Preoperative serum tissue factor pathway inhibitor-2 level as a prognostic marker for endometrial cancer

RYUJI KAWAGUCHI, TOMOKA MAEHANA, SHOICHIRO YAMANAKA, RYUTA MIYAKE, NAOKI KAWAHARA, KANA IWAI, YUKI YAMADA and FUMINORI KIMURA

Department of Obstetrics and Gynecology, Nara Medical University, Kashihara, Nara 634-8522, Japan

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Abstract. Advanced endometrial cancer (EC) often recurs and has a poor prognosis. Various serum markers have been used for EC but their usefulness as biomarkers is still unclear; therefore, identifying new biomarkers is important. The present study aimed to investigate whether the tissue factor pathway inhibitor-2 (TFPI2) level was elevated in the preoperative serum of patients with EC and if it may be a prognostic factor. The present retrospective study included 207 patients who had a confirmed pathological diagnosis of EC and received surgical therapy as the initial treatment between January 2011 and December 2017. Survival analysis was performed using Kaplan-Meier analysis and the Cox proportional hazards regression model. The 5-year disease-free survival and overall survival (OS) rates were 73.3 and 83.7%, respectively. The cut-off value for predicting OS for TFPI2 level was 177 pg/ml as determined from the receiver operating characteristic curve. A TFPI2 value ≥177 pg/ml was significantly associated with age ≥65 years (P<0.001), diabetes (P=0.035), stage (P<0.001), myometrial invasion (P<0.001), lymphovascular invasion (P=0.004), lymph node metastasis (P=0.010), distant metastasis (P<0.001), cancer antigen (CA) 125 ≥36 U/ml (P<0.001) and CA 19-9 ≥38 U/ml (P<0.001). In multivariate analysis, high-grade carcinoma [hazard ratio (HR), 2.439; P=0.041], lymph node metastasis (HR, 2.116; P=0.038), distant metastasis (HR, 3.604; P=0.009) and TFPI2 level ≥177 pg/ml (HR, 2.42; P=0.043) were significant prognostic factors affecting OS in patients with EC. These results suggest that the preoperative serum TFPI2 level, along with its histological type, lymph node metastasis and distant metastasis, was a prognostic factor for OS in patients with endometrial cancer.

Correspondence to: Dr Ryuji Kawaguchi, Department of Obstetrics and Gynecology, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634-8522, Japan
E-mail: kawaryu@naramed-u.ac.jp

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Introduction

The morbidity of endometrial cancer (EC) has been increasing globally, and it is the second most prevalent gynecological cancer in women after cervical cancer (1,2). In 2018, 382,069 new cases and 89,929 deaths from endometrial cancer were reported worldwide (3). Advanced EC often recurs and has a poor prognosis (4,5), whereas early-stage EC is often completely cured (6).

There are several histological types of EC, of which endometrioid carcinoma is the most common, while other histological types include serous cancer, clear cell carcinoma, and mixed carcinoma. In general, low-grade carcinoma is hormone-sensitive and includes endometrial carcinoma grades 1 and 2, and has a good prognosis. In contrast, high-grade carcinoma includes endometrial carcinoma grade 3, serous carcinoma, and clear cell carcinoma and has a poor prognosis (7). Several tumor markers have been used in patients with EC. Cancer antigen 125 (CA 125), cancer antigen 19-9 (CA 19-9), human epididymis protein 4 (HE4), and carcinoembryonic antigen (CEA) are often used as serodiagnostic markers for EC (8-13). However, there is no consensus on the usefulness of these serodiagnostic and prognostic markers for EC, thus, necessitating a need for identifying new biomarkers for EC.

