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Correlation of Caveolin-1 Expression with Prognosis in Patients with Gastric Cancer after Gastrectomy

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Keywords

Caveolin-1 · Prognosis · Gastric cancer · Immunohistochemistry

Summary

Background: Upregulation of caveolin-1 (Cav-1) expression is correlated with histopathological grade and poor prognosis in several human cancers. However, in gastric cancer, its clinical utility as a useful prognostic molecular marker remains unclear. **Methods:** The prognostic importance of Cav-1 expression was retrospectively analyzed by immunohistochemistry in 148 patients with gastric cancer who had undergone radical gastrectomy. **Results:** Cav-1 expression was positive in 23 (15.5%) patients and negative in 125 (84.5%) patients. Tumor location, tumor grade, lymph node involvement, pT stage, pTNM stage, and the presence of recurrence were found to be significantly associated with Cav-1 expression. The median disease-free survival (DFS) of patients with negative Cav-1 expression was significantly better than that of patients with positive Cav-1 expression (not reached vs. 10.2 months, $p < 0.001$). Moreover, patients with positive Cav-1 expression had a worse median overall survival (OS) compared to patients with negative Cav-1 expression (14.2 vs. 40.3 months, $p = 0.004$). In the multivariate analysis, Cav-1 expression (positive vs. negative) was an independent prognostic factor for DFS ($p < 0.001$, hazard ratio (HR) 2.58) and OS ($p = 0.031$, HR 1.87), as was lymph node metastasis. **Conclusion:** Our results suggest that positive Cav-1 expression is associated with progression and poor prognosis in gastric cancer patients after radical gastrectomy. Targeting Cav-1 would be a potential option for future gastric cancer treatment.

Introduction

Caveolae have an important role in cell physiology due to their involvement in the regulation of signaling functions [1–3]. These structures are rich in various signaling molecules and cell surface receptors. Caveolin proteins are the principle component of caveolae membranes and play an important role in caveolar function. The caveolin protein family is composed of 3 isoforms including caveolin-1 (Cav-1), caveolin-2, and caveolin-3 [4, 5]. Cav-1 comprises 178 amino acids and forms the major structural component of caveolae [6–8]. It is found in many mammalian cells such as adipocytes, endothelial cells, pneumocytes, fibroblasts, and smooth muscle cells [9, 10]. Cav-1 has an important role in tumorigenesis due to various functions such as gene regulation, membrane trafficking, and signal transduction [11–13]. Different roles of Cav-1 in cancer pathogenesis have been demonstrated depending on the cancer cell type. While Cav-1 suppresses tumorigenesis in some cancers, it also contributes to tumor progression under certain conditions. For example, while low expression of Cav-1 was found to be related to tumor progression in breast [14, 15] and pancreatic cancer [16], its overexpression was found to be correlated with tumor progression in lung [17], prostate [18], esophageal [19], and renal cell [20] cancer. However, in gastric cancer, the clinical utility of Cav-1 as a useful prognostic molecular marker remains unclear.

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Gastric cancer is one of the leading causes of global cancer mortality [21]. Unfortunately, 5-year survival is approximately 25% for gastric cancer patients despite recent advancements in medical treatment and surgical techniques [22]. While the detection of prognostic markers may enable us to evaluate the precise status of this disease and allow a more effective management, data about prognostic markers in gastric cancer are still limited.

Several studies have been conducted to reveal the relationship between clinicopathological features and prognosis of gastric cancer [23–28]. However, these have yielded conflicting results. The aim of our study was therefore to investigate Cav-1 expression in the tumor cells of gastric cancer patients who have undergone curative resection. Moreover, the correlation between Cav-1 expression and clinicopathological factors as well as disease-free survival (DFS) and overall survival (OS) was evaluated.

Patients and Methods

A total of 148 gastric cancer patients who were treated and followed up at the Department of Medical Oncology, Dr. Lutfi Kirdar Kartal Education and Research Hospital and Medipol University, Medical Faculty between 2006 and 2013 were included in the study. Clinical and pathological factors including age, sex, resection type, tumor location, histopathology, pT stage, tumor size, histological grade, lymph node involvement, presence of lymphatic vessel invasion, blood vessel invasion, perineural invasion, adjuvant chemotherapy, radiation therapy, response to therapy, and survival were obtained from the patients' medical records. Staging of the patients was performed according to available pathological, clinical, and radiological findings at the time of diagnosis using the 2010 7th edition of the American Joint Committee on Cancer (AJCC) system [29]. Eligibility criteria included histologically confirmed R0 resection of gastric cancer and a postoperative survival time of > 3 months. Patients with distant metastasis (M1) at diagnosis were excluded from the study.

