Pre-treatment thrombocytosis predicts prognosis of endometrial cancer: A meta-analysis of 11 studies

QINGJIAN YE[1*], ZHIXI WU[2*], TINGTING XIA[3], DONG LIU[1], YUEBO YANG[1] and HONG TANG[4]

[1]Department of Gynecology, The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, Guangdong 510630;
[2]Department of Obstetrics and Gynecology, Dongguan People's Hospital (Affiliated Dongguan Hospital, Southern Medical University), Dongguan, Guangdong 523000; [3]Center for Reproductive Medicine, The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, Guangdong 510630; [4]Department of Gynecology, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, Guangdong 510120, P.R. China

Abstract. The aim of the present meta-analysis study was to determine the association between pre-treatment thrombocytosis and prognosis of patients with endometrial cancer. Articles published prior to December 2018 containing information on platelet count and endometrial cancer were searched in the PubMed, Embase and the Cochrane Library databases. A platelet count of ≥350 or >400x10^9/l was considered to indicate thrombocytosis. Hazard ratios (HRs) with 95% CI were calculated using a random- or fixed-effects model to assess the strength of the associations. A Funnel plot and Egger's test were used to evaluate the publication bias and sensitivity analyses were performed to estimate the robustness of the present results by using Stata 13.0 software. A pooled analysis of 11 studies that met the inclusion criteria was performed, involving a total of 2,590 patients with endometrial cancer. The overall survival (OS), progression-free survival (PFS) and disease-free survival (DFS) time of patients with endometrial cancer who exhibited pre-treatment thrombocytosis were shorter than those in patients without pre-treatment thrombocytosis (OS, HR=2.25, 95% CI=1.26-4.00; PFS, HR=2.60, 95% CI=1.23-5.50; DFS, HR=2.23, 95% CI=1.45-3.42). However, pre-treatment thrombocytosis was not associated with disease-specific survival time in patients with endometrial cancer (HR=2.17, 95% CI=0.51-9.27; P=0.296). Subgroup analysis indicated that pre-treatment thrombocytosis was not associated with OS time in patients of Asian and European ethnicity. Furthermore, pre-treatment thrombocytosis (platelet count >400x10^9/l) was an independent predictor of OS, PFS and DFS regardless of the clinical stage.

Introduction

Endometrial cancer, originating from the uterine epithelium, is the most common type of gynecological tumor in developed countries (1). It has been indicated that the vast majority of cases of endometrial cancer are not linked with familial inheritance (2). In the year 2016, ~60,050 new cases and 10,470 mortalities associated with endometrial cancer were reported in the USA (3). Furthermore, the incidence of endometrial cancer appears to be rapidly increasing in the USA (4). In addition, numerous previous studies have suggested that endometrial cancer has a higher incidence in developing countries (5,6). For most patients newly diagnosed with endometrial cancer, the prognosis is good and the 5 year survival rate may be as high as 81.1% (7). Stage, grade, histological subtype, myometrial depth invasion and lymphovascular space involvement have been identified as major prognostic factors for endometrial cancer (8,9).

In 1872, Riess *et al* (10) reported the association between elevated platelet counts and malignant tumors. To date, various studies have confirmed that pre-treatment thrombocytosis may be used as a prognostic indicator for patients with numerous solid tumor types, including lung, gastric, colorectal, esophageal, hepatocellular, pancreatic, breast and ovarian cancer, glioblastoma, renal cell carcinoma, oral squamous cell carcinoma, breast cancer and ovarian cancer (11-22). This effect may be due to the role served by platelets in tumor growth, angiogenesis and metastasis (23-26).

To date, whether pre-treatment thrombocytosis is able to predict the prognosis of patients with endometrial cancer remains unclear. To the best of our knowledge, no previous prospective randomized trials have been performed to evaluate the pre-treatment platelet count for predicting the prognosis for endometrial cancer. In addition, in a prior

Correspondence to: Dr Yuebo Yang, Department of Gynecology, The Third Affiliated Hospital of Sun Yat-Sen University, 600 Tianhe Road, Guangzhou, Guangdong 510630, P.R. China
E-mail: yueboyang001@163.com

Dr Hong Tang, Department of Gynecology, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, 111 Dade Road, Yuexiu, Guangzhou, Guangdong 510120, P.R. China
E-mail: happypangxie@126.com

*Contributed equally

retrospective controlled trial investigating this association, the number of patients was limited (27). In the present study, a pooled analysis of a large number of patients was performed to investigate the effect of preoperative thrombocytopenia on the prognosis of endometrial carcinoma. The present study aimed to investigate the association between thrombocytosis and the prognosis of patients with endometrial cancer to provide a reference for clinical therapy.

