between TRIM44 expression and DFS/ RFS. Elevated expression of TRIM44 indicated an inferior DFS/ RFS outcome, with a combined HR of 2.13 (95% CI 1.45–3.11, p=0.000); thus, indicating that patients with elevated TRIM44 protein expression in malignant tissues had a lower DFS rate compared to patients with lower TRIM44 protein expression (Figure 3). The heterogeneity test revealed a medium heterogeneity among four studies (I<sup>2</sup>=64.2%; P<sub>h</sub>=0.016).

## The correlation between increased TRIM44 expression and clinicopathological parameters

The pooled odds ratios (ORs) were calculated to assess the risk of over-expression of TRIM44 protein under different clinicopathological features (Table 2). Tumors with unfavorable clinicopathological parameters were more frequently associated with overexpression of TRIM44 protein. These parameters included deeper tumor invasion (OR=2.72, 95% CI: 1.73-4.30), poor tumor differentiation (OR=1.78, 95% CI: 1.03-3.09), poor clinical stage (OR=2.75, 95% CI: 2.04-3.71), distant metastasis (OR=10.35, 95% CI: 1.01-106.24), lymph node metastasis (OR=2.69, 95% CI: 1.71-4.24), and tumor recurrence (OR=2.30, 95% CI: 1.34–3.95). However, there was no significant association between elevated TRIM44 expression and gender (OR=1.00, 95% CI: 0.78-1.29,  $p=0.990$ ) or vascular invasion (OR=2.43, 95% CI: 0.85-6.94,  $p=0.097$ ) in malignancy patients.

Clinicopathological parameter	Studies (n)	OR (95% CI)	Heterogeneity $I^2$ (P-value)
Gender (male vs. female)	1800	1.00 (0.78-1.29)	0.990 (0.53)
Recurrence (+ vs. -)	2330	2.30 (1.34-3.95)	0.132 (0.71)
Tumor depth (T3-4 vs. T1-2)	2472	2.72 (1.73-4.30)	0.438 (0.50)
Lymph node metastasis (+ vs. -)	2109	2.69 (1.71-4.24)	0.414 (0.51)
Distant metastasis (+ vs. -)	900	10.35 (1.01-106.24)	0.000 (0.00)
TNM stage (III-IV vs. I-II)	2775	2.75 (2.04-3.71)	0.074 (0.79)
Poorly/undifferentiated vs. well/moderately differentiated	1678	1.78 (1.03-3.09)	0.000 (0.00)
Vascular invasion (+ vs. -)	2313	2.43 (0.85-6.94)	0.097 (0.72)

Table 3: Results of the meta-analysis of high TRIM44 and clinicopathological parameters.

## TRIM44 expression in different cancer types

The results from the GEPIA, an online database containing large RNA sequencing expression information from the GTEx and TCGA projects, revealed that the expression of TRIM44 mRNA was higher in most malignant tissues than in the corresponding normal tissues (Figure 4).

### **Validation of the prognostic value of TRIM44 in human solid tumors**

In a survival analysis conducted through the GEPIA database, high levels of TRIM44 mRNA were associated with unfavorable OS and DFS in various malignancies (Figure 5).

### **Publication bias**

The Begg's visible plots are shown in Figure 6, and the p-value of Begg's test was 0.531 for OS. These results suggest that there was no publication bias in the present meta-analysis.

### **Sensitivity analysis**

Figure 7 shows that the pooled results in this meta-analysis were relatively robust.

## **Discussion**

Ubiquitination is a post-translational protein modification that tags proteins for proteolytic degradation. It is involved in intercellular biological behavior, such as signal transduction, cell cycle regulation, DNA repair, antigen processing, and apoptosis [26-29]. RING finger ubiquitin E3 ligases have been previously reported to participate in cell-cycle regulation and carcinogenesis in malignancy [9,30-33]. Recent studies have suggested that some TRIM proteins, which contain a conserved RING finger, B-box, and coiled-coil domains, function as vital regulators of carcinogenesis [1] [34,35]. These TRIM family proteins are associated with wide biological phenomena, including cell cycle regulation, transcriptional regulation, apoptosis, and carcinogenesis [36,37].

