Original Article

Is plasma caveolin-1 level a prognostic biomarker in metastatic pancreatic cancer?

Nebi S. Demirci, Mutlu Dogan, Gokmen U. Erdem, Sabite Kacar[1], Turan Turhan[2], Saadettin Kilickap[3], Lutfi C. Cigirgan[2], Ertugrul Kayacetin[1], Yakup Bozkaya, Nurullah Zengin

Departments of Medical Oncology and [2]Biochemistry, Ankara Numune Training and Research Hospital, [1]Department of Gastroenterology, Turkiye Yuksek Ihtisas Training and Research Hospital, [3]Department of Medical Oncology, Hacettepe University Medical Faculty, Ankara, Turkey

Abstract

Background/Aims: To evaluate the prognostic significance of plasma caveolin (CAV)-1 and its association with survival and treatment response rates in metastatic pancreatic cancer (MPC).

Patients and Methods: Plasma samples were prospectively collected from 41 patients with newly diagnosed MPC. Moreover, plasma samples were collected from 48 patients with chronic pancreatitis and 41 healthy individuals (control groups) for assessing Cav-1 levels. Plasma Cav-1 levels were evaluated at baseline and after three cycles of chemotherapy in the patients with MPC.

Results: The median Cav-1 level was 13.8 ng/mL for the patients with MPC and 12.2 ng/mL for healthy individuals ($P = 0.009$). The Cav-1 cut-off level was calculated as 11.6 ng/mL by using the receiver operating characteristic curve. The median overall survival and progression-free survival rates were 5 and 2.4 months, respectively, for participants with a high basal plasma Cav-1 level; the corresponding values were 10.5 and 9.4 months for participants with a low plasma Cav-1 level ($P = 0.011$ and $P = 0.003$, respectively). Of the 41 patients with MPC, 23 completed at least three cycles of chemotherapy. The median Cav-1 level was 13 ng/mL for post-treatment MPC (r^2: 0.917; $P = 0.001$). High basal plasma caveolin-1 level have continued to remain at high levels even after chemotherapy, showing a trend toward worse response rates ($P = 0.086$).

Conclusion: High basal plasma Cav-1 levels seem to be associated with poor survival and tend to yield worse therapeutic outcomes in patients with MPC. This study is the first to evaluate the prognostic significance of plasma Cav-1 levels as a prognostic factor in patients with MPC. However, larger prospective clinical trials are warranted.

Keywords: Caveolin-1, cisplatin, gemcitabine, pancreatic cancer, prognosis, resistance, treatment response

Address for correspondence: Dr. Nebi S. Demirci, Department of Medical Oncology, Ankara Numune Training and Research Hospital, Ankara, Turkey.
E-mail: drserkannebi@yahoo.com

INTRODUCTION

Pancreatic cancer is one of the most lethal malignant diseases and the fourth leading cause of cancer deaths in developed countries, with a 5-year survival rate of 5%.[1,2] An early diagnosis of pancreatic cancer is difficult because of the absence of specific symptoms.[1] Most patients present with constitutional symptoms, such as abdominal pain or weight loss. Only 10-15% of the patients present with resectable disease.[3] Despite significant advances in treatment modalities, the prognosis of pancreatic cancer remains poor with a median survival of less than 12 months.[4]

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Several blood biomarkers, such as carbohydrate antigen (CA) 19-9, anticarcinoembryonic antigen (CEA), lactate dehydrogenase (LDH), C-reactive protein (CRP), and cathepsin-l, have been shown to have prognostic significance in pancreatic cancer.[5-7] However, novel prognostic and predictive biomarkes are warranted. The evaluation of serum or plasma samples for these biomarkers seems cheaper and easier.