A follow-up schedule was started after completion of treatment. During follow-up, medical histories and physical examinations were completed once every 3 months in the first 2 years, every 6 months for years 3–5, and annually after 5 years. During check-up, along with complete blood counts and biochemistry panels, tumor markers (carcinoembryonic antigen (CEA), cancer antigen 19-9 (CA 19-9)) were also evaluated. Chest X-rays and abdominal computed tomography (CT) scans were performed every 3 months in the first year, every 6 months in the second postoperative year, and annually thereafter for 5 years.

Histological tumor specimens were evaluated by 2 pathologists who are experts in gastrointestinal pathology and had no knowledge of previous pathological findings. Written informed consent was provided by the patients or their relatives. The study was approved by the local ethics committee of our hospital.

Evaluation of Cav-1 Expression

Sections of 3 μm were cut from paraffin blocks and deparaffinized at 60°C. The following stages were performed using a tissue microarray technique (Bond Max, Leica Biosystems, Nussloch, Germany). After 15 min in 0.5% hydrogen peroxide to block endogenous peroxidase, sections were incubated with liquid rabbit polyclonal caveolin antibody (NCL-L-Caveolin-1, 1/200 dilution, Leica Biosystems, Newcastle, UK) for 25 min. Post-primary antibody, polymer antibody, and DAB mixtures (LOT 11776, Leica, Newcastle) were sequentially applied for 10 min. Contrast staining was done with Mayer's hematoxylin, and slides were sealed with a cover substance. Smooth muscle and endothelial cells were used as positive tissue controls.

The immunohistochemical staining of Cav-1 was evaluated using the scoring system by Fine et al. [30]. and calculated based on the ratio of caveolin-positive tumor cells and staining intensity.

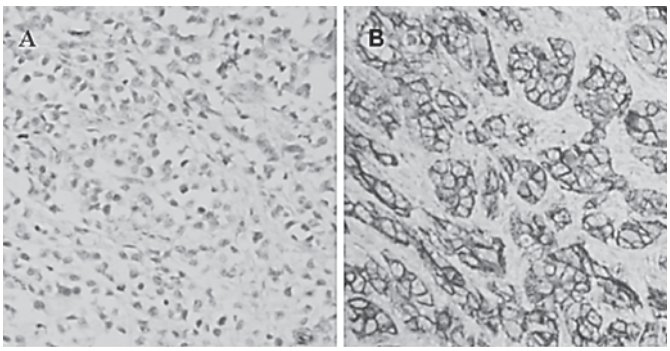

Fig. 1. Immunohistochemical staining of caveolin-1 (Cav-1) in gastric cancer. **A** Poorly cohesive carcinoma without Cav-1 expression. **B** Poorly differentiated tubular adenocarcinoma showing cytoplasmic and/or membranous Cav-1 expression.

0: no staining or weak staining in less than 10% of tumor cells
1: mild staining in 10% or more of tumor cells
2: moderate staining in 10% or more of tumor cells
3: strong staining in 10% or more of tumor cells

Cytoplasmic and/or membranous staining was considered. Estimated scores were stratified into 2 categories; 0 was ranked as negative, ± 1, ± 2, and ± 3 were evaluated as positive. The immunohistochemical staining intensity (no and strong staining) of Cav-1 for gastric specimens in shown in figure 1.

Treatment in the Adjuvant and Metastatic Setting

In total, 98 (66%) patients received adjuvant chemotherapy consisting of leucovorin (LV) and 5-fluorouracil (5-FU) (5-FU 425 mg/m^2 plus LV 20 mg/m^2, each given on days 1–5 every 4 weeks) followed by 4,500 cGy of radiation at 180 cGy per day, given 5 days per week for 5 weeks with modified doses of 5-FU and LV on the first 4 and the last 3 days of radiotherapy, all within 4 weeks after surgery. However, only 75 patients (76.5%) could complete adjuvant therapy. Recurrence occurred in 61 (41.3%) patients. In 39%, the recurrence site was the liver; other sites included the peritoneum, para-aortic lymph nodes, lung, stomach, bone, and ovaries. Of the patients who developed recurrence, 83% received palliative chemotherapy.

