

Investigating the relationship between secreted protein acidic and rich in cysteine expression level and therapeutic efficacy of nab-paclitaxel: a meta-analysis

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Background: Secreted protein acidic and rich in cysteine (SPARC) is always considered as a marker of poor prognosis. However, it helps to transport nab-paclitaxel and may lead better therapeutic ending. This meta-analysis was aimed to assess the relationship between SPARC expression level and clinical efficacy of nab-paclitaxel.

Methods: The PubMed and Embase databases were searched from inception to April 2020, and search terms included nanoparticle albumin-bound paclitaxel, nab-paclitaxel, nab-PTX, Abraxane, ABI-007, secreted protein acidic and rich in cysteine, SPARC, osteonectin, and BM-40. In addition, funnel plots were used to indicate the existence of publication bias.

Results: After further screening the full text, 5 studies that involved 336 patients were finally included in the study, of which, 3 studies concentrated on non-small cell lung cancer (NSCLC) and the other 2 on breast cancer and pancreatic cancer. SPARC status in tumor cells and stromal cells was taken into account. The HR for progression-free survival (PFS) between SPARC high and low groups was 1.25 (95% CI: 0.72–2.14, stromal cell) and 1.51 (95% CI: 0.93–2.46, tumor cell). The HR for OS between SPARC high and low groups was 1.07 (95% CI: 0.57–2.03, stromal cell) and 1.34 (95% CI: 0.74–2.43, tumor cell). It was revealed that SPARC expression level in tumor cells or stromal cells was not significantly correlated with the patient's survival outcomes. No significant publication bias was found in each analysis.

Conclusions: SPARC expression level detected by immunohistochemistry (IHC) cannot predict the efficacy of nab-paclitaxel, while further large-scale clinical trials are required to confirm our findings.

Keywords: Secreted protein acidic and rich in cysteine; nanoparticle albumin-bound paclitaxel; chemotherapy; progression-free survival (PFS); overall survival (OS)

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Introduction

Despite improvements in medical care, tumor remains the second leading cause of death worldwide (1). Combination of chemotherapy with cytotoxic drugs is a promising strategy for the treatment of several malignant tumors. Paclitaxel is a widely used antineoplastic agent

that promotes assembly of microtubules, inhibits tubulin disassembly, and blocks cell cycling at the G2/M stage. Compared with the solvent-based paclitaxel, nanoparticle albumin-bound paclitaxel (nab-paclitaxel) does not require special infusion devices due to different paclitaxel carriers, without necessity of pre-treatment, associating with a lower

incidence of adverse reactions and a higher degree of drug accumulation within the tumor, indicating its broad clinical applicability (2,3).

Secreted protein acidic and rich in cysteine (SPARC), also known as osteonectin, is a bone-specific protein that binds selectively to both hydroxyapatite and collagen (4-6). It is secreted from several types of cancer and tumor-associated stroma cells, and can regulate tumor cell growth and metastasis (3,5,7-9). Studies demonstrated that even in the same type of cancer, a higher SPARC expression level predicts a worse prognosis (10-12). However, a recent meta-analysis found that although SPARC overexpression is an unfavorable prognostic factor in the majority of solid tumors, colon cancer patients with high SPARC expression level in stromal cells can benefit longer disease-free survival (DFS) (13).

Due to high dependence of SPARC to albumin, SPARC can deliver more drug particles to tumors through the unique gp60-caveolin-SPARC pathway (*Figure 1*), thereby causing remarkable anticancer effects (14-17). Besides, it was reported that nab-paclitaxel may be more effective in the treatment of tumors with high SPARC expression level (18). To date, a large number of clinical trials have employed SPARC to predict the efficacy of nab-paclitaxel, while no reliable and unified conclusion has been reached. To our knowledge, there is no meta-analysis specifically targeting the relationship between SPARC level and the efficacy of albumin-bound paclitaxel. Therefore, the present study aimed to investigate the relationship between SPARC expression level and clinical efficacy of nab-paclitaxel.

We present the following study in accordance with the PRISMA reporting checklist (available at <http://dx.doi.org/10.21037/tcr-20-3045>).

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (19) statement was used to report this meta-analysis. Review Manager and Engauge Digitizer software were used for data extraction and analysis.

