Prognostic role of tripartite motif containing 24 in various human solid malignant neoplasms
An updated meta-analysis and systematic review
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Abstract
Background: Currently, clinical studies of tripartite motif containing 24 (TRIM24) on human solid malignant neoplasms were developing, but the prognosis value of TRIM24 continues to be controversial. The aim of our study is to explore the prognostic effect of TRIM24 in various human solid malignant neoplasms.

Methods: We performed a comprehensive research for eligible studies which evaluated the prognostic roles of TRIM24 in cancer patients based on PubMed, Embase, Web of Science, and China National Knowledge Infrastructure. The hazard ratios (HRs) with 95% confidence intervals (CIs) for various malignances were extracted from eligible studies.

Results: A total of 13 studies with 1909 patients were enrolled in this analysis. Combined analyses showed that high expression of TRIM24 significantly predicted poorer overall survival both in univariate analysis (HR = 1.61, 95% CI 1.21–2.15, P = .001) and multivariate analysis (HR = 2.19, 95% CI 1.10–4.38, P = .026). In stratified analyses, high TRIM24 expression level predicted even worse overall survival in hormone-related cancers (HR = 1.92, 95% CI 1.28–2.86, P = .001). Although, expression of TRIM24 failed to show a significant relation with progression-free survival/disease-free survival/recurrence-free survival (HR = 1.42, 95% CI 0.93–2.16, P = .106), high expression predicted significant worse progression-free survival/disease-free survival/recurrence-free survival in hormone-related cancer (HR = 1.71, 95% CI 1.12–2.59, P = .013).

Conclusion: TRIM24 could serve as a new biomarker for patients with solid malignancies and could be a potential therapeutic target for patients especially for hormone-related malignancies.

Abbreviations: CIs = confidence intervals, DFS = disease-free survival, HRs = hazard ratios, OS = overall survival, PFS = progression-free survival, RFS = recurrence-free survival, TRIM = tripartite motif, TRIM24 = tripartite motif containing 24.

Keywords: cancer, meta-analysis, prognosis, tripartite motif containing 24

1. Introduction

Tripartite motif (TRIM) family proteins are reported to have various function in autophagy, immunity, and carcinogenesis.1–4 Most TRIM family proteins have E3 ubiquitin ligase activities which is involved responsible for post-translational modifications.1,5

Tripartite motif containing 24 (TRIM24), also known as transcriptional intermediary factor 1α, is one of the TRIM family.1,5 Three zinc-binding domains of TRIM24 includes a RING, a B-box type 1, and a B-box type 2.1,5 TRIM24 depletion was found to lead p53-dependent apoptosis in breast cancer, suggesting TRIM24 could mediate the ubiquitination of p53 levels.1,5 It has been reported that retinoic acid receptor alpha and TRIM24 co-regulate development of hepatocellular carcinoma in an antagonistic manner.8,9 TRIM24 has also been shown to interact with mineralocorticoid receptor, estrogen receptor α and TRIM33.10,11 Cui et al12 reported proliferation of head and neck squamous cell carcinoma cells could be suppressed upon TRIM24 silencing. TRIM24 could activate PI3K/Akt signaling pathway to promote carcinogenesis and chemoresistance.13 TRIM24 can also promote aggression of malignancy via the Wnt/β-catenin signaling pathway.14 Moreover, TRIM24 was reported to be an important factor in the pathogenesis of human hepatocellular carcinoma by involving in epithelial-mesenchymal transition pathway. Recently Zhou et al15 found a new regulatory pathway that TRIM24 aggravates ovarian cancer by suppressing FOXM1, which is recognized as a “pioneer factor”. These findings indicated that TRIM24 has multiple regulatory mechanisms in the occurrence and development of malignancies. TRIM24 was researched in many cohort studies and was found to have potential role to serve as a prognostic marker and therapeutic target in different types of malignancies.

TRIM24 has been reported to be highly expressed in a variety of malignancies and some studies illustrated that TRIM24 played
an oncogenic role in carcinogenesis.\textsuperscript{[12–24]} However, some other studies demonstrated that TRIM24 act as a tumor suppressor gene.\textsuperscript{[9,23–27]} A recent meta-analysis\textsuperscript{[28]} of 10 studies evaluated the prognostic value of TRIM24 in multiple malignancies. However, the amount of research it contains was small and many high-quality studies of TRIM24 have been published recently. Most importantly, the previous meta-analysis did not include subgroup analysis and lacked the exploration of heterogeneity. Therefore, we performed a systemic review and meta-analysis to discuss the prognostic value of TRIM24 in various malignancies.

