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Expression of tripartite motif-containing 44 and its prognostic and clinicopathological values in human malignancies: a meta-analysis

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Abstract

Background: Previous researches reported that tripartite motif-
containing 44 (TRIM44) were related to prognosis in multiple human tumors. This study was designed to systematically assess the prognostic value of TRIM4

Methods: available databases worldwide were searched for eligible studies that evaluated the clinicopathological and prognostic roles of TRIM44 in patients v

Results: A total of 1,740 patients from thirteen original studies were included in this study finally. 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
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), high 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 GEPIA indicated that the expression of TRIM44 was higher in most tumor tissues than the corresponding normal tissues.Su

Background

Malignant cancers are one of main causes of disease-related death in the world. Advances in detection techniques resulting discovery of early cancer and progress of perioperative treatment have reduced mortality in patients with malignancies. However, after standard treatment, advanced malignancies still suffers from poor survival rates due to consequently recurrence or metastasis. With ongoing intensive tumor research, the mechanisms of tumor occurrence and progression have been gradually been understood, and increasing numbers of therapeutic targets have 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 prognosis. More importantly, these markers can often be used as therapeutic targets, and then 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 bring new progress in tumor therapy.

Recent studies showed that some tripartite motif (TRIM) proteins were involved in tumorigenesis and progression and function as a protein regulator,they were important intersection in the gene pathway [1].TRIM44, which is localized to the cytoplasmic compartment of cells, was reported to contribute to diverse pathological conditions such as cancer, growth disorders,neurodegeneration [2–7]. TRIM44 protein has a zinc-finger domain, which shows the role of ubiquitin-specifc proteases (USPs). Thus, it has been defined as the “USP-like” TRIM [7]. The ubiquitin–proteasome system serves as 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 suggested that TRIM44 plays a cancer-promoting role in the oncogenesis and tumor progression, and increased TRIM44 expression was measured in cancer tissues and was associated with poor prognosis and advanced clinicopathological parameters[10–12].Importantly, recents 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 PI3K/AKT/mTOR pathway [11, 13]. Another report indicated that TRIM44 could activate NF - κB pathway to promote lung cancer cell migration and invasion [14].

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

Methods

Search strategy

A comprehensive search strategy was conducted in multiple 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: 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) about 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 hazard ratio (HR) with 95% CI.

Exclusion criteria: not original studies,studies without control group, articles that only explored the molecular functions of TRIM44; Studies with less than 50 cases included.

Data Extraction

For each study, the general information was collected by two investigators independently: 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, clinicopathological parameters related to tumor progression were collected. For survival data extraction, the HRs and 95% CIs were directly used from multivariate survival analysis or univariate analysis second priority, otherwise, 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 ^ 6 were considered to indicate high-quality studies.

Public Data And Tools

In this study, the GEPIA database was used to display the expression level of TRIM44 in other types of human cancer and to further validate its prognostic value for OS/DFS in TCGA dataset. Patients with cancers were divided into a high or low TRIM44 group according to expression above or below median expression. Box plot was used to represent 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 was adopt to estimate heterogeneity among enrolled studies. $I^2 \geq 50\%$ or a P-value < 0.10 statistically defined as 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 was applied to assess publication bias and sensitivity analysis was adopted to test the stability of the analysis results. $p < 0.05$ was used to identify significant effects.

Results

Characteristics of eligible studies

Studies collection and screening process was shown in Fig. 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, those 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 TRIM44 protein levels and OS, and six of the selected eligible studies presented data on the link between TRIM44 and DFS. Among those studies, 13 different kinds of solid tumors were analysed, 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 with good-quality. The basic characteristic imformation were collected in Table 1.

Table 1
Characteristics of included studies.

Categories	Studies(n)	Number of patients	HR (95% CI)	p-value	Heterogeneity		
					I^2 (%)	P-value	Model
OS	11	1547	2.16(1.65–2.83)	0.000	32.6	0.138	Fixed
Cutoff value							
Final staining scores[1 or 3] (≥ 4 or 5 vs. ＜4)	7	1118	2.03(1.42–2.19)	0.000	40.9	0.119	Fixed
Final staining scores[1] (≥ 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	-	-	-

Figure 1. Flowchart depicting the steps of the literature search and selection process.

Table 1: Characteristics of included studies.

