Combined score of pretreatment platelet count and CA125 level (PLT-CA125) stratified prognosis in patients with FIGO stage IV epithelial ovarian cancer

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Abstract

**Background:** The majority of death-related ovarian cancer is epithelial ovarian cancer (EOC). Regarding the Federation of Gynecology and Obstetrics (FIGO) stage IV EOC, the 5-year overall survival (OS) has not changed in last decades. Platelet (PLT) count and CA125 level are both prognostic markers that related to inflammation and immune evasion in EOC. This study intended to assess the prognostic value of pretreatment PLT count and CA125 level in FIGO stage IV EOC.

**Methods:** The study included 108 patients diagnosed with FIGO stage IV EOC and treated with surgery and/or chemotherapy between January 1995 and December 2016. The PLT counts and CA125 levels of the patients before any treatment were analysed with clinical and pathological parameters, OS and progression-free survival (PFS). The survival of different groups was analyzed using the Kaplan-Meier method. The PLT-CA125 scores (0, 1, and 2) were defined basing on the presence of thrombocytosis (PLT count > 400,000/μL), an elevated CA125 level (CA125 > 1200 U/mL), or both. The prognostic value of PLT-CA125 was assessed with a Cox regression model.

**Results:** Median OS, but not median PFS, was significantly decreased in patients with thrombocytosis or elevated CA125 levels when compared with the others (p = 0.011 & p = 0.004). The median OS was significantly decreased in patients with a PLT-CA125 score of 2 [37.8 months; 95% confidence interval (CI) 20.6–54.9] compared with patients with a PLT-CA125 score of 0 (70.0 months; 95% CI 38.0–101.9, p < 0.001). The median PFS was also significantly decreased in patients with a PLT-CA125 score of 2 (19.6 months; 95% CI 13.0–26.3) compared with patients with a PLT-CA125 score of 0 (32.0 months; 95% CI 23.3–40.7, p = 0.011). Furthermore, multivariate analysis identified both PLT-CA125 scores of 2 and 1 as independent poor prognostic factors for OS (p = 0.004 & p < 0.001) and PFS (p = 0.033 & p = 0.017) compared with a PLT-CA125 score of 0.

**Conclusions:** The pretreatment PLT-CA125 score can be a reliable marker with high accessibility for stratifying prognosis in patients with FIGO stage IV EOC.

**Keywords:** Epithelial ovarian cancer, Thrombocytosis, CA125, Inflammation, Immune evasion, Prognosis
Introduction

Epithelial ovarian cancer (EOC), a lethal gynecologic cancer, accounts for 90% of ovarian malignancies [1, 2]. However, EOC has a high case-fatality ratio among gynecologic cancers [3]. EOC is luring for distinct tumor biology of different histological types and the absence of anatomic barriers. [4] High grade serous carcinoma (HGSC) is the most common histological type with higher malignancy in EOC [3, 4]. The established treatment strategy for advanced EOC includes cytoreductive surgery and chemotherapy. Approximately 70% of EOC patients are diagnosed with advanced Federation of Gynecology and Obstetrics (FIGO) stage III or even higher stage [5]. Although overall survival (OS) has increased over the last decades in stage III EOC, survival of patients with FIGO stage IV has not changed [6]. The prognostic factors of EOC including FIGO stage, age, histological type, performance status, and location of metastases, that predict survival indicate different tumor biology and pave the way for individualization of therapy [7]. However, most prognostic factors were not studied specifically in stage IV EOC patients. There is an urgent need for stratifying prognosis in patients with stage IV EOC.

Thrombocytosis [platelet (PLT) count > 400,000/μL] is associated with various cancers. The rate of thrombocytosis ranges from 31 to 42% in EOC [8]. Thrombocytosis is identified as a prognostic factor in many retrospective studies of EOC [9]. The increase of platelet count is due to tumor-secreted cytokines, such as interleukin (IL-6), which plays a role in stimulating the growth of megakaryocytes and thrombocytosis [10]. IL-6 is overproduced in a variety of malignancies and is related to inflammation and immune suppression [11]. However, it is still unclear whether the poor survival of patients with thrombocytosis is caused by IL-6 itself or is a result of IL-6-induced thrombocytosis [12].

