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ORIGINAL ARTICLE

# Thrombotic events induce the worse prognosis in ovarian carcinomas and frequently develop in ovarian clear cell carcinoma

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## Abstract

**Background** This study aimed to examine the clinical significance and risk factors of thromboembolic events (TEEs) in patients with ovarian carcinoma.

**Methods** Patients with ovarian carcinoma treated at our hospital between 2000 and 2017 were identified. The risk factors of TEEs, including venous TEEs and arterial TEEs, and the association between TEEs and prognosis were investigated. Patients with TEEs were classified into two groups: those with severe TEEs, defined as patients who required urgent treatment for deep vein thrombosis, massive pulmonary embolism, acute myocardial infarction, and symptomatic cerebral infarction, and those with mild TEEs. The risk factors of severe TEEs and the association between severe TEEs and prognosis were investigated.

**Results** A total of 369 patients were enrolled. Among them, 53 patients (14.4%) were complicated with TEEs. Clear cell carcinoma (CCC) was a greater risk factor of TEEs than serous carcinoma (hazard ratio [HR] = 2.81, $p = 0.03$). In multivariate analysis for survival, TEEs were a prognostic factor of poor progression-free survival (PFS; HR = 2.90, $p < 0.01$) and overall survival (OS; HR = 2.89, $p < 0.01$). Among 53 patients with TEEs, 17 (32.1%) developed severe TEEs. CCC was strongly associated with severe TEEs (HR = 42.6, $p = 0.02$). Multivariate analysis for survival demonstrated that severe TEEs were a risk factor of worse PFS (HR = 4.34, $p < 0.01$) and OS (HR = 3.30, $p = 0.03$).

**Conclusion** TEEs induced poor prognosis and was associated with CCC. A standard treatment for CCC should be included in the strategy of TEEs.

**Keywords** Ovarian cancer · Thromboembolic events · Venous thromboembolism · Arterial thromboembolism · Clear cell carcinoma

## Introduction

Ovarian carcinoma is an aggressive tumor with a high mortality that causes cancer-related deaths worldwide [1]. The standard treatment for ovarian carcinoma is the combination of maximum debulking surgery and chemotherapy [1, 2]. Despite aggressive treatments, most patients develop recurrence soon after treatment and die of the disease [3–5]. Histologic subtypes had been identified as one of the poor prognostic factors. Among them, clear cell carcinoma (CCC) has shown resistance to conventional chemotherapy, and its prognosis was reported to be worse than that of prevalent histologic subtypes such as high-grade serous carcinoma [6–10].

Furthermore, recent studies have demonstrated that CCC was a risk factor of thromboembolic events (TEEs). TTEs were detected in 6.8% of patients with other epithelial ovarian cancers. Compared with patients with other histologic types, 27.3% of patients with CCC developed TEEs [11]. Therefore, TEEs were the common complication in patients with ovarian carcinoma, particularly CCC [12], and a strategy for the management of TEEs is needed in the treatment of ovarian carcinoma.

TEEs are classified into two types: venous TEEs (VTEs), such as pulmonary embolism (PE) and deep vein thrombosis (DVT), and arterial TEEs (ATEs), such as acute myocardial

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infarction (AMI) and cerebral infarction [11–13]. The incidence of VTEs in patients with ovarian carcinoma was reported to be 1–26% [11, 13–15], and the incidence of DVT and PE was 11–18% and 1–2.6%, respectively [16–20]. Hence, the incidence of ATEs in patients with ovarian carcinoma was much lower than that of VTEs. Cerebral infarction was detected in approximately 3.8% of patients with ovarian cancer [16, 21]. The exact frequency of AMI is unknown because only a few cases have been reported [22].

The severity of TEEs including VTEs and ATEs ranges from mild, which can be improved by anticoagulant therapy, to severe, which directly causes death after their development [13, 14]. The severity is important because severe TEEs have been shown to induce worsening of the general patient condition, but their management has been limited to the treatments recommended by several guidelines for patients with ovarian cancer. Therefore, knowing the risk factors of not only TEE development but also of severe TEEs is important in the clinical setting; however, there have been no reports about the association between the severity of TEEs and clinicopathologic findings.

The aim of this study was to examine whether CCC is a risk factor of TEEs and whether TEEs affect the prognosis of patients with ovarian cancer. Furthermore, this study also aimed to establish the criteria for grading the severity of TEEs, and to investigate the relationship between TEE severity and the prognosis of patients with TEEs.

