RESEARCH ARTICLE

# Annexin A2 and CD105 Expression in Pancreatic Ductal Adenocarcinoma is Associated with Tumor Recurrence and Prognosis

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## Abstract

**To investigate the value of expression of annexin A2, microvessel density (MVD) and CD105 in pancreatic ductal adenocarcinoma (PDAC) tissues and adjacent normal tissues, immunohistochemical staining was used. The positive expression rate of Annexin A2 and the MVD in pancreatic ductal adenocarcinoma tissues was higher than that in in adjacent normal tissues ($p<0.005$). Expression of Annexin A2 and MVD correlated with histological grade ($p<0.05$). MVD of cancers in TNM stage IIb was higher than that in TNM stageI~IIa ($p<0.026$). Cancerous tissues with Annexin A2 staining grade 3+ had lower MVD than the tissues with the other Annexin A2 staining grade ($p<0.05$). Patients with high MVD had worse prognosis. However , our study did not confirm Annexin A2 was an independent risk factor for patients with PDAC. We confirmed MVD labeled by CD105 was an independent risk factor for patients with PDAC and had moderate predictive value of prognosis.**

**Keywords:** Pancreatic ductal adenocarcinoma - microvessel density - Annexin A2 - CD105

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## Introduction

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive disease with an actuarial mortality rate is about 90% (Cheung, 2013), corresponding to the fourth leading cause of cancer death. Worldwide, the incidence of all types of pancreatic cancer (85% of which are PDAC) ranges from 1 to 10 cases per 100, 000 people (Ryan et al., 2014), Accounted for 2% of all malignant tumor incidence in china. At present, The 5-year survival rate of PDAC was only 3-5%, was the lowest in all cancers. Annexin A2 (ANXA2) also known as LPC2, LIP2, P36, was a member of annexin family. Annexin A2 has been considered to participate in a range of physiological processes, including anti-inflammatory, anti-coagulation, , exocytosis, endocytosis and signal transduction, cell-proliferation, diffrentiation, and apoptosis (Gurluler et al., 2014).

The disorder of Annexin A2 expression is related to the tumorigenesis in a variety of tumor, The data shows Annexin A2 play an important role in the process of tumor invasion and metastasis, and could be used as predictor biomarker of cancer (Alonso-Alconada et al., 2014). Microvessel density (MVD) is the most recognized indicator to evaluate angiogenesis of solid tumors, CD105 (endoglin) was a high affinity coreceptor for transforming growth factor (TGF)-β1 and TGF-β3 (Anderson et al., 2013), and was overexpressed in the tumor-associated vascular endothelium where it modulates angiogenesis (Fonsatti et al., 2010; Fujiwara et al., 2013). Immunostaining of CD105 is used to label MVD.

In the present study, we analyzed the expression of Annexin A2 and CD105 in clinical PDAC specimens and explore the association with disease-free survival and overall survival in patients following surgery.

## Materials and Methods

*Clinical PDAC specimens*

Paraffin-embeded cancer specimens and adjacent normal tissues were collected from 51 patients who underwent surgery between February 2007 and April 2010 in the The first hospital of shanxi medical university, all the specimens were fixed in 10% formaldehyde. The histomorphology of all tissue specimens was confirmed by the Department of Pathology, The first hospital of shanxi medical university. Follow-up information for all of the participants was updated every 3 month using telephone interviews and questionnaires. Overall survival (OS) were defined as the interval between dates of surgery and death, and disease-free survival (DFS) is defined as the interval from surgery to the first occurrence of tumor. The diagnosis of recurrence and distant metastasis was based on imaging methods. Tumors were staged according to the tumor-node-metastasis (TNM) classification system (UICC, 2002). Of All the 51 cases randomly retrieved from a prospectively collected database were identified as having no microscopically observable residual tumor

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(R0). None of them received any preoperative anticancer treatment. Entire tumors were collected. All cases did not received preoperative anticancer treatment, All patients were monitored until September 2013. Treatment were administered according to the NCCN Guideline. 51 cases of patients, 24 cases were male and 27 cases were female, Age 31-78, the median age was 59.15 years old. According to TNM Classification, 16 cases in I, 7 cases in IIA, 28 cases in IIB. According to Histopathological grading, 14 cases in G1, 6 cases in G2, 31 cases in G3.The 1-, 2- and 3-year OS rates were54%, 30%, 20%, respectively. And the 1-, 2-, and 3-year DFS rates were 39.2%, 21.6%, and 13.7% at the same time interval, respectively.

