

## RESEARCH ARTICLE

# Pretreatment Thrombocytosis as a Prognostic Factor in Women with Gynecologic Malignancies: a Meta-analysis

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## Abstract

**Background:** This study was performed to analyze the prognostic implications of pretreatment or preoperative thrombocytosis in women with gynecologic malignancies. **Material and Methods:** We surveyed 2 medical databases, PubMed and EMBASE, to identify all relevant studies. A total of 14 (n=3,490) that evaluated the link between thrombocytosis and 5-year survival were included. REVMAN version 5.1 was used for our analysis and publication bias was evaluated using the Begg's funnel plot and tested by STATA 11.0. Risk ratios (RRs) with 95% confidence intervals (CIs) generated by the random effect model were used to assess the strength of any association. **Results:** 709 (20.3%) of the 3,490 patients exhibited thrombocytosis (platelet counts >400×10<sup>9</sup>/L) at primary diagnosis, and their mortality was 1.62-fold higher compared with the others (RR=1.62, 95% CI= [1.28-2.05], p<0.0001). Thrombocytosis failed to have a stronger effect on the survival of advanced patients of stages III to IV in our study (n=478, RR=1.29, 95% CI= [1.13-1.48], p=0.0003), nor in women with cervical cancer in stage IB (n=1371, RR= 1.73, 95% CI= [1.71-2.58], p=0.007). In addition, when adjusted for different carcinoma, it was associated with worse prognosis for all except the ones with vulvar cancer (n=201, RR= 0.43, 95% CI= [0.14-1.29], p=0.13). **Conclusions:** This meta-analysis indicated that thrombocytosis might be associated with a worse prognosis for patients with gynecologic malignancies but without specificity or sensitivity for the ones in advanced stage. When adjusted for different gynecologic malignancies, it showed a significant effect on survival of all except vulvar cancers.

**Keywords:** Thrombocytosis - gynecologic malignancies - meta-analysis - prognosis

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## Introduction

The clinical observation of thrombocytosis (defined as a platelet counts >400×10<sup>9</sup>/L) and malignancies was described over a century ago (Trousseau et al., 1867; Riess et al., 1872). According to the experimental evidence, it suggested that platelets actively promote cancer cell dissemination by protection of circulating cancer cells from immune surveillance, negotiation of cancer-cell arrest in the microvasculature, and stimulation of angiogenesis (Nieswandt et al., 1999; Borsig et al., 2008). Recent studies have addressed the prevalence and prognostic impact of thrombocytosis in various malignancies, including stomach, lung, kidney, uterus, and gynecologic malignancies (Zeimet et al., 1993; Menczer et al., 1998; Tomita et al., 2008; Heras et al., 2010; Cho et al., 2011). However, up to now, there was no meta-analysis comprehensively analyzing the prognostic value of thrombocytosis in cancer patients. The aim of this study was to comprehensively and quantitatively summarize the evidence for the use of pretreatment or preoperative thrombocytosis to evaluate its prognostic value for women with gynecologic malignancies.

## Materials and Methods

### Identification and Eligibility of Relevant Studies

We identified all studies, published or not, respectively targeting all thrombocytosis in patients with gynecologic malignancies, by an electronic search using online PubMed (MEDLINE) and EMBASE, with the search strategies based on combinations of "ovarian carcinoma", "endometrial carcinoma", "cervical carcinoma", "vulvar carcinoma", "platelet count", "thrombocytosis" and "prognosis". Last query was updated on April 6, 2012. References of retrieved articles were also screened to find out any studies missed by the search strategies.

After reading by two independent reviewers (Yu M. and Ma XL.), the candidate articles were identified for the meta-analysis studies based on title and abstract. Full-text review (Liang CS.) was retrieved when it cannot be categorized and abstract review was restricted to English, and the full-texts not in English were excluded. Reported data required for meta-analysis were then identified. Prespecified quality-related inclusion or exclusion criteria were not used and each study had not been weight by a quality score because no such score had received general

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agreement for meta-analyses of observational studies (Altman et al., 2001). We made an effort to contact investigators by e-mail to get unpublished data regarding thrombocytosis, gynecologic malignancies and survival.

