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Review Article

Prognostic roles of high TIMP-1 expression in patients with solid tumors: a meta-analysis

Hui Liu[1*], Lidong Ji[1*], Wenqing Liu[1], Yunhua Huang[1], Shengze Li[1], Zhen Chen[2*], Jianhua Niu[3*]

[1]Department of General Surgery, The Third People's Hospital of Jiangyin, 999 Wuxing Road, Jiangyin 214400, P.R. China; [2]Department of Urology, The Third Affiliated Hospital of Soochow University, 185 Juqian Street, Changzhou 213003, P.R. China; [3]Department of Gastrointestinal Surgery, The First Affiliated Hospital of Shihezi University, 32 Community, Shibei Road, Shihezi 832000, Xinjiang Province, P.R. China. [*]Equal contributors.

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Abstract: Background: In recent years, many studies have indicated that tissue inhibitor of metalloproteinases-1 (TIMP-1) protein has a close relationship with prognosis in cancer patients. However, other studies have not drawn the same conclusion. Methods: The current systematic review and meta-analysis was conducted to assess the prognostic effects of TIMP1 in cancer patients. Eleven studies were involved in the analysis, including four that evaluated breast cancer, two that evaluated colon cancer, and one each that evaluated epithelial ovarian cancer, lung cancer, gastric cancer, hepatocellular cancer, and laryngeal squamous cell cancer. Results: Results indicate that increased TIMP1 protein levels yield worse overall survival (OS) (hazard ratio (HR) = 1.58, 95% confidence intervals (CI) 1.25-2.01). Subgroup analysis by tumor type showed that high expression of TIMP-1 was associated with poor OS in colon cancer (HR = 2.40, 95% CI 1.35-4.25), rather than in breast cancer (HR = 1.21, 95% CI 0.83-1.74). Subgroup analysis by ethnicity showed that high expression of TIMP-1 was associated with poor OS in Asians (HR = 2.24, 95% CI 1.64-3.06) and Caucasians (HR = 1.32, 95% CI 1.02-1.75). Conclusion: In summary, TIMP-1 is a poor prognostic maker for solid tumors.

Keywords: TIMP-1, cancer, prognosis, meta-analysis

Background

One of the leading causes of death, cancer is a public health problem worldwide [1]. Successful treatment of cancer is dependent not only on early diagnosis, but also proper therapy strategies based on forecasting of patient outcomes. Therefore, new tumor biomarkers with enhanced specificity and sensitivity are necessary for this fatal disease, establishing more accurate prognosis and diagnosis. In recent years, tissue inhibitor matrix metalloproteinase 1 (TIMP-1) has been regarded as a new putative marker for cancer. TIMP-1, a 28.5 kDa glycoprotein that belongs to the TMIPs family, is one of the endogenous inhibitors of matrix metalloproteinases (MMPs) [2]. Various studies have investigated the relationship between TIMP-1 and prognosis of different cancers. TIMP-1 has been considered a possible prognostic biomarker of several cancers, including multiple myeloma and lymphoma, rectal cancer, hepatocellular cancer, gastric cancer, glioblastoma, colon cancer, and breast cancer [3-10]. However, other studies have not drawn the same conclusion. Thus, based on previous findings, it remains controversial whether TIMP-1 plays a prognostic role in cancer. Therefore, the current meta-analysis was carried out to explore the prognostic effects of TIMP-1 in cancer patients.

Materials and methods

The current meta-analysis was conducted according to guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [11].

Search strategy

Relevant studies were searched using PubMed, Embase, and the Cochrane Library (last update by December 21, 2017). Keywords used in the search strategy included "tissue inhibitor of