This study was approved by the research ethics committees of Shan Xi Medical University. The written informed consent was obtained from each patient before participating in this study according to the committees' regulation

*Immunohistochemical assays*

Paraffin-embeded tissue specimens were deparaffinized in xylene for 30mins and dehydrated through a graduated alcohol series, Endogenous peroxidase activity was interrupted by 3% $H_2O_2$ for 15 mins, specimens were rinsed in PBS buffer and microwaved in Citric acid buffer (PH 6.0; 0.01mmol/L)for 15mins to retrieve antigen. Then, the section was washed in PBS buffer for 3 times at room temperature.these sections were incubated with the mouse anti-human Annexin A2 monoclonal antibody (1:100, Santa Cruz)or mouse anti-human CD105 monoclonal antibody (1:100, ZSGB-BIO). All the sections were placed in a moist box at 4°C overnight. And then, the sections were washed by PBS buffer and incubated with Horseradish peroxidase labeled anti-mouse IgG (1:400, ZSGB-BIO) for 45mins at room temperature, then, Join the DAB chromogenic agent. Appropriate positive and negative control groups were set in each experiment.

*Evaluation of staining*

The tissue specimens were viewed separately by two pathologists without prior knowledge of the clinical or clinicopathological status of the specimens. The decision criteria of Annexin A2 protein expression: Positive cells appeared as the cytoplasm and cell membrane was stuned brown or light brown, the immunoreactivity score (IRS) system was based on the proportion and intensity of positively stained cancer cells: A:Staining intensity: colorless, scored 0;pale yellow, scored 1;yellow, scored 2;brown, scored 3.B:Number of positive cells, none, scored 0; ≤25%, scored 1; 26%~50%, scored 2; ≥51%, scored 3. The sum of A and B is the final score, the staining grade was classfied as negative (-, 0 score), weak ( 1+, 1-2 score), moderate (2+, 3-4 score) or strong (3+, 5-6 score). "+"-"3+"was defined as positive immunohistochemical staining. The strategy of counting MVD labeled by CD105: At first, Selecting the most abundant three areas of tumor microvascular number under low magnification (40X), Then, counting the number of tumor microvascular in the above three different areas under high magnification (400X), All brown individual endothelial cells or endothelial cell clusters, as long as they were Separated from the adjacent capillaries, tumor cells, or other connective tissue apart, they were considered as a separate Microvessel, except for the vessels it' s Lumen is greater than eight red blood cell diameter or had wall smooth muscle.

*Statistical analysis*

All statistical analyses were performed with SPSS 19.0 software, The expression of Annexin A2 and it's correlation was analyzed by Chi-square test, rank-sum test and Fisher's exact probability method; MVD was expressed as average±standard deviation (x±sd), to check up the data of all groups with normal test and ANOVA, it' s correlation was analyzed by t-test and variance analysis, ROC curves was performed to assess the cut-off value of MVD in PDAC prognosis analysis. Spearman rank correlation was performed to assess the relationship between two markers. Survival curves were estimated using the Kaplan-Meier method, and differences in survival distributions were evaluated by the log-rank test. Cox's proportional hazards modeling of factors potentially related to survival was performed to identify factors that might have a significant influence on survival. Differences with a *p* value of 0.05 or less were considered statistically significance

## Results

*Annexin A2 Staining*

In pancreatic ductal adenocarcinoma and it's association with Clinicopathological Characteristics.

