Venous thromboembolism, interleukin-6, and survival outcomes in patients with advanced ovarian clear cell carcinoma

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ABSTRACT (243 words)

Background: We compared survival outcomes and risk of venous thromboembolism (VTE) among patients with advanced and early-stage ovarian clear cell carcinoma (OCCC) and serous ovarian carcinoma (SOC), as well as potential links with interleukin-6 (IL-6) levels.

Methods: A multicenter case-control study was conducted in 370 patients with OCCC and 938 with SOC. In a subset of 200 cases, pretreatment plasma IL-6 levels were examined.

Findings: Patients with advanced OCCC had the highest 2-year cumulative VTE rates (advanced OCCC 43.1%, advanced SOC 16.2%, early-stage OCCC 11.9%, and early-stage SOC 6.4%, $P < 0.0001$) and the highest median levels of IL-6 (advanced OCCC 17.8 pg/mL, advanced SOC 9.0 pg/mL, early-stage OCCC 4.2 pg/mL, and early-stage SOC 5.0 pg/mL, $P = 0.006$). Advanced OCCC (hazard ratio [HR] 3.38, $P < 0.0001$), thrombocytosis (HR 1.42, $P = 0.032$), and elevated IL-6 (HR 8.90, $P = 0.046$) were independent predictors of VTE. In multivariate analysis, patients with advanced OCCC had significantly poorer 5-year progression-free and overall survival rates than those with advanced SOC ($P < 0.01$), and thrombocytosis was an independent predictor of decreased survival outcomes ($P < 0.01$). Elevated IL-6 levels led to poorer 2-year progression-free survival rates in patients with OCCC (50% vs. 87.5%, HR 4.89, $P = 0.016$) than in those with SOC (24.9% vs. 40.8%, HR 1.40, $P = 0.07$).

Interpretation: Advanced OCCC is associated with an increased incidence of VTE and decreased survival outcomes, which has major implications for clinical management of OCCC.

INTRODUCTION

Epithelial ovarian cancer comprises various histologic subtypes, including ovarian clear cell carcinoma (OCCC), which represents the second most common histologic subtype.[1,2] Accumulating evidence suggests that OCCC has distinct clinical and molecular characteristics compared with other histologic subtypes of epithelial ovarian cancer.[3,4] Clinically, patients with advanced-stage OCCC have poorer survival outcomes than those with advanced-stage serous ovarian carcinoma (SOC), whereas patients with early-stage OCCC and SOC have similar survival outcomes.[5,6] However, the reasons for this discrepancy and the mechanisms leading to poor survival outcomes in patients with advanced-stage OCCC have yet to be completely elucidated.

Venous thromboembolism (VTE) is a relatively common complication in ovarian cancer and is associated with decreased survival outcomes.[7,8] Epidemiologic studies have shown that patients with OCCC have an increased risk of VTE compared with patients with other histologic subtypes of epithelial ovarian cancer, and VTE adversely affects survival outcomes in patients with OCCC.[9-11] One possible biomarker linking OCCC with the increased risk of VTE is the proinflammatory cytokine interleukin 6 (IL-6). OCCC is known to be associated with higher IL-6 expression than in other subtypes of epithelial ovarian cancer,[12] and IL-6 is a pivotal marker of paraneoplastic thrombocytosis, which is a prognostic factor for decreased survival of ovarian cancer.[13,14] IL-6 could directly increase the risk of VTE by inducing procoagulant factors or indirectly increase the risk by inducing thrombocytosis.[15,16] However, it is unclear whether VTE events and IL-6 levels differ by stage of disease. The aim of our study was to compare the survival outcomes and risk of VTE among patients with early- and advanced-stage OCCC and SOC, as well as to examine the relationship of these outcomes to IL-6 levels.

PATIENTS AND METHODS

Clinical information

A large-scale multicenter international case-control study was conducted in 10 academic institutions, including 5 from the United States, 4 from Japan, and 1 from England. Institutional Review Board approval was obtained at each participating institution. Consecutive patients diagnosed with OCCC and SOC between January 1, 2000 and December 31, 2012 were identified from institutional databases. The STROBE guidelines for case-control studies were followed.[17] All patients had primary OCCC or SOC that was histologically confirmed from surgical specimens obtained in cytoreductive surgery. Those with a mixed histologic type were excluded from our analysis. A fraction of this study population was used in our previous study.[13] Medical records were retrospectively reviewed to obtain the following data: age, tumor markers, cytoreductive status, VTE characteristics, tumor characteristics, and survival outcomes.

Tumor markers included CA-125 levels and the presence of thrombocytosis (based on platelet counts) at the time of diagnosis. The cutoff for thrombocytosis (platelet count ≥400 $\times 10^9$/L) was determined on the basis of prior work.[18] Among those with recurrent or progressive disease, CA-125 levels and platelet counts were also collected at the time of first recurrence or progression. Residual tumor size at the end of cytoreductive surgery was grouped as >1 cm *versus* ≤1 cm. VTE characteristics included type of VTE (deep vein thrombosis [DVT], pulmonary embolism [PE], and others) and date of VTE diagnosis. Information for VTE was searched in both medical records and radiology reports for Doppler study, computed tomography scan, and lung scan. Tumor characteristics included histologic subtype (OCCC or SOC) and cancer stage (early or advanced) based on International Federation of Gynecology and Obstetrics (FIGO) criteria. Early-stage disease

was defined as FIGO stage I-II disease and advanced-stage disease was defined as FIGO stage III-IV disease.[19]

For survival outcomes, we determined progression-free survival (PFS) and overall survival (OS). PFS was defined as the time interval between the date of ovarian cancer diagnosis and the date of the first recurrence or progression of disease or last follow-up if there was no recurrence or progression. OS was defined as the time interval between the date of ovarian cancer diagnosis and the date of death or last follow-up if the patient was still alive. OS after first recurrence or progression was also examined in the subset of patients who experienced recurrence or progression.

IL-6 measurement

Pretreatment plasma samples were available for consecutive patients in 2 institutions. Blood samples were obtained prior to surgery and centrifuged at 3,000 rotations per minute for 10 minutes. Plasma was collected and stored in 1-mL aliquots in a -80°C freezer until it was processed. Plasma levels of IL-6 were examined using a Human IL-6 Quantikine enzyme-linked immunosorbent assay (ELISA) Kit (R&D Systems, Minneapolis, MN), according to the manufacturer's instructions. The ELISA plates were read using Multiskan JX (ThermoFisher Scientific, Waltham, MA). All tests were done in triplicate. Written informed consent was obtained from each subject prior to the blood sampling.

Statistical analysis

The primary outcome of interest was the impact of stage-specific histologic subtype (advanced-OCCC, advanced-SOC, early-OCCC, or early-SOC) on cumulative risk of VTE and survival outcomes. The secondary outcomes of interest were the correlation between

IL-6 levels and VTE incidence and between IL-6 levels and survival outcomes, by stage-specific histologic subtype. Continuous variables were assessed for normality distribution using Kolmogorov–Smirnov test, and results were expressed using mean (±standard deviation) or median (range) as appropriate. Statistical significance of continuous variables was determined using Student *t*-test or Mann-Whitney *U*-test, depending on normality. Median values across the 4 groups were examined using Kruskal-Wallis test. For categorical variables, chi-square test or Fisher exact test was used as appropriate.