Caveolae, 50–100-nm proteins, are localized in mammalian plasma membrane invaginations, and they form vesicles on the plasma membrane.[8] Caveolin-1, -2 and -3 are the isoforms of caveolin. Caveolin-1 (Cav-1) is the major structural protein in caveolae, and the Cav-1 gene is located on chromosome 7q31.1.[9] However, Cav-1 expression varies in different tissues. Cav-1 overexpression is most common in terminally differentiated cells, such as adipocytes, endothelia, smooth muscle cells, and some epithelial cells, as well as type 1 pneumocytes.[10,11] Cav-1 does not only have structural roles but also regulatory roles in cellular differantiation and signaling, tumor progression, endocytosis, lipid homeostasis, and angiogenesis.[12] Cav-1 has been reported to have a potential role in drug resistance.[13-18]

The role of Cav-1 in angiogenesis remains unclear. However, Cav-1 was recently reported to have an antiapoptotic potential, leading to enhanced tumor migration and invasion; thus, it might be a poor prognostic factor in patients with cancer.[19] Notably, Cav-1 seems to act as a tumor suppressor gene and proto-oncogene.[20-23] The lower expression of Cav-1 in breast, colon, and ovarian cancers as well as sarcomas increases the metastatic potential of these tumors, whereas Cav-1 overexpression increases tumor invasion and metastasis through tumor promotion in esophageal, bladder, prostate, and pancreatic cancers in addiiton to nonsmall cell lung cancer, renal cell cancer, and thyroid papillary carcinoma.[23-35] However, the effects of various expression levels of Cav-1 on tumor promotion and metastasis remain unclear.

Cav-1 is little or not expressed in normal pancreatic ductal or acinar cells. However, it is overexpressed in pancreatic tumor cells.[36] Cav-1 overexpression in pancreatic cancer was reported to be associated with poor prognosis. In pancreatic cancer, both progression-free survival (PFS) and overall survival (OS) rates were reported to be higher in patients with lower Cav-1 levels.[37]

Cav-1 is also a critical modulator of multidrug resistance (MDR).[14-17] MDR is an established process involving both biochemical reactions and drug transporter overexpression.[38-42] Cav-1 expression has been reported to be higher in some MDR tumor cells.[15,18] However, the role of Cav-1 overexpression in MDR tumor cells warrants further investigation because Cav-1 plays a complex role in resistance to chemotherapy-induced apoptosis.[39] Nevertheless, the evidence provided by existing literature tends to favor an association of Cav-1 expression with drug resistance rather than sensitization to treatment. Therefore, Cav-1 overexpression has been associated with poor overall response rates in patients with meningioma and malignancies, such as renal, pancreatic, lung, and prostate cancers.[14,37-41] Cav-1 has also been found to be diffrentially overexpressed in multidrug-resistant colon cancer cells, adriamycin-resistant breast cancer cells, and taxane–gemcitabine-resistant lung cancer cells.[13,15,18]

In this study, we evaluated the relationship between pretreatment Cav-1 levels and survival rates with response to the treatment. We also evaluated the correlation between basal plasma Cav-1 levels, LDH, CA19-9, and CEA. The basal plasma Cav-1 levels in patients with metastatic pancreatic cancer (MPC) were compared to those in patients with chronic pancreatitis and healthy individuals.

PATIENTS AND METHODS

Study population

This prospective cross-sectional controlled study was conducted in the Department of Medical Oncology at Numune Training and Research Hospital and Gastroenterology at Turkiye Yuksek Ihtisas Training and Research Hospital in Ankara. Patients with histopathologically proven newly diagnosed MPC who were 18 years or older were enrolled into the study. All patients were required to have a disease that was detectable through computed tomography (CT) or magnetic resonance imaging (MRI). The patients were chemo-naive with Eastern Cooperative Oncology Group scores of 0–2 and adequate hematological, renal, and hepatic functions. Plasma samples of the patients with MPC (group 1) were obtained at baseline and after three cycles of chemotherapy for assessing Cav-1 and other tumor markers (CEA, CA19-9, and LDH). All patients underwent physical examination, complete blood cell count, serum electrolyte, and serum creatinine measurements and liver function tests at baseline. Furthermore, plasma samples of the patients with chronic pancreatitis (group 2) and healthy individuals (group 3; control groups) were collected for assessing the Cav-1 levels.

Chronic pancreatitis was diagnosed based on CT in addition to typical clinical history. The study was approved by

the local institute's ethics committee and all participants provided written informed consent.

