# Prognostic function of platelet-to-lymphocyte ratio in gynecologic cancers: A systematic review and meta-analysis

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# Abstract

Background: Although along with the diagnosis and treatment level enhanced, current situation of the gynecologic malignancies improved, the risk of gynecologic tumor remains high. Nowadays, inflammatory markers increasingly employed as a tumor predictive factor. Herein, we focused on the association between the platelet-to-lymphocyte ratio (PLR) and gynecological cancers, including cervical, ovarian, and endometrial cancer. Methods: In this meta-analysis, we searched systematically on the EMBASE and PubMed databases from June 1, 1989 to May 31, 2019. After excluded some unqualified articles, we calculated the pooled hazard ratio (HR) with 95% confidence interval (CI) mainly to detect the relationship between PLR and prognostic survival, including overall survival (OS) and progression-free survival (PFS). Random-effect model was adopted when I 2 >50% after Higgins I 2 test. Subgroup analysis and funnel plot were used to seek for the possible source of heterogeneity and publication bias, respectively. All statistical tests were two-sided. Results: After a series of searching and selection, twenty-eight literatures containing 8290 participants totally. Among those recruited trials, 26 studies comprising 8109 patients reported HR for OS and 15 researches enrolled 4283 patients for PFS. Overall, a high value of PLR means a worse OS and PFS in women with gynecologic cancer except those with endometrial cancer for OS (pooled HR =1.35, 95% CI =0.73 to 2.53, P =0.33). Subgroup analyses indicated that the source of heterogeneity may be primarily from the sample size, PLR cut-off, study location, published year, and the cut-off year for the study. Publication bias manifested that bias was not evident. Conclusion: Elevated pretreatment PLR portends a poor prognosis among patients with gynecological tumor, as well as in women with cervical and ovarian malignancies for both OS and PFS. However, in patients with endometrial cancer, this connection is broken for OS but still available for PFS.


# Background

Although a great deal of modern therapeutic methods have been expanded for gynecologic cancer, including cervical cancer, ovarian cancer, and endometrial cancer, the estimated deaths are still high last year as before, only after lung, stomach, and liver cancer[1]. Meanwhile, with an estimated over 1,250,000 new gynecological cancer cases in 2018 worldwide[1]. These cancers can result in weight loss, abdominal pain or distension, increased abdominal size, urinary tract symptoms, and subsequently mental discomfort and economic burden[2-6], affecting patient's life quality severely. However, symptoms of these cancers are not obvious in its early stage lead to the early diagnosis rate remains low, while advanced cancer is hard to manage. In addition, current screening methods for gynecological tumors are neither costly nor actual. For ovarian cancer, bimanual pelvic examination and transvaginal ultrasound are short of enough specificity and sensitivity, and the image examination costs are enormous[2, 6]. At the meantime, radioimmunoassay for cancer antigen 125 (CA125) only rises in 50% patients with ovarian cancer[6]. As regards endometrial cancer, clinical examination and ultrasound annually may miss the possible lesions, and the acceptability to women of endometrial biopsy remains in doubt[4]. With respect to cervical cancer, the dominant screening approaches are Papanicolaou (Pap) smear and cervical cytology in the past 60 years, but the same question, limited specificity and sensitivity,

appears[7]. Therefore, seeking for the newly satisfied predictive factors with economical and convenient benefits are warranted.

In the past few decades, systemic inflammation has gradually been associated with cancer pathogenesis and thought as a hallmark of cancer[8-11]. Systemic inflammation usually involves in changes in neutrophil, eosinophil, platelet, lymphocyte, and other peripheral blood cell count[10, 12]. In tumor ambient environment, the cancer cells could recruit inflammatory cells like platelets and lymphocytes[13]. Meanwhile, some researchers have revealed that platelet deposition selectively enhance lymphocyte adhesion in the case of arterial blood flow[14], while the majority of tumor tissues are rich in blood vessel. Thus, it is undoubtedly imperative to explore the potential correlations between the inflammatory associated blood bio-markers with gynecological cancer.

Previous studies have manifested platelet-to-lymphocyte ratio (PLR) can be widely used as a prognostic marker for diverse cancers[15-18]. In these literatures, authors demonstrated that a higher level of preoperative PLR was an indicator of poor survival of different cancers, as well as in most survey results of gynecological cancers. Yet, consequence from Prachratana Nuchpramool and Jitti Hanprasertpong illustrated that PLR could not be applied as a prognostic biomarker in early-stage cervical cancer after receiving primary treatment of radical hysterectomy with pelvic lymph node dissection[19]. Because of lacking the firm uniformity in the field, making the mentioned association above clear is crucial.

In this study, we accomplished a systematic review and meta-analysis to explore the conclusive connection between the PLR and the prognosis, including overall survival (OS) and progression-free survival (PFS), of patients with ovarian, cervical, or endometrial malignancies.

# Methods

### 2.1. Search strategy

A computerized search of EMBASE and PubMed databases was performed for our research. We searched for MeSH terms and keywords in title and abstract and the main search terms were as follows: gynecology, gynecological, cervical, cervix, ovarian, ovary, endometrial, platelet lymphocyte. We included all publications between June 1, 1989 and May 31, 2019.

### 2.2. Study selection

Articles were eligible for inclusion if they met the following criteria: (1) patients diagnosed with cervical, ovarian or endometrial cancer; (2) provided pre-treatment PLR and cut-off values; (3) studies that reported the hazard ratio (HR) and corresponding 95% confidence interval (CI) for overall survival (OS) and/or progression-free survival (PFS), the HR and 95% CI to be calculated via univariate or multivariate analysis. The exclusion criteria were as follows: (1) review articles, guidelines, letters, case reports and

conference proceedings; (2) non-English language publication; (3) title and/or abstract only and no full text provided; (4) only relevant graphic data but not numerical value for HR provided; (5) had no identified gynecologic tumor type.

The literature search and study selection process were conducted by three authors independently. Disagreements between three authors were consulted until a consensus was reached.