CA125 is an extensively studied tumor marker in EOC. The level of CA125 is used in screening test, diagnosis, monitoring of efficacy during chemotherapy, and management of follow up [13, 14]. The dynamic changes of CA125 levels at diagnosis and during chemotherapy were associated with chemosensitivity of drugs and new agents, tumor burden, and time of relapse [15, 16]. In addition, researchers found that glycogen CA125 of tumor cells binds to natural killer (NK) cells and is conducive to immune evasion [17]. As CA125 has been studied in EOC for decades, there are still many puzzles. Stage IV EOC is a systemic disease presenting with parenchymal metastases and metastases of extra-abdominal organs [5]. The poor survival of patients with thrombocytosis was considered to be a result of IL-6-induced thrombocytosis [12]. Currently, the relevance of PLT count and CA125 level was found in EOC [18]. However, the prognostic values of both markers were not comparatively studied. Hence, we combined these markers into a PLT-CA125 score and assessed the prognostic value of this new marker in FIGO stage IV EOC.

Materials and methods

Patients

This study was approved by the institutional review board of Sun Yat-Sen University Cancer Center (2017-FXY-104). The study included patients who were clinically diagnosed with FIGO stage IV primary invasive ovarian-, fallopian tube-, or peritoneal cancer; who are treated with debulking surgery or chemotherapy between January 1995 and December 2016; and who had complete clinical data in the medical record system. Patients were excluded due to (1) histologically reported ovarian tumors other than EOC; (2) serious performance status that contraindicated surgery or platinum-based chemotherapy; and (3) known congenital thrombophilia, deep venous thrombosis, anticoagulant treatment, or pregnancy within 6 months at diagnosis.

Finally, 137 patients were included. Twenty-five Patients treated before operative pathological staging in other hospitals were excluded due to absence of pretreatment PLT count and CA125 level. Tumor staging was conformed based on the FIGO guidelines and four patients were excluded based on only cytology without definite histopathology [5]. As a result, a final study population comprised of 108 patients was used for prognostic analysis. (Fig. 1).

These patients were treated with primary debulking surgery (PDS) followed by adjuvant chemotherapy, neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS), or chemotherapy alone. Debulking surgery was classified as “optimal” if all visible lesions were resected during surgery. In addition to surgery, all patients had two and more cycles of platinum-based chemotherapy. Patients’ characteristics including age at...
diagnosis, histology, metastatic sites, results of complete
blood cells counts and CA125 level were collected in
medical record system. All patients were followed up an-
nually with gynecological examination, pelvic and abdomi-
nal examinations, and tumor marker evaluation.

Criteria of PLT and CA125
PLT count > 400 \times 10^3/\mu L was defined as thrombocyto-
sis. The cut-off value for elevated CA125 levels (>1200
U/mL) was determined from the receiver operating
characteristic analysis. The PLT-CA125 score was de-
defined as 0, 1, or 2 basing on the presence of thrombocy-
tosis, elevated CA125 level, or both.

Statistical analysis
All variables in the lattice table were analyzed using
Pearson’s chi-square test, one-way ANOVA and Fisher’s
exact test. Survival was analyzed using the Kaplan-Meier
method. The end points of the study were OS and pro-
gression-free survival (PFS). The time length of PFS was
from time of diagnosis to progressive disease or relapse.
OS was defined as the length from time of diagnosis to
death or the last follow-up. Survival data of patients alive
without progression or those who died due to other dis-
ease were censored. In the Cox regression model, only
variables that were statistically significant in univariate
analysis were further analyzed in the multivariate ana-
lysis. In addition, Harrell’s C-index was calculated to
evaluate the goodness fit of the Cox model. Software of
statistical analyses included STATA (ver. 20.0; Stata
Corp, College Station, TX, USA), SPSS (ver. 13.0; SPSS
Inc., Chicago, IL, USA), and R statistical software (R
Foundation for Statistical Computing, Vienna, Austria).
In this study, \( p < 0.05 \) was considered statistically
significant.

