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Prognostic Role of Tenascin-C for Cancer Outcome: A Meta-Analysis

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Abstract

Background: The prognostic value of tenascin-C in different types of cancers remains controversial. To clarify its prognostic value on overall survival rates, we have conducted a meta-analysis to quantitatively assess the prognostic roles of tenascin-C for patients with cancer. **Methods:** We systematically searched all published studies about the role of tenascin-C in cancers on PubMed, Web of Science, Cochrane Library, and Embase. The pooled hazard ratio with 95% confidence intervals was used to analyze the association between tenascin-C expression level and overall survival of patients with cancer. The pooled odds ratio with 95% confidence intervals was used to investigate the association between tenascin-C expression level and clinicopathologic features of patients with cancer. Trial sequential analysis was performed to obtain the required information size. **Results:** In this meta-analysis, 18 studies including 2732 patients were incorporated. The pooled hazard ratio of 18 trials was 1.73 (95% confidence interval: 1.29-2.32, $P < .001$) for overall survival, suggesting that elevated tenascin-C expression strongly predicted poor prognosis among patients with various cancers. Simultaneously, elevated tenascin-C expression was also significantly associated with lymph node metastasis (odds ratio = 2.42, 95% confidence interval: 1.79-3.26, $P < .001$). However, no significant correlation was observed between the tenascin-C expression and distant metastasis (odds ratio = 1.72, 95% confidence interval: 0.86-3.44, $P = .127$). **Conclusions:** Tenascin-C is considered as a promising unfavorable prognostic factor in human cancers. Likewise, tenascin-C can be used as a monitoring indicator for poor prognosis in a wide range of cancers.

Keywords

tenascin-C, cancer, prognosis, overall survival, clinicopathological features, monitor, meta-analysis

Abbreviations

AD, assembly domain; APIS, a priori information size; CI, confidence interval; DM, distant metastasis; ECM, extracellular matrix; ELISA, enzyme-linked immunosorbent assay; HR, hazard ratio; IHC, immunohistochemistry; LNM, lymph node metastases; NOS, Newcastle-Ottawa Scale; OS, overall survival; RIS, required information size; TN-C, tenascin-C; TSA, trial sequential analysis

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Introduction

In economically developed countries, cancer leads to a heavy burden on the society. In 2017, 1 688 780 new cancer cases and 600 920 cancer deaths are projected to occur in the United States.[1] Moreover, Bray *et al* predicted an increase in the incidence of all-cancer cases from 12.7 million new cases in 2008 to 22.2 million by 2030.[2] Hence, targeted interventions should be taken to reduce this number through resource dependent interventions. Although there have been significant improvements in diagnostic and therapeutic techniques for cancer, the

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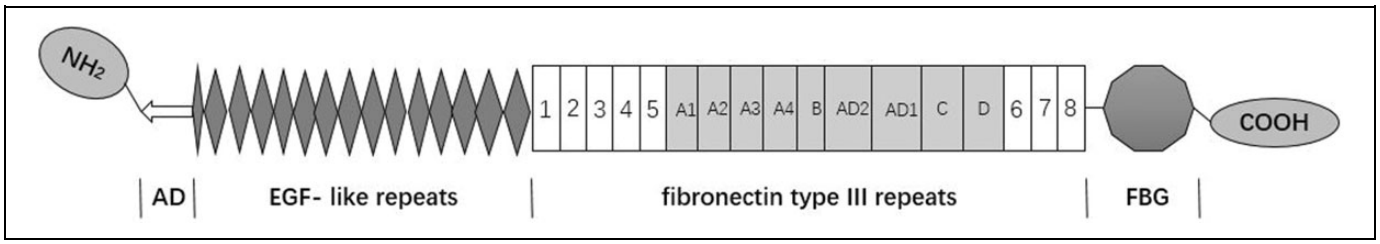

Figure 1. Structural schematic diagram of tenascin-C monomer. Below the structure are the domains: AD, assembly domain; EGF-like repeats, epidermal growth factor-like repeats; FN III, fibronectin type III homology repeats; FBG, the C-terminal fibrinogen globe.

prognosis of patients still remains poor. More and more scientists are committed to finding new effective biomarkers for the early diagnosis of cancer and to predicting the progression and prognosis of patients with cancer.

Tenascin-C (TN-C) is a hexametric glycoprotein that each subunit consists of an assembly domain (AD), epidermal growth factor-like repeats, a variable number of fibronectin type III repeats containing alternative spliced domains and the C-terminal fibrinogen globe[3] (Figure 1). Tenascin-C is a glycoprotein of the extracellular matrix (ECM), whose intricate link to cancer has been recognized since its discovery in the mid-1980s.[4] Recent studies have reported that aberrant expressions of TN-C were found in different types of cancers, such as lung cancer,[5] prostate cancer,[6] colorectal carcinomas,[7] breast carcinoma,[8] posterior fossa ependymoma,[9] clear cell renal cell carcinoma,[10] esophageal squamous cell carcinoma,[11] supratentorial ependymomas,[9] tongue cancer,[12] bladder cancer,[13] pancreatic cancer.[14] Most studies revealed that TN-C played a key role in carcinogenesis and its high expression was associated with poor prognosis in a variety of malignant tumors.[5,11,15] But a recent study reported that high expression of TN-C related to favorable prognosis of patients in supratentorial ependymoma.[9] Because inconsistent evidence and none of published meta-analysis revealed the association of TN-C expression level and prognosis of patients with cancer, these results were still controversial. Therefore, this meta-analysis was performed to further determine whether high expression of TN-C can be served as a novel indicator for the prognosis of patients with cancer.