## Patients and methods

Patients with ovarian carcinoma treated with surgery at our hospital between January 2000 and December 2017 were identified. We excluded patients who were not treated and those without any follow-up. When symptoms suspicious of TEEs (e.g., lower-limb edema, chest pain, and dyspnea) developed, and the D-dimer level suddenly increased without symptoms, ultrasound examination, magnetic resonance imaging, computed tomography, and angiography including cardiac catheterization were performed. TEEs included VTEs such as PE and DVT and ATEs included AMI and cerebral infarction. Patients with or without TEEs throughout the observation period were defined as cases with TEEs and cases without TEEs, respectively. The timing of the development of TEEs was categorized into before primary treatment and after primary treatment (during treatment after the primary treatment).

Furthermore, patients with TEEs were classified into two groups: those with severe TEEs and those with mild TEEs. Severe TEEs were defined as symptomatic TEEs that caused abnormal vital signs or led to death if treatment was delayed, or those that needed to be treated with invasive methods. Mild TEEs were defined as asymptomatic TEEs that needed only anticoagulant therapy. The vital signs of patients with mild TEEs were stable. For example, patients with massive PE or DVT treated with not only anticoagulant therapy but also inferior vena cava filtration and catheter treatment, all patients with AMI, those with cerebral infarction with abnormal vital signs, those with consciousness disturbance, and patients with paralysis were classified into the severe TEE group. Hence, patients with small PE and DVT accidentally detected on computed tomography performed to detect recurrent disease, without abnormal vital signs, and treated with only anticoagulant therapy, as well as patients with cerebral infarction without abnormal vital signs, consciousness disturbance, and paralysis were classified into the mild TEE group. Shortly, using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0., Grade 3, 4, and 5 thromboembolic events, stroke, myocardial infarction was defined as severe TEEs. Other than situation was defined as mild TEEs.

Combined CT venography and pulmonary angiography or ultrasound sonography were performed when the patients had difficulty in breathing, chest pain, lower leg edema, or significant elevation of D-dimer levels without symptoms before, during, and after treatment. As the prevention of TEEs, all patients which received surgery received mechanical thromboprophylaxis with intermittent pneumatic compression from 1 h before the surgery to first ambulation and graduated elastic compression stockings from 1 h before surgery to 1 week after surgery. In addition, all patients received a total of 4000 units of the low-molecular-weight heparin enoxaparin in two separate subcutaneous injections from 24 to 36 h after surgery to 7 days after the surgery. Regardless of patients with contraindication or with the situation which clinicians should not perform these strategies such as massive hemorrhage during surgery, all patients received the prevention mentioned above.

Medical and surgical data were obtained from the medical and surgical records. All cases were staged according to the 2014 International Federation of Gynecology and Obstetrics (FIGO) staging system [23]. The performance status was evaluated using the World Health Organization Performance Status scale. The histologic type was classified into high-grade serous carcinoma, CCC, and other subtypes including endometrioid carcinoma, mucinous carcinoma, carcinosarcoma, and adenocarcinoma. With respect to residual tumor, optimal surgery was defined as $< 1$ cm residual tumor after the primary debulking surgery or interval debulking surgery following neoadjuvant chemotherapy. Suboptimal surgery was defined as $\geqq 1$ cm residual tumor after the primary debulking surgery or interval debulking surgery following neoadjuvant chemotherapy. The chi-square test and Fisher's exact test were used for statistical analysis. Univariate and multivariate analyses for the risk factors of TEEs were conducted

using the logistic regression method. Overall survival (OS) was defined as the interval from the first date of therapy to the date of death. Progression-free survival (PFS) was defined as the interval from the first date of therapy to progression or death. OS and PFS were determined using the Kaplan–Meier method. The significance of the survival distribution in each group was tested using the log-rank test and Cox proportional hazard models. A $p$ value of $<0.05$ was considered statistically significant.

This study was approved by the Ethics Committee of the National Defense Medical College, Tokorozawa, Japan.

## Results

During the study period, 369 patients were included. Among them, 53 patients (14.4%) developed TEEs. The incidence of VTEs and ATEs was 49 (13.3%) and 9 (2.4%), respectively. DVT was detected in 21 patients (5.7%); PE in 14 patients (3.8%); PE and DVT in 9 patients (2.4%); cerebral infarction in 4 patients (1.1%); cerebral infarction and DVT in 3 patients (0.8%); cerebral infarction, DVT, and PE in 1 patient (0.3%) each; and AMI in 1 patient (0.3%).