Materials and methods

Search for relevant studies. On December 17, 2018, studies associated with endometrial cancer and thrombocytosis were systematically searched for using the PubMed (https://www. ncbi.nlm.nih.gov/pubmed/), Embase (https://www.embase. com) and Cochrane Library databases (http://www. cochranelibrary.com/). In addition, references to relevant reviews were manually searched in order to avoid excluding any studies that met the selection criteria. The terms used for the search were as follows: i) 'Thrombocytosis', 'thrombocythemia' or 'platelet count'; and ii) 'endometrial cancer', 'endometrial neoplasm' or 'endometrial carcinoma'. Furthermore, the language was not limited during the search process. Two researchers independently searched for relevant studies and screened the articles according to the inclusion and exclusion criteria applied in the present study.

Inclusion criteria. The inclusion criteria for the present study were as follows: i) The study covered the prognosis of endometrial cancer; ii) the study described the effects of thrombocytosis or platelet count on the prognosis of endometrial cancer; iii) the study contained relevant prognostic data, including hazard ratios (HR) and the corresponding 95% CI for overall survival (OS), progression-free survival (PFS), disease-free survival (DFS) and disease-specific survival (DSS); iv) the relevant HR and corresponding 95% CI were available through conversion.

Exclusion criteria. The following exclusion criteria were applied: i) Subjects did not have endometrial cancer; ii) the study did not include the platelet count or any information regarding thrombocytosis; iii) the study was a case report, review or meta-analysis; iv) required data were unavailable. In addition, studies that did not include any data on the prognosis of patients with endometrial cancer were also excluded.

Data extraction and quality assessment. Two researchers extracted the data, including author, publication year, country, sample size, clinical stage, age, cut-off and follow-up time using a pre-made spreadsheet. In the present study, the effect of thrombocytosis on OS was used as the primary outcome, and the impact of thrombocytosis on PFS, DFS and DSS was considered as a secondary outcome. In the process of calculating the HR and its 95% CI, multivariate analyses were initially performed, followed by univariate analyses, and finally Kaplan-Meier survival curves. Kaplan-Meier survival curve analysis was performed using Engauge Digitizer 4.1 (http://digitizer.sourceforge.net/). For studies in which OR or 95% CI could not be obtained directly, OR and 95% CI were obtained through Kaplan-Meier survival analysis. A

non-randomized study (NRS) rating scale was used to evaluate the quality of the studies included in the present meta-analysis, as previously described (28). If inconsistent results regarding literature searches and data extraction were identified between two researchers, a third researcher was consulted to resolve the discrepancy.

Statistical analysis. Stata statistical software (version 13.0; StataCorp, LLC) was used to perform all statistical analyses and P<0.05 was considered to indicate statistical significance. Cochran's Q and I^2 tests were performed to quantify the heterogeneity of the HR. If the heterogeneity was >50%, random-effects models were selected for pooled analysis; otherwise, a fixed-effects model was used. In addition, Egger's test was performed to assess the publication bias and sensitivity analysis was used to examine the effect of a single study on the final results.

Results

Search and screening of eligible studies. A total of 349 studies were initially identified by searching the PubMed, Embase and Cochrane Library databases and through manual searching. After exclusion of duplicate studies, 77 studies were retained. Subsequently, 64 articles comprising reviews, meta-analyses, case reports and studies investigating other tumor types were removed by analyzing the title and abstracts. The full text of the remaining 13 articles was then reviewed and two studies lacking sufficient data were excluded. Finally, 11 studies (29-39) met the inclusion criteria and were included in the meta-analysis. The process of study selection is illustrated in Fig. 1.

