

Original Article

Prognostic role of epithelial caveolin-1 in cancer: a meta-analysis

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Abstract: Introduction: Recent studies have shown that caveolin-1 (Cav-1) plays a potential role as a prognostic biomarker in cancer. The aim of the present study was to clarify whether Cav-1 could be a prognostic factor for patients with various kinds of cancer. Materials and methods: All eligible studies were identified using PubMed and EMBASE system. The patients' clinical characteristics and survival outcomes were extracted. The primary data was hazard ratio (HR) with 95% confidence interval (CI) of survival outcomes. Results: After full text review, 43 articles were identified as eligible articles. The meta-analysis of all studies for survival outcomes showed significant prognostic value of Cav-1 in tumor samples. The combined HR (95% CI) for OS was 1.81 [1.29, 2.55] ($P < 0.00001$, $I^2 = 74\%$). And the combined HR (95% CI) was 1.66 [1.42, 1.94] ($P = 0.001$, $I^2 = 58\%$) for DFS/PFS/RFS and 1.93 [1.54, 2.43] ($P = 0.07$, $I^2 = 47\%$) for CSS. Considering that Cav-1 could play different roles on different types of tumor, we divided all the selected articles into several groups by the tumor types to analyze separately. Conclusion: Our results indicated that Cav-1 could predict the prognosis of cancer, but its prognostic value varies among different kinds of cancer.

Keywords: Prognostic role, caveolin-1, cancer, meta-analysis

Introduction

With many years' endeavors, though much progress has been made, cancer remains to be a major health problem which occurs at all ages. According to the Global Cancer Statistics, in 2008 alone, the total number of patients suffered from cancer was 12.7 million and 7.6 million of them ended up dead which means cancer is obliged to be responsible for one in every four deaths [1]. One of its biggest challenges lies in the bad prognosis of cancer. It is widely acknowledged that marked difference in prognosis has been found in cancer patients even with the same kind of cancer [2]. With regard to VEGF [3], MVD and LVD [4] which have shown relatively high prognostic value as biomarkers and were widely used in both clinical trials and experimental studies, novel biomarkers with higher sensitivity and wider usage for diagnosis still need to be found.

Caveolin is a specialized lipid raft on the plasma membrane found in mesenchymal cells

such as adipocytes, endothelial cells, and fibroblasts, which serves as membrane organizing centers. The Caveolin family consists of three members, caveolin-1 (Cav-1), Cav-2, and Cav-3. Cav-1 is widely expressed in various tissues. Cav-3 is a muscular specific protein and Cav-2 is co-expressed with Cav-1 which is required for Cav-1 stabilization and plasma membrane localization [5]. Previous studies have confirmed the essential role of Cav-1 in a number of human diseases including cancer, diabetes, atherosclerosis, restrictive lung disease, pulmonary fibrosis, cardiomyopathy, muscular dystrophy, and bladder dysfunction [6]. In terms of tumor tissues, cellular level of Cav-1 has emerged as a regulator of both epithelial and stromal-dependent tumor growth which is associated with cancer progression [7, 8]. During tumor progression, Cav-1 can be secreted into the microenvironment by cancer cells and triggers proliferation and anti-apoptosis process of the tumor cells especially in tumor endothelial cells [7]. Besides, tissue culture and animal

Prognostic role of Cav-1

model experiments have indicated that blocking the secretion of Cav-1 by polyclonal antibodies inhibits tumor cell growth [9, 10]. Stromal autophagic therapies also has been reported to be associated with Cav-1 [11].

In sum, Cav-1 is therefore becoming a potential therapeutic target for cancer treatment. Additionally, Cav-1 have been used to predict the prognosis of breast cancer, genitourinary carcinoma, hepatic cancer, lung cancer, head and neck cancer, colorectal cancer, gastric cancer, cerebral cancer, ovarian cancer, pancreatic cancer and many other cancers in clinical trials. Many researchers have given high expectations on the prognostic role of Cav-1.

The aim of our study is to conduct a meta-analysis to evaluate the prognostic role of Cav-1 in various cancer tissues. We also seek to establish an evidence-based perspective on its clinical value to predict the clinical results of cancer patients.

Materials and methods

Search strategy

We searched PubMed and EMBASE the last time on Oct 19, 2014. The search strategy consisted of the following keywords variably combined by “caveolin”, “cancer” or “tumor” or “neoplasm” and “prognosis” or “prognostic”. After removing the duplications, we got the initial articles.

Study inclusion/exclusion criteria

Studies were considered eligible if they met all of the following inclusion criteria: (i) patients were diagnosed with any types of cancer, (ii) researchers measured the expression of Cav-1 and (iii) investigated the prognostic role of Cav-1 (overall survival, OS or progression free survival, PFS or disease free survival, DFS or recurrence free survival, RFS or cancer specific survival, CSS). Studies were excluded based on the following criteria: (i) studies were review articles, laboratory articles or letters, (ii) researchers described the survival outcomes of other markers, (iii) the papers lacked key information for calculation with methods developed by Parmar [12], Williamson [13], and Tierney [14].

Data extraction

Articles were reviewed independently by two investigators (Jing Zhang and Rubai Zhou) for inclusion and exclusion criteria. Disagreements were resolved by consensus. HR and 95% confidence interval (CI), p value, or the Kaplan-Meier survival curves of survival outcomes, the primary information were extracted by two investigators (Jing Zhang and Yanlin Song) independently. Additional data were obtained from the studies including first author, publication year, study size, patients' age, cancer treatment, diagnostic method, follow-up time, cancer type, methods to detect Cav-1, positive Cav-1 definition, positive site, antibodies and dilution proportion, TNM stage, the attitude of conclusion and other clinical characteristics.

Statistical methods

The logHR and SE (logHR) (SE) were used for aggregation of the survival results, but these statistical variables were not given explicitly in most studies. We calculated the necessary statistics on the basis of available data with methods developed by Parmar, Williamson, and Tierney. Then meta-analysis was performed using OS, DFS/PFS/RFS and CSS. Calculation was accomplished by the software designed by Matthew Sydes and Jayne Tierney with their methods (Medical Research Council Clinical Trials Unit, London, UK) [14].

