Original Article

Plasminogen Activator Inhibitor 1 as a Poor Prognostic Indicator in Resectable Pancreatic Ductal Adenocarcinoma

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Abstract

Background: Plasminogen activator inhibitor 1 (PAI-1) was previously established to impact several phenotypes in many kinds of cancer, including pancreatic cancer. However, its prognostic significance in pancreatic ductal adenocarcinoma (PDAC) needs support of further evidence. This study was designed to address the issue.

Methods: PAI-1 expression was detected by tissue microarray-based immunohistochemical staining in formalin-fixed paraffin-embedded specimens from 93 PDAC patients with surgical resection from September 2004 to December 2008. Its relationships with clinicopathologic variables and tumor-specific survival (TSS) were further evaluated using Chi-square, Kaplan-Meier, log-rank, as well as Cox regression analyses.

Results: Expression of PAI-1 was much higher in tumor than that in nontumor tissues, based on comparison of all samples and 74 matched ones (95 [47.5, 180] vs. 80 [45, 95], $Z = -2.439$, $P = 0.015$ and 100 [46.9, 182.5] vs. 80 [45, 95], $Z = -2.594$, $P = 0.009$, respectively). In addition, tumoral PAI-1 expression was positively associated with N stage (22/35 for N1 vs. 21/51 for N0, $\chi^2 = 3.903$, $P = 0.048$). Univariate analyses showed that TSS of patients with high PAI-1 tumors was significantly poorer than that of those with low PAI-1 tumors (log rank value = 19.00, $P < 0.0001$). In multivariate Cox regression test, PAI-1 expression was identified as an independent predictor for long-term prognosis of resectable PDAC (hazard ratio = 2.559, 95% confidence interval = 1.499–4.367, $P = 0.001$).

Conclusion: These results suggest that expression of PAI-1 is upregulated in PDAC and might serve as a poor prognostic indicator.

Key words: Pancreatic Ductal Adenocarcinoma; Plasminogen Activator Inhibitor 1; Prognosis

Introduction

Pancreatic cancer (PC), especially its main histological type, pancreatic ductal adenocarcinoma (PDAC), has long been well known as one of the most lethal malignant neoplasms worldwide.[1] In China, its incidence and mortality rate have also been reported to be remarkably raised in recent years.[2] Up to now, its overall long-term prognosis remains dismal, although curative resection and adjuvant therapy have achieved some favorable effects in highly selected patients.[3-5] Therefore, survival-associated variables in patients with this malignancy caught much attention. The main identified ones were crucial clinicopathologic and surgical factors, including lymph node metastasis, tumor histology grade, peri-neural invasion, and resection margin.[6-9] On the other hand, data on prognostic biomarkers in PC, particularly for resectable patients, were also accumulated.[10,11] However, further candidates need to be supplemented.

In view of the fact that approximately 70% of PDAC patients died from extensive metastatic disease,[1] invasion-related molecules in this malignancy, such as those previously reported,[12-14] were of particular importance. Plasminogen activator inhibitor-1 (PAI-1), encoded by SERPINE1, is a

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Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.247211

Received: 31-08-2018 **Edited by:** Peng Lyu

How to cite this article: Liu WJ, Zhou L, Liang ZY, Zhou WX, You L, Zhang TP, Zhao YP. Plasminogen Activator Inhibitor 1 as a Poor Prognostic Indicator in Resectable Pancreatic Ductal Adenocarcinoma. Chin Med J 2018;131:2947-52.

specific inhibitory member of plasminogen activation (PA) system.[15] Except for its key role in acute thrombotic events, PAI-1 was also expected to prevent cancer invasion and metastasis through its inhibition of urokinase-type plasminogen activator, which was demonstrated to be involved in malignant dissemination.[15] Indeed, there were some published articles showing this metastasis inhibitory effect.[16-18] However, more articles suggested its pro-oncogenic roles.[19-24] In PC/PDAC, different *in vitro* and *in vivo* experiments also got inconsistent, even opposite results.[17,19,23] However, those for its prognostic significance in PDAC seem to be more consistent. It was shown that PAI-1 mRNA/protein overexpression tended to predict poor patient survival, but not being statistically significant.[25,26] The smaller sample size and incomplete staining evaluation criteria (without staining intensity) might be the main limits of these investigations.