The characteristics of the patients are summarized in Table 1. More patients in groups with TEEs had a histologic type other than CCC and high-grade serous

**Table 1** Characteristics of all patients

| Variables | Patients with thromboembolic events $n=53$ | Patients without thromboembolic events $n=316$ | $P$ value |
|---|---|---|---|
| Age at diagnosis | | | |
| ≧61 years | 26 (49.1%) | 131 (41.5%) | 0.30 |
| <61 years | 27 (50.9%) | 185 (58.5%) | |
| Performance status score | | | |
| 0 | 49 (92.5%) | 303 (95.9%) | 0.26 |
| 1 and 2 | 4 (7.5%) | 13 (4.1%) | |
| FIGO stage | | | |
| I | 18 (34.0%) | 124 (39.1%) | 0.59 |
| II | 8 (15.1%) | 35 (11.0%) | |
| III | 20 (37.7%) | 122 (38.5%) | |
| IV | 7 (13.2%) | 35 (11.0%) | |
| Histology | | | |
| High-grade serous carcinoma | 11 (20.8%) | 131 (41.3%) | <0.01 |
| Clear cell carcinoma | 14 (26.4%) | 81 (25.6%) | |
| Other carcinomasa | 28 (52.8%) | 104 (32.8%) | |
| Timing of the development of thromboembolic events | | | |
| Before primary treatment | 25 (47.2%) | – | |
| After primary treatment | 28 (52.8%) | – | |
| Residual tumor | | | |
| Suboptimal surgery | 33 (62.3%) | 83 (26.3%) | <0.01 |
| Optimal surgery | 20 (37.7%) | 233 (73.7%) | |
| Ascites | | | |
| Yes | 32 (60.4%) | 172 (54.4%) | 0.06 |
| No | 21 (39.6%) | 144 (45.6%) | |
| Tumor size | | | |
| ≧10 cm | 23 (43.3%) | 126 (40.0%) | 0.41 |
| <10 cm | 30 (56.6%) | 190 (60.0%) | |
| Body mass index | | | |
| ≧25 | 10 (18.9%) | 68 (21.5%) | 0.61 |
| <25 | 43 (81.1%) | 248 (78.5%) | |

*FIGO* International Federation of Gynecology and Obstetrics

[a]Other carcinomas include endometrioid carcinoma, mucinous carcinoma, carcinosarcoma, and adenocarcinoma

carcinoma ($p < 0.01$) and had suboptimal surgery ($p < 0.01$). There were no deaths due to TEEs. There were no other statistically different factors between the two groups. Moreover, among patients with TEEs, 13 patients had neoadjuvant chemotherapy followed by interval debulking surgery, 40 patients had primary debulking surgery followed by adjuvant chemotherapy. Hence, among patients without TEEs, 43 patients had neoadjuvant chemotherapy followed by interval debulking surgery and 273 patients had primary debulking surgery followed by adjuvant chemotherapy. All patients received taxane- and platinum-based chemotherapy. To detect the risk factors of TEEs, multivariate analysis was performed (Table 2). Patients with CCC and other subtypes were at a higher risk for TEEs than patients with high-grade serous carcinoma (CCC vs. high-grade serous carcinoma: hazard ratio [HR] = 3.87, $p < 0.01$) (other subtypes vs. high-grade serous carcinoma: HR = 4.05, $p < 0.01$). The PFS and OS data

**Table 2** Univariate and multivariate analysis of the incidence of thromboembolic events

| Variables | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | *p* value | HR | 95% CI | *p* value |
| Age at diagnosis | | | | | | |
| ≧61 years vs. < 61 years | 1.36 | 0.76–2.44 | 0.30 | | | |
| Performance status score | | | | | | |
| ≧ 1 vs. 0 | 1.9 | 0.60–6.07 | 0.28 | | | |
| FIGO stage | | | | | | |
| III/IV vs. I/II | 1.05 | 0.59–1.88 | 0.87 | | | |
| Histology | | | | | | |
| Clear cell carcinoma vs. high-grade serous carcinoma | 2.06 | 1.03–4.75 | 0.04 | 3.87 | 1.58–9.48 | < 0.01 |
| Other carcinomas[a] vs. high-grade serous carcinoma | 3.21 | 1.52–6.74 | < 0.01 | 4.05 | 1.84–8.91 | < 0.01 |
| Residual tumor | | | | | | |
| Suboptimal surgery vs. optimal surgery | 4.63 | 2.52–4.56 | < 0.01 | 6.01 | 3.13–11.5 | < 0.01 |
| Ascites | | | | | | |
| Yes vs. no | 2.27 | 0.22–4.56 | 0.25 | | | |
| Tumor size | | | | | | |
| ≧ 10 cm vs. < 10 cm | 1.11 | 0.61–2.00 | 0.74 | | | |
| Body mass index | | | | | | |
| ≧ 25 vs. < 25 | 0.87 | 0.41–1.81 | 0.71 | | | |