### 2.3. Data extraction

Three reviewers independently extracted the detailed information using predetermined forms from the included studies with disagreements discussed until consensus finished. For each study, we extracted characteristics on first author, year of publication, research location, study duration, number of available patients, median or mean age and age range of participants, stage and grade of diverse cancer, histopathologic subtype of tumor, lymph node metastasis whether or not, treatment methods, median or mean follow-up time. OS, PFS, as well as its HR with associated 95% CI, were also be recorded.

### 2.4. Statistical analysis

Extracted data from the enrolled studies were analyzed using RevMan 5.3 software (Cochrane Collaboration, Copenhagen, Denmark). Survival outcomes, both OS and PFS included, were the primary interests in this meta-analysis. Therefore, the Log (HR) and standard error were calculated according to HRs and their 95% confidence intervals. Heterogeneity was evaluated via Cochran's Q test and the Higgins $I^2$ statistic. While $P < 0.05$ was calculated by Cochran's Q test, heterogeneity between literatures was manifested. In the Higgins $I^2$ test, the value of $I^2$ could considered as a criterion to estimate the degree of heterogeneity and the reference standards were as follows: if $I^2$ no more than 40%, heterogeneity could be negligible; if $I^2$ between 30% and 60%, moderate heterogeneity might be shown; while $I^2$ falls into 50-90%, evident heterogeneity may be presented; when $I^2$ =75-100%, inevitable heterogeneity exists[20]. Meanwhile, $I^2$ >50% in the Higgins $I^2$ test were termed as significant heterogeneity, and then a random effects model was chosen; or else, if $I^2$ <50%, a fixed effects model was performed. We also conducted subgroup analyses to detect the potential sources of heterogeneity though RevMan 5.3 software. And the items of subgroup analysis contain sample size, PLR cut-off, study location, the cut-off year for the research, published year of the articles, median age, and other subgroup that may impact the heterogeneity between the studies. In addition, funnel plots were employed for testing publication bias. P-values <0.05 was considered as statistically significant, and all adopted tests were two-sided.

## Results

### 3.1. Literature search results and characteristics

The literature search results and detailed study selection steps are shown in Figure 1. The database searching yielded 556 publications originally. After removing 154 duplicates, and screening residual titles and abstracts of 402 articles, 83 articles remained. Of the remaining studies, 53 literatures were further excluded for various reasons: eight reviews, two with non-English language, thirteen provided conference summary or abstract only, thirty-one did not offered numerical value for hazard ratio, and one with only gynecologic cancer but no primary cancer. Finally, a total of 28 articles and 8290 participants were included in this review and meta-analysis. Among them, one concerning cervical cancer was disposed separately cause of providing HRs and survival outcomes for patients with two different treatments[21]. As a consequence, fifteen, nine, and four publications regarding to cervical[19, 21-34], ovarian[35-43], and endometrial cancer[44-47] were enrolled, respectively.

Characteristics of all enrolled studies are shown in Table 1. The publication of all enrolled studies ranged from 2011 to 2019 and the duration of experiments were from 1988 to 2016. Six studies were from Europe (Spain, Poland, the United Kingdom, and Italy) and the remained twenty-two were from Asia (Korea, China, Japan, Turkey, and Thailand). The number of study population recruited in each research were ranged from 36 to 795 patients. The outcomes of all included cancer were also recorded. PLR cut-off were extracted from the above-mentioned 28 researches, too.

### 3.2. Overall survival and progression-free survival

Two forest plots of all articles for OS and PFS are displayed as Figure 2A and Figure 2B, respectively. Overall, higher PLR represents worse survival in this data, both for OS (HR =1.49, 95%CI =1.23-1.82) and PFS (HR =1.63, 95%CI =1.30-2.05). Among all included studies, twenty-six studies consisting of 8109 participants reported HR for OS. In the meantime, for PFS, fifteen of the eligible twenty-eight literatures comprising 4283 patients. Thereinto, seven articles reported HR from univariate analysis for OS or PFS and the remained twenty-one were from multivariate analysis. The patients had a median age (age range =18 to 95) from 44 to 63 years old in twenty-four studies which reported the median age. The median cut-off for PLR was 169 (range =138.35 to 300) for OS, while it was 172.50 (range =62.31 to 300) for PFS. Relevant follow-up information (duration of median or mean follow-up) were recorded in nineteen researches, ranged from 0.1 to 175.3 months. A random-effects model was performed since the presence of heterogeneity ($I^2$ =85%, P<0.0001 and $I^2$ =81%, P<0.00001 for OS and PFS, respectively) existed between the applicable literatures.

### 3.3. Overall survival and progression-free survival by primary tumor

The results of subgroup analysis by primary tumor are shown in Figure 3A and Figure 3B. From the Figure 3A and 3B, our work manifested that the lower PLR represented the better prognostic except for OS with

endometrial cancer. In patients with endometrial cancer, the HR and its 95% CI for OS was 1.35(0.73, 2.50). But for PFS, the corresponding outcome was 1.86(1.20, 2.91) and Higgins $I^2$ test declared $I^2$ =0%.

### 3.4. Subgroup analysis of overall survival and progression-free survival

In the subgroup analyses, three details should be stated initially. In the subgroup of median age, one research[42] provided two different median age (60 and 63) for diverse group. However, this did not influence the classification of subgroup in this data due to the cut-off value of median age was 50 years old. Another issue worth noting was that the Turkey was identified as a European country in this data on account of their living habits and ethnics were closer to Europe but not Asia. One last thing to note is that the subgroup analysis of endometrial cancer did not be carried out because of a relatively low number of recruited literatures.