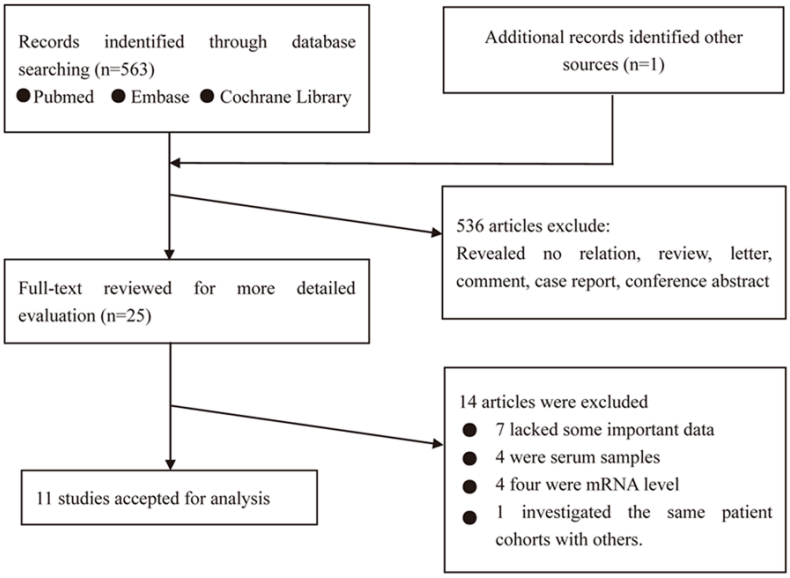

Figure 1. Flow diagram of the study selection process.

metalloproteinases-1 OR TIMP1 OR TIMP-1" (all fields) AND "tumor OR tumour OR neoplasm OR cancer OR carcinoma" (all fields) AND "prognosis OR prognostic OR survival OR outcome" (all fields). Advanced limitations were not imposed in the process of database search. Reference lists of identified articles were also screened, further identifying potential studies. Two authors (H. Liu and L. Ji), comprehensively and independently, searched the databases. **Figure 1** presents a flow diagram of the selection process.

Inclusion and exclusion criteria

Inclusion criteria: (1) Cases including confirmed diagnosis of solid tumor in humans; (2) Clinical research associated TIMP-1 with survival of patients; No animal experiments or basic research; (3) No duplicate data and the same sample in different studies was contained once; (4) Sufficient data were offered to measure the 95% confidence intervals (CI) and hazard ratios (HR); and (5) Letters to editors, reviews, incomplete information, articles published in a book or in languages instead of English, and summaries.

Data extraction and quality assessment

Two researchers, independently, collected necessary information from eligible studies, including first author's surname, origin of population, publication year, tumor type, tumor stage, sample number, detected source, follow-up period, lymph node metastasis, detected methods, cut-off of TIMP1 expression, and HRs and 95% CIs. For studies presenting results of both univariate and multivariate analysis, only the results of multivariate analysis were selected. Articles that offered HRs and 95% CIs were directly extracted. Those that did not offer HRs and 95% CIs were calculated based on the data in these articles. In cases where only Kaplan-Meier curves of TIMP-1 were provided, HRs and 95% CIs were reconstructed from the data in survival plots. Calculation methods mentioned above were proposed by Parmar et al. [12] and Tierney et al. [13].

Quality assessment

The quality of every study was evaluated by two researchers, independently, in accordance with the Newcastle-Ottawa Quality Assessment Scale (NOS) [14]. Scores concerning quality assessment ranged from 0 (the lowest) to 9 (the highest), with scores of 6 or more indicating high quality.

Statistical analysis

The relationship between TIMP1 protein and survival of patients is described by HRs with 95% CIs. An HR less than 1 indicates better prognosis in patients with high TIMP1 protein levels, while an HR greater than 1 indicates worse prognosis. Heterogeneity of combined HRs was tested using Higgins I-squared statistic and Cochran's Q test. Heterogeneity with a P value of less than 0.1 and/or I^2 of more than 50% is regarded as statistically significant. The Der Simonian-Laird method was used or the Mante-Haenszel method was employed. Subgroup analysis was used to analyze factors contributing to heterogeneity. The asymmetry of an inverted funnel plot was used to evaluate publication bias. Moreover, offering quantitative evidence of publication bias, Egger's and Begg's