Basic characteristics of included studies. In order to understand the basic characteristics of the studies included, relevant data, including publication year, country, number of cases, age of the patients and platelet count, were extracted. Detailed basic information on the studies included is provided in Table I. In total, 3 of the 11 studies included in the present meta-analysis analyzed patients exhibiting tumors at stage III-IV and the remaining 8 examined patients with tumors at stage I-IV. These previous studies were published after 2000 and 5 were published after 2015. The study by Gorelick *et al* (37) analyzed platelet counts as continuous variables and the remaining studies analyzed platelet counts as categorical variables with corresponding cut-off values. In total, 9 of the 11 studies reported the effect of pre-treatment thrombocytosis on the OS of patients with endometrial cancer.

Quality assessment. To measure the quality of the studies included, an NRS rating scale was applied. The results of the quality evaluation are provided in Table II. Among the 11 studies included in the present study, the baseline data of three studies were comparable and those of the other 8 studies were only partially comparable. In total, 4 studies did not control for confrontation factor. Finally, 4 articles had a quality score of 7 and the remaining studies had a score of >7.

Pooled analysis for OS. A total of 9 studies comprising 1,715 patients reported the effects of pre-treatment
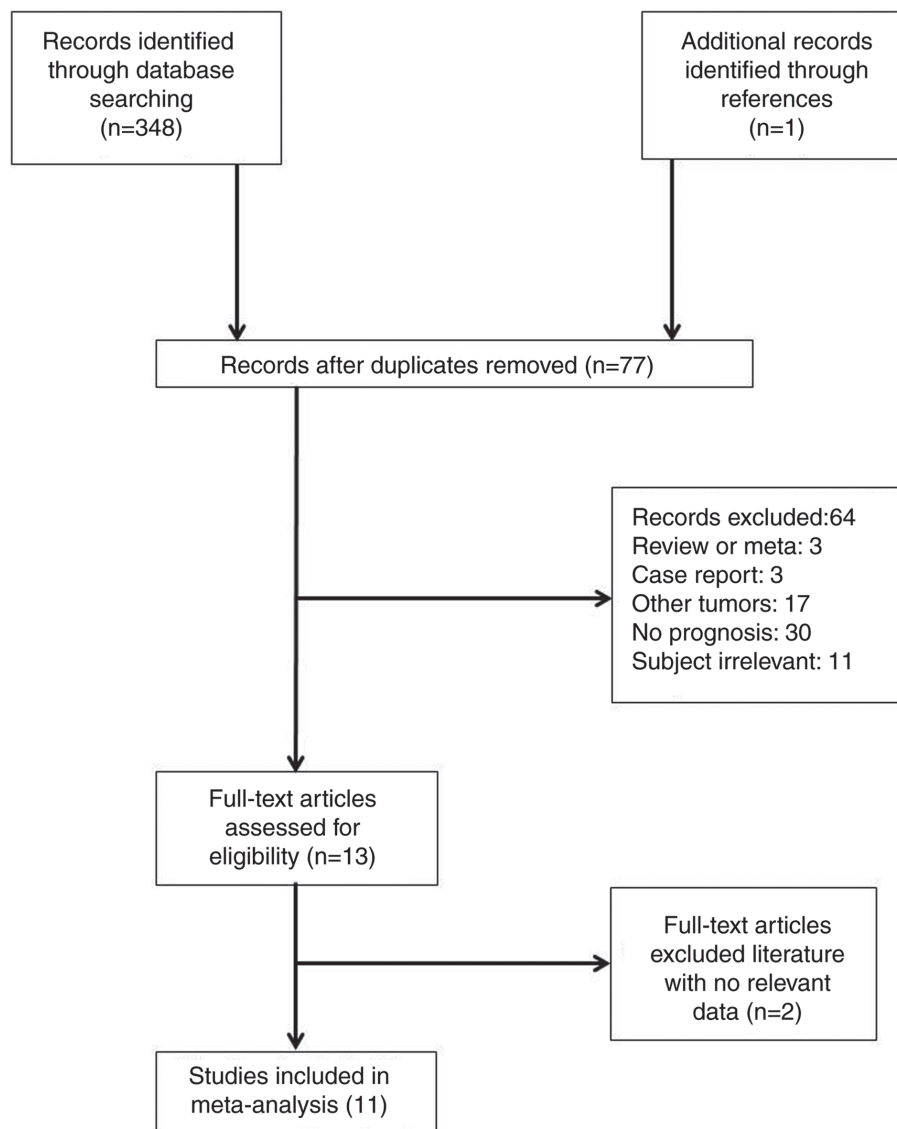
Figure 1. Approach used in the present study to examine previous literature and select studies for inclusion.