#### 3.4.1 Gynecologic cancer

The results of gynecologic cancer subgroup analyses were exhibited in Table 2 and several sources of heterogeneity were found. In women with gynecological tumor, stratified analysis discovered several sources of heterogeneity and almost all heterogeneity decreased after subgroup analyses. Concerning OS, we found heterogeneity reduced in the published year (pooled HR =1.49; 95% CI =1.03 to 1.17; P <0.0001) and median age (pooled HR =1.47; 95% CI =1.18 to 1.82; P =0.0005) subgroup in all 26 eligible literatures containing 27 different trials. However, as for PFS, despite the heterogeneity equally shortened in the subgroup of the published year (pooled HR =1.63; 95% CI =1.30 to 2.05; P <0.0001), heterogeneity switched softly in the median age (pooled HR =1.58; 95% CI =1.22 to 2.06; P =0.0006) stratified group in all 16 trials. Among other subgroup analyses, including PLR cut-off, study location, the cut-off year for the study, and sample size subgroup, significant pooled HR and lessened heterogeneity were also observed visibly for PFS but not so remarkable for OS. Regarding study location, we did further classification and found that $I^2$ dropped to 0% after Higgins $I^2$ test in women who suffered from ovarian cancer and endometrial cancer despite the elevation in the cases with cervical cancer in Asian. With respect to OS, whether it was in Asia or Europe, we failed to explore the exact origin of the heterogeneity even heterogeneity declined to some degree but far from enough.

#### 3.4.2 Cervical cancer

The analytical consequences of cervical cancer were presented in Table 3 and supplement 1. Four subgroups were designed to search the underlying sources of heterogeneity for OS but three for PFS and matching trials were fifteen and eight, respectively. Similar to overall analysis for OS above, the cut-off year for the study (pooled HR =1.48; 95% CI =1.08 to 2.04; P=0.02) and published year subgroup

analytical results displayed the significant heterogeneity reduction in one of the layered groups, whereas in the sample size and the PLR cut-off subgroup the decline did not illustrate significant heterogeneity. For PFS, after three subgroup analyses, opposite change occurred between groups of one subgroup: heterogeneity descended in the groups with sample size ≤200 patients, the cut-off year for the study from 2009 to 2012, and published year between 2011 and 2016, but conversely added in the other group.

### 3.4.3 Ovarian cancer

The corresponding results of ovarian cancer were diplayed in Table 3 and supplement 1. Still four and three subgroups were exploited for heterogeneity analyses for OS and PFS. Heterogeneity of the stratified group of published year (pooled HR =1.51; 95% CI =1.16 to 1.96; P <0.002) from 2011 to 2016 illustrated a shrinkage as before, as well as sample size in spite of group altered. In regard to PFS, several favorable survival results were recognized about ovarian cancer and resembled to women with cervical cancer.

### 3.5. Publication bias analysis

From funnel plot (Figure 4A & 4B), our results suggested that publication bias was low for both OS and PFS.

# Discussion

Accumulating evidence implies that inflammation acts an absolutely required part in the formation of neoplasm possibly via all kinds of transcription factors, chemokines, as well as cytokines[10, 11]. In many published knowledges, the roles of inflammatory factors like neutrophil-to-lymphocyte ratio (NLR) [48], monocyte-to-lymphocyte ratio (MLR)[49], and C-reactive protein (CRP)[50] have always been delineated in patients who suffered from cancer. Given that, we turned our attention on the association between another inflammatory immune factors, platelet-to-lymphocyte ratio (PLR), and gynecological cancer.

According to the present review and meta-analysis, we evaluated the prognostic effects of PLR for ovarian, cervical, and endometrial cancers and ultimately found that an elevated PLR was linked to both shorter OS and poorer PFS in the ovarian cancer and cervical cancer, in keeping with many known outcomes with several other sorts of neoplasm such as early stage classical Hodgkin lymphoma[51], hepatopancreatico-biliary malignancy[52], early stage non–small-cell lung cancer[15], gastric cancer[16], breast cancer[17], and esophageal cancer[18]. But contrary result appeared in endometrial cancer,

pretreatment low or high value of PLR had no impact on OS in endometrial tumor, while higher value of PLR denoted inferior PFS.

After subgroup analyses, we detect some meaningful outcomes likewise. Nearly in all published year subgroups, decreased heterogeneity in stratified group (2011~2016) was observed and P value for all pooled HR in the subgroup for diverse analyses were less than 0.05. Hence, we have adequate reasons to believe that heterogeneity between literatures may come from those which are published later than 2016. Comparably, in the majority of the cut-off year for the study subgroups, our consequences revealed that the relatively later cut-off year for the study, the higher heterogeneity happened to the studies we included these observations. Combined to the published year subgroup analysis, we speculated that the latest researches could exist certain inconsistence since the later the trial stopped, the more recent the study published. And this may be resulted from the rapid medical development particularly in cancer evolution[53] and along with the new controversy appeared, as well as the incompatible evaluation criterion. For this account, inclusion criteria for patients may various and enrolled women with tumor and treatment methods differ followed would have an inherent impact on the outcomes. Additionally, sample size no more than 200 could be taken as another source of the heterogeneity both in cervical and ovarian cancer. Moreover, study location may constitute another sources of heterogeneity for PFS. Heterogeneity was relatively low in Asian patients, especially for endometrial cancer. But this may not make sense because of the few literatures included in our report. Regretfully, for OS, maybe due to the large amount of the studies, we do not ensure sufficient resources of heterogeneity in women with gynecologic tumor.

To our knowledge, this study firstly summarizes the potential prognostic for PLR on overall gynecologic cancer patients, as well as cervical cancer, ovarian cancer, and endometrial cancer. Further, we detected the underlying sources of heterogeneity, and possible causes displayed subsequently. In addition, we recruited the ample researches in the present report. Despite the heavy workload, we furnished the convincing proof, which could offer a reference for clinical management with gynecologic cancer patients.

Some limitations still inevitably exist in this study. First, almost all of the contained observations in this data were retrospective but not prospective cohort study, which may lead to bias in data processing. At the same time, because significant results were easier to be accepted by journal now, the role of PLR may be overestimated virtually. Besides, available data extracted from the above-mentioned articles were gathered instead of specific personal information also further exaggerated the potential bias. Second, PLR was susceptible to influence via other diseases not only gynecological cancer. For example, several authors had reported chronic hepatitis B virus infection[54], *Helicobacter pylori* infection[55], acute kidney injury[56] all had an impact on the value of PLR. But many selected studies did not eliminate such corresponding conditions in our work and subsequently imbalance between groups came. Therefore, PLR cannot be used as an independent judgment prognostic indicator, but can be applied as an auxiliary indicator. Third, the other inconformity between the literatures were that not all researches adopted the multivariate model. Nearly a quarter researches used the univariate model to explore the correlation between the PLR and gynecologic cancer. Meanwhile, not all results from the recruited studies were

statistically significant. Moreover, different therapeutic methods for gynecologic cancer could have influence on the observed index, but this is hard to manage.

