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Original Article

Prognostic value of caveolin-1 in genitourinary cancer: a meta-analysis

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Abstract: We aimed to obtain the most comprehensive picture to date of the prognostic value of caveolin-1 (Cav-1) in genitourinary carcinoma by meta-analyzing all eligible studies in PubMed and EMBASE. Data on patient clinical characteristics, cancer-specific survival (CSS) and recurrence-free survival (RFS) were extracted. The meta-analysis included 6 articles on prostate cancer, 5 on renal cancer, 1 on bladder cancer and 1 on transition cell carcinoma of the upper urinary tract. Two studies examining the association of ELISA-measured Cav-1 levels in serum with RFS in 621 patients with prostate cancer gave a combined hazard ratio (HR) of 1.25 (95% CI 0.36 to 4.36). The other 4 studies on prostate cancer examined the association of immunohistochemically determined Cav-1 levels in cancerous tissue with RFS and gave a combined HR of 1.83 (95% CI 1.36 to 2.47). Three studies on renal cancer examining the association of Cav-1 levels with CSS gave a multivariate HR of 1.98 (95% CI 1.35 to 2.90). The single studies on bladder carcinoma and upper urinary tract carcinoma gave, respectively, a multivariate HR of 2.28 (95% CI 1.09 to 4.74) for the relationship of Cav-1 levels to DFS, and a multivariate HR of 5.08 (95% CI 1.799 to 14.342) for the relationship of Cav-1 levels to CSS. This meta-analysis of available evidence suggests that elevated Cav-1 levels in serum can predict poor survival in patients with genitourinary cancer, which may help identify high-risk patients earlier and guide clinical decision-making.

Keywords: Genitourinary cancer, prognosis, caveolin-1, meta-analysis

Introduction

Genitourinary cancers, which include carcinoma of kidneys, bladder and prostate, as well as cancers of the testicles, urinary tract, and penis, take a large toll on human health and on health care systems. In fact, renal cell carcinoma (RCC) accounts for approximately 2% of all types of cancers, which is growing annually at 1.5-5.9% around the world [1]. In 2008 alone, an estimated 386,300 new cases of bladder cancer and 150,200 deaths from bladder cancer occurred globally. Prostate cancer ranks as the leading genitourinary cancer in the USA, followed by bladder and kidney cancer; it is the second most frequently diagnosed cancer and the sixth leading cause of cancer death among males. In 2008, prostate cancer accounted for 903,500 (14%) of all new cancer cases and 258,400 (6%) of all cancer deaths in males around the world [2].

Carcinomas of the testicles, urinary tract, or penis are relatively less common. Nevertheless, testicular cancer accounts for 1% of malignancies in men and is considered the most common cancer in young men in Western populations. Although the incidence of testicular cancer is increasing globally, mortality rates remain low and most patients are cured [3].

Caveolin (Cav-1) is a transmembrane protein that forms specialized lipid rafts in the plasma membrane of mesenchymal cells such as adipocytes, endothelial cells, and fibroblasts [4]. It has been implicated in a number of human diseases including diabetes, atherosclerosis, restrictive lung disease, pulmonary fibrosis,