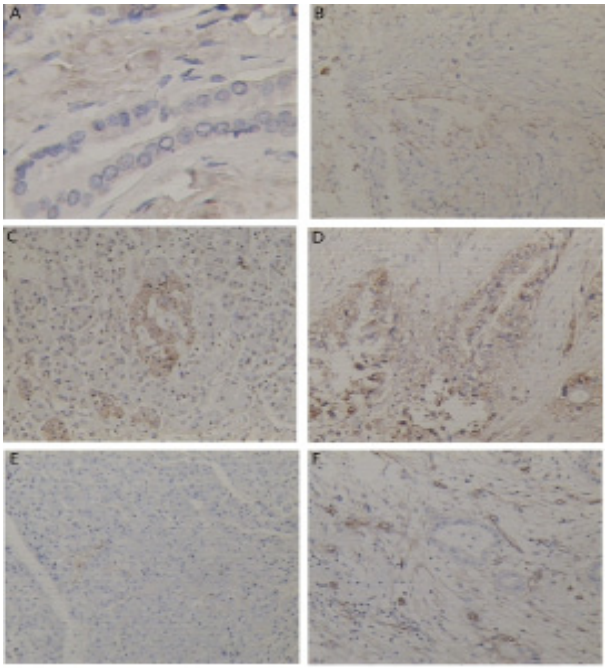


**Figure 1. Immunohistochemistry Staining Pattern of Annexin A2 and CD105 in PDAC and Adjacent Normal tissues A.** The expression of Annexin A2 in adjacent normal tissues (400×) ; B Weak positive staining (+) of Annexin A2 in PDAC tissues (100×); C Moderate positive staining (2+) of Annexin A2 in PDAC tissues (100×); D Strong positive staining (3+) of Annexin A2 in PDAC tissues; E The expression of CD105 in PDAC tissues(100×); F The expression of CD105 in adjacent normal tissues (100×)

**Table 1. Relationship between Annexin A2 and CD105 and Clinicopathological Features**

| | | n | Annexin A2 染色 0 | Annexin A2 染色 +~3+ | P | MVD | P |
|---|---|---|---|---|---|---|---|
| Tumor tissue | | 51 | 6 | 45 | <0.005 | 11.24±3.18 | <0.01 |
| Adjacent normal tissue | | 51 | 34 | 17 | | 1.08±1.163 | |
| Histopathological grading | G1 | 14 | 4 | 10 | =0.029▫ | 8.29±2.43 | <0.05# |
| | G2 | 6 | 1 | 5 | | 10.50±2.59 | <0.05☆ |
| | G3 | 31 | 1 | 30 | | 12.71±2.82 | <0.05△ |
| TNM stage | I~II[a] | 23 | 5 | 18 | 0.079 | 10.17±2.807 | 0.026 |
| | II[b] | 28 | 1 | 27 | | 12.14±3.214 | |

▫: G3versus G1, G2; #: G1versus G2; ☆: G2versusG3; △: G3 versus G1(#, ☆, △: SNK variance analysis method)

**Table 2. Annexin A2 Expression in Tumor and Adjacent Normal Tissues**

| | Annexin A2 stain grading 1+ | 2+ | 3+ | sum | T | P |
|---|---|---|---|---|---|---|
| Tumor tissues | 10 | 20 | 15 | 45 | 1685 | <0.05 |
| Adjacent normal tissues | 15 | 2 | 0 | 17 | 268 | |
| sum | 25 | 22 | 15 | 62 | | |

*rank sum test

**Table 3. The Correlation between Annexin A2 Expression and MVD**

| Group | Annexin A2 staining grading | n | MVD | F | P |
|---|---|---|---|---|---|
| 1 | 0 | 6 | 11.67±2.51 | 13.182 | <0.05 |
| 2 | 1+ | 10 | 12.3±3.19 | | |
| 3 | 2+ | 20 | 13.0±1.75 | | |
| 4 | 3+ | 15 | 8.0±2.67 | | |

*ANOVA

Annexin A2 staining in PDAC tissue was localized at the cell membranes (Figure 1 B~D). Among the 51 PDAC specimens, negative (-) Annexin A2 staining was examined in 6 specimens, weak positive (1+) Annexin A2 staining was examined in 10 specimens, moderate positive (2+) Annexin A2 staining was examined in 20 specimens and strong positive (3+) Annexin A2 staining was examined in 15 specimens. On the contrary, in the 51 adjacent normal tissues, negative (-), weak positive (1+) and moderate positive (2+) Annexin A2 staining was examined in 34 specimens, 15 specimens and 2 specimens, respectively. Strong positive (3+) staining was not detected. The Annexin A2 Expression percentage in tumor tissues was 88.2% (45/51), Is significantly higher than that in adjacent normal tissues (33.3%, 17/51) ($p$<0.005) (Table 1, Table 2). Annexin A2 expression was associated with histopathological grading, Annexin A2 expression in G3 tissues is stronger than that in G1 and G3 tissues ($p$=0.029) (Table 1). However, Annexin A2 staining was not related to TNM classification of PDAC ($p$=0.079).