Proteomics-based secretome analysis identified tissue factor pathway inhibitor-2 (TFPI2) as a biomarker for ovarian clear cell carcinoma (OCCC) in 2013 (14). TFPI2 is a placental glycoprotein and Kunitz-type serine protease inhibitor with extracellular matrix-related protease inhibitory activity (15). A retrospective study carried out by Arakawa *et al* demonstrated that serum TFPI2 is a useful diagnostic marker for ovarian cancer (OC), especially OCCC (16). TFPI2 has also been reported to be immunohistologically positive in laryngeal, breast, gastric, pancreatic, renal, and colorectal cancers; however, the staining intensity is not uniform (17). Based on the immunohistochemical expression of TFPI2 in ovarian clear cell carcinoma, we postulated that TFPI2 is also expressed in endometrial clear cell carcinoma. We then performed immunostaining for TFPI2 in endometrial carcinoma tissues and found that TFPI2 was localized in the cytoplasm and nucleus of endometrial carcinomas, with a staining rate of 63.6%, notably reaching 100% in endometrial clear cell carcinomas (18). Therefore, we hypothesized that TFPI2 flows into blood vessels from endometrial cancer

tissue and its serum level increases. However, there have been no reports to date regarding serum TFPI2 levels. Therefore, in this study, we aimed to investigate the TFPI2 levels in the preoperative serum of patients with EC and its utilization as a prospective prognostic factor.

Materials and methods

Patients. Patients (n=207) who visited the Nara Medical University for treatment of EC between January 2011 and December 2017 were enrolled in this retrospective study. The patient inclusion criteria for the study were as follows-i) confirmed pathological diagnosis of EC, ii) had undergone surgery as an initial treatment and iii) had not received neoadjuvant chemotherapy or radiotherapy. The grading of EC was performed as per the International Federation of Gynecology and Obstetrics (FIGO) classification, 2009. Patients diagnosed with EC via histopathology underwent pelvic magnetic resonance imaging (MRI) and computed tomography (CT) of the chest and abdomen and their CA 125, CA 19-9 and TFPI2 serum levels were measured preoperatively. Anti-TFPI2 monoclonal antibodies were used to measure serum TFPI2 concentrations via E-test Tosoh II (AIA-PACK TFPI2) and an automated immunoanalyzer AIA-2000 (Tosoh Corporation, Yokohama, Japan). Clinical and pathological data of the patients were obtained retrospectively from the medical records; they included age, body mass index (BMI), parity, menopausal status, smoking status, hormone replacement therapy, hyperlipidemia, hypertension, diabetes, histological type, FIGO stage, myometrial invasion, lymphovascular invasion, ascites cytology, lymph node metastasis, and distant metastasis. The acceptable baseline reference values for CA 125 and CA 19-9 at our institute are 36 U/ml and 38 U/ml respectively.

Treatment. The patients diagnosed with EC underwent an open or laparoscopic total hysterectomy and bilateral salpingo-oophorectomy. Abdominal radical hysterectomy was performed in patients with EC invading the cervical stroma. Pelvic lymph node dissection was performed if preoperative pelvic MRI showed <1/2 myometrial invasion of the uterine corpus. In addition, para-aortic lymphadenectomy was performed if preoperative pelvic MRI showed ≥1/2 myometrial invasion, or if the histopathologic type was endometrial carcinoma grade 3, serous/clear cell carcinoma, or carcinosarcoma. Lymphadenectomy was omitted if preoperative pelvic MRI showed no myometrial invasion of the corpus of the uterus and the histopathologic type was endometrial carcinoma grade 1 or 2.

Adjuvant chemotherapy was administered in the following cases: medium risk of recurrence after surgery (endometrial carcinoma grade 1/2 + ≥1/2 myometrial invasion, and endometrial carcinoma grade 3 + <1/2 myometrial invasion) and high risk of recurrence (endometrial carcinoma grade 3 + ≥1/2 myometrial invasion, serous carcinoma/clear cell carcinoma, lymph node metastasis and distant metastasis). Adjuvant chemotherapy was omitted in cases with a low risk of recurrence (endometrial carcinoma grade 1/2 + <1/2 myometrial invasion). The adjuvant chemotherapy regimen consisted of TC therapy (paclitaxel 175 mg/m^2 + carboplatin AUC 5) every 3 weeks for six courses. In case TC therapy was not administered owing to adverse events, AP therapy (doxorubicin 60 mg/m^2 + cisplatin 50 mg/m^2) was administered every 4 weeks for six courses.

