Original Article

Prognostic and clinicopathological value of CD90 expression in cancer patients: a systematic review and meta-analysis

Hyun Min Koh[1], Hyun Ju Lee[2,3], Dong Chul Kim[4,5,6]

[1]Department of Pathology, Gyeongsang National University Changwon Hospital, Changwon, Korea; [2]Department of Pathology, Soonchunhyang University College of Medicine, Cheonan, Korea; [3]Department of Pathology, Soonchunhyang University Cheonan Hospital, Cheonan, Korea; [4]Department of Pathology, Gyeongsang National University School of Medicine, Jinju, Korea; [5]Department of Pathology, Gyeongsang National University Hospital, Jinju, Korea; [6]Gyeongsang Institute of Health Science, Jinju, Korea

Contributions: (I) Conception and design: All authors; (II) Administrative support: HM Koh, DC Kim; (III) Provision of study materials or patients: HM Koh, DC Kim; (IV) Collection and assembly of data: HM Koh, HJ Lee; (V) Data analysis and interpretation: HM Koh, HJ Lee; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Hyun Ju Lee, MD, PhD. Department of Pathology, Soonchunhyang University Cheonan Hospital, Soonchunhyang University College of Medicine, 31 Soonchunhyang 6 gil, Cheonan 31151, Korea. Email: drlhjmd@daum.net; Dong Chul Kim, MD, PhD. Department of Pathology, Gyeongsang National University School of Medicine, 79 Gangnam-ro, Jinju 52727, Korea. Email: kdcjes@gmail.com.

Background: Recent studies have shown that CD90 has an important role in cancer development. Moreover, CD90 is reportedly associated with cancer progression, metastasis, and poor prognosis. Thus, we performed this meta-analysis to investigate the prognostic and clinicopathological value of CD90 expression in patients with cancer.

Methods: Eligible studies were collected by searching PubMed, Embase, and the Cochrane library. The pooled results were analyzed to reveal the association between CD90 expression and survival as well as the clinicopathological characteristics of cancer patients.

Results: CD90 overexpression was associated with poor survival in cancer patients [for overall survival, hazard ratio (HR): 2.56, 95% confidence interval (CI): 1.42–4.62, P=0.002; for disease-free survival, HR: 1.88, 95% CI: 1.08–3.27, P=0.025] and was also significantly correlated with a larger tumor size [odds ratio (OR): 1.97, 95% CI: 1.01–3.85, P=0.048), higher tumor grade (OR: 2.72, 95% CI: 1.33–5.54, P=0.006), lymph node metastasis (OR: 3.66, 95% CI: 1.14–11.78, P=0.029), and higher tumor-node-metastasis stage (OR: 4.79, 95% CI: 2.28–10.04, P<0.001).

Conclusions: CD90 overexpression could predict poor prognosis and may hence be a potential prognostic biomarker for cancer patients.

Keywords: Cancer; CD90; meta-analysis; prognosis

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Introduction

Cancer significantly contributes to overall morbidity and mortality (1). Therefore, it is very important to predict cancer progression and to classify and treat patients accordingly. Recently, there have been numerous attempts to utilize biomarkers in early detection and treatment.

CD90 is a glycophosphatidylinositol-anchored cell surface protein (2). It regulates cell adhesion, migration and proliferation, apoptosis, and cellular communication and is involved in T cell activation, wound healing, and fibrosis (2,3). CD90 is expressed in various cells such as mesenchymal and hematopoietic stem cells, neurons, endothelial cells, and fibroblasts (2,3). Recent studies have shown that CD90 also has an important role in the development of various cancers, including liver, gastric, and

esophageal cancers (4). Moreover, it has been shown that CD90 is related to cancer progression, metastasis, and poor patient survival (4-9).

Nevertheless, little is known about the relationship between CD90 expression and the prognosis of cancer patients. Thus, we systematically investigated the prognostic and clinicopathological value of CD90 expression in cancer.

We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/tcr-21-266).

Methods

Literature search

We performed a literature search in PubMed, Embase, and the Cochrane library until June 2020 using the following keywords: "CD90" and "cancer or carcinoma or malignancy" and "prognosis or survival or outcome". We also performed an additional manual search.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (I) CD90 expression identified in human cancer tissue using immunohistochemistry and (II) the hazard ratio (HR) with 95% confidence interval (CI) between CD90 expression and clinical outcome should be available. The following articles were excluded: (I) duplicate articles, (II) a study of pediatric patients, and (III) reviews, conference abstracts, and non-English articles.