*CD105 staining*

CD105 staining in PDAC tissue was only localized at the cytomembrane and cytoplasm of new Vascular endothelial cells (Figure 1F), These new Vascular endothelial cells mainly located in the edge of cancer tissue and the The lumen formed by them is not obvious (Figure 1E). The mean MVD in PDAC specimens was 10.54±3.35, was greater than that in adjacent normal tissues (1.08±1.163, $p$<0.05) (Table 1). MVD in PDAC specimens was associated with histopathological grading,

**Table 4. Relationship between MVD and Different Annexin A2 Staining Grading**

| Group | Mean difference | $p$ | 95%CI |
|---|---|---|---|
| Annexin A2(-) versus Annexin A2(1+) | -0.633 | 0.609 | -3.11~1.84 |
| Annexin A2(-) versus Annexin A2(2+) | -1.383 | 0.218 | -3.61~0.85 |
| Annexin A2(-) versus Annexin A2(3+) | 3.667 | 0.003 | 1.35~5.98 |
| Annexin A2(1+) versus Annexin A2(2+) | -0.75 | 0.42 | -2.60~1.10 |
| Annexin A2(1+) versus Annexin A2(3+) | 4.3 | 0 | 2.34~6.26 |
| Annexin A2(2+) versus Annexin A2(3+) | 5.05 | 0 | 3.41~6.69 |

*LSD test

the highest in G3, the second in G2 and the lowest in G1 (Table 1) MVD in tissues of TNM staging IIb period was higher than that in I-IIa period ($p$<0.026) (Table 1).

The correlation between Annexin A2 expression and MVD in PDAC tissues: CD105 and Annexin A2 evaluated by spearman rank correlation showed significant correlation between two markers (r= -0.443 $p$=0.001). MVD in strong positive (3+) Annexin A2 staining PDAC specimens Annexin is lower than that in other Annexin A2 staining specimens ($p$<0.05), However, MVD in negative, weak and moderate Annexin A2 staining PDAC tissues had no difference (Table 3, Table 4).

*Prognostic Impact of Annexin A2 Expression on Overall Survival And Disease-Free Survival*

We further analyzed the assosiation of Annexin A2 Expression with overall survival. The median overall survival time and disease-free survival time for all patients was 13.0 months (95%CI: 8.056-17.944 months) and 9months (95%CI: 7.251-10.749 months), respectively. Kaplan-Meier analysis was used to evaluate the overall survival and disease-free survival of patients with pancreatic cancer indicates that: .that patients with Annexin A2 positive tumors (+~3+)had indifferent overall survival compared with patients with Annexin A2 negative tumors (Figure 2, Log Rank test: $p$=0.456), the same with disease-free survival (Figure 2, Log Rank test: $p$=0.143). The median overall survival time and Disease-Free Survival time of patients with Annexin A2 positive tumors (+~3+)was 13 months (95%CI: 9.756-16.235), 10 months (95%CI: 5.627-14.373), respectively, and the median overall survival time and Disease-Free Survival time patients with Annexin A2 negative tumors was 14.0 months (95%CI: 3.198-24.802), 8months (95%CI: 6.868-9.123), respectively. whereas, the different overall survival was observed in different patients with different positive classification of Annexin A2 positive staining tumors (Log Rank test: $p$<0.001), the same with disease-free survival (Figure 2). However, in multivariate analysis,

**Table 5. Multivariate Analysis of Factors Associated with OS and DFS**

| Factors | OS Multivariate | | | DFS Multivariate | | |
|---|---|---|---|---|---|---|
| | HR | 95%CI | *P* | HR | 95%CI | *P* |
| Gender | | | 0.838 | | | 0.915 |
| TNM stage | | | 0.162 | | | 0.188 |
| Histopathological grade | | | 0.174 | | | 0.226 |
| MVD (quantitation) | 1.236 | 1.113~1.373 | <0.001 | 1.227 | 1.107~1.361 | <0.001 |
| Annexin A2 expression | | | 0.071 | | | 0.626 |

*COX Regression(LR)