*HR* hazard ratio, *CI* confidence interval, *FIGO* International Federation of Gynecology and Obstetrics

[a]Other carcinomas include endometrioid carcinoma, mucinous carcinoma, carcinosarcoma, and adenocarcinoma

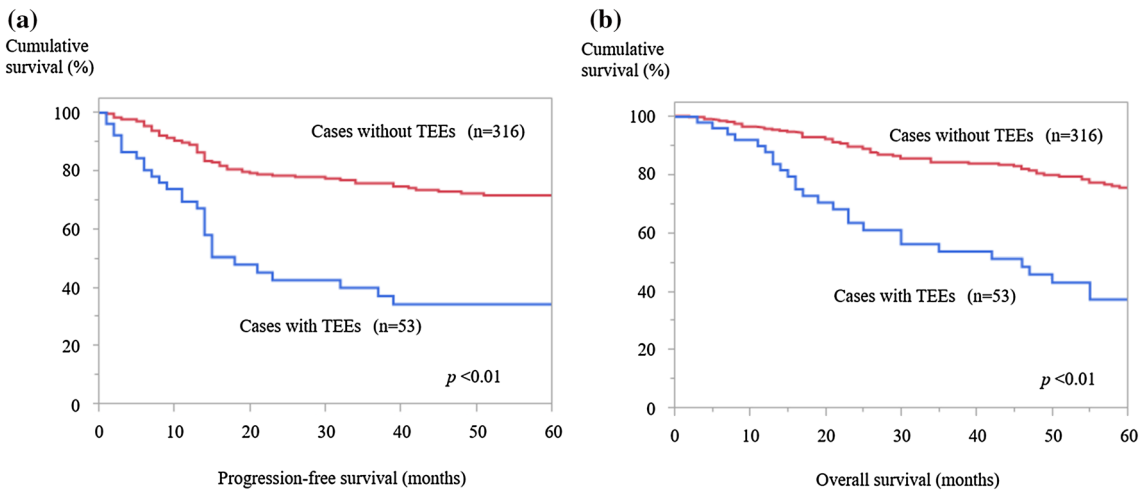


**Fig. 1** Progression-free survival (PFS) and overall survival (OS) in patients with thromboembolic events (TEEs) and in those without TEEs. The PFS (**a**) and OS (**b**) of patients with TEEs were worse than those of patients without TEEs (both $p < 0.01$)

are shown in Fig. 1. The PFS and OS of patients with TEEs were worse than those of patients without TEEs ($p < 0.01$ and $p < 0.01$, respectively). The percentage of 5-year PFS of patients with or without TEEs was 34.2 and 71.6%, respectively. In addition, the percentage of 5-year OS of patients with or without TEEs was 37.3 and 75.4%, respectively. Table 3 shows the results of the multivariate analysis for PFS and OS in all patients. TEEs (HR = 2.41, $p < 0.01$) were a risk factor of PFS in addition to FIGO stage III/IV ovarian carcinoma (HR = 2.07, $p < 0.01$), suboptimal surgery (HR = 3.14, $p < 0.01$) and ascites (HR = 2.59, $p < 0.01$). Similarly, TEEs (HR = 2.45, $p < 0.01$) were a prognostic factor of worse OS in addition to FIGO stage III/IV ovarian carcinoma (HR = 1.73, $p = 0.03$), suboptimal surgery (HR = 3.08, $p < 0.01$), and ascites (HR = 2.39, $p = 0.04$).

In 53 patients with TEEs, there were 17 (32.1%) with severe TEEs and 36 (67.9%) with mild TEEs. The characteristics of the patients with TEEs are shown in Table 4. The distribution of severe TEEs was as follows: DVT was discovered in 3/17 patients (17.6%), PE in 3/17 patients (17.6%), PE and DVT in 3/17 patients (17.6%), cerebral infarction in 6/17 patients (41.2%), and AMI in 1/17 patients (5.9%). Nine patients with DVT or PE required not only anticoagulant therapy but also inferior vena cava filtration or catheter treatment. Seven patients with cerebral infarction showed unstable vital signs or symptoms such as consciousness disturbance, dizziness, or paralysis. Of them, one patient was treated with thrombectomy and six patients were treated with catheter treatment. One patient with AMI was managed with catheterization treatment and anticoagulant therapy such as warfarin and aspirin. The details of mild TEEs were as follows: DVT was detected in 17 patients (47.2%), PE in 11 patients (30.6%), PE and DVT in 7 patients (19.4%), and cerebral infarction in 1 patient (2.8%). All patients with mild TEEs had no symptoms and no abnormal vital signs. Patients with CCC more frequently developed severe thrombosis ($p < 0.03$). There were no statistical differences between the two groups except in histology. More patients in the group with severe TEEs had CCC ($p = 0.03$). In univariate analysis for the risk of severe TEEs, CCC was a greater risk factor than high-grade serous carcinoma (HR = 11.4, $p = 0.04$) (Table 5). Furthermore, the PFS and OS in the group with severe TEEs were worse than those in the group with mild TEEs ($p = 0.01$ and $p < 0.01$, respectively) (Fig. 2). The percentage of 5-year PFS of patients with severe or mild TEEs was 21.0% and 39.5%, respectively. In addition, the percentage of 5-year overall survival of patients with severe or mild TEEs was 19.3% and 43.9%, respectively.