Statistical Method

All statistical analyses were carried out using SPSS 17.0 version (IBM Corp., Armonk, NY, USA). The Mann-Whitney U test was used for comparison of non-categorical data besides descriptive statistical methods (mean, standard deviation, median, frequency, and ratio). The association of Cav-1 expression with clinicopathological factors was analyzed using the chi-square test and Fisher's exact test after Cav-1 expression was categorized. Survival analyses and curves were compared with the log-rank test using the Kaplan-Meier method. DFS was defined as the time from curative surgery to disease progression or recurrence, or to the date of death, or to being lost to follow-up. OS was described as the time interval from the diagnosis to the date of the patient's death or to being lost to follow-up. The prognostic significance of Cav-1 expression and clinicopathological properties was evaluated using univariate and multivariate analyses and the Cox proportional hazards model. 95% confidence interval (CI) was used for determining the relationship between survival time and each independent factor. All p values were 2-sided, and values below 0.05 were accepted as statistically significant.

Results

The median age of the 148 patients was 61 years (range 23–76 years), and 73 patients were older than 60 years. 95 (64.2%) patients were male and 53 (35.8%) were female. The tumor was lo-

Table 1. Correlation between caveolin-1 (Cav-1) expression and clinicopathological factors

Factors	Total, n (%)	Cav-1 negative, n (%)	Cav-1 positive, n (%)	p
Sex				0.64
Female	53 (35.8)	46 (36.8)	7 (30.4)	
Male	95 (64.2)	79 (63.2)	16 (69.6)	
Age, years				0.06
< 60	75 (50.7)	59 (47.2)	16 (69.6)	
> 60	73 (49.3)	66 (52.8)	7 (30.4)	
Tumor location				0.043
Upper	44 (30.0)	40 (32.3)	4 (16.7)	
Middle	25 (17.0)	17 (13.7)	8 (33.3)	
Lower	79 (53.0)	68 (54.0)	11 (50.0)	
Surgery type				0.82
Subtotal gastrectomy	79 (53.4)	66 (52.8)	13 (56.5)	
Total gastrectomy	69 (46.6)	59 (47.2)	10 (43.5)	
Tumor diameter, cm				0.82
< 5	62 (42.2)	53 (42.7)	9 (39.1)	
> 5	85 (57.8)	71 (57.3)	14 (60.9)	
Histology				0.83
Tubular/papillary adenocarcinoma	82 (55.4)	68 (54.4)	14 (60.9)	
Signet ring cells	53 (35.8)	46 (36.8)	7 (30.4)	
Mucinous	13 (8.8)	11 (8.8)	2 (8.7)	
Grade of differentiation				0.041
Well	3 (2.0)	3 (2.4)	0 (0.0)	
Moderate	54 (36.5)	50 (40.0)	4 (17.4)	
Poorly cohesive or undifferentiated	91 (61.5)	72 (57.6)	19 (82.6)	
Lymph node metastases				0.009
No	40 (27.0)	39 (31.2)	1 (4.3)	
Yes	108 (73.0)	86 (68.8)	22 (95.7)	
pT stage				0.003
T1	11 (7.4)	11 (8.9)	0 (0.0)	
T2	9 (6.1)	9 (7.3)	0 (0.0)	
T3	81 (54.7)	72 (58.1)	8 (37.5)	
T4	47 (31.8)	32 (25.8)	15 (62.5)	
pTNM stage				0.022
I	14 (9.5)	14 (11.2)	0 (0.0)	
II	49 (33.1)	45 (36.0)	4 (17.4)	
III	85 (57.4)	66 (52.8)	19 (82.6)	
Vascular invasion				0.79
No	36 (24.5)	30 (24.2)	6 (26.1)	
Yes	111 (75.5)	94 (75.8)	17 (73.9)	
Perineural invasion				0.61
No	33 (22.0)	28 (22.0)	5 (21.7)	
Yes	115 (78.0)	97 (78.0)	18 (78.3)	
Recurrence				0.022
No	87 (58.7)	79 (63.2)	8 (34.8)	
Yes	61 (41.3)	46 (36.8)	15 (65.2)	

cated in the inferior part of the stomach in 53% of patients, in the middle part of the stomach in 17%, and in the upper part in 30%. Subtotal gastrectomy was performed in 53.4% of the patients, while 46.6% underwent total gastrectomy. Histopathological examination revealed tubular/papillary adenocarcinoma in 55.4% of patients, and poorly cohesive or undifferentiated carcinoma in 61.5%. Lymph node involvement was detected in 73% and absent in 27%. According to pTNM staging, 14 (9.5%) patients were classified as stage I, 49 (33.1%) as stage II, and 85 (57.4%) as stage III.

