Pretreatment Thrombocytosis as an Independent Predictive Factor for Chemoresistance and Poor Survival in Epithelial Ovarian Cancer

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Abstract

Background Thrombocytosis is related to tumor stage and survival of ovarian cancer in addition to common complications with malignant diseases, such as anemia and inflammation. The aim of our study was to clarify the precise prognostic impact of pretreatment thrombocytosis in epithelial ovarian cancer. Methods We retrospectively analyzed 280 consecutive patients who were treated for epithelial ovarian cancer at our institution between 2001 and 2011. Results Pretreatment thrombocytosis was observed in 18.9% of all the patients, and was associated with advanced FIGO stage, primary treatment, operation achievement, histologic subtype, microcytic hypochromic anemia (MHA), and non-malignant inflammatory condition (p=0.0018, 0.0028, 0.00050, 0.034, 0.00090 and 0.0022). In the patients who relapsed after primary adjuvant chemotherapy (n=126), thrombocytosis was associated with shorter treatment-free interval (TFI) (p=0.0091). The univariate and multivariate analyses revealed that thrombocytosis was independently associated with TFI and MHA (p=0.021 and 0.0091). Patients with thrombocytosis had worse progression-free survival (PFS) and overall survival (OS) than those without thrombocytosis (p<0.0001 and <0.0001). The multivariate analyses for prognostic factors demonstrated that thrombocytosis was significant for poor PFS and OS (p=0.0050 and p=0.022) independently of stage, histology, primary treatment, operation achievement, non-malignant inflammatory condition and MHA. Conclusions The current findings indicate that the detrimental survival impact of pretreatment thrombocytosis in epithelial ovarian cancer may be independent of tumor extent but rather attributed to chemoresistance, further supporting the therapeutic potential of targeting thrombopoietic cytokines in the disease.

Background

Approximately half of the patients with ovarian cancer are diagnosed as advanced-stage disease(1), as early-stage patients tend to hardly have subjective symptoms due to anatomical location of the ovary as an intraperitoneal organ. The principal treatment for epithelial ovarian cancer is maximal cytoreduction, which typically comprises surgery followed by chemotherapy, and the amount of residual tumor is one of the most important prognostic factors(2–5). Accordingly, the elucidation of mechanisms for tumor growth and metastasis will contribute to improving patient prognosis. Thrombocytosis is traditionally known to be associated with patient prognosis of ovarian cancer(6–15). Platelets are involved in tumor growth, angiogenesis, and metastasis(16). The functions of cytokines on platelet-mediated tumor proliferation and progression have been widely investigated(16). Recently, antiplatelet therapies including molecular agents targeting the thrombopoietic cytokines are investigated by clinical trials in patients with ovarian cancer(17, 18). However, the precise prognostic significance of paraneoplastic thrombocytosis is yet to be determined. Thrombocytosis is known to be induced by iron-deficiency anemia and non-malignant inflammatory conditions in addition to malignant disease, and ovarian cancer patients especially with advanced-stage disease may have these complications. The aim of our study was to investigate detailed prognostic impact of thrombocytosis on ovarian cancer patients in order to elucidate

the underlying mechanism and to identify the target patients who will benefit more from the antiplatelet therapies.

Methods

Patients

We retrospectively reviewed the clinical records of a total of 280 consecutive patients who were treated for epithelial ovarian cancer at the University of Tsukuba Hospital between 2001 and 2011. The study protocol was approved by the Ethics Committee University of Tsukuba Hospital (H27-143). We excluded patients with multiple primary cancers, the past history of cancer, or hepatic disease from our study. Patients diagnosed as malignant transformation of mature cystic teratoma were also excluded. Thrombocytosis was defined as ≥ 400,000/mm³ of platelet count before treatment, which was calculated as the mean value of the initial and pretreatment examinations. For survival analyses, progression-free survival (PFS) was defined as the interval between the dates of the initial treatment and the first recurrence or progression of disease, and overall survival (OS) was defined as the interval between the dates of the initial treatment and the last follow-up. Treatment-free interval (TFI) was defined as the interval between the dates of the end of primary adjuvant chemotherapy and the first disease progression (n = 126). The stages were classified according to the International Federation of Gynecology and Obstetrics system (FIGO, 1988). The median follow-up period excluding patients who died was 81.4 months (range, 0.7–178). The patient demographics are summarized in Table 1.