Materials and Methods

Study Strategy

The present review was based on a standard guideline for meta-analysis and systematic review of the studies of tumor markers in respect to prognosis.[16] In order to get the relevant articles in this review, 2 authors independently used the following research tools: PubMed, Web of Science, Cochrane Library, and Embase to identify all relevant articles about TN-C as a prognostic factor for survival of patients in different types of cancers. The time frame of the literature search was from October 01, 1980 to October 01, 2017. The search strategy using both MeSH terms and text words was to enhance the sensitivity of the search. The core search comprised terms ("Tenascin-C" or "TN-C") AND ("cancer" or "carcinoma" or "tumor" or "adenocarcinoma" or "neoplasm") AND ("prognosis" or "prognostic" or "outcome" or "mortality" or "survival" or "recurrence"). We also used the reference lists of key articles published in English to search manually.

Study Selection

Eligible studies must conform to the following criterions: (1) immunohistochemistry (IHC) or enzyme-linked immunosorbent assay (ELISA) was used to assess TN-C expression; (2) the study provided data on tumor differentiation, distant metastasis (DM), lymph node metastasis (LNM), and tumor-node-metastasis stages; (3) hazard ratios (HRs) and their 95% confidence intervals (CIs) were directly extracted or synthesized; (4) the article language is limited to English. The following exclusion criteria were used: (1) letters, editorials, expert opinions, reviews, and case reports; (2) articles based on cancer cells or animal models but not based on patients.

Data Extraction and Quality Assessment

Two researchers conducted an independent study of all literature searches to identify qualified studies and to extract data from the studies. The data extracted for each study were as follows: (1) general data including primary author, age and gender of the study patients, sample size, and survival month; (2) clinicopathological characteristics including DM and LNM; (3) data for overall survival (OS) or disease-free survival; (5) cutoff value; (6) survival curves. If the only available data were in the form of the survival curves, the Kaplan-Meier curves were read using an Engauge Digitizer version 4.1 (free software down-loaded from http://sourceforge.net) and we extracted the survival rates to calculate the HR and 95% CI.[17] The deviations related to risk assessment from 2 independent researchers were based on PRISMA recommendations.[18] Any potential discrepancies and quality assessment between the authors (X.M. and S.Q.) were resolved through discussion with a third reviewer (J.T.). The Newcastle-Ottawa Scale (NOS) method was applied to evaluate the quality of included studies (Supplemental material table 3).[19] The NOS score ranged from 0 to 9 and a study by the NOS score over 7 was accounted the high quality.

