RESEARCH ARTICLE

Prognostic Value of Caveolin-1 Expression in Gastric Cancer: a Meta-analysis

Yang Ye[1,3&*], Shu-Han Miao[2,3&], Rong-Zhu Lu[1,4], Jian-Wei Zhou[3]

Abstract

The relationship between caveolin-1 (Cav-1) and clinicopathological characteristics of gastric cancer is controversial, although Cav-1 plays an important role in tumor metastasis. To evaluate the clinicopathological and prognostic value of expression in patients with gastric cancer, a meta-analysis was performed to investigate the impact on clinicopathological parameters and prognosis in gastric cancer cases. Studies assessing these parameters for Cav-1 in gastric cancer were identified up to June 2014. Finally, a total of six studies met the inclusion criteria. Our combined results showed that Cav-1 expression was significantly associated with the Lauren classification (pooled OR=0.603, 95% CI: 0.381-0.953, *P*=0.030). Furthermore, we found that Cav-1 expression predicted a better overall survival in gastric cancer patients (pooled OR=0.590, 95% CI: 0.360-0.970, *P*=0.038, fixed-effect). In conclusion, the overall data of the present meta analysis showed that Cav-1 expression was not correlated with clinicopathological features except for the Lauren classification. Simultaneously, Cav-1 overexpression predicted a better overall survival in gastric cancer. Cav-1 expression in tumors is a candidate positive prognostic biomarker for gastric cancer patients.

Keywords: Cav-1 - gastric cancer - clinicopathological characteristics - prognosis

Asian Pac J Cancer Prev, **15 (19)**, 8367-8370

Introduction

Gastric cancer is one of the most common malignancies and remains the second leading cause of cancer related mortality worldwide (Li et al., 2012). Despite recent advances in medical treatment and surgical techniques, the five-year survival rate for gastric cancer patients unfortunately remains poor. Biological prognostic markers in early stages of gastric cancer would have great clinical value.

Caveolin-1 (Cav-1) is mainly expressed by adipocytes, fibroblasts, and endothelial and smooth muscle cells (Scherer et al., 1997). It is involved in signal transduction and transmembrane transport processes (Anderson et al., 1992). In cancers, ambivalent roles of Cav-1 in the pathogenesis have been reported. Cav-1 down-regulation has been found in tumors such as lung, ovarian, mammary carcinomas and mesenchymal sarcomas (Wiechen et al., 2001), whereas its over-expression has been reported in cancers of the prostate, esophagus, bladder and kidney (Williams and Lisanti, 2005; Goetz et al., 2008). Cav-1 amplification is frequently down-regulated in gastric cancer and is associated with better prognosis (He et al., 2012), but recently studies show that high Cav-1 levels predict poor outcome in gastric cancer (Nam et al., 2013). Based on the fact that clinical values of Cav-1 in gastric cancer remain not entirely clear, the present meta-analysis was conducted to provide a better estimation of any association.

Materials and Methods

Publication search

We searched PubMed and CNKI (China National Knowledge Infrastructure) for all articles on the correlation of clinicopathological characteristics and prognosis with Cav-1 expression in gastric cancer to be included in this study up to June 2, 2014. The following key words were used: "gastric cancer" or "gastric caicinoma", "caveolin-1" or "Cav-1". Reference lists of the identified articles were also examined and the literature retrieval was performed in duplication by two independent reviewers (Ye and Miao).

The following criteria were used to include published studies: (1) The search was conducted without restriction on language, but limited to human subjects; (2) The association between Cav-1 expression and clinicopathological parameters or/and survival were assessed. We excluded papers did not meet all inclusion criteria.

*[1]Department of Preventive Medicine, [4]Department of Public Health Laboratory Science, School of Medicine, Jiangsu University, [2]Department of Health Care, the Fourth Affiliated Hospital of Jiangsu University, [3]Department of Molecular Cell Biology and Toxicology, Cancer Center, School of Public Health, Nanjing Medical University, Nanjing, China [&]Equal contributors *For correspondence: jamesnone@163.com*

Data extraction

The following characteristics were extracted from eligible studies: first author's name, name of journal, publication year, population, test method, age, gender, Lauren classification, depth of invasion, lymph node metastasis, TNM-stage and overall survival. We used the software GetData Graph Digitizer 2.24 (http://getdata-graph-digitizer.com/) to digitize and extract the data from Kaplan-Meier curve in the eligible papers.