Search strategy

We used free-text words and MeSH terms to increase sensitivity. The PubMed and Embase databases were searched from inception to April 2020. The following search strategy was used on PubMed: ('nanoparticle albumin-bound paclitaxel' OR nab-paclitaxel OR nab-PTX

OR Abraxane OR ABI-007) AND ('secreted protein acidic and rich in cysteine' OR SPARC OR osteonectin OR BM-40). On Embase database, we combined the search terms in pairs like (Abraxane AND SPARC) or (nab-paclitaxel AND osteonectin).

Inclusion and exclusion criteria

- (I) The inclusion criteria were as follows: (i) studies published in English; (ii) utilizing at least one chemotherapy regimen containing nab-paclitaxel; (iii) measurement of SPARC expression level (regardless of the method or material) and evaluation of relationship between SPARC expression level and survival outcomes [progression-free survival (PFS) or overall survival (OS)].
- (II) We adopted the following exclusion criteria: (i) studies published in form of reviews, editorial guidelines, or expert opinion letters; (ii) duplicate publication; (iii) application of only neoadjuvant therapy; (iv) studies that concentrated on only animal experiments.

Data extraction and quality assessment

Two authors (Xiaobo Zhou and Xin Yang) independently performed and reviewed the data extraction for the least selection bias. And the following data were extracted from the eligible studies: the full name of the authors, study design, patients' demographic and clinical characteristics, type of chemotherapy regimen, SPARC detection method, the type of antibody used for immunohistochemistry (IHC), SPARC positive expression, and patients' survival data (PFS or/and OS).

Statistical analysis

We used hazard ratio (HR) to evaluate the relationship between survival data and SPARC expression level. $HR < 1$ indicates that high SPARC expression level can result in superior survival benefits than low SPARC expression level. For those studies that did not directly present HR, HR was estimated based on the survival curves via data extraction using Engauge Digitizer 11.1 software (20). Since the majority of the included studies reported the relationship between SPARC expression level in tumor cells or stromal cells and patient's survival data, we calculated HR of both tumor cells and stromal cells. Xing *et al.* (21) demonstrated that the tumor tissues were only used for IHC. With assessment of previously reported images achieved by