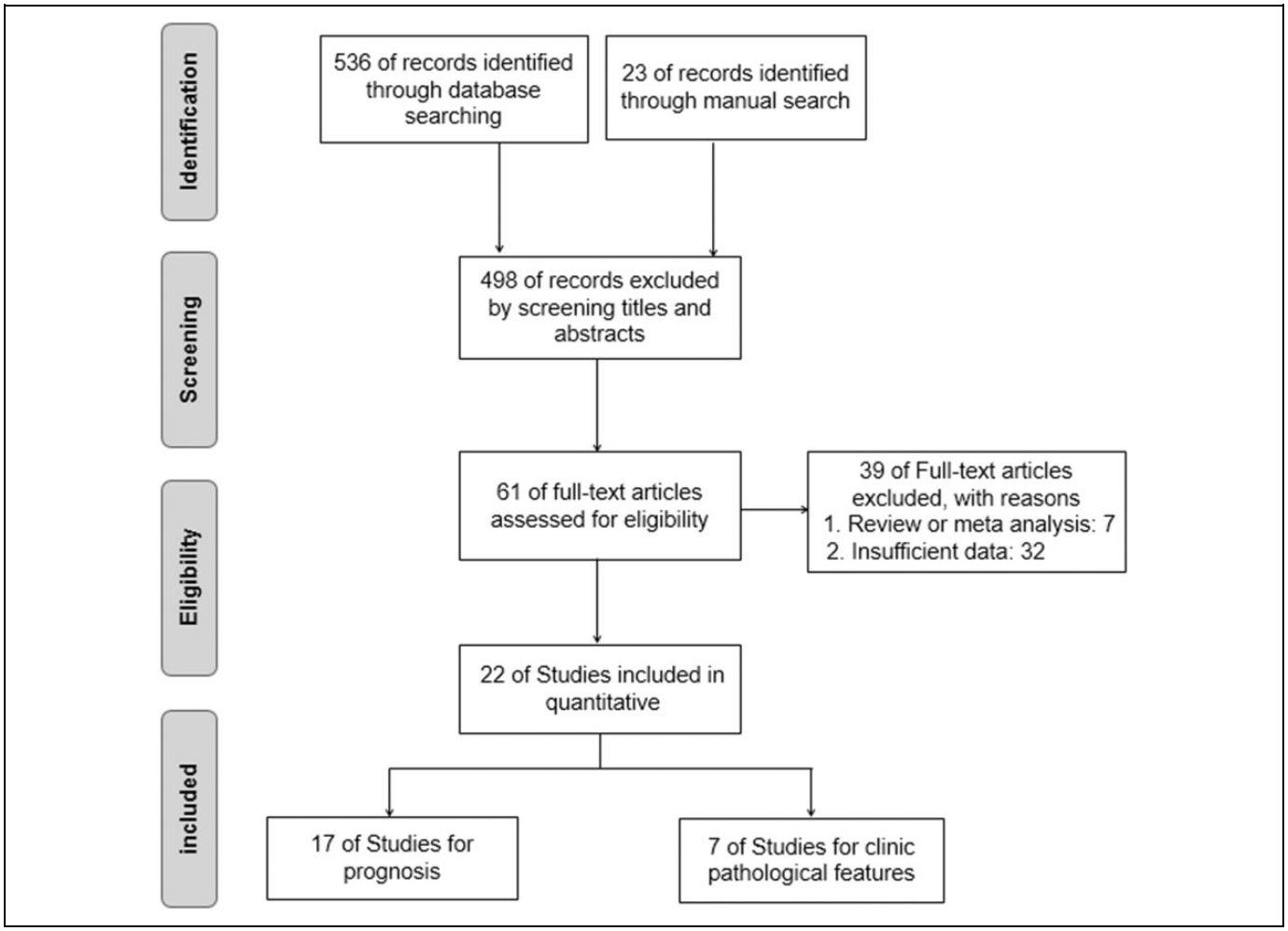

Figure 2. Flow diagram of the study search and selection process.

Statistical Analysis

Meta-analysis was carried out using STATA statistical software package version 12.0 (STATA Corp, College Station, Texas). Pooled HRs and corresponding 95% CIs were calculated to evaluate the impact of TN-C expression on OS. The χ^2-based Q test and I^2 test were used to evaluate the heterogeneity across the studies. Random effect model was used for meta-analysis if there was significant heterogeneity ($P \leq .05$, $I^2 \geq 50\%$), otherwise, fixed effect model was used. Besides, subgroup analysis was performed to explore the sources of heterogeneity. Meanwhile, we used funnel plots and Begg's bias test to analyze the publication bias in this study.[20]

Trial Sequential Analysis

The meta-analyses and systematic reviews are regarded as the best available evidence if all qualified studies are covered. However, "the best available evidence" might not be considered equivalent to "sufficient evidence." In our studies, the trial sequential analysis (TSA) was carried out to assess the robustness of the current conclusions.[21] The O'Brien-Fleming α-spending–function and a priori information size (APIS) are adopted to estimate the required information size (RIS). We defined the sufficient power as the RIS for 80% power, 5% type 1 error, relative risk reduction of 15%, and average survival rates of 40%.[21] According to the required power and risk for type I and type II errors, TSA monitoring boundaries were built. If a TSA monitoring boundary is crossed with Z-curve before the required power is reached, further trials are unnecessary. Otherwise, it is necessary to continue performing trials.

Results

Study Characteristics

As shown in Figure 2, the initial search yielded 536 studies. After reviewing the titles and abstracts, 61 full-text articles were assessed for eligibility. Due to the absence of sample size of different groups, the CI for the HR or survival curves in some studies, 17 articles were ultimately accepted in the current meta-analysis.[5-15,22-27] In these included articles, there were 5 studies from Japan, 7 studies from Europe, and 6 studies from China. Reference 9 which was included 2 times contains

Table 1. Characteristics of Included Studies.