# Conclusions

In conclusion, our currently results manifest that a higher value of pretreatment PLR indicates a worse prognosis among patients with gynecologic malignancies, as well as in patients with cervical, ovarian, and endometrial cancer for both OS and PFS except in those with endometrial cancer for OS. This provides us a therapeutic thought of that we could improve the prognosis of gynecological cancers by reducing the value of PLR, that is to say, attenuating the platelet count within certain range correspondingly should be considered. Though PLR do not set up as an independent prognostic indicator, it can help clinicians judge the prognosis of gynecologic cancer. But for all that, more perspective investigations need to be performed and the appropriate cut-off for PLR remains to be determined in the near future.

# Abbreviations

PLR□platelet-to-lymphocyte ratio; HR: hazard ratio; CI: confidence interval; OS: overall survival; PFS: progression-free survival; CA125: cancer antigen 125; NLR: neutrophil-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio; CRP: C-reactive protein.

# Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Availability of data and materials

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

### Competing interests

The authors declare that they have no competing interests.


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### Authors' contributions

LP and ZX obtained funding for the study and conceptualized and designed the study. FC, DYJ, WYQ, MM and RC collected the data. FC, DYJ and WYQ screened and extracted the data. MM and RC conducted data analysis. WXY, LY, and LT reviewed the data analysis. FC drafted the article. DYJ, WYQ, LP and ZX critically revised the article. All authors have read and approved the final article.


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# Tables

**Table 1**.

Characteristics of recruited studies.

| Study | Published year | Duration of study | Country | Number | Age | Analysis | PLR cut-off |
|---|---|---|---|---|---|---|---|
| **Cervical cancer** | | | | | | | |
| Lee [22] | 2017 | 2011.03-2014.12 | Korea | 377 | 52(29-79) | PFS | 170.00 |
| He [23] | 2018 | 2007.09-2009.03 | China | 229 | 44(28-79) | OS | 149.27 |
| Nakamura [24] | 2018 | 1997.01-2013.07 | Japan | 98 | 65(32-86) | OS | 212.00 |
| Onal [25] | 2016 | 2006.10-2014.09 | Turkey | 235 | 57(21-86) | OS, PFS | 133.02 |
| Zheng [26] | 2016 | 2005.05-2012.12 | China | 795 | 49.5±10.7 | OS, PFS | 128.30 |
| Huang [27] | 2019 | 2006-2015 | China | 328 | 45(22-86) | OS | 118.00 |
| Holub [28] | 2018 | 2009.06-2016.07 | Spain | 151 | 51(25-92) | OS | 210.00 |
| Wang [29] | 2017 | 2012.01-2014.05 | China | 129 | 51(25-79) | OS | 148.90 |
| Zhang [30] | 2017 | 2005.01-2009.12 | China | 235 | 46(29-78) | OS, PFS | 176.50 |
| Nuchpramool [19] | 2018 | 2001.01-2016.06 | Thailand | 460 | 47 | OS, PFS | 119.00 |
| Jonska-gmyrek [31] | 2018 | 2003.11-2008.11 | Poland | 52 | 53(20-81) | OS | 158.00 |
| Zhu [32] | 2018 | 2012.07-2014.12 | China | 339 | 45(21-76) | OS, PFS | 143.79 |
| Haraga(CCRT) [21] | 2016 | 2007.04-2013.03 | Japan | 131 | 61.5(25-88) | OS, PFS | 172.50 |
| Haraga(RT alone) [21] | 2016 | 2007.04-2013.03 | Japan | 131 | 61.5(25-88) | OS, PFS | 128.00 |
| Chen [33] | 2016 | 2006.01-2009.12 | China | 407 | 44 | OS | 138.35 |
| Ida [34] | 2018 | 2004.04-2015.12 | Japan | 79 | 52.4(25-78) | OS | 260.00 |
| **Ovarian cancer** | | | | | | | |
| Miao [35] | 2016 | 2005-2010 | China | 344 | 55(45-84) | OS, PFS | 207.00 |
| Raungkaewmanee [36] | 2012 | 2004.01-2010.12 | Thailand | 166 | 53(23-85) | OS, PFS | 200.00 |
| Badora-Rybicka [37] | 2017 | 2007-2013 | Poland | 315 | 54(22-77) | OS, PFS | 129.78(OS)<br>62.31(PFS) |
| Liu [38] | 2017 | 2006.06-2012.07 | China | 200 | 53(18-83) | OS | 165.00 |
| Supoken [39] | 2014 | 2003.01-2013.10 | Thailand | 36 | 52 | PFS | 300.00 |
| Asher [40] | 2011 | 1988-1998 | The UK | 235 | 62 (24–90) | OS | 300.00 |
| Li [41] | 2017 | 2000-2010 | China | 654 | 63(28-93) | OS | 273.50 |
| Farolfi [42] | 2018 | 2007.01.01-2015.06.30 | Italy | 375 | 60,63(19-85) | OS, PFS | 169.00 |
| Zhang [43] | 2015 | 2000.01-2012.12 | China | 190 | 50.6±11.1(24-76) | OS, PFS | 203.00 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Endometrial cancer** | | | | | | | |
| Cummings [44] | 2015 | 2005.01-2007.12 | The UK | 605 | 65(28-95) | OS | 240.00 |
| Aoyama [45] | 2019 | 2007-2013 | Japan | 197 | 59(31-85) | OS, PFS | 206.00 |
| Haruma [46] | 2015 | 2002.01-2012.12 | Japan | 320 | 57.5(23-86) | OS, PFS | 175.72 |
| Li [47] | 2015 | 2007.09-2009.06 | China | 282 | 53(21-76) | OS | 250.00 |