#### Definitions and Standardizations

We defined thrombocytosis as platelet counts  $>400 \times 10^9/L$  in patients with gynecologic malignancies. For statistical analysis, the value of  $400 \times 10^9$  was used as a cut-off to separate the patients with high versus low platelet count, while the others did not mention.

The main reported data required for our meta-analysis was 5-year overall survival (OS). All of these patients were followed up until death or for at least 60 months. We also listed age, tumor location, number of patients got thrombocytosis, clinical stage and p values.

#### Data Extraction

Two reviewers (Yu M. and Liu L.) independently extracted data from all primary studies. In particular, we recorded each report using a standardized data collection form, with the following items: year of publication, the first author, country of origin, tumor location, number of patients analyzed, number of patients got thrombocytosis, mean or median age, clinical stage, p value, number of events in, OS or cumulative survival and survival curves. Disagreements were also resolved by consensus between the two reviewers, and studies were all retrospective.

#### Statistical Analyses

REVMAN, version 5.1 was used for our analysis and publication bias was evaluated using the Begg's funnel plot and tested by STATA 11.0 (STATA Corporation, College Station, TX) (Yu M., Niu ZM. and Wu YK.). A study was considered significant when the p value was less than 0.05 in univariate analysis. For the quantitative aggregation of survival results, we measured the impact of thrombocytosis on survival by estimating the risk ratio (RR) between the thrombocytosis and normal (defined as a platelet count  $<400 \times 10^9/L$ ) groups. An observed  $RR > 1$  indicated worse outcome and would be considered statistically significant if the 95%CI did not overlap 1, with  $p < 0.05$ . The study was termed "positive" when

pretreatment or preoperative thrombocytosis predicted poorer survival while "negative" did not. The simplest method to get RR and their 95% confidence interval (CI) was to find in the original article, while none of our articles consist. Thus, the numbers of events in groups with and without thrombocytosis and the numbers of patients in each group were used to determine the RR estimate. When the data of the total numbers of events was not available directly in the article but as graphical survival plots, and the number of steps on the curves equaled the number of events given in the publication, the calculations were done, presuming that the rate of censored patients was constant during the study follow-up (Parmar et al., 1998), and we read Kaplan-Meier curves (Yu M. and Qin X.) by Engauge Digitizer version 4.1 (free software down-loaded from <http://sourceforge.net>). Considering the many sources of heterogeneity between studies and consequently between their individual RR estimates, a random-effect model (Der Simonian and Laird's method) was used to calculate the overall RR.

## Results

#### Eligible Studies

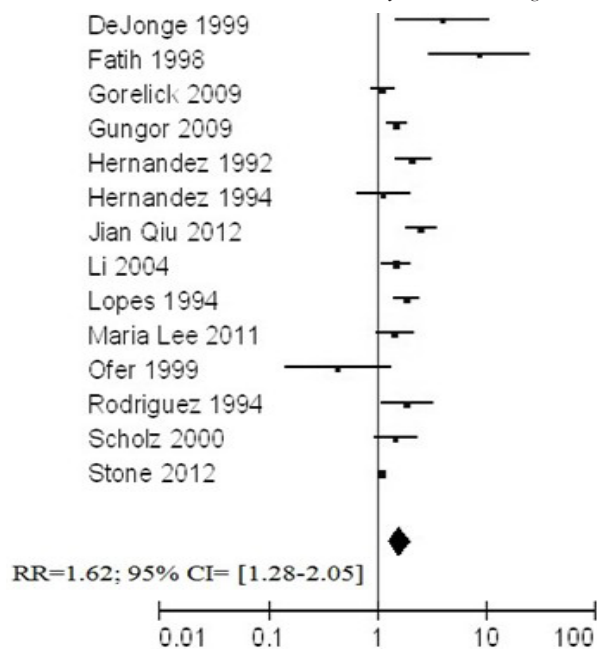
Our electronic search algorithm retrieved a total of 315 references for pretreatment or preoperative thrombocytosis and gynecologic malignancies, and 22 full texts were evaluated. 20 reports were identified with thrombocytosis in patients with gynecologic malignancies while one of excluded was an editorial for another article included (Rodriguez et al., 1994; Rodriguez et al., 1994) and the other was in German (Zeimet et al., 1993). Of all the remaining 20 reports, 6 were excluded: one used  $300 \times 10^9$  to define the thrombocytosis (Lukas et al., 2000), and five lacked informative clinical data (Zeimet et al., 1994; Menczer et al., 1998; Hernandez et al., 2000; Tamussino et al., 2001; Kuyumcuoglu et al., 2010).