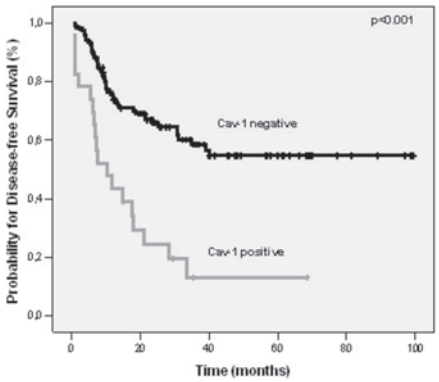

Fig. 2. Disease-free survival according to caveolin-1 (Cav-1) expression status.

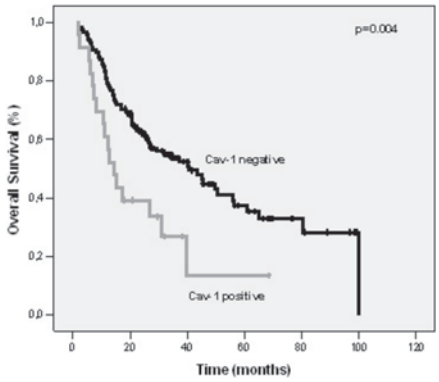

Fig. 3. Overall survival curves show that positive caveolin-1 (Cav-1) expression is associated with worse survival compared to negative Cav-1 expression.

Immunohistochemical analysis of the 148 gastric tumor tissues revealed positive Cav-1 staining in 23 (15.5%) patients and negative staining in 125 (84.5%) patients. A statistically significant relationship was seen between Cav-1 expression and tumor location, grade of differentiation, lymph node involvement, pT stage, pTNM stage, and the presence of recurrence. Compared to negative Cav-1 expression, there was a closer association between positive Cav-1 expression and tumors which were located in the lower part of the stomach ($p = 0.043$), were poorly or undifferentiated ($p = 0.041$), had lymph node involvement ($p = 0.009$), had an advanced pT stage ($p = 0.003$), and had an advanced pTNM stage ($p = 0.022$). The prevalence of recurrence was significantly higher for patients with positive Cav-1 expression than for patients with negative Cav-1 expression ($p = 0.022$). The relationship between clinicopathological factors and Cav-1 expression status is shown in table 1.

The median duration of follow-up was 37 months (range 23–93 months). Patients with negative Cav-1 expression had a significantly better 3-year DFS rate than those with positive Cav-1 expression. (54.6 vs.13.0%, $p < 0.001$) (fig. 2). Likewise, the 3-year OS rate was higher in patients who showed negative Cav-1 expression compared to those with positive Cav-1 expression (60.1 vs. 26.8 months, $p = 0.004$) (fig. 3). In univariate analysis, Cav-1 expression

Table 2. Results of the univariate analysis for disease-free survival (DFS) according to clinicopathological factors

Factors	3-year DFS, %	Log rank, χ^2	p
Sex		0.27	0.59
Male	39.1		
Female	32.3		
Age, years		0.18	0.66
< 60	33.4		
> 60	36.6		
Tumor location		0.37	0.83
Upper	31.3		
Middle	30.8		
Lower	39.5		
Surgery type		0.77	0.37
Subtotal gastrectomy	39.9		
Total gastrectomy	30.5		
Tumor diameter, cm		0.74	0.38
< 5	39.4		
> 5	33.3		
Histology		2.45	0.29
Tubular/papillary adenocarcinoma	38.1		
Signet ring cells	36.7		
Mucinous	11.3		
Grade of differentiation		1.64	0.43
Well	NA		
Moderate	20.9		
Poorly cohesive or undifferentiated	32.0		
Lymph node metastases		12.7	<0.001
No	64.1		
Yes	23.6		
pT stage		17.2	0.001
T1	NA		
T2	NA		
T3	23.0		
T4	18.0		
pTNM stage		19.1	<0.001
I	NA		
II	49.8		
III	18.9		
Vascular invasion		10.8	0.001
No	49.9		
Yes	21.5		
Perineural invasion		12.1	0.001
No	59.1		
Yes	27.6		
Cav-1 expression		21.9	<0.001
Negative	54.6		
Positive	13.0		

Cav-1 = Caveolin-1; NA = not applicable.

