Investigating the efficacy of tissue factor pathway inhibitor-2 as a promising prognostic marker for ovarian cancer

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Abstract. Tissue factor pathway inhibitor-2 (TFPI2) is a tumor marker for diagnosing ovarian cancer and ovarian clear cell carcinoma (OCCC); however, its effectiveness as a prognostic marker remains unclear. The present study aimed to investigate the utility of TFPI2 as a prognostic marker for ovarian cancer. A total of 256 cases of ovarian cancer was collected at Nara Medical University (Kashihara, Japan) from January 2008 to January 2022. The majority of cases were serous carcinoma (109, 42.6%), followed by OCCC (66, 25.8%), mucinous carcinoma (40, 15.6%), endometrial carcinoma (15, 5.9%), and other (26, 10.2%). The median preoperative serum TFPI2 for ovarian cancer was 219.0 (82.5-5,824.2) pg/ml. Overall survival (OS) of patients with non-OCCC and OCCC was calculated using the cut-off value determined obtained through receiver operating characteristic curve analysis. Cut-off values of TFPI2 for OS were 201 for non-OCCC and 255 pg/ml for OCCC. In univariate analysis, OS was significantly elevated in patients with non-OCCC and OCCC who had TFPI2 levels ≥201 pg/ml (P<0.001) and ≥255 pg/ml (P=0.036), respectively. Progression-free survival (PFS) was significantly elevated in patients with non-OCCC and OCCC who had TFPI2 levels ≥201 and ≥255 pg/ml (both P<0.001), respectively. Multivariate analysis revealed that OS was significantly higher in patients with non-OCCC who had TFPI2 levels ≥201 pg/ml (P=0.021), while PFS was significantly higher in patients with OCCC who had TFPI2 levels ≥255 pg/ml (P=0.020). These findings suggest that TFPI2 is a potential prognostic marker for ovarian carcinoma.

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Introduction

Ovarian cancer is the fifth most common cause of cancer-associated mortality in females and has the lowest 5-year survival rate among all types of gynecological cancers (1,2). In 2018, 295,414 new cases of ovarian cancer and 184,799 deaths from ovarian cancer were reported worldwide (3).

The preliminary stages of ovarian cancer are typically asymptomatic and difficult to detect (4,5), resulting in diagnosis at later stages with a worse prognosis due to lack of essential screening tools (1,4,5).

Tissue factor pathway inhibitor-2 (TFPI2), which serves as a tumor suppressor gene in various types of cancer such as gastric (6), colorectal (7) and hepatocellular cancer (8), has been investigated as a diagnostic marker of ovarian clear cell carcinoma (OCCC) in Japan (9-11). TFPI2 can serve as a serum tumor marker for discriminating ovarian cancer from other types of ovarian tumors (12). Accordingly, TFPI2 has been covered by insurance providers in Japan since April 2021 and is gaining popularity nationwide (13,14). TFPI2 cut-off value is ≥191 for ovarian cancer and ≥270 pg/ml for OCCC. Unlike cancer antigen 125 (CA125), TFPI2 levels are not elevated in ovarian endometrial cysts (10,11); therefore, TFPI2 is the optimal single tumor marker for diagnosing ovarian cancer (12). A recent study confirmed that TFPI2 can diagnose venous thromboembolism (VTE) in patients with epithelial ovarian cancer who have positive-D-dimer results (13). Moreover, the combination of D-dimer and TFPI2 levels can be used to rule out VTE and identify patients at high risk of VTE (14).

Despite accumulating evidence regarding the diagnostic accuracy of this tumor marker (10-12), the association between preoperative serum TFPI2 levels and outcomes in patients with ovarian cancer remains unclear. Our previous study demonstrated that TFPI2 levels are associated with survival outcome of patients with endometrial cancer (15) and clarified the potential link between TFPI2 and cancer prognosis. The present study aimed to determine whether serum TFPI2 could be a prognostic marker for overall survival (OS) and progression-free survival (PFS) in patients with ovarian cancer.