Results
Patients characteristics
The study population included 108 patients with FIGO
stage IV EOC treated in our hospital (Fig. 1). The median
age of these patients was 51 years, ranging from 27 to 75
years. The most prevalent histological type was HGSC
(85/108, 78.7%). Seventeen (17/108, 15.4%) patients had
FIGO stage IVA disease, which is pleural effusion with
positive cytology. In terms of treatment, 105 (97.22%) pa-
tients were treated with surgery. PDS was conducted in 53
patients (53/108, 49.1%). NACT and subsequent IDS treat-
ment were performed in 52 patients (52/108, 48.1%). Three
patients were treated with chemotherapy alone.
The primary regimen of chemotherapy was paclitaxel-
platinum combined chemotherapy.

Statistical descriptions of the patients' characteristics is
shown in Table 1. There is no significant difference
detected between groups of patients with different PLA-
CA125 scores, with the exception of metastatic pattern.

Survival analyzes of PLT count, CA125 level, and the PLT-
CA125 score
Thrombocytosis (PLT > 400,000/\mu L) or an elevated
CA125 level (CA125 > 1200 U/mL) was significantly as-
associated with poorer OS in patients with stage IV EOC
(Fig. 2a & c). The appropriate cut-off value of CA125
was calculated from the receiver operating characteristic
curve analysis. However, both thrombocytosis and an
elevated CA125 level were likely to be associated with
shorter PFS without statistical significance (Fig. 2b & d).
OS was shorter in patients with thrombocytosis than in
those without thrombocytosis (40.0 months vs. 57.0
months, \( p = 0.011 \); Fig. 2a). PFS was decreased in pa-
tients with an elevated CA125 level when compared with
patients who had a relatively low CA125 level (66.6
months vs. 41.0 months, \( p = 0.003 \); Fig. 2c).

As the associations of PLT count and CA125 level with
OS were significant, we further calculated the association
of the PLT-CA125 score with OS and PFS. A PLT-CA125
score of 2, indicating the presence of thrombocytosis and
an elevated CA125 level, was associated with a worse
median OS [37.8 months; 95% confidence interval (CI)
20.6–54.9] than that of a PLT-CA125 score of 0 (70.0
months, 95% CI 38.0–101.9, \( p < 0.001 \); Fig. 2e). Interest-
ingly, PFS was also significantly decreased in patients with
a PLT-CA125 score of 2 (19.6 months; 95% CI 13.0–26.3)
compared with those with a PLT-CA125 score of 0 (32.0
months; 95% CI 23.3–40.7, \( p = 0.0115 \); Fig. 2f). These find-
ings imply that the PLT-CA125 score can stratify PFS bet-
ter than both markers alone.

Cox proportional hazards model of FIGO stage IV EOC
The results of the univariate and multivariate Cox re-
gression analyzes for OS and PFS are shown in Table 2.
Univariate analysis of the Cox model for OS identified histological type other than HGSC, suboptimal surgery
or no surgery, and a PLT-CA125 score of 1 or 2 as
prognostic factors. Whereas NACT subsequent IDS or
chemotherapy alone, suboptimal surgery or no surgery,
and PLT-CA125 scores of 1 or 2 were associated with
worse PFS. Multivariate Cox regression analysis identi-
fied PLT-CA125 scores of 1 or 2 as independent poor prognostic factors for OS. PLT-CA125 scores of 1 and 2 were also
independent poor prognostic factors for PFS.

Furthermore, Harrell’s C-index of the Cox propor-
tional hazards model that included the PLT-CA125 score
(C-index: 0.684 for OS; 0.622 for PFS) was relatively
higher than that of the model without the PLT-CA125
score (C-index: 0.633 for OS; 0.581 for PFS).
To identify the specific clinical factors related to survival, we also assessed the prognostic value of the PLT-CA125 score grouped by FIGO stage, age, histology, primary treatment, and surgical satisfaction (Table 3). There was a significant association between PLT-CA125 and OS with regard to the factors of stage ($p = 0.003$ for stage IVB), age ($p = 0.003$ for < 55), histology ($p = 0.002$ for HGSC), treatment ($p = 0.009$ for PDS), and surgical satisfaction ($p = 0.003$ for optimal surgery).