thrombocytosis on the OS of patients with endometrial cancer (29-32,34,36-39). Considering the large heterogeneity, a random-effects model was used to summarize the 9 articles (I^2=81.7%; P<0.001; Fig. 2). The pooled analysis indicated that pre-treatment thrombocytosis was associated with a significantly reduced OS of patients with endometrial cancer (HR=2.25; 95% CI=1.26-4.00; P<0.001; Fig. 2), indicating that thrombocytosis may affect the prognosis of patients with endometrial cancer.

Pooled analysis for PFS, DFS and DSS. To determine the effects of pre-treatment thrombocytosis on other prognostic indicators, PFS, DFS and DSS were also analyzed. Of the 11 studies included in the present meta-analysis, 8 studies included relevant data: 3 Studies reported on PFS, DFS and DSS (32,36,37), 3 on DFS (30,33,34) and 2 on DSS (33,35). The pooled analysis indicated that pre-treatment thrombocytosis was significantly associated with PFS and DFS, but not with DSS (PFS, HR=2.60, 95% CI=1.23-5.50, P=0.013; DFS, HR=2.23, 95% CI=1.45-3.42, P<0.001; DSS, HR=2.17,

95% CI=0.51-9.27, P=0.296; Supplemental Figs. S1-S3). The present results further confirmed that pre-treatment thrombocytosis may be used to predict the prognosis of patients with endometrial cancer.

Subgroup analysis. To further examine the association between pre-treatment thrombocytosis and prognosis of endometrial cancer in different patients and studies, a subgroup analysis was performed based on publication date, the region covered by the study, the number of cases included in the analysis, the type of cancer included in analysis, whether it was a multivariate or single-factor analysis and the platelet count cut-off. Detailed results of the subgroup analyses are provided in Table III. The publication date and the number of cases included in the analysis both had a significant effect on patient prognosis. The results indicated that pre-treatment thrombocytosis was not associated with OS in patients from Asia or Europe, however, there appeared to be some association for patients from America. Patients with uterine serous papillary carcinoma (USPC) and endometrial cancer were

Table I. Basic characteristics of the 11 studies included in the present meta-analysis.

Author (year)	Country	Case number	FIGO stage	Age (years)	Cut-off	Follow-up time[a] (months)	Category	Adjusted[b]	Survival analysis	(Refs.)
Takahashi (2017)	Japan	508	I-IV	58.0±10.5	>400,000	Unclear	Endometrial cancer	Yes	OS	(29)
Abu-Zaid (2017)	Saudi Arabia	162	I-IV	59.0±11.0	>400,000	Unclear	Endometrial cancer	Yes	OS, DFS	(30)
Younes (2016)	Israel	56	I-IV	69.4±15.0	>400,000	76.8	USPC	No	OS	(31)
Nakamura (2016)	Japan	108	I-IV	60.0 (27.0-87.0)[a]	≥350,000	Unclear	Endometrial cancer	No	OS, PFS	(32)
Kizer (2015)	USA	318	I-IV	Unclear	>400,000	25.6/23.1	Endometrial cancer	Yes	DSS, DFS	(33)
Heng (2014)	Thailand	238	I-IV	57.9±10.0	>400,000	59.6 (1.0-98.0)	Endometrial cancer	Yes	OS, DFS	(34)
Njølstad (2013)	Norway	557	I-IV	66.2±11.7	>390,000	55.0 (0.0-97.0)	Endometrial cancer	No	DSS	(35)
Matsuo (2013)	USA	516	I-IV	52.0±10.4	>400,000	43.7	Endometrial cancer	No	OS, PFS	(36)
Gorelick (2009)	USA	29	III-IV	Unclear	Continuous	Unclear	Endometrial cancer	Yes: OS No: PFS	OS, PFS[c]	(37)
Lerner (2007)	USA	39	III-IV	Unclear	>400,000	Unclear	USPC	Yes: OS	OS	(38)
Scholz (2000)	Turkey	59	III-IV	64.8	>400,000	Unclear	Endometrial cancer	No	OS[c]	(39)

[a]Median (range). [b]Adjusted: Data from multivariate analysis with Cox proportional hazards regression model; [c]Data from survival curve. FIGO, International Federation of Gynecologists and Obstetricians; OS, overall survival; DFS, disease-free survival; DSS, disease-specific survival; PFS, progression-free survival; USPC, uterine serous papillary carcinoma.