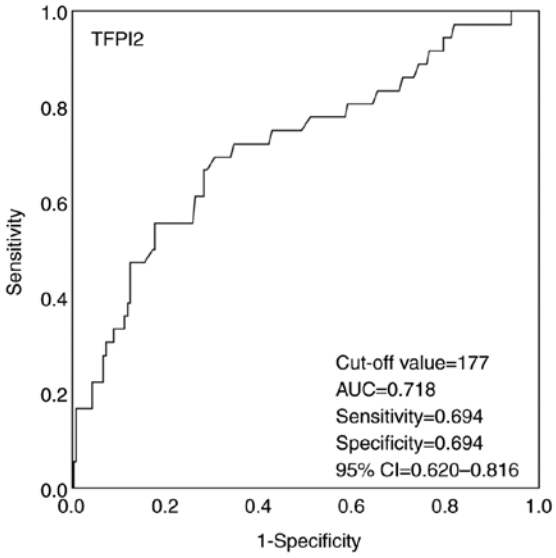

Figure 1. Receiver operating characteristic curve of preoperative serum TFPI2 levels for predicting overall survival. AUC, area under the curve; CI, confidence interval; TFPI2, tissue factor pathway inhibitor-2.

Statistical analysis. Kaplan-Meier life table analysis and log-rank tests were used to assess survival rates and differences based on prognostic factors. Disease-free survival (DFS) is defined as the interval of time after the end of primary cancer treatment where the patient survives without any signs or symptoms of that cancer. Overall survival (OS) is defined as the time span from the start of treatment to death or the last follow-up examination. Multivariate analysis of prognostic factors for DFS and OS was performed using the Cox proportional hazards regression model. Receiver operating characteristic (ROC) curves were used to determine the best cut-off points for serum TFPI2 levels to predict the OS. The outcome in the ROC curve was defined as survival or death. Baseline characteristics, surgical procedure, risk of recurrence and adjuvant chemotherapy in 207 patients with endometrial cancer stratified by the cut-off value of TFPI2 were analyzed using the chi-square test and Fisher's exact test. All statistical analyses were performed using SPSS software version 28.0 for Windows (IBM Corp., Armonk, NY, USA). Statistical significance was set at P<.05.

Results

Patients' clinical characteristics. All 207 patients with EC had a mean age of 60.3±11.4 (mean ± standard deviation) years (range, 32.0 to 92.0), mean BMI of 24.4±5.6 kg/m^2 (range, 15.1 to 47.5), and median follow-up of 68.3 months (range, 5.8 to 158.8). The mean preoperative serum TFPI2, CA 125, and CA 19-9 values were 211.6±27.4 pg/ml (range, 52.0 to 5630.0), 98.8±26.1 U/ml (range, 6.0 to 4019.0), and 86.0±33.1 U/ml (range, 1.0. to 6106.0), respectively. The cut-off value predicting OS for TFPI2 was determined from the ROC curve and was 177 pg/ml (Fig. 1). A TFPI2 value of <177 was defined as negative and a value of >177 as positive. Table I shows the baseline

Table I. Baseline characteristics of 207 patients stratified by the cut-off value of TFPI2.