Study ID	Country	Tumor Type	Total Number	Sample Type	Method	Cutoff	Survival Analysis	Metastasis Analysis	Analysis Type	NOS
Ni *et al*[6]	China	Prostate cancer	145	Tissue	IHC	IHC score ≥ 2	OS	LNM	Multivariate	9
Yang *et al*[22]	China	Breast ductal carcinoma	150	Tissue	IHC	IHC score ≥ 2	OS	LNM	Multivariate	9
Ishiwata *et al*[27]	Japan	Nonsmall cell lung cancer	63	Serum	ELISA	Mean	OS	NR	Kaplan-Meier	6
Takahashi *et al*[7]	Japan	Colorectal carcinoma	170	Tissue	IHC	NR	OS/DFS	DM/LNM	Kaplan-Meier	8
Arak *et al*[23]	Austria	Posterior fossa, ependymoma	52	Tissue	IHC	NR	OS	NR	Multivariate	7
Tastekin *et al*[8]	Turkey	Breast cancer	126	Serum	ELISA	Mean	OS	NR	Multivariate	6
Ohno *et al*[10]	Japan	Clear cell renal cell carcinoma	137	Tissue	IHC	IHC $\geq 10\%$	OS	NR	Kaplan-Meier	8
Florian *et al*[24]	Germany	Nonsmall cell lung cancer	103	Serum	ELISA	mean	OS	LNM	Multivariate	7
Yang *et al*[25]	China	Esophageal squamous cell carcinoma	136	Tissue	IHC	IHC score ≥ 2	OS/DFS	LNM	Multivariate	8
Andreiuolo *et al*[9]	France	Posterior fossa ependymomas	330	Tissue	IHC	IHC score ≥ 2	OS	NR	Multivariate	8
Andreiuolo *et al*[9]	France	Supratentorial ependymoma	148	Tissue	IHC	IHC score ≥ 3	OS	NR	Multivariate	7
Gocheva *et al*[15]	England	Lung adenocarcinoma	458	Tissue	IHC	NR	OS	NR	Kaplan-Meier	7
Sundquist *et al*[12]	Finland	Early stage tongue cancer	196	Tissue	IHC	IHC score ≥ 1	OS	NR	Multivariate	7
Ohtsuka *et al*[11]	Japan	Esophageal squamous cell carcinoma	111	Tissue	IHC	NR	OS	DM/LNM	Kaplan-Meier	8
Guan *et al*[13]	China	Bladder cancer	66	Urine	ELISA	Mean	OS	NR	Multivariate	5
Tang *et al*[5]	China	Lung cancer	133	Tissue	IHC	IHC $\geq 10\%$	OS	NR	Kaplan-Meier	6
Xu *et al*[14]	China	Pancreatic cancer	103	Tissue	IHC	IHC score ≥ 2	OS	DM	Kaplan-Meier	7
Emoto *et al*[26]	Japan	Colorectal carcinoma	105	Tissue	IHC	IHC score ≥ 3	OS	DM/LNM	Kaplan-Meier	7

Abbreviations: DFS, disease-free survival; DM, distant metastasis; ELISA, enzyme-linked immunosorbent assay; IHC, immunohistochemistry; LNM, lymph node metastasis; NR, not reported; NOS, Newcastle-Ottawa Scale; OS, overall survival.

2 separate studies, one is posterior fossa ependymomas and the other is supratentorial ependymoma. Thus, Table 1 summarized the main characteristics of the included 18 studies. The association between TN-C expression level and OS was explored in all studies.[5-15,22-27] In these included studies, the level of TN-C expression was determined in the collected tumor tissue, serum, or urine. Meanwhile, 7 of the 18 studies showed that TN-C expression level was associated with LNM[6,7,11,22,24-26] and 4 studies indicated that TN-C expression level was related to DM.[14,26]

Increased TN-C Expression Level and OS

As indicated in Figure 3, the result was heterogenous indeed ($I^2 = 65.2\%, P < .001$). Therefore, the random effects model was adopted to estimate the pooled HR as well as the corresponding 95% CI. The HR, expressed as the high TN-C expression group versus the low TN-C expression group in various carcinomas was 1.73 (95% CI: 1.29-2.32, $P < .001$). It indicated that the expression of TN-C at high levels was bound up with poor OS.

Thereafter, the analysis was stratified by factors of sample type, sample size, region of participants, and clinicopathological features (LNM and DM) to analyze possible sources of heterogeneity. We showed the pooled HR for OS based on different types of tumor sample and region (Table 2). The high expression of TN-C in serum by ELISA was of no significance (HR = 0.77, 95% CI: 0.24-2.41, $P = .651$). It is possible that the structure of TN-C monomer is easily degraded in the serum. And it was observed that a significant disparity between the subgroup in Asia ($I^2 = 46.8\%, P = .043$) and the subgroup in Europe ($I^2 = .00\%, P = .699$) did exist. Compared to similar research subgroups in Europe, Asian researches had relatively high heterogeneity and a wider range of CIs, suggesting that the quality of Asian research needs to be further strengthened. Depending on subgroup analysis of this study, the impact of tumor sample types and regional factors on heterogeneity is more obvious. The reason for heterogeneity may be that the detection rates of positive results are obviously altered under different types of tumor sample. Additionally, the demographic characteristics (such as race, etc) of patients investigated in different regions are inconsistent and the conditions and level of scientific research varied widely in different regions.

Association Between TN-C Expression and Clinicopathological Features

The association between TN-C expression and clinicopathological features in different types of cancers was assessed. We