All patients with MPC had received cisplatin plus gemcitabine chemotherapy as the first-line treatment; the treatment regimen comprised cisplatin (75 mg/m^2 on day 1, intravenous infusion) plus gemcitabine (1200 mg/m^2 on days 1 and 8, intravenous infusion) every 21 days for a maximum of six cycles. The patients received chemotherapy until disease progression or unacceptable toxicity. The patients who had completed at least one cycle of therapy were enrolled in the study. Tumor responses were evaluated according to Response Evaluation Criteria in Solid Tumors (version 1.1) through CT or MRI at baseline and after chemotherapy.[43]

Determination of plasma Cav-1

All blood samples were obtained by venipuncturing the antecubital vein between 8:00 AM and 9:00 AM, following overnight fasting for 8–10 hours. Within 30 minutes of blood collection, the plasma was separated through centrifugation at 2500 rpm for 20 minutes at room temperature. The plasma Cav-1 levels were measured using the enzyme-linked immunosorbent assay (ELISA; BioTek® Synergy HT, BioTek® Instruments, Vermont 05404-0998 USA). The separated plasma was divided into 200-μL aliquots and stored at −80°C until further processing. The plasma Cav-1 level in groups 1, 2, and 3 was determined using the ELISA kit (Lot no. 201511; Sunred Biological Technology, Shanghai, China) according to the manufacturer's instructions (assay range: 0.5–96 ng/mL). All analyses were performed on the same day. The standard concentrations of 3, 6, 12, 24, and 48 ng/mL were used. As mentioned previously, plasma Cav-1 levels were evaluated at baseline and after three cycles of chemotherapy in group 1.

Statistical analysis

The Kruskal–Wallis and Mann–Whitney U tests were applied to compare the variables among the three groups, whereas Spearman's correlation test was used for comparing the parameters (Cav-1, LDH, CEA, CA19-9, and age) at baseline and after three cycles of chemotherapy (non-normally distributed data). The survival data were analyzed using the Kaplan–Meier method, and the statistical significance was assessed using the log-rank test. The cut-off level was set by constructing the receiver operating characteristic curve. Logistic regression analysis was applied to analyze the effects of plasma Cav-1 levels on the treatment response.

OS was defined as the interval between diagnosis and death; PFS was defined as the duration between chemotherapy initiation and disease progression. The patients lost to follow-up were censored. $P < 0.05$ was considered statistically significant. SPSS 18.0 for Windows (SPSS Inc. Chicago, IL, USA) was used for statistical analysis.

RESULTS

Between March 2013 and April 2015, 41 and 48 patients with MPC (group 1) and chronic pancreatitis (group 2), respectively, and 41 healthy individuals (group 3) were recruited in this study. The median follow-up duration was 4.2 months (0.43–33.8 months). The median age was 59 years (44–80; group 1), 58 years (28–79 years; group 2), and 59 years (27–76 years; group 3). The male to female ratio was 3.1 (31/10), 1.52 (29/19), and 1.27 (23/18) for groups 1, 2, and 3, respectively. The basal levels of Cav-1, LDH, CA19-9, and CEA were examined in plasma samples obtained from group 1. The first-line chemotherapy regimen of cisplatin plus gemcitabine was administered to group 1. A median of three chemotherapy cycles (1–6) were adminstered. Furthermore, 44% ($n = 18$) of the patients in group 1 could not be evaluated after the three cycles of chemotherapy because of either death or loss to follow-up. The remaining 56% ($n = 23$) of them were evaluated after the three cycles.

No significant correlations were observed between basal plasma Cav-1 levels and other basal parameters [Table 1]. The median plasma Cav-1 levels were 13.8 ng/mL (4–96 ng/mL; mean: 27.02 ± 24.93 ng/mL) for group 1, 12.4 ng/mL (8.3–96 ng/mL; mean: 26.82 ± 27.75 ng/mL) for group 2, and 12.2 ng/mL (3.7–30.4 ng/mL; mean: 13.35 ± 5.05 ng/mL) for group 3. Group 1 had significantly higher basal plasma Cav-1 levels than did the control groups ($P = 0.042$). *Post hoc* analysis revealed prominent differences between groups 1 and 3 (groups 1 and 3, $P = 0.009$; groups 2 and 3, $P = 0.135$; groups 1 and 2, $P = 0.39$). The median plasma Cav-1 levels were 13.3 ng/mL (8–96 ng/mL) before treatment in 23 patients who completed three cycles of chemotherapy. At the end of the study, four patients were still alive. The median plasma Cav-1 levels in these patients were 9.85 ng/mL (4–12.5 ng/mL) and 11.7 ng/mL (10.9–13 ng/mL) before and after the treatment, respectively.