**Table 2.**

Subgroup analyses of main outcome for gynecologic cancer

| Subgroups | No. of studies | HR (95% CI) | P value | Heterogeneity | |
|---|---|---|---|---|---|
| | | | | $I^2$ | P value |
| **Overall survival** | | | | | |
| Sample size | 27 | **1.49 (1.23, 1.82)** | <0.0001 | 85% | <0.00001 |
| ≤200 patients | 10 | **1.64 (1.13, 2.39)** | 0.009 | 74% | <0.0001 |
| >200 patients | 17 | **1.42 (1.16, 1.74)** | 0.0008 | 79% | <0.00001 |
| PLR cut-off | 27 | **1.49 (1.23, 1.82)** | <0.0001 | 85% | <0.00001 |
| <200 | 16 | **1.52 (1.15, 2.01)** | 0.004 | 85% | <0.00001 |
| ≥200 | 11 | **1.46 (1.09, 1.95)** | 0.01 | 74% | <0.0001 |
| Study location | 27 | **1.49 (1.23, 1.82)** | <0.0001 | 85% | <0.00001 |
| Asia | 20 | **1.44 (1.15, 1.80)** | 0.002 | 64% | <0.0001 |
| Europe | 7 | **1.63 (1.11, 2.41)** | 0.01 | 92% | <0.00001 |
| The cut-off year for the study | 27 | **1.49 (1.23, 1.82)** | <0.0001 | 85% | <0.00001 |
| 1998~2010 | 10 | **1.85 (1.40, 2.44)** | <0.0001 | 75% | <0.0001 |
| 2011~2016 | 17 | **1.29 (1.02, 1.63)** | 0.04 | 74% | <0.00001 |
| Published year | 27 | **1.49 (1.23, 1.82)** | <0.0001 | 85% | <0.00001 |
| 2011~2016 | 12 | **1.71 (1.44, 2.04)** | <0.00001 | 21% | 0.23 |
| 2017~2019 | 15 | **1.39 (1.07, 1.81)** | 0.01 | 85% | <0.00001 |
| Median age | 22 | **1.47 (1.18, 1.82)** | 0.0005 | 85% | <0.00001 |
| <50 | 6 | **1.85 (1.34, 2.57)** | 0.0002 | 15% | 0.32 |
| ≥50 | 16 | **1.38 (1.09, 1.76)** | 0.008 | 88% | <0.00001 |
| | | | | | |
| **Progression-free survival** | | | | | |
| Sample size | 16 | **1.63 (1.30, 2.05)** | <0.0001 | 81% | <0.00001 |
| ≤200 patients | 7 | **1.95 (1.54, 2.48)** | <0.00001 | 0% | 0.57 |
| >200 patients | 9 | **1.41 (1.09, 1.82)** | 0.008 | 81% | <0.00001 |
| PLR cut-off | 16 | **1.63 (1.30, 2.05)** | <0.0001 | 81% | <0.00001 |
| <200 | 11 | **1.46 (1.14, 1.85)** | 0.002 | 73% | <0.00001 |
| ≥200 | 5 | **1.91 (1.55, 2.35)** | <0.00001 | 0% | 0.65 |
| Study location | 16 | **1.63 (1.30, 2.05)** | <0.0001 | 81% | <0.00001 |
| Asia | 13 | **1.82 (1.55, 2.14)** | <0.00001 | 7% | 0.38 |
| Europe | 3 | 1.07 (0.89, 1.27) | 0.48 | 51% | 0.13 |
| The cut-off year for the study | 15 | **1.63 (1.30, 2.05)** | <0.0001 | 81% | <0.00001 |
| 2009~2012 | 6 | **1.80 (1.51, 2.15)** | <0.00001 | 0% | 0.82 |
| 2013~2016 | 9 | **1.47 (1.11, 1.93)** | 0.007 | 71% | 0.0002 |
| Published year | 16 | **1.63 (1.30, 2.05)** | <0.0001 | 81% | <0.00001 |
| 2011~2016 | 9 | **1.68 (1.43, 1.98)** | <0.00001 | 0% | 0.47 |
| 2017~2019 | 7 | **1.56 (1.12, 2.18)** | 0.009 | 80% | <0.0001 |
| Median age | 12 | **1.58 (1.22, 2.06)** | 0.0006 | 81% | <0.00001 |
| <50 | 3 | 1.81 (0.81, 4.07) | 0.15 | 70% | 0.04 |
| ≥50 | 9 | **1.54 (1.16, 2.05)** | 0.003 | 82% | <0.00001 |

P values <0.05 are in bold.

**Table 3.**

Subgroup analyses of main outcome for cervical and ovarian cancer

| Subgroups | No. of studies | HR (95% CI) | P value | Heterogeneity |
|---|---|---|---|---|