The results of multivariate analysis for PFS and OS in patients with TEEs are shown in Table 6. Severe TEEs were a prognostic factor of worse PFS (HR = 2.91, $p = 0.01$) and OS (HR = 2.46, $p = 0.04$).

## Discussion

In this study, the incidence of TEEs was 14.4%. Specifically, the incidence of VTEs and ATEs was 49 (13.3%) and 9 (2.4%), respectively. A histology other than high-grade serous carcinoma was a risk factor of TEEs, which were associated with poor prognosis. In addition, CCC was a risk factor of severe TEEs, which were related to poor prognosis.

In our study, the incidence of VTEs (14.4%) fell within the range (1–26%) reported in previous studies [11, 13–20]. The ratio of VTEs was relatively low in our study. Satoh et al. demonstrated silent VTE was detected in 18 of 72 patients (25.0%) [19]. Therefore, there is a possibility that silent VTE was missed because our study did not perform combined CT venography and pulmonary angiography or ultrasound sonography. Moreover, the incidence of cerebral infarction (2.2%) in our study was lower than that in previous reports (3.8%) [16, 21]. The incidence of AMI is unclear because there have been few research articles and case reports of AMI in patients with ovarian carcinoma [22]. In our study, the incidence of AMI was 0.3%. Therefore, AMI is a rare complication in patients with ovarian carcinoma.

The mechanism of hypercoagulable states associated with ovarian carcinoma is mediated by tissue factor, cancer procoagulant, and inflammatory cytokines such as interleukin (IL)-6 [11, 19, 24–27]. Among them, tissue factor and IL-6 are overexpressed in CCC [25, 26]. This mechanism was assumed to be associated with the more frequent development of TEEs in patients with CCC [11, 25, 26]. In our study, CCC was a risk factor of TEEs. Thus, our results could support the findings of previous reports. Furthermore, because CCC could induce severe TEEs, which could lead to fatal outcomes, a strategy for the management of TEEs is important, particularly when treating patients with CCC.

In addition, our study demonstrated that both the development of TEEs and the presence of severe TEEs were risk factors of worse PFS and OS. We assumed two explanations for the worse prognosis in cases with TEEs and severe TEEs. First, factors associated with TEEs such as tissue factor or IL-6 in CCC had the potential to activate cancer tumor cells. Tissue factor was reported to form a complex with blood coagulation factor VII, which enhances the pathogenic events in cancer progression such as cell motility, invasion, angiogenesis, and cancer cell survival via the activation of protease-activated receptors in ovarian carcinoma [27]. Furthermore, IL-6 is reported to be associated with angiogenesis and the enhancement of the immune suppression status of the tumor microenvironment by inducing B7-H4 expression and activating