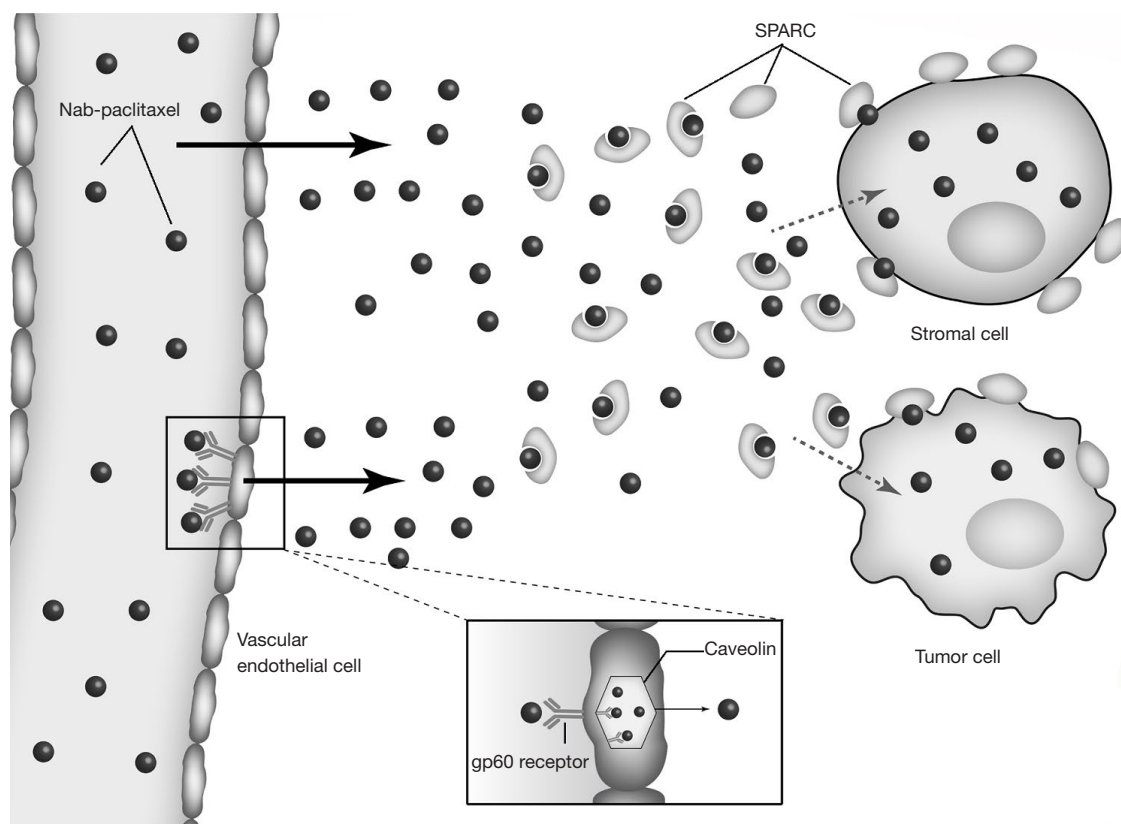


Figure 1 Transport mechanism of albumin-bound paclitaxel. SPARC, secreted protein acidic and rich in cysteine.

IHC, Xing *et al.*'s outcomes were included in our analysis. Heterogeneity between studies was evaluated by using the Cochran's Q-statistic test ($P < 0.05$ was considered statistically significant heterogeneity) and the inconsistency index I^2 statistic ($I^2 > 50\%$ was considered statistically significant heterogeneity). The fixed effects model by Mantel-Haenszel was used in the absence of between-study heterogeneity, and a random effects model by DerSimonian and the Laird would be used to investigate variation both from in-study and between-study. The significance of the pooled HR was determined by the Z test ($P < 0.05$ was considered significant).

Quality control

Because most of the studies that we included were single-arm or non-controlled studies, the Newcastle Ottawa Scale (NOS) was used to evaluate the quality of enrolled studies (22). Studies were divided into three grades: poor,

modest, and high quality, according to scores ranging from 0–3, 4–6, and 7–9, respectively.

Results

Literature screening

A total of 338 studies were included in the preliminary screening. Among them, 315 studies were excluded according to reading their title or abstract. After further screening the full text, 5 studies were finally included in the study, of which, 3 studies concentrated on non-small cell lung cancer (NSCLC) and the other 2 on breast cancer and pancreatic cancer. We created a flowchart to show the details of the inclusion process (Figure 2).