Treatment

The basic surgical procedure for epithelial ovarian cancer consisted of total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and pelvic and para-aortic lymphadenectomy. Following primary debulking surgery (PDS), a combination of paclitaxel (175 mg/ m^2, day1) and carboplatin (AUC = 6, day1) (TC regimen) was administered every 3 weeks. Four cycles of TC were performed in stage IA with clear cell carcinoma. Six to eight cycles were performed in stage IC or more. Neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS) was selected for patients with apparent stage-III/IV disease and chemosensitive tumor histology, i.e. serous or endometrioid as estimated by CT, excessively elevated CA125 level, and cytological findings of ascites(19). As NAC, 4 cycles of TC were administered, and IDS was followed by additional 4 cycles.

Statistical analysis

Differences in proportions were evaluated by the χ^2 test or the Fisher's exact test where appropriate. Differences in continuous variables were evaluated by the Wilcoxon rank-sum test. The logistic regression was used for the univariate and multivariate analyses of clinicopathologic factors associated with thrombocytosis. Kaplan–Meier survival curves were generated and compared statistically by the log-rank test. The Cox proportional hazard model was used for the univariate and multivariate analyses for

prognostic factors. P-values < 0.05 were considered as statistically significant. All statistical analyses were performed using JMP11.0 software (SAS Institute, Cary, NC).

Results

Thrombocytosis was observed in 18.9% (53/280) of all the patients. We first examined the relationships between thrombocytosis and clinicopathologic parameters. The rate of thrombocytosis significantly increased with the progressing FIGO stage: 9.9% (9/91) in stage I, 10.3% (4/39) in stage II, 23.6% (26/110) in stage III, and 35.0% (14/40) in stage IV (p = 0.0018; Table 2). Additionally, thrombocytosis was found to be significantly associated with microcytic hypochromic anemia (MHA), primary treatment (NAC vs. PDS), histologic subtype (serous, clear cell, or others), operation achievement (complete, optimal, or suboptimal resection), non-malignant inflammatory condition, and CA125 (p = 0.00090, 0.0028, 0.034, 0.00050, 0.0022, and < 0.0001, respectively; Table 2).

We subsequently conducted the univariate and multivariate analyses of clinicopathologic factors associated with thrombocytosis. Among the factors significantly associated with thrombocytosis in Table 2, we selected MHA, FIGO stage, histologic subtype, operation achievement, non-malignant inflammatory condition for the factors to be analyzed (Table 3). In order to include the factor of TFI as well, we confined the analyses to the 126 patients who showed disease progression after primary adjuvant chemotherapy. Among the 4 significant factors from the univariate analysis, MHA and TFI were found to be significantly and independently associated with thrombocytosis (p = 0.0091 and 0.021, respectively; Table 3).

Next, we compared PFS and OS according to the presence or absence of thrombocytosis. In the whole patients, those with thrombocytosis showed significantly poorer PFS (5-year PFS rate, 25.2% vs. 61.8%, p < 0.0001; Fig. 1A) and OS (5-year OS rate, 41.4% vs. 75.5%, p < 0.0001; Fig. 1B) compared to those without thrombocytosis. When the analysis was confined to the patients with stage III/IV disease, thrombocytosis was still significantly associated with poor PFS (5-year PFS rate, 0.0% vs. 34.0%, p < 0.0001; Fig. 2A) and OS (5-year OS rate, 26.1% vs. 56.9%, p = 0.0011; Fig. 2B), in contrast with the patients with stage I/II disease showing no difference for PFS (5-year PFS rate, 86.0% vs. 83.9%, p = 0.88; Fig. 2C) and OS (5-year OS rate, 92.0% vs. 90.1%, p = 0.85; Fig. 2D).