TRIM-containing protein 44 (TRIM44: 11p13) contains B-box, coiled-coil domains, and a zinc-finger domain, which was discovered in ubiquitin hydrolases [38]. TRIM44 protein and mRNA have been reported to be significantly upregulated in cancer tissues compared to para-cancerous or normal samples. TRIM44 amplification is correlated with unfavorable prognosis and advanced clinicopathological parameters of malignancies [10,15,39]. Increased expression of TRIM44 could promote cell proliferation, migration, and invasion, whereas down-regulation of TRIM44 could significantly inhibit these pathologic features. TRIM44 may act as a cancer-promoting gene regulating deubiquitination and stabilization of oncogenes.

Tumor metastasis is a multistep process that starts with tumor migration and invasion through endothelial barriers via a process known as EMT, which is characterized by loss of cell-cell adhesion and increased cell motility [40-42]. Loss of E-cadherin expression, a hallmark of EMT, has been noted in many malignancies and is associated with increased metastatic potential [43,44]. Cell motility, migration, and invasion are the malignant biological behaviors of cancer cells and the necessary factors for cancer

metastasis. Knockdown of TRIM44 inhibited the invasion and migration of human NSCLC cells, and it was associated with downregulation of mesenchymal markers (such as vimentin and N-cadherin) and upregulation of epithelial markers (such as E-cadherin) [11]. Overexpression of TRIM44 repressed E-cadherin expression and increased vimentin and N-cadherin expression in NSCLC cell lines [11]. Overexpression of TRIM44 induced EMT and increased the metastatic potential of lung cancer cells. In HCC cell lines, it was found that the ectopic expression of TRIM44 dramatically increased the expression of mesenchymal markers N-cadherin and vimentin, but it decreased the expression of epithelial marker E-cadherin; thus, suggesting that overexpression of TRIM44 could potentiate the EMT program [25]. Overexpression of TRIM44 has been shown to induce a similar change in hallmark characteristics of EMT in other cancers, such as ICC and HEC.

Uncontrolled cell proliferation is the biological characteristic of malignant tumors at the cellular level, and abnormal cell cycle regulation is closely related to uncontrolled cell proliferation [44]. TRIM44 expression positively affects the expression of cyclins and CDKs, suggesting that TRIM44 is involved in the regulation of cell cycle G1/s transformation [11,25]. TRIM44 induced cell proliferation in vitro and tumor growth in vivo by accelerating the G1/S transition via upregulation of cyclins and CDKs. Indeed, ectopic expression of TRIM44 promotes cell proliferation by accelerating the G1/S-phase transition in HCC. In colony formation assays, knockdown of TRIM44 in Huh7 cells significantly decreased the expression levels of cyclin D1 and cyclin E, which have been shown to play a crucial role in accelerating the G1/S-phase transition [25]. p21/p27 was discovered to function as a vital cyclin-dependent kinase inhibitor, and up-regulated expression of p21/p27 can inhibit cell entry into the S phase [45,46]. Knock-down of TRIM44 in glioma cells induces an increase in p21/p27 expression and then it inhibited cell division [47]. Further, the critical p21/p27 regulator AKT is inactivated after TRIM44 is knocked down, but it is activated in glioma cells that overexpress TRIM44 [47].

TRIM44 overexpression leads to high mTOR activity, which is consistent with observations of reduced mTOR signaling in cancer cell lines after siRNA knockdown of TRIM44 [39]. The phosphorylation of downstream mTOR substrates, including p-Akt (Ser473) and p-p70S6K (Thr389), in TRIM44-knockdown cells was markedly inhibited, indicating that TRIM44 functions upstream of the mTOR signaling pathway by phosphorylating mTOR. STAT3 participates in multiple biological behavior regulation, including cell proliferation, apoptosis, and tumorigenesis, and it has been reported to be involved in oncogene regulatory pathways, including AKT/mTOR [48-50].

TRIM44 could function as E3 ubiquitin ligase and has ubiquitination function. TRIM44 can inhibit the role of AMPK in cells by degrading AMPK [7,51]. AMPK has been reported to inhibit mTOR signaling. The upregulated TRIM44 reduced AMPK activity, thus relieving the inhibition of AMPK in the mTOR signaling pathway and it up-regulated mTOR signaling from other mechanisms.

TRIM44-induced mTOR signaling, EMT, and cyclin/CDK upregulation were reversed by treatment with an inhibitor of the mammalian target of rapamycin (mTOR) [11]. Several previous studies have suggested that MAPK signaling pathways can induce EMT in cancer cells [12,53-55]. Inhibition of MAPK signaling

by incubation with a signaling inhibitor significantly repressed ICC cell invasion and metastasis [21]. ERK1/2 has been reported to be involved in the regulation of EMT in ICC cells. TRIM44 could increase the activation of the AKT signaling pathway and activate ERK1/2; thus, suggesting that TRIM44 promotes EMT in ICC cells via the ERK-MAPK pathway.