Variable	Total, n (%)	TFPI2-negative (<177 pg/ml), n (%)	TFPI2-positive (≥177 pg/ml), n (%)	P-value
Age (years)				
<65	133 (64.3)	97 (73.5)	36 (48.0)	<0.001
≥65	74 (35.5)	35 (26.5)	39 (52.0)	
BMI (kg/m^2)				
<25	158 (76.3)	82 (62.1)	45 (60.0)	0.438
≥25	49 (23.7)	50 (37.9)	30 (40.0)	
Parity				
≥1	149 (72.0)	95 (72.0)	54 (72.0)	0.996
0	58 (28.0)	37 (28.0)	21 (28.0)	
Menopausal status				
Pre-menopausal	61 (29.5)	45 (34.1)	16 (21.3)	0.053
Post-menopausal	146 (70.5)	87 (65.9)	59 (78.7)	
Smoking				
Yes	184 (88.9)	14 (10.7)	8 (10.7)	0.996
No	23 (11.1)	117 (89.3)	67 (89.3)	
HRT				
Yes	8 (3.9)	7 (5.3)	1 (1.3)	0.263
No	199 (96.1)	125 (94.7)	74 (98.7)	
Hyperlipidemia				
Yes	33 (15.9)	23 (17.4)	10 (13.3)	0.44
No	174 (84.1)	109 (82.6)	65 (86.7)	
Hypertension				
Yes	51 (24.6)	29 (22.0)	21 (28.4)	0.303
No	156 (75.4)	103 (78.0)	53 (71.6)	
Diabetes				
Yes	30 (14.5)	14 (10.6)	16 (21.3)	0.035
No	177 (85.5)	118 (89.3)	59 (78.7)	
Histological type				
Low-grade carcinoma	129 (62.3)	86 (65.2)	43 (57.3)	0.177
Endometrioid carcinoma G1	90 (43.5)	67 (50.8)	23 (30.7)	
Endometrioid carcinoma G2	39 (18.8)	19 (14.4)	20 (26.6)	
High-grade carcinoma	78 (37.7)	46 (34.8)	32 (42.7)	
Endometrioid carcinoma G3	29 (14.0)	18 (13.6)	11 (14.7)	
Clear cell carcinoma	11 (5.3)	3 (2.3)	8 (10.7)	
Serous carcinoma	19 (9.2)	12 (9.1)	7 (9.3)	
Carcinosarcoma	13 (6.3)	10 (7.5)	3 (4.0)	
Others	6 (2.9)	3 (2.3)	3 (4.0)	
FIGO stage, n (%)				
I/II	158 (76.3)	113 (85.6)	45 (60.0)	<0.001
III/IV	49 (23.7)	19 (14.4)	30 (40.0)	
Myometrial invasion				
<1/2	142 (68.6)	106 (80.3)	36 (48.0)	<0.001
≥1/2	65 (31.4)	26 (19.7)	39 (52.0)	
Lymphovascular invasion				
Positive	128 (61.8)	91 (68.9)	37 (49.3)	0.004
Negative	79 (38.2)	41 (31.1)	38 (50.7)	
Ascites cytology				
Positive	49 (23.7)	26 (19.7)	22 (29.7)	0.102
Negative	158 (76.3)	106 (80.3)	52 (70.3)	

Table I. Continued.

Variable	Total, n (%)	TFPI2-negative (<177 pg/ml), n (%)	TFPI2-positive (≥177 pg/ml), n (%)	P-value
Lymph node metastasis				
Positive	32 (15.5)	14 (10.6)	18 (24.0)	0.010
Negative	175 (84.5)	118 (89.4)	57 (76.0)	
Distant metastasis				
Positive	18 (8.7)	5 (3.8)	13 (17.3)	0.002
Negative	189 (91.3)	127 (96.2)	62 (82.7)	
CA 125 (U/ml)				
<36 U/ml	136 (70.1)	98 (79.0)	38 (54.2)	<0.001
≥36 U/ml	58 (29.9)	26 (21.0)	32 (45.7)	
CA 19-9 (U/ml)				
<38 U/ml	120 (62.2)	85 (69.1)	35 (50.0)	0.009
≥38 U/ml	73 (37.8)	38 (30.9)	35 (50.0)	

BMI, body mass index; HRT, hormone replacement therapy; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; CI, confidence interval; TFPI2, tissue factor pathway inhibitor-2; CA, cancer antigen.

Table II. Surgical procedure, risk of recurrence and adjuvant chemotherapy performed on a patient with endometrial cancer.