Table 1: The relationship of the pretreatment caveolin-1 plasma levels with age and other biochemical markers

	n	Median (range)	r^2	*P*
Pre-treatment cav-1	41	13,8000 (3.7-96)	-	-
Age	41	58 (27-80)	0.027	0.76
Pre-treatment CA 19-9	41	486 (4.8-2048)	0.133	0.408
Pre-treatment CEA	41	5.4 (0.6-1000)	-0.018	0.911
Pre-treatment LDH	38	363 (135-1549)	0.096	0.567
Post-treatment Cav-1	23	13 (9.4-96)	0.917	<0.001

Group 1 was evaluated for post-treatment Cav-1 levels after three cycles of chemotherapy. The median post-treatment Cav-1 level was 13 ng/mL (9.4–96 ng/mL). A positive correlation was observed between pretreatment and post-treatment plasma Cav-1 levels. The post-treatment plasma Cav-1 levels remained significant even after chemotherapy in patients with MPC having higher basal plasma Cav-1 levels [Table 1].

The patients in group 1 were subgrouped according to the basal plasma Cav-1 levels. The cut-off level was estimated to be 11.6 ng/mL for Cav-1 levels, where the optimal sensitivity and specificity were 83.4% and 75%, respectively, according to ROC analysis [Figure 1]. The patients with low basal Cav-1 levels (<11.6 ng/mL) were subgrouped as group 1a, whereas those with high basal Cav-1 levels (≥11.6 ng/mL) were subgrouped as group 1b. A complete response was not achieved, whereas partial (PR) and stable (SD) responses were reported in 6 (14.6%) and 10 (24.4%) patients, respectively, with a disease control rate of 39%. Twenty-five patients (61%) exhibited disease progression. In group 1 (patients with MPC), higher plasma Cav-1 levels (group 1b) also tended to be associated with lower objective response rates [Table 2]. The patients with low basal Cav-1 levels (group 1a) had more clinical benefits than did those with high basal Cav-1 levels (PR: 40% vs. 6.5% and SD: 20% vs. 25.8%).

The median PFS rate was significantly shorter in patients with higher basal plasma Cav-1 levels [hazard ratio: 3.41; 95% confidence interval (CI): 1.49–7.76; $P = 0.003$). The median PFS rate was 9.4 months (95% CI: 4.37–14.5) in group 1a, whereas it was 2.4 months (95% CI: 1.09–3.89) in group 1b [Figure 2 and Table 2]. However, high basal levels of LDH, CEA, and CA19-9 had no effects on survival [Table 3].

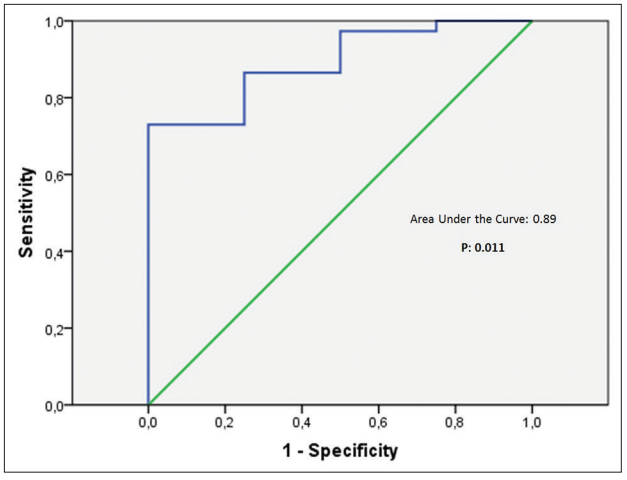

Figure 1: ROC curve of plasma Caveolin-1 level

The median OS rate for group 1 was 5.6 months (95% CI: 2.09–9.27). The median OS rate was significantly shorter in patients with higher basal plasma Cav-1 levels (hazard ratio: 2.99; 95% CI: 1.28–6.97; $P = 0.011$). The median OS rate was 10.5 months (95% CI: 1.35–19.67) in group 1a, whereas it was 5 months (95% CI: 3.01–7.1) in group 1b [Figure 3 and Table 2]. High basal Cav-1 levels were associated with poor survival in patients with MPC.

