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# Expression, Intracellular Localization, and Prognostic Value of Plasminogen Activator Inhibitor 1 and PAI-1 RNA-Binding Protein 1 in Primary and Recurrent Ovarian Cancer: A Study of the Tumor Bank Ovarian Cancer Network

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**Keywords**
Plasminogen activator inhibitor 1 · PAI-1 RNA-binding protein 1 · Gene expression · Ovarian cancer · Intracellular localization

**Abstract**
***Background:*** The plasminogen activator system plays a key role in ovarian cancer (OC) tumor progression. The plasminogen activator inhibitor type 1 (PAI-1) and the recently identified PAI-1 RNA binding protein 1 (PAI-RBP1) are primary regulators of plasminogen activation and thus are putative biomarkers for OC progression. ***Methods:*** One hundred fifty six OC patients were analyzed to identify the presence of PAI-1 and PAI-RBP1 and subsequently correlated to clinicopathological parameters. Primary cells obtained from OC patient samples were applied in fluorescence microscopy analysis for examination of PAI-1 and PAI-RBP1 distribution. ***Results:*** PAI-1 and PAI-RBP1 have been found to be predictive markers for OC patients' outcome. PAI-1 levels significantly correlated with volume of ascites, FIGO staging, and lymph node status. PAI-RBP1 expression significantly correlated with age at first diagnosis, histological tumor type, presence of distant metastasis (pM), and recurrence. PAI-1 showed a trend toward association and PAI-RBP1 was significantly associated with progression-free survival. Notably, PAI-1 protein in recurrent OC tissues was exclusively localized in the nucleus. ***Conclusion:*** This study has shown that a combination of PAI-1 and PAI-RBP1 may represent novel prognostic factor for OC. Prospective trials are needed.


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## Introduction

Although ovarian cancer (OC) ranks eighth among the most common female malignancies, it is the fifth cause of death due to cancer in women [1]. This discrepancy is largely attributed to the fact that the majority of patients present with advanced disease at the time of diagnosis. Furthermore, only one molecular marker exists for OC therapy. Patients with mutations of breast cancer types 1 and 2 susceptibility protein (BRCA1/2) genes most likely benefit from olaparib treatment [2]. Therefore, the identification of novel molecular biomarkers could potentially lead to improvement in prognosis and development of novel therapeutic approaches using targeted therapy.

In solid tumors, motility and invasiveness of cancer cells require the activation of proteolytic enzymes leading to the degradation of the extracellular matrix and basement membrane. The urokinase plasminogen activator (uPA) system plays a key role in tumor cell invasion and metastasis. Plasminogen activator inhibitor type 1 (PAI-1) is the primary regulator of plasminogen activation and a member of the serpin superfamily. PAI-1 plays crucial roles in promoting tumor progression by regulating cell motility, extracellular matrix remodelling, and intracellular signaling pathways [3]. Consequently, elevated PAI-1 levels have been detected in numerous carcinomas [4, 5]. Moreover, a relationship between uPA and PAI-1 and clinical prognostic factors in primary breast cancer has been demonstrated and the clinical utility of uPA/PAI-1 as a dual-biomarker concept has been confirmed in level-of-evidence-1 studies [6, 7].

Performing a computational expressed sequence tag database analysis, we previously identified the PAI-1 RNA-binding protein 1 (PAI-RBP1) being upregulated in OC cells and verified this finding by in situ hybridization and immunohistochemistry in OC tissue samples [8]. As PAI-RBP1 exerts PAI-1 mRNA-binding capacity, it is most likely that PAI-RBP1 modulates mRNA translation by affecting the mRNA turn-over or the translational complex functionality [9]. Some data provide evidence that PAI-RBP1 activity is regulated by cyclic nucleotides and by the subcellular localization of the protein. In this study, we analyzed intracellular protein levels and subcellular protein localization of PAI-1 and PAI-RBP1 in primary and recurrent OC tissue samples. Subsequently, protein alterations were statistically correlated to clinical parameter. The aim of this study was to evaluate the usefulness of PAI-1 and PAI-RBP1 expression and cellular distribution as prognostic biomarkers, particularly in the concept of a PAI-1/PAI-RBP1 dual-biomarker strategy.