Data extraction and quality assessment

Each of the two authors extracted basic data such as the first author, year of publication, country, cancer type, sample size, sex, mean or median age of patients, study period, follow-up period, clinical outcome, and cutoff value of CD90 expression. The Newcastle-Ottawa Scale was used to assess the quality of the included studies. In case of a disagreement, the authors reached an agreement through discussion.

Statistical analysis

Data were analyzed using StataSE12 (Stata, College Station, TX, USA), and statistical significance was determined only if the P value was less than 0.05. I^2 statistics were used to check for heterogeneity between the included studies. A random effects model was applied if the I^2 statistic was >50% or the P value was <0.1; otherwise, a fixed model was applied. The pooled HR and odds ratio (OR) were calculated to evaluate the prognostic and clinicopathological value of CD90 expression. A funnel plot (using Egger's test) and a filled funnel plot were constructed to check for publication bias, and sensitivity analysis was performed to prove the reliability of the pooled HR.

Results

Study selection and basic data

We included six eligible studies through the process presented in *Figure 1*. The basic data of these studies are given in *Table 1*. The reports consisted of hepatocellular carcinoma (n=2), intrahepatic cholangiocarcinoma (n=1), gallbladder cancer (n=1), breast cancer (n=1), and chondrosarcoma (n=1). Four studies originated from China, and the other two studies were published in Brazil and Japan, respectively. The minimum, maximum, and total number of samples was 50, 278, and 676, respectively. All of the studies were verified to be of good quality with eight scores.

The association between CD90 expression and overall survival (OS)

Of the included studies, five reported the relationship between CD90 expression and OS. Zhang *et al.* (8) reported the relationship between CD90 expression and OS in squamous cell/adenosquamous cell carcinoma (SC/ASC) and adenocarcinoma (AC) of the gallbladder. This analysis was conducted to include each HR reported by Zhang *et al.* (8).

There was high heterogeneity between the included studies, with an I^2 value of 75.6% (P=0.001) (*Figure 2A*). Thus, a random effects model was applied in this analysis. The pooled HR with 95% CI between CD90 expression and OS was 2.56 (95% CI: 1.42–4.62, P=0.002), implying that the overexpression of CD90 was significantly associated with a poor OS in cancer patients (*Figure 2A*). When grouped according to cancer type, the subgroup with hepatobiliary cancers showed significant results (HR: 2.96, 95% CI: 1.66–5.28, P<0.001) (*Figure 2B*).

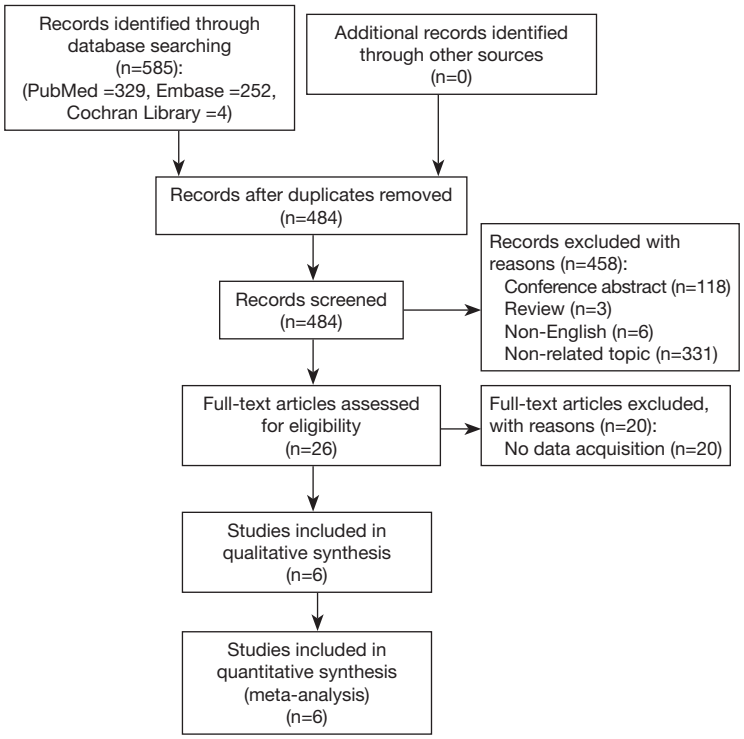

Figure 1 Flow diagram for the selection of studies to be included in the meta-analysis.