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DISCUSSION

Numerous studies have shown an association between pancreatic cancer and Cav-1 overexpression in tumor tissues; however, no study has reported an association between plasma Cav-1 levels and prognosis in pancreatic cancer. In the present study, we demonstrated that high plasma Cav-1 levels were significantly associated with a poor prognosis of patients with MPC and that a cisplatin plus gemcitabine chemotherapy regimen showed a decreasing trend in response rates.

Cav-1 is overexpressed on tumor tissues in pancreatic cancer; however, it is weakly or even not expressed in chronic pancreatitis specimens or normal ductal epithelium.[33,44,45] Notably, in the current study, plasma Cav-1 levels were significantly higher in the patients with pancreatic cancer than in the healthy individuals.

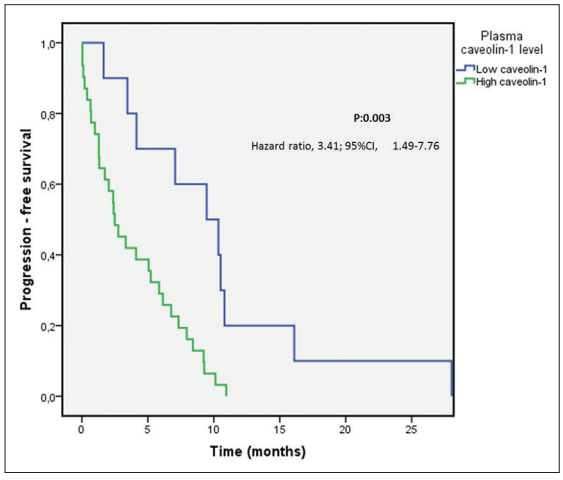

Figure 2: Kaplan-Meir curve of free survival period according to plasma caveolin-1 level

Table 2: Low and high baseline caveolin-1 plasma levels in relation to disease outcome

Variable	Patients with pancreatic cancer (*n*=41)	Low basal Cav-1 levels (*n*=10)	High basal Cav-1 levels (*n*=31)	Hazard ratio or odds ratio (95% CI)	*P*
Survival months†	5.6 (2.09-9.27)	10.5 (1.35-19.67)	5 (3.01-7.1)	Hazard ratio, 2.99 (1.28-6.97)	0.011
Overall Progression-free	4.1 (1.22-6.99)	9.4 (4.37-14.5)	2.4 (1.09-3.89)	Hazard ratio, 3.41 (1.49-7.76)	0.003
Response to therapy *n*	15	6	9	Odds ratio, 0.27 (0.06-1.2)	0.086‡
Disease control* progression	26	4	22		

†The number of months was estimated with the use of the Kaplan-Meier method. ‡The *P* value was calculated with the use of the logistic regression test. *Disease control includes complete response, partial response, and stable disease. Comparison of low and high plasma Cav-1 levels for outcome variables. Data in the treatment columns are median (95% CI)

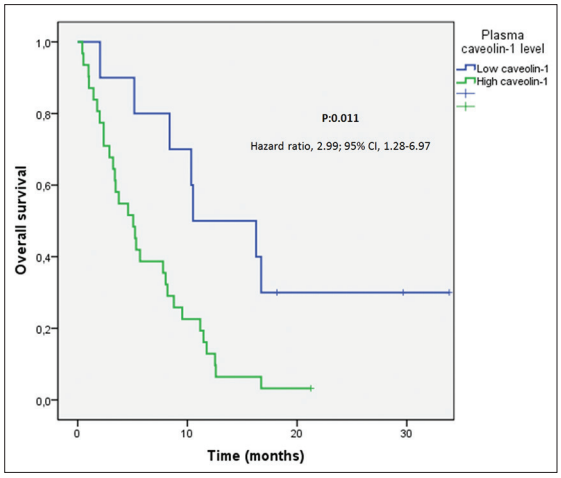

Figure 3: Kaplan-Meier plots illustrate the shorter time to overall survival in the high caveolin-1 group compared with low caveolin-1 group

Cav-1 expression was significantly correlated with the monoclonal antibody Ki-67, CEA, CA19-9, LDH, and p53 as well as serum levels of CA19-9.[37,44] In contrast, in our study, plasma Cav-1 levels and biochemical markers did not correlate [Table 1]. This may partly be because of the small sample size in this study.