The correlation between increased TRIM44 expression and overall survival (OS)

Eleven studies involving 1,547 malignancy patients reported the HRs for OS. The pooled results for OS are displayed in Fig. 2. High expression of TRIM44 protein in malignant tissues was indicated strongly to be 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 an 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,indicating significant diference (Table 2).

Table 2
Pooled HR for OS according to subgroup analysis

Clinicopathological parameter	Studies(n)	OR (95% CI)	p-value	Heterogeneity		
				I^2 (%)	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

Figure 2. Forest plot of HR for the relationship between increased TRIM44 expression and OS.

Table 2 Pooled HR for OS according to subgroup analysis

The correlation between increased TRIM44 expression and disease-free survival (DFS/ 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) ,indicating that patients with elevated TRIM44 protein expression in malignant tissues had lower DFS rate compared to patients with lower expression(Fig. 3). The heterogeneity test revealed a medium heterogeneity among the four studies (I^2 = 64.2%; P_h =0.016).

Figure 3. Forest plot of HR for the relationship between increased TRIM44 expression and DFS/RFS.

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 connected with overexpression of TRIM44 protein more frequently.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: 2.30).However, there was no siginificant 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.

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 the corresponding normal tissues (Fig. 4).

Figure 4. TRIM44 mRNA expression in malignant tissues and the corresponding normal tissues.

Validation of 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 (Fig. 5).

Figure 5. Kaplan–Meier plotter of patients with different level of TRIM44 mRNA.

Publication Bias

The Begg's visible plots are shown in Fig. 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.

Figure 6. Funnel plot analysis of potential publication bias.

Sensitivity Analysis

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

Clinicopathological parameter	Studies (n)	OR (95% CI)	p Value	Heterogeneity	
				I^2	Model
Gender (male vs. female)	18	1.00 (0.78-1.29)	0.990	0.0%	Fixed
Recurrence (+ vs. -)	2	3.30 (1.34-8.15)	0.009	0.0%	Fixed
Tumor depth (T3-4 vs. T1-2)	24	2.72 (1.73-4.30)	0.000	0.0%	Fixed
Lymph node metastasis (+ vs. -)	2	2.69 (1.71-4.24)	0.000	0.0%	Random
Distant metastasis (+ vs. -)	2	10.35 (1.01-106.24)	0.049	90.0%	Random
TNM stage (III-IV vs. I-II)	2	2.75 (2.04-3.71)	0.000	0.0%	Fixed
Poorly/undifferentiated vs. well/moderately	4	1.78 (1.03-3.09)	0.040	68.2%	Random
Vascular invasion (+ vs. -)	2	2.43 (0.85-6.94)	0.097	0.0%	Random

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

Discussion

Ubiquitination is a post-translational protein modification that tags proteins for proteolytic degradation. It involves in intercellular biological behavior such as signal transduction,cell cycle regulation, DNA repair, antigen processing, and apoptosis [26–29]. RING finger ubiquitin E3 ligases were 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 associate 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,that was discovered in ubiquitin hydrolases [38]. TRIM44 protein and mRNA was 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 the 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 Ecadherin 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 was associated with downregulation of mesenchymal markers (such as vimentin and Ncadherin) and upregulation of epithelial markers (such as Ecadherin) [11]. Overexpression of TRIM44 repressed Ecadherin expression and increased vimentin and Ncadherin 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 ectopic expression of TRIM44 dramatically increased the expression of mesenchymal markers N-cadherin and vimentin but decreased the expression of epithelial marker E-cadherin, 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 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 were discovered function as a vital cyclin-dependent kinase inhibitors, 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 of p21/p27 expression,and then inhibited cell division[47]. Further, the critical p21/p27 regulator AKT is inactivated after TRIM44 is knocked down, but is activated in cells that overexpress TRIM44 in glioma cells [47].

TRIM44 overexpression leads to high mTOR activity ,consistent with observations of reduced mTOR signaling in cancer cell lines after siRNA knockdown of TRIM44 [39]. The phosphorylation of downstream mTOR substrates, including pAkt (Ser473) and pp70S6K (Thr389), in TRIM44knockdown 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 which is reported to be involved in oncogene regulatory pathways, including AKT/mTOR[48–50].