The association between CD90 expression and disease-free survival (DFS)

Of the included studies, four reported the relationship between CD90 expression and metastasis-free or recurrence-free or DFS. Here, metastasis-free or recurrence-free survival was considered and analyzed as DFS. There was high heterogeneity between the included studies, with an I^2 value of 73.1% (P=0.011) (*Figure 3A*). Thus, a random effects model was used. The pooled HR with 95% CI between CD90 expression and DFS was 1.88 (95% CI: 1.08–3.27, P=0.025), suggesting that the overexpression of CD90 is related to poor DFS in cancer patients (*Figure 3A*). In the subgroup analysis, hepatobiliary cancer revealed significant results (HR: 2.45, 95% CI: 1.25–4.78, P=0.009) (*Figure 3B*).

The association between CD90 expression and clinicopathological characteristics

CD90 overexpression was significantly correlated with a larger tumor size (OR: 1.97, 95% CI: 1.01–3.85, P=0.048), higher tumor grade (OR: 2.72, 95% CI: 1.33–5.54, P=0.006), lymph node metastasis (OR: 3.66, 95% CI: 1.14–11.78, P=0.029), and higher tumor-node-metastasis (TNM) stage (OR: 4.79, 95% CI: 2.28–10.04, P<0.001) but not with age and sex (*Table 2*, *Figure 4*).

Publication bias

In the funnel plots, the distribution of the included studies was skewed to one side (*Figure 5A*,*B*). The Egger's test confirmed that there was publication bias (for OS, P=0.001; for DFS, P=0.021). Thus, we constructed filled funnel plots. The pooled HRs were still statistically significant (for OS, P=0.004; for DFS, P=0.013) (*Figure 5C*,*D*).

Sensitivity analysis

The sensitivity analysis revealed that the study published by Lobba *et al.* (4) had a significant impact on the initial pooled results (for OS, HR: 2.75, 95% CI: 1.86–4.07; for DFS, HR: 2.16, 95% CI: 1.43–3.26) (*Figure 6*). However, the pooled results were still statistically significant, implying that even after excluding the effects of individual studies, our initial results were meaningful.

Table 1 Basic data of the included studies

Study (year)	Country	Cancer type	Sample size	Sex (male/ female)	Mean or median age (years)	Study period	Follow-up (months)	Clinical outcome	CD90 detection	CD90 expression associated with poor prognosis	Cut-off value of CD90 expression	Survival analysis	NOS
Lobba *et al.* (2018)	Brazil	Breast cancer	278	–	55	1976–2005	Median 98.16 (OS), 87.36 (MFS)	OS, MFS	IHC	High	Mean positivity value	MVA	8
Yamaoka *et al.* (2018)	Japan	Intrahepatic cholangiocarcinoma	77	46/31	65	2001–2013	Median 31.92	OS, RFS	IHC	Positive	≥5%	MVA	8
Zhao *et al.* (2016)	China	Hepatocellular carcinoma	86	67/19	NA	2009–2011	Median 31.5	OS, DFS	IHC	High	≥4 (immunoreactivity score with staining intensity and percentage of positive staining areas)	MVA	8
He *et al.* (2016)	China	Chondrosarcoma	59	30/29	NA	2001–2011	Until 134	OS	IHC	Positive	≥25%	MVA	8
Zhang *et al.* (2016)	China	Gallbladder cancer	126 (46 SC/ASC and 80 AC)	45/81	NA	1995–2009	Until 24	OS (SC /ASC and AC respectively)	IHC	Positive	≥25%	MVA	8
Guo *et al.* (2014)	China	Hepatocellular carcinoma	50	NA	46	2007–2009	Until 36	RFS	IHC	Positive	≥5%	MVA	8

AC, adenocarcinoma; DFS, disease-free survival; IHC, immunohistochemistry; MFS, metastasis-free survival; MVA, multivariate analysis; NA, not available; NOS, Newcastle-Ottawa Scale; OS, overall survival; RFS, recurrence-free survival; SC/ASC, squamous cell/adenosquamous cell carcinoma.

