Clinical implication of Tiam1 overexpression in the prognosis of patients with serous ovarian carcinoma

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Abstract. T lymphoma invasion and metastasis 1 (*Tiam1*), a guanine nucleotide exchange factor, was originally identified as an invasion- and metastasis-inducing gene in T lymphoma cells. High expression levels of the human *Tiam1* gene have been found in numerous human malignancies, suggesting a potential role as a modifier of tumor initiation and progression. However, little is known about the status of *Tiam1* in ovarian carcinoma. The present study aimed to investigate the clinicopathological significance of high *Tiam1* expression in serous ovarian carcinoma. Immunohistochemical staining for Tiam1 was performed in 182 patients with serous ovarian carcinoma, in 76 patients with ovarian borderline tumors and in 72 patients with benign ovarian tumors. Immunofluorescence staining was also performed to detect the subcellular localization of Tiam1 protein in SK-OV-3 ovarian carcinoma cells. The correlations between high Tiam1 expression and the clinicopathological features of the ovarian carcinomas were evaluated by the χ^2 test and Fisher's exact test. The overall survival (OS) rates were calculated by the Kaplan-Meier method, and the association between prognostic factors and patient survival was analyzed by the Cox proportional hazard model. Tiam1 protein showed a cytoplasmic and nuclear staining pattern in ovarian carcinoma. Strongly-positive Tiam1 protein expression was observed in 59.3% (108/182) of ovarian carcinomas, which was significantly higher than in benign serous tumors (12.5%; 9/72). Moreover, the rate of strongly-positive Tiam1 expression in borderline serous tumors (31.6%; 24/76) was also significantly higher than that in benign serous tumors. High Tiam1 protein expression was closely associated with a high histological grade, metastasis, advanced clinical stage and lower OS rates in ovarian carcinoma. Multivariate analysis indicated that Tiam1 was an independent prognostic factor, along with metastasis and clinical stage, in patients with ovarian carcinoma. In conclusion, Tiam1 expression is strongly associated with grade and outcome in ovarian carcinoma, and may serve as a useful molecular marker for clinical management.

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Introduction

Detecting carcinoma at an early stage or tackling it at the late stage in an efficient way is always a challenge in clinical oncology. As one of the most frequently occurring gynecological malignancies, ovarian carcinoma is the fifth most common cause of cancer-associated mortality in women (1). The poor clinical outcome is likely to be caused, at least in part, by the high percentage of cases diagnosed at an advanced stage. Tumor recurrence and chemoresistance are common reasons for carcinoma-related mortality (2). Understanding the possible mechanisms underlying the aggressive progression of ovarian carcinoma may, therefore, provide better prognostic and predictive factors for this disease.

T lymphoma invasion and metastasis protein (Tiam1) was first identified as a gene that induces invasion and metastasis using T lymphoma cells by proviral tagging and *in vitro* selection for invasiveness (3,4). Tiam1 is a guanine nucleotide exchange factor that mediates the specific activation of Rac1 (5-7). Tiam1 maintains the specificity of Rac1 toward specific downstream effector pathways, whereas Rac1 regulates cell survival and cell cycle progression (8,9). Together, Tiam1-Rac1 is a critical component in the biology of human tumors, affecting the transformed cells themselves and the tumor microenvironment (10-12). Tiam1 is a potent modifier of oncogenic Ras-induced skin tumor initiation, promotion and progression (13). Moreover, numerous studies have demonstrated that the upregulation of Tiam1 is associated with an aggressive phenotype and a poor clinical outcome in several types of malignant tumors, including breast (14), colon (15), prostate (16), liver (17) and nasopharyngeal (11) tumors, and

esophageal squamous cell carcinoma (18). However, to date, the correlation between Tiam1 expression and ovarian carcinoma has not been adequately investigated.

The current study was undertaken to investigate the expression of Tiam1 in human ovarian benign, borderline and malignant tumors, and to investigate whether Tiam1 expression is associated with the clinicopathological features of ovarian carcinoma. Furthermore, the prognostic value of high Tiam1 expression in patients with serous ovarian carcinoma was also assessed.