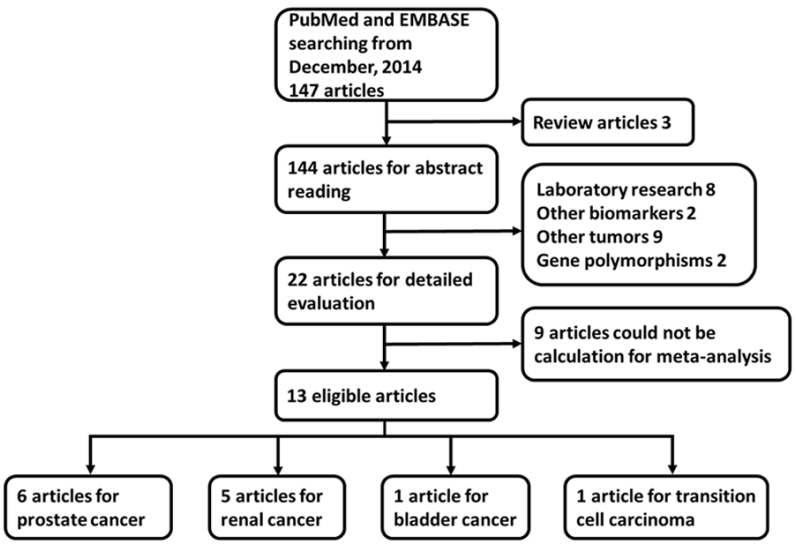

Figure 1. Flow chart of study selection and meta-analysis.

cardiomyopathy, and muscular dystrophy [5]. Cav-1 has recently been shown to play an important role in the tumorigenesis and metastasis of certain cancers, including cancers of the renal cells [6], prostate [7], lung [8], and esophageal squamous cells [9]. This molecule is postulated to support these cancer processes because its caveolin scaffold domain binds proteins containing a caveolin-binding domain (CBD), such as the Rho-GTPases. These GTPases are important regulators of $p130^{Cas}$, which is crucial for both normal cell migration and Src kinase-mediated metastasis [10]. In this way, Cav-1 mediates endo- and transcytosis of molecules attached to the cell surface and organizes signaling proteins involved in tumor cell proliferation, adhesion, and migration, among numerous other biological processes [11]. Thus higher serum levels of Cav-1 have been predicted to increase risk of onset or metastasis of certain cancers.

The implication of Cav-1 in numerous oncogenic processes led investigators to examine its prognostic value for cancer patients. Elevated serum levels of the protein show significant correlation with poor prognosis in patients with breast cancer [12], hepatic cancer [13], or lung cancer [14, 15]. Various studies have reported that serum levels of Cav-1 predict prognosis in patients with genitourinary carcinoma, whereas at least one study has concluded that this marker has no prognostic value [16].

To help resolve this controversy, we systematically reviewed and meta-analyzed the literature on the ability of serum or tissue levels of Cav-1 to predict the clinical outcomes of patients with genitourinary cancer.

Materials and methods

Search strategy

PubMed and EMBASE were searched for the last time on December, 2014 using the search terms "genitourinary cancer" OR "urogenital cancer" AND "caveolin-1" AND "prognosis". In subsequent searches, the term "genitourinary cancer" was replaced with "renal cell carcinoma", "bladder cancer", "prostate cancer", "testicular carcinoma", "penis cancer" or "carcinoma of urinary tract". We combined the search results and removed duplicates in order to obtain an initial set of potentially eligible studies.

Study inclusion/exclusion criteria

Studies were considered eligible if they met all the following inclusion criteria: (i) patients showed any manifestation of genitourinary cancer; (ii) researchers measured the expression of Cav-1 in serum or tissue, and (iii) the study investigated the association between Cav-1 levels and either clinical variables or survival outcomes [overall survival (OS), cancer-specific survival (CSS), progression-free survival (PFS), recurrence-free survival (RFS) or disease-free survival (DFS)]. Studies were excluded if they (i) were review articles, basic laboratory studies or letters to the editor; (ii) described the association of survival outcomes with other types of tumors or markers; or (iii) failed to report sufficient data to calculate desired meta-analysis outcomes using methods developed by Parmar [17], Williamson [18], and Tierney [19].

Data extraction

Articles were assessed independently by two authors for possible inclusion, and disagree-

Table 1. Characteristics of all studies included in our systematic review and meta-analysis