Research features

The main characteristics of the eligible studies are presented

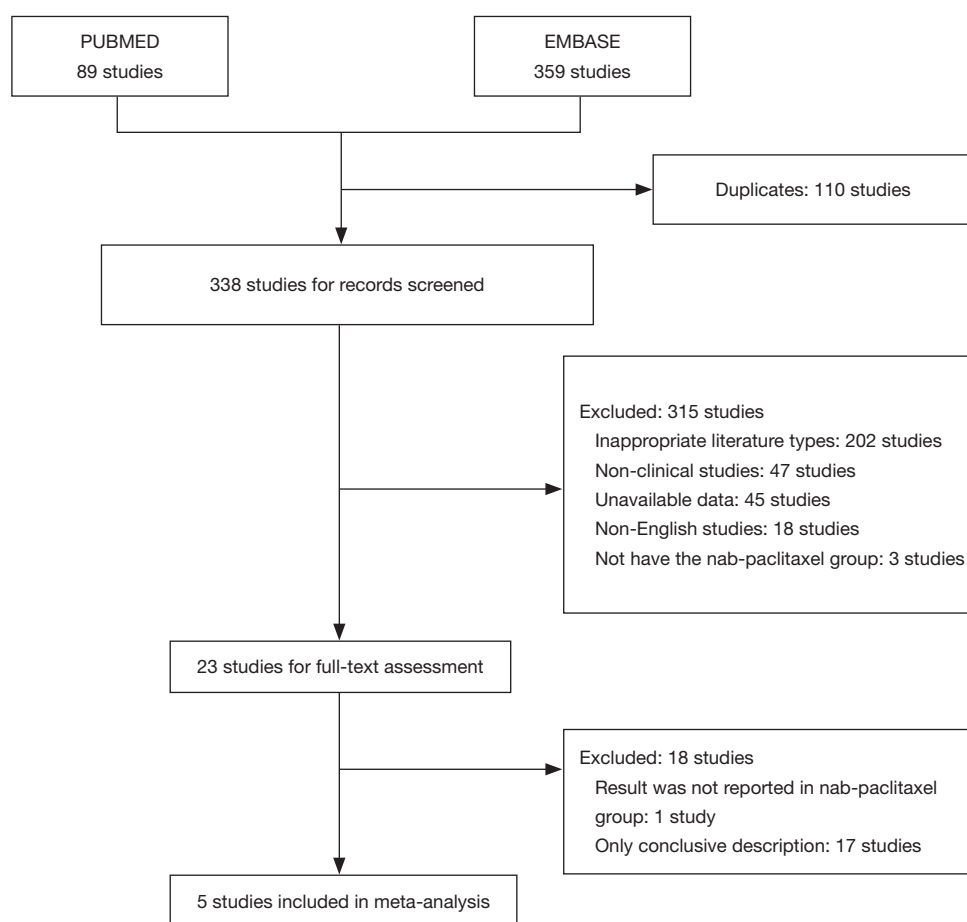


Figure 2 The flowchart of selection of studies.

in *Tables 1-3*. And the results of NOS were shown on *Table 4*.

Meta-result

Since no significant heterogeneity was found in each study group, we used the fixed effects model to combine HR and 95% confidence interval (CI) through Review Manager 5.3 software.

The results showed that SPARC expression level in tumor cells or stromal cells (*Figures 3 and 4*) were not associated with the survival data (PFS or OS) of patients who were treated with nab-paclitaxel. The HR for PFS between SPARC high and low groups was 1.25 (95% CI: 0.72–2.14, stromal cell) and 1.51 (95% CI: 0.93–2.46, tumor cell). The HR for OS between SPARC high and low groups was 1.07 (95% CI: 0.57–2.03, stromal cell) and 1.34 (95%

CI: 0.74–2.43, tumor cell).

Sensitivity analysis

Sensitivity analysis was performed to examine the potential impact of uncertain factors in this study. Removing any single study or using another effects model did not significantly alter our results, which indicates that the survival influences of SPARC level were still undetected when the potential study with a high risk of bias was omitted.

Publication bias

We did not evaluate the risk of publication bias by using any integrated testing tools, because the included studies were

Table 1 The main characteristics of the eligible studies

Study name	Number of patients	Tumor type	Type of chemotherapy regimen	Type of survival data
Bertino <i>et al.</i> , 2015	63	NSCLC	Carboplatin plus nab-paclitaxel	PFS and OS
Duan <i>et al.</i> , 2017	64	NSCLC	Nab-paclitaxel	PFS and OS
Schneeweiss <i>et al.</i> , 2014	44	Brest cancer	Nab-paclitaxel	PFS and OS
Von Hoff <i>et al.</i> , 2011	67	Pancreatic cancer	Nab-paclitaxel	OS
Xing <i>et al.</i> , 2017	98	NSCLC	Nab-paclitaxel	PFS and OS

PFS, progression-free survival; OS, overall survival; NSCLC, non-small cell lung cancer.

Table 2 SPARC-related characteristics of the eligible studies

Study name	Number of patients	Detection method	Antibody used for IHC	Positive expression
Bertino <i>et al.</i> , 2015	37	IHC (TC+SC)	Osteonectin, mouse monoclonal antibody, ON1-1, Invitrogen, 33–5,500	TC: 10/31, 32%; SC: 11/32, 34%
Duan <i>et al.</i> , 2017	28	IHC (TC+SC)	Invitrogen, Carlsbad, CA, USA	TC: 16/28, 57%; SC: 16/28, 57%
Schneeweiss <i>et al.</i> , 2014	37	IHC (TC+SC)	NCL-O-NECTIN, 1:100, Novocastra	TC: 5/37, 14%; SC: 28/37, 76%
Von Hoff <i>et al.</i> , 2011	36	IHC (TC)	1:500; Abcam, Cambridge, UK	19/36, 53%
Xing <i>et al.</i> , 2017	24	IHC (TT)	R&D system, MAB941	7/24, 29%

IHC, immunohistochemistry; TC, tumor cell; SC, stromal cell; TT, tumor tissue.