Lastly, we performed the multivariate analysis of pretreatment thrombocytosis for OS and PFS, adjusted for age, MHA, histologic subtype, FIGO stage, primary treatment, non-malignant inflammatory condition, and operation achievement (Table 4). Pretreatment thrombocytosis was found to be an independent prognostic factor for poor PFS and OS (p = 0.0050 and 0.022, respectively; Table 4).

Discussion

We observed pretreatment thrombocytosis, defined as platelet count ≥ 400,000/mm³, in 18.9% of the patients with epithelial ovarian cancer in stage I-IV, being in line with previous reports of the same cutoff

value as ours (7.4–42.5%)(10–12, 15). Our analyses for relationships between thrombocytosis and clinicopathologic parameters showed that thrombocytosis was significantly associated with MHA, primary treatment, FIGO stage, histologic subtype, operation achievement, non-malignant inflammatory condition, CA125, and TFI (Tables 2 and 3). Among these significant factors, FIGO stage, CA125, operation achievement, and primary treatment are considered to reflect the tumor extent, which has been reportedly associated with pretreatment thrombocytosis(6, 20). MHA and non-malignant inflammatory condition are clinically well known to induce thrombocytosis. We subsequently conducted the univariate and multivariate analyses for associations with thrombocytosis in the patients who relapsed after adjuvant chemotherapy, excluding the 2 factors, CA125 and primary treatment, which are considered to be closely related with FIGO stage. We found that MHA and TFI were significantly and independently associated with thrombocytosis (Table 3). Accordingly, thrombocytosis is suggested to possibly contribute to chemoresistance, as TFI is known to be an important surrogate marker for chemosensitivity of ovarian cancer(21–23). As regards MHA, iron deficiency anemia caused by intratumoral hemorrhage in ovarian cancer is likely to be involved.

Our survival analyses showed that patients with thrombocytosis had worse PFS and OS compared to those without thrombocytosis (Figs. 1A, B). Besides, when the analysis was confined to the stage-III/IV patients, there was still significant difference in PFS and OS (Figs. 2A, B), whereas the stage-I/II patients showed no difference in survival according to presence/absence of pretreatment thrombocytosis (Figs. 2C, D). These findings indicate that thrombocytosis affects survival mainly in advanced diseases, being consistent with our above finding that thrombocytosis was significantly and independently associated with TFI, an established predictor for chemosensitivity in recurrence therapies, as recurrence is prone to occur in advanced diseases. Furthermore, our multivariate analysis for prognostic factors demonstrated that thrombocytosis was significant for unfavorable PFS and OS independently of age, histology, and FIGO stage (Table 4). These findings indicate that pretreatment thrombocytosis may be an ideal predictive biomarker for treatment outcome and a reasonable therapeutic target in epithelial ovarian cancer.

Tumor cells firstly increase and activate platelets via various cytokines including interleukin-6 (IL-6)(16). Activated platelets in turn facilitate tumor growth and angiogenesis through growth factors and angiogenic factors including VEGF and PDGF(16, 24). Activated platelets also promote metastasis through epithelial mesenchymal transition (EMT) and defense by platelet-tumor interaction against blood flow and immune system including NK cells in circulation(16, 24). Besides, platelets contribute to chemoresistance through MAPK and PI3-kinase/Akt pathways and drug efflux proteins(24). Therefore, thrombocytosis can possibly affect patient prognosis via both tumor progression and chemoresistance. However, we found that thrombocytosis was significantly and independently associated with TFI, but not with FIGO stage (Table 3), and that thrombocytosis was significantly associated with PFS independently of FIGO stage (Table 4). These findings suggest that prognostic impact of thrombocytosis may be independent of tumor extent but rather attributed to chemoresistance. Indeed, platelets have been reported to be involved in chemoresistance in ovarian cancer by basic studies in vitro and in vivo. Radziwon-Balicka et al. reported that platelets decreased paclitaxel-induced apoptosis of human ovarian