Table 1. Main characteristics of all studies included in the meta-analysis

Study	Year	Country	Cancer	Case number	Tumor stage (I/II/III/IV)	Follow-up (months)	High expression (%)	Detected method	Cut-off value	Multivariate analysis	Survival analysis	HR
Steffensen et al.	2010	Denmark	Epithelial ovarian cancer	163	0/26/123/14	3-220	20 (12.3)	IHC	> 25%	NO	OS	SC
Aljada et al.	2003	America	Lung cancer	160	100/60 (I/II-III)	Low median > 53.4, high 37.1	43 (26.9)	IHC	> 10%	NO	OS	SC
Song et al.	2016	China	Colon cancer	94	42/52 (I+II/III+IV)	> 60	50 (53.2)	IHC	IRS > 2	NO	OS	SC
Joo et al.	1999	Korea	Colon cancer	54	8/21/22/3	NR	31 (57.4)	IHC	IRS > 2	NO	OS	SC
Yoshikawa et al.	2006	Japan	Gastric cancer	86	24/4/24/13	Median 60	31 (36.0)	IHC	≥ 10 ng/mg	NO	OS	SC
Song et al.	2015	China	Hepatocellular cancer	87	63/24 (I+II/III+IV)	Median 25	63 (72.4)	IHC	NR	NO	OS	SC
Ma 2014	2014	China	Laryngeal squamous cell cancer	109	65/44 (I+II/III+IV)	NR	56 (51.4)	IHC	IHS ≥ 4	YES	OS	Report
Ridnour et al.	2012	America	Breast cancer	207	164/39 (I+II/III+IV)	12-166	87 (42.0)	IHC	IHS ≥ 4	NO	OS	SC
Jørgensen et al.	2014	Denmark	Breast cancer	264	NR	0-250	210 (79.5)	IHC	NR	YES	OS	Report
Schrohl et al.	2004	Denmark, Holland	Breast cancer	2984	NR	1-231	1769 (59.3)	IHC	> 11.71 ng/mg	YES	OS	Report
Dechaphunkul et al.	2012	Canada	Breast cancer	145	31/102/12 (I/II/III)	2.9-108.3	94 (64.8)	IHC	IRS > 2	NO	OS	SC

Abbreviation: IHC: immunohistochemistry; HR: hazard ratio; CI: confidence intervals; IRS: immunoreactivity score; HIS: immunohistochemistry; NR: not report; SC: survival curve.

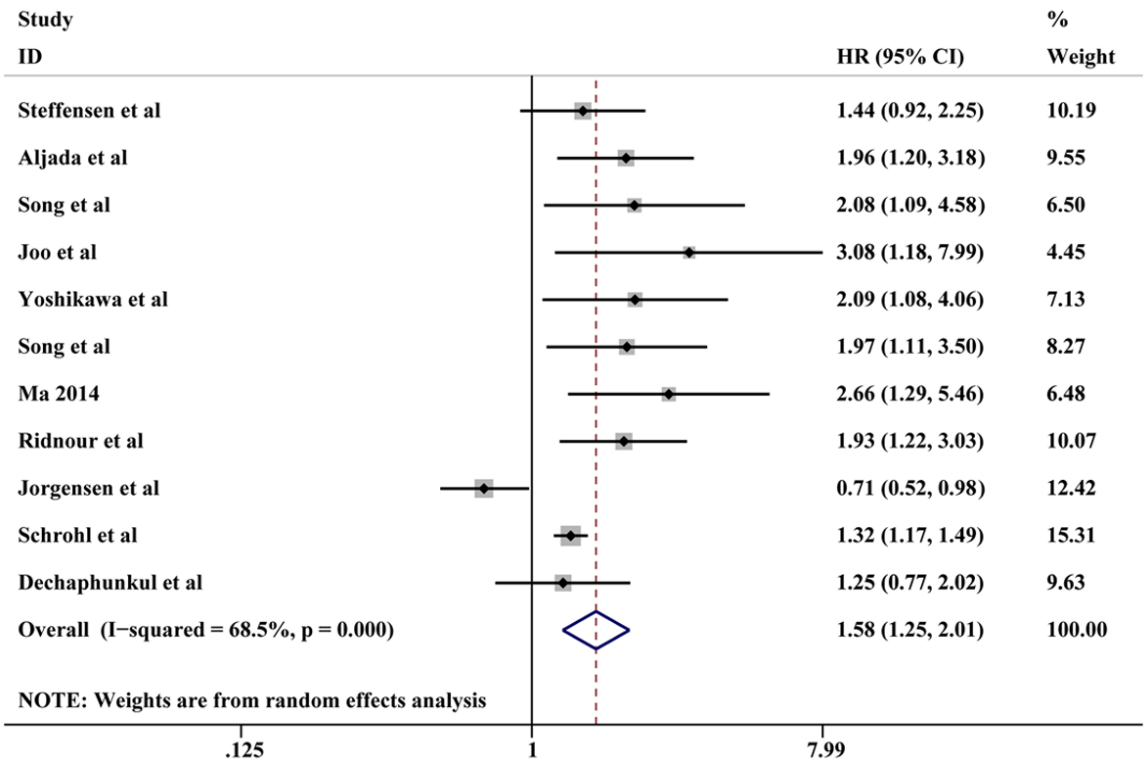

Figure 2. Forest plots of studies evaluating hazard ratios of high TIMP-1 expression in solid cancers for overall survival.