**Table 3** Multivariate analysis of progression-free survival and overall survival in all patients

| Variables | Progression-free survival | | | | | | Overall survival | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Univariate analysis | | | Multivariate analysis | | | Univariate analysis | | | Multivariate analysis | | |
| | HR | 95% CI | *p* value | HR | 95% CI | *p* value | HR | 95% CI | *p* value | HR | 95% CI | *p* value |
| Age at diagnosis | | | | | | | | | | | | |
| ≧61 years vs. < 61 years | 1.44 | 0.97–2.12 | 0.69 | | | | 1.55 | 0.89–2.29 | 0.09 | | | |
| Performance status score | | | | | | | | | | | | |
| ≧ 1 vs. 0 | 2.17 | 0.85–4.56 | 0.46 | | | | 3.95 | 0.95–6.42 | 0.06 | | | |
| FIGO stage | | | | | | | | | | | | |
| III/IV vs. I/II | 3.18 | 2.10–4.90 | < 0.01 | 2.07 | 1.26–3.41 | < 0.01 | 2.75 | 1.83–4.23 | < 0.01 | 1.71 | 1.04–2.82 | 0.03 |
| Histology | | | | | | | | | | | | |
| Clear cell carcinoma vs. high-grade serous carcinoma | 1.39 | 0.85–2.37 | 0.19 | | | | 1.22 | 0.74–1.75 | 0.09 | | | |
| Other carcinomas[a] vs. high-grade serous carcinoma | 1.31 | 0.78–2.26 | 0.78 | | | | 1.13 | 0.73–1.75 | 0.30 | | | |
| Residual tumor | | | | | | | | | | | | |
| Suboptimal surgery vs. optimal surgery | 4.8 | 3.24–7.16 | < 0.01 | 3.14 | 1.97–5.04 | < 0.01 | 4.56 | 3.01–6.78 | < 0.01 | 3.08 | 1.95–4.92 | < 0.01 |
| Ascites | | | | | | | | | | | | |
| Yes vs. no | 2.56 | 1.62–4.24 | < 0.01 | 2.59 | 1.47–3.19 | < 0.01 | 2.32 | 1.52–3.63 | < 0.01 | 2.39 | 1.28–3.01 | 0.04 |
| Tumor size | | | | | | | | | | | | |
| ≧10 cm vs. < 10 cm | 1.24 | 0.84–1.83 | 0.27 | | | | 1.29 | 0.88–1.91 | 0.19 | | | |
| Body mass index | | | | | | | | | | | | |
| ≧25 vs. < 25 | 1.07 | 0.66–1.67 | 0.77 | | | | 1.01 | 0.62–1.58 | 0.86 | | | |
| Thromboembolic events | | | | | | | | | | | | |
| Yes vs. no | 3.2 | 2.05–4.87 | < 0.01 | 2.41 | 1.44–3.89 | < 0.01 | 3.14 | 2.00–4.79 | < 0.01 | 2.45 | 1.51–3.96 | < 0.01 |

[a]Other carcinomas include endometrioid carcinoma, mucinous carcinoma, carcinosarcoma, and adenocarcinoma

*HR* hazard ratio, *CI* confidence interval, *FIGO* International Federation of Gynecology and Obstetrics

**Table 4** Characteristics of patients with thromboembolic events

| Variables | Patients with severe thromboembolic events ($n=17$) | Patients with mild thromboembolic events ($n=36$) | $p$ value |
|---|---|---|---|
| Age at diagnosis | | | |
| ≧ 61 years | 8 (47.1%) | 18 (50.0%) | 0.84 |
| < 61 years | 9 (52.9%) | 18 (50.0%) | |
| Performance status score | | | |
| 0 | 14 (82.4%) | 35 (97.2%) | 0.06 |
| 1 and 2 | 3 (17.6%) | 1 (2.8%) | |
| FIGO stage | | | |
| I | 5 (29.4%) | 13 (36.1%) | 0.75 |
| II | 4 (23.5%) | 4 (11.1%) | |
| III | 7 (41.2%) | 13 (36.1%) | |
| IV | 1 (5.9%) | 6 (16.7%) | |
| Histology | | | |
| High-grade serous carcinoma | 1 (5.9%) | 10 (27.8%) | 0.03 |
| Clear cell carcinoma | 8 (47.1%) | 7 (19.4%) | |
| Other carcinomas[a] | 8 (47.1%) | 19 (52.8%) | |
| Timing of the development of thromboembolic events | | | |
| Before primary treatment | 8 (47.1%) | 17 (47.2%) | 0.66 |
| After primary treatment | 9 (52.9%) | 19 (52.8%) | |
| Residual tumor | | | |
| Suboptimal surgery | 4 (23.5%) | 16 (44.4%) | 0.14 |
| Optimal surgery | 13 (76.5%) | 20 (55.6%) | |
| Ascites | | | |
| Yes | 11 (64.7%) | 23 (63.9%) | 0.40 |
| No | 6 (35.3%) | 13 (6.1%) | |
| Tumor size | | | |
| ≧ 10 cm | 8 (47.1%) | 16 (44.4%) | 0.59 |
| < 10 cm | 9 (52.9%) | 20 (55.6%) | |
| Body mass index | | | |
| ≧ 25 | 4 (23.5%) | 8 (22.2%) | 0.92 |
| < 25 | 13 (76.5%) | 28 (77.8%) | |

*FIGO* International Federation of Gynecology and Obstetrics

[a]Other carcinomas include endometrioid carcinoma, mucinous carcinoma, carcinosarcoma, and adenocarcinoma

cancer cells through the Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) pathway in ovarian carcinoma [26, 28–32]. Second, patients with worse general conditions due to TEEs were unable to receive effective therapy [33]. Moreover, once severe TEEs had developed, they require urgent treatment, thus delaying the treatment of ovarian cancer. Furthermore, patients with severe TEEs could not receive the most appropriate treatment such as maximum cytoreductive surgery because a long duration of surgery could increase the risk of new TEEs [34]. Therefore, factors associated with TEEs and TEEs themselves negatively affected both the tumor cells and the patients.