Statistical analysis

The pooled estimates of odds ratios (OR) and 95% confidence intervals (CI) were performed to estimate the correlation of Cav-1 expression and the clinical features, including age, gender, Lauren classification, Depth of invasion, Lymph node metastasis, TNM stage and overall survival. Heterogeneity assumption was made with the chi-squared based Q-test (P>0.10) and I^2 (I^2<50%, no heterogeneity), ORs were pooled according to fixed-effects model. Otherwise, the random-effects model was used. A diagnosis of publication bias were provided by Egger test and inverted funnel plots. The significance of the intercept was assessed by the t-test with a significance level of 0.05 suggested by Egger. All statistical tests were conducted with Stata/SE 10.0 for Windows (Stata Corporation, College Station, TX, USA).

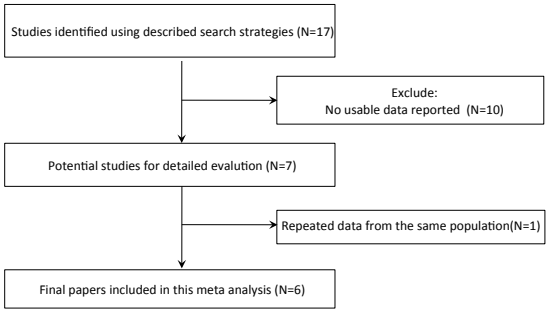

Figure 1. Flow Chart for Selection of Studies for Inclusion in this Meta-Analysis

Results

Description of studies

At the beginning, 17 records were examined according to the search strate¬gies. Next, 10 articles were excluded because of the insufficient correlation data of Cav-1 with clinicopathological parameters and/or overall survival. 1 record was eliminated data of the repeated data from the same population. Thus, a total of 6 papers met the inclusion criteria for the present meta-analysis (Gao et al., 2005; Barresi et al., 2008; He et al., 2012; Sun et al., 2012; Nam et al., 2013; Zhao et al., 2013) (Figure 1). We

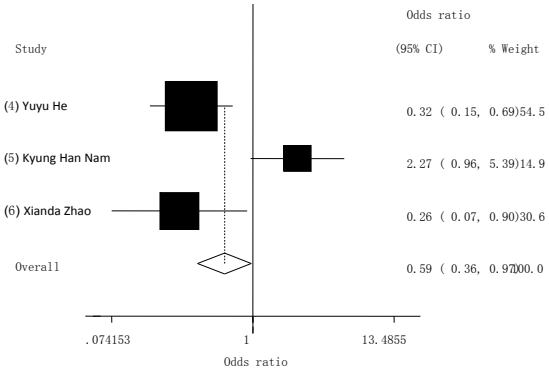

Figure 2. Forest Plot Showed that the Cav-1 Expression wasAssociated with Overall Survival of Gastric Cancer

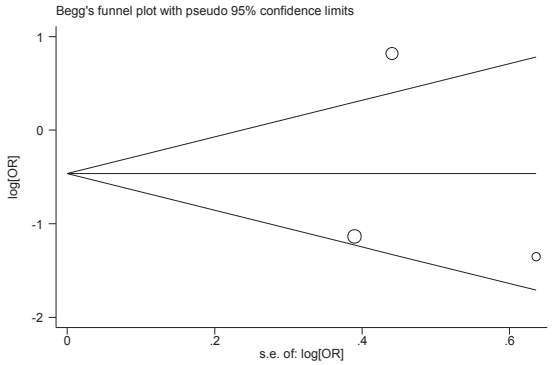

Figure 3. Begg's Funnel Plot Estimated The Publication Bias of the Included Literature

Table 1. Main Characteristics and Results of the Eligible Studies

No. of paper	First author	Journal	Year	Population	methods	Number of patients
1	Xue Gao	Chinese Journal of Cancer	2005	China	IHC	56
2	V. Barresi	Virchows Arch	2008	Italy	IHC	49
3	Guoyang Sun	Chin J Cancer Res	2012	China	IHC	58
4	Yuyu He	International Journal of Molecular Sciences	2012	China	IHC	118
5	Kyung Han Nam	Pathobiology	2013	Korea	IHC	405
6	Xianda Zhao	PLoS ONE	2013	China	IHC	286

Abbreviations: IHC, immunohistochemistry.