Finally, 14 studies (n =3490 patients) were eligible for the meta-analysis, and 12 of the 14 reports found an inverse relationship between 5-year overall survival and thrombocytosis, that is positive studies (Hernandez et al., 1992; Lopes et al., 1994; Rodriguez et al., 1994; Gücer et al., 1998; De Jonge et al., 1999; Scholz et al., 2000;

**Table 1. Characteristics of the Eligible Studies**

year	author	country	location	No.	no. of thrombocytosis	clinical stage	P value
1992	Hernandez	U.S.	cervix	113	20	I-IV	<0.0001
1994	Rodriguez	U.S.	cervix	219	19	IB	NR
1994	Lopes*	England	cervix	643	109	I-IV	<0.01
	Lopes*	England	cervix	436	56	IB	NS
	Lopes*	England	cervix	65	25	III-IV	NS
1994	Hernandez	U.S.	cervix	623	59	IB	0.4
1999	DeJonge	Norway	cervix	93	6	IB	0.0012
1999	Ofer Lavie	England	vulva	201	30	I-IV	0.586
1998	Fatih Gücer	Turkey	endometrium	135	19	I-IV	<0.0001
2000	Scholz	Austria	endometrium	59	12	III-IV	0.035
2009	Gorelick	U.S.	endometrium	29	8	III-IV	0.015
2004	Li	U.S.	ovary	146	39	III-IV	<0.0004
2009	Gungor	Turkey	ovary	292	124	I-IV	<0.0004
2011	Maria Lee	Korea	ovary	179	62	III-IV	0.005
2012	Stone	U.S.	ovary	619	192	I-IV	<0.001
2012	Jian Qiu	China	ovary	139	10	I-IV	<0.001

\*they were from the same study; NR, not reported; NS, no significant



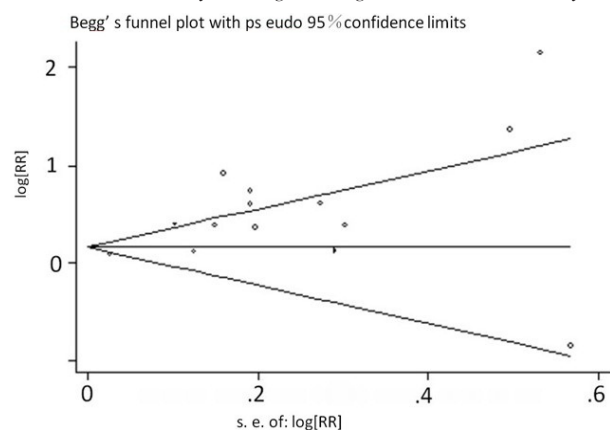
**Figure 1. Meta-analysis of the Association Between Thrombocytosis and the Risk of Death at 5 Years.** Each study is shown by the name of the lead author and the RR with 95% CIs. The summary RR and 95% CIs (according to random effect calculations) are also shown (ALL)

Taucher et al., 2003; Li et al., 2004; Gorelick et al., 2009; Gungor et al., 2009; Lee et al., 2011; Qiu et al., 2012; Stone et al., 2012), leaving only 2 studies negative (Hernandez et al., 1994; Lavie et al., 1999).