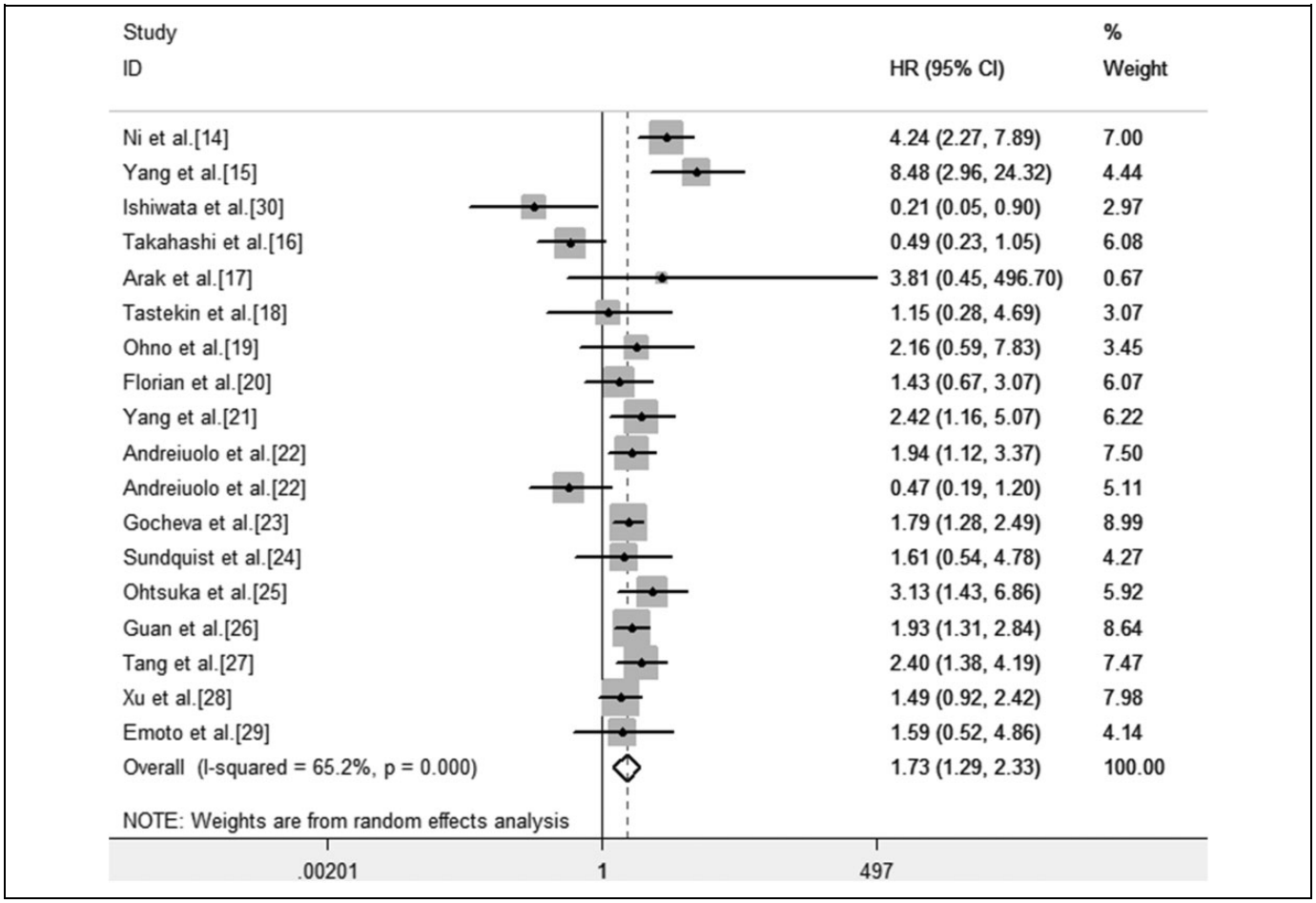

Figure 3. Forest plot for the association between TN-C expression level with OS. CI indicates confidence interval; HR, hazard ratios; OS, overall survival; TN-C, tenascin-C.

Table 2. Subgroup Analysis of the Pooled HRs of Overall Survival With TN-C Expression in Patients With Cancer.

					Heterogeneity		
Subgroup Analysis	Studies (n)	Number of Patients	HR (95% CI)	*Q* Value	I^2 (%)	*P*	τ^2
Sample type							
Tissue	14	2374	1.92 (1.33, 2.78)	16.72	22.20	.213	0.1085
Serum	3	292	0.77 (0.24, 2.41)	3.47	42.40	.176	0.4370
Residence region							
Asian	11	1319	1.90 (1.15, 3.13)	18.79	46.80	.043	0.3273
European	7	1413	1.49 (1.06, 2.09)	3.83	0.00	.699	0.0000
Clinicopathological features							
LNM	7	920	2.42 (1.79,3.26)	9.27	35.30	.159	0.0960
DM	4	489	1.72 (0.86,3.44)	1.59	0.00	.662	0.0000
Sample size							
<115	7	603	0.53 (0.28, 0.78)	11.48	47.80	.075	0.0000
>115	11	2129	0.64 (0.44, 0.83)	36.91	72.90	.000	0.0000

Abbreviations: CI, confidence interval; DM, distant metastasis; HR, hazard ratios; LNM, lymph node metastasis; OS, overall survival; TN-C, tenascin-C.

found that the TN-C expression level was significantly associated with lymph node metastasis (OR = 2.42, 95% CI: 1.79-3.26, $P < .001$; Figure 4). However, no significant correlation was observed between TN-C expression level and DM (OR = 1.72, 95% CI: 0.86-3.44, $P = .127$).