Materials and methods

Ethics statement. This study complied with the Declaration of Helsinki and was approved by the Human Ethics and Research Ethics committees of Yanbian University Medical College (Yanji, Jilin, China) and The People's Hospital of Beijing University (Beijing, China). Through the use of surgical consent forms, patients were informed that the resected specimens would be stored by the hospital and potentially used for scientific research, and that their privacy would be maintained. Follow-up survival data were collected retrospectively through medical record analyses.

Patients and tissue specimens. A total of 330 human ovarian tumor specimens, including 182 serous carcinomas, 76 borderline serous tumors and 72 benign serous tumors, were used for this study. These tumors were selected randomly from female patients undergoing surgery between February 2006 and October 2010, and stored in the Tumor Tissue Bank of Yanbian University Medical College. Pathological parameters, including age, menopausal status, grade, metastasis and survival data, were carefully reviewed in all 182 serous ovarian carcinomas.

In these 182 cases, the patients ages ranged from 16 to 75 years, with a mean age of 48.3 years, and the patient age ratio between ≥ 48 years to <48 years was 101:81. All samples were routinely fixed in 10% buffered formalin and embedded in paraffin, and tissue sections (4-μm) were stained with hematoxylin and eosin (H&E). The H&E-stained slides of the different biopsies were reviewed by two experienced pathologists and one appropriate paraffin block was selected for this study. Histopathological grading was performed using the World Health Organization (Pathology and Genetics Tumors of Gynecological System) criteria (with 72 low-grade tumors and 110 high-grade tumors) (19). All the ovarian carcinoma patients were clinically staged according to the International Federation of Gynecology and Obstetrics (FIGO) staging system [with 86 early-stage tumors (FIGO stages I and II) and 96 late-stage tumors (FIGO stages III and IV)] (19). None of the ovarian carcinoma patients received pre-operative radiation or chemotherapy prior to surgery. All ovarian carcinoma patients had follow-up records of longer than 5 years.

Immunohistochemical (IHC) analysis. IHC analysis was performed using the DAKO LSAB kit (DAKO A/S, Glostrup, Denmark). Briefly, to eliminate endogenous peroxidase activity, 4-μm thick tissue sections were deparaffinized, rehydrated and incubated with 3% H_2O_2 in methanol for 15 min at room temperature (RT). The antigen was retrieved at 95˚C for 20 min by placing the slides in 0.01 M sodium citrate buffer (pH 6.0). The slides were then incubated with the polyclonal anti-C-terminal Tiam1 antibody (1:100 dilution; catalog no. SC-872; Santa Cruz Biotechnology Inc., Dallas, TX, USA) at 4˚C overnight. Following incubation with the biotinylated secondary antibody (catalog no. PV9000; ZSGB-Bio, Beijing, China) at RT for 30 min, the slides were incubated with streptavidin-peroxidase complex at RT for 30 min. Immunostaining was developed using 3,3'-diaminobenzidine, and Mayer's hematoxylin was used for counterstaining (20). Rabbit immunoglobulin G (IgG) (1:2,500 dilution; catalog no. GTX35035; GeneTex Inc., Irvine, CA, USA) was used as an isotope control. In addition, positive tissue sections were processed while omitting the primary antibody (rabbit anti-Tiam1) for negative controls.

As described previously (21), expression was scored by two pathologists who did not possess knowledge of the clinical data. In case of discrepancies, a final score was established by reassessment on a double-headed microscope. Briefly, the immunostaining for Tiam1 was semi-quantitatively scored as follows: -, no or <5% positive cells; +, 5-25% positive cells; ++, 26-50% positive cells; and +++, >50% positive cells). The cytoplasmic and nuclear expression patterns were each considered as a positive staining result. Tissue sections scored as ++ and +++ were considered as strong positive results (high expression) for Tiam1. For the survival data analysis, ++ or +++ samples were considered as high Tiam1 expression and - or + samples were considered as low Tiam1 expression.