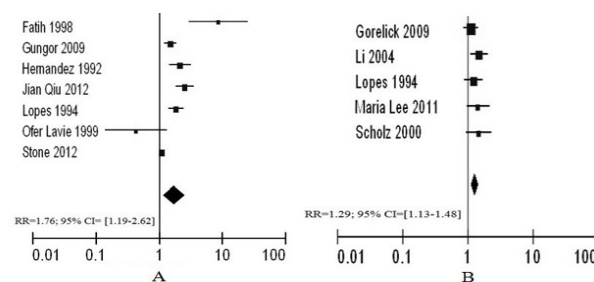
Characteristics of the 14 eligible studies are listed in Table 1. 6 reports originated from U.S., 2 from England, 2 from Turkey, 1 from Australia, 1 from China, 1 from Norway and 1 from Korea. All of the eligible studies were observational retrospective studies. According to the information, the median or mean age of the enrolled patients ranged from 45.5 to 68.1 years. In the 14 studies included for meta-analysis, only 1 study was about vulvar cancer, 3 were about endometrial cancer, 5 were cervical cancer and 5 were ovarian cancer. Meanwhile, the tumor was located in the cervix in 1691 patients (48.5%), endometrium in 223 patients (6.4%), ovary in 1375 patients (39.4%), and vulva in 201 patients (5.8%). Of the 3490 women with gynecologic malignancies, 709 (20.3%) had thrombocytosis at primary diagnosis, indicating platelet counts  $>400 \times 10^9/L$ . The incidence of thrombocytosis was 14.9% (30/201) for vulva cancer, 17.5% (39/223) for endometrial cancer, 12.6% (213/1691) for cervical cancer and 31.1% (427/1375) for ovarian cancer, respectively.

#### Meta-analysis: 5-year overall survival

Thrombocytosis was associated with worse prognosis regarding the risk of death within 5 years. As between-study heterogeneity was significant ( $I^2 > 50\%$ ,  $p < 0.0001$ ), random model was used. Mortality was 1.62-fold higher in patients with thrombocytosis compared to the others with normal platelet count ( $n=3490$ ,  $RR=1.62$ ,  $95\% CI= [1.28-2.05]$ ,  $p < 0.0001$ ; Figure 1). Begg's test and funnel was used to evaluate publication bias. No significant publication biases were found in results of meta-analyses

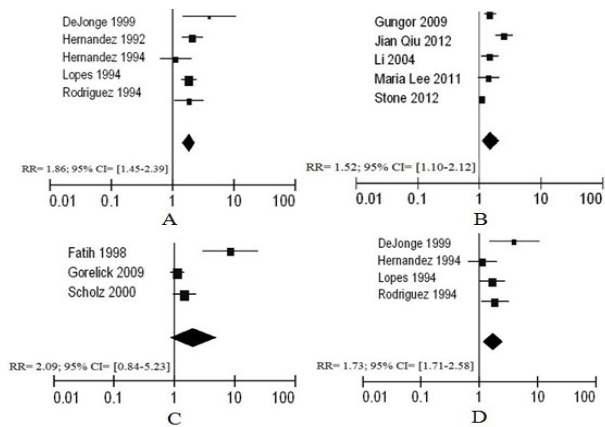


**Figure 2. Begg's Funnel Plot Showing the Relation Between RR and 1/SE Larger Studies (Those with Larger 1/SE) Show Generally Smaller RRs**