The aim of this study was to discover the clinicopathologic and prognostic implications of PAI-1 expression in PDAC, through improvements of aforementioned limits.

Methods

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Ethics Committee of Peking Union Medical College Hospital (No. JS1178). Being a retrospective study and since data analysis was performed anonymously, this study was exempted from the informed consent from patients.

Patients

This study enrolled 93 resected patients with PDAC from September 2004 to December 2008. The inclusion criteria included: (1) without chemo-/chemo-radiation therapy before surgery; (2) underwent curative resection; and (3) histologically confirmed. Fifty-eight patients were male and 35 were female. The age ranged from 34 to 85 years (median: 62 years). The main clinical and pathologic variables of patients are summarized in Table 1.

Tissue microarray construction

The tissue microarray was constructed using formalin-fixed paraffin-embedded blocks. The construction method was same as our previous report.[27]

Immunohistochemistry

A mouse monoclonal antibody for human PAI-1 (Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA) and a two-step staining kit (EnVision™ plus kit, Dako, Denmark) were used for staining. First, 4-μm-thick slides were mounted, deparaffinized, and rehydrated. After antigen retrieval in an autoclave, sections were incubated with 3% hydrogen peroxide (10 min) to block endogenous peroxidase. Then, slides were sequentially incubated with the primary antibody (dilution: 1: 50) overnight at 4°C and horseradish peroxidase-labeled secondary antibody (30 min). Diaminobenzidine was applied as a chromogen. Finally, those were counterstained with hematoxylin. Nonimmune mouse serum at the same dilution was used as the negative control.

Table 1: Relationships between PAI-1 expression and clinicopathologic variables of resectable PDAC

Variables	*n*	PAI-1 expression, *n*		χ^2	*P*
		High	Low		
Gender					
Male	58	30	28	0.001	0.978
Female	35	17	18		
Age (years)					
≥62	47	24	23	0.011	0.915
<62	46	24	22		
Tumor site					
Head	57	30	27	0.061	0.805
Nonhead	36	18	18		
Tumor size (cm)					
>4	54	27	27	0.016	0.899
≤4	37	19	18		
Histological grade					
G1–G2	64	33	31	<0.001	0.988
G3–G4	29	15	14		
T stage					
T1–T2	71	39	32	2.479	0.115
T3	20	7	13		
N stage					
N0	51	21	30	3.903	0.048
N1	35	22	13		

Partial data were not available, and statistics were based on available data. *P* values were derived from the Pearson's Chi-square test (two tailed). PAI-1: Plasminogen activator inhibitor 1; PDAC: Pancreatic ductal adenocarcinoma; G1: Well differentiated; G2: Moderately differentiated; G3: Poorly differentiated; G4: Undifferentiated; T: Tumor; N: Lymph node.

Staining evaluation

Two experienced pathologists who had no clinicopathologic and follow-up information evaluated the sections, according to the H-score,[28] a widely used immunostaining evaluation criterion.[29,30] Similar to a previous study,[31] the H-score with the largest Youden index (YI) within the receiver operating characteristic (ROC) curve for survival status was adopted as the cutoff value.

Follow-up

All patients accepted the postsurgical follow-up (range: 2–87 months; median: 11 months). A total of 61 patients (65.6%) died, and the other 32 (34.4%) were alive.