Table 3 Hazard ratios of each study

Study name	HR (PFS), 95% CI	HR (OS), 95% CI	HR source
Bertino <i>et al.</i> , 2015	TC: 1.08, 0.39–3.02; SC: 1.37, 0.52–3.62	TC: 0.89, 0.30–2.64; SC: 1.00, 0.32–3.08	Estimated
Duan <i>et al.</i> , 2017	SC: 2.71, 0.83–8.82	SC: 1.05, 0.37–2.95	Estimated
Schneeweiss <i>et al.</i> , 2014	TC: 0.68, 0.25–1.85; SC: 0.94, 0.39–2.26	TC: 2.343, 0.31–17.67; SC: 1.795, 0.46–0.71	Original
Von Hoff <i>et al.</i> , 2011	N/A	TC: 0.59, 0.19–1.84	Estimated
Xing <i>et al.</i> , 2017	TT: 1.62, 0.50–5.21	TT: 2.19, 0.61–7.82	Estimated

HR, hazard ratio; CI, confidence interval; PFS, progression-free survival; OS, overall survival.

Table 4 NOS score of each study

Study name	NOS score			
	Selection	Comparability	Exposure	Total
Bertino <i>et al.</i> , 2015	4	1	2	7
Duan <i>et al.</i> , 2017	3	1	2	6
Schneeweiss <i>et al.</i> , 2014	4	2	2	8
Von Hoff <i>et al.</i> , 2011	4	2	2	8
Xing <i>et al.</i> , 2017	3	1	2	6