| | | | | $I^2$ | P value |
|---|---|---|---|---|---|
| **Overall survival** | | | | | |
| **Cervical Cancer** | | | | | |
| Sample size | 15 | **1.48 (1.08, 2.04)** | 0.02 | 71% | <0.00001 |
| ≤200 patients | 6 | 1.47 (0.47, 2.94) | 0.27 | 85% | <0.00001 |
| >200 patients | 9 | **1.52 (1.23, 2.05)** | 0.006 | 41% | 0.09 |
| PLR cut-off | 15 | **1.70 (1.46, 1.99)** | <0.00001 | 71% | <0.00001 |
| <200 | 12 | **1.89 (1.60, 2.25)** | <0.00001 | 57% | 0.007 |
| ≥200 | 3 | 0.94 (0.63, 1.40) | 0.77 | 85% | 0.001 |
| The cut-off year for the study | 15 | **1.48 (1.08, 2.04)** | 0.02 | 71% | <0.00001 |
| 1998~2010 | 4 | **2.60 (2.05, 3.29)** | <0.00001 | 0% | 0.59 |
| 2011~2016 | 11 | 1.18 (0.82, 1.69) | 0.37 | 59% | 0.006 |
| Published year | 15 | **1.48 (1.08, 2.04)** | 0.02 | 71% | <0.00001 |
| 2011~2016 | 5 | **1.56 (1.20, 2.03)** | 0.0010 | 3% | 0.39 |
| 2017~2019 | 10 | 1.35 (0.83, 2.20) | 0.22 | 80% | <0.00001 |
| **Ovarian Cancer** | | | | | |
| Sample size | 8 | **1.51 (1.16, 1.96)** | 0.002 | 88% | <0.00001 |
| ≤200 patients | 3 | **1.91 (1.47, 2.49)** | <0.00001 | 0% | 0.50 |
| >200 patients | 5 | **1.36 (1.03, 1.80)** | 0.03 | 88% | <0.00001 |
| PLR cut-off | 8 | **1.51 (1.16, 1.96)** | 0.002 | 88% | <0.00001 |
| <200 | 3 | 1.33 (0.90, 1.97) | 0.15 | 86% | 0.0009 |
| ≥200 | 5 | **1.64 (1.17, 2.32)** | 0.005 | 77% | 0.002 |
| The cut-off year for the study | 8 | **1.51 (1.16, 1.96)** | 0.002 | 88% | <0.00001 |
| 1998~2010 | 4 | **1.53 (1.04, 2.25)** | 0.03 | 77% | 0.005 |
| 2011~2016 | 4 | 1.51 (1.00,2.28) | 0.05 | 90% | <0.00001 |
| Published year | 8 | **1.51 (1.16, 1.96)** | 0.002 | 88% | <0.00001 |
| 2011~2016 | 4 | **1.97 (1.60, 2.43)** | <0.00001 | 0% | 0.56 |
| 2017~2019 | 4 | 1.22 (0.97, 1.54) | 0.09 | 80% | 0.002 |
| | | | | | |
| **Progression-free survival** | | | | | |
| **Cervical Cancer** | | | | | |
| Sample size | 8 | **1.68 (1.21, 2.33)** | 0.002 | 48% | 0.06 |
| ≤200 patients | 3 | **2.17 (1.35, 3.47)** | 0.001 | 4% | 0.35 |
| >200 patients | 5 | **1.49 (0.99, 2.24)** | 0.06 | 55% | 0.06 |
| The cut-off year for the study | 8 | **1.68 (1.21, 2.33)** | 0.002 | 48% | 0.06 |
| 2009~2012 | 2 | **1.85 (1.19, 2.87)** | 0.006 | 25% | 0.25 |
| 2013~2016 | 6 | **1.63 (1.03, 2.56)** | 0.04 | 55% | 0.05 |
| Published year | 8 | **1.68 (1.21, 2.33)** | 0.002 | 48% | 0.06 |
| 2011~2016 | 4 | **1.43 (1.05, 1.95)** | 0.02 | 12% | 0.33 |
| 2017~2019 | 4 | **2.04 (1.08, 3.88)** | 0.03 | 65% | 0.03 |
| **Ovarian Cancer** | | | | | |
| Sample size | 6 | **1.49 (1.08, 2.07)** | 0.02 | 87% | <0.00001 |
| ≤200 patients | 3 | **1.80 (1.33, 2.43)** | 0.0002 | 0% | 0.40 |
| >200 patients | 3 | 1.31 (0.90, 1.91) | 0.15 | 91% | <0.0001 |
| The cut-off year for the study | 6 | **1.49 (1.08, 2.07)** | 0.02 | 87% | <0.00001 |
| 2009~2012 | 3 | **1.84 (1.48, 2.29)** | <0.00001 | 0% | 0.73 |
| 2013~2016 | 3 | 1.15 (0.85, 1.56) | 0.35 | 74% | 0.02 |
| Published year | 6 | **1.49 (1.08, 2.07)** | 0.02 | 87% | <0.00001 |
| 2011~2016 | 4 | **1.87 (1.51, 2.32)** | <0.00001 | 0% | 0.58 |
| 2017~2019 | 2 | 1.09 (0.86, 1.38) | 0.49 | 76% | 0.04 |

P values <0.05 are in bold.