Immunofluorescence (IF) staining analysis. IF staining was used to detect the subcellular localization of Tiam1 protein in ovarian carcinoma SK-OV-3 cells (Korean Cell Line Bank, Seoul, Korea). All steps were performed at RT. SK-OV-3 cells were grown to 70-80% confluence on coverslips, then fixed with 4% paraformaldehyde for 10 min and permeabilized with 0.5% Triton X-100 for 10 min after 24 h. Subsequent to being blocked with 3% Albumin Bovine V (catalog no. A8020; Solarbio, Beijing, China) for 1 h, the slides were quickly and gently washed with phosphate-buffered saline (PBS). The cells were then incubated with the Tiam1 antibody (1:100 dilution) at 4˚C overnight, followed by incubation with Alexa Fluor® 488 goat anti-rabbit IgG (H+L) (catalog no. A11004; 1:1,000 dilution; Invitrogen; Thermo Fisher Scientific, Inc., Waltham, MA, USA) for 1 h. After washing with PBS, the cells were counterstained with 4',6-diamidino-2-phenylindole (catalog no. C1006; Beyotime, Shanghai, China) and the coverslips were mounted with Antifade Mounting Medium (catalog no. P0126; Beyotime) (21). Finally, the IF signals were visualized and recorded using a Leica SP5II confocal microscope (Leica Microsystems GmbH, Wetzlar, Germany).

Statistical analysis. Statistical analyses included descriptive statistics with determination of minimal and maximal values, means and medians, with 95% confidence intervals (CIs) for particular variables. The χ^2 test and Fisher's exact test were used to assess correlations between clinicopathological characteristics and the expression of the studied protein. The Kaplan-Meier method was used to calculate the survival rates after tumor removal and the Log-rank test was used to analyze the differences in survival curves. Multivariate survival

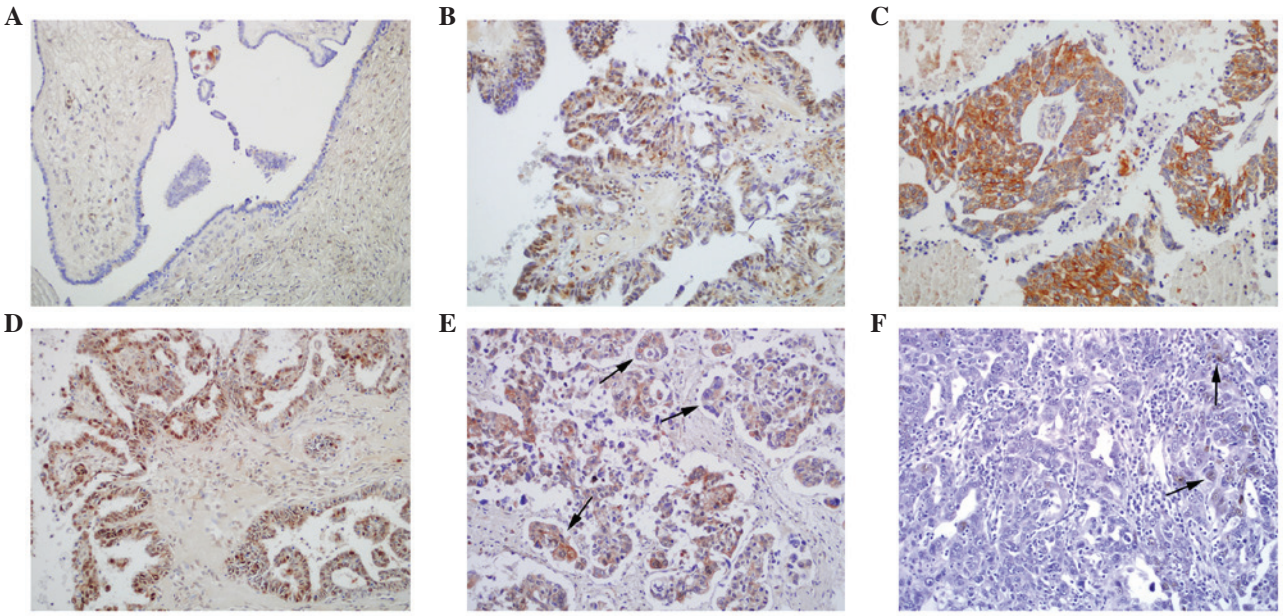

Figure 1. Immunohistochemical staining of T lymphoma invasion and metastasis 1 (Tiam1) protein in ovarian tumor samples. (A) Negative expression of Tiam1 protein in a benign serous tumor. (B) Positive expression of Tiam1 protein in a borderline serous tumor. (C) Strong positive expression of Tiam1 protein in serous carcinoma cells, showing a cytoplasmic staining pattern. (D) A mainly nuclear staining pattern in serous carcinoma cells. (E) Positive expression of Tiam1 protein in the metastatic serous carcinoma cells in the vascular/lymphatic vessels (arrows). (F) Negative or weakly-positive expression of Tiam1 protein in serous carcinoma without metastasis. Original magnification, x200.

analysis was performed on all the characteristics measured by univariate survival analysis (age, menopausal status, histological grade, metastasis, FIGO stage and Tiam1 expression) through the Cox proportional hazard regression model. Statistical analyses were performed using the SPSS software program for windows, version 17.0 (SPSS, Inc, Chicago, IL, USA), and the JMP software program for Mac, version 10.0.0 (SAS Institute Inc, Cary, NC, USA). P<0.05 was considered to indicate a statistically significant difference.