Parameter	Total, n (%)	TFPI2-negative (<177 pg/ml), n (%)	TFPI2-positive (≥177 pg/ml), n (%)	P-value
Surgical procedure				
TAH + BSO	53 (25.6)	25 (18.9)	28 (37.3)	0.012
TAH + BSO + PLA	75 (36.2)	54 (11.4)	21 (13.3)	
TAH + BSO + PLA + PALA	79 (35.9)	52 (39.4)	23 (30.7)	
Risk of recurrence				
Low risk	84 (40.6)	64 (47.7)	20 (26.7)	<0.001
Median risk	72 (34.8)	47 (35.6)	25 (33.3)	
High risk	51 (24.6)	21 (15.9)	30 (40.0)	
Adjuvant chemotherapy				0.037
No	84 (40.6)	64 (48.5)	20 (26.7)	
Yes	123 (59.4)	68 (51.5)	55 (73.3)	

TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; TLH, total laparoscopic hysterectomy; PLA, pelvic lymphadenectomy; PALA, para-aortic lymphadenectomy; ARH, abdominal radical hysterectomy.

characteristics of the 207 EC patients stratified according to the cut-off value of TFPI2. A TFPI2 value of ≥177 pg/ml was significantly correlated with age ≥65 years (P<0.001), diabetes (P=0.035), FIGO stage (P<0.001), myometrial invasion (P<0.001), lymphovascular invasion (P=0.004), lymph node metastasis (P=0.010), distant metastasis (P=0.002), CA 125 ≥36 U/ml (P<0.001) and CA 19-9 ≥38 U/ml (P<0.001).

Treatment and risk of recurrence for 207 endometrial cancer patients. Table II shows the surgical procedures performed on 207 patients, hysterectomy (including total abdominal and laparoscopic hysterectomy) and bilateral salpingo-oophorectomy in 53 patients (25.3%). Hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy were performed in 75 patients (35.9%). Hysterectomy, bilateral salpingo-oophorectomy, pelvic lymphadenectomy, and para-aortic lymphadenectomy were performed in 79 patients (37.8%, including 4 abdominal radical hysterectomies). The risk of recurrence was assessed from postoperative pathology and patients were stratified as low risk (n=84, 40.6%), medium risk (n=72, 34.8%), and high risk (n=51, 24.6%). Medium and high risk of recurrence were more common in the group with TFPI2 levels ≥177 pg/ml (P<0.001) (Table II). Patients with medium risk and high risk of recurrence received postoperative adjuvant chemotherapy. A total of 123 patients (59.4%) received adjuvant chemotherapy after surgery due to medium or high risk of recurrence (Table II); 111 patients (90.2%) received TC therapy, and 12 patients (9.8%) received AP therapy.

Table III. Univariate and multivariate analysis of prognostic factors for disease free survival.

	Univariate analysis		Cox multivariate analysis		
Parameter	Patients, n	P-value	HR	95% CI	P-value
Age (years), n					
<65	23				
≥65	31	<0.001	2.550	1.260-5.161	0.009
BMI (kg/m^2)					
<25	39				
≥25	15	0.058			
Parity					
≥1	40				
0	14	0.76			
Menopausal status					
Pre-menopausal	7				
Post-menopausal	47	0.002	3.645	1.263-10.525	0.017
Smoking					
Yes	7				
No	47	0.577			
HRT					
Yes	0				
No	54	0.116			
Hyperlipidemia					
Yes	8				
No	46	0.746			
Hypertension					
Yes	16				
No	38	0.335			
Diabetes					
Yes	8				
No	46	0.881			
Histological type					
Low-grade carcinoma	20				
High-grade carcinoma	34	<0.001	2.188	1.074-4.460	0.031
Myometrial invasion					
<1/2	21				
≥1/2	33	<0.001	0.762	0.347-1.675	0.499
Lymphovascular invasion					
Negative	18				
Positive	35	<0.001	4.628	1.118-4.628	0.023
Ascites cytology					
Negative	30				
Positive	24	<0.001	1.857	0.904-3.813	0.092
Lymph node metastasis					
Negative	35				
Positive	19	<0.001	3.075	1.434-6.594	0.004
Distant metastasis					
Negative	40				
Positive	14	<0.001	2.88	1.255-6.605	0.013
TFPI2					
<177 pg/ml	23				
≥177 pg/ml	31	<0.001	2.328	1.165-4.650	0.017

Table III. Continued.