Forrest plots were used to estimate the effect of Cav-1 expression on survival outcomes. Heterogeneity was defined as $P < 0.10$ or $I^2 > 50\%$. When homogeneity was fine ($P \leq 0.10$, $I^2 \leq 50\%$), a fixed effect model was used for secondary analysis. If not, a random effect model was used instead [15]. An observed HR > 1 indicated worse outcome for the positive group, meanwhile it would be considered statistically significant if the 95% CI did not overlap 1. The Begg's test and funnel plot were also applied to assess the potential publication bias, and $P > 0.05$ was considered that there was no potential publication bias [16]. All above calculations were performed using RevMan 5.1 (Cochrane collaboration, Oxford, UK). Publication biases were evaluated using the Begg's funnel plot by STATA 11.0 (STATA Corporation, College Station, TX).

Prognostic role of Cav-1

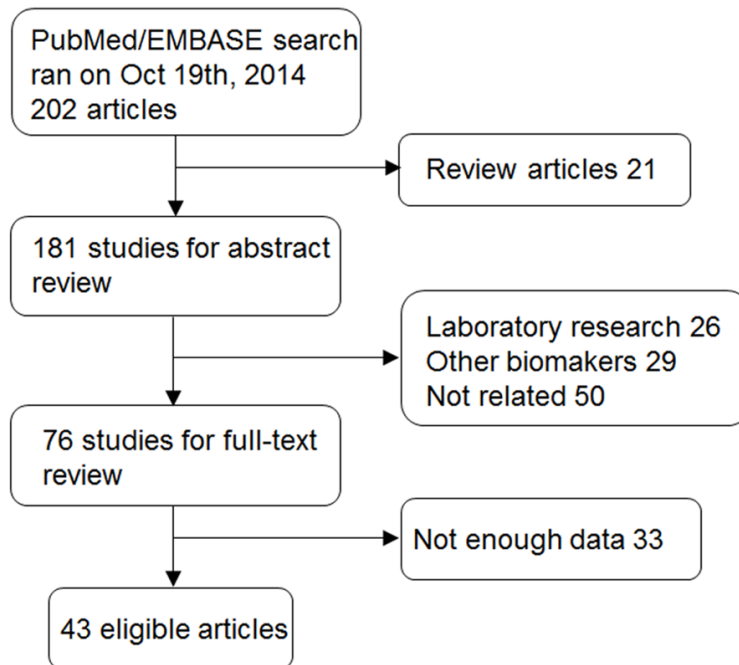


Figure 1. Selection of studies.

Results

Eligible studies

We got 202 records for Cav-1, cancer and prognosis in PubMed and EMBASE. After screening titles and abstracts, we found that 29 articles referred to other markers, 21 referred to review articles, 26 referred to laboratory studies and 50 did not center on the association between cav-1 and prognosis. Finally, 76 potentially relevant studies were identified as eligible studies. After full text review, 43 article [8, 17-58] were identified as eligible ones, 33 studies were excluded for short of the necessary data for calculation (Figure 1).

The eligible studies included 12 articles for genitourinary cancer [20, 23, 29, 31, 33, 36, 38, 44, 45, 48, 55, 56], 11 articles for breast cancer [8, 22, 25, 26, 30, 33, 35, 39, 43, 47, 57], 4 articles for gastrointestinal cancer [17, 19, 32, 46], 2 articles for head and neck cancer [24, 40], 5 articles for lung cancer [27, 28, 50, 52, 53], 4 articles for liver cancer [49, 51, 54, 58], 3 articles for brain cancer [18, 41, 42], 1 article for pancreatic cancer [37] and 1 article for osteosarcoma [21]. The 43 eligible studies were published from 1999 to 2011. These studies included a total of 7205 patients

(ranged 21-924). The patients' clinical characteristics and other useful information have been extracted in Table 1.

Correlation between Cav-1 and the survival outcome

Most of the primary researches discovered high cav-1 level in tumor epithelial tissue. The meta-analysis of all studies for survival outcome showed significant prognostic value of Cav-1 in tumor samples. The combined HR (95% CI) of 21 studies [8, 17-19, 21, 27, 28, 32, 33, 35, 37, 39, 41, 42, 46, 49, 50, 52-54, 58] for OS was 1.81 [1.29, 2.55] ($P < 0.00001$, $I^2 = 74\%$) (Figure 2A). And the combined HR (95% CI) of 17 studies [20-22, 25, 26, 28, 30, 31, 33, 35, 40, 44, 45, 47, 50, 55, 56] for DFS/PFS/RFS was

1.66 [1.42, 1.94] ($P = 0.001$, $I^2 = 58\%$) (Figure 2B) as well as the ones of 9 studies [23, 24, 26, 29, 38, 43, 48, 51] for CSS was 1.93 [1.54, 2.43] ($P = 0.07$, $I^2 = 47\%$) (Figure 2C). All above results indicated that Cav-1 in tumor epithelial tissue could predict the prognosis of patients with cancer.

We grouped the results by the cut-off value, detecting method, III&IV% and statistical analysis in all cancer and displayed detailed subgrouped results in Table 2. All studies evaluated caveolin levels by immunohistochemistry (IHC) [8, 17-19, 24, 27, 28, 32, 37, 39-42, 46, 49-54, 58] and tissue microarray (TMA) [33, 35], the combined HRs (95% CI) for OS were 1.95 [1.36, 2.80] and 0.67 [0.19, 2.33], for DFS/PFS/RFS were 1.90 [1.54, 2.33] and 1.41 [1.10, 1.80], for CSS were 2.08 [1.58, 2.72] and 1.62 [1.06, 2.48], respectively. The pooled HRs (95% CI) using multivariate analysis was 1.81 [0.85, 3.86] for OS [17, 18, 27, 28, 32, 39, 49, 50, 53, 58], 1.89 [1.51, 2.36] for DFS/PFS/RFS [20, 25, 28, 31, 36, 40, 44, 45, 47, 50, 55, 56] and 1.93 [1.49, 2.50] for CSS [23, 29, 38, 43, 48, 51] while 1.58 [0.99, 2.50], 1.47 [1.18, 1.83] and 1.94 [1.20, 3.14] in univariate analyzing studies separately. When grouped by cut-off value of individual studies, the combined HRs (95% CI) of less than 30% staining group