adenocarcinoma cells in vitro(25). Bottsford-Miller et al. reported that combined administration of platelet-depleting antibody with docetaxel caused 62% decrease in tumor weight compared to docetaxel treatment in orthotopic mouse models of human ovarian cancer(6). They further found that platelet transfusion blocked the effect of docetaxel on tumor growth, and aspirinization blocked the effect of transfusion. However, clinical evidence suggesting the link between thrombocytosis and chemoresistance in ovarian cancer is very few, as most studies only correlated thrombocytosis with survival after chemotherapy. Bottsford-Miller et al. reported on change of platelet count during first-line chemotherapy in the responsive and refractory groups matched for stage, histology, grade, and primary therapy(26). In patients with durable response, only 50% had pretreatment thrombocytosis and all of them achieved normal platelet count during therapy, whereas all had pretreatment thrombocytosis and only 50% of them achieved normal count during therapy in patients with refractory disease. However, the possibility that platelet count only reflects the real-time residual tumor amount cannot be excluded. Feng et al. reported that preoperative thrombocytosis was significantly associated with chemoresistance determined based on the interval between disease progression and adjuvant chemotherapy in high-grade serous ovarian cancer(20). However, thrombocytosis was not significant after stratification based on residual tumor after surgery. In our study, pretreatment thrombocytosis was not associated with operation achievement, and was significantly associated with TFI independently of FIGO stage (Table 3). Moreover, pretreatment thrombocytosis was a significant prognostic factor for poor PFS and OS independently of FIGO stage and operation achievement (Table 4). These observations strongly support the involvement of thrombocytosis in chemoresistance, implicating that molecular therapy targeting thrombocytosis may improve prognosis via attenuating chemoresistance. Based on the current findings, we assume that combination of chemotherapeutics and antiplatelet therapies may be efficacious for the ovarian cancer patients with thrombocytosis. Notably, patients with MHA or non-malignant inflammatory condition may have to be excluded from the treatment subjects, as the pathways for thrombocytosis in those patients must be different from paraneoplastic thrombocytosis.

Stone et al. proposed that increased hepatic thrombopoietin synthesis in response to tumor-derived IL-6 was a mechanism for paraneoplastic thrombocytosis(27). They further reported that treatment with siltuximab, anti-IL-6 antibody, significantly enhanced therapeutic efficacy of paclitaxel in mouse models of epithelial ovarian cancer. As regards clinical trials, a phase II study in patients with platinum-resistant ovarian cancer reported that siltuximab treatment showed partial response in one patient and disease stabilization in 7 among 18 evaluable patients(28). Regarding combination with chemotherapeutics, a phase I trial in patients with recurrent epithelial ovarian cancer reported that combined carboplatin/doxorubicin with tocilizumab, anti-IL-6 receptor antibody, and interferon-α2b showed complete response in 3, partial response in 8, and stable disease in 6 among 21 evaluable patients, and that toxicity was tolerable(29). More clinical trials and examination of clinical samples are warranted to evaluate usefulness and to investigate the underlying mechanism of anti-IL-6 therapies in ovarian cancer.

Our study has the following limitations. First, the sample size of the subset analyses is relatively small. Second, the strengthening of our hypothesis by basic study data is lacking. Third, the retrospective study design potentially causes selection biases. Prospective studies are required to verify our proposal.

Conclusions

We have reported here on the precise prognostic impact of pretreatment thrombocytosis in epithelial ovarian cancer. The univariate and multivariate analyses exhibited that thrombocytosis was independently associated with TFI and MHA. Thrombocytosis correlated with poor OS and PFS in advanced stages but showed no difference in early stages. The multivariate analysis for prognostic factors demonstrated that thrombocytosis was significant for OS and PFS independently of stage, histology, primary treatment, operation achievement, non-malignant inflammatory condition, and MHA. The current findings implicate that the unfavorable prognostic impact of thrombocytosis may be ascribed to chemoresistance, further supporting the therapeutic potential of targeting thrombopoietic cytokines in epithelial ovarian cancer.