Author	Year	Study site	Study design	N	No. (%) positive	disease	No. males	Age, yr (range)
Langeberg WJ	2010	USA	R	202	-	PC	202	median 57 (35-64)
Tahir SA	2006	USA	R	419	120	PC	419	mean 62.6 (42.6-78.9)
Karam JA	2007	USA	P	232	70	PC	232	median 62.6
Satoh T	2003	Japan	P	152	46 (30.3)	PC	152	mean 64.3, median 64.5 (49-74)
Yang G	1999	USA	P	189	47 (25)	PC	189	mean 63 (43-78)
Yang G	2005	USA	P	104	21	PC	104	mean 64.2 (49.6-78.5)
Campbell L	2003	UK	P	114	21	RCC	76	median 63.6 (33-84)
Campbell L	2008	UK	P	174	28	RCC	119	median 65 (34-88)
Joo HJ	2004	South Korea	P	67	34	RCC	53	mean 54.5 (33-81)
Phuoc NB	2007	Japan	P	119	66	RCC	78	median 61 (23-86)
Sandra Steffens	2011	Germany	P	289	57	RCC	159	median 60.4
Ruan Jiang	2010	China	P	85	34 (40)	BC	64	mean 57 (39-81)
Cho DS	2008	South Korea	P	98	9	TCC-UUT	76	mean 61.7 (33-85)

Author	Sample type	Follow up, mo. (range)	Assay type	Cut-off	Survival outcome	Kaplan-Meier survival curves	Uni- or multivariate
Langeberg WJ	serum	144	ELISA	0.13 ng/ml	RFS	yes	uni
Tahir SA	serum	mean 52, median 48	ELISA	0.13 ng/ml	RFS	yes	both
Karam JA	tissue	120	IHC	50%	RFS	yes	both
Satoh T	tissue	median 48.2 (1.3-103.3)	IHC	50%	RFS	yes	uni
Yang G	tissue	60	IHC	50%	RFS	yes	multi
Yang G	tissue	mean 62.7 (0.5-144.9)	IHC	50%	RFS	yes	both
Campbell L	tissue	median 44 (1-99)	IHC	-	DFS	yes	multi
Campbell L	tissue	median 44 (1-99)	IHC	-	DFS	yes	multi
Joo HJ	tissue	median 46 (12-91)	IHC	25%	CSS	yes	multi
Phuoc NB	tissue	median 69.3 (3.6-215.2)	IHC	50%	DFS	yes	multi
Sandra Steffens	tissue	median 80.5 (24.5-131.7)	IHC	5%	CSS	yes	multi
Ruan Jiang	tissue	median 45 (36-60)	IHC	5%	DFS	yes	multi
Cho DS	tissue	-----[a]	IHC	10%	CSS	yes	multi

Abbreviations: BC, bladder cancer; CSS, cancer-specific survival; DFS, disease-free survival; ELISA, enzyme-linked immunosorbent assay; IHC, immunohistochemistry; PC, prostate cancer; RCC, renal cell carcinoma; RFS, recurrence-free survival; TCC-UUT, transitional cell carcinoma of the upper urinary tract. [a]70 patients were disease-free at a median follow-up of 52.5 months (range, 12-162 months). The other 28 patients developed metastases at a median of 28 months (range, 4-86 months).

ments were resolved by consensus. The same two authors independently extracted data on hazard ratios (HRs) and 95% confidence intervals (CIs), *p* values, and Kaplan-Meier survival curves. They also extracted data on first author, publication year, study design, study size, ethnicity of study population, patient age and gender, TNM stage, diagnosis, method used to assay Cav-1, definition (threshold) of Cav-1 positivity, conclusions and other clinical characteristics.

Statistical methods

All calculations and data manipulations were performed using RevMan 5.1 (Cochrane Collaboration, Oxford, UK). Survival data were log-transformed and pooled results were expressed in terms of the log (HR) and standard error of the log (HR). Since most studies in our meta-analysis did not report these values directly, we used available data to calculate them according to the methods developed by Parmar [17], Williamson [18], and Tierney [19]. We then meta-analyzed data for OS, CSS, PFS, RFS or DFS using software designed by Matthew Sydes and Jayne Tierney of the Medical Research Council Clinical Trials Unit, London, UK [19].

Forrest plots were used to meta-analyze the association between Cav-1 levels and survival outcomes, as well as the association between Cav-1 levels and clinical variables. Heterogeneity was defined as $P<0.10$ or $I^2>50\%$. When homogeneity was adequate ($P\leq50\%$. $Wh^2\leq50\%$. When homogeneity was adequate (z fixed-effects model. Otherwise, data were meta-analyzed using a random-effects model [20]. A pooled HR >1 indicated poorer survival for patients with higher levels of Cav-1, and it was considered statistically significant if the corresponding 95% CI did not include 1.