VTE is a time-dependent event after ovarian cancer diagnosis. Therefore, the statistical significance of cumulative risk of VTE was determined using log-rank test in univariate analysis. Cox proportional hazards regression modeling in multivariate analysis was also performed to identify independent predictors of VTE. For survival analysis, log-rank test in univariate analysis and Cox proportional hazards regression modeling in multivariate analysis were used, and results were expressed as hazard ratios (HR) and 95% confidence intervals (CI). In multivariate analysis, variables used in the final model were based on clinical relevance and impact in ovarian cancer; these included age (≥60 or <60 years), CA-125 levels (>35 or ≤35 IU/L), thrombocytosis (yes or no), residual tumor size (≤1 cm or >1 cm), VTE (yes or no), and stage-specific histologic subtype (advanced-OCCC, advanced-SOC, early-OCCC, or early-SOC). Kaplan-Meier method was used to construct survival curves. $P < 0.05$ was considered statistical significant (two-tailed test). Statistical Package for the Social Sciences (SPSS, Inc., version 12.0, Chicago, IL) was used for all statistical analyses.

RESULTS

Patient characteristics

We evaluated the records of 1,308 patients with ovarian cancer for the current study. Although most of the 938 patients with SOC had advanced disease (n=836, 89.1%), most of the 370 patients with OCCC had early-stage disease (n=264, 71.4%; Table S1).

Stage-specific characteristics are shown in Table 1. The mean age of the entire cohort was 58.5 years. Both the advanced-OCCC and advanced-SOC groups had a high proportion of patients with elevated CA-125 levels at the initial cancer diagnosis (advanced-OCCC 96.2%, and advanced-SOC 87.0%). The advanced-SOC group had the highest proportion of patients with thrombocytosis at initial diagnosis (41.6%), followed by the advanced-OCCC group (32.1%). The advanced-SOC group had the highest proportion of patients with residual tumor size >1 cm at cytoreductive surgery (37.6%), followed by advanced-OCCC (26.4%). The median follow-up time of the entire cohort was 31.3 months, and there were 787 cases of recurrent or progressive disease (60.2%) and 487 deaths (37.2%) reported in the records.

Characteristics of VTE

There were 215 VTEs reported in the entire cohort (16.4%). DVT alone (n=102, 47.4%) was the most common type of VTE, followed by PE alone (n=56, 26.0%) and DVT+PE (n=51, 23.7%). The advanced-OCCC group had the highest incidence of any VTE (36.8%) among the 4 groups, as well as the highest incidence of DVT+PE (11.3%, $P<0.0001$, Table 1).

The cumulative prevalence of VTE was examined by stage-specific histologic subtype (Table 2). In univariate analysis, advanced-OCCC was associated with the highest

cumulative risk of VTE among the 4 groups (2-year cumulative VTE rates, advanced-OCCC 43.1%, advanced-SOC 16.2%, early-OCCC 11.9%, and early-SOC 6.4%, *P*<0.0001, Fig. 1A). In addition, age ≥60 years (19.3% vs. 14.1%, *P*=0.009), elevated CA-125 levels (17.0% vs. 5.8%, *P*=0.003), and thrombocytosis (22.3% vs. 13.8%, *P*=0.0001) were associated with increased risk of VTE. Residual tumor size ≤1 cm at cytoreductive surgery showed a protective effect against VTE (13.6% vs. 20.2%, *P*=0.028).

To identify independent risk factors for VTE, we performed multivariate analysis (Table 2). After controlling for age, CA-125 levels, thrombocytosis, cytoreductive status, and stage-specific histologic subtype, we found that advanced-OCCC remained an independent risk factor for VTE compared with advanced-SOC (HR 3.38, 95%CI 2.28-5.01, *P*<0.0001). Thrombocytosis also remained an independent risk factor for VTE (HR 1.42, 95%CI 1.03-1.96, *P*=0.032).

Survival analysis

In the univariate analysis for 5-year PFS rates, age ≥60 years (24.6% vs. 38.4%), CA-125 >35 IU/L (27.4% vs. 81.3%), thrombocytosis (15.3% vs. 40.7%), and VTE (15.7% vs. 35.3%) were associated with decreased PFS (*P*<0.0001; Table 3). Five-year PFS rates were 13.3% for advanced-OCCC, 19.7% for advanced-SOC, 84.7% for early-OCCC, and 66.9% for early-SOC (*P*<0.0001).

In the multivariate analysis controlling for age, CA-125, thrombocytosis, cytoreductive status, VTE, and stage-specific histologic subtype, patients with advanced-OCCC had poorer 5-year PFS rates than those with advanced-SOC (HR 1.45, 95%CI 1.12-1.86, *P*=0.004; Table 3). Thrombocytosis (HR 1.39, 95%CI 1.18-1.64, *P*<0.0001) and VTE

(HR 1.28, 95%CI 1.04-1.58, *P*=0.02) also remained independent prognostic factors for decreased 5-year PFS rates.

For 5-year OS rates, in the univariate analysis, age ≥60 years (44.7% vs. 58.0%), CA-125 >35 IU/L (49.1% vs. 90.7%), thrombocytosis (35.8% vs. 60.7%), and VTE (33.0% vs. 55.8%) were associated with decreased 5-year OS rates (*P*<0.0001; Table 4). Five-year OS rates were 28.2% for advanced-OCCC, 39.8% for advanced-SOC, 89.5% for early-OCCC, and 82.1% for early-SOC (Fig 1B, *P*<0.0001).

In the multivariate analysis controlling for age, CA-125, thrombocytosis, cytoreductive status, VTE, and stage-specific histologic subtype, those with advanced-OCCC had poorer 5-year OS rates than those with advanced-SOC (HR 2.15, 95%CI 1.60-2.88, *P*<0.0001; Table S2). In addition, thrombocytosis (HR 1.45, 95%CI 1.18-1.79, *P*=0.001) remained an independent prognostic factor for decreased 5-year OS rates. In a post-hoc multivariate analysis, 5-year OS rates did not differ between those with early-OCCC and those with early-SOC (HR 0.62, 95%CI 0.27-1.39, *P*=0.24).

Recurrent or progressive tumors

In our cohort, 787 patients experienced recurrence or progression. Among these patients, prognostic factors for OS after the first recurrence or progression of the tumor were examined (Table 4). Patterns of CA-125 and thrombocytosis at recurrence or progression were distinctively different from those at the initial ovarian cancer diagnosis. Specifically, CA-125 levels were similar across the 4 stage-specific histologic subtype groups (*P*=0.38; Table 1). Although thrombocytosis was more common in those with advanced-SOC (41.6%) than in those with advanced-OCCC (32.1%) at the time of the initial cancer diagnosis, at the time of the first recurrence or progression, thrombocytosis was more

common in those with advanced-OCCC (27.0%) than in those with advanced-SOC (13.6%, *P*=0.028). Splenectomy at the time of cytoreductive surgery (n=15, 1.1%) was not associated with thrombocytosis at the time of the first recurrence or progression of disease (9.1% vs. 15.1%, *P*=1.0).