	Univariate analysis		Cox multivariate analysis		
Parameter	Patients, n	P-value	HR	95% CI	P-value
CA 125					
<36 U/ml	22				
≥36 U/ml	28	<0.001	1.465	0.661-3.244	0.347
CA 19-9					
<38 U/ml	26				
≥38 U/ml	24	<0.001	2.195	1.019-4.725	0.045

BMI, body mass index; HRT, hormone replacement therapy; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; CI, confidence interval; TFPI2, tissue factor pathway inhibitor-2; CA, cancer antigen.

Prognostic factors for disease-free survival. The 5-year DFS rate and OS rates were 73.3 and 83.7%, respectively. The log-rank test was used to assess the risk factors affecting the DFS and OS in patients with EC. In the univariate analysis, age ≥65 years (P<0.001), postmenopausal status (P=0.002), high-grade carcinoma (P<0.001), myometrial invasion ≥1/2 (P<0.001), lymphovascular invasion (P<0.001), positive ascites cytology (P<0.001), lymph node metastasis (P<0.001), distant metastasis (P<0.001), TFPI2 level ≥177 pg/ml (P<0.001), CA 125 level ≥36 U/ml (P<0.001) and CA 19-9 level ≥38 U/ml (P<0.001) were shown to be significantly associated with DFS (Table III). When Cox multivariate analysis was applied, age ≥65 years (P=0.009), postmenopausal status (P=0.017), high-grade carcinoma (P=0.031), lymphovascular invasion (P=0.023), lymph node metastasis P=0.004), distant metastasis (P=0.013), TFPI2 level ≥177 pg/ml (P=0.017) and CA 19-9 level ≥38 U/ml (P=0.045) were found to be significant independent prognostic factors affecting DFS in patients with EC (Table III).

Prognostic factors for overall survival. As per univariate analysis, age ≥65 years (P<0.001), BMI ≥25 kg/m^2 (P=0.019), postmenopausal status (P=0.009), high-grade carcinoma (P<0.001), myometrial invasion ≥1/2 (P<0.001), lymphovascular invasion (P<0.001), positive ascites cytology (P<0.001), lymph node metastasis (P<0.001), distant metastasis (P<0.001), TFPI2 level ≥177 pg/ml (P<0.001), CA 125 level ≥36 U/ml (P<0.001) and CA 19-9 level ≥38 U/ml (P<0.001) were found to have significant effects on OS (Table III). However, as per multivariate analysis, high-grade carcinoma (P=0.041), lymph node metastasis (P=0.038), distant metastasis (P=0.009) and TFPI2 level ≥177 pg/ml (P=0.043) were found to be significant prognostic factors affecting OS in patients with EC (Table IV). The DFS and OS curves for patients with EC according to preoperative TFPI2 levels are shown in the Fig. 2A and B), respectively. Patients with positive TFPI2 levels had significantly worse DFS and OS than those with negative TFPI2 levels (P<0.001).

Discussion

Several studies have been carried out on tumor markers in patients with EC, and CA 125, CA 19-9, human epididymis protein 4 (HE4), and carcinoembryonic antigen (CEA) are the often used serodiagnostic markers for EC (8-13). CA 125 is the most widely used tumor marker for EC, and there have been several reports stating that preoperative CA 125 can be a prognostic factor for the OS of EC patients (19-22). Chao *et al* reported that a preoperative CA 125 level of 105 U/ml in patients under 49 years of age and 35 U/ml in patients over 50 years of age are prognostic factors for EC (19). Furthermore, Pinar *et al* reported that a preoperative CA 125 level ≥35 U/ml is a poor prognostic factor for EC (20). Yilmaz *et al* also reported that a CA 125 level of 35 U/ml was the cut-off value for the OS (21) and in other studies, the reported cut-off value for CA 125 was 20 U/ml for EC (23,24). Previous studies have shown that CEA (12,22) and CA 19-9 (22) are potential prognostic factors for OS in patients with EC. In addition, several recent reports have suggested HE4 as a useful biomarker for EC as well as OC (25,26). Moreover, serum HE4 is an independent risk factor for decreased DFS and OS in patients with EC and has been reported to be a more useful biomarker than CA 125 (25).