Results

Tiam1 protein is overexpressed in serous ovarian carcinoma. IHC staining for the Tiam1 protein was performed in 182 ovarian carcinoma tissues. The analysis of Tiam1 expression in the ovarian carcinoma cells from the 182 patients revealed predominantly cytoplasmic and nuclear expression patterns in the positive cases (Fig. 1). The IF staining results also showed that Tiam1 protein was localized in the cytoplasm and nuclei of the ovarian carcinoma SK-OV-3 cells (Fig. 2).

IHC staining indicated that the rate of positive Tiam1 protein expression was significantly higher in serous carcinomas (75.8%; 138/182) than in benign serous tumors (36.1%; 26/72) (P<0.01). Similarly, the rate of strongly positive Tiam1 protein expression was significantly higher in serous carcinomas (59.3%; 108/182) than in benign serous tumors (12.5%; 9/72) (P<0.01). Moreover, the rates of positive (51.3%; 39/76) and strongly-positive (31.6%; 24/76) Tiam1 protein expression in borderline serous tumors were significantly higher than those in benign serous tumors (P<0.05 and P<0.01, respectively) (Table I).

Correlations between Tiam1 expression status and clinicopathological features of serous ovarian carcinoma. To evaluate the association between Tiam1 protein and ovarian carcinoma progression, the correlations between high Tiam1 expression and the clinicopathological features of ovarian carcinomas were analyzed. The rate of strongly-positive Tiam1 protein expression was significantly higher in high-grade (66.4%; 73/110) ovarian carcinomas than in low-grade cases (48.6%; 35/72) (P=0.017), and in ovarian carcinomas with metastasis (73.2%; 71/97) than in cases without metastasis (43.5%; 37/85) (P<0.001). Regarding FIGO clinical stages, the rate of strongly-positive Tiam1 expression was 69.8% (67/96) in the late-stage (IIB-IIIC) ovarian carcinomas, but only 47.7% (41/86) in the early-stage (I-IIA) cases (P=0.002). However, high expression of Tiam1 protein was not associated with the age or menopausal status of the patients with ovarian carcinoma (Fig. 3; Table II).

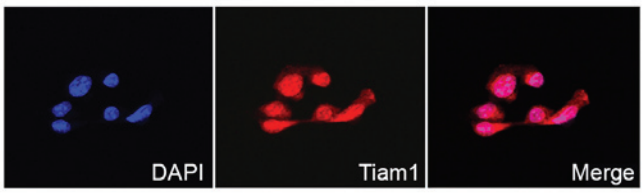

Figure 2. Immunofluorescence staining of the T lymphoma invasion and metastasis 1 (Tiam1) protein in ovarian carcinoma SK-OV-3 cells. The Tiam1 protein was localized in the cytoplasm and the nucleus of the cells [red indicates Tiam1 staining, blue indicates 4',6-diamidino-2-phenylindole (DAPI) staining].

High Tiam1 expression is an independent biomarker of a poor prognosis in patients with serous ovarian carcinoma. To further substantiate the importance of high Tiam1 expression in ovarian carcinoma progression, the overall survival (OS) rate of 182 ovarian carcinoma patients was assessed

Table I. T lymphoma invasion and metastasis 1 protein expression in ovarian carcinoma.

Diagnosis	No. of cases	Positive cases, n				Positive cases, %	Strongly-positive cases, %
		-	+	++	+++		
Serous carcinoma	182	44	30	72	36	75.8[a]	59.3[a]
Borderline serous tumor	76	37	15	19	5	51.3[b]	31.6[a]
Benign serous tumor	72	46	17	9	0	36.1	12.5

[a]P<0.01 and [b]P<0.05 compared with benign serous tumor.