2. Methods

This systematic review and meta-analysis were carried out according to the preferred reporting items for systematic reviews and meta-analyses statement\textsuperscript{[29]} and the checklist of preferred reporting items for systematic reviews and meta-analyses was provided (see Table S1, Supplemental Digital Content, http://links.lww.com/MD/G549). The research does not involve patients, so ethical approval was not necessary.

2.1. Search strategy

We conducted the literature research via PubMed, Embase, Web of science, and China National Knowledge Infrastructure up to June 2020. The literature published until July 15, 2020 was searched. The following keywords were adopted in various combination: “TRIM24”, “RNF82”, “tripartite motif-containing protein 24”, “TIF1A”, “Transcriptional Intermediary Factor 1”, “PTC6”, “cancer”, “carcinoma”, “tumor”, “neoplasm”, “malignancy”, “survival”, “incidence”, “risk”, and “mortality”. Eligible research for relevant references were also reviewed.

2.2. Criteria of inclusion and exclusion

Inclusion criteria: studies were dealing with human solid malignancies; the expression of TRIM24 was measured from tissue; associations between different expression level of TRIM24 and survival were evaluated; and hazard ratios (HRs) and 95% confidence intervals (CIs) of survival data could be directly or indirectly extracted from studies. Articles were excluded if the study was not original; there were no comparison between different expression level of TRIM24 and survival data; and lacking data for estimating HRs with 95% CIs.

2.3. Data extraction

All eligible studies were independently collected by Yifeng Xue and Wei Ge. The general information was as follows: author’s name, publication year, number of patients, number of low and high TRIM24 expression patients, cancer types, maximum follow-up time, and method of detection. The characteristics of the studied patients were also collected, including the ethnicity, age, and gender. For survival data, we gave priority to using the HRs with 95% CI provided in the article. For studies only provided Kaplan–Meier curves, the data were extracted by using the Engauge Digitizer version 4.1.\textsuperscript{[30]}

2.4. Quality assessment

Three investigators (Yifeng Xue, Wenhua Shi, and Rong Wang) independently assessed all included studies referring to the Newcastle–Ottawa Quality Assessment Scale.\textsuperscript{[9]} Study with scores ≥6 in total was considered as high-quality research.

2.5. Statistical analysis

HRs with 95% CIs for overall survival (OS), progression-free survival (PFS), disease-free survival (DFS), and recurrence-free survival (RFS) were extracted from eligible studies. We combined these HRs and 95% CIs of OS and PFS/DFS/RFS separately for further analyses.

Heterogeneity was measured by Q statistics and if inconsistency index (I²) > 50% and P < .10, a random-effect model would be used. If P < .50% and P > .10, a fixed-effect model would be selected.\textsuperscript{[31]} Publication bias was tested by funnel plot and Begg bias indicator test.\textsuperscript{[32]} The stability of analysis was tested by sensitivity analysis. Analysis in this study were performed with STATA/SE 12.0 (Stata Corporation, College Station, TX) and P < .05 was considered statistical significance.

3. Results

3.1. Characteristics of included studies

A flow chart of study identification and screening process was shown in Figure 1. A total of 1909 patients in 14 studies published from 2011 to 2019 were included for this meta-analysis.\textsuperscript{[12–25]} The features of the 14 eligible studies were listed in Tables 1 and 2. Twelve studies provided data between OS and TRIM24 expression level while 6 studies present data between PFS/DFS/RFS and TRIM24 expression. In this meta-analysis, 10 different kinds of neoplasms were analyzed, including breast cancer, head and neck squamous cell carcinoma, hepatocellular carcinoma, glioblastoma multiforme, gastric cancer, esophageal squamous cell carcinoma, cervical cancer, colorectal cancer, prostate cancer, and ovarian cancer. All studies were designed retrospective.

3.2. Association between TRIM24 expression and OS

A total of 12 studies were applied for OS analysis. Univariate analysis and multivariate analysis of HR for OS were pooled separately (Fig. 2). Random-effects model was used because of significant heterogeneity (univariate analysis: P = .023, I² = 51.8%; multivariate analysis: P = .000, I² = 87.6%). Both univariate and multivariate analysis showed that high TRIM24 expression level predicted poorer OS significantly (HR = 1.61, 95% CI 1.21–2.15, P = .001; HR = 2.19, 95% CI 1.10–4.38, P = .026).