## Methods

*Patients*

This study was conducted within the framework of the Tumorbank Ovarian Cancer Network (http://www.toc-network.de) and has been approved by the Ethics Committees of the participating centers (University Medicine Greifswald, Germany; Charité Medical University Berlin, Germany; Medical Center University of Freiburg, Germany; Clinic Bayreuth, Germany; Oncological Institute Chisinau, Moldova). All patients signed informed consent forms. For the study, patients with primary and recurrent OC were included. The majority of patients with primary OC underwent radical surgery. Surgical treatment in patients with recurrent OC involved maximal tumor debulking.

*Data Collection*

All clinical data, including age, FIGO stage, prior surgical procedures, all surgical procedures, postoperative residual tumor and histopathological diagnosis were collected with the help of a standardized systematic documentation tool (IMO) [10]. The attending physician performed standard follow-up visits according to the established protocols, that is, every 3 months during standard follow-up examinations or by checking the regional tumor registry or by telephone interview all clinical data were collected. Progress was defined by confirmed imaging or clinical examination.

*Preparation of Snap-Frozen Samples of OC*

Tissue specimens were collected immediately after the removal of the tumors, and samples were immediately snap-frozen and stored in liquid nitrogen. Histopathological evaluation of tumor samples was performed by an independent pathologist at the Institute of Pathology, Charité Medical University, Berlin, Germany. Histopathological evaluation was carried out on hematoxylin and eosin (H&E) stained 2–3 mm thick cryosections. Tumor origin, histological type of tumor, and tumor grading according to the Silverberg grading system of epithelial ovarian tumors were evaluated.

*Western Blot Analysis*

Fifty milligram of OC tissue ($n$ = 106) in 200 µL TPER buffer (Thermo Fisher Scientific, Bonn, Germany) was lyzed (Precyllis-24 homogenizer; Peqlab, Erlangen, Germany), 50 µg of total protein were separated by SDS-PAGE (10% polyacrylamide gel; Bio-rad) and blotted onto a Immobilon-FL Transfer Membrane (MerckMillipore, Darmstadt, Germany). Target proteins were detected by antibodies directed against PAI-1 (Cell Signaling Technology, Danvers, MA, USA; 1:1,000), PAI-RBP1 (Sigma-Aldrich; 1:1,000), and β-actin (Cell Signaling Technology; 1:1,000) as loading control in combination with fluorescent dye-labeled antibodies goat-anti-rabbit 680 (LI-COR Biotechnology, Bad Homburg, Germany; 1:10,000) and goat-anti-rabbit 800 (LI-COR Biotechnology; 1:10,000). Proteins were visualized using the Odyssey Imager (LI-COR Biotechnology) and quantified applying the Image Studio Lite V4.0 software (LI-COR Biotechnology). PAI-1 and PAI-RBP1 expression was normalized to β-Actin and signal intensity was expressed in densitometric arbitrary units (AU).

*Preparation of Primary OC Cells*

OC tissue samples (5–10 $mm^3$) from 24 patients were maintained in PBS (Biochrom, Berlin, Germany) supplemented with 50 µg/mL gentamicin (Ratiopharm, Ulm, Germany), digested with

collagenase I (Biochrom) for 1 h, and filtrated through a 40-μm nylon sieve (BD Falcon, Heidelberg, Germany). Separated cells were propagated in DMEM/F-12 supplemented with 10% fetal bovine serum (Invitrogen, Karlsruhe, Germany) and 50 μg/mL gentamicin (Ratiopharm). Primary ovarian cells from nonmalignant women undergoing a hysterectomy were used as control cells.

*Indirect Immunofluorescence Microscopy Analysis*

Primary OC cells were grown in 8-chamber LAB-TEK slides (NalgeNunc International, Naperville, USA), fixed with 3.7% PFA, and stained with Hoechst 33258 dye (5 μg/mL). Subsequently, cells were incubated with antibodies against PAI-1 (Santa Cruz; 1:75) and PAI-RBP1 (Sigma-Aldrich; 1:100) followed by staining with Alexa Fluor 488- and Alexa Fluor 546-conjugated antibodies, respectively (each Invitrogen, Karlsruhe, Germany; 1:200). Expression of mesothelin (Abcam, Frankfurt; Germany; 1:100) and vimentin (Santa Cruz; 1:100) was used as OC-specific marker. Indirect immunofluorescence analysis was performed using an Axio Observer Z1 fluorescence microscope with Axio Vision 4.8 software (Zeiss, Jena, Germany).