Materials and methods

Patient population. In the present retrospective study, 256 patients (age range, 22-88 years) with a confirmed

diagnosis of ovarian cancer at Nara Medical University Hospital (Kashihara, Japan) were recruited between January 2008 and January 2022. The inclusion criteria were as follows: i) Confirmed pathological diagnosis of ovarian cancer and ii) received treatment, not only supportive care. The exclusion criteria were as follows: i) Combined with other malignancies; ii) pregnant women; and iii) patients with concomitant serious comorbidities. The ovarian cancer staging was determined using the International Federation of Gynecology and Obstetrics (FIGO) classification 2014 (16). Patients were diagnosed with ovarian cancer based on histopathology, pelvic magnetic resonance imaging and chest and abdominal computed tomography (Definition Flash, Siemens AG; Definition AS, Siemens AG; and Aquilion ONE, Canon, Inc.). Histopathology involved primary staining with hematoxylin-eosin (room temperature, hematoxylin for 5 min and eosin for 2 min), with additional p53 staining [primary antibody at 4˚C for 12 h (rabbit polyclonal anti-p53; dilution, 1:200; cat no. NCL-L-p53-CM5p; Leica Biosystems, Ltd.); secondary antibody at room temperature for 1 h (mouse anti-rabbit IgG-HRP; dilution, 1:25; cat no. sc-2357; Santa Cruz Biotechnology, Inc.)] for high-grade serous carcinoma and HNF-1β staining [primary antibody at 4˚C for 12 h (rabbit polyclonal anti-HNF1β; dilution, 1:200; cat no. 12533-1-AP, Proteintech Group, Inc.); secondary antibody at room temperature for 1 h (mouse anti-rabbit IgG-HRP; dilution, 1:25; cat no. sc-2357; Santa Cruz Biotechnology, Inc.)] for OCCC as an auxiliary diagnosis. CT images were evaluated using 5 mm thick axial images. Patient clinical data were collected, including age, body mass index (BMI), parity, menopausal status, histological type and FIGO stage. Proteins of interest were quantified using a fluorescence or chemiluminescence immunoassay, including TFPI2 [E-Test TOSOH II (TFPI2); Tosoh Corporation; cat. no. #0025245], CA125 (CL AIA-PACK® OVCA; Tosoh Corporation, cat. no. #0029114; ARCHITECT CA125 II; Abbott Japan LLC, cat. no. #2K45-28), carbohydrate antigen (CA) 19-9 (CL AIA-PACK® Sla; Tosoh Corporation, cat. no. #0029112) and carcinoembryonic antigen (CEA) (CL AIA-PACK® CEA; Tosoh Corporation, #0029108) according to the manufacturer's instructions. TFPI2, CA125 (CL AIAPACK OVCA), CA19-9, and CEA concentrations were determined by Tosoh Corporation using serum obtained before the surgery. Tumor marker concentrations were measured by clinical laboratory technologists blinded to the study. The present study adhered to the guidelines of the Declaration of Helsinki. This was a single-center retrospective study based on medical records and all patient information was anonymized. The research project was announced on an opt-out basis.

Only variables that could be assessed preoperatively were included in uni- and multivariate analyses, including age, BMI, menopausal status and tumor marker levels. The analysis was performed in patients with OCCC and non-OCCC separately because diagnostic cut-off value differs between OCCC and ovarian cancer (11). The cut-off value for OS was applied to analyze PFS and OS. OS was defined as the period from treatment initiation until death or the last follow-up examination. PFS was defined as the period from treatment initiation until date of diagnosis as a progressive disease or the last follow-up examination.

Treatment. Patients diagnosed with ovarian cancer underwent primary debulking surgery (PDS) if optimal surgery was possible. If the surgery was more extensive than bilateral oophorectomy and no second surgery was performed, it was considered PDS. If surgery was performed following chemotherapy, it was considered as an interval debulking surgery (IDS). If surgery was minor relative to bilateral oophorectomy, it was considered as no surgery.