Sensitivity Analysis and Publication Bias

For conducting the meta-analysis of the relation between TN-C expression level and OS, we removed each study in turn from the pooled analysis to perform the sensitivity

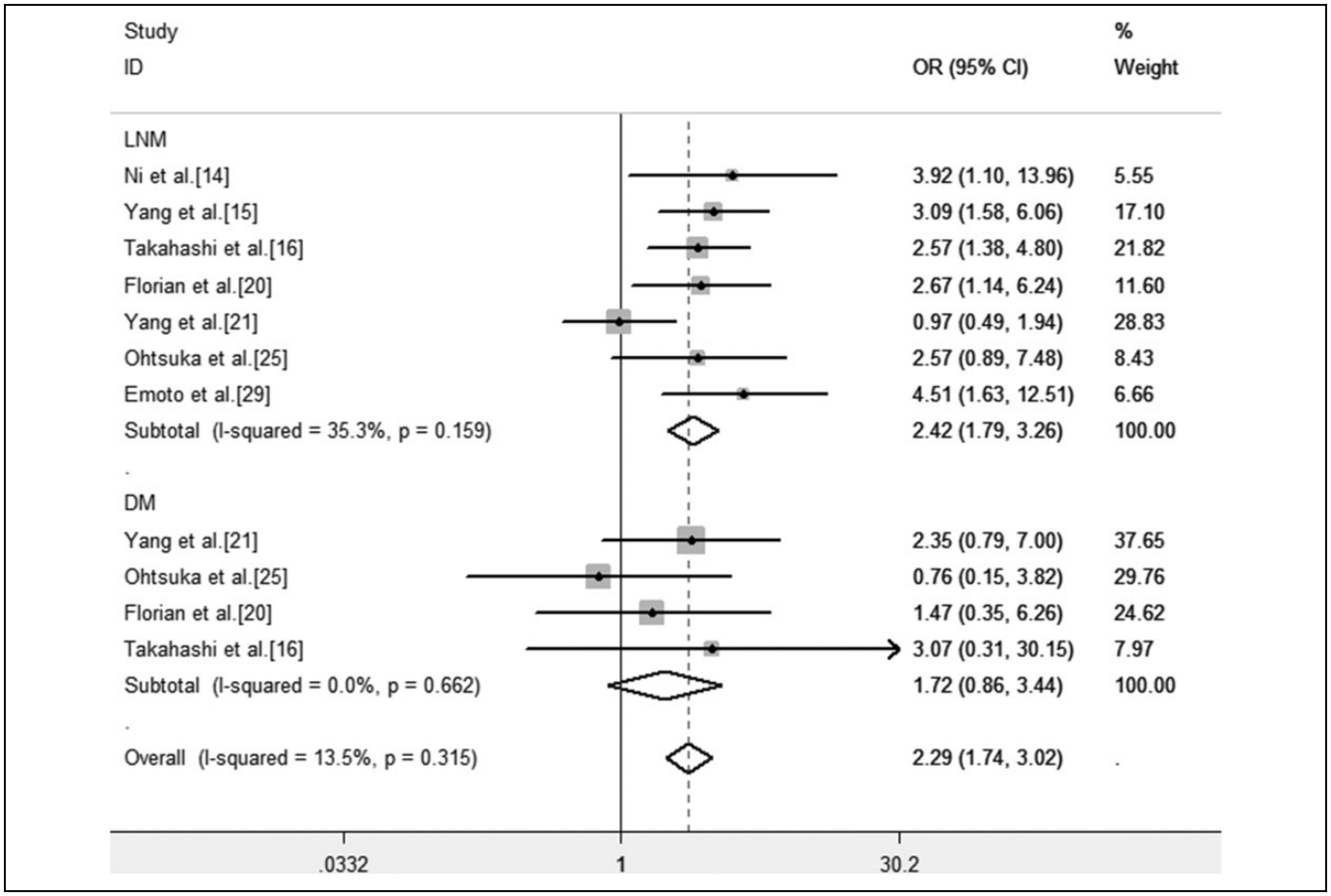

Figure 4. Forest plots of OR for the association between TN-C expression level and clinicopathological features in patients with cancer.
Note: Weights are from fixed effects analysis. CI indicates confidence interval; DM, distant metastasis; LNM, lymph node metastases; OR, odds ratios; TN-C, tenascin-C.

analysis, which was intended to assess the impact of the deleted data set on the overall HR. It turned out that individual study had little effect on our final results (Figure 5), indicating that our analysis was relatively stable and trustworthy. Furthermore, we evaluated the publication bias by funnel plot and Begg bias test. The shape of funnel was relatively symmetrical (Figure 6), and the *P* value of the Begg test was .606 for OS of all selected studies, demonstrating that there was no significant publication bias in the meta-analysis.

Trial Sequential Analysis

Eighteen trials (2732 patients) were used to investigate the relevance of TN-C expression level with the prognosis of patients with cancer. Therefore, we performed TSA and found that the APIS was 1990 patients (Figure 7). Figure 7 demonstrated that the cumulative Z-curve surpassed the conventional boundary and the TSA boundary based on APIS before reaching APIS, which indicated that the cumulative evidence was sufficient and the above results between TN-C expression level and OS were conclusive.