TRIM44 could function as E3 ubiquitin ligase and 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 on mTOR signaling pathway,and up-regulated mTOR signaling from other mechanisms.TRIM44induced mTOR signaling, EMT, and cyclin/CDK upregulation were reversed by treatment with an inhibitor of 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 signifcantly repress ICC cell invasion and metastasis [21]. ERK1/2 was 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, suggesteing that TRIM44 promotes EMT in ICC cells via the ERK-MAPK pathway.

Furthermore, overexpression of TRIM44 was reported to be associated with inhibition of apoptosis in esophageal cancer [13]. A microarray analyses showed that TRIM44 knockdown is associated with the dysregulation of NUPR1, CDK19, CADM1, INHBA, TNFSF10, and DDIT4, which could normally activate apoptic cell pathways [24].Bax and Bcl-2 are closely related to apoptosis. Elevated TRIM44 expression signifcantly repressed Bax and promoted Bcl-2 expression.Thus, TRIM44 has vital role in inhibiting cellular apoptosis.NF-κB,function as a vital nuclear transcription factor,was reported to be closely related to inflammatory response, cellular apoptosis, and stress responses. NF-κB is the melocular target of some antitumor drugs [58]. The transcription factor NF-κB has been reported to inhibit apoptosis and to induce drug resistance in cancer cells [59]. Of note, it has been reported that TRIM44 promotes non-small cell

lung cancer development through activation of NF-κB signaling [14]. Previous studies indicated that cIAP1, c-IAP2, and XIAP are the antiapoptotic transcriptional targets of NF-κB signaling [60]. A previous report showed that silencing of TRIM44 could decrease c-IAP1, c-IAP2, and XIAP expression, especially in the presence of doxorubicin [25]. High expression of TRIM44 could enhance resistance of HCC cells to doxorubicin via accelerating NF-κB activation. Increased NF-κB-mediated transcriptional activity was detected in TRIM44-transfected breast cancer cells[16].

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

Ki67 has been reported to be a promoter in 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 deubiquitinates 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 discussed the possible role of TRIM44 in tumor progression. Pooled results indicated that expression level of TRIM44 protien 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 lower DFS rate than patients with low TRIM44 expression. Furthermore, malignancy patients with unfavorable clinicopathological parameters were connected with overexpression of TRIM44 protein more frequently.Comprehensive analysis results show that TRIM44 is frequently overexpressed in malignancies and functions as a crucial oncogenic role. Malignancy patients with increased tissue TRIM44 expression had an unfavorable prognosis.TRIM44 is involved in the malignant biological behavior of tumor cells and plays an intersection role in 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 would be helpful. Third, several HRs and their corresponding 95% CIs were extracted from the survival curves and 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 investigated that TRIM44 is involved in the malignant biological behavior of tumor cells and plays an intersection role in gene regulatory pathways.TRIM44 may be an important molecular marker for determining 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 surviva;NR: not report;M: multivariate analysis; C:curves;immunohistochemistry (IHC); 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 small cell lung cancer.

Declarations

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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 proces

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Availability of data and materials

Meta-analysis is a secondary analysis, which the data are all fully available without restriction, and all the material 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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Figures