The completion of surgery was considered optimal if the diameter of the remaining tumor was <1 cm. The surgery was considered suboptimal if the diameter of the remaining mass was ≥1 cm. Furthermore, information regarding lymphadenectomy was collected. Unless the patient had a poor performance status and was considered incapable of enduring a high invasive surgery, both paraaortic and pelvic lymphadenectomy were performed. Adjuvant chemotherapy, mostly comprised of taxane and carboplatin (TC) therapy, was generally performed upon obtaining consent from the patient.

Statistical analysis. The receiver operating characteristic (ROC) curve was used to determine optimal cut-off points of TFPI2, CA125, CA19-9, and CEA levels to predict OS for OCCC and non-OCCC. The optimal cut-off value was determined using the Youden index to predict OS. The outcome on the ROC curve was defined as survival or death. The Kaplan-Meier life table analysis and the log-rank tests were used to assess survival rates and differences based on prognostic factors. Multivariate analysis of prognostic factors for PFS and OS was performed using the Cox proportional hazard regression model where univariate analysis revealed significant differences. All statistical analyses were performed using SPSS software (version 29.0, IBM Corp.). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patients' clinical characteristics. The present study included 256 patients with ovarian cancer with a median age of 60 years (range, 22-88 years). The median follow-up period was 52.4 months (range, 0.8-190.8 months).

A total of 121 cases (47.3%) were FIGO stage I or II while 135 (52.7%) were stage III or IV (Table I). There were 109 cases (42.6%) of serous carcinoma, 40 cases of mucinous carcinoma (15.6%), 15 cases of endometrial carcinoma (5.9%), 66 cases of OCCC (25.8%) and 26 cases of others (10.2%; Table SI). Other histological types included carcinosarcoma, malignant Brenner tumor, seromucinous carcinoma, mixed epithelial tumor, neuroendocrine carcinoma and undifferentiated carcinoma (data not shown). The median preoperative serum levels of TFPI2, CA125, CA19-9 and CEA were 219.0 (82.5-5,824.2) pg/ml, 278.6 (0.5-43,170.9) U/ml, 21.5 (0.0-217,474.9) U/ml and 2.1 (0.4-142.9) ng/ml, respectively (Table I).

Treatment. A total of 163 (63.7%) patients underwent PDS, 75 (29.3%) underwent IDS and 18 (7.0%) underwent biopsy (Table II). Moreover, surgery was optimal and suboptimal in 184 (71.9%) and 72 (28.1%) patients, respectively.

Among the 256 patients, 106 (41.4%) underwent lymphadenectomy while 150 (58.6%) did not. The adjuvant first-line chemotherapy regimen mostly comprised TC therapy (n=198,

Table I. Clinicopathological characteristics of patients.

Characteristic	All patients (n=256)	Patients with OCCC (n=66)	Patients with non-OCCC (n=190)	P-value
Age, years[a]	60 (22-88)	56 (35-79)	61 (22-88)	0.032
BMI, kg/m^2[a]	21.8 (15.2-40.8)	21.8 (16.2-40.8)	21.8 (15.2-34.3)	0.547
Parity[b]				0.011
0	64 (29.0)	23 (34.8)	41 (26.5)	
1	38 (17.2)	12 (18.2)	26 (16.8)	
≥2	119 (53.8)	31 (47.0)	88 (56.8)	
Menopausal status[b]				0.825
Pre-menopause	71 (27.7)	19 (28.8)	52 (27.4)	
Post-menopause	185 (72.3)	47 (71.2)	138 (72.6)	
Tumor marker[a]				
TFPI2, pg/ml	219.0 (82.5-5,824.2)	255.0 (82.5-5,824.2)	214.5 (88.9-1,336.9	0.029
CA125, U/ml	278.6 (0.5-43,170.9)	55.4 (0.5-5,727.1)	413.1 (5.9-43,170.9)	<0.001
CA19-9, U/ml	21.5 (0.0-217,474.9)	22.85 (0.0-11,588.4)	20.3 (0.5-217,474.9)	0.448
CEA, ng/ml	2.1 (0.4-142.9)	2.1 (0.7-11.5)	2.1 (0.4-142.9)	0.007
FIGO stage[b]				<0.001
I/II	121 (47.3)	53 (80.3)	68 (35.8)	
III/IV	135 (52.7)	13 (19.7)	122 (64.2)	