Table 2. Main Results for Meta-Analysis between Cav-1 and Clinicopathological

Clinical parameters	No. of studies	overall OR (95%CI)	Heterogeneity test (Q, I^2, P)
Age (<60 *vs*. ≥60)	(2), (3), (4), (5), (6)	0.721 (0.473-1.097)	1.53, 0.0%, 0.127 (fixed-effect)
Gender (male vs. female)	(2), (3), (4), (5), (6)	0.994 (0.628-1.572)	6.32, 36.8%, 0.978 (fixed-effect)
Lauren classification (Diffuse-type *vs*. Intestinal-type)	(1), (2), (4), (5), (6)	0.603 (0.381-0.953)	7.36, 45.6%, 0.030 (fixed-effect)
Depth of invasion (T1+T2 *vs*. T3+T4)	(2), (3), (4), (6)	1.124 (0.683-1.851)	10.99, 72.7%, 0.646 (fixed-effect)
Lymph node metastasis (Yes *vs*. No)	(1), (3), (4) , (5), (6)	0.960 (0.630- 1.463)	15.63, 74.4%, 0.850 (fixed-effect)
TNM stage (I+II vs. III+IV)	(3), (4) , (5), (6)	1.108 (0.717-1.712)	15.25, 80.3%, 0.643 (fixed-effect)

Abbreviations: OR, odds ratios

used the different extracted clinicopathological features to assess the correlation with Cav-1 expression. The sample sizes ranged from 49 to 405 patients of all the papers. Of these studies, expression of Cav-1 was evaluated by immunohistochemistry (IHC). The detail of all the studies included in the meta-analysis were summarized in Table 1.

Association between Cav-1 expression and clinicopathological parameters

As Table 2, the meta-analysis was preformed only when the extracted date of the correlation of Cav-1 expression and clinical features exceeded 3 papers. In gastric cancer patients, there was no association between Cav-1 expression and clinicopathological characteristics such as age, gender, depth of invasion, lymph node metastasis and TNM stage. However, Cav-1 expression was correlated with Diffuse-type compared with Intestinal-type (pooled OR=0.603, 95%CI: 0.381-0.953, *P*=0.030)

Impact of Cav-1 expression on overall survival of gastric cancer

The different results obtained from previous eligible studies on the impact of Cav-1 expression on overall survival outcome. The accumulative overall survival rates of Cav-1-positive and Cav-1-negative gastric cancer patients were 70% (72/103) and 64% (453/706), respectively. The overall survival pooled OR was 0.590 (95% CI: 0.360-0.970, *P*=0.038, fixed-effect, Figure 2), with an I^2 of 85.2%.

Publication bias

Begg's funnel plot and Egger's test were performed to assess the publication bias of the literature (Figure 3). The results did not reveal any evidence of publication bias in the overall meta-analysis of all papers.

Discussion

To our best knowledge, this is the first meta-analysis demonstrating the prognostic role of Cav-1 for gastric cancer clinical outcome. Prognostic studies of gastric cancer biomarkers are great valuable as they assist in the improvement of prevention, diagnosis and treatment of malignancies (Bulanov, 2007). The presence of significant or non-significant studies regarding the importance of Cav-1 expression in gastric cancer made it necessary to perform a meta-analysis of the overall survival results.

Cav-1 is a suggested tumor suppressor gene involved in cell signalling (Syeed et al., 2012). Roles of Cav-1 protein in carcinoma development are compartment-dependent and tumor dependent (Williams and Lisanti, 2005; Sotgia et al., 2012). Moreover, Cav-1 can influence the inhibition of cytokine receptor through its scaffolding domain (Goetz et al., 2008), indicating the tumor suppressor role of Cav-1, whereas an opposing role of Cav-1 in tumorigenesis has been shown. Indeed, even if it may play a role of tumor suppressor by inhibiting the signalling transduction products of some proto-oncogenes (Razani et al., 2001), its tyrosine-14 phosphorylation leads to growth stimulation (Lee et al., 2000), demonstrating that Cav-1 may also make an effect as a pro-tumorigenic factor. In the prognosis of gastric cancer, it has been reported that Cav-1 expression may serve as a promising molecular biomarker recently (Gao et al., 2005; Barresi et al., 2008; He et al., 2012; Sun et al., 2012; Nam et al., 2013; Zhao et al., 2013). However, these results were controversial. Therefore, the present meta-analysis, is a quantitative method to analyze the relationship between Cav-1 expression and gastric cancer clinicopathological features and overall survival statistically.

Recent results show that Cav-1 is more frequently down-regulated in Diffuse-type than Intestinal-type gastric cancer patients (Gao et al., 2005; Barresi et al., 2008; He et al., 2012; Zhao et al., 2013), which is consistent with our meta-analysis. Though Cav-1 over-expression was documented to associate with Lymph node metastasis and TNM stage (Sun et al., 2012; Nam et al., 2013), here our results suggested that Cav-1 positive expression was not correlated with these clinicopathological features. Simultaneously, studies also demonstrate that Cav-1 amplification has ambivalent association with survival outcome in gastric cancer (He et al., 2012; Nam et al., 2013; Zhao et al., 2013), whereas our results concluded that high Cav-1 expression was a positive prognostic biomarker.