*Statistical Analysis*

Statistical analysis was performed using SPSS statistical software package (SPSS Inc. Version 19.0, Chicago, IL, USA). For categorical variables, chi-square, and 2-sided Fisher's exact test were used in order to detect differences between groups, a parametric 2-tailed test for comparisons between mean values and a nonparametric Kruskal-Wallis test for group differences in non-normal or ordinal data. Pearson's correlations were calculated to assess associations between continuous variables. The Cox proportional hazards regression model was used for univariate and multivariate analyses. $p$ values and 95% CIs were calculated. $p$ values <0.05 were considered statistically significant. Survival analyses were carried out by the Kaplan-Meier test with log rank test for determining the comparison of differences in survival curves.

## Results

Details of the main clinicopathological characteristics of the patients are shown in Table 1. The median age at first diagnosis of OC was 57 years (range 22–85 years). The majority of patients were diagnosed when they were in an advanced tumor stage (FIGO III and IV; 83.3%), formed ascites (85.2%), and exhibited peritoneal carcinomatosis (77.6%). Sufficient tumor resections (tumor residual ≤1 cm) were achieved in 79.1% (primary OC) and 54.1% (recurrent OC) of patients. In total, 66.7% of recurrent OC patients received a salvage surgery and serous type was the predominant histological OC subtype (80.1%). Furthermore, 91.6% of all tumors demonstrated intermediate (28.8%) and poorly (62.8%) differentiated tumor grading. The median progression-free survival (95% CI) and overall survival (95% CI) were 14 months (range 11.6–16.4 months) and 37 months (range 29.7–44.3 months), respectively.

Endogenously expressed PAI-1 and PAI-RBP1 protein demonstrated the calculated protein weight of approximately 50 and 53 kDa, respectively (Fig. 1). The mean relative densitometric intensity of both proteins was 0.161 ± 0.198 AU (PAI-1) and 0.361 ± 0.303 AU (PAI-RBP1), respectively. Comparison of primary and recurrent OC samples demonstrated no significant differences in PAI-1 expression (0.156 ± 0.200 AU vs. 0.167 ± 0.195 AU; Fig. 2a), however, the expression of PAI-RBP1 was significantly higher in primary OC compared to recurrent OC tissue (0.432 ± 0.265 AU vs. 0.291 ± 0.324 AU; $p = 0.005$; Fig. 2b).

Data from fluorescence microscopy performing triple staining for PAI-1 (green), PAI-RBP1 (red), and Hoechst staining of nuclei (blue; Fig. 3) of primary OC cells showed PAI-1 protein being diffusely localized throughout the nuclei and the perinuclear area of cells obtained from primary OC tissue. Notably, cells prepared from recurrent OC tissue exhibited PAI-1 exclusively localized in the nucleus and, therefore, suggesting a PAI-1 translocation from the perinuclear compartment to the nucleus. In case of PAI-RBP1, the protein was found to be exclusively distributed in the cytoplasm of both primary as well as recurrent OC tissue cells.

Correlation analysis demonstrated a statistically significant association between the densitometric intensity of PAI-1 and volume of ascites ($p = 0.011$), FIGO tumor stage ($p = 0.028$), lymphnode status ($p = 0.002$), and pM ($p = 0.016$). In case of PAI-RBP1 analysis, a statistically significant correlation between PAI-RBP1 and diagnosis (primary OC vs. recurrent OC, $p < 0.001$), age at first diagnosis ($p = 0.025$), histological tumor type ($p = 0.026$), and pM ($p = 0.020$) was found.

In univariate analysis, PAI-1 expression showed a trend toward association with progression-free survival ($p = 0.065$), but it showed no correlation to overall survival ($p = 0.636$). PAI-RBP1 was found to have a statistically significant association with progression-free survival ($p = 0.047$) and no correlation to overall survival ($p = 0.709$).