Data are presented as [a]median (range) and [b]n (%). OCCC, ovarian clear cell carcinoma; BMI, body mass index; TFPI2, tissue factor pathway inhibitor-2; CA125, cancer antigen 125; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; FIGO, International Federation of Gynecology and Obstetrics.

Table II. Type of surgical treatment.

Characteristic	n (%)
Surgery	
Primary debulking	163 (63.7)
Interval debulking	75 (29.3)
None	18 (7.0)
Completion	
Optimal	184 (71.9)
Suboptimal	72 (28.1)
Lymphadenectomy	
Yes	106 (41.4)
No	150 (58.6)

77.3%). Of the remaining patients, most cases underwent platinum-based chemotherapy, including docetaxel and carboplatin (n=5, 2.0%), TC and bevacizumab (n=5, 2.0%), dose-dense TC (n=5, 2.0%), weekly TC (n=2, 0.8%) and irinotecan and cisplatin therapy (n=2, 0.8%). Weekly paclitaxel therapy was performed in two patients (0.8%), while docetaxel and gemcitabine therapy was performed in one patient (0.4%). However, 36 patients (14.1%) did not receive adjuvant chemotherapy (Table SII).

Analysis of non-OCCC. For non-OCCC, the cut-off value of TFPI2 for predicting OS was 201 pg/ml based on the Youden index [area under the curve (AUC), 0.646; sensitivity, 73.1%; specificity, 59.8%; 95% confidential interval (CI), 0.568-0.724], while that for CA125 was 394 U/ml (AUC, 0.648; sensitivity, 69.2%; specificity, 60.7%; 95% CI, 0.569-0.727; Fig. 1). CA19-9 and CEA were excluded because they showed negative associations with OS based on ROC curve results. TFPI2 values <201 and ≥201 pg/ml were defined as negative and positive, respectively. Similarly, CA125 values <394 and ≥394 U/ml were defined as negative and positive, respectively.

In the univariate analysis, TFPI2 ≥201 pg/ml was significantly associated with PFS (Fig. 2A) and OS (Fig. 2B). Table III shows uni- and multivariate analyses of prognostic factors for PFS and OS. For PFS. Univariate analysis showed significant differences in age ≥60 years, post-menopausal status, TFPI2 ≥201 pg/ml and CA125 ≥394 U/ml. For OS, univariate analysis showed significant differences in age ≥60 years, post-menopausal status, TFPI2 ≥201 pg/ml and CA125 ≥394 U/ml. Cox multivariate analysis revealed that TFPI2 was a significant independent prognostic factor affecting OS.

Analysis of OCCC. Next, analysis was conducted for patients with OCCC. The Youden index was used to calculate a cut-off value of 255 pg/ml for TFPI2 for predicting OS (AUC, 0.653; sensitivity, 87.5%; specificity, 55.2%; 95% CI, 0.494-0.812) and 363 U/ml for CA125 (AUC; 0.655, sensitivity; 62.5%, specificity; 82.8%, 95% CI; 0.421-0.890; Fig. 3). TFPI2 levels <255 and ≥255 pg/ml were defined as negative and positive, respectively. Similarly, CA125 values <363 and ≥363 U/ml were defined as negative and positive, respectively. In univariate analysis, TFPI2 ≥255 pg/ml was significantly associated with PFS (Fig. 4A) and OS (Fig. 4B). Table IV shows univariate and multivariate analyses of prognostic factors for PFS and OS.