The most appropriate treatment for TEEs associated with ovarian carcinoma is not anticoagulant therapy but the treatment of the underlying disease (i.e., ovarian carcinoma). However, among all histologic types of ovarian carcinoma, CCC is the phenotype that is resistant to conventional chemotherapy [5–10]. To date, several candidates for the new target therapy have been reported [6–10, 33–36]. Among them, we considered that the best treatment candidate for patients with CCC complicated with TEEs is IL-6 target therapy. IL-6 target therapy not only could reduce TEEs but also has an antitumor effect in CCC by reducing the IL-6 level [28, 30, 32]. Therefore, future studies should consider dual treatment for patients with ovarian carcinoma and TEEs.

**Table 5** Unitivariate analysis of the incidence of severe thromboembolic events

| Variables | Univariate analysis | | |
|---|---|---|---|
| | HR | 95% CI | *p* value |
| Age at diagnosis | | | |
| ≧ 61 years vs. < 61 years | 0.89 | 0.28–2.82 | 0.84 |
| Performance status score | | | |
| ≧ 1 vs. 0 | 7.50 | 0.72–78.4 | 0.07 |
| FIGO stage | | | |
| III/IV vs. I/II | 0.80 | 0.25–2.53 | 0.70 |
| Histology | | | |
| Clear cell carcinoma vs. high-grade serous carcinoma | 11.4 | 1.15–113.1 | 0.04 |
| Other carcinomas[a] vs. high-grade serous carcinoma | 0.37 | 0.10–1.36 | 0.14 |
| Timing of development of thromboembolic events | | | |
| Before primary treatment vs. after primary treatment | 0.76 | 0.23–2.52 | 0.66 |
| Residual tumor | | | |
| Suboptimal surgery vs. optimal surgery | 2.60 | 0.71–9.53 | 0.15 |
| Ascites | | | |
| Yes vs. no | 1.83 | 0.46–7.23 | 0.39 |
| Tumor size | | | |
| ≧ 10 cm vs. < 10 cm | 1.40 | 0.44–4.48 | 0.57 |
| Body mass index | | | |
| ≧ 25 vs. < 25 | 0.89 | 0.20–3.96 | 0.88 |

*HR* hazard ratio, *CI* confidence interval, *FIGO* International Federation of Gynecology and Obstetrics

[a]Other carcinomas include endometrioid carcinoma, mucinous carcinoma, carcinosarcoma, and adenocarcinoma

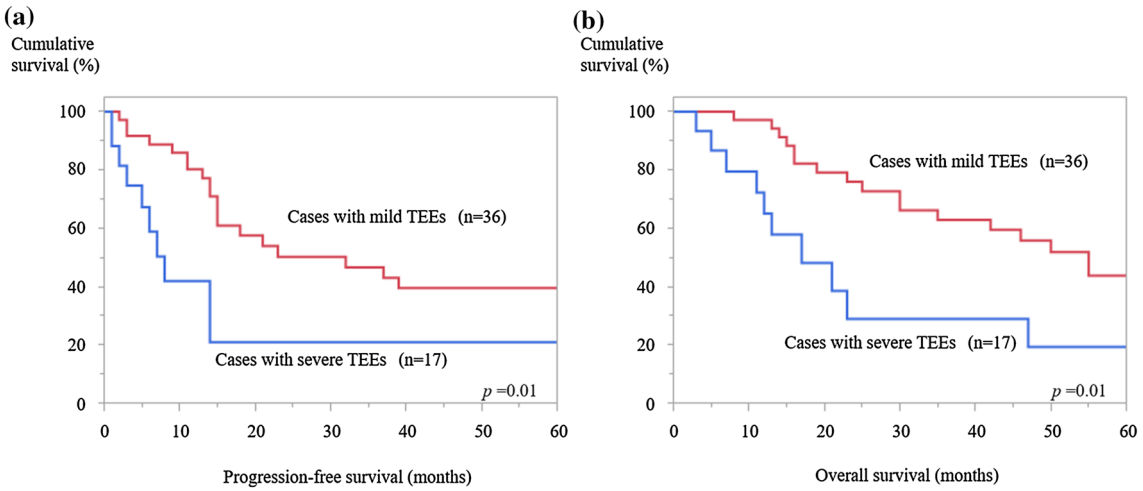


**Fig. 2** Progression-free survival (PFS) and overall survival (OS) in patients with severe thromboembolic events (TEEs) and in those with mild TEEs. The PFS (**a**) and OS (**b**) of patients with severe TEEs were worse than those of patients with mild TEEs (both $p = 0.01$)

Our results demonstrated no association between treatment and TEEs. Tateo et al. demonstrated none of the considered risk factors were found to be predictors of VTE postoperatively [17]. In addition, Chavan et al. showed neoadjuvant chemotherapy was not associated with venous thromboembolism [37]. Matuura et al. showed the incidence of deep venous thrombosis postoperatively and during chemotherapy was almost the same [38]. Therefore, our results could support these results. However, Kröger et al. and De Martino et al. demonstrated operation and chemotherapy increased the risk of TEEs. Further study should examine the association between treatment and the development of TEEs [39, 40].