tests were carried out. In cases of observed publication bias, the Duval and Tweedie trim-and-fill method was used to adjust for effects [15]. STATA version 12.0 (Stata Corporation, College Station, TX, USA) was used to analyze all data. Statistical testing had two aspects, with $P < 0.05$ indicating statistical significance.

Results

Study characteristics

A total of 563 references were retrieved, initially, with application of the abovementioned search strategy. After titles, abstracts, publication types, and full texts of every article were screened, only 25 articles explored the relationship between expression of TIMP-1 and outcomes of patients with different malignant tumors. Thus, 14 articles were ruled out. Six lacked crucial data, four concerned mRNA levels, three concerned serum samples, and one explored the same patient cohorts with others. Finally, 11 articles were applied for the current meta-analysis [16-26]. A total of 4,353 patients from China, Korea, Japan, Athens, America, Canada, Denmark, and Holland were diagnosed with various cancers, including breast cancer, laryngeal squamous cell cancer, hepatocellular cancer, gastric cancer, colon cancer, lung cancer, and epithelial ovarian cancer. Patients were Caucasian in 6 studies and Asian in 5 studies. In all studies, immunohistochemistry (IHC) was used for assessment of TIMP-1 protein expression. HRs were shown directly in 3 studies and measured indirectly in 8 studies. **Table 1** presents the main features of the 11 eligible studies.

Quality assessment

A total of 11 eligible studies were evaluated for quality, in accordance with NOS. The quality of all mentioned studies averaged 6.4, varying from 4 to 9, with higher values showing better methodology. Thus, all 11 studies were included in the following analysis.

Meta-analysis results

The major findings of the current meta-analysis are presented in **Table 1**. Since few studies involved an evaluation of disease-free survival (DFS) and cancer-specific survival (CSS), meta-analysis was conducted only for OS. Subgroup