Statistical analysis

The H-scores of PAI-1 in tumor and nontumor tissues were compared using Mann-Whitney *U*-test. Chi-square test was applied to determine the relationships between PAI-1 expression and clinicopathologic variables. The prognostic significance of PAI-1 was explored by Kaplan-Meier method and log rank test. Univariate and multivariate

Cox regression (proportional hazard model) analysis was adopted for prognostic factor identification. Statistical software package Statistical Package for the Social Sciences version 11.5 (SPSS Inc., Chicago, IL, USA) was employed for all the analyses. A statistical significance was defined when $P < 0.05$.

Results

Expression pattern of plasminogen activator inhibitor 1 in resectable pancreatic ductal adenocarcinoma

As shown in Figure 1a and 1b, the positive staining of PAI-1 was mainly located in the cytoplasm of both tumor and nontumor tissues. In all patients and 74 with matched tumor and nontumor samples, the H-scores in tumor tissues were much higher than those in nontumor ones (95 [47.5, 180] vs. 80 [45, 95], $Z = -2.439$, $P = 0.015$ and 100 [46.9, 182.5] vs. 80 [45, 95], $Z = -2.594$, $P = 0.009$, respectively) [Figure 1c and 1d].

Prognostic value of plasminogen activator inhibitor 1 in resectable pancreatic ductal adenocarcinoma

In the first, the H-score value of PAI-1 (cutoff value: 94.375) with the largest YI in the ROC curve for survival status was selected as the cutoff one [Figure 2a]. In contrast to patients' low tumoral PAI-1 expression, those with high PAI-1 expression carried significantly poorer tumor-specific survival (TSS) [log rank value = 19.00, $P < 0.0001$, Figure 2b].

Relationships of plasminogen activator inhibitor 1 with clinicopathologic variables of resectable pancreatic ductal adenocarcinoma

Using Chi-square analysis, high tumoral PAI-1 expression, based on the same cutoff value, was associated with N1 stage [22/35 for N1 vs. 21/51 for N0, $\chi^2 = 3.903$, $P = 0.048$, Table 1]. No significant associations between PAI-1 expression and other clinicopathologic parameters were found [$P > 0.05$, Table 1].

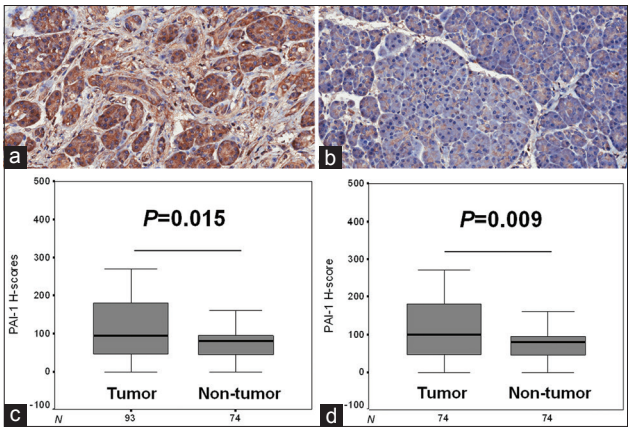

Figure 1: PAI-1 expression in resectable PDAC. (a) High expression in tumor tissue (immunohistochemistry, ×200); (b) Low expression in nontumor tissue (immunohistochemistry, ×200); (c) Comparison of PAI-1 H-scores between all tumor and nontumor tissues (Mann-Whitney *U*-test; $Z = -2.439$, $P = 0.015$); (d) Comparison of PAI-1 H-scores between matched tumor and nontumor tissues (Mann-Whitney *U*-test; $Z = -2.594$, $P = 0.009$). PAI-1: Plasminogen activator inhibitor 1; PDAC: Pancreatic ductal adenocarcinoma.

Identification of prognostic indicators in resectable pancreatic ductal adenocarcinoma

It was revealed by univariate Cox regression analysis that histological grade, N stage, and PAI-1 expression were predictors of TSS [$P < 0.05$, Table 2]. Multivariately, these factors remained to be significant, thus being independent prognostic determinants [$P < 0.05$, Table 2].