Abbreviations

FIGO: International Federation of Gynecology and Obstetrics

IDS: Interval debulking surgery

MHA: Microcytic hypochromic anemia

NAC: Neoadjuvant chemotherapy

OS: Overall survival

PDS: Primary debulking surgery

PFS: Progression-free survival

TC: Paclitaxel and carboplatin

TFI: Treatment-free interval

Declarations

Ethics approval and consent to participate

The present study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee University of Tsukuba Hospital (H27-143) with a waiver of informed consent.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Authors' contributions

SN and KM contributed to the conception and design; SN analyzed the data and drafted the manuscript; TM revised the manuscript; HI, YH, AS, NT, AA, HO, KM and TS critically reviewed the manuscript; SN, TM, HI, YH, AS, NT, AA, HO, KM and TS treated patients; TS supervised the study. All authors read and approved the final manuscript.

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Tables

Due to technical limitations the Tables are available as a download in the Supplemental Files.

Table 1. Patient characteristics.

Table 2. Relationships between pretreatment thrombocytosis and clinicopathologic parameters.

Table 3. Univariate and multivariate analyses of risk factors for pretreatment thrombocytosis.

Table 4. Univariate and multivariate analyses of prognostic factors for PFS and OS.

Figures

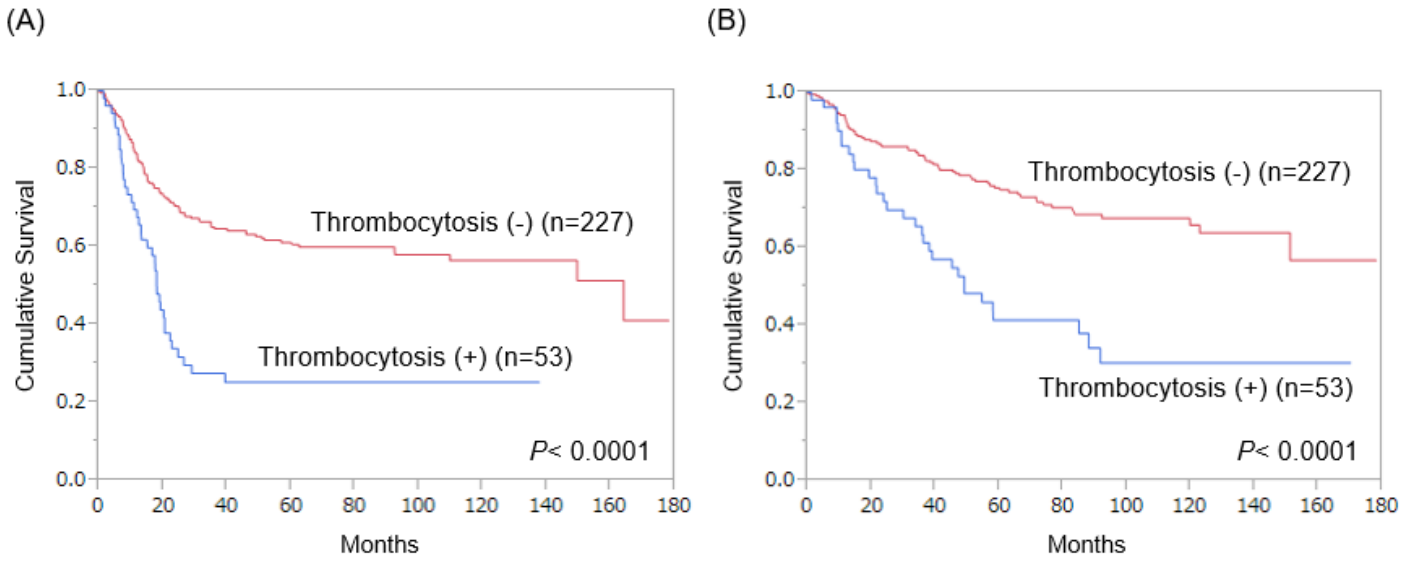

Figure 1

Univariate and multivariate analyses of prognostic factors for PFS and OS. Figure 1. Survival curves in the whole patients according to presence/absence of pretreatment thrombocytosis (n= 280). A, PFS in the whole patients. B, OS in the whole patients.