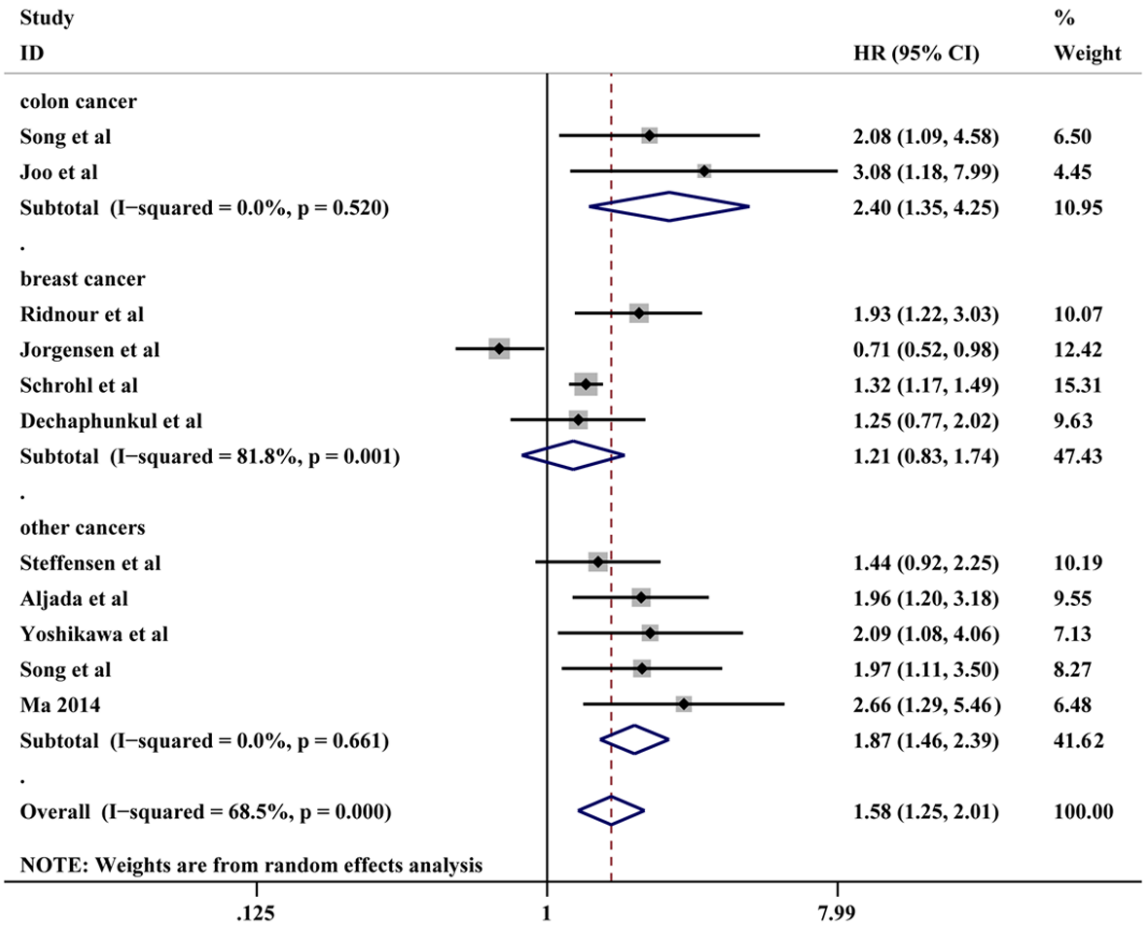

Figure 3. Forest plot of the relationship between high TIMP-1 expression and overall survival in patients with a variety of cancers.

analysis was further used for evaluation of the importance of TIMP-1 expression based on major characteristics, including detecting method, source of HR, and analysis type, as well as ethnicity. As shown in **Figure 2**, worse OS (HR = 1.58, 95% CI 1.25-2.01, P < 0.001) was related to increased levels of TIMP-1 protein. In the ethnicity subgroup, it was found that high TIMP-1 expression was closely related to worse OS in Asian patients (HR = 2.24, 95% CI 1.64-3.06, P < 0.001) and Caucasian patients (HR = 1.32, 95% CI 1.01-1.75, P = 0.049). As shown in **Figure 3**, in the tumor type subgroup, high TIMP-1 expression levels yielded worse OS in colon cancer populations (HR = 2.40, 95% CI 1.35-4.25, P = 0.003) and other cancer populations (laryngeal squamous cell cancer, hepatocellular cancer, gastric cancer, lung cancer, and epithelial ovarian cancer) (HR = 1.87, 95% CI 1.46-1.39, P < 0.001), but better OS in breast cancer populations (HR = 1.21, 95% CI 0.83-1.74, P = 0.320). Subgroup analysis by analysis type showed that high expression of TIMP-1 was associated with poor OS, according to multivariate analysis (HR = 1.77, 95% CI 1.46-2.14, P < 0.001), as opposed to univariate analysis (HR = 1.25, 95% CI 0.72-2.16, P = 0.426), as shown in **Table 2**.

Sensitivity analysis

Sequential omission of individual studies was used for sensitivity analysis, applying a fixed-effects model. Single studies did not significantly impact results. Results of sensitivity analyses indicate the robustness of present findings.

Publication bias

Funnel plots, along with Begg's and Egger's tests, were used to evaluate publication bias of all studies included. Evidence of publication bias was revealed by visual inspection of the funnel plot, as shown in **Figure 4**, verified by

Table 2. The pooled associations between different situations of TIMP-1 expression and the overall survival of patients with solid tumors

Outcome subgroup	No. of patients	No. of studies	HR (95% CI)	*P* value	Model	Heterogeneity	
						I^2 (%)	P
All	4353	11	1.58 (1.25-2.01)	< 0.001*	Random	68.5	< 0.001*
Cancer Types							
Breast cancer	3600	4	1.21 (0.83-1.74)	0.320	Random	81.8	0.001*
Colon cancer	148	2	2.40 (1.35-4.25)	0.003*	Random	0	0.520
Other cancer	605	5	1.87 (1.46-1.39)	< 0.001*	Random	0	0.661
Ethnicity							
Asian	430	5	2.24 (1.64-3.06)	< 0.001*	Fixed	0	0.922
Caucasian	3923	6	1.32 (1.02-1.75)	0.049*	Random	74.8	0.001*
Analysis type							
Univariate	3357	3	1.25 (0.72-2.16)	0.426	Random	88.4	< 0.001*
Multivariate	996	8	1.77 (1.46-2.14)	< 0.001*	Fixed	0	0.662

Abbreviation: HR: hazard ratio, CI: confidence intervals. *indicates that the difference was statistically significant.