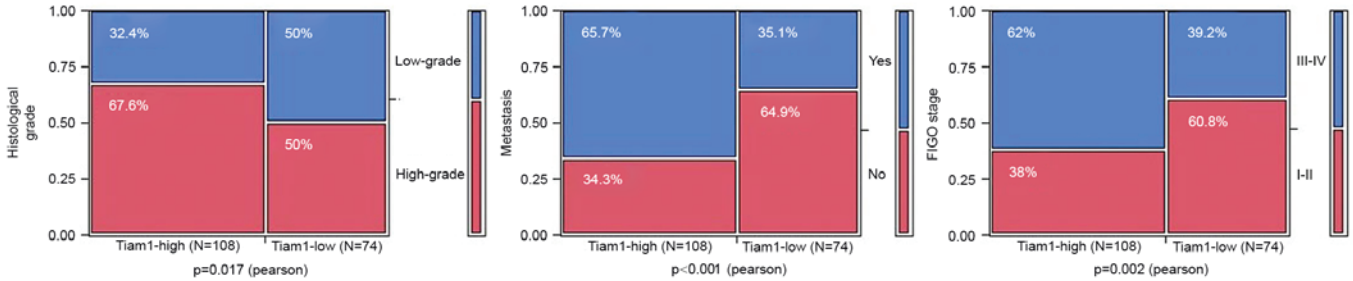

Figure 3. Correlations between T lymphoma invasion and metastasis 1 (Tiam1) expression and the clinicopathological significance of ovarian carcinoma. The expression level of Tiam1 protein was significantly associated with histological grade (P=0.017), metastasis (P<0.001) and International Federation of Gynecology and Obstetrics (FIGO) stage (P=0.002).

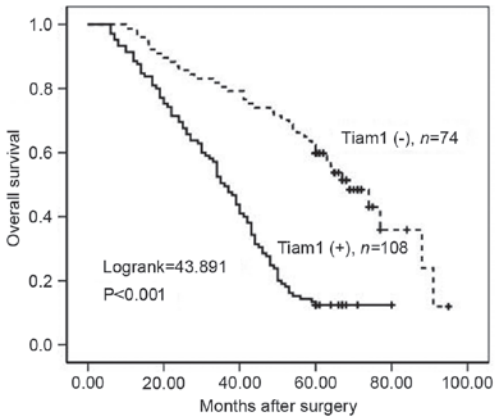

Figure 4. Kaplan-Meier survival curves illustrating the significance of T lymphoma invasion and metastasis 1 (Tiam1) expression in ovarian carcinomas. Overall survival rates of patients with high and low Tiam1 expression.

using the Kaplan-Meier method. Patients with high Tiam1 expression exhibited a lower OS rate than those with low Tiam1 expression (Log-rank=43.891, P<0.001) (Fig. 4). Similarly, ovarian carcinoma patients with high Tiam1 expression exhibited decreased OS rates compared with those with low Tiam1 expression in early-stage cases (Log-rank=14.430, P<0.001) and late-stage cases (Log-rank=23.562, P<0.001) (Fig. 5). Notably, high Tiam1 expression was associated with significantly lower OS rates in cases with metastasis (Log-rank=15.087, P<0.001) and without metastasis (Log-rank=17.337, P<0.001) (Fig. 6). Moreover, the survival rate of patients with low-grade (Log-rank=19.293, P<0.001) and high-grade (Log-rank=21.038, P<0.001) ovarian carcinoma was significantly lower in patients with tumors exhibiting high Tiam1 expression compared with those exhibiting low expression (Fig. 7).

Univariate analysis demonstrated that histological grade (P=0.019), metastasis (P<0.001), FIGO stage (P<0.001) and Tiam1 expression status (P<0.001) were all significantly associated with OS rate in patients with ovarian carcinoma. These data suggested that Tiam1 may be a valuable prognostic factor in ovarian carcinoma. Multivariate analysis was subsequently performed using the Cox proportional hazards model for all variables examined in the univariate analysis. It was found that the high expression of Tiam1 (HR, 2.559; 95% CI, 1.788-3.663; P<0.001), FIGO stage (HR, 2.530; 95% CI, 1.835-3.488; P<0.001) and metastasis (HR, 2.088; 95% CI, 1.493-2.919; P<0.001) were significant independent prognostic factors for survival in ovarian carcinoma (Table III).