Prognostic role of Cav-1

Table 1. Baseline characteristics of the studies

Author	Date	Marker	Attitude	N (P/N)	Age	Treatment	Time	Site	Cut-off value	Antibody	Dilution	Method	Disease	Survival outcome
FRANZ RODEL [1]	2009	Cav-1	P	44 (17/27)	61.8	RCT	41.8M	epithelial	cav score: ≤ 3 ; ≥ 4	anti-Cav-1, Santa Cruz	1:50	IHC	adenocarcinoma of the rectum	OS
V. Barresi [2]	2008	Cav-1	NC	47 (13/34)	63	NR	58.8M	epithelial	ID score 4	rabbit polyclonal anti-Cav-1, Santa Cruz	1:500	IHC	gastric carcinomas	OS
Kentaro Kato [3]	2002	Cav-1	P	130 (58/72)	NR	S	NR	epithelial	50% staining	rabbit polyclonal anti-Cav-1, Santa Cruz	1:400	IHC	ESCC	OS
Lu Shi [4]	2007	Cav-1	N	75 (34/41)	38	S	61M	epithelial	score of 6	rabbit polyclonal anti-Cav-1, Santa Cruz	1:125	IHC	Mucoepidermoid Carcinoma of the Salivary Glands	DFS
TAKUYA ANDO [5]	2007	Cav-1	P	47 (13/34)	NR	S	26.2M	epithelial	10% staining	monoclonal anti-Cav-1, BD	1:150	IHC	ESCC	OS
TAKUYA ANDO [5]	2007	Cav-2	P	47 (22/25)	NR	S	26.2M	epithelial	10% staining	monoclonal anti-Cav-2, BD	1:50	IHC	ESCC	OS
Zi-Ming Du [6]	2009	Cav-1	P	194 (96/98)	46	S&R	NR	epithelial	\geq mean value	anti-Cav-1, Santa Cruz	1:500	IHC	nasopharyngeal carcinoma	CSS
Yu Tang [7]	2011	Cav-1	P	160 (95/65)	52.5	S	NR	epithelial	no staining	anticav-1 monoclonal antibody, Dako	1:100	IHC	HCC	OS
S Murakami [8]	2003	Cav-1	N	60 (22/38)	66.2	S	28.8	epithelial	50% staining	anti-cav-1 rabbit polyclonal; Santa Cruz	1:400	IHC	EBDC	OS
Zhi-Bo Zhang [9]	2009	Cav-1	P	75 (26/49)	45.6	S	NR	epithelial	ID score 6	anti-cav-2 rabbit polyclonal; Santa Cruz	1:500	IHC	HCC	CSS
SHEAU-FANG YANG [10]	2010	Cav-1	N	73 (39/34)	57.3	S	39.04 M	epithelial	10% staining	mouse anti-human CAV1, Santa Cruz	1:200	IHC	HCC	OS
Seong-Ho Yoo [11]	2003	Cav-1	P	107 (34/73)	62	S	27.5M	epithelial	20% staining	mouse monoclonal anti-caveolin-1	1:250	IHC	squamous cell carcinoma of the lung	
KYUNG CHUL MOON [12]	2005	Cav-1	P	21 (10/11)	60	S	NR	epithelial	50% staining (mean value)	mouse monoclonal anti-caveolin-1	1:250	IHC	PCL	OS
KYUNG CHUL MOON [12]	2005	Cav-1	P	21 (10/11)	60	S	NR	epithelial	50% staining (mean value)	mouse monoclonal anti-caveolin-1	1:250	IHC	PCL	DFS
Chao-Chi Hoa [13]	2008	Cav-1	P	73 (12/61)	57	C	NR	epithelial	30% staining	anti-cav-1, BD	1:500	IHC	NSCLC	OS
Chao-Chi Hoa [13]	2008	Cav-1	P	73 (12/61)	57	C	NR	epithelial	30% staining	anti-cav-1, BD	1:500	IHC	NSCLC	DFS
Chao-Chi Ho [14]	2002	Cav-1	P	35 (4/31)	58.4	S	NR	epithelial	30% staining	anti-human caveolin-1 antibody, BD	1:1000	IHC	Lung Adenocarcinoma	OS
PING ZHAN [15]	2012	Cav-1	NC	115 (60/55)	NR	S	22 M	epithelial	50% staining	rabbit polyclonal anti-Cav-1, Santa Cruz	1:400	IHC	lung cancer	OS
V. Barresi [16]	2006	Cav-1	P	62 (33/29)	63.5	S	96 M	epithelial	ID score 4	rabbit polyclonal anti-Cav-1, Santa Cruz	1:500	IHC	meningioma	OS
Rebecca Senetta [17]	2011	Cav-1	P	22 (11/11)	38.7	S&R	58.5 M	epithelial	30% staining	rabbit polyclonal anti-Cav-1, Santa Cruz	1:350	IHC	supratentorial ependymomas	OS