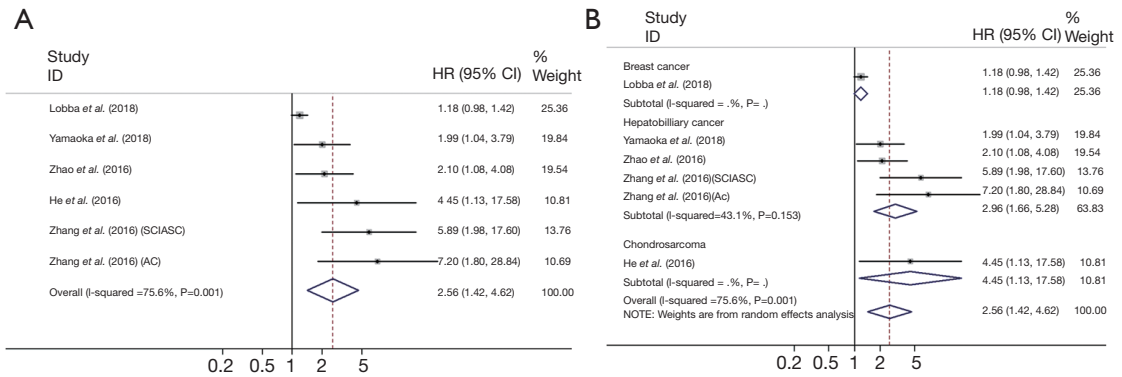

Figure 2 Forest plot of the association between CD90 expression and OS (A), stratified by cancer type (B).

Figure 3 Forest plot of the association between CD90 expression and DFS (A), stratified by cancer type (B).

Table 2 The association between CD90 expression and clinicopathological characteristics in cancer patients

Characteristic	Number of studies	Number of patients	Pooled OR (95% CI)	P value	Heterogeneity		
					I^2 (%)	P value	Model
Age (old *vs.* young)	3	423	0.68 (0.44–1.05)	0.078	0.0	0.552	Fixed
Sex (male *vs.* female)	3	222	0.74 (0.41–1.33)	0.315	0.0	0.466	Fixed
Tumor size (large *vs.* small)	6	676	1.97 (1.01–3.85)	0.048	70.2	0.003	Random
Tumor grade (high *vs.* low)	6	676	2.72 (1.33–5.54)	0.006	62.7	0.013	Random
Lymph node metastasis (present *vs.* absent)	3	481	3.66 (1.14–11.78)	0.029	84.1	<0.001	Random
TNM stage (III, IV *vs.* I, II)	2	185	4.79 (2.28–10.04)	<0.001	0.0	0.774	Fixed

CI, confidence interval; OR, odds ratio; TNM, tumor-node-metastasis.