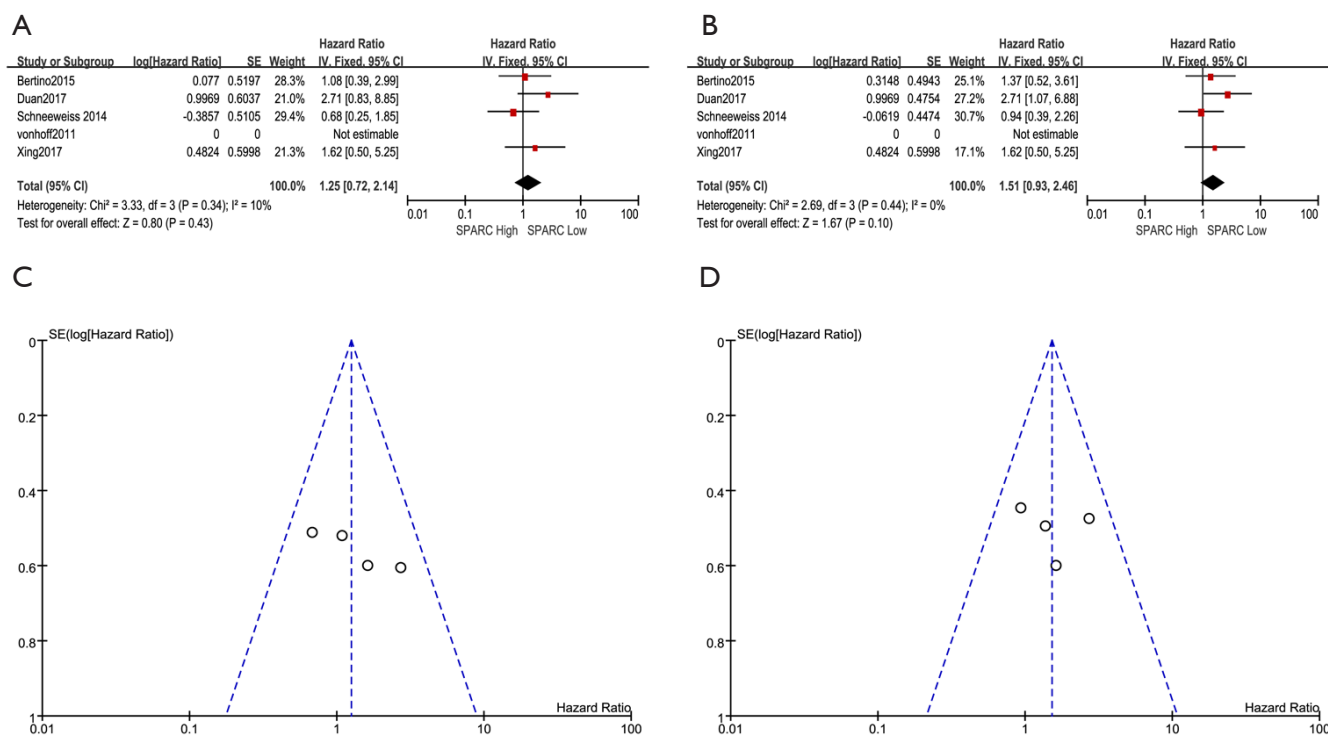


Figure 3 Investigation results of the relationship between SPARC expression level and PFS: (A) relationship between SPARC expression level in tumor cells and PFS; (B) relationship between SPARC expression level in stromal cells and PFS; (C) funnel plot of group A; (D) funnel plot of group B. SPARC, secreted protein acidic and rich in cysteine; PFS, progression-free survival.

neither randomized controlled trials nor non-randomized studies of interventions. Simultaneously, regarding the small number of studies included in our meta-analysis, conduction of a standard publication bias test was found inefficient. Therefore, we used funnel plots to indicate the existence of publication bias. And the results (*Figures 3 and 4*) did not show asymmetric images, indicating that there was no significant publication bias in the literature used in each analysis.

Discussion

The present meta-analysis, for the first time, indicated the predictive effect of SPARC expression level on the therapeutic efficacy of nab-paclitaxel. The results showed that there was no significant association between SPARC expression level and the therapeutic efficacy of nab-paclitaxel. It is noteworthy that 2 of 4 included studies (23,24) indicated that the difference between SPARC expression level and patient's survival data was statistically

significant. However, our findings revealed that even a high level of SPARC seemed to lead to a worse outcome ($HR > 1$ in each group), there was no statistically significant difference between them. This may be due to the small sample size and the estimated HR. Since the survival curves were used to estimate the survival number in our study, and the survival curve represents the survival ratio, the number of survivors will remain stable for a long time because of the small study sample size. The above-mentioned findings indicated inconsistency between our findings and those reported previously. We attempted to increase the number of patients in the same proportion, and the results showed the same conclusion with no significant difference with the original literature, suggesting the importance of high-quality, large sample size studies in the future.

According to previously conducted studies, SPARC contributes to tumorigenesis by promoting migration and epithelial-mesenchymal transition (EMT) of lung cancer cells (25). Therefore, it is almost regarded as a poor prognostic marker (26,27) for patients with different