The Begg's test was performed and funnel plots were generated in STATA 11.0 (STATA Corp., College Station, USA) to assess the potential publication bias; $P>0.05$ was interpreted to indicate the absence of significant publication bias [21].

Results

Characteristics of included studies

We initially identified 147 potentially eligible publications in PubMed and EMBASE, and we eliminated 101 after determining from the titles and abstracts that they did not focus on our research question. Of the remaining 46 studies, 9 were excluded because they analyzed tumors other than genitourinary ones; 2, because they examined markers other than Cav-1; 3, because they were review articles; 8, because they were basic laboratory studies; and 2, because they examined genetic polymorphisms. This left 22 potentially relevant studies that were read in full. After full-text review, 9 studies were excluded because they reported insufficient data to meta-analyze desired outcomes, leaving 13 studies in the final meta-analysis [6, 16, 22-32] (**Figure 1**).

The 13 eligible studies were published between 1999 and 2011 and they included 2,244 patients with a median of 152 patients per study (range, 67-419). Some data were duplicated between two studies [23, 29], so they were extracted only once in the meta-analysis. Patient clinical characteristics and other useful information are summarized in **Table 1**.

The final set of publications included 6 studies on prostate cancer [16, 22, 24-27], 5 on RCC [6, 23, 28, 29, 32], 1 on bladder cancer [31] and 1 on transition cell carcinoma of the upper urinary tract [30]. Two of the included publications on prostate cancer involved a similar team of investigators [22, 25] but they involved different study populations, so they were both included in the meta-analysis. We were unable to identify any eligible studies investigating the prognostic value of Cav-1 levels in testicular carcinoma, penis cancer, or other types of genitourinary carcinoma.

Survival outcomes reported in the included studies

All studies on prostate cancer (n=1298) examined survival in terms of RFS. Of the 5 studies on RCC (n=763), two reported survival in terms of DFS [23, 29], 2 in terms of CSS [6, 32] and 1 in terms of DSS [28]. Since CSS and DSS are equivalent in our case, we meta-analyzed all these data as CSS (**Table 1**). The one eligible study on bladder cancer [31] (n=85) examined survival in terms of DFS and the one study on upper urinary tract carcinoma [30] (n=98) reported survival in terms of CSS.