Cox proportional hazard ratios (HR) adjusted for age, tumor stage, histological type, and response to platinum therapy were calculated for PAI-1 and PAI-RBP1. PAI-1 was not found to be an independent predictor for progression-free survival (HR 0.34, 95% CI 0.01–7.89; $p = 0.50$) and overall survival (HR 1.66, 95% CI 0.39–7.14; $p = 0.49$). The HR for progression-free survival remained not significant for PAI-RBP1 with a HR of 0.53 (95% CI 0.18–1.50; $p = 0.23$), however, PAI-RBP1 turned out to be an independent prognostic factor for overall survival (HR

**Table 1.** Clinicopathological characteristics of OC patients

| | Clinicopathological characteristics | | |
|---|---|---|---|
| | total | primary OC | recurrent OC |
| Number of patients, *n* | 156 | 84 | 72 |
| Age at first diagnosis, years, median (range) | 57 (22–85) | 61 (22–85) | 54 (26–75) |
| *Tumor* | | | |
| FIGO tumor stage, *n* (%) | | | |
| I | 10 (6.4) | 8 (9.5) | 2 (2.8) |
| II | 9 (5.8) | 6 (7.1) | 3 (4.2) |
| III | 108 (69.2) | 47 (56) | 61 (84.7) |
| IV | 22 (14.1) | 16 (19) | 6 (8.3) |
| na | 7 (4.5) | 7 (8.3) | 0 |
| Volume of ascites, *n* (%) | | | |
| No | 6 (3.8) | 3 (3.6) | 3 (4.2) |
| ≤500 mL | 66 (42.3) | 28 (33.3) | 38 (52.8) |
| >500 mL | 67 (42.9) | 36 (42.9) | 31 (43.1) |
| na | 17 (10.9) | 17 (20.2) | 0 |
| Peritoneal carcinomatosis, *n* (%) | | | |
| No | 16 (10.3) | 10 (11.9) | 6 (8.3) |
| Yes | 121 (77.6) | 56 (66.7) | 65 (90.3) |
| na | 19 (12.2) | 18 (21.4) | 1 (1.4) |
| Tumor residual, *n* (%) | | | |
| No | 48 (30.8) | 31 (36.9) | 17 (23.6) |
| ≤1 cm | 38 (24.3) | 22 (26.2) | 16 (22.2) |
| ≤2 cm | 6 (3.8) | 0 | 6 (3.8) |
| >2 cm | 47 (30.1) | 14 (16.7) | 33 (45.9) |
| na | 17 (10.9) | 17 (20.2) | 0 |
| *Histo-pathology* | | | |
| Histological subtype, *n* (%) | | | |
| Serous | 125 (80.1) | 59 (70.2) | 66 (91.7) |
| Mucinous | 4 (2.6) | 3 (3.6) | 1 (1.4) |
| Endometrioid | 8 (5.1) | 6 (7.1) | 2 (2.8) |
| Clear cell | 1 (0.6) | 0 | 1 (1.4) |
| Mixed | 6 (3.8) | 6 (7.1) | 0 |
| Undifferentiated | 7 (4.5) | 6 (7.1) | 1 (1.4) |
| na | 5 (3.2) | 4 (4.8) | 1 (1.4) |
| Grading, *n* (%) | | | |
| G1 | 3 (1.9) | 3 (3.6) | 0 |
| G2 | 45 (28.8) | 24 (28.6) | 21 (29.2) |
| G3 | 98 (62.8) | 48 (57.1) | 21 (29.2) |
| na | 10 (6.4) | 9 (10.7) | 1 (1.4) |
| *Follow-up* | | | |
| Response to chemotherapy, *n* (%) | | | |
| Non-responder | 34 (21.8) | 14 (16.7) | 20 (27.8) |
| Responder | 82 (52.6) | 41 (48.8) | 41 (56.9) |
| No chemotherapy | 15 (9.6) | 8 (9.5) | 7 (9.7) |
| na | 25 (16.0) | 21 (25) | 4 (5.6) |
| Survival, years, median (95% CI) | | | |
| PFS | 14 (11.6–16.4) | 18 (13.3–22.7) | 12 (8.5–15.5) |
| OS | 37 (29.7–44.3) | 27.5 (13.9–41.1) | 45 (32–58) |

na, not available.