**Figure 3. A. Meta-analysis of the association between thrombocytosis and the risk of death at 5 years for patients in stage I to IV. B. Meta-analysis of the association between thrombocytosis and the risk of death at 5 years for patients in stage III to IV.** Each study is shown by the name of the lead author and the RR with 95% CIs. The summary RR and 95% CIs (according to random effect calculations) are also shown

of thrombocytosis prediction value for 5-year overall survival ( $p=0.870$ ; Figure 2). We analyzed the link between thrombocytosis and the prognosis of patients in stage I to IV (Hernandez et al., 1994; Lopes et al., 1994; Gücer et al., 1998; Lavie et al., 1999; Hernandez et al., 2000; Gungor et al., 2009; Qiu et al., 2012; Stone et al., 2012), and found the mortality was 1.76-fold higher in patients with thrombocytosis ( $n=1974$ ,  $RR=1.76$ ,  $95\% CI= [1.19-2.62]$ ,  $p=0.005$ ; Figure 3A). However, the patients in stage III to IV did not have a higher mortality (Lopes et al., 1994; Scholz et al., 2000; Li et al., 2004; Gorelick et al., 2009; Lee et al., 2011) but a much lower ( $n=478$ ,  $RR=1.29$ ,  $95\% CI= [1.13-1.48]$ ,  $p=0.0003$ ; Figure 3B). The result of studies (Hernandez et al., 1994; Lopes et al., 1994; Rodriguez et al., 1994; De Jonge et al., 1999) for relation of thrombocytosis and survival of patients in stage IB cervical cancer was not far-off ( $n=1371$ ,  $RR=1.73$ ,  $95\% CI= [1.71-2.58]$ ,  $p=0.007$ ; Figure 4D). And unfortunately, we did not get enough data to evaluate the link between thrombocytosis and survival of patients in stage I to II. For different gynecologic malignancies, we also found a great difference of their relationship. The thrombocytosis failed to have a significant effect on the 5-year overall survival for the patients with vulva cancer ( $n=201$ ,  $RR=0.43$ ,  $95\% CI= [0.14-1.29]$ ,  $p=0.13$ ), while the relation for patients with endometrial cancer ( $n=223$ ,  $RR=2.09$ ,  $95\% CI= [0.84-5.23]$ ,  $p < 0.0001$ ; Figure 4C) were much more strong. And the mortality was closer to



**Figure 4.** A. Meta-analysis of the association between thrombocytosis and the risk of death at 5 years for patients with cervical cancer. B. Meta-analysis of the association between thrombocytosis and the risk of death at 5 years for patients with ovarian cancer. C. Meta-analysis of the association between thrombocytosis and the risk of death at 5 years for patients with endometrial cancer. D. Meta-analysis of the association between thrombocytosis and the risk of death at 5 years for patients with cervical cancer in stage IB. Each study is shown by the name of the lead author and the RR with 95% CIs. The summary RR and 95% CIs (according to random effect calculations) are also shown

the average for the patients with cervical ( $n=1691$ ,  $RR=1.86$ ,  $95\% CI=[1.45-2.39]$ ,  $p<0.00001$ ; Figure 4A) and ovarian cancer ( $n=1375$ ,  $RR=1.52$ ,  $95\% CI=[1.10-2.12]$ ,  $p=0.01$ ; Figure 4B).

## Discussion

There has been great interest in identifying prognostic markers for patients with gynecologic malignancies as these markers can help guide clinical decision-making regarding therapy and outcomes. In this paper, we examined the correlation of thrombocytosis (platelet counts  $>400 \times 10^9/L$ ) with OS before any curative treatment or surgery of gynecologic malignancies. Our meta-analysis for the 14 primary studies from the published literature according to the survival data in patients with gynecologic malignancies, showed that the thrombocytosis (platelet counts  $>400 \times 10^9/L$ ) at primary diagnosis is associated with worse overall survival ( $RR=1.62$ ) and proved to be a significant but weaker prognostic factor for patients in stage III to IV in comparison with the entire group ( $RR=1.29$ ), although it had evidence that thrombocytosis is more frequent in advanced disease in patients with ovarian cancer, endometrial cancer and cervical cancer (Gücer et al., 1998; Gücer et al., 2004; Gorelick et al., 2009). For the cervical cancer patients in stage IB, especially, it showed a significant effect on the survival too ( $RR=1.73$ ). When adjusted for different gynecologic malignancies, all three of the meta-analyses for endometrial cancer ( $RR=2.09$ ), cervical cancer ( $RR=1.86$ ) and ovarian cancer ( $RR=1.52$ ) gave statistically significant results, favoring a link between thrombocytosis and poor survival, while the vulvar cancer did not ( $RR=0.43$ ).