TFPI2 is a 32-kDa protein that was reported for the first time by Miyagi *et al* as a protease inhibitor that is exclusively expressed in the placenta of pregnant women (15). However, further studies showed that TFPI2 is produced in vascular endothelial cells, platelets, and macrophages (27). Moreover, immunohistochemistry studies have revealed that TFPI2 is localized in normal muscular, skeletal, breast, liver, kidney, pancreas, stomach, and colon tissues (17). In normal human tissues, TFPI2 is thought to be involved in the processes of coagulation, angiogenesis, inflammation, and apoptosis (28). Using proteomic analysis technology, Arakawa *et al* analyzed the culture medium of OC cells and found that OCCC specifically produces TFPI2 (14). Previously, we have reported the diagnostic accuracy and usefulness of TFPI2 in differentiating OC from benign ovarian tumors (29). At a cut-off value of 191 pg/ml for TFPI2 levels, the sensitivity, specificity, and area under the curve (AUC) for discriminating OC from benign ovarian tumors were 64.7, 91.5%, and 0.893, respectively (29). The Ministry of Health, Labor and Welfare in Japan has officially approved the use of TFPI2 by as a serodiagnostic marker for OC.

Table IV. Univariate and multivariate analysis of prognostic factors for overall survival.

	Univariate analysis		Cox multivariate analysis		
Parameter	Patients, n	P-value	HR	95% CI	P-value
Age (year)					
<65	21				
≥65	15	<0.001	1.575	0.653-3.799	0.312
BMI (kg/m^2)					
<25	28				
≥25	8	0.019	0.555	0.229-1.345	0.192
Parity					
≥1	29				
0	7	0.203			
Menopausal status					
Pre-menopausal	4				
Post-menopausal	32	0.009	2.981	0.802-11.079	0.103
Smoking					
Yes	5				
No	31	0.557			
HRT					
Yes	0				
No	36	0.256			
Hyperlipidemia					
Yes	11				
No	25	0.463			
Hypertension					
Yes	7				
No	29	0.48			
Diabetes					
Yes	5				
No	31	0.935			
Histological type					
Low-grade carcinoma	11				
High-grade carcinoma	25	<0.001	2.439	1.038-5.714	0.041
Myometrial invasion					
<1/2	11				
≥1/2	25	<0.001	1.226	0.440-3.643	0.662
Lymphovascular invasion					
Negative	12				
Positive	23	<0.001	1.46	0.579-3.684	0.423
Ascites cytology					
Negative	18				
Positive	18	<0.001	1.173	0.469-2.935	0.733
Lymph node metastasis					
Negative	22				
Positive	14	<0.001	2.116	1.049-5.702	0.038
Distant metastasis					
Negative	24				
Positive	12	<0.001	3.604	1.376-9.439	0.009
TFPI2					
<177 pg/ml	12				
≥177 pg/ml	24	<0.001	2.42	1.021-5.928	0.043

Table IV. Continued.

Parameter	Univariate analysis		Cox multivariate analysis		
	Patients, n	P-value	HR	95% CI	P-value
CA 125					
<36 U/ml	15				
≥36 U/ml	19	<0.001	1.044	0.385-2.829	0.933
CA19-9					
<38 U/ml	16				
≥38 U/ml	18	<0.001	2.193	0.848-5.668	0.105

BMI, body mass index; HRT, hormone replacement therapy; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; CI, confidence interval; TFPI2, tissue factor pathway inhibitor-2; CA, cancer antigen.