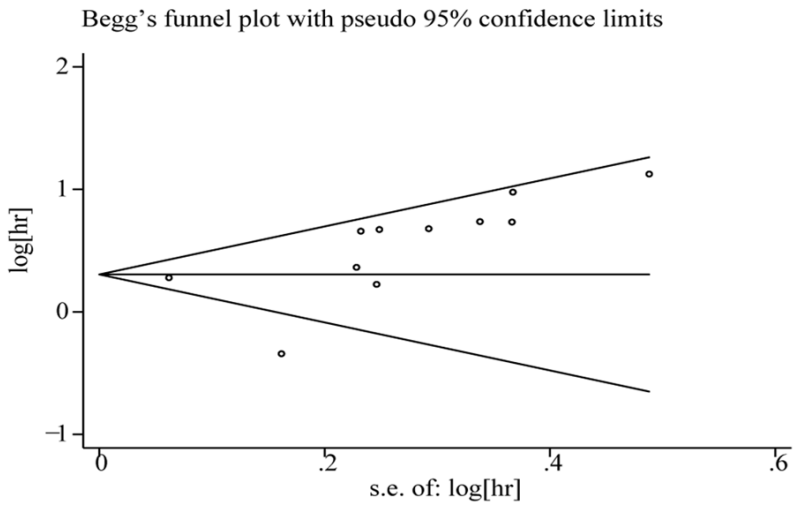

Figure 4. Funnel plots for evaluation of potential publication bias.

Egger's tests (P < 0.001). Using a random-effects model, with application of the "Trim and Fill" approach to adjust for publication bias, the corrected pooled multivariable-adjusted HR was 1.43 for OS (95% CI 1.15-1.78).

Discussion

Recent studies have compiled informative evidence, identifying reliable prognostic biomarkers for cancer patients, with an aim of guiding clinical decision-making. Based on many studies, TIMP-1 protein levels have been suggested to be closely related to prognosis, indicating that TIMP-1 is of potential value as an effective prognostic biomarker. This meta-analysis was performed to investigate the prognostic roles of TIMP-1 protein levels in 4,353 cancer patients from 11 studies. The current study is the first to assess the relationship between expression levels of TIMP-1 and outcomes of cancer patients. Present results indicate that increased TIMP-1 protein levels yield worse OS (HR = 1.58, 95% CI 1.25-2.01). Based on subgroup analysis, HRs in Caucasian and Asian subgroups were both obviously at risk, suggesting that the carcinogenic effects of TIMP1 overexpression are not territorially-specific. High TIMP-1 expression has been shown to have a significant relationship with worse OS in laryngeal squamous cell cancer, hepatocellular cancer, lung cancer, gastric cancer and epithelial ovarian cancer. Therefore, TIMP-1 can be used as a new prognostic marker for cancer patients.

Although TIMP-1 has been proven, in some studies, to be an inhibitor of MMPs [27], its role seems more complicated in tumor progression. Apart from its MMP-inhibitory function, it can enhance tumoral effects via many mechanisms [28, 29]. First, based on several studies, cancer proliferation can be stimulated by TIMP-1. Possible mechanisms are as follows. TIMP-1 directly interacts with a not-yet-identified cell

receptor, which stimulates intracellular pathway enhancing cell proliferation. Increased proliferation and apoptosis inhibition caused by TIMP-1 commonly lead to uncontrolled growth and spread of cancer cells [30]. Several intracellular pathways related to cancer proliferation can be stimulated by TIMP-1. According to the study of Yamashita et al., tyrosine kinase is of great importance to the signal transduction of TIMP-1 and mitogen-activated protein (MAP) kinase is significant in TIMP-1-dependent growth signaling [31]. Wang et al. demonstrated that Ras pathways are activated by TIMP-1 in cell lines of osteosarcoma [32]. Secondly, TIMP-1 works as an inhibitor of apoptosis. It has been shown that TIMP-1 binds to a cell surface protein complex, such as beta 1 integrin and CD63 [33], induces intracellular signaling cascades via phosphorylation of PI-3 kinase, and activates Akt survival pathways [34]. Li et al. demonstrated that antiapoptotic activity of TIMP-1 was independent of its capability to make cell-matrix interactions stable in cell lines of breast cancer. Third, TIMP-1 is of crucial significance in cancer metastasis. According to the study of Zhang et al., overexpression of TIMP-1 has a close relationship with activation of focal adhesion kinase (FAK) related in the pathways of cell conglutination and metastasis [35]. Song et al. demonstrated that downregulation of TIMP1 effectively weakens tumorigenicity and metastasis *in vivo* in animal experiments. Based on the abovementioned findings, expression of TIMP-1 is of great significance to the malignant progression of cancer. TIMP-1 may be a new target for cancer-targeted therapy in the future.