# Figures

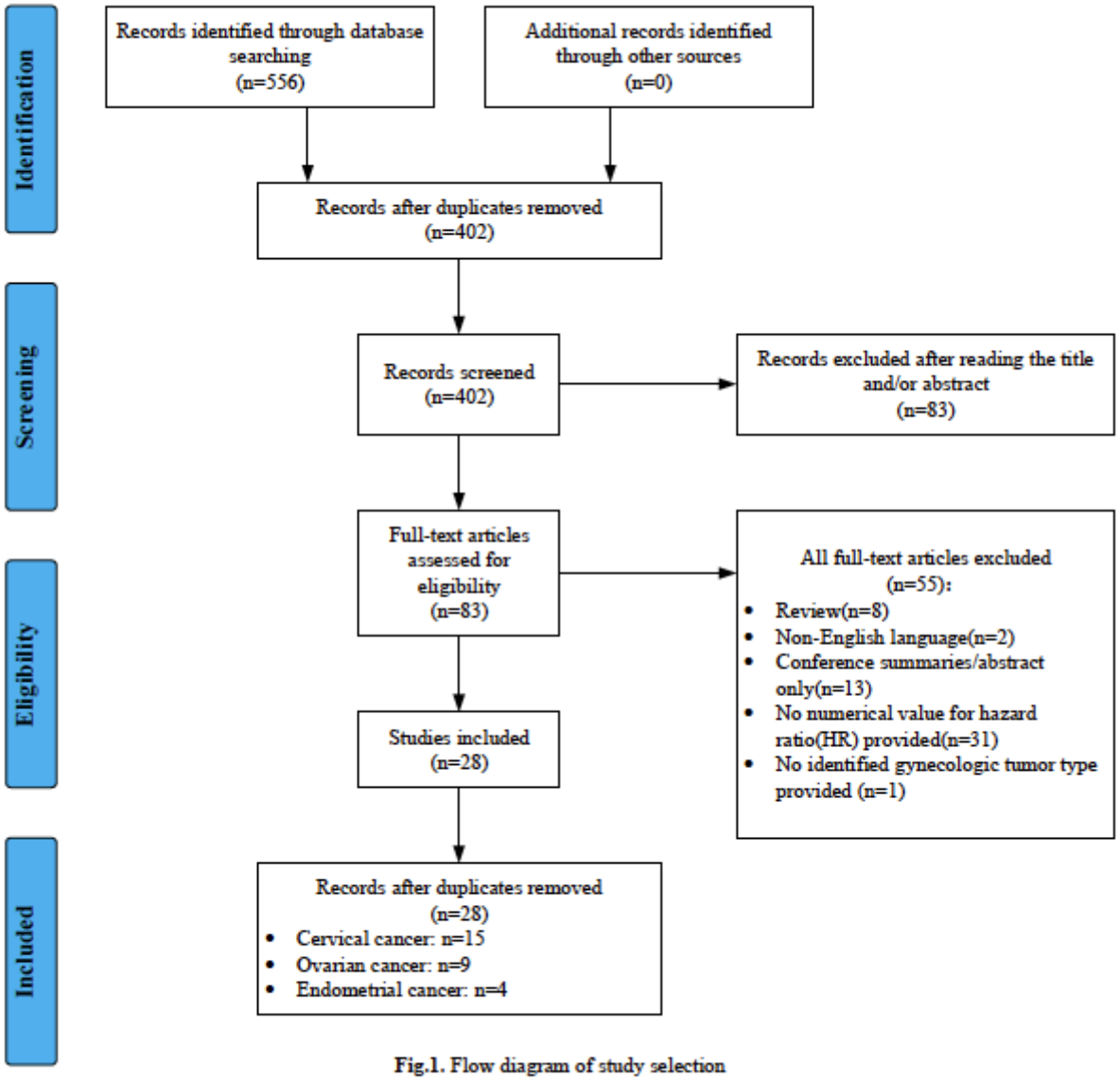
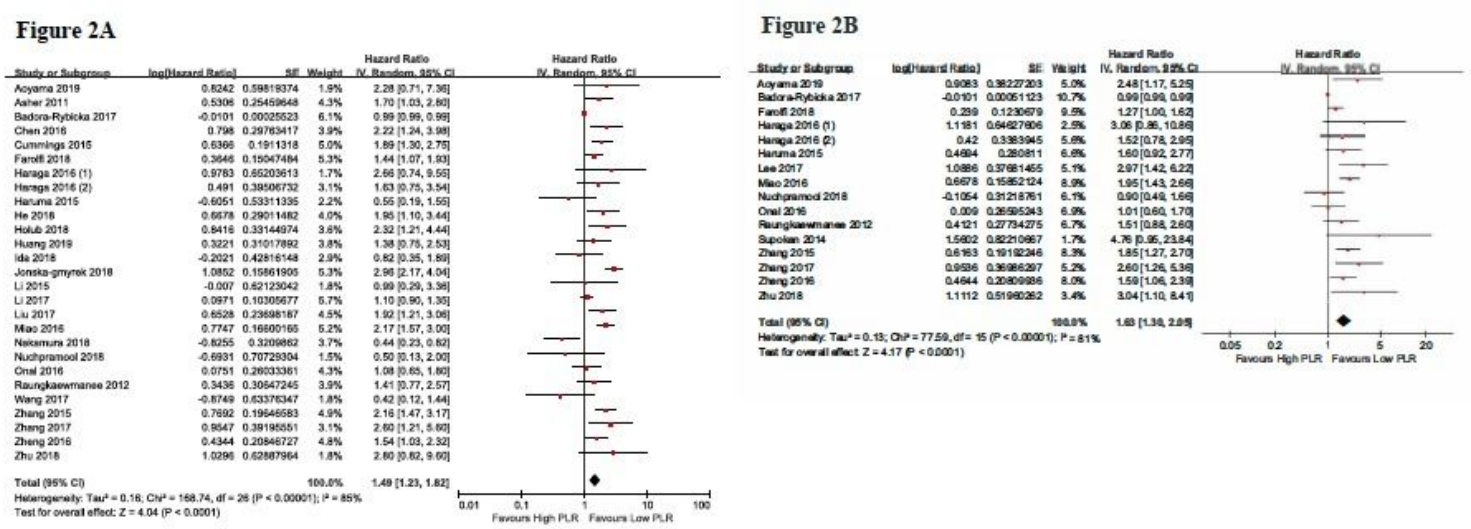



**Fig.1.** Flow diagram of study selection

## Figure 1

Flow diagram of study selection




## Figure 2

2A & 2B. Forest plots showing hazard ratio for overall survival (A) and progression-free survival (B) in all studies for platelet-to-lymphocyte ratio greater or less than the cut-off. Hazard ratio for each study are represented by the squares, the size of the square represents the weight of the study in the meta-analysis, and the horizontal line crossing the square represents the 95% confidence interval (CI). All statistical tests were two-sided.