Furthermore, overexpression of TRIM44 has been reported to be associated with inhibition of apoptosis in esophageal cancer [13]. A microarray analysis showed that TRIM44 knockdown is associated with the dysregulation of NUPR1, CDK19, CADM1, INHBA, TNFSF10, and DDIT4, which could normally activate the apoptotic cell pathways [24]. Bax and Bcl-2 are closely related to apoptosis. Elevated TRIM44 expression significantly repressed Bax and promoted Bcl-2 expression. Thus, TRIM44 has a vital role in inhibiting cellular apoptosis. NF- $\kappa$ B, functioning as a vital nuclear transcription factor, has been reported to be closely related to the inflammatory response, cellular apoptosis, and stress responses. NF- $\kappa$ B is the molecular target of some antitumor drugs [58]. The transcription factor NF- $\kappa$ B has been reported to inhibit apoptosis and to induce drug resistance in cancer cells [59]. Of note, it has been reported that TRIM44 promotes NSCLC development through activation of NF- $\kappa$ B signaling [14]. Previous studies have indicated that cIAP1, c-IAP2, and XIAP are the antiapoptotic transcriptional targets of NF- $\kappa$ B signaling [60]. A previous report has shown that silencing of TRIM44 could decrease the c-IAP1, c-IAP2, and XIAP expression levels, especially in the presence of doxorubicin [25]. High expression of TRIM44 could enhance resistance of HCC cells to doxorubicin via accelerating NF- $\kappa$ B activation. Increased NF- $\kappa$ B-mediated transcriptional activity was detected in TRIM44-transfected breast cancer cells [16].

Elevated TRIM44 protein expression enhanced proliferation and migration of TGCT cells, while TRIM44 protein knockdown repressed this biological behavior and promoted cell apoptosis.

Ki67 has been reported to be a promoter of cell proliferation [61]. TRIM44 modulates Ki67 expression and promotes HEC cell proliferation. Amplified TRIM44 expression was also discovered in melanoma tissues, and overexpression of TRIM44 is associated with a malignant phenotype of melanoma [23]. TRIM44 ubiquitinates and stabilizes TOLL-like receptor 4 (TLR4), which activates the AKT/mTOR pathway and induces cellular EMT. Moreover, miR-26b-5p is the upstream regulatory gene of TRIM44, which acts as a suppressor [23].

We believe that this study is the first meta-analysis to provide a systematic assessment of the prognostic value of TRIM44 in malignancies. Further, we have discussed the possible role of TRIM44 in tumor progression. Pooled results indicated that the expression level of TRIM44 protein is an independent prognostic factor of cancer-specific survival in patients with malignancies. Malignancy patients with increased tissue TRIM44 expression had a significantly shorter OS and a lower DFS rate than patients with low TRIM44 expression. Furthermore, malignancy patients with unfavorable clinicopathological parameters more frequently showed overexpression of TRIM44 protein. Comprehensive analysis results showed that TRIM44 was frequently overexpressed in malignancies and it functions as a crucial oncogenic role. Malignancy patients with increased tissue TRIM44 expression had an unfavorable

prognosis. TRIM44 was involved in the malignant biological behavior of tumor cells and played an intersection role in the gene regulatory pathways.

However, there are several possible limitations of our research that may interfere with the generalizability of these conclusions. First, more samples need to be included to confirm the reliability of the conclusion. Second, all patients were from Asian countries, and studies including patients from other countries and races are required. Third, several HRs and their corresponding 95% CIs were extracted from the survival curves and they might be less accurate than those directly obtained from the studies in multivariate analysis. In addition, heterogeneity still exists in some results of clinicopathological characteristics.

## Conclusion

The present study demonstrated that elevated expression of TRIM44 is significantly correlated with disease progression and unfavorable prognosis in patients with malignancies. We found that TRIM44 is involved in the malignant biological behavior of tumor cells and it plays an intersection role in the gene regulatory pathways. TRIM44 may be an important molecular marker for determining the malignant properties and an attractive therapeutic target for patients with malignancies.