The median OS duration after the first recurrence or progression was 13.0 months. In the multivariate analysis controlling for age, CA-125, thrombocytosis, VTE, and stage-specific histologic subtype, thrombocytosis at the first recurrence or progression remained an independent prognostic factor for decreased 2-year OS rates after the first recurrence or progression (28.7% vs. 46.3%; HR 1.67, 95%CI 1.21-2.30, *P*=0.002). In addition, advanced-OCCC (17.0% vs. 46.3%; HR 2.68, 95%CI 1.90-3.79, *P*<0.0001) and early-OCCC (29.5% vs. 46.3%; HR 2.12, 95%CI 1.30-3.44, *P*=0.002) remained independent prognostic factors for decreased 2-year OS rates after the first recurrence or progression compared to advanced-SOC (Table 4 and Fig. 1C).

IL-6 levels

Plasma samples were available for 200 patients in the cohort (OCCC n=38, and SOC n=162). The median plasma IL-6 level among these 200 patients was 7.6 pg/mL, and 85 of the patients (42.5%) had IL-6 levels ≥10 pg/mL. Thrombocytosis was associated with IL-6 levels ≥10 pg/mL (66.7% vs. 27.0%; HR 5.39, 95%CI 2.91-10.0, *P*<0.0001). Patients with VTE had significantly higher IL-6 levels than those without VTE (median IL-6 levels: 14.4 vs. 7.1 pg/mL, *P*=0.003).

In a multivariate analysis controlling for age, CA-125 levels, thrombocytosis, cytoreductive status, and stage-specific histologic subtype, high pretreatment IL-6 levels remained an independent predictor of VTE compared with lower IL-6 levels (2-year

cumulative VTE rates, 5-19.9 vs. <5 pg/mL, 14.0% vs. 1.4%; HR 7.98, 95%CI 0.99-64.0, *P*=0.051; and ≥20 vs. <5 pg/mL, 17.1% vs. 1.4%; HR 8.90, 95%CI 1.04-76.0, *P*=0.046; Table 5).

Across the 4 stage-specific histologic subtype groups, the advanced-OCCC group had the highest proportion of IL-6 levels ≥10 pg/mL (advanced-OCCC 83.3%, advanced-SOC 47.7%, early-OCCC 15.6%, and early-SOC 27.3%, *P*=0.001, Fig. 1D). Similarly, the advanced-OCCC group had the highest median IL-6 levels among the 4 groups (advanced-OCCC 17.8 pg/mL, advanced-SOC 9.0 pg/mL, early-OCCC 4.2 pg/mL, and early-SOC 5.0 pg/mL, *P*=0.006). Similar to the results from the entire cohort, advanced-OCCC was associated with the highest risk of VTE across the 4 groups (2-year cumulative VTE risk: advanced-OCCC 40%, advanced-SOC 13.4%, early-OCCC 17.5%, and early-SOC 0%, *P*=0.039).

Among the 200 patients in whom IL-6 levels were examined, IL-6 levels ≥10 pg/mL were associated with decreased 2-year PFS rates (27.4% vs. 47.6%; HR 1.58, 95%CI 1.11-2.26, *P*=0.013). However, when the patients were stratified by histologic subtype, the magnitude of the difference was larger in those with OCCC (2-year PFS rates, IL-6 ≥10 vs. <10 pg/mL, 50% vs. 87.5%, HR 4.89, 95%CI 1.17-20.5, *P*=0.016, Fig. 1E) than in those with SOC (24.9% vs. 40.8%, HR 1.40, 95%CI 0.97-2.03, *P*=0.07, Fig. 1F).

DISCUSSION

In the current study, advanced-OCCC, but not early-OCCC, was associated with a substantially increased risk of VTE compared with advanced-SOC. Patients with advanced-OCCC also had the highest frequency of elevated IL-6 levels, and those with advanced-OCCC had poorer survival outcomes than those with advanced-SOC. These findings suggest that the IL-6 pathway plays a pivotal role in the progression of OCCC. A proposed schema of the role of IL-6 in OCCC, based on our results, is shown in Figure S1.

A recent study showed that paraneoplastic thrombocytosis contributed to poor outcomes in ovarian cancer. The authors showed that IL-6 stimulates hepatocytes to induce thrombopoietin, which further induces megakaryocytes in bone marrow to produce platelets.[13] These IL-6–induced platelets promote tumor progression by providing platelet-related cancer cell protection from the host immune system, providing growth factors, and promoting tumor angiogenesis. In our study, survival analyses showed that both advanced-OCCC and thrombocytosis were the common prognostic factors for decreased survival outcomes (Table 3-4). In addition, elevated IL-6 levels were associated with thrombocytosis and advanced disease. These findings provide evidence for the existence of IL-6–mediated paraneoplastic thrombocytosis in advanced-OCCC.

Although IL-6–mediated paraneoplastic thrombocytosis is a proposed mechanism for tumor progression in advanced-OCCC, our study showed that thrombocytosis was less common in patients with advanced-OCCC than in those with advanced-SOC (32.1% vs. 41.6%, Table 1). This implies that the IL-6–mediated paraneoplastic thrombocytosis is more prominent in SOC, and there may be an alternative IL-6–related pathway that contributes to tumor progression in OCCC, such as a direct autocrine pathway. Recently, the tumor microenvironment was reported to be a source of IL-6 in certain types of

malignancy.[20,21] Some researchers have even speculated that the tumor microenvironment may supply IL-6 in SOC.[22] Therefore, hypothetically, there are 2 possible pathways for IL-6 interaction in ovarian cancer: *(i)* direct pathway via autocrine IL-6 signaling and *(ii)* IL-6–mediated indirect pathway via paraneoplastic thrombocytosis.[13,22] In the IL-6 autocrine pathway in OCCC, downstream signaling of the IL-6 receptor is activated via the HIF1A-STAT3 cascade and ultimately induces VEGF, a key mediator for tumor angiogenesis.[12, 23, 24] Indeed, VEGF expression in OCCC is significantly higher than in other histologic types of epithelial ovarian cancer.[25] Collectively, our findings suggest that both direct and indirect IL-6 pathways may lead to tumor progression in OCCC, and the direct pathway may be more active in OCCC.

VTE is a common issue in OCCC.[10] Quality of life in cancer patients can be compromised as a result of the VTE itself and from drug injections, treatment costs, and decreased survival outcomes. In our study, those with VTE had significantly higher levels of IL-6 than those who did not have VTE, and this association has not been well studied in cancer patients.[26] In addition, VTE was associated with thrombocytosis (Table 2), which has recently been recognized in the oncology field.[27] Our findings also showed that elevated IL-6 is associated with thrombocytosis, and those with advanced-OCCC had the highest frequency of multiple-site VTE (DVE+PE; 11.3%) compared with the other groups. Taken together, our findings indicate that VTE in OCCC is a clinical manifestation and surrogate marker of the aggressiveness of IL-6–driven tumor progression, and the decreased survival outcomes in those who develop VTE among OCCC patients is more likely from the aggressive tumor behavior than from cardiovascular collapse.