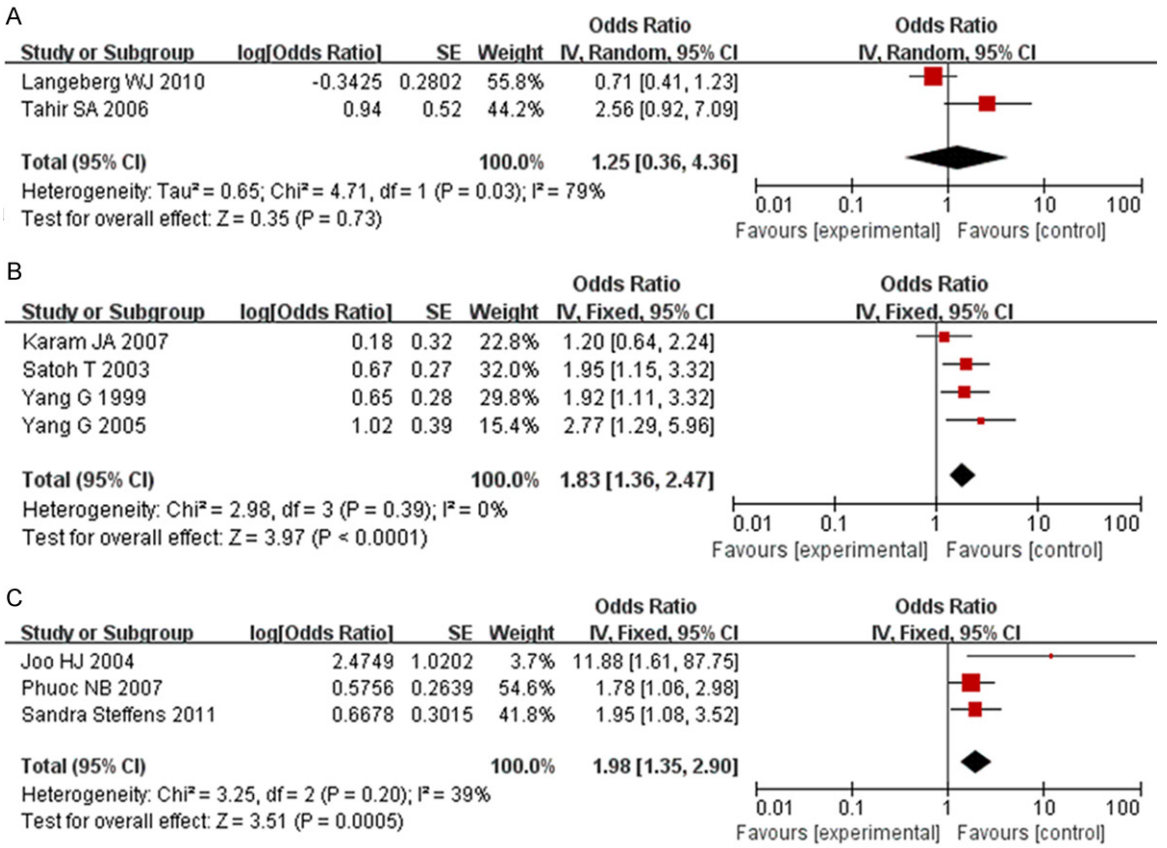

Figure 2. (A, B): Meta-analysis of studies assessing the relationship of levels of caveolin-1 in tissue (A) and serum (B) with recurrence-free survival of prostate cancer patients. (C): Meta-analysis of studies assessing the relationship of caveolin-1 levels in xxx with cancer-specific survival of patients with renal cell carcinoma. HR >1 indicates an association between higher caveolin-1 level and poorer survival. HRs were estimated using a DerSimonian and Laird random-effects model.

Correlation between Cav-1 levels and survival

All studies on prostate cancer examined the possible correlation of Cav-1 levels with RFS. To analyze their data in detail, we performed subgroup analysis based on whether Cav-1 was assayed in serum using enzyme-linked immunosorbent assay (ELISA) or cancer tissue using immunohistochemistry (IHC). Two studies used ELISA to assay Cav-1 in serum [16, 26]; the pooled HR relating Cav-1 levels to RFS was 1.25 (95% CI 0.36 to 4.36) (**Figure 2A**). The remaining 4 studies used IHC to examine Cav-1 levels in cancer tissue [22, 24, 25, 27]; the pooled HR was 1.83 (95% CI 1.36 to 2.47) (**Figure 2B**). These results suggest that higher Cav-1 levels can predict shorter RFS in prostate cancer, at least in the case of Cav-1 assays based on IHC of tumor tissue.

Meta-analysis of 3 studies on RCC [6, 28, 32] gave a multivariate HR relating Cav-1 levels to CSS of 1.98 (95% CI 1.35 to 2.90) (**Figure 2C**). This analysis suggests that higher Cav-1 levels predict shorter CSS in patients with RCC.

Data from the one study on bladder cancer [31] gave a multivariate HR relating Cav-1 levels to DFS of 2.28 (95% CI 1.09 to 4.74). Data from the one study on upper urinary tract carcinoma [30] gave a multivariate HR relating Cav-1 levels to CSS of 5.08 (95% CI 1.799 to 14.342). This analysis suggests that higher Cav-1 levels predict shorter DFS or CSS in patients with transitional cell carcinoma.