**Table 6** Univariate and multivariate analysis of progression-free survival and overall survival in patients with thromboembolic events

| Variables | Progression-free survival | | | | | | Overall survival | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Univariate analysis | | | Multivariate analysis | | | Univariate analysis | | | Multivasriate analysis | | |
| | HR | 95% CI | *p* value | HR | 95% CI | *p* value | HR | 95% CI | *p* value | HR | 95% CI | *p* value |
| Age at diagnosis | | | | | | | | | | | | |
| ≧ 61 years vs. < 61 years | 1.19 | 0.58–2.49 | 0.63 | | | | 1.07 | 0.51–2.24 | 0.86 | | | |
| Performance status score | | | | | | | | | | | | |
| ≧ 1 vs. 0 | 3.53 | 0.81–10.8 | 0.08 | | | | 8.65 | 1.90–29.0 | < 0.01 | 3.32 | 0.69–12.6 | 0.09 |
| FIGO stage | | | | | | | | | | | | |
| III/IV vs. I/II | 1.87 | 0.90–4.02 | 0.09 | | | | 2.10 | 0.99–4.60 | 0.06 | | | |
| Histology | | | | | | | | | | | | |
| Clear cell carcinoma vs. high-grade serous carcinoma | 1.35 | 0.48–3.88 | 0.57 | | | | 1.00 | 0.33–3.11 | 0.99 | | | |
| Other carcinomas[a] vs. high-grade serous carcinoma | 1.28 | 0.54–3.36 | 0.59 | | | | 1.28 | 0.52–3.60 | 0.60 | | | |
| Timing of development of thromboembolic events | | | | | | | | | | | | |
| Before primary treatment vs. after primary treatment | 1.12 | 0.45–3.24 | 0.54 | | | | 1.20 | 0.38–3.40 | 0.56 | | | |
| Residual tumor | | | | | | | | | | | | |
| Suboptimal surgery vs. optimal surgery | 2.4 | 1.12–5.56 | 0.02 | 2.58 | 1.19–6.09 | 0.02 | 3.50 | 1.57–8.63 | < 0.01 | 3.48 | 1.50–8.81 | < 0.01 |
| Ascites | | | | | | | | | | | | |
| Yes vs. no | 1.64 | 0.68–4.53 | 0.28 | | | | 2.37 | 0.94–7.20 | 0.07 | | | |
| Tumor size | | | | | | | | | | | | |
| ≧ 10 cm vs. < 10 cm | 0.89 | 0.41–1.86 | 0.77 | | | | 1.18 | 0.53–2.50 | 0.66 | | | |
| Body mass index | | | | | | | | | | | | |
| ≧ 25 vs. < 25 | 0.85 | 0.29–2.06 | 0.74 | | | | 1.00 | 0.34–2.43 | 0.66 | | | |
| Thromboembolic events | | | | | | | | | | | | |
| Severe vs. mild | 2.65 | 1.16–5.66 | 0.02 | 2.91 | 1.25–6.43 | 0.01 | 2.62 | 1.15–5.63 | 0.02 | 2.46 | 1.02–5.69 | 0.04 |

*HR* hazard ratio, *CI* confidence interval, *FIGO* International Federation of Gynecology and Obstetrics

[a]Other carcinomas include endometrioid carcinoma, mucinous carcinoma, carcinosarcoma, and adenocarcinoma

The limitation of this study is its single-institutional and retrospective design with a small sample size. However, the development of TEEs and the presence of severe TEEs were poor prognostic factors and more frequently detected in patients with CCC.

In conclusion, the incidence of TEEs, and that of severe TEEs in patients with TEEs, is associated with CCC. Furthermore, the survival outcome is poorer in patients with TEEs, and in those with severe TEEs, than in patients without TEEs. Patients with CCC need treatment not only for the tumor but also for TEEs.

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## Compliance with ethical standards

**Conflicts of interest** All authors declare no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

**Informed consent** Informed consent was not obtained because our study was a retrospective analysis.

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