Discussion

Tiam1 exhibits a number of roles in the regulation of cellular functions depending on the specific cell type, substratum and other factors (17). As a guanine nucleotide exchange factor, Tiam1 has been shown to be essential in a range of tumor signaling pathways through the regulation of Rho GTPase functions (22). It has been shown that Tiam1 is involved in the rearrangement of the cytoskeleton, the migration of cells, and the mobility of T-lymphoma cells, fibroblasts and epithelial cells (5,6,23,24). Moreover, studies have indicated that Tiam1 is involved in anti- and pro-apoptotic mechanisms (25). Accordingly, alterations in Tiam1 expression/function may contribute to tumorigenesis and carcinoma progression of common types of human cancer.

Table II. Correlations between Tiam1 protein expression and the clinicopathological parameters of ovarian carcinoma.

Variables	No. of cases	Tiam1 strongly positive cases, n (%)	χ^2	P-value
Age, years				0.777
≥48	101	59 (58.4)	0.080	
<48	81	49 (60.5)		
Menopausal status				0.371
Premenopausal	86	54 (62.8)	0.804	
Postmenopausal	96	54 (56.3)		
Histological grade				0.017[a]
Low-grade	72	35 (48.6)	5.684	
High-grade	110	73 (66.4)		
Metastasis				<0.001[b]
No	85	37 (43.5)	16.525	
Yes	97	71 (73.2)		
FIGO stage				0.002[b]
I-II	86	41 (47.7)	9.197	
III-IV	96	67 (69.8)		

[a]P<0.05 and [b]P<0.01. Tiam1, T lymphoma invasion and metastasis 1; FIGO, International Federation of Gynecology and Obstetrics.

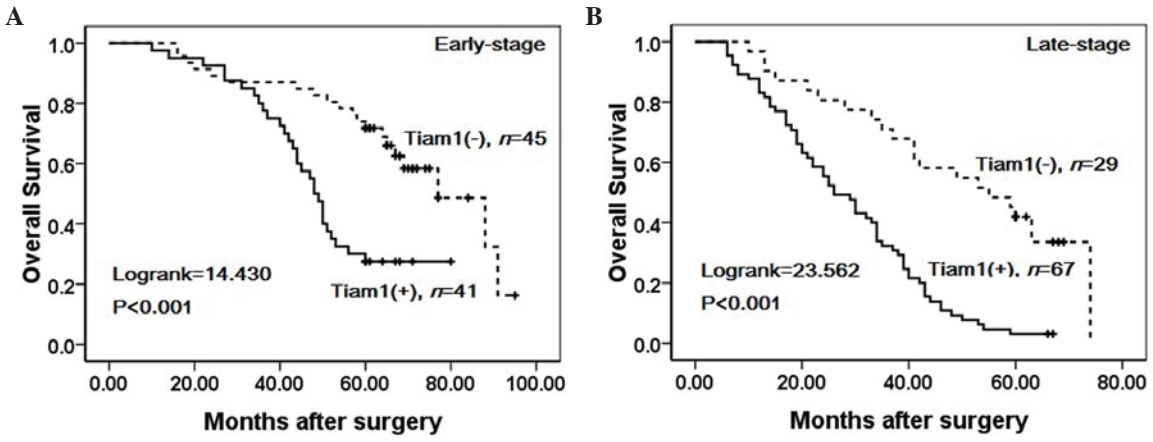

Figure 5. Kaplan-Meier survival curves illustrating the significance of T lymphoma invasion and metastasis 1 (Tiam1) expression in the early and late stages of ovarian carcinomas. High Tiam1 expression was strongly associated with the poor overall survival of patients with (A) early- or (B) late-stage ovarian carcinoma.