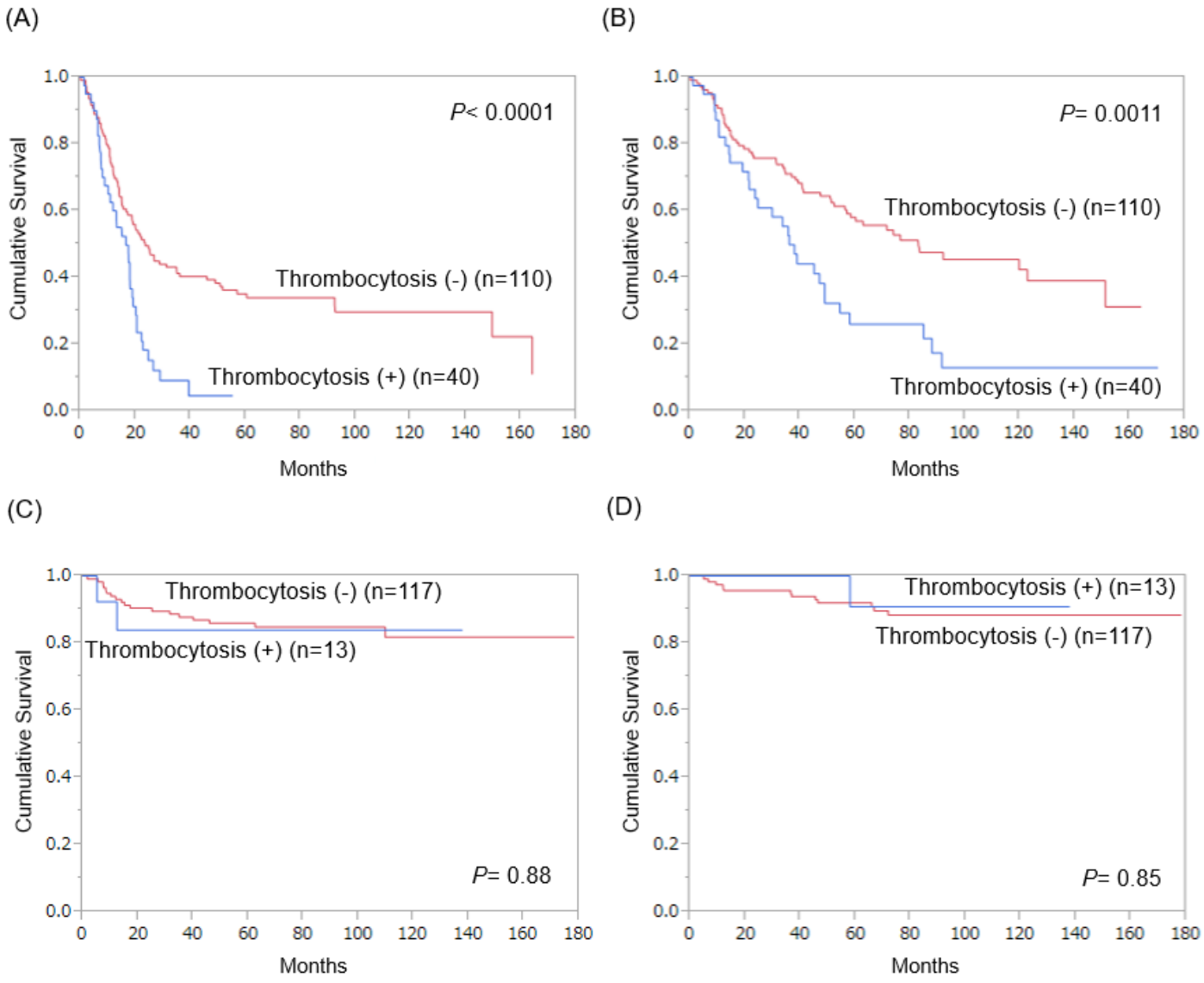

Figure 2

Survival curves in patients with stage III/IV (n=150) or I/II (n=130) diseases according to presence/absence of pretreatment thrombocytosis. A, PFS in stage III/IV patients. B, OS in stage III/IV patients. C, PFS in stage I/II patients. D, OS in stage I/II patients.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PlateletsTable1.xlsx
- PlateletsTable3.xlsx
- PlateletsTable4.xlsx
- PlateletsTable2.xlsx