Moreover, stratified analyses were performed by sample size, data source, cancer type, and patient ethnicity in univariate analyses group. Interestingly, patients sample size < 100 showed significant poor OS (HR = 1.90, 95% CI 1.31–2.75, P = .001) where group of sample size > 100 failed to predict significant results (HR = 1.47, 95% CI 0.95–2.27, P = .086) (Fig. 3A). We used the Engauge Digitizer version 4.1 to get HR data for studies which did not provide HR directly. We divided studies to 2 groups according to source of HR. Surprisingly, significant effect was observed between the high level of TRIM24 in survival curve group (HR = 1.88, 95% CI 1.39–2.54, P = .000) but not in reported group (HR = 1.51, 95% CI 0.83–2.74, P = .020) (Fig. 3B). When stratified by the cancer type, we found a significantly worse OS (HR = 1.92, 95% CI 1.28–2.86, P = .001) in hormone-related cancer with no heterogeneity (F = 0.0%, P = .636) (Fig. 3C). No significant relationship was observed...
between TRM24 and other type cancers (HR = 1.47, 95% CI 1.21–2.15, \( P = .069 \)). This suggested that heterogeneity of analyses was probably due to the tumor type. In subtotal analyses of data source, significant worse OS both in Caucasian (HR = 2.36, 95% CI 1.15–4.84, \( P = .020 \)) and Asian (HR = 1.50, 95% CI 1.08–2.09, \( P = .016 \)) (Fig. 3D).
In addition, we performed subgroup analyses for cancer type and sample size in multivariate analyses of OS. Consistent with univariate analyses, when stratified by cancer type, hormone-related cancer group showed significant worse OS (HR = 5.50, 95% CI 1.63–18.56, P = .006) and other cancer type did not exhibit a significant association with poor OS (HR = 1.76, 95% CI 0.82–3.77, P = .145) (Fig. 4A). Subgroup analysis according to sample size showed the combined HR = 5.39 (95% CI 1.31–22.19, P = .020) for <100 group but with high heterogeneity (I² = 79.6%, P = .007) (Fig. 4B).

### 3.4. Publication bias

Begg funnel plot and Egger test were used to detect publication bias. Among for 11 studies evaluating OS by univariate analysis and 6 studies evaluating OS by multivariate analysis, no obvious asymmetry was observed (P = .775, P = .524, separately) (Fig. 6). No potential publication bias was observed in PFS/DFS/RFS study (P = .907) (see Figure S1A, Supplemental Digital Content, http://links.lww.com/MD/G549).

### Table 1

**Characteristics of eligible studies.**

| First author, Publication year | Dominant ethnicity | Malignant disease | Detected sample | Outcome measurement | Source of HR | Maximum months of follow-up | Assay method | NOS score |
|-------------------------------|---------------------|-------------------|-----------------|--------------------|--------------|-----------------------------|--------------|-----------|
| Monique Chambon, 2011         | Caucasian           | Breast cancer     | Tissue          | OS                 | Reported     | 110                         | IHC          | 6         |
| Monique Chambon, 2011         | Caucasian           | Breast cancer     | Tissue          | OS/PFS             | Reported     | 60                          | IHC          | 6         |
| Zhibin Cui, 2013              | Asian               | HNSCC             | Tissue          | OS                 | SC           | 46                          | IHC          | 6         |
| Xiao Liu, 2014                | Asian               | Hepatocellular carcinoma | Tissue          | OS/PFS             | Reported     | 90                          | IHC          | 6         |
| Luhua Zhang, 2015             | Asian               | Glioblastoma multiforme | Tissue          | OS/PFS             | SC           | 99.3                        | IHC          | 5         |
| Zhifeng Miao, 2015            | Asian               | Gastric cancer    | Tissue          | OS/PFS             | Reported/SC  | 60                          | IHC          | 6         |
| Jun Chi, 2016                 | Asian               | ESCC              | Tissue          | OS                 | SC           | 80                          | IHC          | 6         |
| Li Lin, 2017                  | Asian               | Cervical cancer   | Tissue          | OS                 | SC           | 96                          | IHC          | 6         |
| Fengqin Wang, 2017            | Asian               | Colorectal cancer | Tissue          | OS                 | Reported     | 184                         | IHC          | 6         |
| Li Ma, 2016                   | Asian               | Breast cancer     | Tissue          | OS                 | SC           | 220                         | qRT-PCR      | 6         |
| Li Ma, 2016                   | Asian               | Breast cancer     | Tissue          | OS                 | SC           | 25                          | IHC          | 6         |
| Ziling Fang, 2017             | Asian               | Prostate cancer   | Tissue          | OS                 | Reported     | 150                         | IHC          | 7         |
| Honger Zhou, 2019             | Asian               | Ovarian cancer    | Tissue          | OS                 | SC           | 75                          | NA           | 5         |