**Figure 3B**

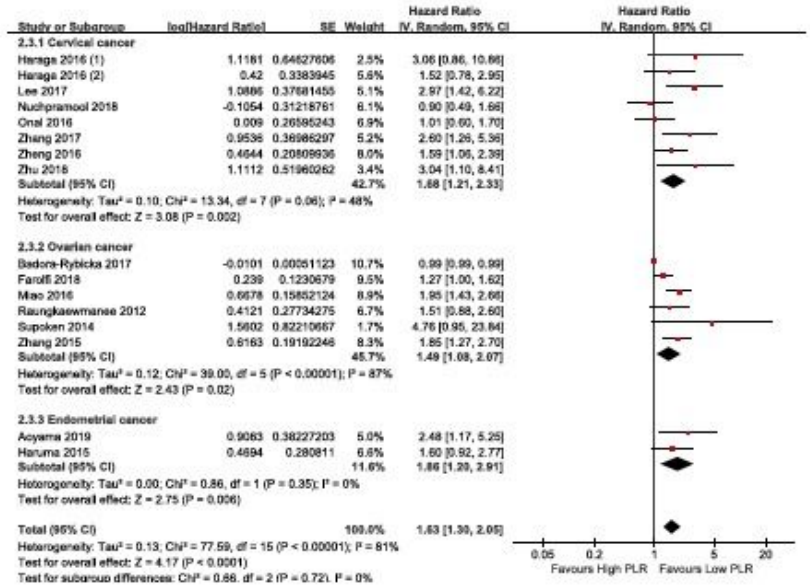
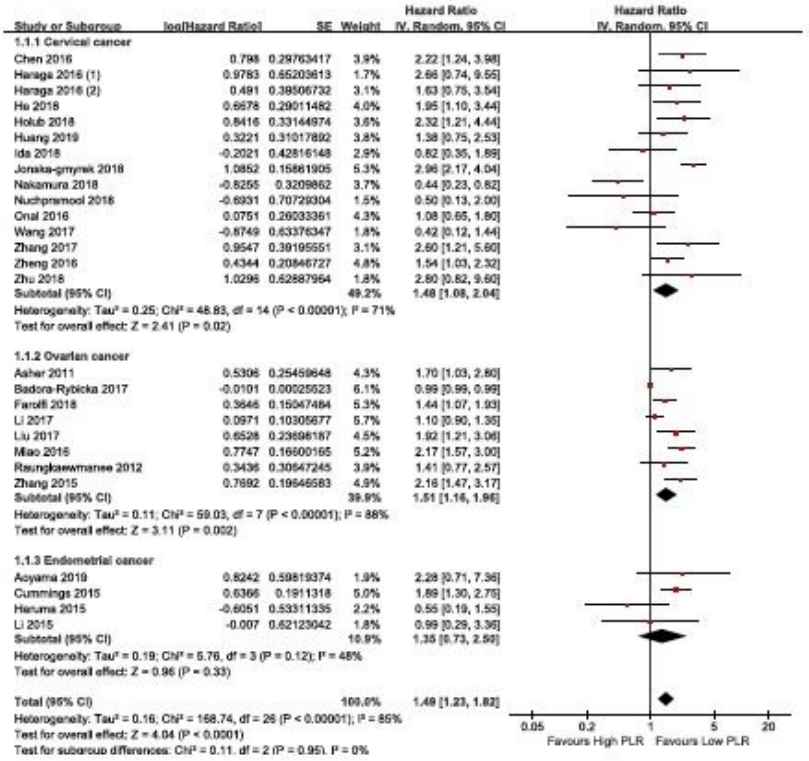
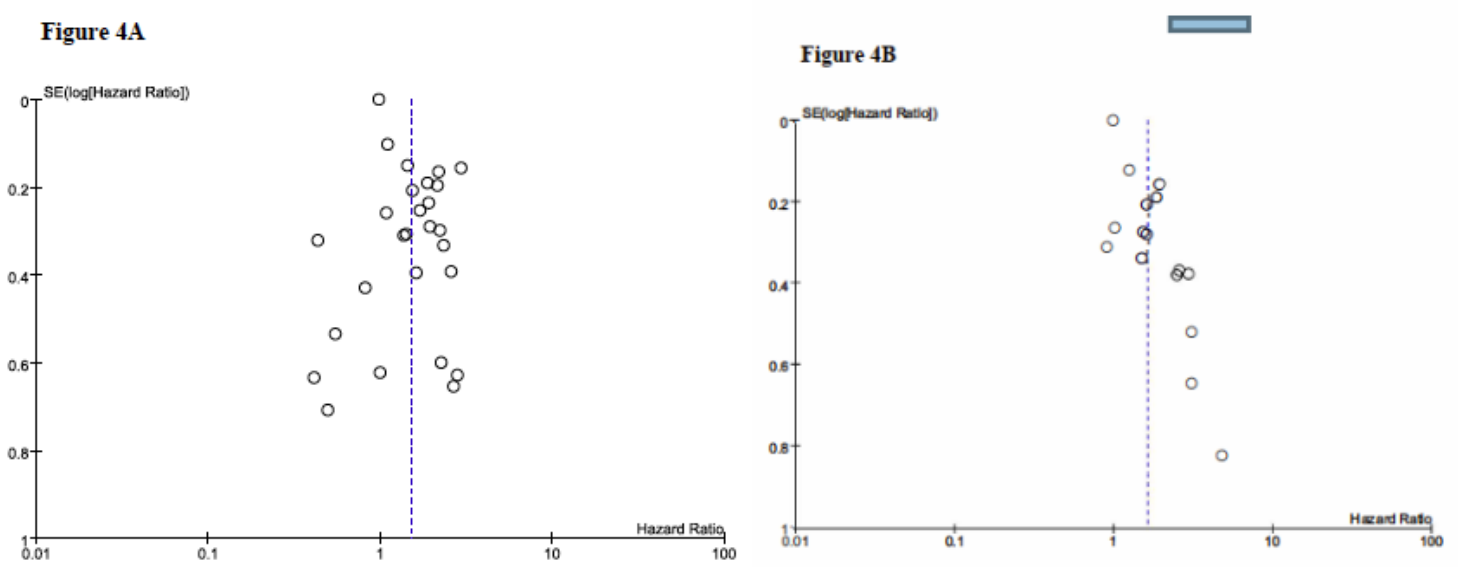



**Figure 3A**




## Figure 3

3A & 3B. Forest plots showing hazard ratio for overall survival (A) and progression-free survival (B) by primary tumor for platelet-to-lymphocyte ratio greater or less than the cut-off. Hazard ratio for each study are represented by the squares, the size of the square represents the weight of the study in the meta-analysis, and the horizontal line crossing the square represents the 95% confidence interval (CI). All statistical tests were two-sided.




## Figure 4

Funnel plot of hazard ratio for overall survival (A) and progression-free survival (B) for high platelet-to-lymphocyte ratio (horizontal axis) and the standard error (SE) for the hazard ratio (vertical axis). Each study is represented by one circle. The vertical line represents the pooled effect estimate.