Although overexpression of IL-6 in OCCC has been reported by various investigators, the exact mechanism driving IL-6 overexpression in OCCC has yet to be

determined.[28] Although a fraction of IL-6 may come from the tumor microenvironment, a substantial fraction of IL-6 is speculated to come from tumor cells in OCCC given its high IL-6 expression. To date, ARID1A mutation (loss of function) and PIK3CA mutation (gain of function) have been identified as common occurrences in OCCC (40-60%).[2,29] Available evidence suggests a possible link between the PIK3CA mutation and IL-6 overexpression. Specifically, the PIK3CA mutation upregulates NF-κB, which leads to IL-6–dependent STAT3 activation.[30] Moreover, a recent pre-clinical study has shown that additional loss of ARID1A function in the setting of PIK3CA overexpression is a key step in pathogenesis of OCCC.[31] Interestingly, IL-6 transcription in this OCCC model of ARID1A and PIK3CA mutation is found to be elevated. Therefore, it is paramount to see if this correlation seen in pre-clinical study also exists in human samples of OCCC by sequencing ARID1A and PIK3CA correlating with plasma IL-6 level.

The unique characteristics of recurrent or progressive OCCC deserve further discussion. Generally, recurrent OCCC is resistant to therapy, with a response rate of <10%.[32] This was also true in our study, and those with advanced-OCCC had poorer 2-year OS rates after recurrence or progression than those with advanced-SOC (Table 5). The advanced-OCCC group had a higher proportion of patients with thrombocytosis at the first recurrence or progression than the other groups, and this may represent a role for paraneoplastic thrombocytosis in the setting of advanced-OCCC. Interestingly, 2-year OS rates after recurrence or progression were also shorter in those with early-OCCC than in those with advanced-SOC. This implies that recurrent or progressive OCCC is quite chemoresistant regardless of original disease status. Our study did not have information for chemotherapy treatment after the first recurrence or progression and therefore we were unable to address this question.

A potential limitation of our study is that this is a retrospective study that may have some confounding factors. For example, we did not use the standard case record form to capture VTE events; however, all the participating institutions are tertiary care cancer centers and patient follow-up is quite consistent. In addition, central pathology review to confirm OCCC was not performed for the study. A potential weakness of our study is that central histopathologic slide review was not available for grading serous tumors.[33,34] Nevertheless, in post-hoc analysis, high-grade SOC cases (n=768) were compared to CCC cases (Table S3-6). The results were consistent in that advanced-OCCC was significantly associated with increased risk of VTE (HR 3.34, 95%CI 2.23-4.99, *P*<0.0001), decreased PFS (HR 1.55, 95%CI 1.20-2.01, *P*=0.002), decreased OS (HR 2.19, 95%CI 1.62-2.97, *P*<0.0001), and decreased OS after the first recurrence or progression of disease (HR 2.73, 95%CI 1.89-3.96, *P*<0.0001) compared to advanced high-grade SOC in multivariate analysis. Lastly, a relatively small sample size for IL-6 assessment may limit generalizability.

In summary, our results indicate that advanced-OCCC is thrombogenic and may be a surrogate marker of tumor-biologically more aggressive disease. Treatment involving both anti-thrombotic agents and blocking of IL-6 signaling may be an attractive approach in advanced-OCCC. A phase II study examining the efficacy of the combination of a monoclonal antibody against IL-6 with siltuximab for platinum-resistant ovarian cancer showed that the combination had some therapeutic activity; however, this study was not solely for patients with OCCC.[35] Statin therapy is also suggested to reduce IL-6 activity and VTE risk by inhibiting inflammatory cytokines, resulting in reduced cancer-related mortality.[36,37] Currently (as of April 8, 2015), no ongoing clinical trial of a treatment targeting IL-6 for

OCCC has been registered at clinicaltrials.gov. Further preclinical and clinical studies are warranted.

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Table 1. Patient characteristics by stage-specific histologic subtype in our cohort (n = 1,308)

	No. (%)				
	OCCC (n = 370)		SOC (n = 938)		
Characteristic	**Advanced**	**Early**	**Advanced**	**Early**	***P*-value[†]**
No. of patients	106 (28.6)	264 (71.4)	836 (89.1)	102 (10.9)	
Mean age (±standard deviation)	57.6 years (± 10.2 years)	53.1 years (± 10.2 years)	60.3 years (± 11.2 years)	58.5 years (± 10.6 years)	< 0.0001
<60 years	62 (58.5)	194 (73.5)	394 (47.1)	55 (53.9)	
≥60 years	44 (41.5)	70 (26.5)	442 (52.9)	47 (46.1)	
Median CA-125 levels at diagnosis (range)	358 IU/L (17-21120 IU/L)	59 IU/L (6-20887 IU/L)	841 IU/L (8-86591 IU/L)	223 IU/L (4-21634 IU/L)	< 0.0001
≤35 IU/L	3 (2.8)	87 (33)	16 (1.9)	26 (25.5)	
>35 IU/L	102 (96.2)	167 (63.3)	727 (87)	65 (63.7)	
Unknown	1 (0.9)	10 (3.8)	93 (11.1)	11 (10.8)	
Median CA-125 levels at first recurrence or progression (range)*	108 IU/L (7-1019 IU/L)	180 IU/L (6-1320 IU/L)	351 IU/L (4-12957 IU/L)	170 IU/L (5-681 IU/L)	0.38
≤35 IU/L	15 (18.8)	11 (33.3)	80 (12.5)	8 (25)	
>35 IU/L	47 (58.8)	19 (57.6)	262 (40.8)	18 (56.3)	
Unknown	18 (22.5)	3 (9.1)	300 (46.7)	6 (18.7)	
Median platelet counts at diagnosis (range)	336 × 10^9/L (145-696 × 10^9/L)	287 × 10^9/L (115-834 × 10^9/L)	368 × 10^9/L (82-979 × 10^9/L)	269 × 10^9/L (97-594 × 10^9/L)	< 0.0001
<400 × 10^9/L	71 (67)	217 (82.2)	480 (57.4)	92 (90.2)	
≥400 × 10^9/L	34 (32.1)	43 (16.3)	348 (41.6)	9 (8.8)	
Unknown	1 (0.9)	4 (1.5)	8 (1.0)	1 (1.0)	
Median platelet counts at first recurrence or progression (range)*	271 × 10^9/L (54-1329 × 10^9/L)	234 × 10^9/L (96-739 × 10^9/L)	243 × 10^9/L (34-1178 × 10^9/L)	239 × 10^9/L (127-779 × 10^9/L)	0.028
<400 × 10^9/L	46 (57.5)	26 (78.8)	287 (44.7)	23 (71.9)	
≥400 × 10^9/L	17 (21.3)	3 (9.1)	45 (7.0)	2 (6.3)	
Unknown	17 (21.3)	4 (12.1)	310 (48.3)	7 (21.9)	
Residual tumor size after surgery					< 0.0001
> 1 cm	28 (26.4)	3 (1.1)	314 (37.6)	8 (7.8)	
≤ 1 cm	72 (67.9)	261 (98.9)	470 (56.2)	94 (92.2)	
Unknown	6 (5.7)	0 (0)	52 (6.2)	0 (0)	
Recurrent or progressive disease					< 0.0001
No	26 (24.5)	231 (87.5)	194 (23.2)	70 (68.6)	
Yes	80 (75.5)	33 (12.5)	642 (76.8)	32 (31.4)	
Death					< 0.0001
No	44 (41.5)	244 (92.4)	444 (53.1)	89 (87.3)	
Yes	62 (58.5)	20 (7.6)	392 (46.9)	13 (12.7)	
Type of venous thromboembolism					< 0.0001
None	67 (63.2)	230 (87.1)	704 (84.2)	92 (90.2)	
DVT alone	17 (16.0)	13 (4.9)	69 (8.3)	3 (2.9)	
PE alone	9 (8.5)	4 (1.5)	41 (4.9)	2 (2.0)	