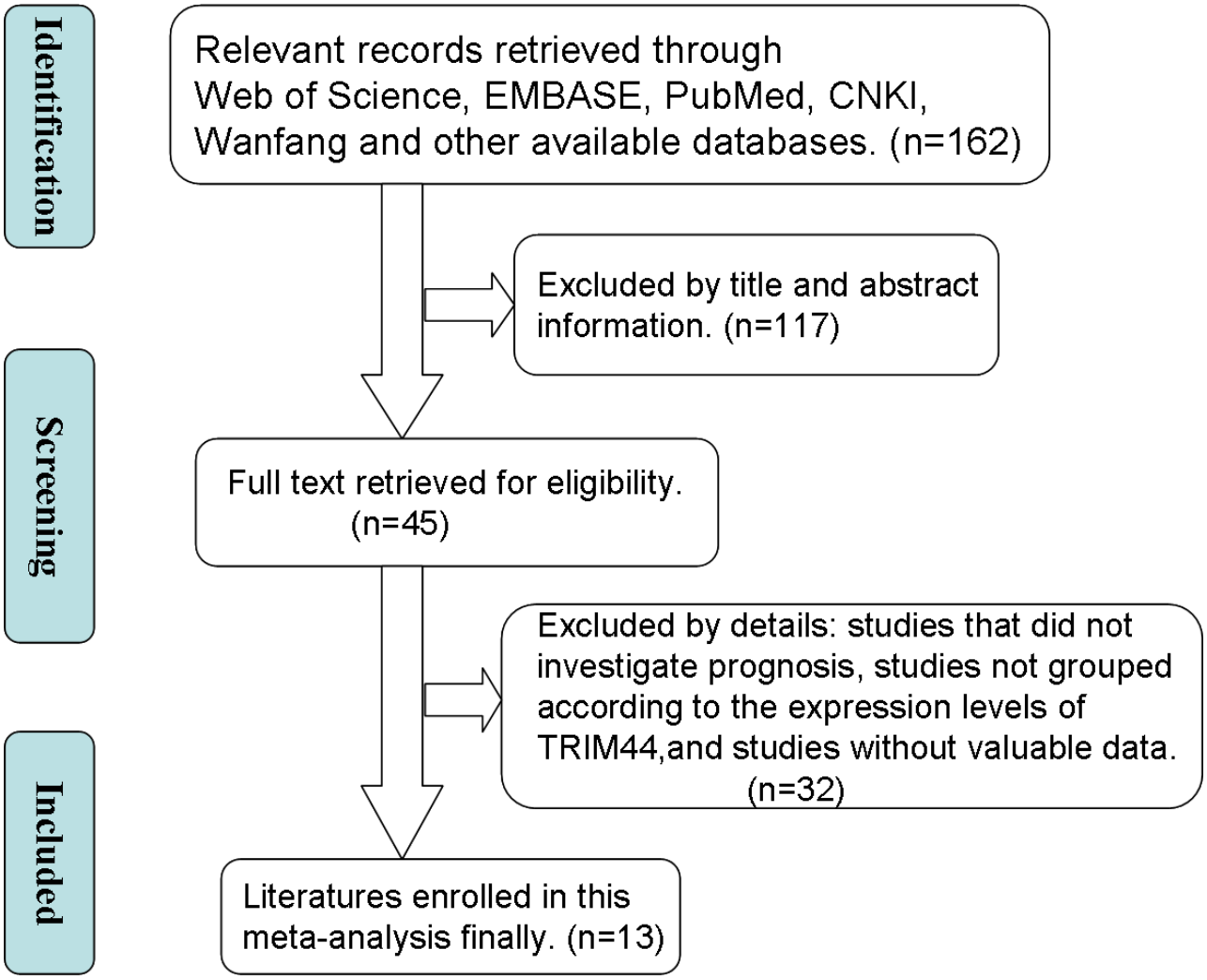

Figure 1

Flow diagram of included studie.