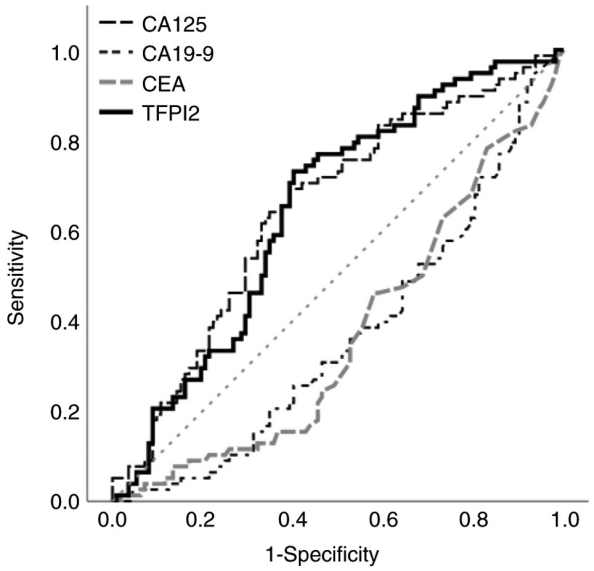

Figure 1. Receiver operating characteristic curve of preoperative serum TFPI2, CA125, CA19-9 and CEA levels for predicting overall survival in non-OCCC. OCCC, ovarian clear cell carcinoma; TFPI2, tissue factor pathway inhibitor-2; CA125, cancer antigen 125; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen.

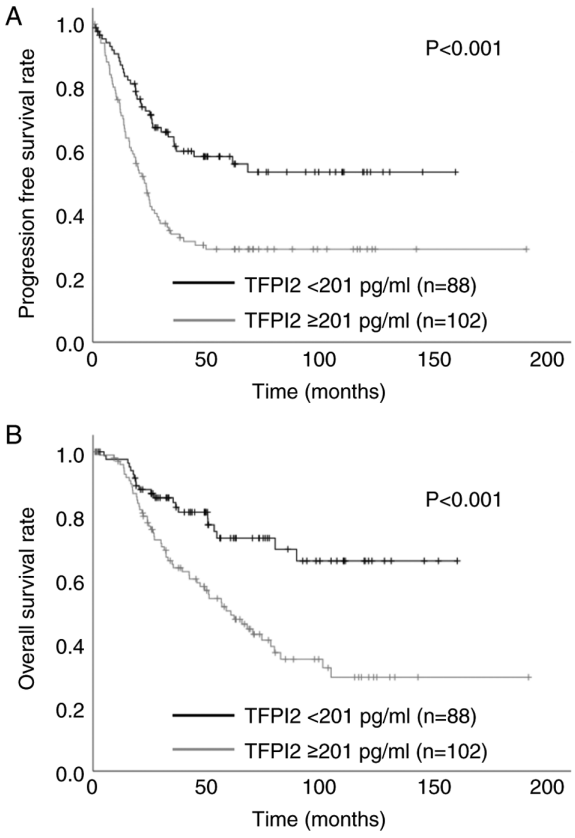

Figure 2. Survival in patients with non-OCCC according to preoperative serum TFPI2 levels. (A) Progression-free and (B) overall survival in patients with non-OCCC according to preoperative serum TFPI2 levels. OCCC, ovarian clear cell carcinoma; TFPI2, tissue factor pathway inhibitor-2.

For PFS, univariate analysis showed significant differences in TFPI2 ≥255 pg/ml and CA125 ≥363 U/ml. Contrastingly, for OS, univariate analysis showed significant differences in BMI ≥25, TFPI2 ≥255 pg/ml and CA125 ≥363 U/ml. When Cox multivariate analysis was applied, only TFPI2 was a significant independent prognostic factor affecting PFS in patients with OCCC.