Discussion

It was long unexpectedly found that PAI-1 promoted many malignant behaviors of several kinds of cancer cells,[19-24] although it is one of the specific inhibitory members of PA system and was thus thought to inhibit cancer invasion/metastasis.[16-18] Therefore, its biological roles in cancer might vary largely. In PC/PDAC, previous articles revealed that high PAI-1 expression at mRNA and protein levels all tended to be associated with poor patient survival,[25,26] unlike inconsistent data from *in vitro* and *in vivo* experiments.[17,19,23] The possible reasons of imperfect statistical results might be attributed to smaller sample size (46 cases)[26] and defective staining evaluation criteria (absence of staining intensity).[25] In the present study, we included relatively more patients and used the H-score that considered both positive cell ratio and staining intensity[28] and wished to make it more comprehensive and reliable than aforementioned ones.[25,26] Our data showed that PAI-1 expression was remarkably higher in tumor than that in nontumor tissues of PDAC, based on the comparison of all samples and 74 matched ones. Moreover, PAI-1 expression positively correlated with N stage, an important factor that reflects tumor cell dissemination and predicts dismal prognosis in PC,[6,7] similar with evidence from other cancers.[32,33] Thus, the data preliminarily provide the histological evidence of PAI-1 as a proto-oncogene in PDAC. However, detailed mechanistic explorations remain to be in need.

More importantly, the prognostic value of PAI-1 expression remains to be elucidated in PDAC, on the basis of previous clues.[25,26] Using H-score and reasonable cutoff value determination method,[25,28] we showed that high tumoral PAI-1 expression was significantly related to poor TSS [Figure 2b]. Furthermore, PAI-1 expression plus the key clinicopathologic parameters of PDAC, histological grade and N stage, were significant prognostic factors, estimated by univariate Cox regression analysis. In view of its positive correlation with N stage, its influence on patient survival might easily be understood. Subsequent multivariate Cox regression analysis identified PAI-1 expression as one of the independent predictors of postsurgical survival of PDAC. These findings, which are largely consistent with those from other tumor types,[32-39] suggested that PAI-1 might be a strong biomarker for

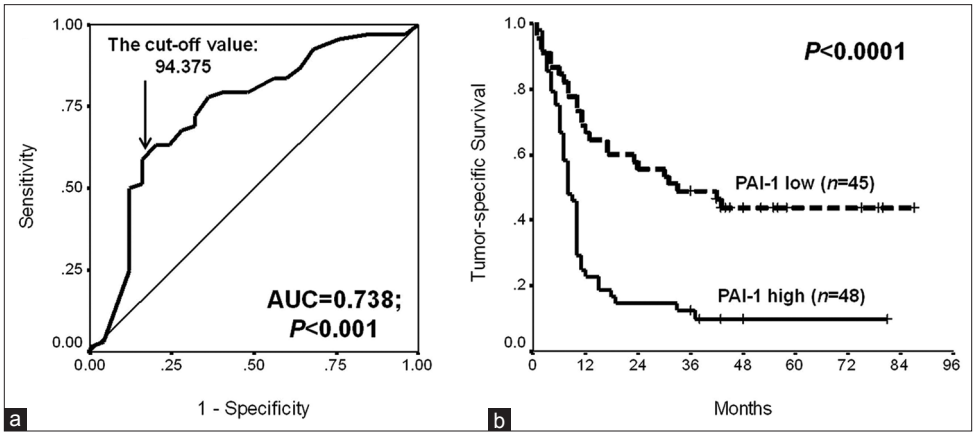

Figure 2: Prognostic value of PAI-1 in resectable PDAC. (a) The cutoff value determination using the ROC curve of tumoral PAI-1 H-scores for tumor-specific survival status; (b) Tumor-specific survival curves of patients with high or low tumoral PAI-1 expression (log rank value = 19.00, $P < 0.0001$). PAI-1: Plasminogen activator inhibitor 1; PDAC: Pancreatic ductal adenocarcinoma; ROC: Receiver operating characteristic.