0.27, 95% CI 0.10–0.72; $p = 0.009$). Besides the correlation of PAI-1/PAI-RBP1 and clinicopathological parameters in OC patients, progression-free survival within the cohort was strongly correlated to tumor residual mass ($p = 0.001$), FIGO tumor stage ($p < 0.001$), pT ($p = 0.001$), pN ($p = 0.002$), pM ($p = 0.010$), grading ($p = 0.002$), and response to chemotherapy ($p < 0.001$).

Additionally, a significant association with overall survival was found for age ($p = 0.013$), peritoneal carcinomatosis ($p = 0.007$), volume of ascites ($p = 0.024$), tumor re-

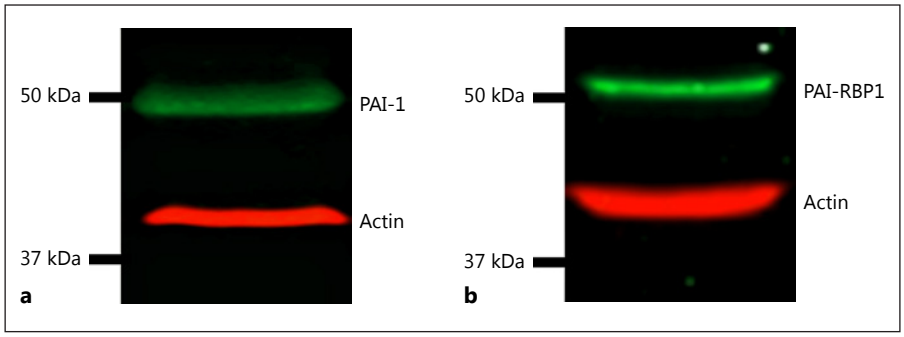


**Fig. 1.** PAI-1 (**a**) and PAI-RBP1 (**b**) expression in OC patient samples.

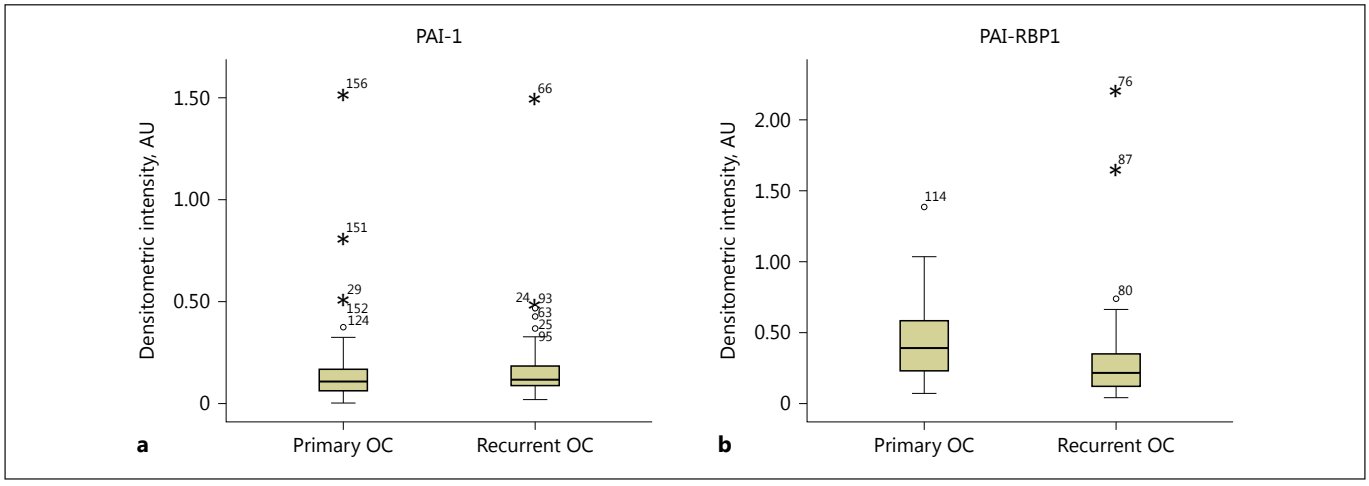


**Fig. 2.** Densitometric quantification of Western blot analysis. PAI-1 (**a**) and PAI-RBP1 (**b**) signals from primary and recurrent OC patient are shown as mean ± SD of signal intensity.