Table II. Quality evaluation results of 11 studies included in the present meta-analysis.

Study	Grouping method	Blinding	ITT	Baseline data	Diagnostic criteria	Confrontation factor control	Quality level[a]	(Refs.)
Takahashi (2017)	2	0	2	2	2	2	10	(29)
Abu-Zaid (2017)	2	0	2	1	2	2	9	(30)
Younes (2016)	2	0	2	1	2	0	7	(31)
Nakamura (2016)	2	0	2	1	2	0	7	(32)
Kizer (2015)	2	0	2	2	2	2	10	(33)
Heng (2014)	2	0	2	1	2	2	9	(34)
Njølstad (2013)	2	0	2	1	2	0	7	(35)
Matsuo (2013)	2	0	2	1	2	0	7	(36)
Gorelick (2009)	2	0	2	2	2	1	9	(37)
Lerner (2007)	2	0	2	1	2	1	8	(38)
Scholz (2000)	2	0	2	1	2	2	9	(39)

ITT, intention to treat; [a]A score of 1 to 6 indicated low quality, whereas a score of 7 to 12 indicated higher quality.
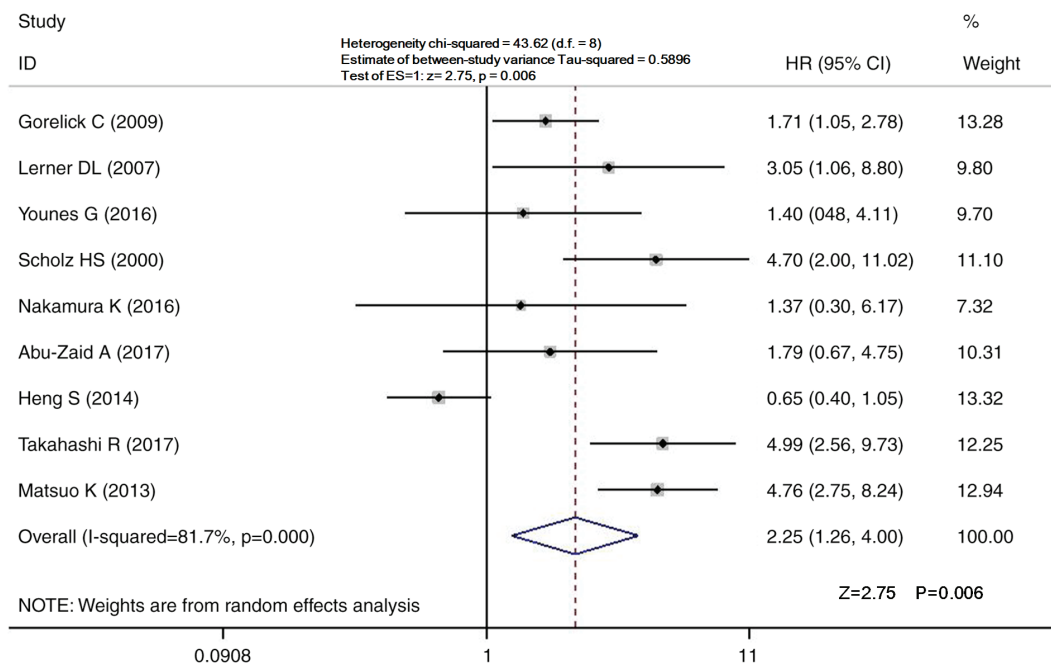

Figure 2. Forest plot of studies evaluating the association between pre-treatment thrombocytosis and overall survival in patients with endometrial cancer. HR, hazard ratio.

included in the study cohort. There was no association for USPC patients, but endometrial cancer patient prognosis was related to pre-operative thrombocytopenia. No association between pre-operative thrombocytopenia and prognosis was noted for patients with a platelet count of $\geq 350 \times 10^9/l$, however, the total survival time of patients with a cut-off >400 was related to pre-operative thrombocytopenia (Table III).

