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ORIGINAL RESEARCH

Clinicopathological and prognostic significance of pretreatment thrombocytosis in patients with endometrial cancer: a meta-analysis

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Background: The prognostic and clinicopathological role of pretreatment thrombocytosis in cancer has been widely studied, but conclusions in endometrial cancer (EnCa) remain controversial. Therefore, we conducted a meta-analysis to assess the pathologic and prognostic impacts of pretreatment thrombocytosis in patients with EnCa.

Methods: We searched PubMed, Embase, SpringerLink, ScienceDirect and China National Knowledge Infrastructure databases. Pooled HR or OR with their 95% CIs were applied to assess the association of pretreatment thrombocytosis with survival outcomes and clinical parameters of EnCa patients.

Results: In total, 10 studies containing 2,995 cases of EnCa met the criteria. The results suggested that pretreatment thrombocytosis was significantly associated with high International Federation of Gynecology and Obstetrics (FIGO) stage (pooled OR 3.45, 95% CI 1.68–7.08, *P*=0.001), poor tumor differentiation (pooled OR 2.00, 95% CI 1.22–3.29, *P*=0.006), lymph-vascular space invasion (pooled OR 2.04, 95% CI 1.35–3.07, *P*=0.001); myometrial invasion (pooled OR 2.14, 95% CI 1.39–3.32, *P*=0.001); cervical involvement (pooled OR 2.54, 95% CI 1.56–4.15, *P*=0.000) and lymph node metastasis (OR 3.15, 95% CI 1.71–5.80, *P*=0.001). No significant difference existed between pretreatment thrombocytosis and overall survival (*P*=0.012), cancer/disease-specific survival (*P*=0.07) or disease-free survival (*P*=0.25).

Conclusion: pretreatment thrombocytosis was associated with advanced clinicopathological features in patients with EnCa, which may serve as a potential therapeutic target for EnCa.

Keywords: thrombocytosis, endometrial cancer, prognosis, meta-analysis

Introduction

Endometrial cancer (EnCa) is the most common gynecological malignancy with a rising incidence in developed countries.[1] Most patients (80%) are commonly diagnosed at the early stage and can be surgically cured. However, patients with metastatic or recurrent disease portend a poor prognosis, with a 5-year survival rate of 5.3–20.1%, as there are limited treatment options.[2,3] Prognostic assessment is essential for treatment decision-making. Clinically, the prognosis of EnCa is heterogeneous due to variations in tumor biology.[4] Some patients with the same stage or pathologic prognostic factors have various clinical courses and survival outcomes.[5] Therefore, additional prognostic markers are needed to guide therapeutic options and surveillance strategies.

Recently, studies have shown that tumor–platelet interactions is associated with tumorigenesis. Specifically, elevated platelet count or thrombocytosis has been

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identified as a marker of cancer prognosis and may reflect tumor burden. Todenhöfer T et al reported thrombocytosis could be used as a prognostic parameter and constructed a more accurate prognostic model according to pretreatment platelet count and established pathological factors.[6] Several studies have suggested that preoperative thrombocytosis associated with poor survival in gynecological malignancies, such as ovarian and cervicalcancer.[7,8] So the relationship between thrombocytosis and prognosis of EnCa is worth further study Pretreatment thrombocytosis has been reported by most researches to be correlated with poor prognosis of EnCa. However, conflicting results exist and a consensus cannot be achieved. Takahashi et al[9] suggested that pretreatment thrombocytosis significantly predicted unfavorable survival. Heng and Benjapibal[10] reported that thrombocytosis was not a prognostic factor of EnCa in the multivariate analysis. Against this background, we performed a comprehensive and quantitative evaluation of the literature about the relationships between pretreatment thrombocytosis and survival and clinicopathological features in EnCa.

Methods

The study was performed according to the PRISMA statement.[11]

Search strategy

Our search was restricted to the English and Chinese using databases from PubMed, Embase, SpringerLink, ScienceDirect and China National Knowledge Infrastructure up to July 15, 2018. Both medical subject heading (Mesh) terms and free-text terms included EnCa, thrombocytosis and prognosis. The full search strategy is available in the Supplementary materials. The bibliographies of the retrieved articles were also manually scrutinized for potential related articles.

Selection criteria

The criteria for inclusion were as follows: 1) prospective or retrospective studies analyzed the relationship between thrombocytosis and clinicopathological factors or prognosis of EnCa; 2) the cutoff values of thrombocytosis were reported; and 3) the most complete study was included if multiple studies described the same cohorts studies were excluded based on the following criteria: (1) studies for the lack of information for further analysis; (2) laboratory articles; and (3) non-research articles (abstracts, letters, comments or reviews).

Definitions and data extraction

Overall survival (OS) was defined as the interval between the initial surgical procedure and the death or the last follow-up. Cancer/disease-specific survival (DSS) was defined as the time from initial diagnosis to date of death attributed to EnCa. Disease-free survival (DFS) was measured from the day of surgery to the time of local/distant disease progression or the date of last follow-up. The following data were collected: (1) publication details: first author's surname, publication year, country of study, age and sample size; (2) study design: study type (prospective/retrospective study), cutoff points; (3) patients characteristics (patients number and age); and (4) follow-up data (median/mean follow-up duration, survival analysis).