Discussion

Epithelial ovarian cancer is divided into two classes based on the criteria of Kurman and Shih (17). Type I includes low-grade serous, endometrial and mucinous carcinoma and OCCC, which are low-grade and relatively slow-growing (18,19). Type II includes high-grade serous, endometrial and undifferentiated carcinoma as well as carcinosarcoma, which are high-grade and relatively fast-growing (18,19). Type I ovarian cancer is genetically stable and is often detected in the initial stages.

Compared with type I, type II ovarian cancer has a high frequency of TP53 mutations and is usually genetically unstable (17,20). High-grade serous carcinoma, which is a type II ovarian cancer, accounts for >70% of epithelial ovarian cancers worldwide (21-23). However, because type I ovarian cancer is relatively rare, there may be a less urgent need for research into its mechanism and treatment in non-East Asian countries (22,24). OCCC is a type I ovarian cancer that is more prevalent in Japan (11.7-26.9%) than in North American and Western countries (4.6-12.0%) (22,24-26). Moreover, because the initial stages of OCCC are more prognostically favorable compared with other histological types of ovarian cancer (25,27), there is a need to determine a method for diagnosing these cancer types in the initial stages (26).

Arakawa *et al* (9) identified TFPI2 as a diagnostic marker for OCCC. TFPI2 is produced in vascular endothelial cells, platelets and macrophages (26). Moreover, an immunohistochemical study revealed that TFPI2 is localized in normal muscle, skeletal, breast, liver, kidney, pancreas, stomach and colon tissue (28). It can also be detected in both OCCC and endometrial clear cell carcinoma cells using immunohistochemical staining (26,28,29). Serum TFPI2 has a high specificity for OCCC and is often negative in patients with endometriosis (9-12,26). All histological types of ovarian cancer are associated with TFPI2 as a tumor marker (12). TFPI2 levels are elevated in other histological types, although not as high as in OCCC (10,12). In Japan, measuring TFPI2 serum levels is already covered by insurance (13,14), and the official cut-off values for diagnosing ovarian cancer and OCCC are 191 and 270 pg/ml, respectively. Therefore, TFPI2 shows different features between OCCC and non-OCCC.

Jacobs and Oram suggested that CA125 is an important tumor marker for distinguishing benign from malignant tumors (30). Other than CA125, various tumor markers are used in gynecology, including CA19-9, CEA and human epididymis protein (HE) 4 (12,19,25,31). However, CA125 is affected by various factors, such as menopausal status, pregnancy, infection and endometriosis (10,11,32). Furthermore, there have been studies on the association between tumor markers and cancer prognosis: CA125 is a prognostic tool for predicting relapse and progression of ovarian cancer; however, since CA125 is also known to be influenced by tumor histology and clinical stage, it remains controversial (33,34).

Table III. Univariate and multivariate analysis of prognostic factors for progression-free survival and overall survival in patients with non-ovarian clear cell carcinoma.

	Progression-free survival				Overall survival			
	Univariate analysis	Cox multivariate analysis			Univariate analysis	Cox multivariate analysis		
Variable	P-value	HR	95% CI	P-value	P-value	HR	95% CI	P-value
Age, years								
<60 (n=87)	0.011	1.285	0.807-2.046	0.290	0.021	1.306	0.763-2.236	0.331
≥60 (n=103)								
BMI, kg/m^2								
<25 (n=144)	0.125	-			0.176			
≥25 (n=46)								
Menopausal status								
Pre-menopausal (n=52)	0.049	1.238	0.720-2.128	0.440	0.043	1.300	0.682-2.475	0.425
Post-menopausal (n=138)								
TFPI2, pg/ml								
<201 (n=88)	<0.001	1.513	0.966-2.370	0.071	<0.001	1.890	1.100-3.247	0.021
≥201 (n=102)								
CA125, U/ml								
<394 (n=92)	<0.001	2.093	1.332-3.288	0.001	<0.001	1.772	1.052-2.983	0.031
≥394 (n=98)								

HR, hazard ratio; CI, confidential interval; BMI, body mass index; TFPI2, tissue factor pathway inhibitor-2; CA125, cancer antigen 125.