sidual mass ($p \leq 0.001$), FIGO tumor stage ($p = 0.008$), pT ($p = 0.001$), pN ($p = 0.005$), pM ($p < 0.001$), grading ($p = 0.019$), histological type ($p = 0.036$), and response to chemotherapy ($p < 0.001$). In multivariate analysis, various clinical factors were found to be independent prognostic factors for progression-free survival (tumor residual, HR 2.29, 95% CI 1.01–5.19; $p = 0.047$) and overall survival (age, HR 2.12, 95% CI 1.31–3.44; $p = 0.002$; pT, HR 4.89, 95% CI 1.34–17.89; $p = 0.016$; pM, HR 5.34, 95% CI 2.09–13.66; $p < 0.001$; histological type, HR 4.59, 95% CI 2.07–10.19; $p < 0.001$ and platinum sensitivity, HR 2.56, 95% CI 1.45–4.51; $p = 0.001$).

## Discussion

Originally, PAI-RBP1 has been characterized as a PAI-1 mRNA binding factor that potentially controls or contributes to PAI-1 mRNA turn-over [9]. Lemos and Kobarg [11] examined the localization of PAI-RBP1 in cervical HeLa cells and observed PAI-RBP1-GFP expression in the cytoplasm as well as in the nucleus. This is in contrast to our own findings reported here, in which PAI-RBP1 has been expressed exclusively in the cytoplasm of primary and relapsed OC tissue samples. However, this may depict differential PAI-RBP1 functions depending on the cellular context in cervix and ovary tissue. Notwithstanding, the putative properties of PAI-RBP1 in mature mRNA turn-over [12, 13] do not strictly require the protein's presence in the nucleus.

In contrast to PAI-RBP1, there is less information available about PAI-1's functionality in physiology as well as in pathology of mammalian cells. Notably, we found intense signals for PAI-1 in the nucleus of primary OC cells originated from relapsed OC patient samples. This is in line with previous reports of nuclear PAI-1 localization [14, 15], however, to the best of our knowledge, there are no studies in which the nuclear import of PAI-1 has