DVT + PE	12 (11.3)	14 (5.3)	21 (2.5)	4 (3.9)
Other	1 (0.9)	3 (1.1)	1 (0.1)	1 (1.0)
Any	39 (36.8)	34 (12.9)	132 (15.8)	10 (9.8)

† The chi-square test was used for *P* values

* Advanced OCCC: n = 80; early-stage OCCC: n = 33; advanced SOC: n = 642; early-stage SOC: n = 32.

. Abbreviations: OCCC, ovarian clear cell carcinoma; SOC, serous ovarian carcinoma; CA-125, cancer antigen 125; DVT, deep vein thrombosis; PE, pulmonary embolism.

Table 2. Risk factors for venous thromboembolism in our cohort (n = 1,308)

Variable	No.	2-year cumulative rate, %	Univariate		Multivariate	
			HR (95%CI)	*P*-value†	HR (95%CI)	*P*-value†
Age				0.009		0.016
<60 years	705	14.1	1		1	
≥60 years	603	19.3	1.42 (1.09-1.86)		1.46 (1.07-1.99)	
CA-125 levels				0.003		0.025
≤ 35 IU/L	132	5.8	1		1	
> 35 IU/L	1061	17.0	2.52 (1.33-4.76)		2.38 (1.11-5.07)	
Thrombocytosis*				0.0001		0.032
No	860	13.8	1		1	
Yes	434	22.3	1.66 (1.26-2.18)		1.42 (1.03-1.96)	
Residual tumor size after surgery				0.028		0.52
> 1 cm	353	20.2	1		1	
≤ 1 cm	897	13.6	0.72 (0.53-0.97)		0.89 (0.63-1.27)	
Stage-specific histologic type				< 0.0001		
Advanced SOC	836	16.2	1		1	
Advanced OCCC	106	43.1	2.74 (1.92-3.92)		3.38 (2.28-5.01)	< 0.0001
Early-stage SOC	102	6.4	0.54 (0.28-1.03)		0.80 (0.38-1.68)	0.55
Early-stage OCCC	264	11.9	0.73 (0.50-1.06)		1.23 (0.77-1.95)	0.39

† The log-rank test was used for univariate analysis and Cox proportional hazards regression modeling was used for multivariate analysis.

* Platelet count ≥400 × 10^9/L.

Abbreviations: HR, hazard ratio; CI, confidence interval; CA-125, cancer antigen 125; SOC, serous ovarian carcinoma; OCCC, ovarian clear cell carcinoma.

Table 3. Factors influencing 5-year progression-free survival (PFS) rates in our cohort (n = 1,308)

Variable	No.	5-year PFS, %	Univariate		Multivariate	
			HR (95%CI)	*P*-value†	HR (95%CI)	*P*-value†
Age				< 0.0001		0.35
<60 years	705	38.4	1		1	
≥60 years	603	24.6	1.45 (1.26-1.67)		1.08 (0.92-1.27)	
CA-125 levels				< 0.0001		0.002
≤35 IU/L	132	81.3	1		1	
>35 IU/L	1061	27.4	6.95 (4.40-11.0)		2.29 (1.35-3.88)	
Thrombocytosis*				< 0.0001		< 0.0001
No	860	40.7	1		1	
Yes	434	15.3	2.09 (1.80-2.41)		1.39 (1.18-1.64)	
Residual tumor size after surgery				< 0.0001		< 0.0001
> 1 cm	353	8.5	1		1	
≤ 1 cm	897	43.3	0.35 (0.30-0.41)		0.64 (0.54-0.76)	
VTE				< 0.0001		0.02
No	1093	35.3	1		1	
Yes	215	15.7	1.78 (1.49-2.12)		1.28 (1.04-1.58)	
Stage-specific histologic type				< 0.0001		
Advanced SOC	836	19.7	1		1	
Advanced OCCC	106	13.3	1.31 (1.04-1.66)		1.45 (1.12-1.86)	0.004
Early-stage SOC	102	66.9	0.23 (0.16-0.32)		0.36 (0.24-0.55)	< 0.0001
Early-stage OCCC	264	84.7	0.09 (0.06-0.13)		0.14 (0.10-0.21)	< 0.0001

† The log-rank test was used for univariate analysis and Cox proportional hazards regression modeling was used for multivariate analysis.

* Platelet count ≥400 × 10^9/L.

Abbreviations: HR, hazard ratio; CI, confidence interval; CA-125, cancer antigen 125; VTE, venous thromboembolism; SOC, serous ovarian carcinoma; OCCC, ovarian clear cell carcinoma.

Table 4. Factors influencing overall survival (OS) after recurrence or progression in a portion of our cohort (n = 787)

Variable	No.	2-year OS rate after recurrence, %	Univariate		Multivariate	
			HR (95%CI)	*P*-value†	HR (95%CI)	*P*-value†
Age				0.046		0.15
<60 years	384	46.8	1		1	
≥60 years	403	39.4	1.20 (1.00-1.44)		1.21 (0.94-1.56)	
CA-125 levels*				< 0.0001		< 0.0001
≤35 IU/L	114	64.0	1		1	
>35 IU/L	346	41.8	1.97 (1.43-2.72)		2.02 (1.44-2.84)	
Thrombocytosis*				< 0.0001		0.002
No	382	49.3	1		1	
Yes	67	28.7	2.00 (1.47^2.71)		1.67 (1.21-2.30)	
VTE				0.05		0.97
No	625	45.3	1		1	
Yes	162	35.2	1.24 (1.00-1.54)		1.01 (0.74-1.37)	
Stage-specific histologic subtype				< 0.0001		
Advanced SOC	642	46.3	1		1	
Advanced OCCC	80	17.0	2.24 (1.70-.94)		2.68 (1.90-3.79)	< 0.0001
Early-stage SOC	32	61.3	0.59 (0.33-1.05)		0.84 (0.44-1.60)	0.60
Early-stage OCCC	33	29.5	1.20 (0.77-1.89)		2.12 (1.30-3.44)	0.002

† The log-rank test was used for univariate analysis and Cox proportional hazards regression modeling was used for multivariate analysis.

