**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 glycophaspatidylinositol-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,
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. I² statistics were used to check for heterogeneity between the included studies. A random effects model was applied if the I² 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 I² 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).
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.
| Study (year) | Country | Cancer type | Sample size | Sex (male/female) | Mean or median age (years) | Study period | 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).

Study ID | HR (95% CI) | % | Weight |
--- | --- | --- | --- |
Lobba et al. (2018) | 1.18 (0.98, 1.42) | 25.36 |
Yamakawa et al. (2018) | 1.18 (0.98, 1.42) |
Zhao et al. (2016) | 2.10 (1.06, 4.06) | 19.34 |
He et al. (2016) | 4.45 (1.13, 17.58) | 10.81 |
Zhang et al. (2016) (SCIASC) | 5.89 (1.98, 17.60) | 13.76 |
Zhang et al. (2016) (AC) | 7.20 (1.80, 28.84) | 10.69 |
Overall (l-squared = 75.6%, P = 0.001) | 2.56 (1.42, 4.62) | 100.00 |

NOTE: Weights are from random effects analysis

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 |
| --- | --- | --- | --- | --- | --- |
| 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.
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 thrombi, and recurrence and that high CD90 expression could predict unfavorable prognosis in hepatocellular carcinoma. Guo et al. (2016) could be an independent prognostic factor in intrahepatic cholangiocarcinoma. Zhang et al. (2018) 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. (2016) 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. (2015) also showed CD90 expression to be significantly associated with early recurrence in hepatocellular carcinoma. He et al. (2016) identified that CD90 expression facilitates the migration of cancer cells by inducing cancer initiation and metastasis (2).

In hepatocellular carcinoma, CD90 expression is related to the prognosis of cancer patients. Yamaoka et al. (2017) reported that CD90 expression was significantly associated with lymph node metastasis and could be an independent prognostic factor in intrahepatic cholangiocarcinoma. Zhang et al. (2016) 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. (2016) 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.
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

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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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