Discussion

As the earliest discovered protein and the most important member of the tenascin gene family, TN-C is attracting increasing attention. Current evidence shows that TN-C plays a role in the pathogenesis of various cancers. Therefore, it is important and necessary to combine these published data through meta-analysis and evaluate the association between expression of TN-C and prognosis as well as clinicopathological characteristics in patients with cancer. In this research, 2732 patients were incorporated. Its results indicated that high expression of TN-C was relevant to poor prognosis in 14 types of cancer and provided sufficient evidence for the association between TN-C expression and clinicopathological features of various cancers. The analysis showed a pooled HR was 1.73 (95% CI: 1.29-2.32, $P < .001$) for OS, and a pooled OR was 2.42 (95% CI: 1.79-3.26, $P < .001$), and 1.72 (95% CI: 0.86-3.44, $P = .127$) for LNM and DM, respectively. Besides, subgroup analysis was used to investigate the association between HRs and these variables, such as sample type, sample size, region of participants, and clinicopathological features (LNM and DM), these factors are sources of heterogeneity. From the perspective of τ^2

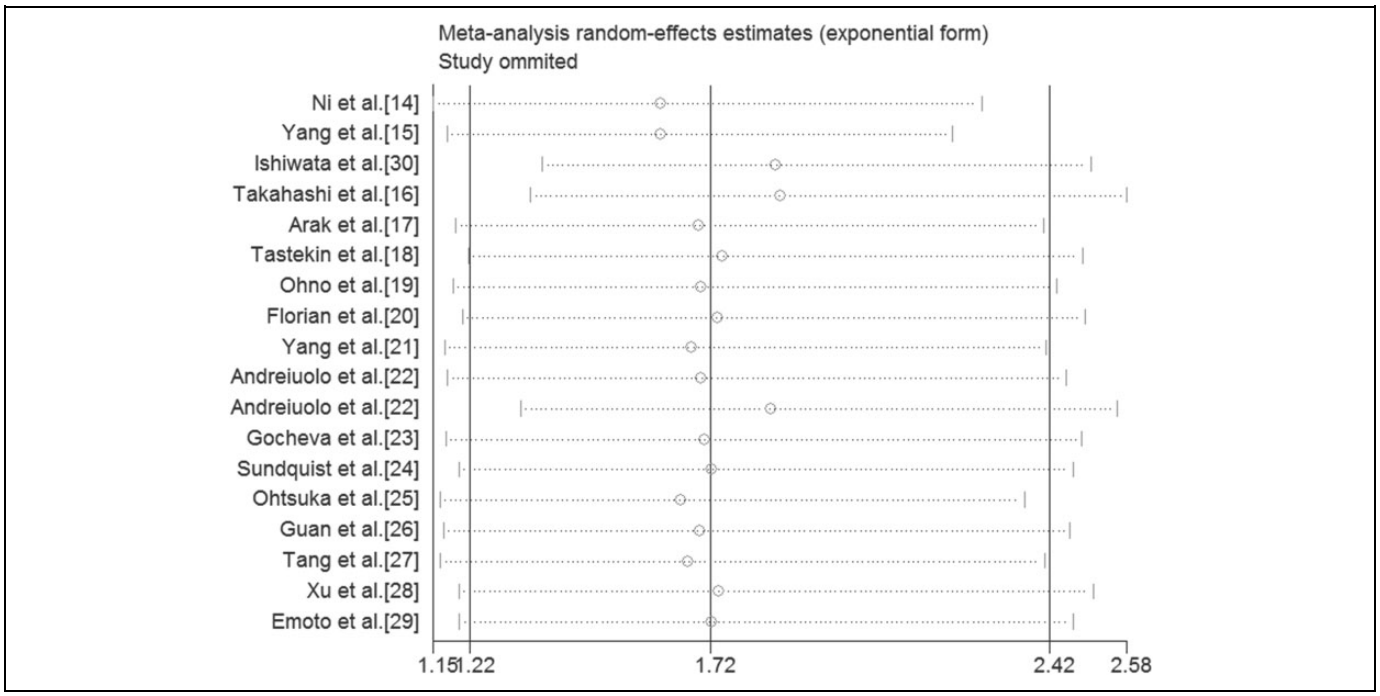

Figure 5. Sensitivity analyses of studies concerning TN-C and OS. OS indicates overall survival; TN-C, tenascin-C.

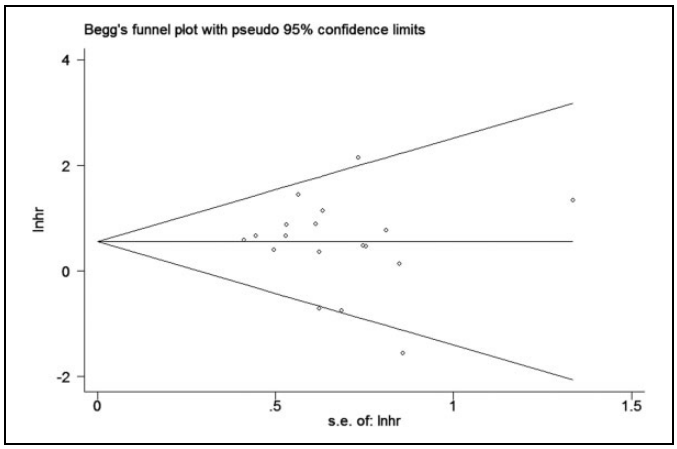

Figure 6. Funnel plot for TN-C expression level and OS in patients with cancers. OS indicates overall survival; TN-C, tenascin-C.