Assessment of publication bias

The likelihood of publication bias was assessed by applying Begg's test and generating funnel plots. No significant publication bias appeared in the meta-analysis of Cav-1 levels and RFS in prostate cancer (P=0.851) (**Figure 3A**), or in the

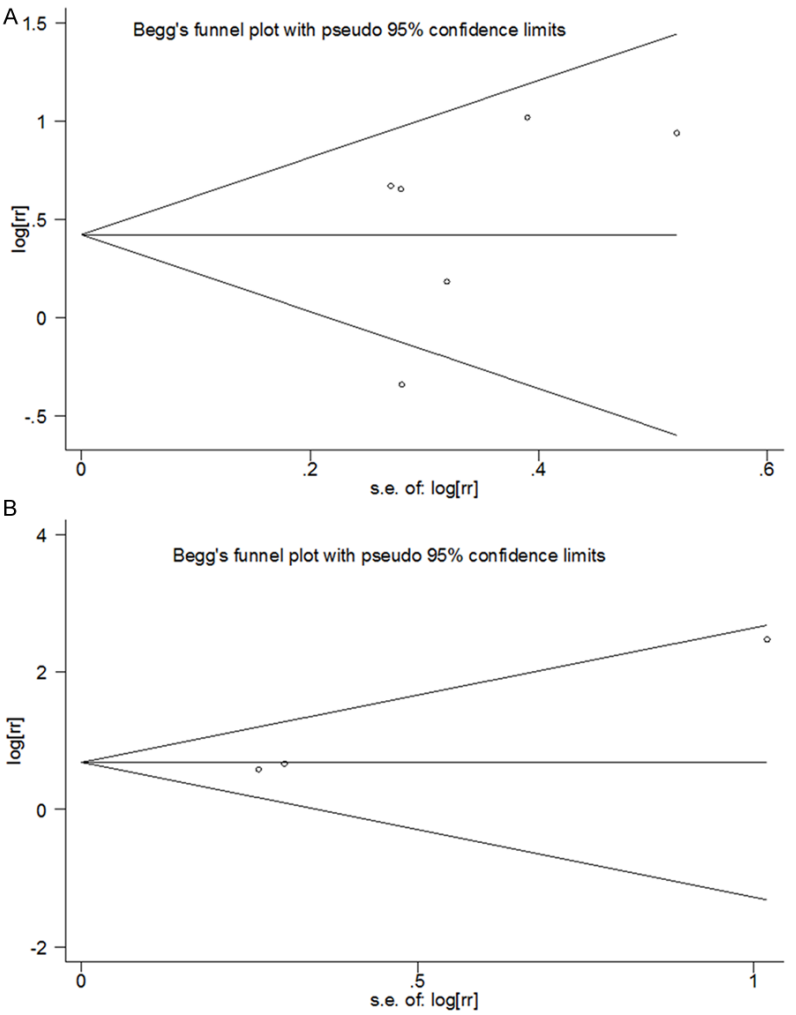

Figure 3. Begg's funnel plots to assess bias among studies in the meta-analysis of caveolin-1 levels and (A) recurrence-free survival in patients with prostate cancer or (B) cancer-specific survival in patients with renal cell carcinoma.

meta-analysis of Cav-1 levels and CSS in renal cell carcinoma (P=0.117) (**Figure 3B**).

Discussion

For the past decade, Cav-1 has been considered a potential biomarker for cancer prognosis because its expression is upregulated in numerous types of cancer, including genitourinary carcinoma [33]. However, studies on the prognostic value of Cav-1 levels for patients with genitourinary cancer have given conflicting results, leading us to conduct what we believe to be the first meta-analysis of this question. Our findings suggest that higher Cav-1 levels in serum or cancer tissue may predict worse survival in patients with various types of genitourinary cancer.

Our data further suggest that at least in the case of prostate cancer, the assay format can make a difference. When Cav-1 levels were assayed in serum using ELISA, the measurements did not show a significant association with survival. However, when Cav-1 levels were assessed in tumor tissue using IHC, a significant association did emerge between higher Cav-1 expression and shorter survival. Nearly all studies in our meta-analysis analyzing other types of genitourinary cancer relied on IHC to measure Cav-1 levels in tumor tissue, suggesting that this approach may be more reliable and effective than current ELISA-based approaches.