## Abbreviations

TRIM44: Tripartite motif-containing 44; OS: overall survival; RFS: recurrence-free survival; DFS: disease-free survival; NR: not reported; M: multivariate analysis; C: curves; IHC: immunohistochemistry; HR: hazard ratio; DFS: disease-free survival; BC: breast cancer; CC: cervical cancer; GC: gastric cancer; HCC: hepatocellular carcinoma; EC: endometrial carcinoma; ESCC: esophageal squamous cell carcinoma; ICC: intrahepatic cholangiocarcinoma; HEC: human esophageal cancer; EOC: epithelial ovarian cancer; TGCT: testicular germ cell tumor; NSCLC: non-small cell lung cancer.

## Declarations

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Not applicable.

### Authors' contributions

XGL and YQX initiated and promoted the study. XGL and BZW implemented data analysis and completed the manuscript. Z Y reviewed the data analysis process and proofread the manuscript.

### Funding

Not applicable.

### Availability of data and materials

Meta-analysis is a secondary analysis, in which all data are fully available without restriction and all materials can be found in the included original studies.

### **Ethics approval and consent to participate**

Not applicable.

### **Consent for publication**

Not applicable.

### **Competing interests**

No competing interests.

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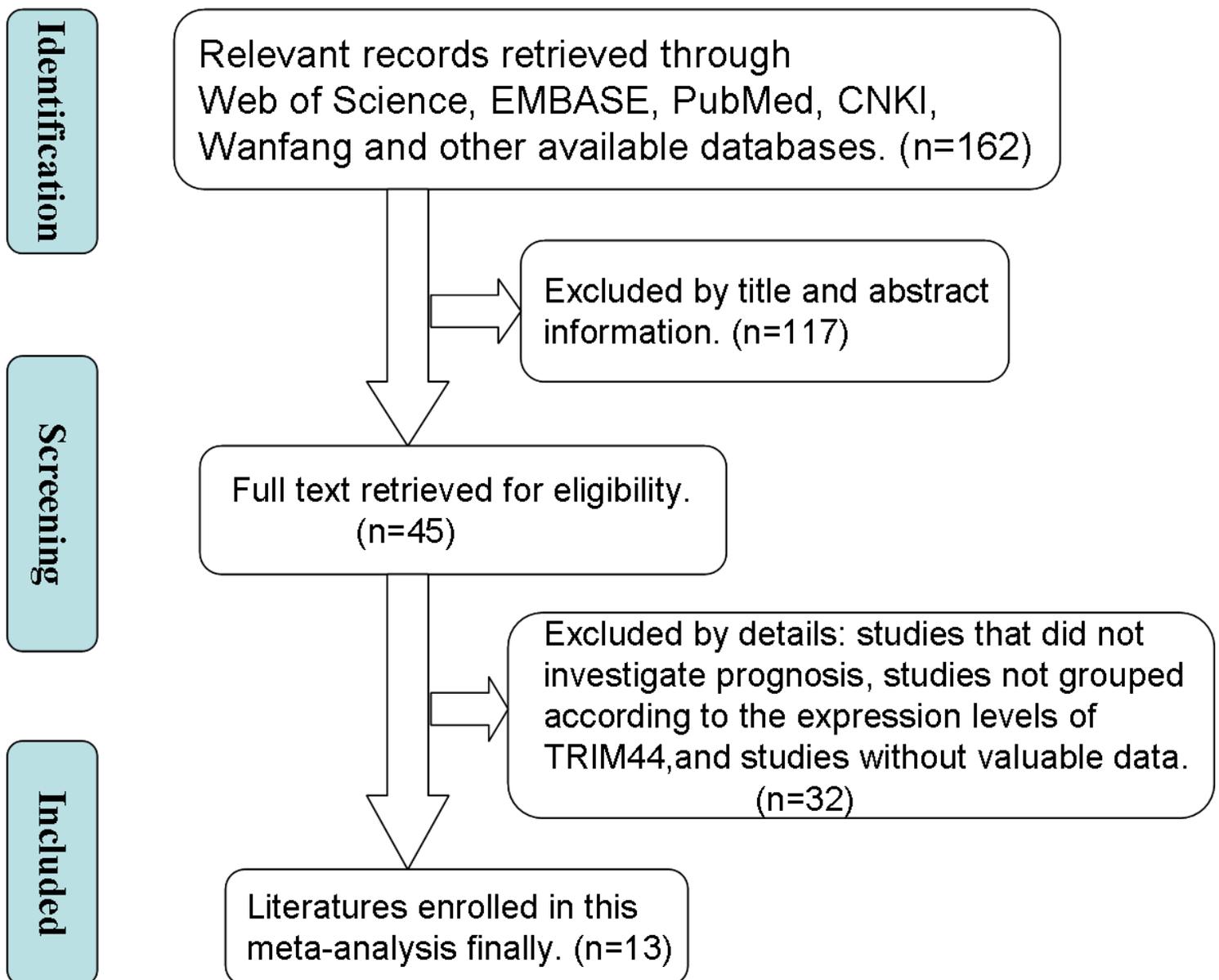
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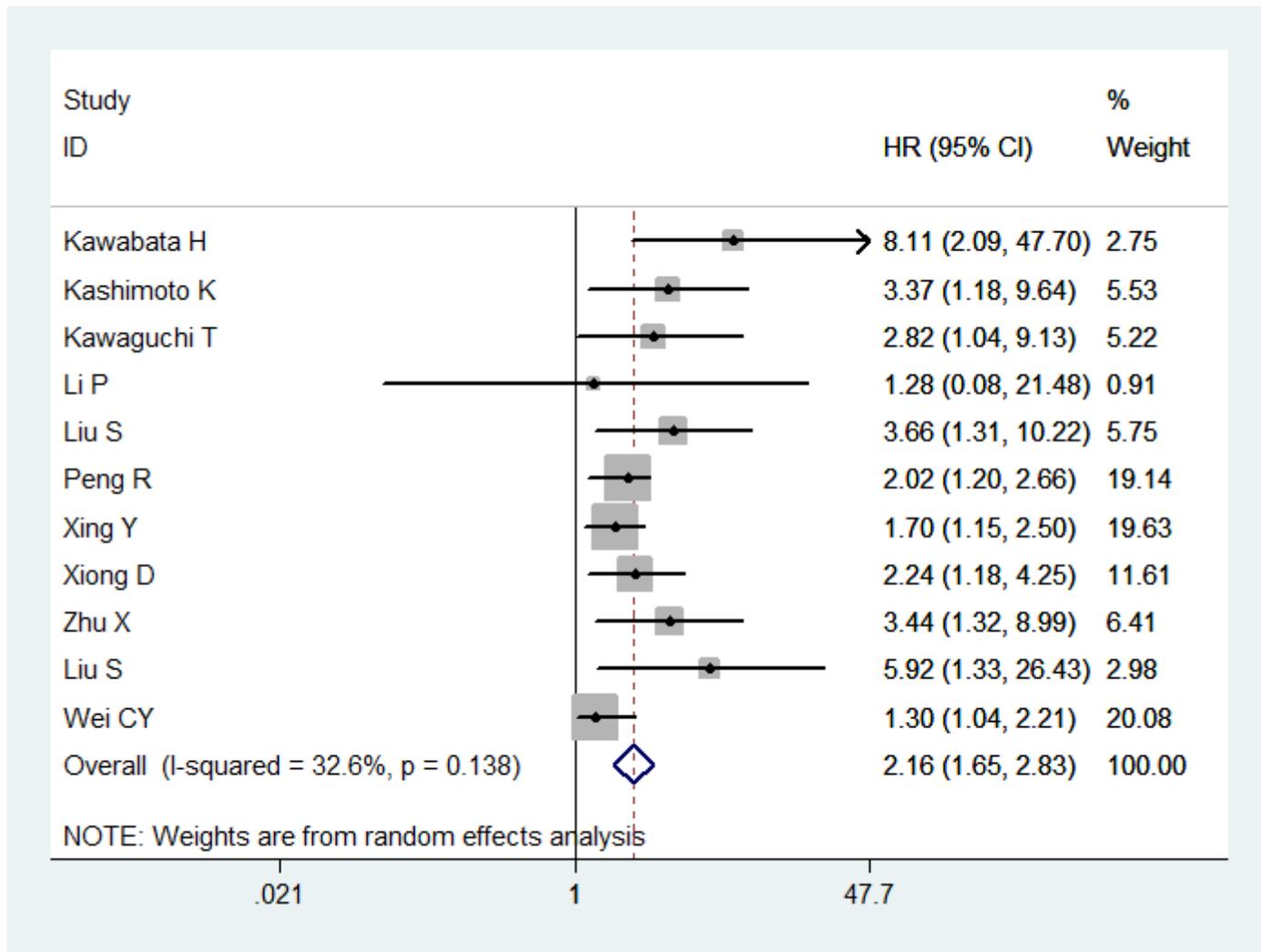
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## Figures