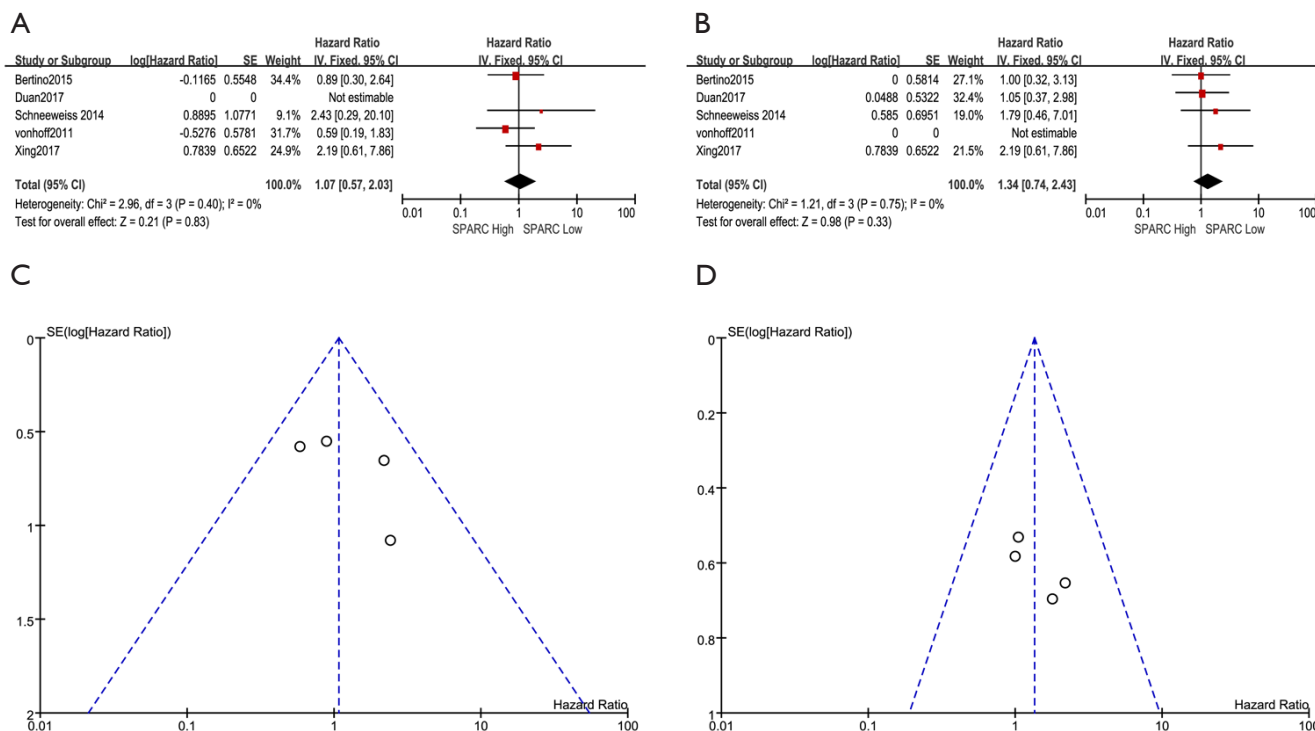


Figure 4 Investigation results of the relationship between SPARC expression level and OS: (A) relationship between SPARC expression level in tumor cells and OS; (B) relationship between SPARC expression level in stromal cells and OS; (C) funnel plot of group A; (D) funnel plot of group B. SPARC, secreted protein acidic and rich in cysteine; OS, overall survival.

types of cancer. Although nab-paclitaxel improves patient's survival compared with traditional taxanes (28,29), the side effect of SPARC makes it a contradictory prognostic factor in treatment with albumin-bound paclitaxel. Although a number of studies demonstrated that SPARC overexpression indicates a higher pathologic complete response (pCR) rate in neoadjuvant therapy with nab-paclitaxel (15,30), our study that included patients who received only systemic chemotherapy did not reveal any survival benefits with nab-paclitaxel. We will dynamically monitor the changes in SPARC expression levels with the treatment progress, which may be more significant to clarify the relationship between SPARC expression level and efficacy of nab-paclitaxel-related antitumor therapy.

Additionally, SPARC, as a secreted protein, not only exists in the cell surface, but also is discharged into the intercellular matrix and enters into the circulatory system. Giallongo *et al.* (31) investigated the variations in SPARC production by peripheral blood cells from chronic myeloid leukemia patients at the time of diagnosis and after

treatment, and identified the subpopulation of cells that were the prevalent source of SPARC. We also included a study (32) that concluded efficacy of nab-paclitaxel in metastatic breast cancer does not associate with SPARC expression level in tumor tissues, while no statistical significant difference was noted in patients with higher plasma SPARC level and longer survival.

IHC was employed for the detection of SPARC expression level in all of the studies included in the current meta-analysis. Even in the 3 studies concentrating on NSCLC (21,23,33), the difference in the proportion of SPARC positive expression was remarkable (29–57%). We noticed that the reagents used in the IHC, as well as the scoring methods and cut-off values were also different, which may lead to differences in experimental results. The determination of the transcriptional mRNA level of SPARC may be more significant to evaluate SPARC expression level. Nakazawa *et al.* (14) confirmed the consistency between SPARC mRNA and protein levels. Although none of the studies included in the present meta-analysis

had concentrated on SPARC mRNA level, in other nab-paclitaxel-based therapies, especially in neoadjuvant therapy, studies have shown that high SPARC mRNA level can often predict worse therapeutic effects (14,34).

Conclusions

According to the results of the current meta-analysis, SPARC expression level in patients who were treated with nab-paclitaxel was not significantly associated with prognosis of such patients. As matters stand, SPARC is not a reliable biomarker to predict the prognosis of patients who were treated with nab-paclitaxel-related chemotherapy. However, the studies included in the current meta-analysis all had small sample sizes, were conducted in phase I/II and used IHC for detection. Therefore, further relevant prospective studies are required to confirm our findings. With the use of a standard method for detection of SPARC expression level, the accuracy of findings will be improved.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr-20-3045>). 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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