Prognostic role of Cav-1

Rebecca Senetta [18]	2009	Cav-1	P	63 (13/50)	48.6	S	NR	epithelial	no staining	rabbit polyclonal anti-Cav-1, Santa Cruz	1:350	IHC	Oligodendrogliomas	OS
Lara Cantiani [19]	2007	Cav-1	N	36 (18/18)	NR	C	6 Y	epithelial	median value	anti-Cav-1 polyclonal antibody, BD	1:10000	RT-PCR	osteosarcoma	OS
Lara Cantiani [19]	2007	Cav-1	NC	36 (18/18)	NR	C	6 Y	epithelial	median value	anti-Cav-1 polyclonal antibody, BD	1:10000	RT-PCR	osteosarcoma	DFS
M Suzuoki [20]	2002	Cav-1	P	79 (32/47)	63	S	57.6 M	epithelial	50% staining	rabbit polyclonal anti-Cav-1, Santa Cruz	1:400	IHC	pancreatic carcinomar	OS
Langeberg WJ [21]	2010	Cav-1	P	202	57		144 M	serum	0.13 ng/ml			ELSIA	PC	RFS
Tahir SA [22]	2006	Cav-1	P	419 (120/299)	62.6		52 M	serum	0.13 ng/mL			ELSIA	PC	RFS
Karam JA [23]	2007	Cav-1	P	232 (70/163)	62.6		120 M	epithelial	50% staining			IHC	PC	RFS
Satoh T [24]	2003	Cav-1	P	152 (46/106)	64.3		48.2 M	epithelial	50% staining			IHC	PC	RFS
Yang G [25]	1999	Cav-1	P	189 (47/142)	63		60 M	epithelial	50% staining			IHC	PC	RFS
Yang G [26]	2005	Cav-1	P	104 (21/83)	64.2		62.7 M	epithelial	50% staining			IHC	PC	RFS
Campbell L [27]	2008	Cav-1	N	174 (28/146)	65		44 M	epithelial	NR			IHC	RCC	DFS
Joo HJ [28]	2004	Cav-1	P	67 (34/33)	54.5		46 M	epithelial	25% staining			IHC	RCC	CSS
Phuoc NB [29]	2007	Cav-1	P	119 (66/53)	61		69.3 M	epithelial	50% staining			IHC	RCC	CSS
Sandra Steffens [30]	2011	Cav-1	P	289 (57/232)	60.4		80.5 M	epithelial	5% staining			IHC	RCC	CSS
Ruan Jiang [31]	2010	Cav-1	N	85 (34/51)	57		45 M	epithelial	5% staining			IHC	BC	DFS
Cho DS [32]	2008	Cav-1	N	98 (9/89)	61.7		NR	epithelial	10% staining			IHC	TCC-UUT	CSS
Witkiewicz AK [33]	2010	Cav-1	P	85	NR		33.8 M	stroma	no staining	rabbit polyclonal anti-Cav-1, BD	1/4000	IHC	TNBC	OS
Witkiewicz AK [33]	2010	Cav-1	P	85	NR		33.8 M	stroma	no staining	rabbit polyclonal anti-Cav-1, BD	1/4000	IHC	BLBC	OS
Witkiewicz AK [33]	2010	Cav-1	P	85	NR		33.8 M	epithelial	no staining	rabbit polyclonal anti-Cav-1, BD	1/4000	IHC	breast cancer	OS
Witkiewicz AK 3 [34]	2009	Cav-1	positive	154	59.5		100.8 M	stroma	no staining	rabbit polyclonal anti-Cav-1, Santa Cruz	1/500	IHC	breast cancer	PFS
El-Gendi SM [35]	2011	Cav-1	positive	91	50.1		21.94 M	stroma	no staining	rabbit monoclonal anti-Cav-1, Abcam	1/100	IHC	NR	PFS
El-Gendi SM [35]	2011	Cav-1	positive	91	50.1		21.94 M	epithelial	no staining	rabbit monoclonal anti-Cav-1, Abcam	1/100	IHC	NR	PFS
Koo JS [36]	2011	Cav-1	P	722	NR		71 M	stroma	30% staining	monoclonal anti-Cav-1, BD; anti-Cav-2, Abcam; polyclonal anti-Cav-3, Abcam	1/50, 1/200 and 1/100	TMA	breast cancer	OS
Koo JS [36]	2011	Cav-1	NC	722	NR		71 M	epithelial	30% staining	monoclonal anti-Cav-1, BD; anti-Cav-2, Abcam; polyclonal anti-Cav-3, Abcam	1/50, 1/200 and 1/100	TMA	breast cancer	OS
Koo JS [36]	2011	Cav-1	P	722	NR		71 M	stroma	30% staining	monoclonal anti-Cav-1, BD; anti-Cav-2, Abcam; polyclonal anti-Cav-3, Abcam	1/50, 1/200 and 1/100	TMA	breast cancer	DFS
Koo JS [36]	2011	Cav-1	NC	722	NR		71 M	epithelial	30% staining	monoclonal anti-Cav-1, BD; anti-Cav-2, Abcam; polyclonal anti-Cav-3, Abcam	1/50, 1/200 and 1/100	TMA	breast cancer	DFS
Liedtke C [37]	2007	Cav-1	NC	109	NR		82 M	epithelial	no staining	mouse monoclonal anti-Cav-1, BD	1/200	TMA	breast cancer	OS
Liedtke C [37]	2007	Cav-1	NC	109	NR		82 M	epithelial	no staining	mouse monoclonal anti-Cav-1, BD	1/200	TMA	breast cancer	DFS

Prognostic role of Cav-1

Qian N [38]	2011	Cav-1	P	86	NR	74 M	stroma	5% staining	monoclonal anti-Cav-1, Cell Signaling	1/800	IHC	breast cancer	DFS
Qian N [38]	2011	Cav-1	P	86	NR	74 M	epithelial	5% staining	monoclonal anti-Cav-1, Cell Signaling	1/800	IHC	breast cancer	DFS
Savage K (Break-through) [39]	2008	cav-2	N	210	NR	67 M	epithelial	no staining	mouse monoclonal anti-Cav-2, BD	1/100	TMA	breast cancer	CSS
Savage K (Vancouver) [39]	2008	cav-2	NC	310	NR	129.6 M	epithelial	no staining	mouse monoclonal anti-Cav-2, BD	1/100	TMA	breast cancer	CSS
Elsheikh SE [40]	2008	Cav-1	NC	516	NR	NR	epithelial	no staining	mouse monoclonal antibodies, BD	1/150 and 1/50	TMA	breast cancer	DFS
Elsheikh SE [40]	2008	cav-2	P	516	NR	NR	epithelial	no staining	mouse monoclonal antibodies, BD	1/150 and 1/50	TMA	breast cancer	CSS
Sloan EK [41]	2009	Cav-1	P	173	54	146.8 M	stroma	no staining	mouse monoclonal anti-Cav-1, BD	1/50	IHC	breast carcinomas	OS
Sloan EK [41]	2009	Cav-1	NC	173	54	146.8 M	epithelial	no staining	mouse monoclonal anti-Cav-1, BD	1/50	IHC	breast carcinomas	OS
Charpin C [42]	2009	Cav-1	P	924	NR	79 M	epithelial	NR	rabbit polyclonal anti-Cav-1, Santa Cruz	NR	TMA	breast carcinomas	DFS
Joshi B [43]	2008	Cav-1	P	438	NR	180 M	epithelial	25% staining	mouse anti-Cav-1, Transduction	NR	TMA	breast carcinomas	DFS