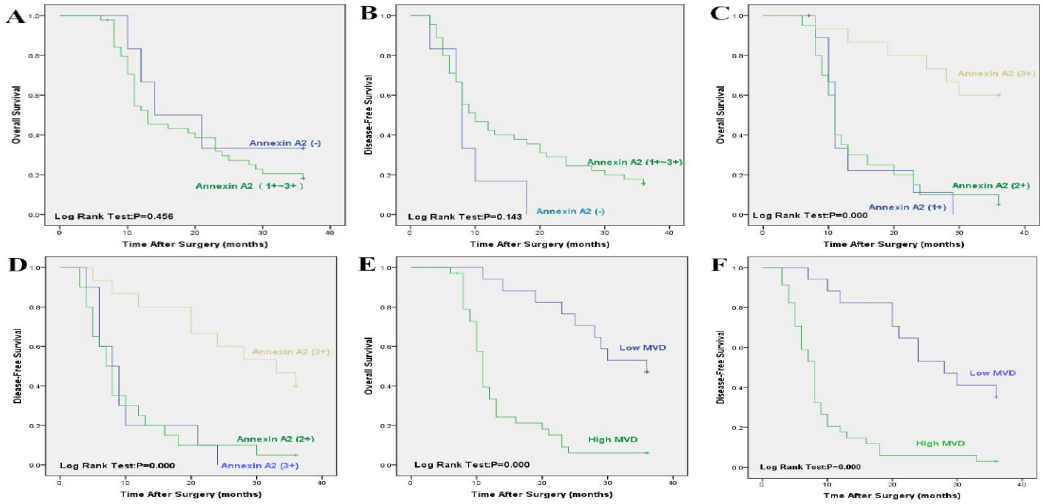


**Figure 2. Cumulative Overall Survival (OS) and Recurrence-free Survival (RFS) Curves of Patients with Different Annexin A2 Expression and Low or High Microvessel Density (MVD).** (A, B) The Annexin A2 expression was associated with neither OS nor RFS. (C, D) The patients with different positive staining of Annexin A2 had different OS and DFS (log-rank test: P<0.001). (E, F) Low MVD was associated with prolonged OS and RFS(log-rank test: *p*<0.001).

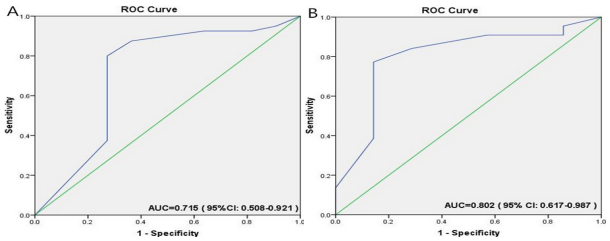


**Figure 3. Receiver Operating Characteristic Curve (ROC) of MCD for OS and DFS.** A: receiver operating characteristic curve (ROC) of MCD for OS with AUC: 0.715 (95% CI: 0.508-0.921). B: receiver operating characteristic curve (ROC) of MCD for OS with AUC: 0.802 (95% CI: 0.617-0.987)

Cox proportional hazards model indicated that Annexin A2 expression was not an independent prognostic factor of overall survival of patients with pancreatic cancer (Table 5).

*Prognostic impact of MVD on Overall Survival and Disease-Free Survival*

The mean MVD of PDAC was 10.54±3.35, and the cut-off value of MVD was 9.5 with sensitivity for OS and RFS was 80.0%, 77.3% and specificity for OS and DFS was 72.7%, 85.7%, respectively. The area under receiver operating characteristic curve was 0.715 (95%CI: 0.508-0.921) for OS and 0.802 (95%CI: 0.617-0.987) for DFS (Figure 3), indicated that MVD had a moderate predictive value of prognosis for patients with PDAC. The Low MVD was defined as MVD below9.5 or contain 9.5, on the contrary, MVD above 9.5 was defined as High MVD. Log-Rank test shows: The median OS survival for patients with Low MVD is 29 months (95%CI: 26.311.~31.689), Higher than that of High MVD patients (11 Months, 95%CI: 10.084~11.916, Log Rank test: *p*=0.143) (Figure 2). The median DFS survival for patients with Low MVD is 25 months (95%CI: 19.958.~30.042), Higher than that of High MVD patients (8 Months, 95%CI: 6.812~10.188, Log Rank test:*p*=0.000) (Figure 2). The COX regression confirmed that furthermore, The High MVD was an independent risk factor of OS and DFS for PDAC patients (HR of OS=1.236, 95%CI:1.113~1.373;HR of DFS=1.227, 95%CI:1.107~1.361) (Table 5)