Quality assessment

The Newcastle-Ottawa Scale (NOS) criterion[12] was used to evaluate the quality of the included studies (Table S1). The scores were judged based on the three aspects of NOS, namely, selection, comparability and outcomes. Studies achieving scores ≥6 were defined as high quality (Table S2).

Statistical analyses

For the quantitative aggregation of results, pooled OR with 95% CI were used to evaluate the association of thrombocytosis with clinicopathological features of patients. The HR with 95% CI were used to analyze postoperative OS, cancer/DSS, or DFS, which was directly retrieved from each of included article. Pooled OR and HR were calculated using random-effect model. Heterogeneity was performed by using chi-square-based Q-test. The I^2 value indicated the degree of heterogeneity. A P-value <0.10 or I^2>50% indicated significant heterogeneity. All statistical analyses were carried out by Review Manager 5.3 (Cochrane Collaboration, London, UK).

Results

Characteristics of included studies

The detail search process is shown in Figure 1. The initial search retrieved a total of 339 published studies. Out of which, 146 studies were excluded due to duplicate records. After screening titles and abstracts, we removed 162 publications including 148 irrelevant studies and 14 reports without clinical specimens. Further evaluating, finally, we included 10 studies in the final meta-analysis.[9,10,13–20] Sample sizes ranged from 68 to 1166 patients. All included studies including 2995 patients were counted for the incidence of thrombocytosis ranged from 2.3% to

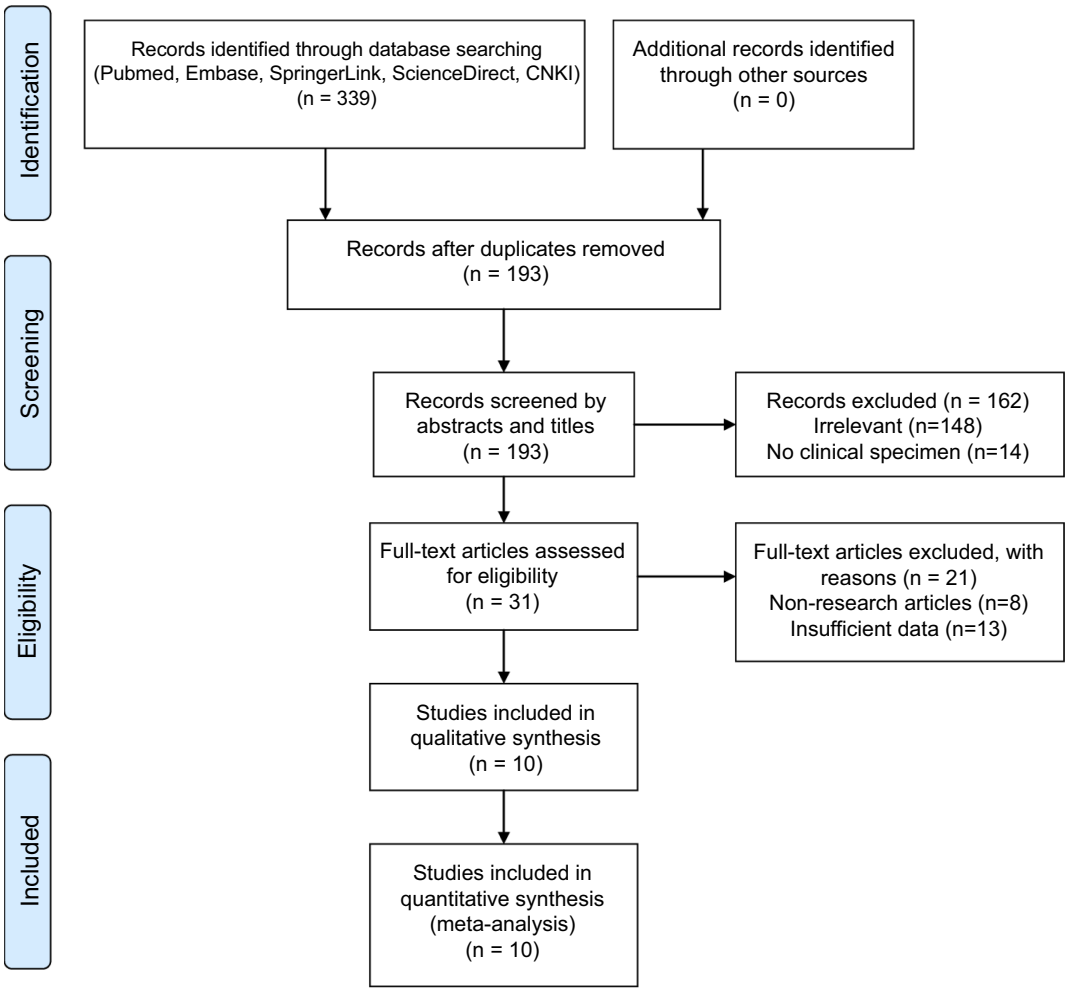

Figure 1 Flow diagram of the search strategy.

18.2%. The study by Njølstad et al[15] was a prospective study. The remaining studies were retrospective. All the included studies did not report the methods to measure pretreatment thrombocytosis in detail. Three studies[10,16,19] stated that platelet count in each case was obtained within 14 days before surgery. The detailed characteristics of eligible studies are described in Table 1.

Correlation of preoperative thrombocytosis and clinicopathological feature

Four studies[9,10,13,17] involving 1133 patients reported the association of FIGO stage with preoperative thrombocytosis. The pooled OR revealed that patients with preoperative thrombocytosis were more likely to have high FIGO stage categories (OR 3.45, 95% CI 1.68–7.08, *P*=0.001; Figure 2A). Five studies[9,10,13,15,17] including 1261 patients provided information regarding histological grade. The pooled analysis showed that thrombocytosis was linked to high histological grading (pooled OR 2.00, 95% CI 1.22–3.29, *P*=0.006; Figure 2B). Four studies[9,10,15,17] described preoperative thrombocytosis according to histologic subtype and lymph-vascular space invasion (LVSI). The pooled data showed thrombocytosis correlated with LVSI (pooled OR 2.04, 95% CI 1.35–3.07, *P*=0.001; Figure 2C), but there were no significant associations of histologic subtype (pooled OR 0.79, 95% CI 0.39–1.60, *P*=0.52; Figure 3A). The combined results showed that thrombocytosis was significantly associated with cervical involvement (pooled OR 2.54, 95% CI 1.56–4.15, *P*=0.000; Figure 3B) and myometrial invasion (pooled OR 2.14, 95% CI 1.39–3.32, *P*=0.001; Figure 3C) and in three studies.[9,10,15] The pooled OR revealed that preoperative thrombocytosis was associated with lymph node metastasis (OR 3.15, 95% CI 1.71–5.80, *P*=0.001 Figure 3D) by analyzing two studies.[9,10]

Table 1 Baseline characteristics of studies included in the meta-analysis

Study (year)	Study period	Country	Study design	Participants	Mean/median age (years)	Cutoff value	Outcomes	Incidence	NOS score	Variable type	Median follow-up (months)
Abu-Zaid et al[13] 2017	2010–2013	Saudi Arabia	R	162	59	>400×10^9/L	OS, DFS	8.6%	7	Multi	NR
*Andersen et al[14] 2015	2000–2010	Denmark	R	218	NR	400–550×10^9/L	OS, DSS	9.2%	6	Multi	NR
*Andersen et al[14] 2015	2000–2010	Denmark	R	218	NR	>550×10^9/L	OS, DSS	2.3%	6	Multi	NR
Gücer et al[15] 1998	1987–1991	Austria	R	135	64	>400×10^9/L	OS	14%	7	Multi	53 (1–124)
Gorelick et al[16] 2009	1998–2006	USA	R	77	65.5	>400×10^9/L	OS, DFS	18.2%	6	Multi	NR
Heng and Benjapibal[10] 2014	2005–2008	Thailand	R	238	57.88	>400×10^9/L	OS, DFS	18.06%	8	Multi	59.6 (1–98)
Kizer et al[17] 2015	1999–2009	USA	R	318	NR	>400×10^9/L	DFS, DSS	16.7	8	Multi	25.6 normal group 23.1 thrombocytosis group
Lerner et al[19] 2007	1996–2004	USA	R	68	NR	>400×10^9/L	OS, DFS	12%	8	Multi	NR
Moeini et al[20] 2016	2000–2013	USA	R	714	53.1	>400×10^9/L	DFS, OS	11.1%	7	Multi	28.8
Njølstad et al[18] 2013	2001–2011	Norway	P	557	66.2	>390×10^9/L	DSS	12.1%	9	Multi	55 (0–97)
Takahashi et al[9] 2017	2000–2010	Japan	R	508	58	>400×10^9/L	OS	6.9%	7	Multi	NR

Note: *Data were from the same study.

Abbreviations: NR, not report; R, retrospective; P, prospective; multi, multivariate analysis; OS, overall survival; DSS, cancer/disease-specific survival; DFS, disease-free survival; NOS, Newcastle-Ottawa Scale.

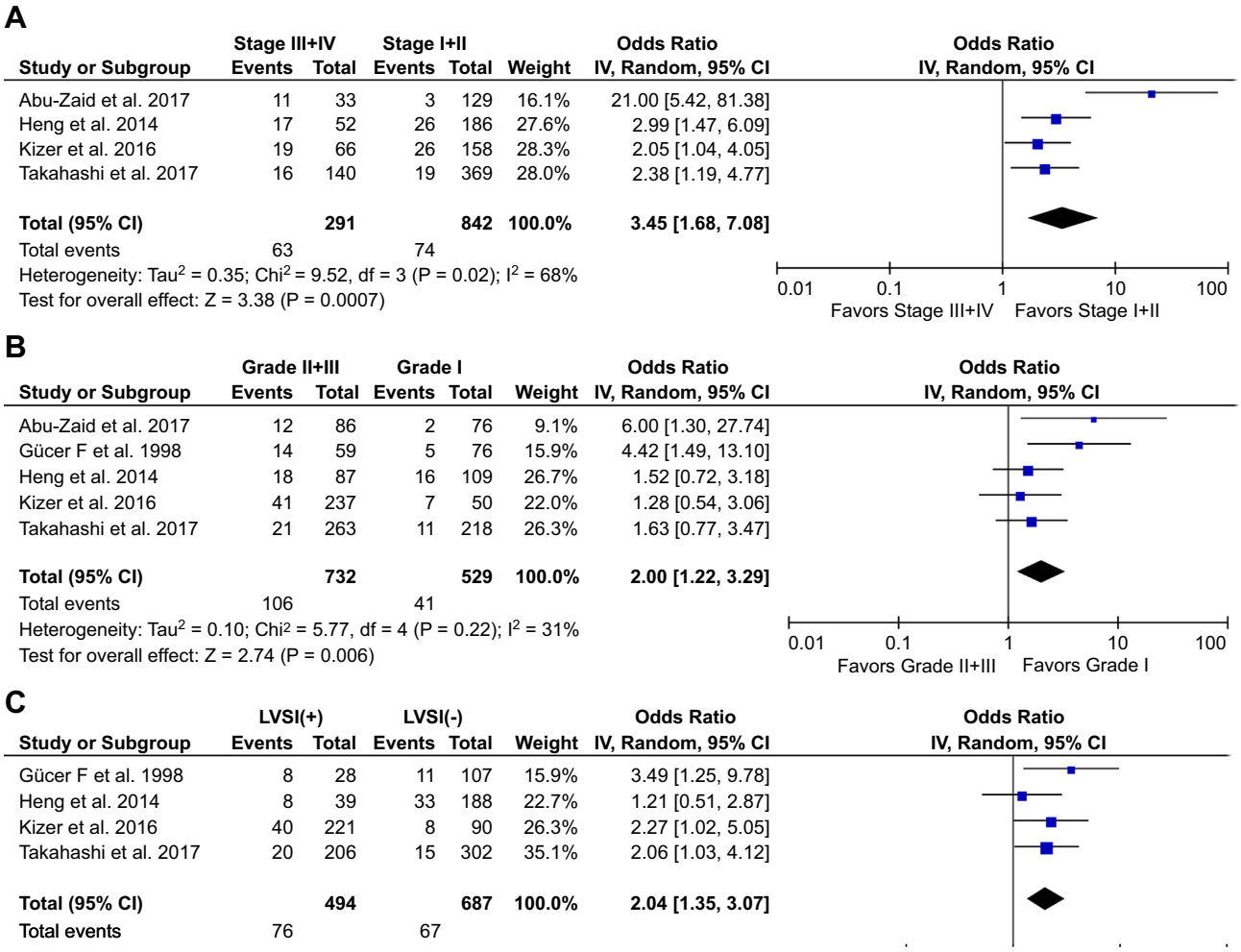

Figure 2 Association of pretreatment thrombocytosis with clinicopathological parameters. (**A**) FIGO stage; (**B**) tumor differentiation; and (**C**) lymph-vascular space invasion.

Impact of preoperative thrombocytosis on survival

As seen in Figure 4, six[9,10,13,16,19,20] of the included studies showed was preoperative thrombocytosis was not associated with OS in EnCa patients (pooled HR =1.65, 95% CI: 0.88–3.11, P=0.012, I^2=82%, Figure 4A). The synthesized data from four studies[10,13,17,20] suggested that thrombocytosis did not correlate with poor DFS (pooled HR =1.66, 95% CI: 0.96–2.89, P=0.07, I^2=59%, Figure 4B). There was no association between preoperative thrombocytosis and DSS (pooled HR =1.37, 95% CI: 0.80–2.36, P=0.25, I^2=40%, Figure 4C). Particularly, Andersen et al[14] divided the preoperative platelet count into two categories of thrombocytosis (mild, platelet count=400–550×10^9/L; severe, platelet count >550×109/L). The study reported that mild and severe preoperative thrombocytosis was all not associated with cancer-specific mortality.

Subgroup and sensitivity analysis

Stratified analysis was conducted to assess the prognostic value of thrombocytosis on OS and DFS according to geographic region, sample size, and NOS score. As shown in Table 2, stratified analysis did not alter the prognostic role of preoperative thrombocytosis on OS, except for the subgroup small sample size (pooled HR =1.88, 95% CI: 1.26–2.80, P=0.002, I^2=0%). However, the EnCa patients with preoperative thrombocytosis showed a significant worse DFS in subgroups of Asian patients (pooled HR =2.21, 95% CI: 1.17–4.21, P=0.02, I^2=0%), NOS scores >7 (pooled HR=2.16, 95% CI: 1.34–3.56, P=0.002, I^2=0%). We further performed a sensitivity analysis to gauge the stability of the results. The pooled effects of OS was significantly altered when the study by Heng and Benjapibal[10] was omitted (pooled HR=2.04, 95% CI=1.11–3.73, P=0.02, Table 3). When the study by Moeini et al[20] was removed, the pooled results for

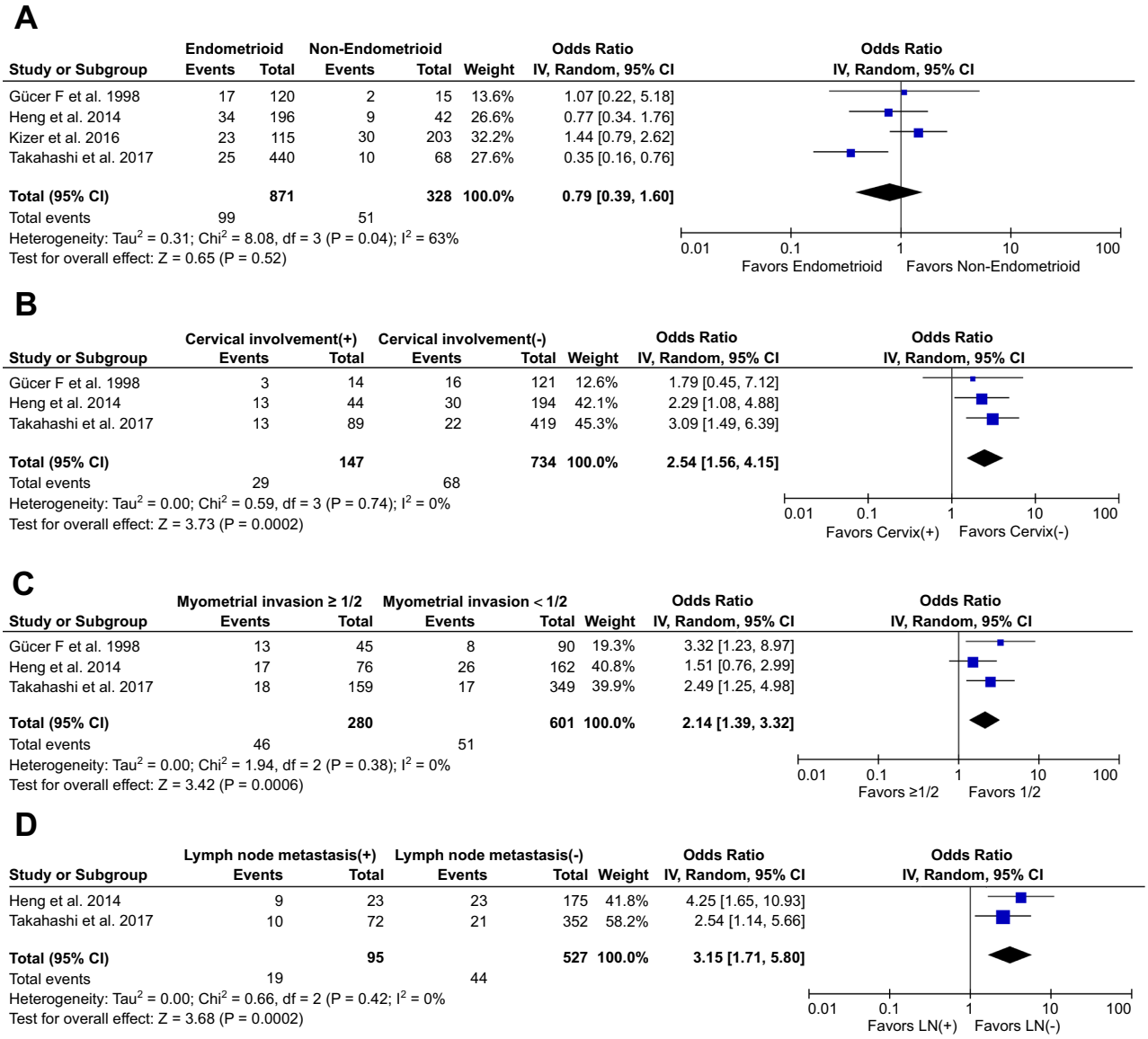

Figure 3 Association of pretreatment thrombocytosis with clinicopathological factors. (**A**) histologic subtype; (**B**) cervical involvement; (**C**) myometrial invasion; and (**D**) lymph node metastasis.

DFS were significantly altered (pooled HR=2.23, 95% CI=1.45–3.42, *P*=0.000, Table 3). We did not evaluate publication bias since the number of included studies was limited.

Discussion

Thrombocytosis in cancer patients is a common finding and preoperative thrombocytosis has a strong connection to cancer outcomes.[21,22] However, conflicting studies exist regarding the prognostic effects of thrombocytosis on EnCa patients.[9,10] So we performed the meta-analysis to reassess the association of preoperative thrombocytosis with clinicopathological factors and prognosis of EnCa. In the current study, the pooled effects indicated that preoperative thrombocytosis was positively correlated with high FIGO stage, high histological grading, LVSI, myometrial invasion, cervical involvement and lymph node metastasis in EnCa patients. Nonetheless, preoperative thrombocytosis was not associated with poor OS, DFS, and DSS (all included studies were used multivariate analysis). According to NOS quality assessment, all included studies were high quality and the scores of ranged from 6 to 9 (median 7). So we defined the cutoff value of NOS quality as 7 when performing stratification analysis. EnCa patients with preoperative thrombocytosis showed a reduced DFS in subgroups of Asian patients and studies with NOS scores larger than 7.

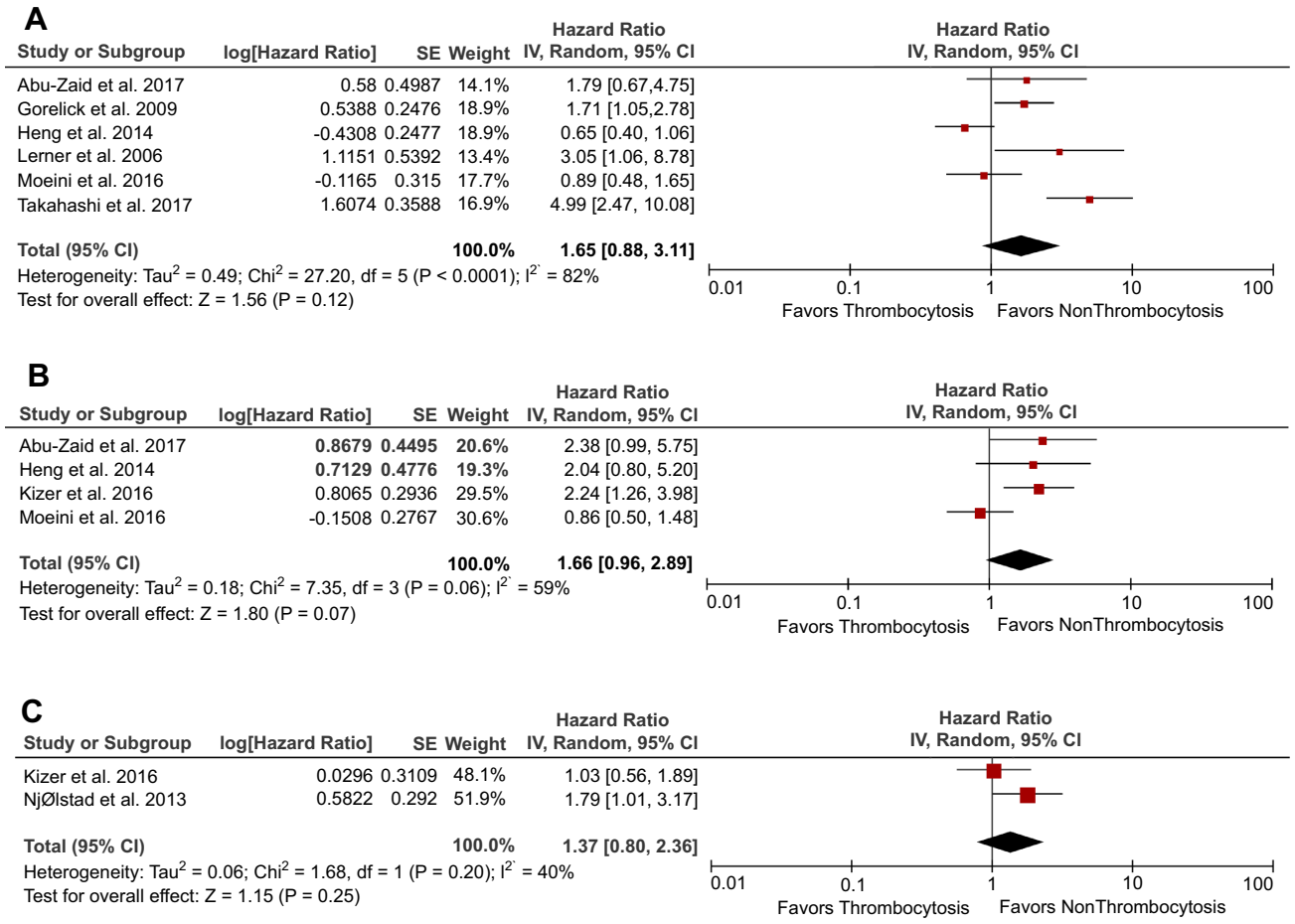

Figure 4 The association between thrombocytosis and survival outcomes (all multivariate analysis). (**A**) overall survival; (**B**) disease-free survival; and (**C**) cancer/disease-specific survival.

Table 2 Subgroup analyses for OS and DFS

Subgroups	N	Pooled OS			I^2	N	Pooled DFS			I^2
		HR	95% CI	*P*-value			HR	95% CI	*P*-value	
Geographic region										
Asian	3	1.77	0.46–6.79	0.41	91%	2	2.21	1.17–4.21	0.02	0%
Non-Asian	3	1.52	0.83–2.79	0.17	58%	2	1.38	0.54–3.53	0.50	82%
NOS score										
≤7	4	1.90	0.94–3.81	0.07	77%	2	1.35	0.50–3.63	0.56	73%
>7	2	1.31	0.29–5.91	0.73	85%	2	2.18	1.34–3.56	0.002	0%
Sample size										
Small (≤200)	3	1.88	1.26–2.80	0.002	0%	1	2.38	0.99–5.75	0.05	NA
Large (>200)	3	1.39	0.44–4.45	0.57	91%	3	1.52	0.77–3.00	0.22	68%

Abbreviations: DFS, disease-free survival; NOS, Newcastle-Ottawa Scale; OS, overall survival.

The prognosis remains dismal for patients with recurrent or metastatic EnCa. In order to improve survival, it is imperative that we identify the tumors with aggressive behaviors and treat them appropriately. Recently, studies have been reported that circulating biomarkers can predict the course of EnCa. Indices of systemic inflammation such as elevated platelet/lymphocyte ratio, platelet count and platelet volume have shown potential for prognostic

Table 3 Sensitivity analysis for OS and DFS

Outcomes	Study omitted	Pooled results		
OS		HR	95% CI	*P*-value
	Abu-Zaid et al[13] 2017	1.64	0.80–3.38	0.18
	Gorelick et al[16] 2009	1.66	0.73–3.79	0.23
	Heng and Benjapibal[10] 2014	2.04	1.11–3.73	0.02
	Lerner et al[19] 2007	1.50	0.75–3.00	0.25
	Moeini et al[20] 2016	1.90	0.89–4.04	0.10
	Takahashi et al[9] 2017	1.27	0.75–2.16	0.37
DFS	Abu-Zaid et al[13] 2017	1.52	0.77–3.00	0.22
	Heng and Benjapibal[10] 2014	1.60	0.79–3.22	0.19
	Kizer et al[17] 2015	1.49	0.74–3.00	0.27
	Moeini et al[20] 2016	2.23	1.45–3.42	0.000

Abbreviations: DFS, disease-free survival; OS, overall survival.

surveillance.[23,24] In addition, such circulating markers are readily monitored by relatively noninvasive means. Therefore, it is of great clinical significance to identify new circulating markers, combining with the established clinicopathologic prognostic factors, to improve the outcomes of patients with EnCa.

The mechanisms by which preoperative thrombocytosis correlates clinicopathological features of EnCa patients remains to be not fully elucidated. Several studies which put forward to plausible hypotheses may explain the correlations. Platelets can infiltrate into tumor tissue and contribute to tumor growth by secreting pro-angiogenic and pro-tumorigenic factors including vascular endothelial growth factor, insulin-like growth factor 1 and 2 .[25] Platelet-tumor cell adhesion established a pro-metastatic microenvironment that protects cancer cells from immune surveillance.[26] Orellana et al[27] found that platelets acted as chemo-attractants to facilitate cancer cells migration through co-cultivating cancer cells with human platelets. The authors concluded that platelet–cancer interactions contributed to the cancer metastasis. On the one hand, a variety of tumor-related cytokines stimulates thrombopoiesis in cancer. Among them are IL-1, IL-6, and thrombopoietin (TPO).[28] Stone et al[29] established mouse models of ovarian cancer and demonstrated that tumor-derived IL-6 stimulates hepatic production of TPO, which stimulates megakaryocyte growth and thrombopoiesis. In addition, Inhibition of IL-6 by neutralizing antibody reduced tumor growth and enhanced the therapeutic efficacy of paclitaxel. Recently, Guillem-Llobat et al[30] reported that low-dose aspirin which inhibits platelet activation prevented colorectal cancer metastasis in mice. Other antiplatelet agents such as heparinoids may be beneficial for cancer patients.

Limitations

Certain limitations exist in the current study. First, the cutoff point of preoperative thrombocytosis is still not established. Most of the included studies set cutoff point as platelet count >400×10^9/L, but Njølstad et al[18] report thrombocytosis as platelet count >390×10^9 platelets/L, which may lead to inter-study heterogeneity. Besides, the majority of included studies were retrospective, so the possibility of selection bias cannot be ruled out. Second, several disease conditions such as inflammatory hematological diseases may affect platelet count, but some included studies did not control these confounding factors. Third, the sample size of the included studies ranged from 68 to 714, which may result in between-study heterogeneity. The limited number of included studies might impact the validity of our analysis, so further studies are warranted. These limitations may also contribute to the conflicting results of the prognostic significance of thrombocytosis in EnCa. Besides, a study by Oge T et al[24] reported that platelet volume can be used as a parameter for platelet activation and prediction of advanced-stage EnCa. All included studies highlighted on platelet count, rather than function. Thus, the association of platelet volume with the survival of EnCa deserves further investigation.

Conclusion

In summary, the current meta-analysis shows that preoperative thrombocytosis is correlated with high FIGO stage, poor tumor differentiation, LVSI, myometrial invasion, cervical involvement, and lymph node metastasis. No significance was found between thrombocytosis and OS, DFS, and DSS. However, further studies are needed to update our results.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Newcastle-Ottawa quality assessment scale

Selection
(1) Representativeness of the exposed cohort
(a) Truly representative of the average "endometrial cancer patient" in the community (1 star)
(b) Somewhat representative of the average 'endometrial cancer patient in the community (1 star)
(c) Selected group of users (eg, nurses, volunteers)
(d) No description of the derivation of the cohort
(2) Selection of the non-exposed cohort
(a) Drawn from the same community as the exposed cohort (1 star)
(b) Drawn from a different source
(c) No description of the derivation of the non-exposed cohort
(3) Ascertainment of exposure
(a) Secure record (eg, surgical records) (1 star)
(b) Structured interview (1 star)
(c) Written self-report
(d) No description
(4) Demonstration that outcome of interest was not present at start of study
(a) Yes (1 star)
(b) No
Comparability
(1) Comparability of cohorts on the basis of the design or analysis
(a) Study controls for confounder factor (factors that may affect hematologic parameters) (1 star)
(b) Study controls for any additional factor (1 star) (age, gender, stage, etc.)
Outcome
(1) Assessment of outcome (death or recurrence or progression)
(a) Independent blind assessment (1 star)
(b) Record linkage (1 star)
(c) Self-report
(d) No description
(2) Was follow-up long enough for outcomes to occur?
(a) Yes (1 star)
(b) No
(3) Adequacy of follow-up of cohorts
(a) Complete follow-up – all subjects accounted for (1 star)
(b) Subjects lost to follow-up unlikely to introduce bias – small number lost "(25%)" or description provided of those lost (1 star)
(c) Follow-up rate less than "75%" and no description of those lost
(d) No statement

Notes: Reproduced with permission from Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in metaanalyses. Ottawa Hospital Research Institute. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.[1]

Table S2 Assessment of Newcastle-Ottawa Scale methodological quality of cohort studies

Study[a]	Selection				Comparability	Outcome			Score[b]
	Representativeness of the exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Outcome not present at start		Assessment of outcome	Follow-up length	Follow up adequacy	
Abu-Zaid et al[2] 2017	⋆	⋆	⋆	-	⋆⋆	⋆	-	⋆	7
Andersen et al[3] 2015	⋆	⋆	⋆	-	⋆⋆	⋆	-	-	6
Gücer et al[4] 1998	⋆	⋆	⋆	-	⋆⋆	-	⋆	⋆	7
Gorelick et al[5] 2009	⋆	⋆	-	-	⋆⋆	⋆	-	⋆	6
Heng and Benjapibal[6] 2014	⋆	⋆	⋆	-	⋆⋆	⋆	⋆	⋆	8
Kizer et al[7] 2015	⋆	⋆	⋆	-	⋆⋆	⋆	⋆	⋆	8
Lerner et al[8] 2007	⋆⋆	⋆	⋆		⋆⋆	⋆	-	⋆	8
Moeini et al[9] 2016	⋆	⋆	-	-	⋆⋆	⋆	⋆	⋆	7
Njølstad et al[10] 2013	⋆	⋆	⋆	⋆	⋆⋆	⋆	⋆	⋆	9
Takahashi et al[11] 2017	⋆	⋆	⋆	-	⋆⋆	⋆	-	⋆	7

Notes: [a]Newcastle-Ottawa Quality Assessment Scale: a study can have one star (*) for meeting each criterion, except that comparability (design or analysis) can have a maximum of two stars. For comparability in this study: one star if controlled for age; two stars if also controlled for other important variables such as age, histology, stage, etc. [b]Quality evidence score, study met criteria for selection (four items), comparability (one star; upgraded a level for two stars), and outcome assessment.

Search strategy

PubMed:

#1: Search ((((((((((((((((((Endometrial Neoplasm[Title/Abstract]) OR Neoplasm, Endometrial[Title/Abstract]) OR Neoplasms, Endometrial[Title/Abstract]) OR Endometrial Carcinoma[Title/Abstract]) OR Carcinoma, Endometrial [Title/Abstract]) OR Carcinomas, Endometrial[Title/Abstract]) OR Endometrial Carcinomas[Title/Abstract]) OR Endometrial cancer[Title/Abstract]) OR Cancer, Endometrial [Title/Abstract]) OR Cancers, Endometrial[Title/Abstract]) OR Endometrial Cancers[Title/Abstract]) OR Endometrium Cancer[Title/Abstract]) OR Cancer, Endometrium[Title/Abstract]) OR Cancers, Endometrium[Title/Abstract]) OR Cancer of the Endometrium[Title/Abstract]) OR Carcinoma of Endometrium[Title/Abstract]) OR Endometrium Carci noma[Title/Abstract]) OR Endometrium Carcinomas[Title/Abstract]) OR Cancer of Endometrium[Title/Abstract]) 38,079

#2: Search (((((((Thrombocytosis[Title/Abstract]) OR Thrombocytoses[Title/Abstract]) OR Thrombocythemia [Title/Abstract]) OR Thrombocythemias[Title/Abstract]) OR Increased platelets[Title/Abstract]) OR Increased platelet[Title/Abstract]) OR platelets count[Title/Abstract]) OR platelet count[Title/Abstract] 29,942

#3: Search ((((((((((((((“Prognosis”[Mesh]) OR Prognosis [Title/Abstract]) OR Prognoses[Title/Abstract]) OR Prognostic[Title/Abstract]) OR Outcome[Title/Abstract]) OR Survival[Title/Abstract]) OR Overall survival[Title/Abstract]) OR OS[Title/Abstract]) OR Cancer-specific survival[Title/Abstract]) OR CSS[Title/Abstract]) OR Progression-free survival[Title/Abstract]) OR PFS[Title/Abstract]) OR Disease-free survival[Title/Abstract]) OR DFS[Title/Abstract]) OR Mortality[Title/Abstract]) OR Recurrence[Title/Abstract] 3,215,415

#4: #1 and #2 and #3 **38**

Embase:

(“thrombocytosis”:ab,ti OR “thrombocytoses”:ab,ti OR “thrombocythemia”:ab,ti OR “thrombocythemias”:ab,ti OR “increased platelets”:ab,ti OR “increased platelet”:ab,ti OR “platelets count”:ab,ti OR “platelet count”:ab,ti) AND [1966-2018]/py 49,707

“prognosis”/exp/mj OR prognosis:ab,ti OR prognoses:ab,ti OR prognostic:ab,ti OR outcome:ab,ti OR survival:ab,ti OR “overall survival”:ab,ti OR os OR “cancer-specific survival”:ab,ti OR css:ab,ti OR “progression-free survival”:ab,ti OR pfs:ab,ti OR “disease-free survival”:ab,ti OR dfs:ab,ti OR mortality:ab,ti OR recurrence:ab,ti 3,462,505

(“endometrial cancer”:ab,ti OR “endometrial neoplasm”:ab,ti OR “neoplasm, endometrial”:ab,ti OR “neoplasms, endometrial”:ab,ti OR “endometrial carcinoma”:ab,ti OR “carcinoma, endometrial”:ab,ti OR “carcinomas, endometrial”:ab,ti OR “endometrial carcinomas”:ab,ti OR “cancer, endometrial”:ab,ti OR “cancers, endometrial”:ab,ti OR “endometrial cancers”:ab,ti OR “cancer, endometrium”:ab,ti OR “cancers, endometrium”:ab,ti OR “cancer of the endometrium”:ab,ti OR “carcinoma of endometrium”:ab,ti OR “endometrium carcinoma”:ab,ti OR “endometrium carcinomas”:ab,ti OR “cancer of endometrium”:ab,ti) AND [1966-2018]/py 31,021

#4: #1 and #2 and #3 **35**

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