Despite the predominance of ICH-based assays to measure Cav-1 levels in the studies in our meta-analysis, circulating biomarkers are usually much more desirable than tissue markers because they can be monitored easily and non-invasively before surgery and afterwards. Our findings highlight the need to improve existing ELISA-based methods to measure Cav-1 levels in order to improve the prognostic value.

Our finding that Cav-1 levels can predict prognosis of patients with prostate cancer is consistent with laboratory studies suggesting that Cav-1 has oncogenic activity in prostate cancer cells. Overexpression of Cav-1 in prostate cancer cells increased binding of that protein to the serine/threonine phosphatases PP1 and PP2A, inhibiting their activity so that levels of phospho-Akt remained high, causing sustained activation of downstream oncogenic Akt targets [34] that promote the growth, survival and progression of prostate cancer cells [35]. Cav-1 in lipid rafts co-localizes with the oncogenic tyro-

sine kinase Src and an Akt-regulated metabolic oncogene encoding a fatty acid synthase [36]. In prostate cancer, Cav-1 participates in Src- and Rho/ROCK-dependent regulation of tumor cell motility and invasion [37]. Cav-1 may also potentiate the PI3-K/Akt signaling pathway to promote the production and release of VEGF-A in prostate cancer cells and thereby stimulate tumor angiogenesis [38].

If we take RR"_ENREF_38" \o "Li, 2009 #53" signaling pathway to [39], then the multivariate pooled HR relating high Cav-1 levels and shorter CSS of 1.98 (95% CI 1.46 to 2.80) is near this threshold, suggesting that assaying Cav-1 levels holds potential for predicting prognosis of RCC patients in the clinic. In renal carcinoma cells, Cav-1 enhances secretion of VEGF-A, thereby stimulating angiogenesis [38]. In addition, Cav-1 interacts with phospho-ERK-1/2 to promote tumor survival and growth, facilitating metastasis and early relapse [40].

Our findings that high Cav-1 levels can predict poor survival in patients with bladder cancer or upper urinary tract carcinoma should be interpreted cautiously because they are based on only one study for each cancer type [30, 31]. Cav-1 and Src expression in human bladder cancer cells show a surprising inverse correlation, which may relate to the fact that Cav-1 is a substrate of Src [41]. Depleting Cav-1 or overexpressing active Src in UMUC-3 metastatic bladder cancer cells decreases their migration and metastasis; conversely, overexpressing Cav-1 or depleting Src increases the migration of RT4 non-metastatic bladder cancer cells [42].

The findings of our meta-analysis should be interpreted carefully given the relatively small numbers of studies that we identified for each type of genitourinary cancer. In fact, we were able to analyze in detail results only for prostate cancer and RCC. Even these analyses were problematic because although studies on prostate cancer shared a detection threshold of 50% for measuring Cav-1 levels, detection thresholds varied in studies on RCC. In addition, studies differed in whether they performed Cav-1 IHC on stromal or epithelial tissue. In fact, the majority of IHC-based studies in our meta-analysis examined epithelial tissue, but similar experiments to measure Cav-1 levels in other types of tumors typically rely on stromal tissue. Future studies should examine whether stromal or epithelial tissue provides Cav-1 measurements with greater prognostic value. The answer may lie in the combination of both: in breast cancer, assaying Cav-1 in both stromal and epithelial tissues provides better predictive value than assaying either type of tissue on its own [12].

Another limitation of our meta-analysis is that several studies did not report survival data directly, forcing us to back-calculate it from Kaplan-Meier survival curves, which can over- or underestimate actual survival [17]. We also cannot exclude publication bias from our review, especially since we searched only two literature databases and meta-analyzed only studies in English. Nevertheless, Begg's funnel plot analyses suggest a low risk of bias.

In conclusion, this meta-analysis suggests that elevated Cav-1 levels can predict poor survival in patients with genitourinary cancer, which may help identify patients at high risk of poor outcomes and guide clinical decision-making. These findings should be confirmed in adequately designed, prospective, multi-center studies.

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Declaration of conflict of interest

None.

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