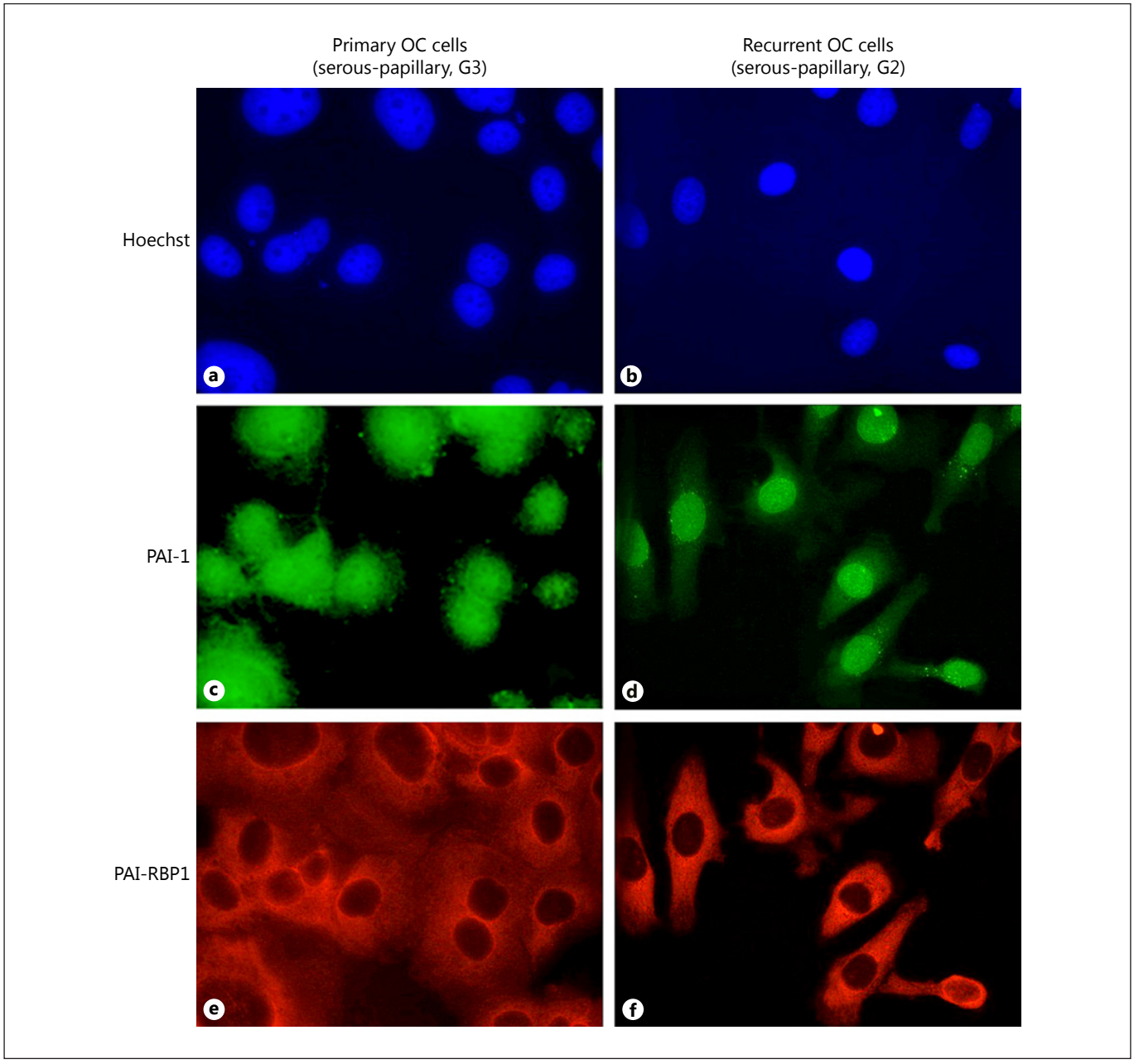


**Fig. 3.** Fluorescence microscopy (magnification ×60) and analysis of Hoechst staining (**a**, **b**), PAI-1 (**c**, **d**), and PAI-RBP1 (**e**, **f**) in primary cells obtained from primary (**a**, **c**, **e**) and recurrent (**b**, **d**, **f**) OC patients.

been induced during cancer development. In this respect, the possibility that a so far unknown nuclear activity of PAI-1 is induced during OC recurrence cannot be excluded. Thus, the activation of PAI-1's nuclear import may serve as a new prognostic biomarker for OC recurrence.

Apart from molecular and cellular aspects, our study revealed a statistically significant impact of PAI-1 and PAI-RBP1 protein expression on OC patient's clinical prognosis. While former studies on PAI-1 expression in OC demonstrated controversial data regarding its clinical relevance [16–18], however, our study significantly correlated PAI-1's expression levels with a more aggressive OC phenotype (volume of ascites, FIGO staging, lymph node status) and thus highlighting PAI-1's prognostic value. These findings are similar to those found in a re-

cent study of Ren et al. [19], which showed PAI-1 being correlated to advanced FIGO stage, poor histological differentiation, and lymph node metastasis. Even though PAI-1 demonstrated a trend toward progression-free survival ($p = 0.065$) but no correlation with overall survival, PAI-1 may serve as a suitable prognostic biomarker for OC.

PAI-RBP1 expression significantly correlates with OC diagnosis (age at first diagnosis, histological tumor type, presence of distant metastasis, recurrence) and, moreover, PAI-RBP1 might be an independent predictor for overall survival (HR 0.27, $p = 0.009$). These data confirmed our initial study [8] and demonstrated for the first time a prognostic value of PAI-RBP1 in OC. Our data, taken together with recent studies, demonstrated for the first time at the level of protein expression that PAI-RBP1 may represent a prognostic biomarker for OC, particularly in advanced metastatic stages. The most important limitation of the study presented here is its low number of included patients. Reevaluation of the dual-biomarker PAI-1/PAI-RBP1 within a larger cohorte would be desirable. A further limitation of the study is the short follow-up of patients as well as the not randomized, single-arm design of the study.

In conclusion, we have shown that PAI-1 and PAI-RBP1 may play a mechanistic role in OC progression and that expression levels of both proteins are associated with patient outcome. A combination of both factors, PAI-1 as well as PAI-RBP1, may represent a novel prognostic factor in OC including progression-free survival and overall survival. Moreover, PAI-1's nuclear import may serve as an innovative prognostic biomarker for OC recurrence.


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## Disclosure Statement

No potential conflicts of interest were disclosed.

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