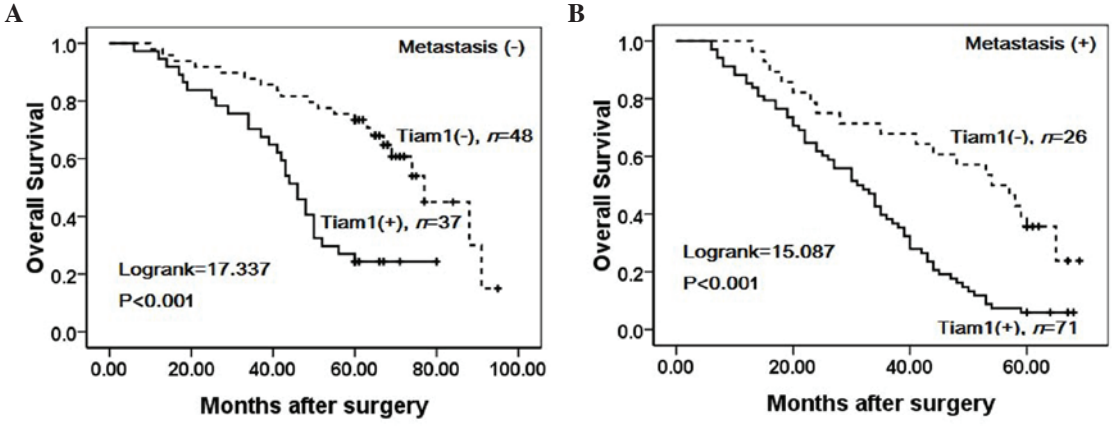

Figure 6. Kaplan-Meier survival curves illustrating the significance of T lymphoma invasion and metastasis 1 (Tiam1) expression in ovarian carcinomas with or without metastasis. High Tiam1 expression predicted poor overall survival in (A) patients without metastasis or (B) in those with metastasis of ovarian carcinoma.

Table III. Univariate and multivariate analysis of clinicopathological factors for the overall survival rate of 182 patients with ovarian carcinoma.

	Univariate analysis		Multivariate analysis	
Characteristics	HR (95% CI)	P-value	HR (95% CI)	P-value
Age, years	1.079 (0.802-1.453)	0.615	0.979 (0.715-1.340)	0.894
Menopausal status	1.093 (0.811-1.472)	0.559	0.920 (0.660-1.283)	0.624
Histological grade	1.436 (1.062-1.942)	0.019[a]	1.147 (0.831-1.582)	0.405
Metastasis	2.739 (1.981-3.787)	<0.001[b]	2.088 (1.493-2.919)	<0.001[b]
FIGO stage	2.705 (1.978-3.699)	<0.001[b]	2.530 (1.835-3.488)	<0.001[b]
Tiam1	2.854 (2.075-3.927)	<0.001[b]	2.559 (1.788-3.663)	<0.001[b]

[a]P<0.05 and [b]P<0.01. HR, hazard ratio; CI, confidence interval; Tiam1, T lymphoma invasion and metastasis 1; FIGO, International Federation of Gynecology and Obstetrics.

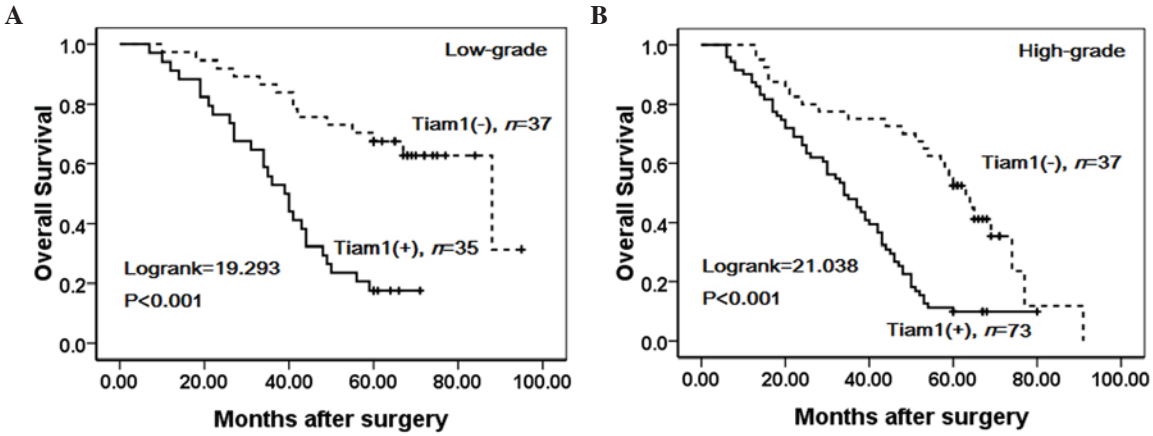

Figure 7. Kaplan-Meier survival curves illustrating the significance of T lymphoma invasion and metastasis 1 (Tiam1) expression in low- or high-grade ovarian carcinomas. High Tiam1 expression was strongly associated with poor overall survival in patients with (A) low- or (B) high-grade ovarian carcinoma.