The PFS of patients with different PLT-CA125 scores, which were 0, 1, and 2, were significantly different in the subgroups of patients with histology of HGSC ($p = 0.021$) and those who received suboptimal surgery or no surgery ($p = 0.046$).

## Discussion

In our study, the PLT-CA125 score was an independent prognostic factor for both OS and PFS in stage IV EOC. However, neither thrombocytosis nor elevated CA125 level was significantly associated with short PFS. The survival for stage IV patients can be more specifically stratified using combined PLT-CA125 scoring model compared with using PLT or CA125 alone. These findings imply that both thrombocytosis and an elevated CA125 level may equally contribute to the poor survival of patients with stage IV EOC.

Currently, there are evidences from retrospective studies that suggest a potential relationship between platelet count and CA125 level [19]. Platelet is an important modulator in many physiological functions of cancer, and thrombocytosis is identified as a prognostic factor in
many studies of EOC [20]. IL-6, which is commonly ele-
vated in patients with EOC and is known to be an impor-
tant cytokine of inflammation and immune suppression, can
stimulate megakaryocyte growth and thrombopoiesis [8].
Platelets take part in the process of haematogenous metas-
tasis by parcelling tumor cell in the vasculature system [21].
On the other hand, platelets can promote tumor cell meta-
tasis by breaking the membrane of vessels through the
release of enzymes [22]. In addition, tumor cells expressing
glycogen can aggregate platelets and induce tumor-platelet
aggregation, which help tumor cells survive from immune
clearance [21]. Recently, the dual role of platelets in im-
mune functions and inflammation has gained more and
more attention in infectious disease and cancer [23].

Inflammation plays an important role of tumorgenesis
and tumor progression in EOC, especially in advanced
disease [24, 25]. At the same time, inflammatory cyto-
kine, IL-6, can stimulate megakaryocyte growth and
induce thrombocytosis [8]. Although EOC is considered
unresponsive to immune therapy, there are increasing
evidences suggesting that EOC is, in fact, an immuno-
genic tumor with highly heterogeneous subtypes [26].
Diverse clinical and epidemiological data have shown
that a natural antitumor immune response of tumor in-
filtrating lymphocytes and NK cells in EOC [27]. Emer-
ging evidence about inflammation and tumor immune
suppression mechanisms may pave the way for immune
therapy.

Over the last decades, CA125 is extensively investi-
gated and widely used in the diagnosis and follow-up of
EOC [18]. In addition, elevated CA125 is noted in
inflammatory diseases and several benign diseases.
Expression of CA125 in EOC plays important roles in cell growth, transformation, and invasion of tumor cells [28]. As a large glycoprotein, the CA125 glycogen is an important molecule contacting with other cells, including NK cells and fibroblasts [17]. The immune evasion mechanism of NK cell suppression through binding to CA125 has been reported in EOC [29]. Both CA125 and platelets are related to inflammation and play important roles in the pathological status of immune surveillance in EOC. In our study, we combined these markers as a novel scoring model to stratify OS and PFS in stage IV EOC, which were shown to be better than using PLT or CA125 alone. This result implies that the PLT-CA125 score, reflecting inflammation and immune suppression, could be used to predict survival and determine potential therapeutic strategies targeting inflammatory and immune surveillance in advanced EOC.