Table 2: Univariate and multivariate analyses for prognostic indicators of resectable PDAC

Variables	*n*	Univariate			Multivariate		
		HR	95% *CI*	*P*	*HR*	95% *CI*	*P*
Gender							
Male	58	1.182	0.718–1.945	0.510			
Female	35	1					
Age (years)							
≥62	47	1.341	0.832–2.159	0.228			
<62	46	1					
Tumor site							
Head	57	1		0.980			
Nonhead	36	0.994	0.611–1.616				
Tumor size (cm)							
>4	54	0.807	0.496–1.313	0.387			
≤4	37	1					
Histological grade							
G1–G2	64	1		0.018	1		0.001
G3–G4	29	1.824	1.106–3.005		2725	1.495–4.968	
T stage							
T1–T2	71	1		0.941			
T3	20	0.978	0.541–1.766				
N stage							
N0	51	1		0.010	1		0.004
N1	35	1.940	1.169–3.221		2.372	1.327–4.241	
PAI-1 expression							
High	48	2.874	1.727–4.782	<0.001	2.559	1.499–4.367	0.001
Low	45	1			1		

Partial data were not available, and statistics were based on available data. *P* values were derived from the univariate and multivariate Cox regression analyses. PDAC: Pancreatic ductal adenocarcinoma; *HR*: Hazard ratio; *CI*: Confidence interval; G1: Well differentiated; G2: Moderately differentiated; G3: Poorly differentiated; G4: Undifferentiated; T: Tumor; N: Lymph node; PAI-1: Plasminogen activator inhibitor 1.

long-term prognosis of PDAC. All our data support its promoting role in PDAC invasion.[19,23] In the future, combined evaluation of this molecule and other variables might be of interest. On the other hand, relative molecular mechanisms are also worth further investigation.

However, this work has some limitations, such as its retrospective design and single detection method. Therefore, subsequent prospective and more comprehensive validations might be necessary.

In conclusion, our data indicate that PAI-1 expression is upregulated in PDAC and might serve as a poor prognostic marker.

Financial support and sponsorship

This work was supported by a grant from the National Natural Science Foundation (No. 81402027).

Conflicts of interest

There are no conflicts of interest.

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可切除胰腺导管腺癌中纤溶酶原激活物抑制物1作为不良预后指标

摘要

背景：之前研究发现纤溶酶元激活物抑制物1（PAI-1）在多种癌症，包括胰腺癌中影响许多表型。然而，其在胰腺导管腺癌(PDAC)中的预后意义需要进一步证据支持。本研究意在阐述这个问题。

方法：采用基于组织芯片的免疫组化染色检测2004年9月至2008年12月93例行外科切除的胰腺导管腺癌福尔马林固定石蜡包埋标本中PAI-1的表达。其与临床病理参数和肿瘤特异性生存（TSS）的关系以卡方检验、Kaplan-Meier和Log-rank检验以及Cox回归进行评价。

结果：在所有标本和74例配对标本中，癌组织PAI-1表达显著高于非癌组织（95 [47.5, 180] vs 80 [45, 95] ,Z=-2.439，P=0.015和100 [46.875, 182.5] vs 80 [45, 95]，Z=-2.594，P=0.009）。而且，肿瘤组织PAI-1表达与N分期呈正相关（N1组22/35比N0组21/51，χ^2=3.903，P=0.048）。单因素分析显示癌组织PAI-1高表达患者肿瘤特异性生存显著差于低表达者（Log-rank值=19.00，P<0.0001）。在多因素Cox回归中，PAI-1表达被鉴定为可切除胰腺导管腺癌长期预后的独立预测因素（相对危险度[HR]=2.559，95%可信区间[CI]=1.499–4.367，P=0.001）。

结论：这些结果提示胰腺导管腺癌中PAI-1表达上调，并可能作为不良预后的指标。