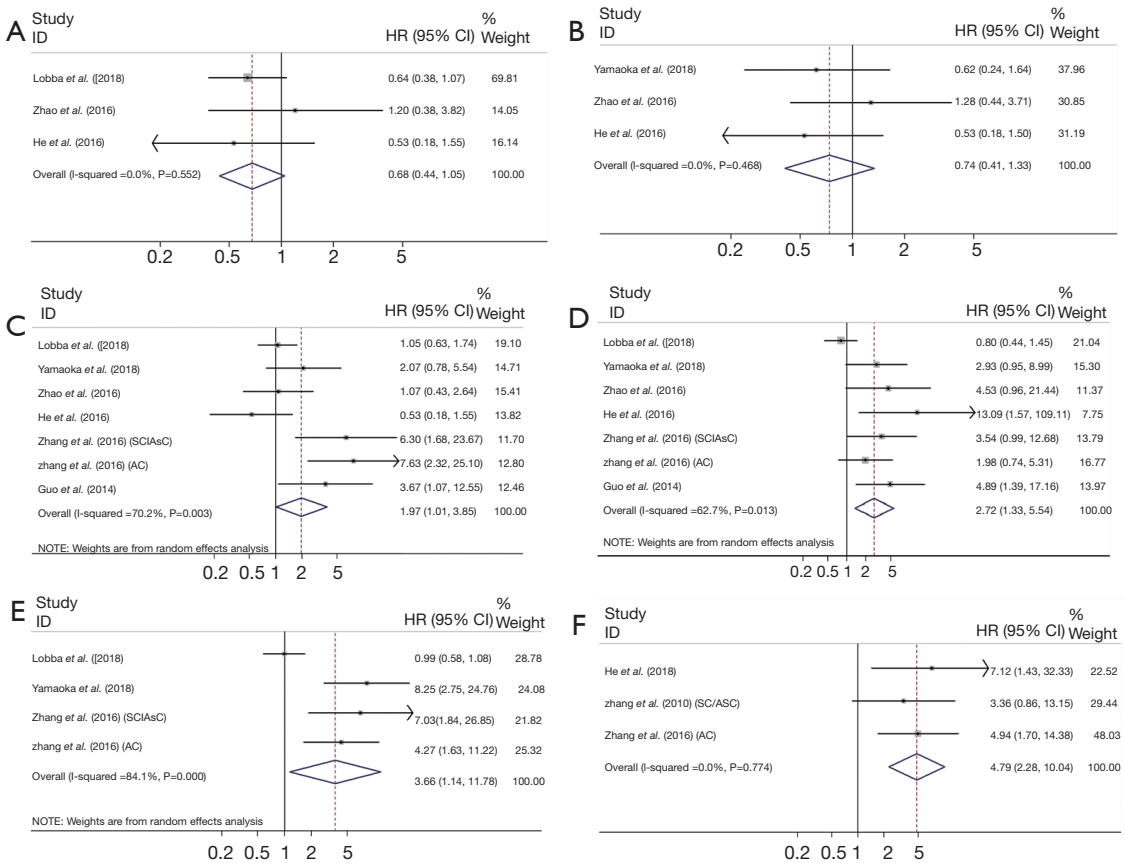

Figure 4 Forest plot of the association between CD90 expression and clinicopathological characteristics: (A) age, (B) sex, (C) tumor size, (D) tumor grade, (E) lymph node metastasis, and (F) tumor-node-metastasis stage.

Discussion

CD90 is a cell surface glycoprotein located on chromosome 11q22.3 (10). Although the function of CD90 has not been fully identified, it is involved in intercellular and cell-to-matrix interactions, apoptosis, cell adhesion and migration, and neurite overgrowth modulation (10).

In various cancers, CD90 expression has been associated with cancer stem cells, which induce cancer initiation and metastasis (2). For example, several researchers have reported that CD90 expression is increased in hepatic cancer tissue compared with normal or cirrhotic liver tissue and is higher in poorly differentiated than in well-differentiated cancer (2). In hepatocellular carcinoma, CD90 expression facilitates the migration of cancer cells by causing the upregulation of EpCAM and downregulation of E-cadherin (2). In melanoma, CD90 is expressed in endothelial cells, promoting the metastasis of melanoma cells with integrin (2). CD90 is also expressed in the tumor front by invading breast cancer cells (2).

In addition, recent studies have shown that CD90 expression is related to the prognosis of cancer patients. Yamaoka *et al.* (7) reported that CD90 expression was significantly associated with lymph node metastasis and could be an independent prognostic factor in intrahepatic cholangiocarcinoma. Zhang *et al.* (8) revealed that CD90 overexpression was correlated with a poor differentiation, large tumor size, lymph node metastasis, and substantial invasiveness in SC/ASC and AC of the gallbladder and that patients with positive CD90 expression had shorter OS than those with negative CD90 expression. Moreover, Zhao *et al.* (9) demonstrated that CD90 expression was correlated with the pathologic grade, stellate lesion, portal vein tumor thrombi, and recurrence and that high CD90 expression could predict unfavorable prognosis in hepatocellular carcinoma. Guo *et al.* (5) also showed CD90 expression to be significantly associated with early recurrence in hepatocellular carcinoma. He *et al.* (6) identified that