* CA-125 and platelet counts were measured at the time of first recurrence or progression of disease.

Abbreviations: HR, hazard ratio; CI, confidence interval; CA-125, cancer antigen 125; VTE, venous thromboembolism; SOC, serous ovarian carcinoma; OCCC, ovarian clear cell carcinoma.

Table 5. Interleukin-6 (IL-6) and risk of venous thromboembolism in a portion of our cohort (*n* = 200)

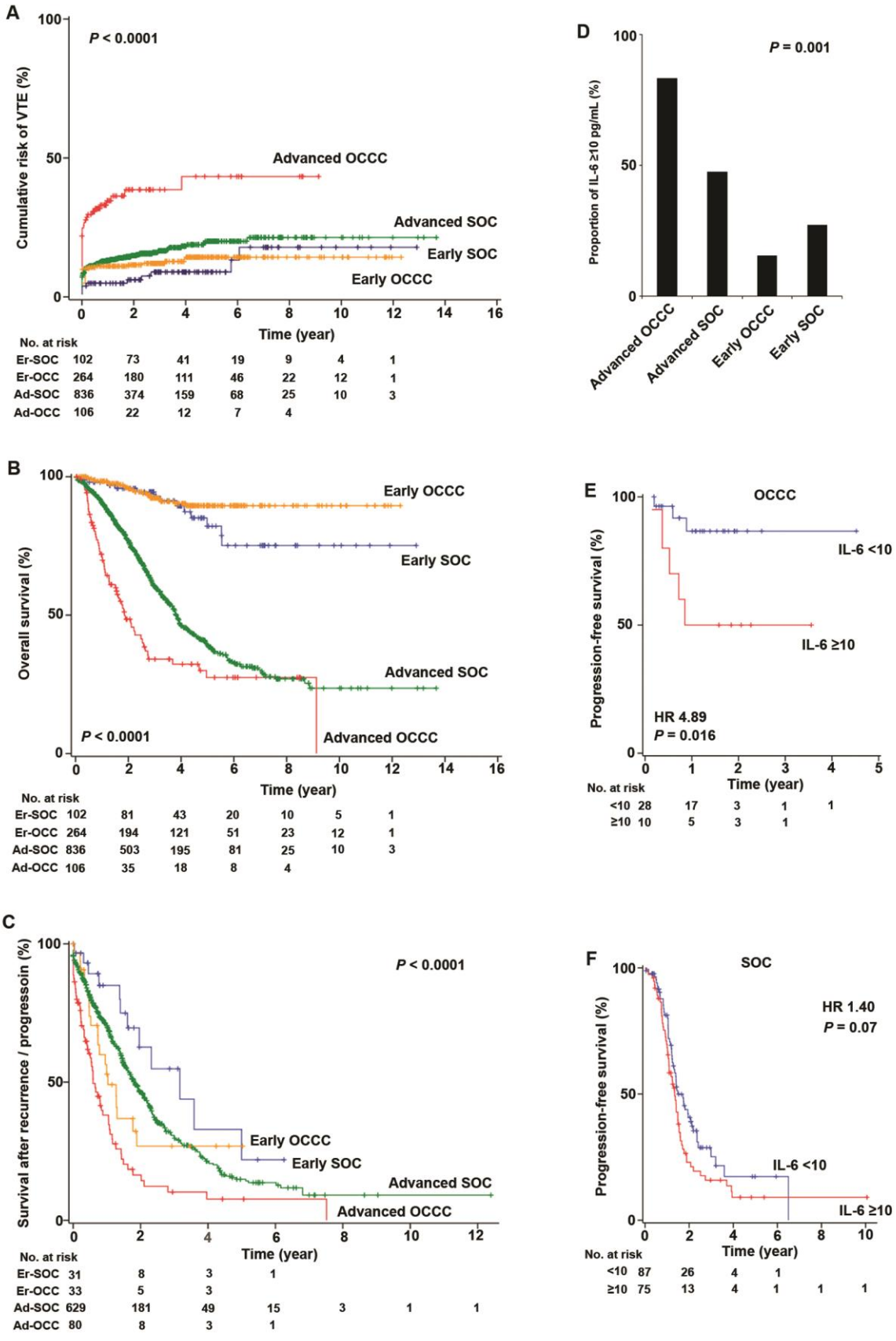
Variable	No.	2-year cumulative rate, %	Univariate		Multivariate	
			HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age				0.57		0.78
<60 years	99	12.4	1		1	
≥60 years	101	9.1	0.78 (0.33-1.86)		0.87 (0.34-2.22)	
CA-125 levels				0.19		0.95
≤35 IU/L	15	0.0	1		1	
>35 IU/L	185	11.6	22.7 (0.02-28568)		na	
Thrombocytosis*				0.028		0.31
No	122	7.0	1		1	
Yes	78	16.7	2.58 (1.07-6.22)		1.65 (0.63-4.33)	
Residual tumor size after surgery				0.96		0.84
> 1 cm	63	11.5	1		1	
≤ 1 cm	137	10.0	1.03 (0.39-2.67)		1.11 (0.41-3.04)	
Stage-specific histologic subtype				0.039		
Advanced SOC	151	13.4	1		1	
Advanced OCCC	6	40.0	5.07 (1.13-22.7)		3.43 (0.76-15.6)	0.11
Early-stage SOC	11	0.0	0		na	0.99
Early-stage OCCC	32	17.5	2.17 (0.77-6.13)		4.00 (1.25-12.8)	0.019
IL-6 levels prior to treatment**				0.012		
<5 pg/mL	68	1.4	1		1	
5-19.9 pg/mL	79	14.0	9.66 (1.25-74.9)		7.98 (0.99-64.0)	0.051
≥20 pg/mL	53	17.1	12.1 (1.53-95.5)		8.90 (1.04-76.0)	0.046

The log-rank test was used for univariate analysis and Cox proportional hazards regression modeling was used for multivariate analysis. Abbreviations: HR, hazard ratio; CI, confidence interval; CA-125, cancer antigen 125; VTE, venous thromboembolism; SOC, serous ovarian cancer; OCCC, ovarian clear cell carcinoma; na, not available.

*Platelet count ≥400 × 10^9/L.

**IL-6 levels were grouped into lower third (1-33%ile, <5 pg/mL), mid third (34-66%ile, 5-19.9 pg/mL), and upper third (≥67%ile, ≥20 pg/mL).

Figure 1. Venous thromboembolism (VTE), interleukin-6 (IL-6), and survival of ovarian cancer.