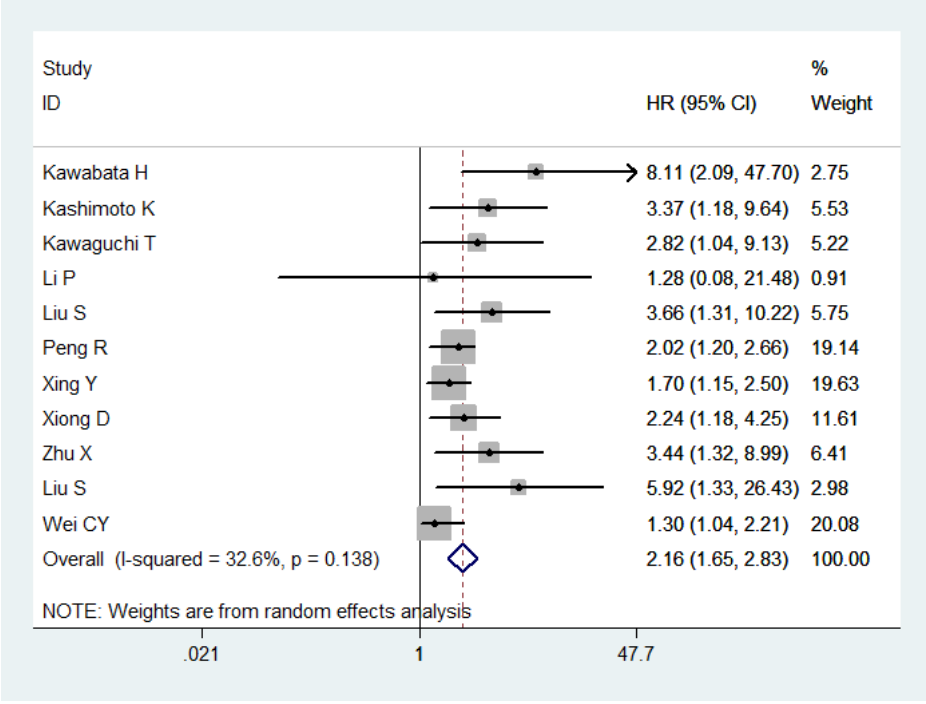

Figure 2

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

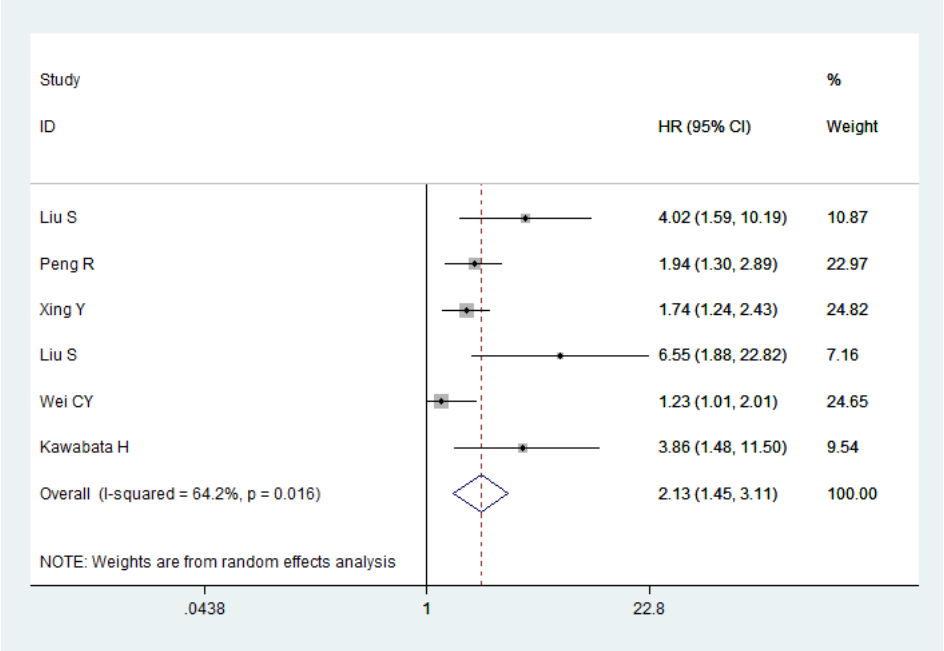

Figure 3

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

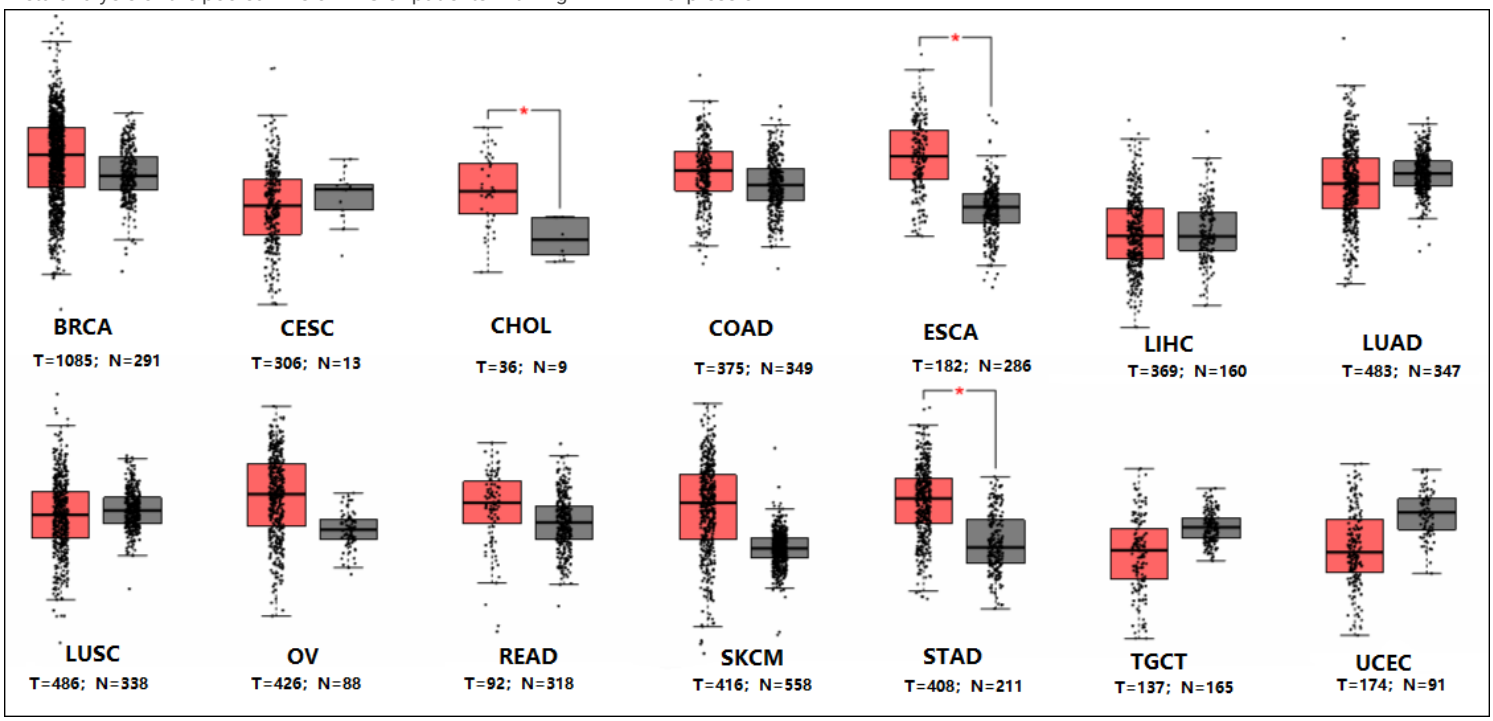

Figure 4

TRIM44 mRNA expression in different types of human malignancies.