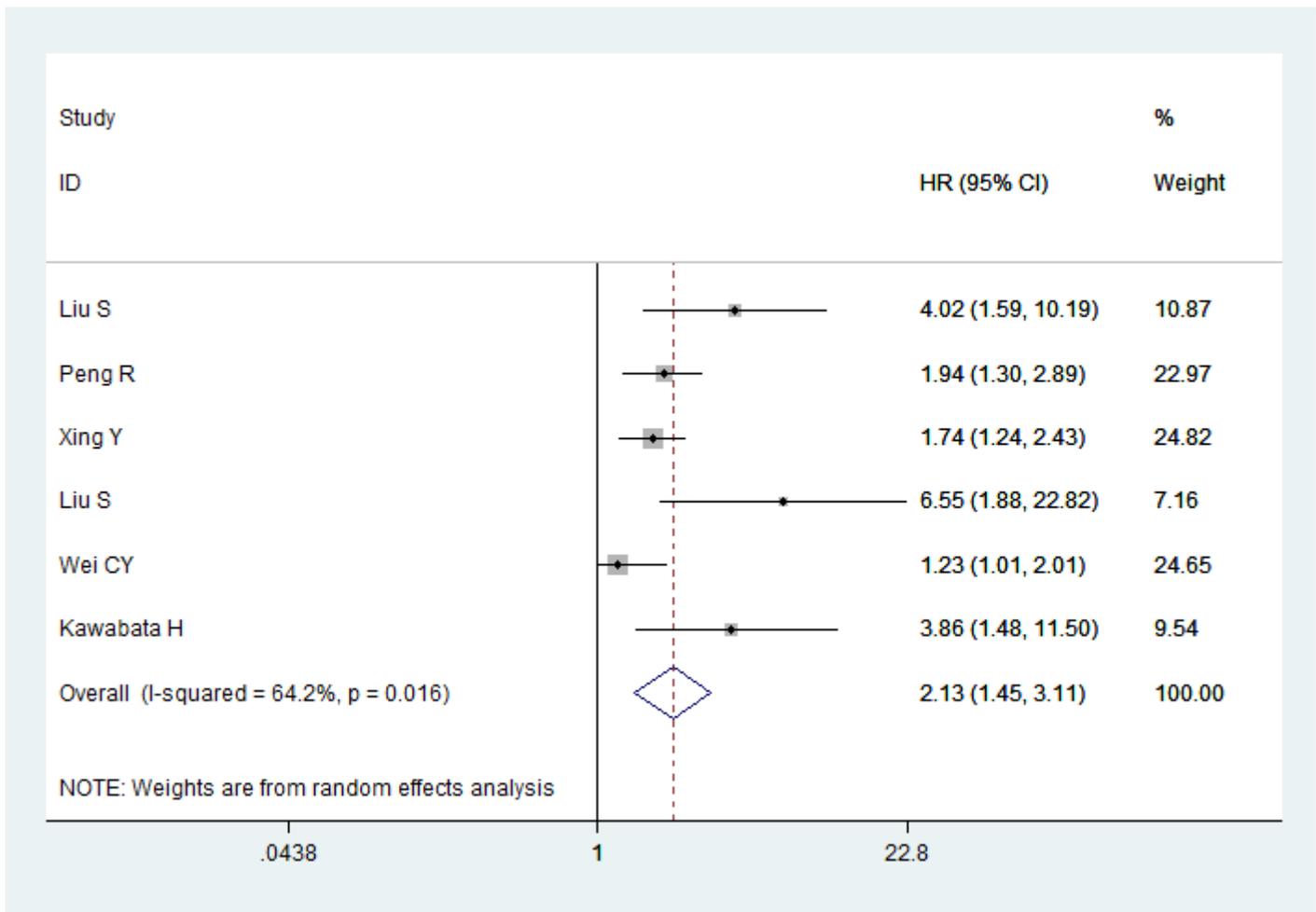
**Figure 1**

Flow diagram of included studie.



**Figure 2**

Meta-analysis of the pooled HRs of OS of patients with high TRIM44 expression.



**Figure 3**

Meta-analysis of the pooled HRs of DFS of patients with high TRIM44 expression.