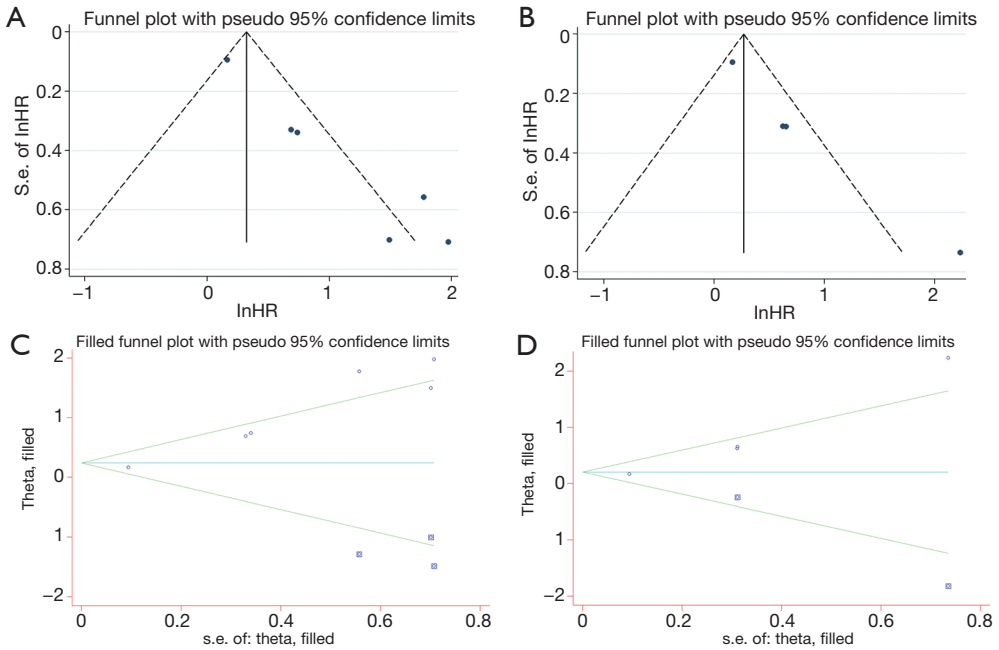

Figure 5 Funnel plot and filled plot of the association between CD90 expression and OS (A,C) and DFS (B,D).

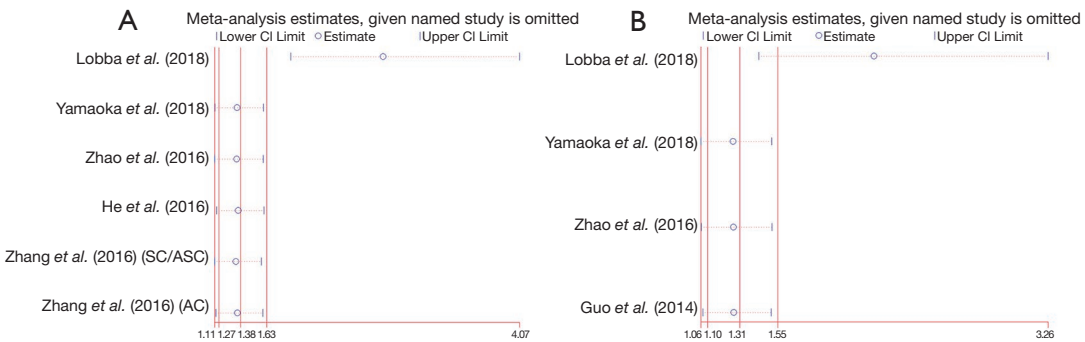

Figure 6 Sensitivity analysis of the association between CD90 expression and OS (A) and DFS (B).

CD90 expression was negatively correlated with OS in chondrosarcoma, and Lobba *et al.* (4) reported the relationship between CD90 expression and the prognosis of breast cancer patients.

In the present study, we performed a meta-analysis for OS and DFS and demonstrated that CD90 overexpression was associated with a poor prognosis in cancer patients. We also found that CD90 overexpression was significantly correlated with a larger tumor size, higher tumor grade, lymph node metastasis, and higher TNM stage.

There are some limitations to the present study. First, the number of studies included was small, and all of them were published in Asia, with the exception of one study. Moreover, the heterogeneity among the included studies was significant probably because several baseline characteristics varied, such as cancer type, sample size, and criteria for determining CD90 expression. However, the source of the heterogeneity was not revealed because of the limited number of studies. Second, the criteria for determining CD90 expression differed from study to study. Four studies evaluated CD90 expression by positive fraction, two of which were based on 25%, and the other two were based on 5%. Among the other two studies, CD90 expression was determined by combining the staining intensity and the percentage of positive staining areas, whereas the other applied CD90 expression based on the

mean positive value. Finally, there have been recent reports that the expression and function of CD90 are dependent on the cellular context and the tumor microenvironment, so our analysis may be limited. We hope that further research on the relationship between CD90 expression and the prognosis of cancer will be conducted and that better meta-analyses could be conducted.

In summary, we systematically analyzed the prognostic and clinicopathological value of CD90 expression in patients with cancer. CD90 overexpression could predict poor prognosis in patients with cancer and may hence be a potential prognostic biomarker.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://dx.doi.org/10.21037/tcr-21-266

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/tcr-21-266). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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