Prognostic role of Cav-1

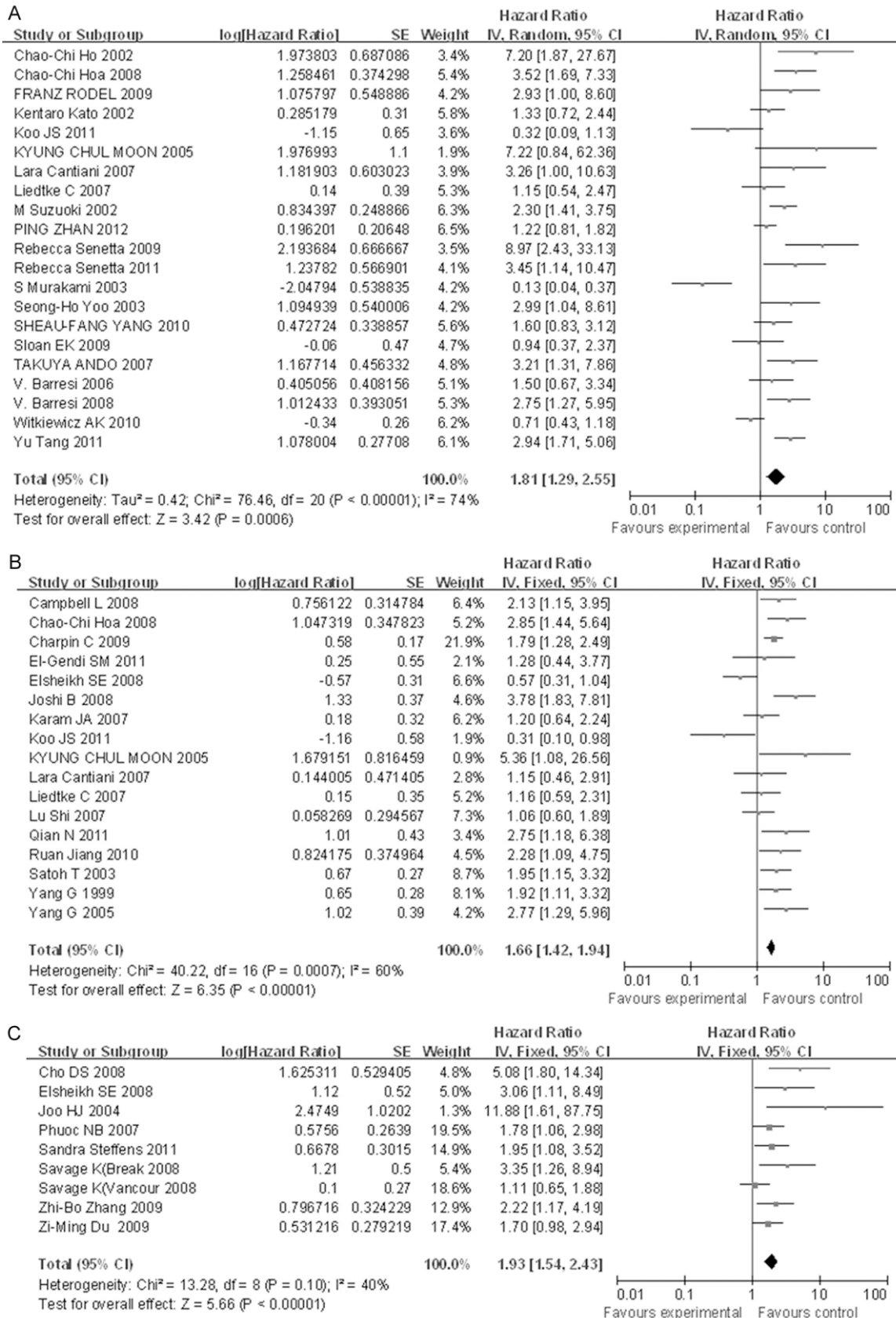


Figure 2. A. Assessed Hazard Ratios (HRs) Summary for OS for all the studies; B. Assessed Hazard Ratios (HRs) Summary for DFS/PFS/RFS for all the studies; C. Assessed Hazard Ratios (HRs) Summary for CSS for all the studies.

Prognostic role of Cav-1

Table 2. Sub-grouped results

		OS	DFS/PFS/RFS	CSS
Total		1.81 [1.29, 2.55] (n = 21; P < 0.00001; I ² = 74%)	1.66 [1.42, 1.94] (n = 17; P = 0.0007; I ² = 60%)	1.93 [1.54, 2.43] (n = 9; P = 0.10; I ² = 40%)
Cut-off value	Less than 30% staining	1.88 [1.10, 3.19] (n = 8; P = 0.0004; I ² = 74%)	1.51 [1.11, 2.04] (n = 6; P = 0.001; I ² = 75%)	2.01 [1.46, 2.78] (n = 6; P = 0.03; I ² = 61%)
	not less than 30% staining	1.41 [0.73, 2.70] (n = 9; P < 0.00001; I ² = 84%)	1.83 [1.41, 2.38] (n = 7; P = 0.02; I ² = 62%)	1.78 [1.06, 2.98] (n = 1)
Detecting method	IHC	1.95 [1.36, 2.80] (n = 18; P < 0.00001; I ² = 75%)	1.90 [1.54, 2.33] (n = 11; P = 0.32; I ² = 13%)	2.08 [1.58, 2.72] (n = 6; P = 0.24; I ² = 26%)
	TMA	0.67 [0.19, 2.33] (n = 2; P = 0.09; I ² = 65%)	1.41 [1.10, 1.80] (n = 5; P = 0.001; I ² = 75%)	1.62 [1.06, 2.48] (n = 3; P = 0.06; I ² = 64%)
Statistical analysis method	Multivariate analysis	1.81 [0.85, 3.86] (n = 10; P < 0.00001; I ² = 82%)	1.89 [1.51, 2.36] (n = 10; P = 0.24; I ² = 22%)	1.93 [1.49, 2.50] (n = 7; P = 0.06; I ² = 51%)
	Univariate analysis	1.58 [0.99, 2.50] (n = 9; P = 0.0003; I ² = 73%)	1.47 [1.18, 1.83] (n = 7; P = 0.0002; I ² = 77%)	1.94 [1.20, 3.14] (n = 2; P = 0.32; I ² = 0%)

OS overall survival, DFS disease free survival, PFS progression free survival, RFS recurrence free survival, CSS cancer specific survival, IHC immunohistochemistry, TMA tissue microarray.

Table 3. Results grouped by cancer type

Disease	Survival outcome	Study n.	Patient n.	Model	HR (95% CI)	P value	Heterogeneity (I ² , p)	Conclusion
Genitourinary cancer	RFS	6	1298	Random	1.60 [1.05, 2.43]	0.03	61%, 0.02	P
Genitourinary cancer	CSS	3	475	Fixed	1.98 [1.35, 2.90]	0.0005	39%, 0.20	P
Breast cancer	OS	4	1089	Fixed	0.78 [0.54, 1.12]	0.18	6%, 0.36	NC
Breast cancer	DFS/PFS	7	2886	Random	1.32 [0.76, 2.29]	0.33	78%, 0.0001	NC
Lung cancer	OS	5	351	Random	1.81 [1.22, 2.69]	0.005	70%, 0.010	P
Lung cancer	DFS	2	94	Fixed	3.14 [1.68, 5.88]	0.0003	0%, 0.48	P
Gastrointestinal cancer	OS	4	213	Fixed	1.81 [1.22, 2.69]	0.003	16%, 0.31	P
Liver cancer	OS	3	293	Random	0.91 [0.20, 4.14]	0.9	92%, < 0.00001	NC
Brain cancer	OS	3	147	Fixed	3.66 [2.07, 6.46]	< 0.00001	15%, 0.31	P

RFS recurrence free survival, CSS cancer specific survival, OS overall survival, DFS disease free survival, PFS progression free survival, P positive, NC not conclusive.