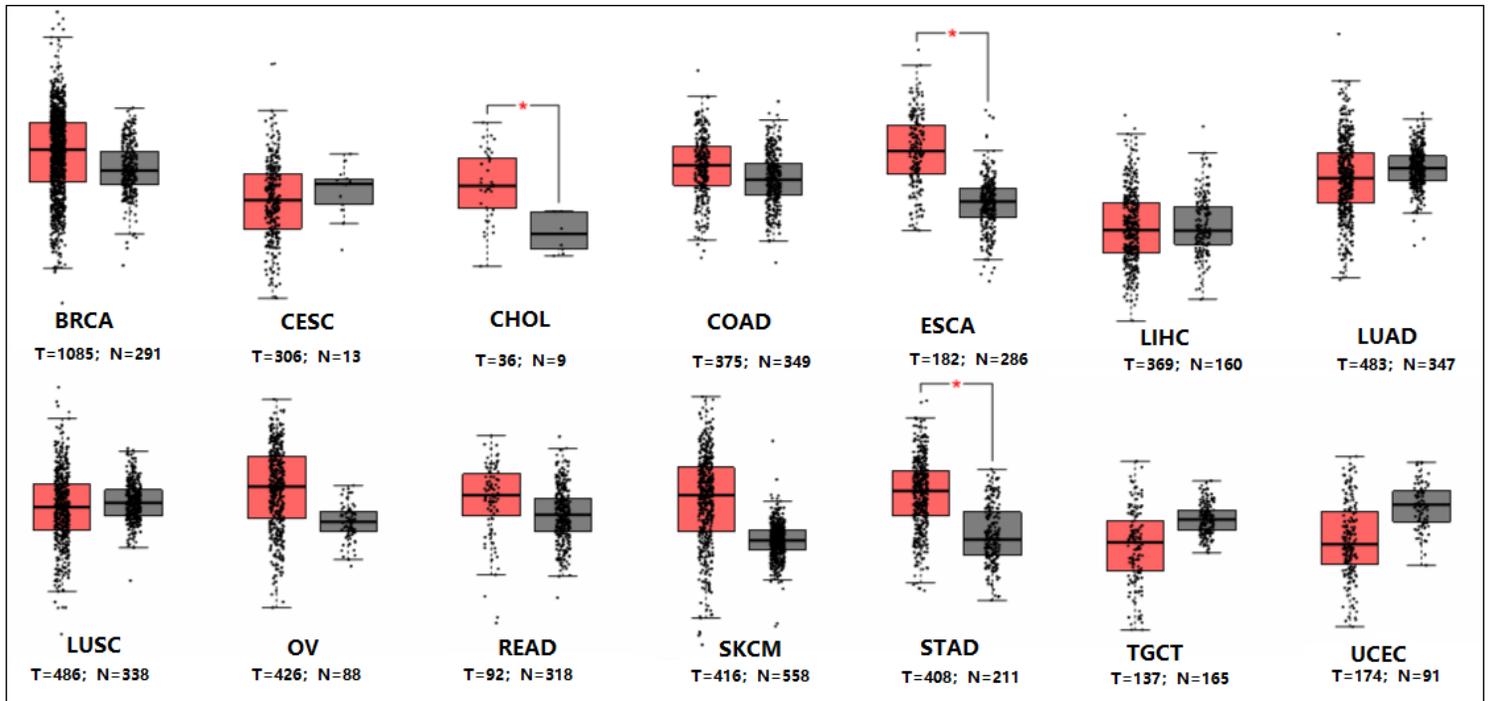


Figure 4

TRIM44 mRNA expression in different types of human malignancies.