However, several limitations might be included in this meta-analysis. First, the number of cases and controls in included studies was limited, further well designed studies with large sample sizes are warranted to confirm our findings. Secondly, though no significant heterogeneity across study was detected in the present meta-analysis, potential heterogeneity could not be neglected. When the meta-regression and subgroup analysis were used to assess the sources of heterogeneity, the pooled results were not influenced though the heterogeneity was decreased, which suggested these data are stable.

In conclusion, the overall data of the present meta analysis showed that Cav-1 expression was not correlated with clinicopathological features except for Lauren classification. Simultaneously, Cav-1 overexpression predicted a better overall survival in gastric cancer. Therefore, Cav-1 may represent a novel biomarker for the prognosis of gastric cancer.

Acknowledgements

This work was supported by the Natural Science Foundation of Jiangsu Province (BK20140576), the Research Foundation for Advanced Talents of Jiangsu University (No. 14JDG044) and the open project of Key Lab of Modern Toxicology (NJMU), Ministry of Education (NMUMT201410).

References

Anderson RG, Kamen BA, Rothberg KG, et al (1992). Potocytosis: sequestration and transport of small molecules by caveolae. *Science*, **255**, 410-1.

Barresi V, Giuffre G, Vitarelli E, et al (2008). Caveolin-1 immuno-expression in human gastric cancer: histopathogenetic hypotheses. *Virchows Arch*, **453**, 571-8.

Bulanov D (2007). Gastric cancer - current state of the problem.

Part I. Epidemiology. Pathology. Classification. Staging. *Khirurgiia*, 48-59 (in Bulgarian).

Gao X, Sun Y, Huang L, et al (2005). Down-regulation of caveolin-1 in gastric carcinoma and its clinical biological significance. *Ai Zheng*, **24**, 311-6 (in Chinese).

Goetz JG, Lajoie P, Wiseman SM, et al (2008). Caveolin-1 in tumor progression: the good, the bad and the ugly. *Cancer Metastasis Rev*, **27**, 715-35.

He Y, Zhao X, Gao J, et al (2012). Quantum dots-based immunofluorescent imaging of stromal fibroblasts caveolin-1 and light chain 3B expression and identification of their clinical significance in human gastric cancer. *Int J Mol Sci*, **13**, 13764-80.

Lee H, Volonte D, Galbiati F, et al (2000). Constitutive and growth factor-regulated phosphorylation of caveolin-1 occurs at the same site (Tyr-14) *in vivo*: identification of a c-Src/Cav-1/Grb7 signaling cassette. *Mol Endocrinol*, **14**, 1750-75.

Li BR, Zhou GW, Bian Q, et al (2012). Lack of association between the hOGG1 Ser326Cys polymorphism and gastric cancer risk: a meta-analysis. *Asian Pac J Cancer Prev*, **13**, 1145-9.

Nam KH, Lee BL, Park JH, et al (2013). Caveolin 1 expression correlates with poor prognosis and focal adhesion kinase expression in gastric cancer. *Pathobiology*, **80**, 87-94.

Razani B, Engelman JA, Wang XB, et al (2001). Caveolin-1 null mice are viable but show evidence of hyperproliferative and vascular abnormalities. *J Biol Chem*, **276**, 38121-38.

Scherer PE, Lewis RY, Volonte D, et al (1997). Cell-type and tissue-specific expression of caveolin-2. Caveolins 1 and 2 co-localize and form a stable hetero-oligomeric complex *in vivo*. *J Biol Chem*, **272**, 29337-46.

Sotgia F, Martinez-Outschoorn UE, Howell A, et al (2012). Caveolin-1 and cancer metabolism in the tumor microenvironment: markers, models, and mechanisms. *Annu Rev Pathol*, **7**, 423-67.

Sun GY, Wu JX, Wu JS, et al (2012). Caveolin-1, E-cadherin and beta-catenin in gastric carcinoma, precancerous tissues and chronic non-atrophic gastritis. *Chin J Cancer Res*, **24**, 23-8.

Syeed N, Hussain F, Husain SA, et al (2012). 5'-CpG island promoter hypermethylation of the CAV-1 gene in breast cancer patients of Kashmir. *Asian Pac J Cancer Prev*, **13**, 371-5.

Wiechen K, Diatchenko L, Agoulnik A, et al (2001). Caveolin-1 is down-regulated in human ovarian carcinoma and acts as a candidate tumor suppressor gene. *Am J Pathol*, **159**, 1635-43.

Williams TM, Lisanti MP (2005). Caveolin-1 in oncogenic transformation, cancer, and metastasis. *Am J Physiol Cell Physiol*, **288**, 494-506.

Zhao X, He Y, Gao J, et al (2013). Caveolin-1 expression level in cancer associated fibroblasts predicts outcome in gastric cancer. *PLoS One*, **8**, 59102.