Publication bias and sensitivity analysis. In order to evaluate the potential publication bias, the articles included in the present meta-analysis were subjected to Egger's test. The results indicated no significant publication bias in the present

study (P=0.565). A sensitivity analysis was also performed to assess the effect of a single study on the final results. The analysis suggested that the impact of individual studies on the results of the pooled analysis was negligible, indicating that the present conclusions are not influenced by individual articles and exhibit high robustness (Fig. 3).

Discussion

Identification of prognostic markers for patients with endometrial cancer is important and may facilitate clinical decisions regarding potential treatments and disease outcome. The

Table III. Subgroup analyses of the association between pre-treatment thrombocytosis and overall survival.

Variable	Number of studies	HR (95%)	Z	P-value	I^2 (%)	P-value
Year of publication						
2000-2014	5	2.916 (1.534-5.543)	3.26	0.001	56.9	0.055
2015-2017	5	2.296 (1.002-5.262)	1.96	0.049	88.7	<0.001
Region						
Asia	5	2.207 (0.772-6.311)	1.48	0.140	89.0	<0.001
Europe	2	2.687 (0.823-8.774)	1.64	0.102	66.6	0.084
America	3	2.874 (1.388-5.952)	2.84	0.004	73.4	0.023
Number of cases						
<150	5	2.202 (1.388-3.492)	3.35	0.001	26.5	0.245
>150	5	2.779 (1.041-7.420)	2.04	0.041	91.2	<0.001
Type of cancer						
USPC	2	2.078 (0.969-4.457)	1.88	0.060	2.1	0.312
Endometrial cancer	8	2.598 (1.355-4.982)	2.88	0.004	86.0	<0.001
Analysis						
Multivariate	9	1.733 (1.430-2.100)	5.61	<0.001	50.9	0.038
Single factor	4	1.886 (1.117-3.186)	2.37	0.018	63.8	0.040
Platelet count cut-off ($x10^3/mm^3$)						
≥350	1	1.367 (0.303-6.171)	0.41	0.684	-	-
>400	8	2.771 (1.382-5.557)	2.87	0.004	85.7	<0.001
Continuous	1	1.714 (1.055-2.785)	2.18	0.030	-	-

Pooled analysis was performed by generic inverse variance. USPC, uterine serous papillary carcinoma; HR, hazard ratio; FIGO, International Federation of Gynecology and Obstetrics.
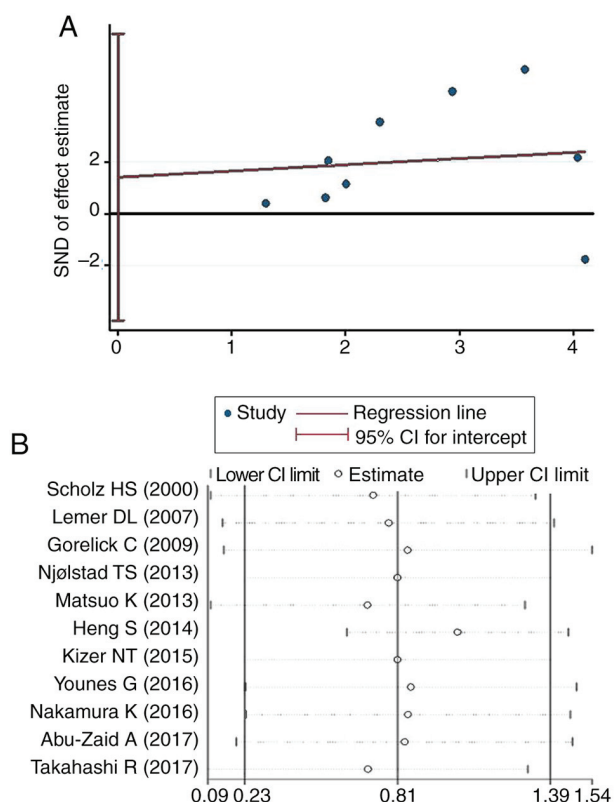

Figure 3. Egger's test and sensitivity analysis chart. (A) Egger's test of studies evaluating the potential publication bias. (B) Graph indicating the impact of a single study on the results. SND, standard error.