[8, 23, 25, 26, 29, 30, 35, 38, 39, 41, 43, 45, 47, 53, 54, 57, 58] and no less than 30% staining group [28, 29, 32-34, 36, 41, 43, 45, 47-49, 51, 54, 55] for OS were 1.88 [1.10, 3.19] and 1.41 [0.73, 2.70], for DFS/PFS/RFS were 1.51 [1.11, 2.04] and 1.83 [1.41, 2.38] as well as for CSS were 2.01 [1.46, 2.78] and 1.78 [1.06, 2.98], respectively. We try all these subgroup analysis to decline the heterogeneity. Unfortunately, we could not find a fine homogeneity. The *P*-value for heterogeneity and I² have been listed in **Table 2**. Considering that Cav-1 could play different roles on different types of tumor, we divided all the selected articles into several groups by the tumor types.

Genitourinary cancer

All results below indicated that Cav-1 could be used as a prognostic marker of patients with genitourinary cancer. For prostate cancer, the

combined HR (95% CI) of 6 studies [31, 34, 36, 44, 55, 56] for RFS was 1.60 [1.05, 2.43] (*P* = 0.02, I² = 61%). In the studies of renal cancer, the combined HR (95% CI) of 3 studies [31, 34, 47] for CSS was 1.98 [1.35, 2.90] (*P* = 0.20, I² = 39%). The multivariate HR (95% CI) of bladder carcinoma for DFS was 2.28 [1.09, 4.74]. And the multivariate HR (95% CI) of upper urinary tract carcinoma for CSS was 5.08 [1.799, 14.342].

Breast cancer

Both the tissue and stromal Cav-1 have been developed as an important factor in breast cancer prognosis. The results for survival outcome suggested no significant prognostic value of Cav-1 in tumor epithelia. The pooled HR (95% CI) of 4 studies [8, 33, 35, 39] for OS was 0.78 [0.54, 1.12] (*P* = 0.36, I² = 6%). And the combined HR (95% CI) of 7 studies [22, 25, 26, 30,

Prognostic role of Cav-1

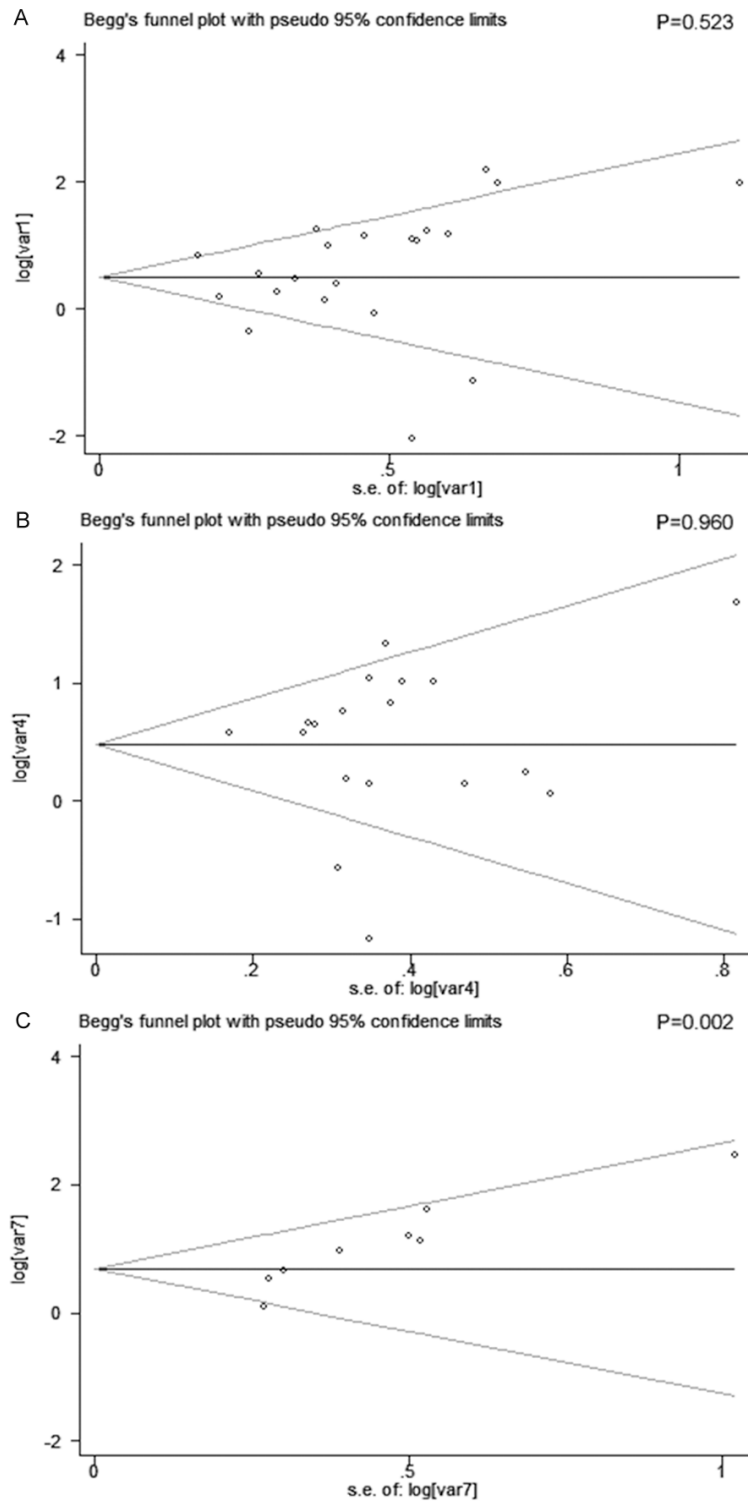


Figure 3. Funnel Plots of Publication Bias for OS (A), DFS/PFS/RFS (B) and CSS (C).

33, 35, 47] for DFS/PFS was 1.32 [0.76, 2.29] ($P = 0.0001$, $I^2 = 78\%$). Additionally, 7 studies have been made to evaluate the relationship

There are 4 related studies [49, 51, 54, 58] found on liver cancer about survival outcomes including 3 ones [51, 54, 58] on HCC and 1 [49]

between the loss of stromal Cav-1 expression and overall survival. The combined HR (95% CI) of 3 studies [8, 33, 39] for OS was 4.12 [2.05, 8.28] ($P = 0.0009$, $I^2 = 82\%$). While the HR (95% CI) of 4 studies [25, 33, 47, 57] for DFS/PFS was 3.69 [2.57, 5.31] ($P = 0.50$, $I^2 = 0\%$). These results showed that loss of stromal Cav-1 could be considered as a promising and effective predictor for an adverse survival outcome in breast cancer.