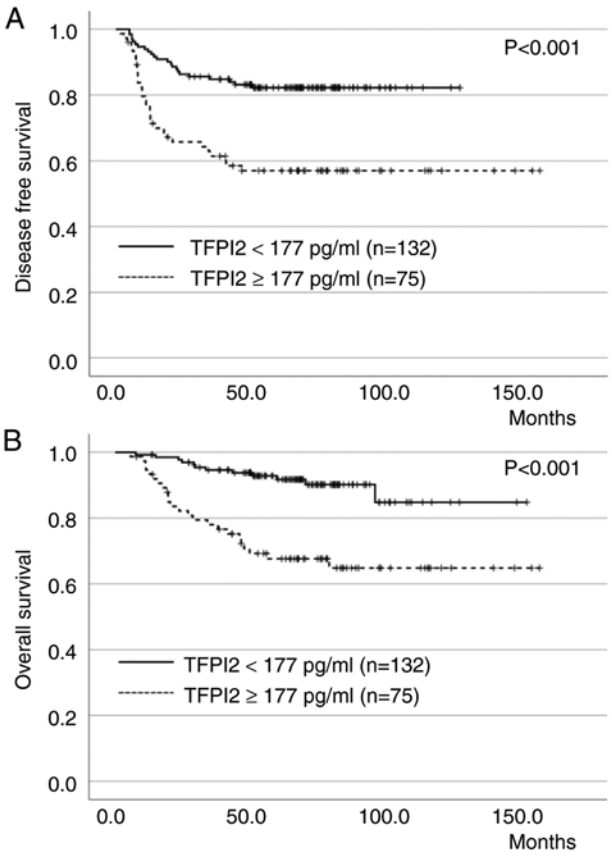

Figure 2. Disease-free survival and overall survival in patients with endometrial cancer according to preoperative serum TFPI2 levels. (A) Disease-free survival and (B) overall survival for 207 patients with endometrial cancer according to preoperative serum TFPI2 levels. TFPI2, tissue factor pathway inhibitor-2.

TFPI2 was reported to be stained in the nucleus, cytoplasm, and extracellular matrix in OCCC, whereas TFPI2 was not expressed in non-ovarian clear cell carcinomas (27). However, serum TFPI2 levels were elevated in non-ovarian clear cell carcinoma patients, suggesting that non-tumor cells such as macrophages, platelets, and vascular endothelial cells produce TFPI2 (17). Moreover, elevated serum TFPI2 levels in patients with EC are thought to be derived from EC cells (18). Therefore, more studies need to be conducted to reveal the potential source of TFPI2 in different cancers. The usefulness of serum TFPI2 as a tumor marker in EC has never been reported. In this study, we determined the serum TFPI2 levels in uterine EC and evaluated whether TFPI2 could be a prognostic factor. Additionally, we investigated the association between various parameters and serum TFPI2 levels. In patients with EC, serum TFPI2 levels were associated with clinicopathological factors, such as the FIGO stage, myometrial invasion, lymphovascular invasion, lymph node metastasis, and distant metastasis. These findings suggest that serum TFPI2 levels reflect the aggressiveness and progression of EC. Therefore, patients with high TFPI2 levels are considered to have a poor prognosis. Although TFPI2 values were also correlated with CA 125 and CA 19-9 values, multivariate analysis revealed that TFPI2 was superior to CA 125 and CA 19-9 as a prognostic marker for OS in uterine cancer.

Thus, to the best of our knowledge, this is the first report of elevated serum TFPI2 levels in patients with EC and its use as an independent prognostic factor for EC. In this study, a preoperative serum TFPI2 level of 177 pg/ml was found to be the cutoff value predicting a worse OS. The prognosis of patients with EC with high-grade carcinoma, lymph node metastasis, distant metastasis and preoperative TFPI2 level ≥177 pg/ml was poor in multivariate analysis. A previous retrospective cohort study of 2,948 patients with EC also reported distant metastasis, particularly to the brain, as an independent prognostic factor for OS and multiple distant metastases were associated with a poor prognosis (30). Our study had few limitations. Although serum TFPI2 levels are elevated in patients with EC, the biological properties and role of TFPI2 in EC remain unclear. Therefore, further studies on TFPI2, including a large prospective study involving the collection of EC samples from more institutions, are required.

In summary, in this study we have demonstrated for the first time that the preoperative serum TFPI2 level, along with histological type, lymph node metastasis and distant metastasis, can be used as a potential prognostic factor for OS in patients with EC.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

RK conceived and designed the study and drafted the manuscript. TM, SY, RM, KI and YY collected and analyzed the data and produced the tables and figures. RK, FK and NK analyzed and interpreted the data. RK and TM confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was approved by the Institutional Ethics Committee of Nara Medical University, Kashihara, Japan (approval no. 3401). This study was 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 survey 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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