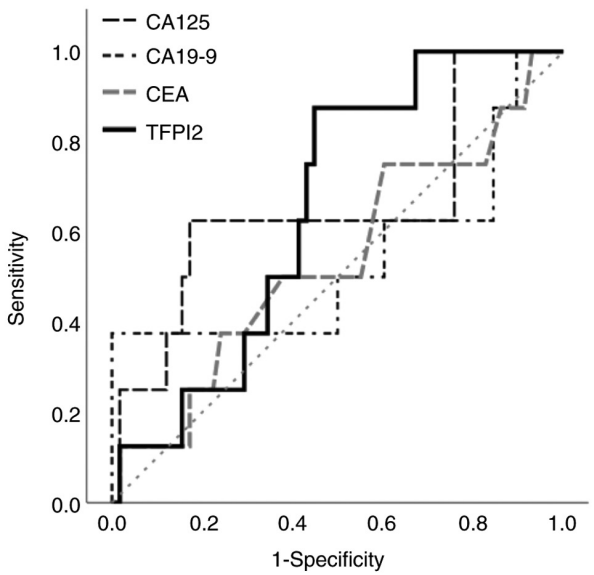

Figure 3. Receiver operating characteristic curve of preoperative serum TFPI2, CA125, CA19-9 and CEA levels for predicting overall survival in OCCC. OCCC, ovarian clear cell carcinoma; TFPI2, tissue factor pathway inhibitor-2; CA125, cancer antigen 125; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen.

Other studies have shown that pretreatment serum CA125 level is associated with disease progression of ovarian cancer (33-35). According to a previous study, serum CA19-9 levels >70.3 U/ml decrease the odds of survival in OCCC, whereas CA125 and HE4 levels do not (25). Our previous study found that preoperative serum TFPI2 levels serve as a prognostic marker for endometrial cancer (15). TFPI2 levels ≥177 pg/ml significantly increase the risk of recurrence and death (15). The present study investigated the utility of TFPI2 as a prognostic marker of OS and PFS in patients with ovarian cancer and showed that elevated serum TFPI2 levels were linked to cancer progression and indicated poor prognosis.

Although results of the univariate analysis showed significant differences in both OS and PFS in OCCC and non-OCCC, those of the multivariate analysis only showed significant differences in PFS in OCCC and OS in non-OCCC. In a previous study, early-stage detection is more often achieved in OCCC than in non-OCCC; (36). Likewise, in our study, most patients with OCCC were in the early stages and did not die during the study period. This may explain why OS did not show significant differences in OCCC. Including a higher number of cases may yield better multivariate analysis results regarding OS.

To the best of our knowledge, the present study is the first to demonstrate that high preoperative serum levels of TFPI2 are associated with ovarian cancer progression. TFPI2 levels ≥201 pg/ml for predicting OS for non-OCCC and ≥255 pg/ml for predicting PFS were the cut-off values. The present results highlighted the effectiveness of TFPI2 as a prognostic marker for ovarian cancer.

Table IV. Univariate and multivariate analysis of prognostic factors for progression free survival and overall survival in ovarian clear cell carcinoma.