Lung cancer

We found 5 relevant studies on lung cancer for survival outcomes with the combined HR (95% CI) for OS being 1.81 [1.22, 2.69] ($P = 0.010$, $I^2 = 70\%$). In Ho.C.C.'s [28] study and MOON.K.C.'s study [50], the combined HR (95% CI) for DFS was 3.14 [1.68, 5.88] ($P = 0.48$, $I^2 = 0\%$). All these results for meta-analysis presented remarkable prognostic value of Cav-1 in lung cancer.

Gastrointestinal cancer

In the studies of gastrointestinal cancer, the meta-analysis for OS revealed a significant prognostic value of epithelial Cav-1. We included 4 studies [17, 19, 32, 46] in this subgroup analysis which consisted of 2 studies [17, 32] for esophageal squamous cell cancer, one study [19] for gastric carcinoma and one study [46] for rectal adenocarcinoma. The combined HR (95% CI) for OS was 1.81 [1.22, 2.69] ($I^2 = 64\%$, $P = 0.06$).

Liver cancer

Prognostic role of Cav-1

on EBDC, among which the combined HR (95% CI) of HCC for OS was 0.91 [0.20, 4.14] ($P < 0.00001$, $I^2 = 92\%$) and the HR (95% CI) of Zhang Z.B.'s study for CSS was 2.61 [1.21, 5.60].

Other cancers

Moreover, 3 studies on brain cancer involving meningioma [18], supratentorial ependymoma [42] and oligodendroglioma [41] with the combined HR (95% CI) for OS was 3.66 [2.07, 6.46] ($P = 0.31$, $I^2 = 15\%$).

We integrated 2 relevant studies on head and neck cancers in our meta-analysis. One study [40] is on mucoepidermoid carcinoma of the salivary glands with HR (95% CI) for DFS being 1.063 [0.342, 3.304] and the other one [24] is on nasopharyngeal carcinoma with HR (95% CI) for CSS being 1.701 [0.984, 2.940].

In M Suzuoki's study [37], the HR (95% CI) of pancreatic carcinoma for OS was 1.701 [0.984, 2.940]. And one study [21] concentrated on osteosarcoma with HR (95% CI) for OS being 3.26 [1.00, 10.63] and for EFS 1.15 [0.46, 2.91].

Results grouped by cancer types have been displayed in **Table 3**.

Assessment of publication bias

Begg's test and funnel plot were used to evaluate publication bias. No significant publication bias was found in the meta-analysis of Cav-1 for OS ($P = 0.523$) and DFS/PFS/RFS ($P = 0.960$) in cancer. However, the eligible studies for CSS yielded a Begg's test score of $P = 0.002$. Meanwhile according to the Begg's funnel plot of these studies, the publication bias was found (**Figure 3**).

Discussion

As far as we know, it is the first meta-analysis summarizing the prognostic role of epithelial Cav-1 of all kinds of solid human tumors and we hope this article could make a contribution to the exploration about the clinical value of Cav-1 on cancer patients. In the past two decades, caveolin family has become a hot research subject, involving diagnosis, therapy and prognosis. In this study, we focused on Cav-1 with its potential prognostic value in many kinds of cancer as a biomarker, including genitourinary can-

cer, breast cancer, gastrointestinal cancer, head and neck cancer, lung cancer, liver cancer, brain cancer, pancreatic cancer and osteosarcoma. Our results suggest that detected Cav-1 expression in epithelial and stromal cells could predict worse survival in patients with a variety of cancer.

Categorizing groups according to tumor types, we found that Cav-1 showed strong prognostic significance on genitourinary cancer, gastrointestinal cancer, lung cancer, brain cancer and osteosarcoma while just weak prognostic effect on breast cancer, liver cancer, head and neck cancer, pancreatic cancer. When analysis was strictly restricted to studies with detecting method of IHC, we found that the combined HR for OS (1.95), DFS/PFS/RFS (1.90) and CSS (2.08) were higher than the combined HR for total results (1.81; 1.66; 1.93) while the TMA group were lower. This subgroup result suggested that CAV-1 expression could be an important prognostic marker using IHC method to measure, while the TMA may be premature as a more advanced and complicated detecting method at the present stage. Other subgroup classifications have been tried using cut-off value and statistical analysis method etc., but we did not obtain ideal statistically significant results.

Significant heterogeneity has been found in the meta-analysis for OS and DFS/PFS/RFS of the prognostic role of epithelial Cav-1. To exclude the heterogeneity, subgroup analysis were performed by country, detecting method, and publishing year. All above attempts could not eliminate the heterogeneity. Then we found that the heterogeneity for OS group mainly came from the Koo JS's study [33], Murakami S's study [49] and Witkiewicz AK's study [8] and for DFS/PFS/RFS was from the Koo JS's study [33]. When these groups were removed from the meta-analysis, the adjusted HR for OS was 2.23 [1.72, 2.89] ($P = 0.02$, $I^2 = 47\%$) and for DFS/PFS/RFS was 1.74 [1.39, 2.18] ($P = 0.01$; $I^2 = 50\%$). These three articles mainly described the prognostic role of breast cancer and liver cancer. It suggested that the prognostic role of epithelial Cav-1 might be variable among different cancers, especially in terms of breast cancer and liver cancer.

In the subgroup analysis of genitourinary cancer, we found that the combined HR for prostate cancer was 1.60 [1.05, 2.43] indicating

Prognostic role of Cav-1

that the Cav-1 had a good prognostic significance on PC. Among these studies, 4 [31, 44, 55, 56] of them measured the Cav-1 level in tumor tissue while the other two [34, 36] detected the Cav-1 in serum and their combined HR (95% CI) was 1.25 [0.36, 4.36]. The 95% CI of serum group overlapped 1, which showed that the serum Cav-1 had no prognostic significance on prostate cancer. The detecting results in serum changed greatly due to many different factors. Two studies [34, 36] have the opposite opinion on the predictive role of serum Cav-1. When we observed the two studies further, we found that the association with PC recurrence was not significant when 0.13 ng/ml was used to define high Cav-1 values (HR = 0.71, 95% CI [0.41, 1.23]; log rank P (P) = 0.23); while the median level for the controls in our dataset (0.69 ng/ml) was used as the cut-off value, the association approached statistical significance in the opposite direction as previously reported (HR = 0.68; 95% CI [0.46, 0.99]; P = 0.04). Some more studies need to focus on the serum Cav-1 to identify a better cut-off value. Evaluation of level of serum Cav-1 could be considered as a novel, convenient and non-invasive method for us doctors to follow up the profiles of patients. Further studies to confirm the prognostic role of Cav-1 in serum remain in demand.