## Discussion

Annexin A2 (ANXA2) was a member of annexin family Annexin A2 and Widely exists in many kinds of cells in the human body (Liu et al., 2014), and had been reported to participate in processes localised to the cell surface including extracellular protease regulation and cell cell interactions (Bharadwaj et al., 2013). Studies had shown that Annexin A2 played an important role in tumorigenesis (Okuse et al., 2002). Annexin A2 tetramers. (AIIt) can be used as co-receptor of t-PA and PLG, to regulate the produce of Plasmi and promote the tumor invasion and was correlated with clinical outcomes (Yang et al., 2014). Annexin A2 is reported to be overexpressed in a variety of cancers including lung cancer, colon cancer, gastric cancer, hepatocellular carcinoma and malignant glioma (Zheng and Jaffee, 2012). Many research showed

that Annexin A2 was a kind of differential protein in pancreatic cancer tissue using proteomics analysis (Shen et al., 2004). Our present study found that Annexin A2 had high expression in PDAC tissues compared with adjacent normal tissues and was associated with pathological grade of PDAC, indicating that Annexin A2 may be used as a diagnostic marker of PDAC. Ercument Gurluler, et al verified the promise of serum levels of Annexin A2 as a distinct biomarker with diagnostic value in patients with colon cancer (Gurluler et al., 2014). We speculated that Annexin A2 was an important role in tumor invasion and could be used as a target for the treatment of PDAC. However, the present study showed that the Annexin A2 was not an independent risk factor for patients with PDAC, The finding may be attributed to little scale of patients in our study. As a result, a research with larger scale of patient should be performed in the future.

CD105 (Endoglin) was a member of transforming growth factor β (TGFβ) superfamily, Related to angiogenesis and maintaining vascular. CD105was highly expressed on endothelial cells of nascent tumor blood vessels and vascular endothelial cells of the tumor margin and was considered to be an ideal target in tumor therapy to inhibit tumor angiogenesis (Li et al., 2014), CD105 strongly overexpressed in the endothelial cells of arteries and veins surrounding tumor tissues contrasted with tumor cell (Ling et al., 2004), Our experiment confirmed CD105 is mainly expressed in the vascular endothelial cells around tumor tissues. Microvessel density (MVD) in tumor tissues is directly correlated with the prognosis of patients with cancer, some research showed that in breast cancer, cervical cancer and other malignant tumor tissues, MVD labeled by CD105 is better than that labeled by CD34, VIII factor related antigen, Etc. And MVD was associated with survival of patients with prostate cancer, As a consequence, it can be used as an independent prognostic factor (Miyata et al., 2014). The present experiment proved MVD labeled by CD105 in PDAC tissues was obviously higher than MVD in adjacent normal tissue, and was associated with histopathological grading and TNM staging of tumor tissue. MVD increased with exacerbation of histopathological grading, MVD of tumor tissue in TNM IIb stage is higher than that in I~IIa stage, the present study proved MVD maight be an independent risk factor of prognosis for patients with PDAC and had moderate predictive value. Tumor growth and metastasis was depended on angiogenesis, and CD105 is necessary for neovascularization, Azadeh Andisheh Tadbir1 et al. observed that there was a higher expression of CD105 in malignant salivary tumors compared to benign tumor (Tadbir et al., 2012). Fonsatti et al. comfirmed that CD105 monoclonal antibody showed anti-cancer efficiency in breast cancer cells with no serious adverse reaction (Fonsatti et al., 2001), speculated that CD105 may be a target of PDAC treatment to improve the prognosis of pancreatic cancer.

The present study confirmed that there was significant correlation between two markers and MVD in tissues of strong positive (3+) Annexin A2 staining was lower compared with negative (-), weak positive (1+) and moderate positive (2+) Annexin A2 staining, and the difference between negative (-), weak positive (1+) and moderate positive (2+) Annexin A2 staining showed no significance. In consequence of Annexin A2 could promote new blood vessels endothelial cells to form tube-like structure (Kumar et al., 1999; Ling et al., 2004), resulted in decrease of isolated vascular endothelial cells and lower MVD in specimens of strong positive (3+) Annexin A2 staining, Of course, the specific reason and mechanism needed further research.

In conclusion, Annexin A2 overexpressed in PDAC tissues, and was associated with tumor differentiation. And Annexin A2 had correlation with MVD labeled by CD105. PDAC tissues had higher MVD labeled by CD105 than that of adjacent normal tissues, and MVD is associated with histopathology grading and TNM stage. Our study also proved MVD labeled by CD105 was an independent risk factor and had moderate predictive value of prognosis for patients with PDAC.

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