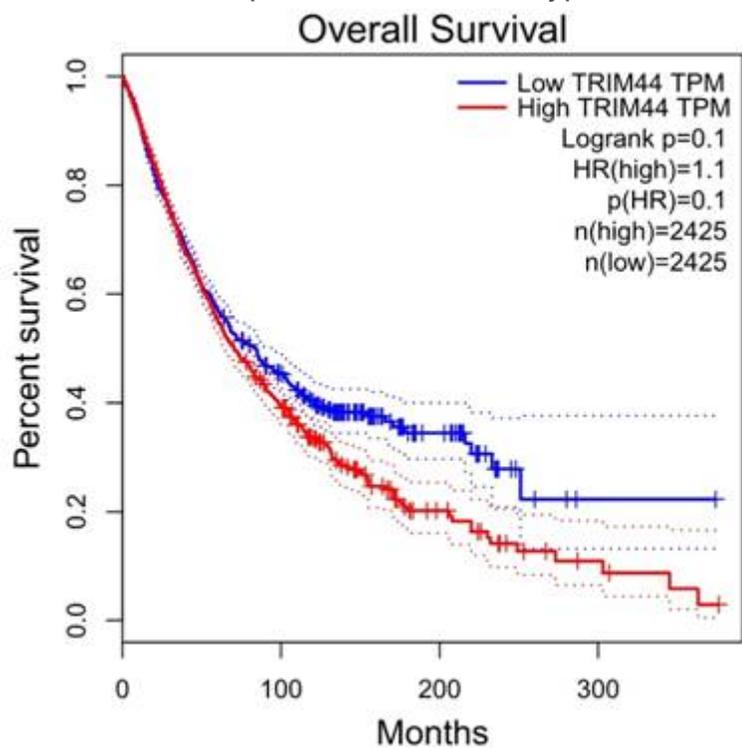


Figure 5

Validation of prognostic value of TRIM44 mRNA in various malignancies.

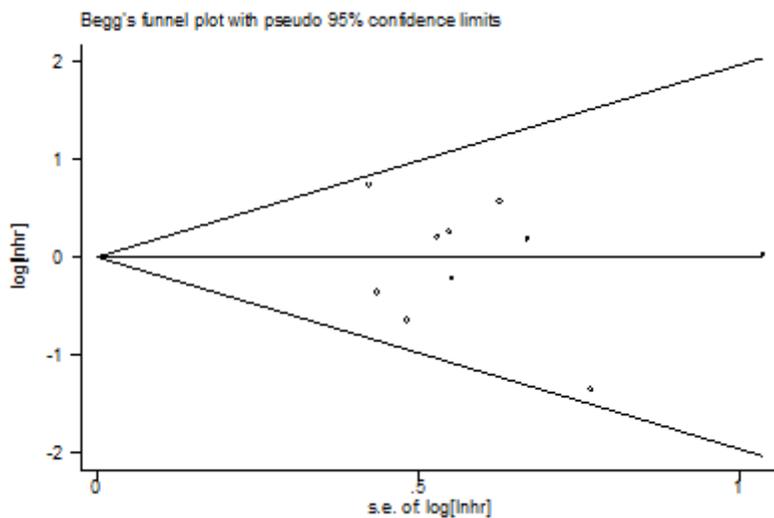
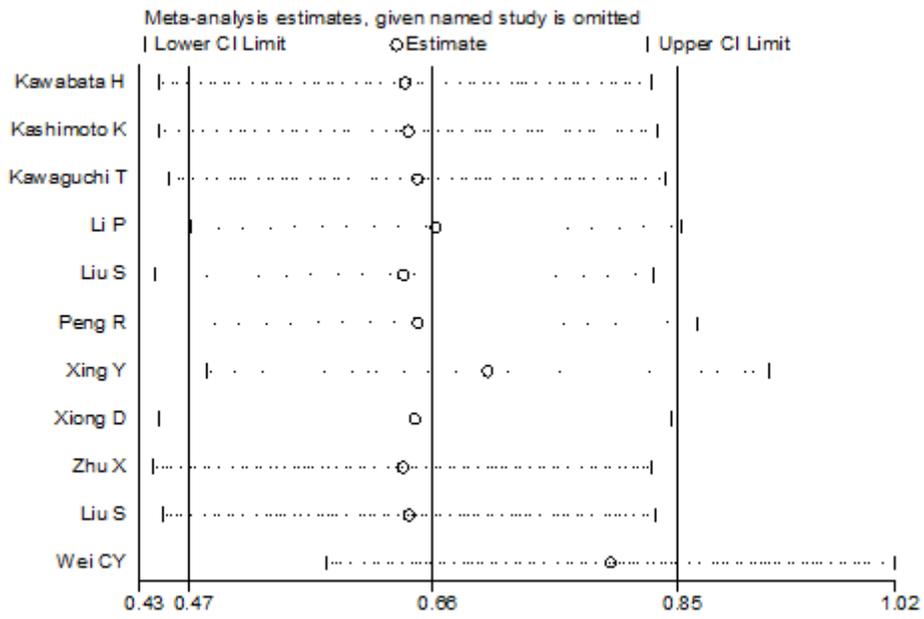


Figure 6

Publication bias assessment of TRIM44 expression and OS.



**Figure 7**

Sensitivity analysis of TRIM44 expression and OS.