Table 3. Results of the univariate analysis for overall survival (OS) according to clinicopathological factors

Factors	3-year OS, %	Log rank, χ^2	p
Sex		0.20	0.87
Male	48.7		
Female	50.7		
Age, years		0.24	0.62
< 60	52.7		
> 60	46.2		
Tumor location		0.65	0.72
Upper	51.9		
Middle	46.1		
Lower	49.5		
Surgery type		0.55	0.45
Subtotal gastrectomy	52.2		
Total gastrectomy	46.8		
Tumor diameter, cm		0.88	0.34
< 5	54.4		
> 5	45.2		
Histology		2.26	0.32
Tubular/papillary adenocarcinoma	55.7		
Pure signet ring cells	37.8		
Mucinous	57.0		
Grade of differentiation		5.57	0.06
Well	NA		
Moderate	59.9		
Poorly cohesive or undifferentiated	42.6		
Lymph node metastases		22.9	<0.001
No	83.1		
Yes	34.8		
pT stage		13.9	0.003
T1	NA		
T2	88.9		
T3	45.3		
T4	37.5		
pTNM stage		25.0	<0.001
I	91.7		
II	70.0		
III	30.7		
Vascular invasion		13.1	<0.001
No	73.1		
Yes	42.5		
Perineural invasion		12.1	<0.001
No	77.2		
Yes	42.3		
Cav-1 expression		8.34	0.004
Negative	60.1		
Positive	26.8		

Cav-1 = Caveolin-1; NA = not applicable.

status, lymph node involvement, pT stage, pTNM stage, and vascular and perineural invasion were found to be statistically significant prognostic factors both for DFS and for OS. The results of univariate analysis according to DFS and OS are summarized in tables 2 and 3.

A multivariate analysis using the Cox proportional hazards model was performed in order to further evaluate the significant prognostic factors detected in the univariate survival analysis. It showed that Cav-1 expression status (p = 0.001, hazard ratio (HR) 2.58 (1.47–4.52)) was seen to be an independent prognostic factor for DFS, as was lymph node involvement (p = 0.01, HR 2.07 (0.83–

Table 4. Results of the multivariate analysis for overall OS and DFS

Factors	p	HR	95% CI
Disease-free survival			
Lymph node metastases	0.01	2.07	0.83–5.12
pT stage	0.12	1.37	0.91–2.07
pTNM stage	0.91	0.96	0.47–1.94
Vascular invasion	0.06	1.95	0.95–3.99
Perineural invasion	0.08	2.14	0.89–5.15
Cav-1 expression (negative vs. positive)	0.001	2.58	1.47–4.52
Overall survival			
Lymph node metastases	0.03	2.98	1.11–3.12
pTNM stage	0.24	1.57	0.73–3.35
pT stage	0.14	1.33	0.90–1.94
Vascular invasion	0.22	1.62	0.74–3.56
Perineural invasion	0.23	0.57	0.22–1.43
Cav-1 expression (negative vs. positive)	0.031	1.87	1.05–3.31

HR = Hazard ratio; CI = confidence interval; Cav-1 = caveolin-1.

5.12)). Similarly, both lymph node involvement (p = 0.03, HR 2.98 (1.11–3.12)) and Cav-1 expression status (p = 0.031, HR 1.87 (1.05–3.31)) were found to be independent prognostic factors for OS in multivariate analysis. Table 4 shows the results of the multivariate analysis for DFS and OS.

There was no correlation between the presence of adjuvant treatment and Cav-1 expression (p = 0.63). In a subgroup analysis of patients having received adjuvant treatment, 83% showed no Cav-1 expression, while 17% were Cav-1-positive. We did not detect any relationship between adjuvant treatment and Cav-1 expression, similar to the overall cohort (p = 0.73).

Discussion

In the present study, positive Cav-1 expression was found to be significantly correlated with tumor location, grade of differentiation, lymph node involvement, pT stage, pTNM stage, and the presence of recurrence. Furthermore, we detected that positive Cav-1 expression is an independent prognostic factor for both DFS and OS in gastric cancer patients who have undergone radical surgery.