Increasing evidence has focused on the regulation of Tiam1, as well as its role in carcinoma progression and metastasis. Liu *et al* found that Tiam1 expression was upregulated in lung carcinoma compared with normal lung tissues, and analysis further showed that Tiam1 overexpression was correlated with the lymph node metastasis of patients with lung carcinoma (22). Yu *et al* demonstrated that Tiam1 was upregulated in colorectal carcinoma tissues and provided evidence that Tiam1 was closely correlated to the metastatic potential of colorectal carcinoma. Depletion of Tiam1 significantly reduced the tumor growth and metastatic ability of colorectal carcinoma cells (26). However, its role in ovarian carcinoma remains to be elucidated. In the present study, IHC and IF staining of Tiam1 protein was performed in ovarian carcinoma tissues. It was found that positive staining of Tiam1 was mainly localized in the cytoplasm and nucleus. Compared with benign serous tumors, the positive and strongly-positive Tiam1 staining were significantly higher in serous carcinomas (both P<0.01), which is consistent with the result of a previous study by Li *et al* (27), and it was also indicated that Tiam1 expression was markedly increased in primary and metastatic ovarian carcinoma tissues relative to normal ovarian tissues in a smaller group. These observations suggest that the high expression of Tiam1 may be correlated with the potential malignancy of ovarian carcinomas. Notably, a significant difference was also observed in the rates of positive and strongly-positive Tiam1 expression between borderline tumors and benign tumors (P<0.05 and P<0.01), which may represent tumor progression. Nonetheless, studies have shown that borderline tumors and high-grade serous tumors have completely different etiologies rather than being high-grade tumors arising from borderline tumors (28). Accordingly, the present study did not compare the expression of Tiam1 in borderline tumors with that in serous carcinomas. Compatible with these findings, it was also observed that the strongly-positive Tiam1 protein expression rate was significantly higher in patients with late-stage serous ovarian carcinomas compared with that in patients with early-stage cancer. The analysis further showed that high Tiam1 expression correlates with the metastasis of patients with ovarian carcinoma, which suggests that Tiam1 may play an important role in the progression and invasion of ovarian carcinoma. Similarly, the strongly-positive Tiam1 protein expression rate was higher in patients with high-grade ovarian carcinoma compared with low-grade cases. High-grade serous ovarian carcinoma is the most lethal form of gynecological malignant carcinoma, and the majority of patients present with late clinical stages (FIGO stages III and

IV) of disease at the time of diagnosis. These results demonstrate that the high expression of Tiam1 may assist in more accurate outcome prediction in serous ovarian carcinoma.

Despite the strong association between Tiam1 expression and cancer, reports of Tiam1 expression-based outcome analysis in tumor patients are limited. Nevertheless, several reports have indicated that the high expression of Tiam1 is significantly associated with the shortened survival of patients with malignancies. For example, Engers *et al* reported that high Tiam1 expression is an independent predictor of decreased disease-free survival for patients with prostate cancer (16). Yang *et al* demonstrated that the high expression of Tiam1 correlates with a poor prognosis in hepatocellular carcinoma (29). Recently, Du *et al* suggested that high Tiam1 expression is associated with poor overall survival in patients with primary gallbladder carcinoma (10). With respect to survival, the present study found that ovarian carcinoma patients exhibiting high Tiam1 expression had lower OS rates compared with patients with low Tiam1 expression ($P<0.01$). Univariate survival analysis revealed that histological grade, metastasis, FIGO stage and Tiam1 expression status were all significantly associated with the OS of patients with serous ovarian carcinoma ($P<0.05$). Furthermore, multivariate survival analysis revealed that Tiam1 expression was an independent prognostic factor, as were metastasis and FIGO stage ($P<0.01$). These clinical and experimental data indicate that Tiam1 may be a useful prognostic factor and a potential therapeutic target in patients with serous ovarian carcinoma.

In conclusion, the high expression of Tiam1 appears to be significantly associated with ovarian carcinoma progression and is an independent prognostic factor, along with metastasis and clinical stage. Additional studies are warranted to further our understanding of the role that Tiam1 plays in ovarian carcinoma tumorigenesis.

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