### Table 2

**HRs and 95% CIs for patient survival in association with TRIM24 expression in included studies.**

| First author, Publication year | High expression | Low expression | Number of cases | OS (Univariate) | OS (Multivariate) | PFS/DFS/RFS |
|-------------------------------|-----------------|----------------|----------------|-----------------|-------------------|-------------|
| High expression               | Low expression  | N/A            | N/A            | N/A             | N/A               | N/A         |
| Monique Chambon, 2011         | N/A             | 1.91 (1.088–3.352) | .024           | 1.90 (1.064–3.428) | .03 | N/A         |
| Monique Chambon, 2011         | N/A             | 1.60 (1.39–1.83) | .001           | 1.50 (1.30–1.72) | .001 | N/A         |
| Zhibin Cui, 2013              | N/A             | 2.54 (1.39–4.66) | .001           | 1.05 (0.354–0.810) | .003 | 0.586 (0.398–0.863) | .007 |
| Xiao Liu, 2014                | N/A             | 0.498 (0.220–0.770) | .001           | 0.550 (0.354–0.810) | .003 | 0.586 (0.398–0.863) | .007 |
| Luhua Zhang, 2015             | N/A             | 1.17 (0.47–2.93) | .05            | N/A             | N/A               | 1.28 (0.8–2.08) | .05 |
| Zhifeng Miao, 2015            | N/A             | 3.754 (2.059–5.909) | .012           | 3.383 (2.246–4.989) | .026 | N/A         |
| Jun Chi, 2016                 | N/A             | 13.782 (4.087–46.476) | < .001         | 13.782 (4.087–46.476) | < .001 | N/A         |
| Li Ma, 2016                   | N/A             | 1.68 (0.93–3.04) | .01            | N/A             | N/A               | N/A         |
| Li Lin, 2017                  | N/A             | 1.21 (0.22–6.79) | .05            | N/A             | N/A               | N/A         |
| Fengqin Wang, 2017            | N/A             | 5.0 (1.10–23.3) | .025           | 8.1 (1.6–41.8) | .003 | N/A         |
| Ziling Fang, 2017             | N/A             | 1.97 (1.16–3.34) | < .001         | N/A             | N/A               | N/A         |
| Qinbo Zhang, 2017             | N/A             | 1.78 (1.12–6.87) | .002           | N/A             | N/A               | 2.78 (1.12–6.87) | .002 |
| Anne Offermann, 2019          | N/A             | 106 (133)       | N/A            | N/A             | N/A               | 2.17 (1.28–3.68) | .004 |
| Honger Zhou, 2019             | N/A             | 17 (22)         | 2.18 (0.46–10.25) | N/A             | N/A               | N/A         |
3.5. Sensitivity analysis

In both univariate and multivariate analysis of OS studies, sensitivity analyses did not show any alterations (Fig. 7). In PFS/DFS/RFS study, no single study affected the pooled HR (see Figure S1B, Supplemental Digital Content, http://links.lww.com/MD/G549).

4. Discussion

TRIM24, as one of the TRIM family, was reported to be associated with clinical outcomes for multiple cancers. As a transcriptional intermediary factor, TRIM24 may participate in various mechanism in development and progression of cancers and serve as a potential marker for prognosis.\(^{12-25}\) TRIM24 was found to be highly expressed in many malignant solid tumors such as: head and neck squamous cell carcinoma, glioma, gastric cancer, breast cancer, cervical cancer, colorectal cancer, hepatocellular carcinoma, prostate cancer, and ovarian cancer,\(^{12-24}\) indicating TRIM24 as a oncogene. However, TRIM24 was reported to be downregulated in esophageal squamous cell carcinoma as a tumor suppressor gene.\(^{25}\)

Previous meta-analysis of 10 studies evaluated the prognosis value of TRIM24.\(^{28}\) However, because of limited sample size, they failed to find significant relationship between OS and TRIM24 expression. In addition, in case of high heterogeneity, they did not apply the stratified analysis to find where heterogeneity from. Moreover, we analysis PFS/DFS/RFS to further evaluate the prognostic role of TRIM24.