The pooled risk of high TIMP-1 expression for OS in breast cancers was not statistically significant, with a combined HR of 1.21 (95% CI 0.83-2.74, P > 0.05). According to the study of Roy et al., poor prognosis in breast cancer is related to increased levels of TIMP-1 [36], while the opposite conclusion was made by Nakopoulou et al. [37]. Combined with this controversy, the roles and functions of TIMP-1 in breast cancer are quite complex. Ridnour et al. suggested that TIMP-1 exerts oncogenic effects via binding of CD63 cell surface receptors and activation of pro-survival PI3k/Akt signaling [38]. However, Henriet et al. [39] presented an opposing point of view. They indicated that preservation of the contact between an intact extracellular matrix (ECM) and cells and maintenance of restrictive growth signals produced by such a contact are involved in the mechanisms. Also, malignant cells are possibly sensitive to restrictive growth signals produced by ECM components when they contact the ECM. Growth-negative signals are likely to be removed by excessive proteolytic degradation of ECM tumor tissues. TIMP-1 has been considered to inhibit the progression of breast cancer via pathways. Thus, more deep and objective studies should be carried out, revealing the roles of TIMP-1 in breast cancer. In a sense, the roles and functions of TIMP-1 in breast cancer may vary widely because of different pathological types and different clinical stages. According to univariate subgroup analysis, there was no statistical significance (P = 0.426). This may be less relevant to the single-factor studies included. However, this study mainly focused on the results of multivariate analysis. It has increased precision, due to accounting for confounding factors.

The current meta-analysis had some limitations. First, the sample size was comparatively small, with only 4,353 patients from 11 studies involved. Second, different cut-off values were applied in these studies because of a lack of a unified cut-off value for TIMP-1 expression. The availability of TIMP-1 was possibly influenced by incorrect cut-off values, regarding its function as a predictive biomarker in cancer prognosis. Third, some HRs were measured using data from survival curves, resulting in small statistical errors. Fourth, great heterogeneity existed in the current meta-analysis, possibly because of differences in publication years, tumor stages, tumor types, patient origins, follow-up times, TIMP-1 methods, and cut-off values.

Conclusion

In conclusion, current results suggest that increased levels of TIMP-1 lead to poor prognosis in cancer patients. Considering the limitations of this analysis, conclusions should be judged cautiously. Further adequately designed and prospective multi-center studies, with larger sample sizes, are necessary to confirm the prognosis value of TIMP-1 in cancer patients.

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Disclosure of conflict of interest

None.

Abbreviations

TIMP-1, tissue inhibitor of metalloproteinases-1; OS, overall survival; HR, hazard ratio; 95% CI, 95% confdence interval; MMPs, matrix metalloproteinases; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; NOS, Newcastle-Ottawa Quality Assessment Scale; IHC, immunohistochemistry; DFS, disease free survival; CSS, cancer-specific survival; IHC, immunohistochemistry; IRS, immunoreactivity score; HIS, immunohistochemistry; NR, not report; SC, survival curve; MAP, mitogen-activated protein; FAK, focal adhesion kinase; EMC, extracellular matrix.

Address correspondence to: Zhen Chen, Department of Urology, The Third Affiliated Hospital of Soochow University, 185 Juqian Street, Changzhou 213003, P.R. China. Tel: +86-519-68871251; E-mail: chenzhen168@126.com; Jianhua Niu, Department of Gastrointestinal Surgery, The First Affiliated Hospital of Shihezi University, 32 Community, Shibei Road, Shihezi City 832000, Xinjiang Province, P.R. China. Tel: +86-189-0993-0916; E-mail: 525554703@qq.com

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