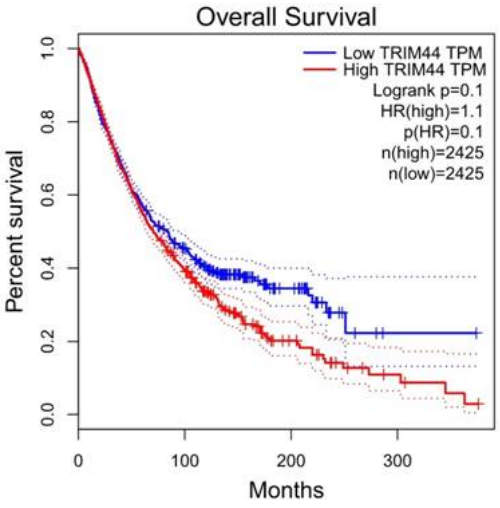

Figure 5

Validation of prognostic value of TRIM44 mRNA in various malignancies.

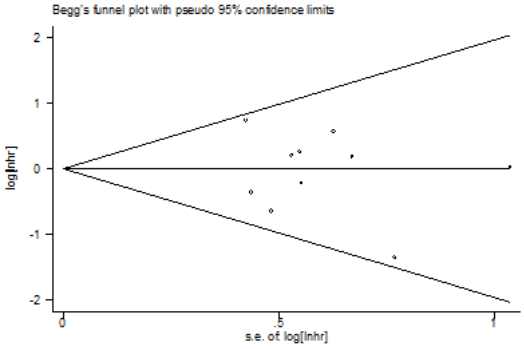

Figure 6

Publication bias assessment of TRIM44 expression and OS.

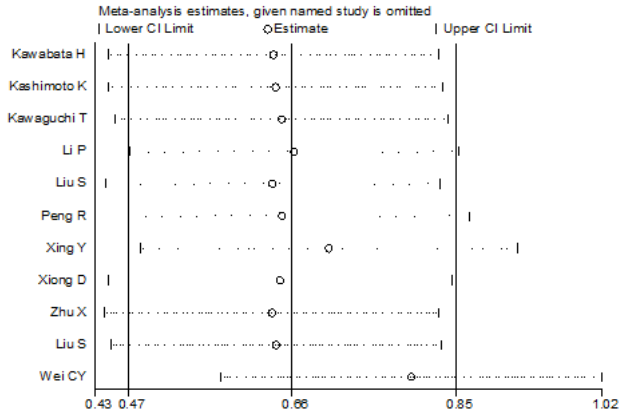

Figure 7

Sensitivity analysis of TRIM44 expression and OS.