The log-rank test or chi-square test were used to generate the *P* values. **A)** Cumulative risk of thromboembolism after diagnosis of ovarian cancer. **B)** Overall survival by stage-specific histologic subtype. **C)** Overall survival after recurrence or progression by stage-specific histologic subtype. **D)** Proportion of patients with IL-6 levels ≥10 pg/mL (prior to treatment), by stage-specific histologic subtype. **E)** Progression-free survival by IL-6 level in patients with ovarian clear cell carcinoma (OCCC). **F)** Progression-free survival by IL-6 level in patients with serous ovarian carcinoma (SOC). Abbreviations: HR, hazard ratio.

Supplemental Table S1. Patient characteristics in our cohort (*N* = 1,308)

Characteristic	No. (%) OCCC	No. (%) SOC	*P* value
No. of patients	370	938	
Mean age (± standard deviation)	54.4 years (±10.4 years)	60.1 years (±11.1 years)	<0.0001
<60 years	256 (69.2)	449 (47.9)	
≥60 years	114 (30.8)	489 (52.1)	
Median CA-125 levels at diagnosis (range)	117 IU/L (6-21120 IU/L)	754 IU/L (4-865591 IU/L)	<0.0001
≤35 IU/L	90 (24.3)	42 (4.5)	
>35 IU/L	269 (72.7)	792 (84.4)	
Unknown	11 (3.0)	104 (11.1)	
Median CA-125 levels at first recurrence or progression (range)*	95 IU/L (6-1320 IU/L)	101 IU/L (4-12957 IU/L)	0.45
≤35 IU/L	26 (23.0)	88 (13.1)	
>35 IU/L	66 (58.4)	280 (41.5)	
Unknown	21 (18.6)	306 (45.4)	
Median platelet counts at diagnosis (range)	294 × 10^9/L (115-834 × 10^9/L)	353 × 10^9/L (82-979 × 10^9/L)	<0.0001
<400 × 10^9/L	288 (77.8)	572 (61.0)	
≥400 × 10^9/L	77 (20.8)	357 (38.0)	
Unknown	5 (1.4)	9 (1.0)	
Median platelet counts at first recurrence or progression (range)*	252 × 10^9/L (54-1329 × 10^9/L)	242 × 10^9/L (34-1178 × 10^9/L)	0.40
<400 × 10^9/L	72 (63.7)	310 (46.0)	
≥400 × 10^9/L	20 (17.7)	47 (7.0)	
Unknown	21 (18.6)	317 (47.0)	
Stage			<0.0001
I	225 (60.8)	57 (6.1)	
II	39 (10.5)	45 (4.8)	
III	87 (23.5)	652 (69.5)	
IV	19 (5.1)	184 (19.6)	
Residual tumor size after surgery			<0.0001
> 1 cm	31 (8.4)	322 (34.3)	
≤ 1 cm	333 (90.0)	564 (60.1)	
Unknown	6 (1.6)	52 (5.5)	
Recurrence			<0.0001
No	257 (69.5)	264 (28.1)	
Yes	113 (30.5)	674 (71.9)	
Death			<0.0001
No	288 (77.8)	533 (56.8)	
Yes	82 (22.2)	405 (43.2)	
Type of venous thromboembolism			0.002
None	297 (80.3)	796 (84.9)	

DVT alone	30 (8.1)	72 (7.7)
PE alone	13 (3.5)	43 (4.6)
DVT + PE	26 (7.0)	25 (2.7)
Other	4 (1.1)	2 (0.2)
Any	73 (19.7)	142 (15.1)

The Student *t* test, Mann-Whitney *U* test, or chi-square test were used for *P* values. Abbreviations: OCCC, ovarian clear cell carcinoma; SOC, serous ovarian cancer; CA-125, cancer antigen 125; DVT, deep vein thrombosis; PE, pulmonary embolism.

* OCCC: *n* = 113; SOC: *n* = 674.

Table S2. Factors influencing 5-year overall survival (OS) rates in our cohort (n = 1,308)

Variable	No.	5-year OS, %	Univariate		Multivariate	
			HR (95%CI)	*P*-value†	HR (95%CI)	*P*-value†
Age				< 0.0001		0.18
<60 years	705	58.0	1		1	
≥60 years	603	44.7	1.47 (1.23-1.76)		1.15 (0.94-1.41)	
CA-125 levels				< 0.0001		0.007
≤35 IU/L	132	90.7	1		1	
>35 IU/L	1061	49.1	8.80 (4.37-17.7)		3.20 (1.38-7.45)	
Thrombocytosis*				< 0.0001		0.001
No	860	60.7	1		1	
Yes	434	35.8	2.17 (1.81-2.60)		1.45 (1.18-1.79)	
Residual tumor size after surgery				< 0.0001		<0.0001
> 1 cm	353	28.0	1		1	
≤ 1 cm	897	64.4	0.33 (0.28-0.40)		0.57 (0.46-0.70)	
VTE				< 0.0001		0.15
No	1093	55.8	1		1	
Yes	215	33.0	1.84 (1.49-2.28)		1.22 (0.93-1.58)	
Stage-specific histologic type				< 0.0001		
Advanced SOC	836	39.8	1		1	
Advanced OCCC	106	28.2	1.83 (1.40-2.39)		2.15 (1.60-2.88)	< 0.0001
Early-stage SOC	102	82.1	0.19 (0.11-0.34)		0.33 (0.17-0.63)	0.001
Early-stage OCCC	264	89.5	0.12 (0.08-0.19)		0.23 (0.14-0.39)	< 0.0001

† The log-rank test was used for univariate analysis and Cox proportional hazards regression modeling was used for multivariate analysis.

* Platelet count ≥400 $\times 10^9$/L.

Abbreviations: HR, hazard ratio; CI, confidence interval; CA-125, cancer antigen 125; VTE, venous thromboembolism; SOC, serous ovarian cancer; OCCC, ovarian clear cell carcinoma.

Table S3. Risk factors for venous thromboembolism in sub-analysis (n =1,138)

Variable	No.	2-year cumulative rate, %	Univariate		Multivariate	
			HR (95%CI)	*P*-value†	HR (95%CI)	*P*-value†
Age				0.006		0.012
<60 years	616	18.9	1		1	
≥60 years	522	26.4	1.48 (1.12-1.95)		1.51 (1.10-2.08)	
CA-125 levels				0.005		0.038
≤ 35 IU/L	120	9.1	1		1	
> 35 IU/L	912	22.8	2.52 (1.33-4.77)		2.24 (1.05-4.79)	
Thrombocytosis*				0.002		0.23
No	744	18.0	1		1	
Yes	380	31.8	1.55 (1.17-2.05)		1.23 (0.88-1.72)	
Residual tumor size after surgery				0.001		0.001
> 1 cm	834	25.0	1		1	
≤ 1 cm	247	11.5	0.49 (0.33-0.75)		0.52 (0.32-0.86)	
Stage-specific histologic type						
Advanced HG-SOC	701	23.6	1		1	
Advanced OCCC	106	47.1	2.50 (1.74-3.59)	<0.0001	3.34 (2.23-4.99)	<0.0001
Early-stage HG-SOC	67	13.9	0.74 (0.39-1.41)	0.35	1.10 (0.53-2.32)	0.79
Early-stage OCCC	264	14.5	0.66 (0.45-0.97)	0.033	1.47 (0.88-2.44)	0.13

† The log-rank test was used for univariate analysis and Cox proportional hazards regression modeling was used for multivariate analysis.