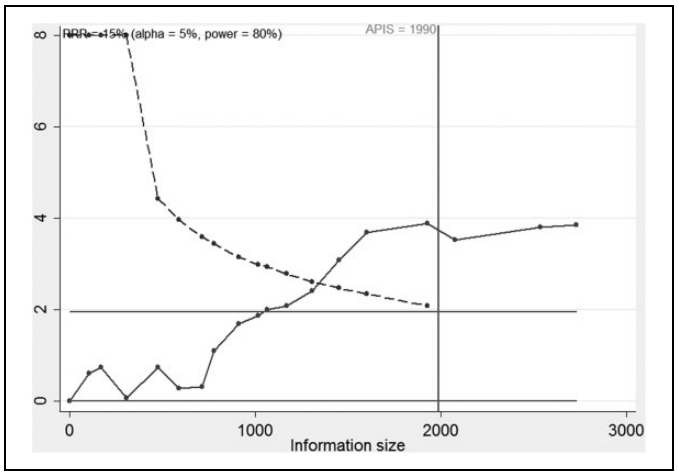

Figure 7. Trial sequential analysis of all included studies. APIS indicates a priori information size; RRR, relative risk reduction.

that reflects the heterogeneity between studies, the impact of tumor sample types and regional factors on heterogeneity is more obvious. Then we found that high expression of TN-C in cancer was significantly correlated with clinicopathological variables including LNM and DM. As a result, these findings indicated that TN-C may be a hopeful prognostic biomarker to predict patients' survival in different types of cancers. Through the TSA, the result of the cumulative z-curve showed the cumulative evidence was sufficient and this meta-analysis was convincing.

Potential mechanism can be inferred from research results. Abundant TN-C could not only affect cell adhesion and migration but also influence the expression of tumor suppressor genes, oncogenes, and genes involved in the maintenance of genomic stability capable of influencing cancer growth.[28,29] Tenascin-C could mediate loss of intercellular adhesion,[30] through which it enhanced migration and metastasis of tumor cells. There were various molecular mechanisms affecting both the structure of ECM and functions of cancer cells. The ECM is increasingly recognized as a major player in cancer progression and metastasis, providing important regulatory cues for cellular responses.[31] The cellular movement can be controlled by ECM networks that are rich with TN-C, which enhances migration and metastatic progression of tumor cells.[32,33] They might interact with each other to form synergies for the association of high expression of TN-C with poor cancer prognosis.

Some of the previous studies had found that TN-C expression was obviously upregulated comparing with adjacent normal lung tissues in nonsmall cell lung carcinoma and the highest TN-C expression could be observed in the recurrent patients with nonsmall cell lung carcinoma.[34] Saupe *et al* demonstrated that TN-C promoted tumor cell survival, proliferation, invasion, and metastasis by establishing a kind of tumor mouse model that imitated the high expression of TN-C detected in human cancer.[33] Furthermore, Juhasz A *et al* detected that expression of TN-C in laryngeal and hypo pharyngeal cancers was linked to early metastatic recurrence and poor OS,[35] which were related to tumor patient's prognosis and clinicopathological features. However, TN-C has also been demonstrated to restrain cell migration, such as in the case of growth cones.[36] So far, it was not rare to detect the high TN-C expression in both primary and metastasized tumors of patients with cancer and TN-C was also reported to be an effective novel prognostic biomarker for patients with cancer. However, previous studies were moderately limited because of relatively small sample sizes and these results were still controversial. The current comprehensive meta-analysis was performed to get more detailed and reliable results via large sample size, updated data, and reasonable subgroup analysis.

Undoubtedly, it should be emphasized that there would be some limitations in our meta-analysis. Above all, the number of samples was unevenly distributed and most of the included patients were from Asia, with a small part from Europe. Moreover, because of the dispersed data, the assessment between TN-C expression level and the prognosis of various patients with cancers might lead to a lack of specificity for clinical evaluation. Once more, the HR and 95% CI were estimated from the Kaplan-Meier survival curves in 8 studies, which might be less accurate than the data acquired directly from published statistics. Furthermore, there were only about 14 types of cancer, which couldn't fully represent all the cancers. Finally, the cutoffs and methods of low or high expression levels of TN-C were different in the included studies, which might lead to heterogeneity of results. As a semiquantitative measurement, IHC was adopted in most studies. However, only a few studies picked the ELISA which belonged to the quantitative approach. Inevitably, there existed indefinable heterogeneity in this meta-analysis. Consequently, all studies of larger sample size, multicenter, and higher quality with uniform standard for determining the expression level of TN-C are necessary conditions to validate the results of this study.

Conclusion

Despite the above limitations, we can draw a preliminary conclusion based on TSA. There is a dramatic correlation between high expression of TN-C and OS of various patients with cancer and it might be considered as a potential and promising unfavorable prognostic factor in human cancers. From another point of view, TN-C, which can be used as a monitoring indicator for poor prognosis, may be widely applied into different types of cancers. Tenascin-C may have a good clinical application prospect for monitoring of therapeutic efficacy, prognosis evaluation, and individualized treatment of patients with cancer.

Authors' Note

The authors Xinliang Ming and Shili Qiu contributed equally to this work. The ethical permission was not applicable. The reasons are that we analyzed published data and our study did not involve human or animal research.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental Material

Supplemental material for this article is available online.

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