Both epithelial and stromal Caveolin have been evaluated in patients to predict the prognosis in breast cancer. The pooled HR of epithelial group for OS was 0.78 [0.54, 1.12] and for DFS/PFS was 1.32 [0.76, 2.29], both results overlapped 1. These results could only be interpreted as that epithelial Cav-1 expression is not qualified to be a good biomarker to predict the prognosis of breast cancer. However, the combined HRs of stromal Cav-1 expression for OS and DFS/PFS was significantly greater than two which suggested that loss of stromal Cav-1 indicated an adverse prognosis in breast cancer. These articles [59, 60] considered that Cav-1 expression in stromal cells might have a protective effect against tumor progression.

Despite the above two kinds of cancer, many studies [49, 51, 54, 58] have some different opinions on the prognostic role of Cav-1 in patients with liver cancer, which give rise to a combined HR spanning 1. We included 4 studies on liver cancer altogether comprising 3 on HCC as well as 1 on extrahepatic bile duct can-

cer (EBDC). In Murakami, S's studies [49], the multivariate Cox regression analysis of HR was 0.13 [0.04, 0.37] in contrast to the total outcome, suggesting that Cav-1 had an opposite prognostic significance on extrahepatic bile duct cancer, further studies on classified liver cancer were still needed. Among the studies centering on HCC, the 95% CI of YANG.S.F's study [54] overlapped 1, which showed that the Cav-1 had no prognostic significance on HCC. YANG.S.F's study only hammered at primary HCC with III&IV% 27.4 while the other 2 studies [51, 58] contained mixed tumors with III&IV% 60, which may indicated that Cav-1 expression could predict worse survival in patients especially with advanced HCC. Further studies could selectively analyze the prognostic role of epithelial Cav-1 in advanced HCC.

Furthermore, when referred to head and neck squamous cell carcinoma (HNSCC), the conclusions of 2 relevant studies [24, 40] both brought doubts to our total results. Shi L's study [46] about mucoepidermoid carcinoma of the salivary glands provided HR (95% CI) for DFS as 1.063 [0.342, 3.304] and the HR (95% CI) in Du ZM's study [24] on nasopharyngeal carcinoma for CSS was 1.701 [0.984, 2.940]. Additionally, the HR (95% CI) of M Suzuoki's study [37] about pancreatic carcinoma for OS stepped astride 1. Neither of above 3 studies presented significant prognostic value of Cav-1, which might indicate that the prediction function of Cav-1 varies in different kinds of HNSCC.

Many researchers reported that Cav-1 could facilitate the proliferation and metastasis of tumor cells recently. Lin 's studies [61] revealed that the expression of Cav-1 (P132L) improved the invasiveness and resistance of tumor cells. Besides, it is confirmed that phosphorylation of serine/threonine in Cav-1 could boost viability of tumors which are autocrine or paracrine and repress the anti-tumor aspect of Cav-1. Hayashi [62] considered that Caveolin-1 132nd codon mutations also made main contributions to metastasis and invasiveness of tumor cells. Furthermore, Cav-1 held back cell apoptosis which may facilitate tumor occurrence too. In spite of these studies, Cav-1 was also covered to suppress tumor growth by inhibiting the activity of VEGFR-2 and restraining Ras2p42/44 MARK signal pathway [63]. In recent years, there existed some researches concentrating upon the value of stromal Cav-1 on breast can-

cer, prostate cancer. Unlike in epithelial tumor tissue, Cav-1 suggested an adverse prognostic value in tumor stromal and many researchers have given their opinions on the mechanism. Sloan and colleagues [39] hypothesized that stromal Cav-1 modulated paracrine signaling with tumor cells, leading to a permissive environment for tumor cell proliferation, migration, and local invasion. Sotgia [64] hold the opinion that loss of Cav-1 induced the lethal metabolic reprogramming of the tumor microenvironment by favoring stromal aerobic glycolysis and autophagy. Loss of stromal caveolin-1 is associated with early tumor recurrence, metastasis, and drug resistance, which could lead to poor clinical outcomes. Anyhow, the mechanism by which stromal Cav-1 suppressed cancer progression remained to be discussed.

At the same time, this meta-analysis has some limitations. First and foremost, the statistics of some studies were obtained from calculation based on the Kaplan-Meier survival curve instead of the given data. Tierney has proven the method not perfect [14]. And we deliberated the statistics of every article intensively in order to find unreasonable results to rule out. Secondly, we used the software designed by Matthew Sydes and Jayne Tierney to calculate the logHR and SE which retained only percentile. At the same time, we verified the data again by STATA 11.0, only minimal bias was observed. Thirdly, when we analyzed every kind of cancer separately so as to explore their prognostic value meticulously, we thought the number of prognostic studies dealing with several types of cancers, such as osteosarcoma and pancreatic carcinoma, was not enough. More studies were need in the future to confirm the prognostic role of Cav-1. Fourthly, the cut-off value of Cav-1 expression could not reach an agreement. Lack of abundant Cav-1 expression data in global population makes it difficult to set a standard cut-off value. As the subgroup results set by cut-off value were consistent with the comprehensive result, it did not have significant influence on the whole study.

The publication bias was a major concern for all forms of meta-analysis. Positive results tend to be accepted by journals, while negative results are often rejected. Therefore, we conducted analyses for publication bias using Begg's method. Results showed no statistically signifi-

cant publication bias was found in the analysis of outcomes for OS and DFS/ PFS/ RFS, whereas the publication bias for CSS could not reach an ideal value. Three articles contributed to the publication bias consisting of Cho DS's study, Joo HJ's study and Savage K's study [23, 29, 43]. After excluding these statistics, the adjusted publish bias was 0.10.

In conclusion, this meta-analysis suggested that elevated Cav-1 could predict poor survival outcomes of various cancers, including genitourinary cancer, gastrointestinal cancer, lung cancer, brain cancer and osteosarcoma, which could be used to identify the high-risk patients earlier and guide the clinical decision. Some other tumors with weak predictive value such as breast cancer, liver cancer, head and neck cancer, pancreatic cancer need to be further investigated. All these results should be confirmed by multi-center designed prospective studies in the future.

Disclosure of conflict of interest

None.

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