Cav-1 expression contributes to chemoresistance because Cav-1 was shown to be overexpressed in some human MDR tumor cells.[46] Additionally, it regulates angiogenesis and vascular remodeling in endothelial cells.[21,47] Cav-1 overexpression has been reported to be associated with chemoresistance in some malignancies, such as adriamycin resistance in breast cancer, taxan and platin resistance in ovarian cancer, and etoposide resitance in lung and pancreatic cancer.[13-17,47-49] Gemcitabine and platin are commonly used in advanced pancreatic cancer. Cav-1 depletion has been shown to increase chemosensitivity via the intrinsic pathway of apoptosis in MPC.[13,37] Cav-1 has been reported to be upregulated with chemotherapy in pancreatic cancer cells, leading to decreased chemosensitivity.[50-52]

We indicated that patients with higher plasma Cav-1 levels (group 1a) showed a trend toward worse response rates with cisplatin plus gemcitabine ($P = 0.086$). Patients with higher basal plasma Cav-1 levels also showed higher post-treatment levels despite chemotherapy. This result may have been related to the aggressive pattern of pancreatic cancer, particularly in the advanced stage [Table 4]. However, it is difficult to comment on the prognostic significance of plasma Cav-1 levels in all malignancies because of the lack of relevant data on its sensitivity and specificity rates.

Table 3: The relationship between pretreatment biochemical markers and survival in pancreatic cancer patients

	HR (%95 CI)	*P*
High pre treatment Cav-1	2.993 (1.285-6.970)	0.011
High pre treatment CA 19-9	0.731 (0.254-2.106)	0.562
High pre treatment CEA	1.154 (0.602-2.210)	0.666
High pre treatment LDH	1.827 (0.845-3.951)	0.125

Cav-1 overexpression on tumor tissues has been reported to be associated with worse PFS and OS outcomes.[33,37] Limited data report the prognostic significance of plasma Cav-1 levels, whereas Cav-1 tissue levels have previously been shown to be important. Higher plasma Cav-1 levels have been shown to have prognotic significance in prostate cancer and melanoma.[53-55] We demonstrated higher progression rates with shorter OS rates in patients with MPC having higher basal plasma Cav-1 levels. The risk of pancreatic cancer-related death, estimated according to the hazard ratio, was 2.993 times higher in group 1a than in group 1b ($P = 0.011$).

The study has certain limitations. Multivariate analyses could not be performed because of the limited number of patients in our study. The Cav-1 levels could not be determined in all patients at the end of the three cycles of chemotherapy. On the other hand, study also has several strengths. According to our review of relevant literature, this study is the first to measure the plasma Cav-1 levels and the study design was more homogenous because all patients received cisplatin plus gemcitabine regimen. In addition, plasma Cav-1 levels of patients with pancreatic cancer were compared to the control groups (patients with chronic pancreatitis and healthy individuals).

The prognostic significance of plasma Cav-1 levels are unclear becasue of Cav-1 overexpression on tumor tissues,

Table 4: Pretreatment plasma basal caveolin-1 levels of patients with pancreatic cancer correlated with post treatment levels

	n	Mean	Median (range)	r^2	*P*
Pre-treatment Cav-1	41	27,02	13,8 (3.7-96)	0.903	<0.001
Post-treatment Cav-1	23	28.6	13 (9.4-96)	1	<0.001

as previously mentioned. Therefore, the correlation between plasma levels and Cav-1 overexpression should be evaluated in future studies.

CONCLUSION

High plasma Cav-1 levels seem to be associated with poor survival and tend to yield worse therapeutic responses in MPC. The evaluation of plasma Cav-1 levels is both easier and cheaper compared with the assesment of Cav-1 overexpression on tumor tissues. Plasma CAV-1 levels may be used as a cost-effective potential prognostic biomarker for MPC. However, larger prospective clinical trials are warranted.

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Conflicts of interest
There are no conflicts of interest.

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