	Progression-free survival				Overall survival			
	Univariate analysis	Cox multivariate analysis			Univariate analysis	Cox multivariate analysis		
Variable	P-value	HR	95% CI	P-value	P-value	HR	95% CI	P-value
Age, years								
<60 (n=38)	0.316				0.541			
≥60 (n=28)								
BMI, kg/m^2								
<25 (n=50)	0.157				0.049	4.171	1.008-17.264	0.049
≥25 (n=16)								
Menopausal status								
Pre-menopausal (n=19)	0.534				0.702			
Post-menopausal (n=47)								
TFPI2, pg/ml								
<255 (n=33)	<0.001	11.627	1.476-91.597	0.020	0.036	5.280	0.611-45.616	0.130
≥255 (n=33)								
CA125, U/ml								
<363 (n=51)	0.014	2.223	0.728-6.786	0.161	<0.001	6.320	1.317-30.325	0.021
≥363 (n=15)								

HR, hazard ratio; CI, confidential interval; BMI, body mass index; TFPI2, tissue factor pathway inhibitor-2; CA125, cancer antigen 125.

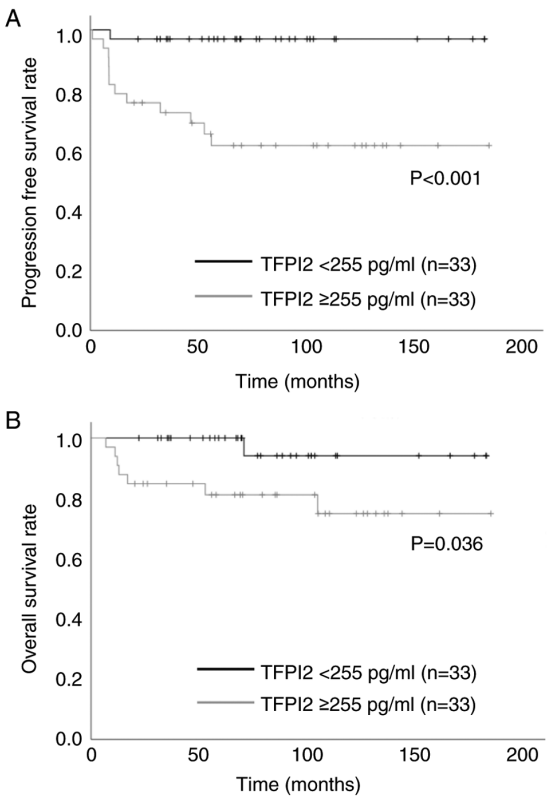

Figure 4. Survival in patients with OCCC according to preoperative serum TFPI2 levels. (A) Progression-free and (B) overall survival in patients with OCCC according to preoperative serum TFPI2 levels. OCCC, ovarian clear cell carcinoma; TFPI2, tissue factor pathway inhibitor-2.

A strength of the present study is that the prognostic factors included in the analysis could be preoperatively measured. Accordingly, determining the pre-treatment prognosis may help patients decide on treatment plans.

The present study has certain limitations. First, this was a single-center, small-scale retrospective study. Second, the present study did not measure serum HE4 levels and thus could not employ the risk of ovarian malignancy algorithm. Compared with CA125 and HE4, TFPI2 is less sensitive in detecting serous carcinoma (12) and the present results may be different, especially in the non-OCCC group. Third, the present study did not consider tumor size in the multivariate analysis because it only included items that could be assessed preoperatively. Although it remains controversial, preoperative serum levels of CA125 are positively associated with tumor size (37). Therefore, TFPI2 may also be related to tumor size and affect the results regarding OS and PFS.

In conclusion, TFPI2 is a potential reliable biomarker for predicting the prognosis of ovarian cancer. With insurance coverage, more cases can be assessed, which will facilitate elucidation of the utility of TFPI2 as a prognostic marker.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

TM, RK and YY conceived and designed the study. TM and YY collected data and produced the tables and figures. TM and YY confirmed the authenticity of all the raw data. TM wrote the manuscript. TM, RK, KN, NK, YY and FK analyzed and interpreted data and revised the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Ethics Committee of Nara Medical University, Kashihara, Japan (approval no. 3115) and conducted in accordance with the guidelines of the Declaration of Helsinki. This was a single-center retrospective study based on medical records and histopathological findings. All patient information was anonymized; thus, the need for informed consent was waived and information regarding the implementation of the study was disclosed by the opt-out method.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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