* Platelet count ≥400 × 10^9/L.

Abbreviations: HR, hazard ratio; CI, confidence interval; CA-125, cancer antigen 125; HG-SOC, high-grade serous ovarian cancer; OCCC, ovarian clear cell carcinoma.

Table S4. Factors influencing 5-year progression-free survival (PFS) rates in sub-analysis (n = 1,138)

Variable	No.	5-year PFS, %	Univariate		Multivariate	
			HR (95%CI)	*P*-value†	HR (95%CI)	*P*-value†
Age				<0.0001		0.43
<60 years	616	40.0	1		1	
≥60 years	522	25.3	1.46 (1.25-1.70)		1.07 (0.90-1.28)	
CA-125 levels				<0.0001		0.006
≤35 IU/L	120	81.3	1		1	
>35 IU/L	912	28.8	6.90 (4.26-11.2)		2.20 (1.26-3.85)	
Thrombocytosis*				<0.0001		0.001
No	744	42.2	1		1	
Yes	380	16.4	2.10 (1.80-2.46)		1.35 (1.13-1.62)	
Residual tumor size after surgery				<0.0001		0.059
> 1 cm	834	22.5	1		1	
≤ 1 cm	247	74.7	0.19 (0.14-0.25)		1.24 (0.99-1.54)	
VTE				<0.0001		0.044
No	935	37	1		1	
Yes	203	16.2	1.79 (1.49-2.15)		1.25 (1.01-1.56)	
Stage-specific histologic type						
Advanced HG-SOC	701	13.3	1		1	
Advanced OCCC	106	19.7	1.28 (1.01-1.62)	0.041	1.55 (1.20-2.01)	0.001
Early-stage HG-SOC	67	68.4	0.22 (0.14-0.35)	<0.0001	0.34 (0.21-0.56)	<0.0001
Early-stage OCCC	264	84.7	0.09 (0.06-0.13)	<0.0001	0.17 (0.12-0.26)	<0.0001

† The log-rank test was used for univariate analysis and Cox proportional hazards regression modeling was used for multivariate analysis.

* Platelet count ≥400 × 10^9/L.

Abbreviations: HR, hazard ratio; CI, confidence interval; CA-125, cancer antigen 125; VTE, venous thromboembolism; HG-SOC, high-grade serous ovarian cancer; OCCC, ovarian clear cell carcinoma.

Table S5. Factors influencing 5-year overall survival (OS) rates in sub-analysis (n =1,138)

Variable	No.	5-year OS, %	Univariate		Multivariate	
			HR (95%CI)	*P*-value†	HR (95%CI)	*P*-value†
Age				<0.0001		0.13
<60 years	616	57.3	1		1	
≥60 years	522	43.1	1.49 (1.23-1.79)		1.19 (0.95-1.47)	
CA-125 levels				<0.0001		0.013
≤35 IU/L	120	89.9	1		1	
>35 IU/L	912	47.4	8.42 (4.18-17.0)		2.93 (1.26-6.80)	
Thrombocytosis*				<0.0001		0.005
No	744	59.2	1		1	
Yes	380	35.5	2.12 (1.75-2.55)		1.37 (1.10-1.71)	
Residual tumor size after surgery				<0.0001		<0.0001
> 1 cm	834	42.8	1		1	
≤ 1 cm	247	84.8	0.20 (0.14-0.29)		0.42 (0.28-0.64)	
VTE				<0.0001		0.29
No	935	54.9	1		1	
Yes	203	32.4	1.80 (1.44-2.24)		1.16 (0.88-1.52)	
Stage-specific histologic type						
Advanced HG-SOC	701	37.5	1		1	
Advanced OCCC	106	28.2	1.71 (1.30-2.24)	<0.0001	2.19 (1.62-2.97)	<0.0001
Early-stage HG-SOC	67	81.3	0.20 (0.11-0.37)	<0.0001	0.31 (0.15-0.64)	0.001
Early-stage OCCC	264	89.5	0.11 (0.07-0.17)	<0.0001	0.27 (0.16-0.45)	<0.0001

† The log-rank test was used for univariate analysis and Cox proportional hazards regression modeling was used for multivariate analysis.

* Platelet count ≥400 $\times 10^9$/L.

Abbreviations: HR, hazard ratio; CI, confidence interval; CA-125, cancer antigen 125; VTE, venous thromboembolism; HG-SOC, high-grade serous ovarian cancer; OCCC, ovarian clear cell carcinoma.

Table S6. Factors influencing overall survival (OS) after recurrence or progression in sub-analysis (n = 681)

Variable	No.	2-year OS rate after recurrence, %	Univariate		Multivariate	
			HR (95%CI)	*P*-value†	HR (95%CI)	*P*-value†
Age				0.12		0.31
<60 years	331	43.2	1		1	
≥60 years	350	35.8	1.18 (0.96-1.44)		1.17 (0.86-1.59)	
CA-125 levels*				0.001		0.001
≤35 IU/L	90	58.2	1		1	
>35 IU/L	282	38.1	1.94 (1.30-2.89)		2.00 (1.31-3.04)	
Thrombocytosis*				0.002		0.021
No	305	20.5	1		1	
Yes	58	11.3	1.75 (1.24-2.48)		1.55 (1.07-2.24)	
VTE				0.036		0.65
No	528	42.4	1		1	
Yes	153	31.4	1.28 (1.02-1.62)		1.08 (0.77-1.52)	
Stage-specific histologic subtype						
Advanced HG-SOC	546	43.3	1		1	
Advanced OCCC	80	16.1	2.20 (1.67-2.92)	<0.0001	2.73 (1.89-3.96)	<0.0001
Early-stage HG-SOC	22	66.3	0.58 (0.30-1.13)	0.11	0.97 (0.46-2.01)	0.92
Early-stage OCCC	33	31.1	1.12 (0.70-1.78)	0.64	2.00 (1.19-3.35)	0.009

† The log-rank test was used for univariate analysis and Cox proportional hazards regression modeling was used for multivariate analysis.

* CA-125 and platelet counts were measured at the time of first recurrence or progression of disease.

Abbreviations: HR, hazard ratio; CI, confidence interval; CA-125, cancer antigen 125; VTE, venous thromboembolism; HG-SOC, high-grade serous ovarian cancer; OCCC, ovarian clear cell carcinoma.

Supplemental Figure S1. Proposed schema for the role of interleukin-6 (IL-6) in ovarian clear cell carcinoma. The dashed line indicates the clinical manifestation of venous thromboembolism (VTE) in advanced ovarian clear cell carcinoma. Abbreviations: HIF1, hypoxia-inducible factor 1; STAT3, signal transducer and activator of transcription 3; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha.