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REVIEW

Platelet–lymphocyte ratio as a potential prognostic factor in gynecologic cancers: a meta-analysis

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Abstract

Purpose Cancer-related inflammation plays an important role in tumor development and progression. Platelet–lymphocyte ratio (PLR) has been studied as a biomarker for prognosis in gynecologic cancers. But, the results of previous studies were controversial, so we performed this meta-analysis.

Methods We searched the scientific database of PubMed, Embase, Web of Science, Wanfang, and China National Knowledge Infrastructure (CNKI) using free text and MeSH keywords. Crude HR (hazard ratio) with 95% confidence interval was used to evaluate the risk association between PLR and overall survival (OS) or progression-free survival (PFS) in gynecologic neoplasms.

Results There totally 23 studies, including 6869 patients who were eligible, most of which are published after 2015 or later. PLR greater than the cut-off was associated with poorer survival prognosis in ovarian cancer [OS: HR 1.80 (95% CI 1.37–2.37), $p = 0.000$; PFS: HR 1.63 (95% CI 1.38–1.91), $p = 0.000$] and cervical cancer [OS: HR 1.36 (95% CI 1.10–1.68), $p = 0.005$; PFS: HR 1.40 (95% CI 1.16–1.70), $p = 0.002$], but not in endometrial cancer [OS: HR 1.95 (95% CI 0.65–5.84), $p = 0.234$].

Conclusions The current meta-analysis revealed that pretreatment PLR was a simple, promising prognostic indicator for OS and PFS in ovarian and cervical cancers. But, its significance of prognosis did not agree with endometrial neoplasm. However, due to the limited number of original studies, future large-scale studies with more well-designed, high-quality studies are still needed.

Keywords Platelet–lymphocyte ratio · Ovarian neoplasm · Endometrial neoplasm · Cervical neoplasm · Prognosis · Meta-analysis

Introduction

Cancer-related inflammation has been hypothesized to increase the risk of tumor development and angiogenesis [1, 2]. Tumor-associated inflammatory response, as being a potential and accessible preoperative prognostic marker, is composed of inflammatory cells and a series of inflammatory mediators. These inflammatory mediators often manifests as neutrophilia, thrombocytosis and relative lymphocytopenia in the peripheral blood [3, 4]. As a member of systemic inflammatory response family, lymphocytes and platelets have been noted significant positive relations of carcinogenesis and tumor progression [5, 6]. Alterations in anti-tumor immunity are considered to have significant value in the pathogenesis of gynecologic neoplasms [7, 8]. In recent years, there was increasingly interest in elucidating the significant relationship between the disease load of cancer inflammation and tumor prognosis. As is known to all that inflammatory reaction and immune status have played a pivotal role in tumorigenesis and cancer progression [9–11]. Together, these generate a tumor-related

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inflammatory microenvironment which exert an important value in the pathogenesis and development of tumors [10]. Platelets are associated with the generation of vascular endothelial growth factor (VEGF), which plays an important role in the production of blood vessel and endothelial proliferation [12–14]. Neutrophil–lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR) are mostly easy and readily available tests in the clinic. NLR and PLR can also be considered as a simple marker to predict cancers and premalignant lesions [15–17]. Ethier et al. [18] previously reported that NLR greater than 2.95 were correlated with adverse OS (HR 1.65, 95% CI 1.44–1.89; $p < 0.001$) and EFS (event-free survival) (HR 1.57, 95% CI 1.35–1.82; $p < 0.001$) in gynecologic malignancies. An elevated peripheral PLR has been recognized as an adverse indicator in different cancers. There were many meta-analyses presenting that greater PLR has been considered to increase the risk of mortality in non-small cell lung cancer [19], colorectal cancer [20], breast cancers [21, 22], and esophageal cancer [23]. But until now, there is rare systematical analysis on the prognostic effect of PLR in gynecologic malignancies. Disagreement of prognostic value between PLR and gynecologic cancers is still obvious [24, 25]. Therefore, we systematically searched scientific databases to recognize relevant publications and explore the relationship between preoperative peripheral blood PLR and OS or PFS in gynecologic cancers.

Materials and methods

Data sources and search strategy

Eligible studies were selected by searching PubMed, Embase, and Web of Science databases. We used free text and MeSH keywords as search strategy: [(PLR) or (platelet-to-lymphocyte ratio) or (platelet–lymphocyte ratio) or (platelet–lymphocyte ratio)] AND (cancer or neoplasm or malignancy) AND (outcome or prognosis). All articles were published up to February 28 2019. This meta-analysis was complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [26].

Inclusion and exclusion criteria

The qualified literature should meet the inclusion criteria: (1) studies were investigated the relationship between preoperative peripheral blood PLR and OS or PFS; (2) studied population with ovarian, cervical, and endometrial neoplasms was confirmed by pathology; (3) PLR were collected without any treatments (surgery and/or systemic chemotherapy and/or radiotherapy); (4) PLR assessed by cut-off value or median into different risk strata; (5) studies reported a hazard ratio (HR) with 95% CI for OS or PFS; (6) full articles were published using English or Chinese. Studies were deleted according to exclusion criteria: letters to editor, systematic reviews, case reports or laboratory research. All the eligible studies were evaluated by two reviewers independently and disagreements were reconciled via discussion.

Data extraction

Data were extracted using predesigned abstraction forms as following: the first author name, publication year, country, cancer type, sample of individual qualified study, cut-off value, FIGO stage, follow-up time, outcome of interests, HR for OS or PFS with corresponding 95% CI or p value.

There were three methods to extract HRs according to the report in previous publications [27, 28]. First and foremost, the HRs were directly acquired from the original article or indirectly calculated from the O–E statistic and variance. Second, the estimate was calculated using the relevant data, such as the number of patients at risk in each group, the number of events, and the log-rank statistics or its p value. Third, when these data were also unavailable, the HR was determined by the Kaplan–Meier survival curves under the assumption that the rate of patients with censored data was constant during the follow-up. We calculated an approximate HR by extracting several survival rates at specified times from survival curves using the Engauge Digitizer version 4.1 (https://digitizer.sourceforge.net/, free downloaded software).

Study quality score

In this meta-analysis, the quality assessment for the non-randomized studies was evaluated by two reviewers independently based on the Newcastle–Ottawa quality assessment scale (NOS) [29]. The assessed items included selection (four stars maximum), comparability (two stars maximum), and the ascertainment of outcome of interests (three stars maximum). In this scale, studies were awarded a maximum score of 9 points; a moderate-to-high-quality study with low risk of bias was awarded 7 or greater score, and those with a NOS value less than 7 points were considered poor-quality studies with high risk of bias. This cut-off value was evaluated by the distribution of relative quality scores of all the eligible studies.

Data synthesis and statistic analysis

We used STATA SE12.0 (STATA Corporation, College Station, Texas, USA) to pool the extracted data into this meta-analysis. Hazard ratios with 95% CI were collected from individual studies, then combined using random or fixed effects model, and finally presented in forest plots. Statistical heterogeneity was quantified by I^2 statistics

[30]. A random effects modeling based on the DerSimonian and Laird method would be used [31] with prominent heterogeneity ($I^2 > 50\%$ or p for heterogeneity < 0.1); on the contrast ($I^2 < 50\%$ and p for heterogeneity > 0.1), a fixed effects model using the Mantel–Haenszel method was adopted [32]. Risk of publication bias was assessed by visual inspection of Begg's funnel plot and Egger's linear regression test. All statistical tests were two-sided, and $p < 0.05$ were statistically significant.

Results

Study selection

As shown in Fig. 1, through the electronic searching on PubMed, Web of Science, Embase, Wang Fang, and CNKI, 1919 potential articles were screened. Records after excluding duplicate studies were 1055. Then, the titles and abstracts were screened, and 1023 publications were removed as irrelevant, not for gynecologic neoplasms, non-English studies, reviews, and meta-analysis. Finally, 32 full-text articles were identified for qualification, and 9 ineligible papers were eliminated, because it did not provide primary outcome measurements (OS and/ or PFS) or PLR which is not pretreatment. In the final, a total of 23 studies with 6869 cases were eligible for the current meta-analysis [33–55].

Study characteristics

The main characteristics of included studies are presented in Table 1. In this study, all necessary data were extracted from 23 studies, which were consisted of multiple countries including China (11 studies), Japan (4 studies), United Kingdom (2 studies), Thailand (2 studies), Turkey (2 studies), Italy (1 study), and Korea (1 study). All included studies were retrospective studies, and more than half of the studies were published in 2015 or later. Among these articles, ten studies were reported about cervical cancers, ten studies were reported about ovarian cancers, and three studies were reported about endometrial cancers. There were 7 studies that were reported disease stage at early (I–II), and 15 studies were reported in mixed stage (I–IV) according to International Federation of Gynaecology and Obstetrics (FIGO) Criteria. The cut-off points for PLR were calculated by ROC curves according to maximum joint sensitivity and specificity or the median cut-off values. Among the 23 eligible studies, 16 studies were scored more than 7 based on NOS, and general details about NOS score are displayed in Table 2.

PLR and OS

The pooled results indicated that PLR more than cut-off value was correlated with negative OS in ovarian cancers [HR 1.80 (95% CI 1.37–2.37), $p = 0.000$] and cervical cancers [HR 1.36 (95% CI 1.10–1.68), $p = 0.005$], but no significant association in endometrial cancers [HR 1.95 (95% CI

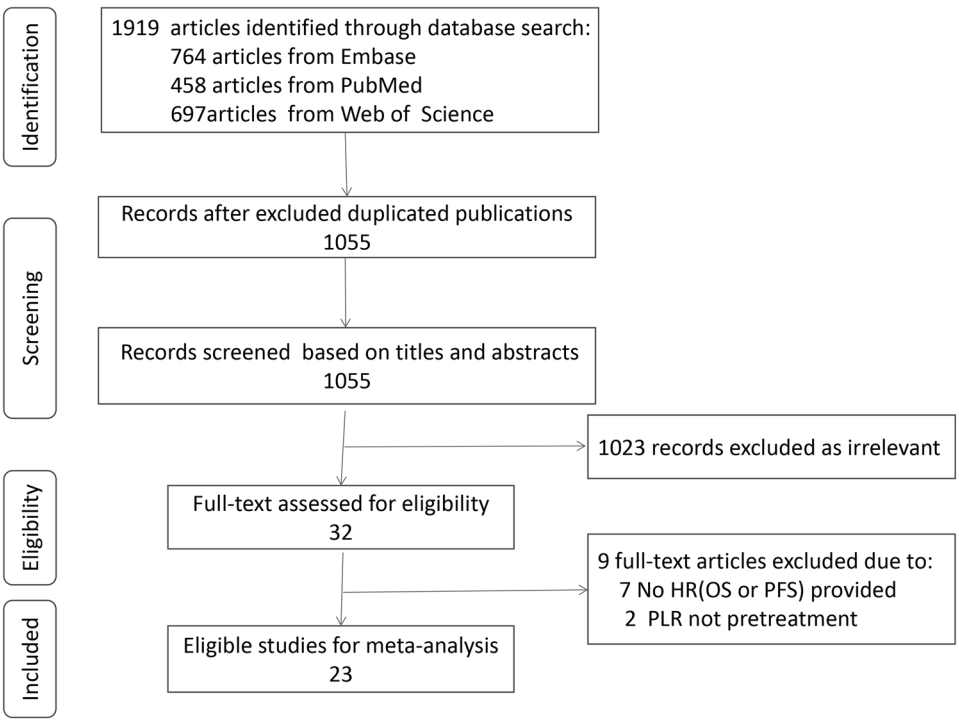

Fig. 1 The flowchart of included studies

Table 1 Characteristics of included studies

Authors	Year	Country	Cancer type	Sample size	Cut-off value	Outcome	FIGO stage	Treatment	Follow-up time (months)
Li et al.	2015	China	Endometrial	282	250	OS	I–II	S + CT	< 60
Li et al.	2017	China	Ovarian	654	273	OS	I–IV	S + CT	< 60
Hu et al.	2016	China	Ovarian	103	188	OS	I–IV	S	< 60
Onal et al.	2016	Turkey	Cervical	235	133	OS, PFS	I–IV	S + CRT	< 60
Chen et al.	2016	China	Cervical	407	143	OS	I–II	S + CRT	≥ 60
Zhou et al.	2014	China	Cervical	75	123	OS	I–II	S + CT	< 60
Miao et al.	2016	China	Ovarian	344	207	OS, PFS	I–IV	S + CT	≥ 60
Wang et al.	2016	China	Ovarian	143	201	OS, PFS	I–IV	S	≥ 60
Wang et al.	2013	China	Cervical	111	142	OS, PFS	I–II	S + CT	≥ 60
Asher et al.	2011	UK	Ovarian	235	300	OS	I–IV	S + CT	< 60
Zhang et al.	2014	China	Cervical	460	150	OS, PFS	I–II	S + RT	≥ 60
Zhang et al.	2015	China	Ovarian	190	203	OS, PFS	I–IV	S + CT	< 60
Zheng et al.	2016	China	Cervical	795	128	OS	I–II	S + CRT	≥ 60
Supoken et al.	2014	Thailand	Ovarian	36	300	PFS	I–IV	S + CT	< 60
Cummings et al.	2015	UK	Endometrial	605	240	OS	I–IV	S + CRT	≥ 60
Raungkaewmanee et al.	2012	Thailand	Ovarian	166	200	OS, PFS	I–IV	S + CT	< 60
Haraga et al.	2016	Japan	Cervical	95	171/172	OS, PFS	I–IV	CRT	≥ 60
Haraga et al.	2016	Japan	Cervical	36	128/130	OS, PFS	I–IV	RT	≥ 60
Kozasa et al.	2017	Japan	Cervical	684	125	OS, PFS	I–IV	S/RT	NA
Wang et al.	2017	China	Cervical	129	149	OS	I–II	S	≥ 60
Lee et al.	2017	Korea	Cervical	145	170	PFS	I–IV	S + CRT	< 60
Haruma et al.	2015	Japan	Endometrial	320	175	OS	I–IV	S + CT	≥ 60
Farolfi et al.	2018	Italy	Ovarian	375	169	PFS	III–IV	CT + B	NA
Ceran et al.	2019	Turkey	Ovarian	244	231	OS	I–IV	S	≥ 60

OS overall survival, *PFS* progression-free survival, *S* surgery, *CT* chemotherapy, *CRT* chemoradiotherapy, *RT* radiotherapy, *B* bevacizumab

0.65–5.84), $p = 0.234$]. Meanwhile, prominent heterogeneity [*P* for heterogeneity (P_h) < 0.1, $I^2 = 85.3\%$] between studies was observed in endometrial cancers (Fig. 2). Analysis of sensitivity was performed by omitting one study at a time to measure its effect on pooled HRs. Deletion of the study by Li et al. [45] significantly reduced the heterogeneity in the analysis of high PLR expression and OS. No other individual study influenced the results (Fig. 3). Publication bias was investigated by Begg's funnel plots and Egger's test. The *p* values for the Begg's test and Egger's test were $p = 0.695$ and $p = 0.410$, respectively. Visual inspection of the Begg's funnel plot was almost symmetry (Fig. 4), suggesting no evidence of publication bias.

PLR and PFS

The results indicated that higher PLR was correlated with adverse PFS in ovarian cancers [HR 1.63 (95% CI 1.38–1.91), $p = 0.000$] and cervical cancers [HR 1.40 (95% CI 1.16–1.70), $p = 0.002$] (Fig. 5). No heterogeneity existed in ovarian cancers ($I^2 = 15.9\%$, $P_h = 0.312$) and cervical cancers ($I^2 = 18.2\%$, $P_h = 0.291$) between the studies, and thus, the fixed effect modeling was adopted. Sensitivity analysis for the effect of the pooled result showed that none of the individual studies substantially altered the combined HRs, suggesting that the conclusion was reliable (Fig. 6). Begg's funnel plots were almost symmetry when all data were viewed on a funnel plot (Fig. 7). Egger's tests also showed that no significant publication bias existed. The *p* values for Begg's test and Egger's test were $p = 0.127$ and $p = 0.121$, respectively.

Discussion

Inflammation has previously been recognized to be an important factor in the development of tumor in humans [56]. PLR was considered as an accurate, readily obtained and low-cost indicator to evaluate patient status and prognosis, which could allow patients and physicians to make sensible decisions in the treatment process before clinical

Table 2 Details about NOS scores of eligible studies

First author, year	Representativeness of exposed cohort	Selection of unexposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Comparability based on the design or analysis	Ascertainment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up	Total quality scores
Wang (2013)	–	–	*	*	**	*	*	*	7
Li (2015)	–	–	*	*	**	*	*	*	7
Li (2017)	–	–	*	*	**	*	*	–	6
Zhang (2014)	–	–	*	*	**	*	*	*	7
Asher (2011)	–	–	*	*	**	*	*	*	7
Raungkaewmanee (2012)	–	–	*	*	**	*	*	*	7
Onal (2016)	*	*	*	*	**	*	*	*	9
Zheng (2016)	–	–	*	*	**	*	*	*	7
Chen (2016)	–	–	*	*	**	*	*	*	7
Cummings (2015)	*	*	*	*	**	*	*	–	8
Miao (2016)	*	*	*	*	–	*	*	–	6
Zhang (2015)	*	*	*	*	**	*	*	–	8
Supoken (2014)	–	–	*	*	**	*	*	–	6
Wang (2016)	–	–	*	*	**	*	*	*	8
Hu (2016)	–	–	*	*	**	*	*	*	7
Zhou (2014)	–	–	*	*	*	*	*	*	6
Haraga (2016)	–	–	*	*	*	*	*	*	6
Haraga (2016)	–	–	*	*	*	*	*	*	6
Kozasa (2017)	–	*	*	*	**	*	–	–	6
Wang (2017)	–	–	*	*	**	*	*	*	7
Lee (2017)	–	*	*	*	**	*	*	*	8
Haruma (2015)	–	–	*	*	**	*	*	*	7
Farolfi (2018)	*	*	*	*	**	*	–	–	7
Ceran (2019)	–	*	*	*	**	*	*	*	8

Asterisk represents a point

intervention. The preoperative high PLR has been previously hypothesized to be associated with negative survival endpoints of several types of cancer [57]. However, people were confused about the link between great PLR and adverse outcome in cancer patients. Research has discovered that platelets can produce inflammatory cytokines and chemokines leading to tumor progression [56]. Platelets can promote angiogenesis through the cytokine VEGF which contributes to tumor growth [14]. IL-6 can stimulate the differentiation of megakaryocytes to platelets and participate in recruitment of neutrophils [58]. Several studies have shown that IL-6 can stimulate thrombopoietin production and can lead to increase of platelet counts in cancer patients [59].

Here, in the current meta-analysis, we explored the significant prognostic role for PLR on both OS and PFS in patients with gynecologic neoplasms. We identified 23 studies with 6869 patients who underwent platelet–lymphocyte ratio testing to determine OS or PFS. The pooled HRs for OS maintained the significant prognostic effect for cervical and ovarian cancers, but not for endometrial cancers. The reason for the above result may be that few studies about endometrial cancers have been included. The pooled HRs for PFS were associated with ovarian cancers and cervical cancers. Sensitivity analysis found that the combined HRs of the PFS were credible, and there was no the risk of publication bias by Begg's funnel plot and the Egger's linear regression test. Taken together, greater PLR

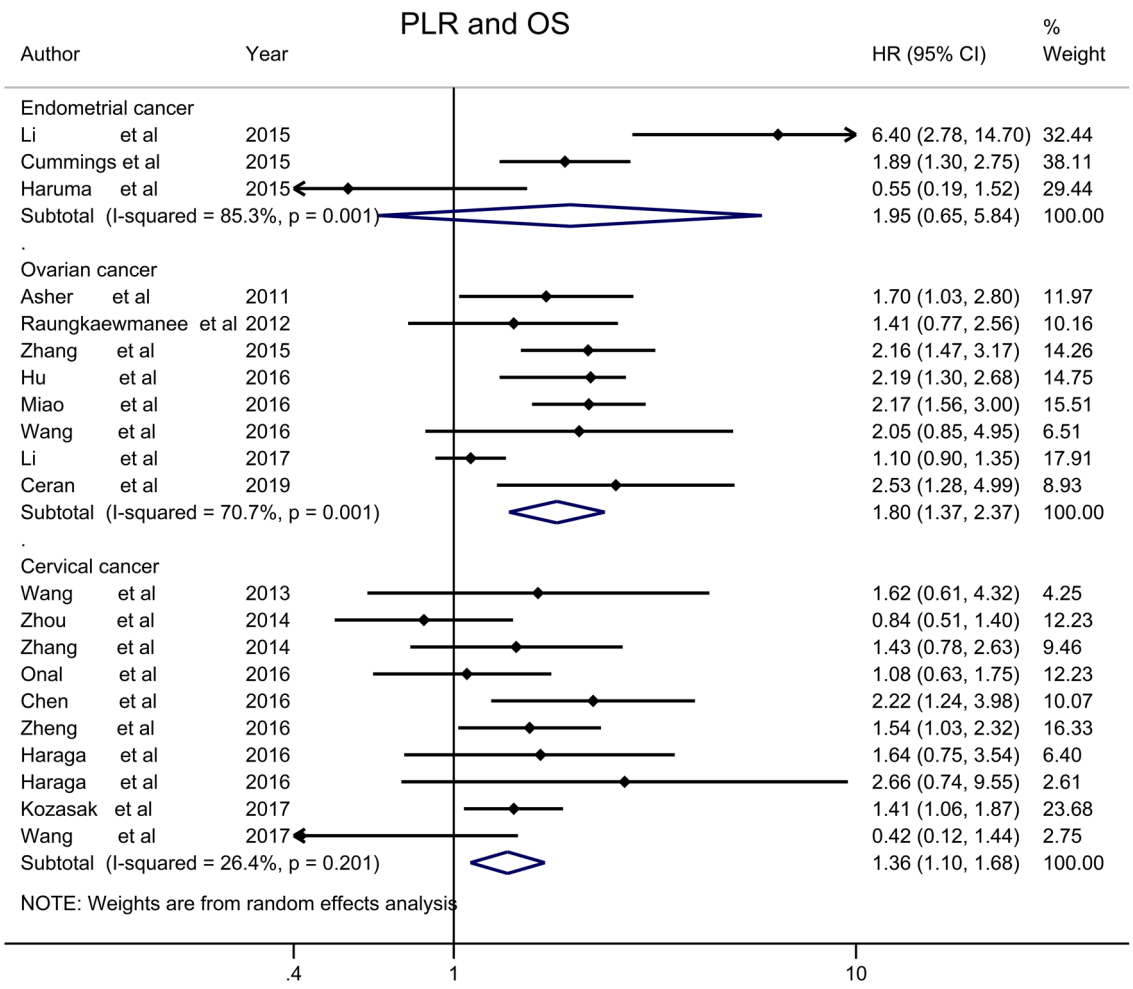

Fig. 2 Meta-analysis higher PLR was associated with worse OS

tends to be related to negative OS and PFS in cases with ovarian cancers and cervical cancers. The results, however, need to be further studied.

In recent years, lots of studies discovered that a systemic inflammatory response could contribute to the growth of tumor [10, 56, 60, 61]. Inflammation is a sign of tumor [3], and the relationship between host tumor and inflammatory cells or mediators is very sophisticated in the microenvironment [10, 11]. Fortunately, there are widely used indicators that not only can assess systemic inflammation, but also can be a prognostic marker in tumors. There were meta-analyses indicated that high level of C-reactive protein (CRP) was inclined to great risk of cancers [62, 63]. Greater NLR was associated with negative prognostic effect in patients with gastrointestinal cancers [64] and pancreatic cancers [65]. PLR may prove to be a readily available and cost-effective biomarker with patient stratification and individual prognostic risk assessment in solid tumors including gynecologic cancers. But more evidences are needed to confirm through larger, prospective, randomized clinical trials of gynecologic cancers, especially for endometrial cancers.

Strengths and limitations

We systematically searched 5 electronic engines aggregating data from 23 gynecologic cancer studies with more than 6800 patients. All included studies were assessed by NOS quality scale on methodological, and the quality of each study was more than 6 scores. We first reported the pooled results of PLR for OS and PFS in gynecologic cancers. The findings displayed that greater PLR was obviously associated with adverse OS and PFS in ovarian and cervical cancers. Though the meta-analysis showed that PLR had an important role in predicting survival outcome in gynecologic cancers, there were several limitations. First, eligible publications in this meta-analysis were limited to articles published in English or Chinese. There could be publication bias. Second, the included study number was small and

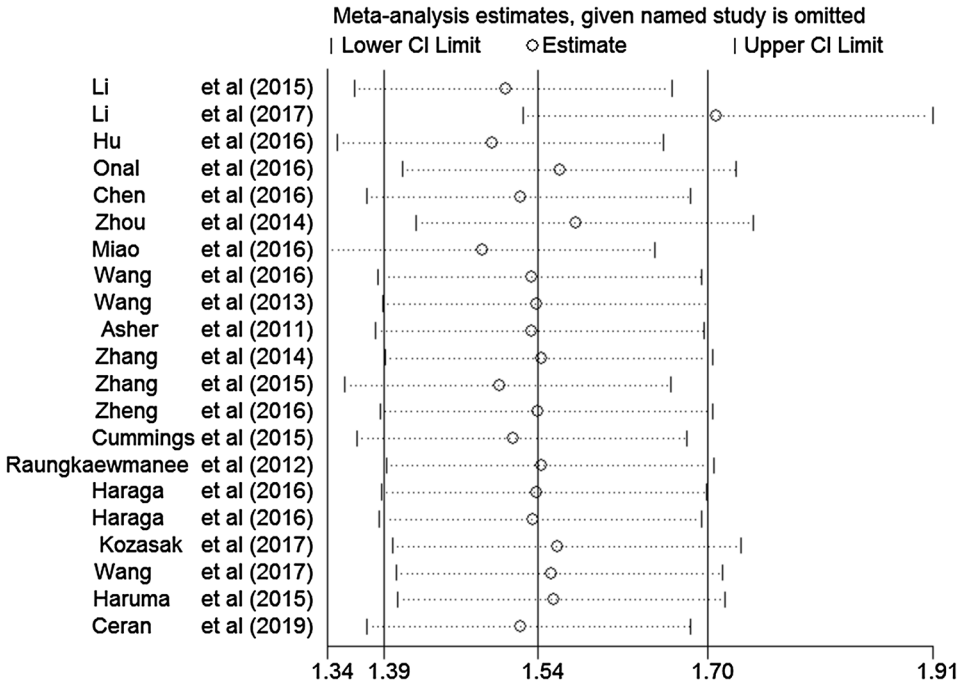

Fig. 3 Sensitivity analysis for the OS

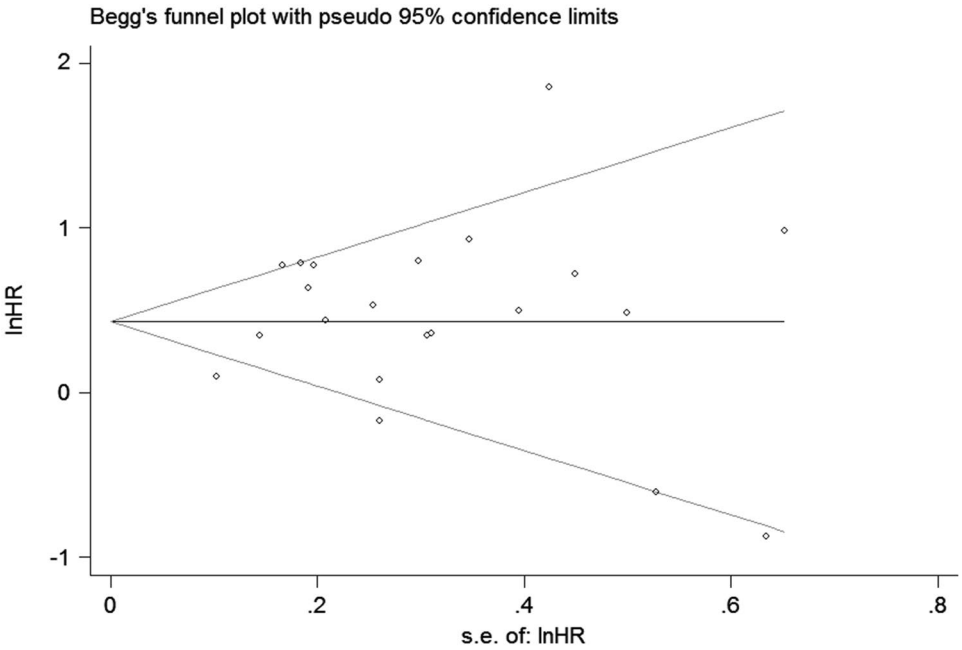

Fig. 4 Begg's funnel plot for the high PLR on the pooled HRs of OS

increasing studies should be performed to improve credibility, especially to increase the studies of endometrial cancers. Third, there was markedly statistical heterogeneity in several pooled results. Studies may have differed with regard to the baseline characteristics of the patients including age, histological type, differentiation, disease stage, the duration of follow-up, and adjustments for other cofactors. By the way, as the data limitation, we did not perform meta-regression analyses to explore the sources of heterogeneity further. Fourth, some included studies were not clearly interpreted the variables, and this may contribute to uncertain explanation of the independent prognostic value of PLR. Finally, this meta-analysis included the predominance of retrospective studies and lacked of random control test studies, and the retrospective studies may bring confounding variables. Therefore, prospective studies with large-scale patients are needed to further clarify the prognostic function of PLR and to ascertain its role in tumor progression.