Previous studies in the literature investigating the relationship between Cav-1 expression and gastric cancer yielded conflicting results. In the largest study, Nam et al. [28] evaluated 405 gastric cancer tissue specimens. While no staining was seen in non-neoplastic mucosa, positive staining was observed in the gastric cancer mucosa of 22 (5.4%) patients. Moreover, a significant correlation was found between Cav-1 staining and advanced pTNM stage and lymph node involvement. Their survival analyses showed that Cav-1 expression is an independent risk factor for poor survival. Similarly, in our study, Cav-1 expression was an independent prognostic factor for poor survival, and a significant correlation was found between positive Cav-1 staining and tumor location, grade of differentiation, pT stage, presence of recurrence, advanced pTNM stage, and lymph node involvement. Our results were thus compatible with those of Nam et al. [28]. However, stage IV patients were included in their study, while we analyzed only patients without distant metastasis. In our view, this difference makes our study a noteworthy contribution to the literature.

Furthermore, the rate of positive staining for Cav-1 was higher in our study compared to the study by Nam et al. [28] (15.5 vs. 5.4%).

In contrast, other studies available in the literature report different conclusions with respect to Cav-1 staining rates and their relationship with prognosis. In a study by Sun et al. [26], Cav-1 expression was evaluated in 5 gastric cancer tissues, 40 precancerous gastric tissues (19 intestinal metaplasia and 21 dysplasia), and 42 non-atrophic gastritis tissues. They showed that Cav-1 positivity was significantly lower in the gastric cancer tissues compared to precancerous gastric and non-atrophic gastritis tissues [26]. Moreover, different from our study, low Cav-1 expression was found to be significantly correlated with lymph node metastasis and advanced pTNM stage. Similarly, Cav-1 was immunohistochemically evaluated both in gastric cancer cells and cancer-associated fibroblasts (CAFs) in a study by Zhao et al. [27] examining a total of 286 gastric cancer tissues. While low expression of Cav-1 in CAFs was found to be an independent predictor for poor prognosis in gastric cancer patients (p = 0.034 and 0.005, respectively, for DFS and OS), no association was found between Cav-1 expression levels in tumor cells and prognosis. In the same study, Cav-1 expression in tumor cells and CAFs showed no significant correlation with classical clinicopathological features such as T stage or pTNM stage [27]. In another study conducted by Barresi et al. [24] in which Cav-1 expression was immunohistochemically investigated in gastric cancer and adjacent normal tissues, staining was observed in 94% of gastric cancer tissues but no association was found between Cav-1 expression and stage or prognosis. In the present study, Cav-1 expression was not analyzed in the stroma and/or in CAFs. Due to heterogeneous expression levels, we evaluated Cav-1 expression in tumor cells only, and calculated it based on the ratio of caveolin-positive tumor cells. Our strategy of detecting Cav-1 expression was thus different from that of Zhao et al. [27].

In a recent meta-analysis of 6 studies performed by Yang et al. [31], no relationship was found between Cav-1 expression and clinicopathological characteristics in 972 resected gastric cancer tissues. However, Cav-1 expression was found at a higher ratio in diffuse type gastric cancer compared to intestinal type. Contrary to our study, this meta-analysis showed that Cav-1 expression had a positive predictive value for better OS in gastric cancer patients (pooled odds ratio = 0.590, 95% CI 0.360–0.970, p = 0.038). In our study, the small sample size might have influenced the results.

As seen in the above-mentioned studies and meta-analysis, there are conflicting results about the relationship between Cav-1 expression and prognosis of gastric cancer. On the other hand, our findings regarding Cav-1 expression and its association with clinicopathological factors and prognosis in gastric cancer are consistent with those of Nam et al. [28] which is the largest study in the literature. One of the reasons for the conflicting results may be methodological differences in the determination of Cav-1 expression levels. Different scores have been used both for intensity and proportion in most of the studies, and different cut-off values were applied for expression level. Another reason may be the discrepancy between the role of Cav-1 as a tumor promoter versus a tumor suppressor with an underlying tumor stage dependency.

The retrospective nature of our study is an important limitation and might have influenced our results. Other limitations are the small sample size and short follow-up interval. Although our results should be confirmed by prospective studies with larger sample sizes, we believe that our study is a noteworthy contribution to the literature and to the knowledge of prognosis and progression in gastric cancer, especially since our results are supported by the largest comparable study in the literature [28].

In conclusion, our findings show that positive Cav-1 expression was correlated with poor prognosis in patients with gastric cancer who had undergone radical gastrectomy. To validate these findings, further studies are needed which may reveal an association between Cav-1 and a diversity of signaling pathways and provide exciting anti-cancer treatment options targeting Cav-1 and caveolae both in primary and metastatic disease.

Disclosure Statement

The authors declare that they have no conflict of interest.

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