In addition to the prognostic significance of the PLT-CA125 score, the high accessibility makes it practical in clinical use. Platelets count and CA125 level can be easily obtained in all patients suspected with ovarian cancer. Stage IV EOC is a systemic disease and is often diagnosed with parenchymal metastases and metastases of extra-abdominal organs [5]. Our study demonstrated that the combined score of systemic inflammatory marker, PLT, and EOC tumor marker CA125 was a reliable prognostic factor for stage IV EOC. In addition, other prognostic factors of stage IV EOC, including histological type and satisfaction of surgery, were demonstrated in our study.
As a retrospective study, there are several limitations. Firstly, the sample size of the study was relatively small. Thus, confirmation of results in other cohorts and centers is necessary for further research. Secondly, the cut-off value for CA125 may vary in different study cohorts. Although the cut-off value of CA125 has been confirmed in our study cohort, the value may vary in different cohorts and centers. Finally, the performance statuses of the patients were not included in our study, which may affect the daily life abilities of the patients.

### Table 3: Subgroup analysis of prognostic factors

| Groups                  | PLT-CA125 | OS (months) | PFS (months) |
|-------------------------|-----------|-------------|--------------|
|                         | N (%)     | Median (SD) | 95% CI | p | Median (SD) | 95% CI | p |
| FIGO stage              |           |             |       |   |             |       |   |
| IVA                     |           |             |       |   |             |       |   |
| 0                       | 5 (29.4)  | 48.3 (14.6) | 19.6–77.0 | 0.600 | 11.17 |       | 0.185 |
| 1                       | 7 (41.2)  | 47.4 (13.4) | 21.1–73.7 | 31.8 | 13.6 | 5.14–58.5 |
| 2                       | 5 (29.4)  | 41.7 (10.1) | 21.9–61.5 | 13.3 | 5.59 | 2.32–24.2 |
| IVB                     |           |             |       |   |             |       |   |
| 0                       | 34 (37.4) | 90.4 (18.9) | 53.2–127.6 | 0.003 | 32.0 | 4.37 | 0.107 |
| 1                       | 41 (45.1) | 42.7 (2.99) | 36.8–48.5 | 20.0 | 3.12 | 13.9–26.1 |
| 2                       | 16 (17.6) | 37.8 | 21.2–54.4 | 19.7 | 3.15 | 13.5–25.8 |
| Age                     |           |             |       |   |             |       |   |
| < 55                    |           |             |       |   |             |       |   |
| 0                       | 19 (32.8) | 90.4 (29.2) | 33.2–147.6 | 0.003 | 35.4 | 8.95 | 0.101 |
| 1                       | 25 (43.1) | 42.7 (0.71) | 41.3–44.1 | 21.0 | 2.89 | 15.4–26.6 |
| 2                       | 14 (24.1) | 40.7 (8.2) | 24.7–47.1 | 16.2 | 3.98 | 8.43–24.0 |
| ≥55                     |           |             |       |   |             |       |   |
| 0                       | 20 (40.0) | 70.0 (13.0) | 44.6–95.4 | 0.183 | 32.0 | 6.29 | 0.404 |
| 1                       | 23 (46.0) | 28.7 (9.13) | 10.8–46.6 | 16.9 | 5.01 | 7.11–26.7 |
| 2                       | 7 (14.0)  | 37.8 | 21.2–54.4 | 19.7 | 3.45 | 18.2–28.4 |
| Histology               |           |             |       |   |             |       |   |
| HGSC                    |           |             |       |   |             |       |   |
| 0                       | 29 (34.1) | 111.6 (26.6) | 59.4–163.8 | 0.002 | 35.4 | 4.45 | 0.021 |
| 1                       | 39 (45.9) | 42.7 (4.88) | 33.1–52.2 | 20.0 | 4.61 | 10.9–29.0 |
| 2                       | 17 (20.0) | 41.7 (2.77) | 36.3–47.1 | 21.5 | 2.82 | 18.9–27.0 |
| Non-HGSC                |           |             |       |   |             |       |   |
| 0                       | 10 (43.5) | 20.4 (20.5) | 0.00–60.5 | 0.189 | 9.57 | 11.4 | 0.117 |
| 1                       | 9 (38.3)  | 43.2 (5.55) | 32.3–54.1 | 33.5 | 15.8 | 2.52–64.5 |
| 2                       | 4 (17.4)  | 15.6 | 8.83 (20.8) | 4.75–12.9 |
| Primary treatment       |           |             |       |   |             |       |   |
| PDS + chemotherapy      |           |             |       |   |             |       |   |
| 0                       | 21 (39.6) | 90.4 (31.5) | 28.7–152 | 0.009 | 40.1 | 3.71 | 0.104 |
| 1                       | 24 (45.3) | 42.7 (6.04) | 30.8–54.5 | 21.1 | 4.42 | 12.4–29.8 |
| 2                       | 8 (15.1)  | 40.7 (15.7) | 9.87–71.5 | 17.5 | 5.47 | 6.79–28.25 |
| NACT+IDS/ Chemotherapy alone |     |             |       |   |             |       |   |
| 0                       | 18 (32.7) | 70.0 (29.1) | 12.9–127 | 0.254 | 23.3 | 4.97 | 0.571 |
| 1                       | 24 (45.3) | 43.2 (3.87) | 35.6–50.8 | 20.0 | 2.68 | 14.74–25.26 |
| 2                       | 13 (23.6) | 37.8 (7.67) | 22.8–52.8 | 19.7 | 4.46 | 10.9–28.4 |
| Surgery                 |           |             |       |   |             |       |   |
| Optimal surgery         |           |             |       |   |             |       |   |
| 0                       | 30 (36.6) | 80.4 (20.2) | 50.8–130 | 0.003 | 32.0 | 6.14 | 0.167 |
| 1                       | 35 (42.7) | 43.9 (3.21) | 37.6–50.2 | 23.6 | 6.23 | 11.4–35.8 |
| 2                       | 17 (20.7) | 40.7 (10.2) | 20.8–60.6 | 21.5 | 6.07 | 11.6–31.4 |
| Suboptimal surgery/no surgery | |             |       |   |             |       |   |
| 0                       | 9 (34.6)  | 45.7 (23.6) | 0.00–91.86 | 0.175 | 35.4 | 17.4 | 0.046 |
| 1                       | 13 (50.0) | 23.2 (13.5) | 0.00–49.7 | 12.8 | 4.26 | 4.49–21.2 |
| 2                       | 4 (15.4)  | 37.8 (12.4) | 13.6–62.0 | 12.6 | 4.68 | 3.44–21.8 |