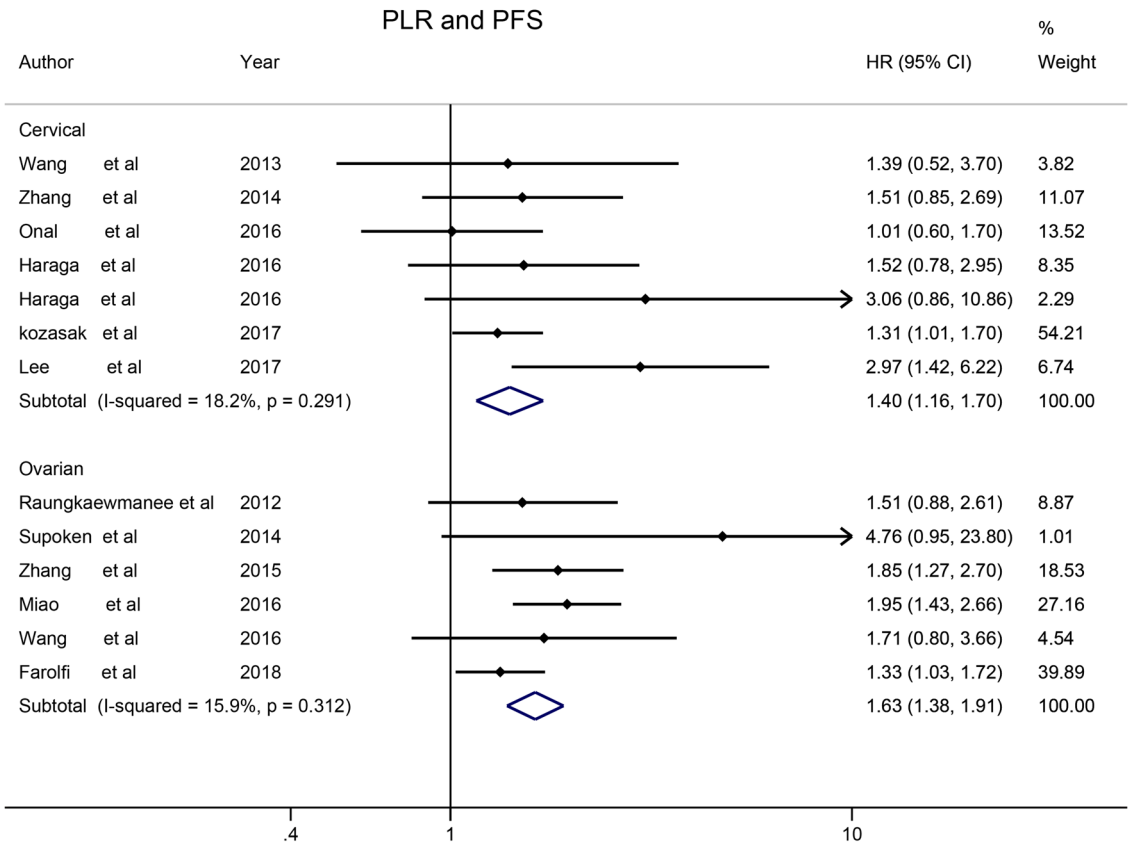

Fig. 5 Meta-analysis higher PLR was associated with worse PFS

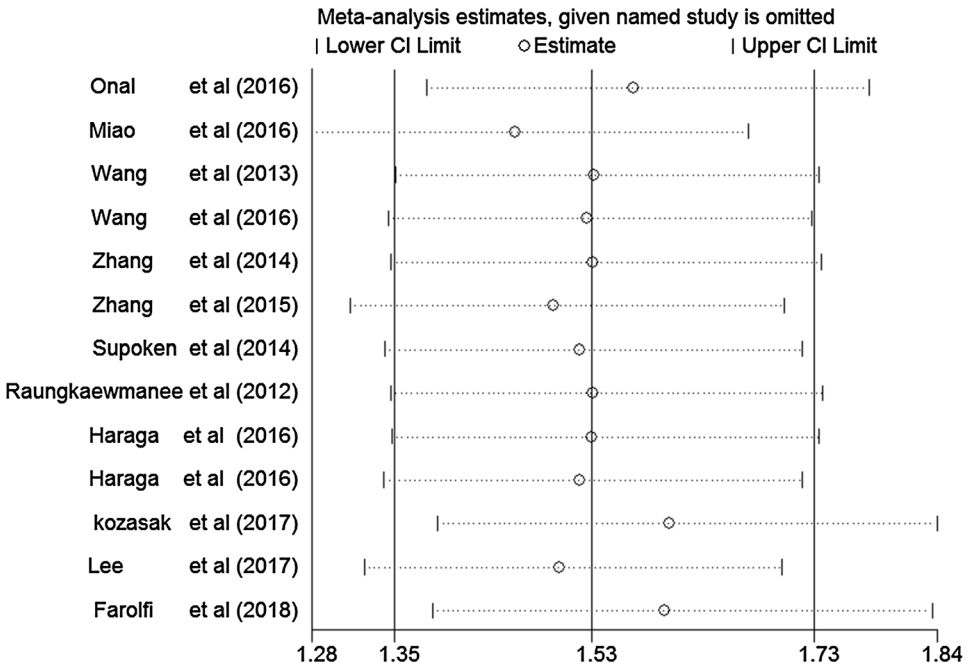

Fig. 6 Sensitivity analysis for the OS

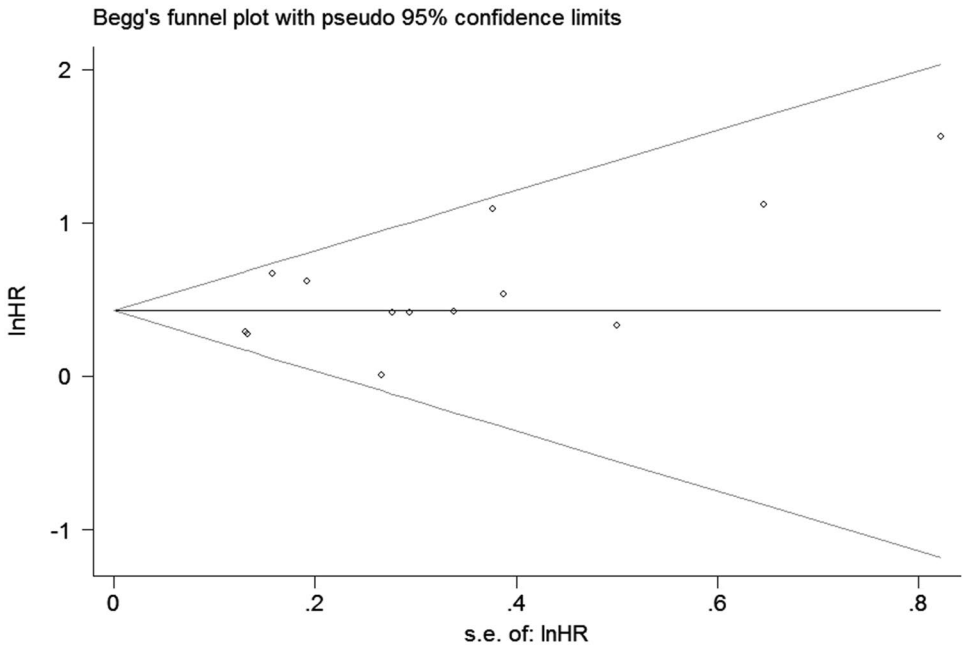

Fig. 7 Begg's funnel plot for high PLR of the pooled HRs of PFS

Conclusions

Higher PLR is correlated with negative OS and PFS in patients with ovarian and cervical malignancies, and it plays a pivotal role in predicting survival outcome in patients with gynecologic cancers. Preoperative PLR will be an easily available prognostic marker for patients and clinicians. However, more prospective clinical trials of PLR on prognostic value are still needed to discern its potential significance.

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Author contributions SSJ: project development, data collection, management data, analysis, and manuscript writing; JDL: data collection, management data, analysis, and manuscript writing; XYC: management data, analysis, and editing; XFZ: management data, analysis, and editing; JHR: management data, analysis, and editing; AHYE: management data, analysis, and editing; SFZ: management data, analysis, and editing; LLZ: management data, analysis, and editing; ZXK: management data, analysis, and editing; RQL: management data, analysis, and editing.

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Compliance with ethical standards

Conflict of interest We declare that we have no conflict of interest.

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