Our findings were consistent with the outcome on the link between thrombocytosis and survival in patients with another common cancer for women, breast cancer,

which showed an incidence of 3.7% (161/4300) and a strong relation ( $n=4300$ ,  $RR=2.04$ ,  $95\% CI=[1.43-2.92]$ ,  $p<0.0001$ ) (Taucher et al., 2003). We finally got the only study about breast cancer and it got the maximum sample size ( $n=4300$ ). To avoid bias, four malignancies were ultimately included in our study, as endometrial, cervical, ovarian and vulvar cancer. However, only one study had evaluated the correlation between thrombocytosis and survival for patients with vulva cancer, and reported that thrombocytosis had no effect on 5-year survival rate in 201 patients with primarily surgical treatment (Lavie et al., 1999). Compared to the others, the studies about prognosis of patients with ovarian cancer lagged behind (2004-2012), and the earliest studies were all about cervical cancer (1992-1999). The overall statistical link we got between thrombocytosis and survival was rather weak, with a global RR of 1.62. While as a rule of the thumb, a prognostic factor with a  $RR<2$  is of limited practical use (Hayes et al., 2001), only the breast and endometrial cancer subgroup got a  $RR>2$ .

There were no studies which had analyzed the prognostic value of thrombocytosis in tumors yet, and thrombocytosis has repeatedly been identified as a marker of gynecologic malignancies with independent prognostic value. Our study aimed to summarize the evidence for the use of pretreatment or preoperative thrombocytosis to evaluate its prognostic value for women with gynecologic malignancies. According to the International Federation of Gynecologists and Obstetricians (FIGO) guidelines, all patients had received surgery, on the basis of primary surgical staging with the intent of optimal tumor cytoreduction, radiotherapy or chemotherapy.

The precise mechanisms underlying the cancer-associated thrombocytosis are not clearly understood. Although the thrombocytosis should not be thought of as an isolated factor involved in the cancer growth and metastatic process, it might represent an important therapeutic prospect. For example, heparin given as thromboembolic prophylaxis in the perioperative period may incidentally act to reduce the assistance of platelets to tumor spread (Nash et al., 2002). However, it could also result in a lowering of the platelet count by administration of cytotoxic drugs in chemotherapy and is currently unclear whether decreasing platelet counts has a place in the treatment of malignant disease.

Though we attempted to minimize publication bias by searching completely, it is unavoidable that some data was missing for various reasons such as publishing language only in German (Zeimet et al., 1993), failing to get the survival data in the full-text or the authors (Zeimet et al., 1994; Menczer et al., 1998; Hernandez et al., 2000; Tamussino et al., 2001; Kuyumcuoglu et al., 2010), or unpublished or ignored studies. All of our studies are retrospective observational studies, which are more prone to many biases than prospective randomized controlled studies (Grimes et al., 2002). Between-study heterogeneity is significant in our study, but we tried to reduce the variability by screening the literature using the same standard, such as the same experimental design and definition of thrombocytosis in prognostic meta-analysis. Furthermore, results should be interpreted with caution

for the probable contribution of the clinical stage, age, pathology and location to its prognostic effect.

On the basis of the results of this analysis, we believe that the thrombocytosis is associated with worse prognosis for patients with gynecologic malignancies but do not have specificity or sensitivity for a variety of staging. When adjusted for different gynecologic malignancies, it showed a significant effect on survival except the vulvar cancer. Although briefly discussed in one study (Lavie et al., 1999), additional investigations evaluating thrombocytosis as a marker of vulva cancer progression or response to therapy would be a valuable addition to the literature. In the interim, this meta-analysis appears to initially support the hypothesis that thrombocytosis is associated with a reduced probability of overall survival from gynecologic malignancies.

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The authors declare that they have no competing interests.

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