Abbreviations: PLT platelet, OS overall survival, PFS Progress-free survival, SD standard deviation, CI confidence interval, HGSC high grade serous carcinoma, Non-HGSC non-high grade serous carcinoma, PDS primary debulking surgery, NACT neoadjuvant chemotherapy, IDS interval debulking surgery, LNM lymph nodes metastasis beyond abdominopelvic cavity.
and help determine treatment strategies, as well as prognosis. However, this is an inevitable defect of retrospective study.

In conclusion, the PLT-CA125 score is an independent prognostic factor in patients with stage IV EOC. It is a useful and highly accessible marker for predicting clinical outcomes and suggesting for potential therapeutic strategies in patients with stage IV EOC.

Abbreviations
CI: Confidence interval; HGSC: High grade serous carcinoma; HR: Hazard ratio; IDS: Interval debulking surgery; LNM: Lymph node metastasis beyond the abdominopelvic cavity; NA: Not applicable; NACT: Neoadjuvant chemotherapy; Non-HGSC: Non-high grade serous carcinoma; OS: Overall survival; PDS: Primary debulking surgery; PFS: Progression-free survival; PLT: Platelet; SD: Standard deviation

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Authors’ contributions
JPC and QDH analyzed and interpreted the patient data. JPC and JYC performed the histological confirmation. TW, HT and JHL organized the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets generated in this study are available in the Research Data Deposit. (http://www.researchdata.org.cn), with the approval number of RDDA2019001031.

Ethics approval and consent to participate
All procedures in studies involving human participants were performed in accordance with the ethical standards of the institutional review board of Sun Yat-Sen University Cancer Center (2017-FXY-104) basing on the 1964 Helsinki declaration and its later amendments.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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