Pooled HRs of OS from both univariate analysis and multivariate analysis showed that increased TRIM24 expression predicted poor OS significantly \((P = .001, P = .026, \text{respectively})\). In consistent with OS, PFS/DFS/RFS analysis demonstrated that high TRIM24 expression was correlated with worse outcome but not significant \((P = .106)\). Recent studies revealed that TRIM24 played an important role in develop, invasion, and metastasis of multiple tumors.\(^{33}\)

Next, in subgroup analysis, the results focused on whether the relationship between TRIM24 expression and OS was affected by sample size, data source, cancer type and patient ethnicity. First, we found that high TRIM24 expression level was significantly related with a worse OS in studies which sample size was \(<100\) while not significant in cohort which sample size was \(>100\). As the sample size increases, study bias may become less while cohort of small sample size may lead to greater bias. Next in subgroup analysis of cancer type, we found OS of hormone-related cancer was related with TRIM24 expression while OS of other cancer types showed no significant relationship with TRIM24 expression. Consistent with this result, subgroup analysis of PFS/DFS/RFS for hormone-related cancer types also revealed a significant correlation between PFS/DFS/RFS and TRIM24 expression. The hormone-related cancer involved in our meta-analysis included breast cancer, cervical cancer, ovarian cancer and prostate cancer. This result strongly suggested that TRIM24 may be involved in steroid receptor function. It is reported that TRIM24 expression was positively correlated with acetylated H3 lysine23, HER2, estrogen receptor, and progesterone receptor statuses.\(^{17}\) In addition, studies showed that TRIM24 acted as a cofactor of various steroid hormone receptors such as androgen receptor, retinoic acid receptor.\(^{8,9,34,35}\) TRIM24 can augment AR signaling and act as an oncogenic transcriptional activator in prostate cancer.\(^{36}\) TRIM24 was found even higher in castrate resistant prostate cancer,\(^{36}\) indicating TRIM24 was attributed in prostate cancer progression and may be a potential drug target. When grouped by ethnicity, both Caucasian and Asian have a significant correlation between worse OS and high TRIM24 expression. Notably, Caucasian patients seemed have higher HR than Asian patients. More studies for Caucasian are needed for further analysis.
Figure 3. Forest plots of subgroup univariate analyses for OS associated with TRIM24 expression. Subgroup analysis for (A) sample size >100 or not; (B) data extracted from SC or provided directly; (C) hormone-related cancer or other cancer types; (D) Caucasian or Asian. CI = confidence interval, HR = hazard ratio, OS = overall survival, SC = survival curve.

Figure 4. Forest plots of subgroup multivariate analyses for OS associated with TRIM24 expression. Subgroup analysis for (A) hormone-related cancer or not; (B) sample size >100 or not. CI = confidence interval, HR = hazard ratio, OS = overall survival.
Figure 5. Forest plots of merged analyses for PFS/DFS/RFS associated with TRIM24. (A) Forest plot for the PFS/DFS/RFS analysis. (B) Subgroup analysis for hormone-related cancer or other cancer types. CI = confidence interval, DFS, disease free survival, HR = hazard ratio, PFS = progression free survival, RFS = recurrence free survival.

Figure 6. Begg funnel plots of the publication bias. Begg funnel plot for (A) merged univariate analysis of OS and (B) merged multivariate analysis of OS. OS = overall survival.

Figure 7. Sensitivity analysis of each included study. Sensitivity analysis for OS for individual studies in (A) univariate analysis and (B) multivariate analysis. OS = overall survival.
It is undeniable that heterogeneity is a potential issue in meta-analysis that cannot be neglected. In this meta-analysis, moderate heterogeneity was observed in univariate OS analysis and high heterogeneity was observed in multivariate OS analysis and PFS/DFS/RFS analysis. In stratified analysis, we found the heterogeneity was largely decreased when grouped by sample size, data source, cancer type, and patient ethnicity. However, some limitations in our meta-analysis may have an impact on our results. First, there was no exact cutoff value when evaluating expression level of TRIM24. Even using the same scoring system for immunohistochemistry, bias still exist because the percentage and intensity of immunohistochemistry were evaluated by different pathologists. Second, because of limited sample size in PFS/DFS/RFS analysis, the statistical power may be reduced. Third, several HRs in our study were extracted from survival curve and original data were not available. Finally, data extracted from univariate analysis without adjustment for multiple factors may lead confounding bias.

5. Conclusion
In summary, we concluded that TRIM24 expression level was related with survival time and tumor progression for patients with cancer. Furthermore, TRIM24 may serve as a new biomarker for predicting survival and progression of malignant diseases especially in hormone-related cancers.

Author contributions
Conceptualization: Rong Wang.
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