present study performed a pooled analysis of the results of previously published studies to assess whether pre-treatment thrombocytosis may be a prognostic indicator for patients with endometrial cancer. The meta-analysis suggested that pre-treatment thrombocytosis was significantly associated with OS, PFS and DFS in patients with endometrial cancer, but was not significantly associated with DSS. Furthermore, quality assessments, publication bias analysis and sensitivity analysis of the studies included confirmed that the present results were reliable. Of note, only two previous studies reported an association between pre-treatment thrombocytosis and DSS (33,35). Further studies with more patients are required in order to investigate the association between pre-treatment thrombocytosis and DSS.

Previous studies have reported that 7-41% of patients with endometrial cancer suffer from thrombocytosis with different cut-offs (29,34,35,37-44). In addition, one previous study indicated a significant correlation between thrombocytosis and clinical stages, suggesting that patients with advanced clinical stage are more likely to suffer from thrombocytosis (29). Thrombocytosis may reduce the rate of chemotherapy response in patients with endometrial cancer, and this effect may explain why patients with thrombocytosis have a poor prognosis (33). A retrospective study by Borges *et al* (45) analyzed ~1,000 patients with lung cancer and indicated that a platelet count of $>440x10^3/mm^3$ significantly reduced the chemotherapy response rate (45). Furthermore, a previous study suggested that an increase in the platelet count may

reduce the resistance to docetaxel-induced apoptosis in a mouse model of ovarian cancer (46). In addition, previous studies suggested that thrombocytosis may increase the risk of thromboembolism in cancer patients (35,46). The present study suggested that a platelet count of $\geq 400 \times 10^3/mm^3$ was significantly associated with a reduced OS of patients with endometrial cancer. Further studies are required to investigate the molecular mechanisms underlying the effect of thrombocytosis on the prognosis of patients with endometrial cancer.

A previous study demonstrated that various cytokines and growth factors, including thrombopoietin, interleukin-1 (IL-1), IL-3, IL-6, IL-11 and leukemia inhibitory factors are able to enhance platelet production (23). Elevated levels of IL-6 were previously identified to be associated with poor prognosis of patients with ovarian cancer (47). Various previous studies have indicated that thrombocytosis may be a paraneoplastic syndrome in patients with ovarian cancer, and thrombocytosis may stimulate angiogenesis and lead to tumor progression via increased secretion of IL-6 from tumor cells (46,48,49). Due to limited information provided by the studies included, the present study did not investigate the association between multiple growth factors and platelet formation in patients with endometrial cancer. Further studies are required to investigate whether IL-6 is involved in platelet formation in patients with endometrial cancer and IL-6 may be a novel potential therapeutic target for treating endometrial cancer, providing a novel direction for future studies. To the best of our knowledge, the present study was the first meta-analysis investigating the association between pre-treatment thrombocytosis and prognosis in patients with endometrial cancer. Pooled analysis of prognostic indicators for OS, PFS, DFS and DSS in patients with endometrial cancer was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (50) and reliable results were obtained. However, the present study has certain limitations. First, the analysis included a small number of studies on uterine serous papillary carcinoma and further studies are required to examine this type of tumor. In addition, the results of the present meta-analysis suggested that pre-treatment thrombocytosis was not associated with the prognosis of patients with endometrial cancer and a platelet count of $\geq 350 \times 10^3/mm^3$, and this result requires further investigation using a larger sample size. Furthermore, it is necessary to analyze the association between thrombocytosis and the prognosis of stage I-II endometrial cancer. This was not analyzed in the present study due to the lack of previous studies reporting on this.

The results of the present systematic review and meta-analysis indicated that pre-treatment thrombocytosis was significantly associated with OS in patients with endometrial cancer at stage III-IV. Furthermore, pre-treatment thrombocytosis ($>400 \times 10^3$ platelets/mm^3) was an independent predictor of OS regardless of the clinical stage. In addition, patients with pre-treatment thrombocytosis had poor DFS and PFS.

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Availability of data and materials

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Authors' contributions

QY and ZW performed the literature search and selection, performed the data analysis and wrote the manuscript. TX and DL helped with the data analysis. YY and HT designed and supervised the present study and revised the manuscript.

Ethical approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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