Predictive Values of Programmed Cell Death-Ligand 1 Expression for Prognosis, Clinicopathological Factors, and Response to Programmed Cell Death-1/Programmed Cell Death-Ligand 1 Inhibitors in Patients With Gynecological Cancers: A Meta-Analysis

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Background: The prognostic value of programmed cell death-ligand 1 (PD-L1) in gynecological cancers has been explored previously, but the conclusion remains controversial due to limited evidence. This study aimed to conduct an updated meta-analysis to re-investigate the predictive significance of PD-L1 expression.

Methods: PubMed, EMBASE and Cochrane Library databases were searched. The associations between PD-L1 expression status and prognosis [overall survival (OS), progression-free survival (PFS), recurrence-free survival (RFS), cancer-specific survival (CSS) or disease-free survival (DFS)], clinical parameters [FIGO stage, lymph node metastasis (LNM), tumor size, infiltration depth, lymphovascular space invasion (LVSI) or grade] and response to anti-PD-1/PD-L1 treatment [objective response rate (ORR)] were analyzed by hazard ratios (HR) or relative risks (RR).

Results: Fifty-five studies were enrolled. Overall, high PD-L1 expression was not significantly associated with OS, PFS, RFS, CSS and DFS of gynecological cancers. However, subgroup analysis of studies with reported HR (HR = 1.27) and a cut-off value of 5% (HR = 2.10) suggested that high PD-L1 expression was correlated with a shorter OS of gynecological cancer patients. Further sub-subgroup analysis revealed that high PD-L1 expressed on tumor-infiltrating immune cells (TICs) predicted a favorable OS for ovarian (HR = 0.72), but a poor OS for cervical cancer (HR = 3.44). PD-L1 overexpression was also correlated with a lower OS rate in non-Asian endometrial cancer (HR = 1.60). High level of PD-L1 was only clinically correlated with a shorter PFS in Asian endometrial cancer (HR = 1.59). Furthermore, PD-L1-positivity was correlated with LNM (for overall, ovarian
and endometrial cancer expressed on tumor cells), advanced FIGO stage (for overall, ovarian cancer expressed on tumor cells, endometrial cancer expressed on tumor cells and TICs), LVSI (for overall and endometrial cancer expressed on tumor cells and TICs), and increasing infiltration depth/high grade (only for endometrial cancer expressed on TICs). Patients with PD-L1-positivity may obtain more benefit from anti-PD-1/PD-L1 treatment than the negative group, showing a higher ORR (RR = 1.98), longer OS (HR = 0.34) and PFS (HR = 0.61).

**Conclusion:** Our findings suggest high PD-L1 expression may be a suitable biomarker for predicting the clinical outcomes in patients with gynecological cancers.

**Keywords:** gynecological cancers, programmed death ligand 1, prognosis, immunotherapy, clinicopathological features

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**BACKGROUND**

Gynecological cancers have been a significant global health burden for women (1, 2). According to the statistics by the American Cancer Society in 2020, uterine corpus endometrial cancer accounts for approximately 65,620 new cases and 12,590 deaths, followed by ovarian cancer (21,750 new cases and 13,940 deaths) and cervical cancer (13,800 new cases and 4,290 deaths) (3). Although several therapeutic options (i.e. surgery, chemoradiotherapy and immunotherapy) have been recommended recently, some patients exhibit a poor response to these management strategies and experience relapses or metastases, ultimately dying from their diseases (4). Therefore, predictive biomarkers may be urgently necessary to early stratify these patients at a high risk of poor responses and unfavorable outcomes and then guide more individualized treatment regimens to further improve overall survival (OS).

Recently, accumulating evidence has revealed that immune escape represents a crucial hallmark for malignant transformation and tumor progression (5, 6). The programmed death-ligand 1 (PD-L1, also called B7-H1 or CD274)/programmed cell death-1 (PD-1) axis is a major immune checkpoint pathway (7). PD-L1 distributed on tumor cells or tumor-infiltrating immune cells (TICs) can bind with the co-inhibitory molecule PD-1 on T cells and then promote T-cell exhaustion (8). Exhausted CD8+ T cells have significantly reduced cytotoxicity, which facilities the cancer cells escape from T cell-mediated immune surveillance (7, 9). These findings suggest that overexpressed PD-L1 may serve as a potential biomarker to predict the tumor progression, poor prognosis and therapeutic response. This hypothesis has been proved by meta-analyses on several cancers, including gynecological cancer types (10–12). For example, Gu et al., synthesized 7 studies of cervical cancer and found that PD-L1 overexpression was related with poor OS.

**MATERIALS AND METHODS**

This meta-analysis followed the guidelines of the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA). Patient consent and ethical approval were waived because this study collected the data from published articles.

**Literature Search**

The online databases of the PubMed, the Cochrane Library and Embase were systematically searched up to April, 2020. The following key words were applied for searches: ("gynecological" OR "cervical" OR "ovarian" OR "endometrial") AND ("cancer" OR "carcinoma" OR "tumor") AND ("PD-L1" OR "programmed
death ligand-1” OR “B7-H1” OR “CD274”). The reference lists in the retrieved papers and relevant reviews were also checked to identify additional publications.

Inclusion and Exclusion Criteria
Two reviewers independently evaluated potential articles. Studies which met the following inclusion criteria were considered eligible: 1) patients were diagnosed as any one type of gynecological cancers by pathological analyses (regardless of epithelial cancers, sarcomas or neuroendocrine tumors); 2) tumor samples for detection of PD-L1 expression were collected during primary tumor removal surgery or diagnostic biopsy before any treatment (such as neoadjuvant chemotherapy, PD-1/PD-L1 inhibitor); 3) the protein expression of PD-L1 on tumor cells or TICs of cancer tissues was determined using immunohistochemistry (IHC); 4) prognosis [OS, PFS, recurrence-free survival (RFS), cancer-specific survival (CSS) or disease-free survival (DFS)], clinicopathological parameters [FIGO stage, lymph node metastasis (LNM), tumor size, depth of infiltration, lymphovascular space invasion (LVSI), FIGO grade] and therapeutic response outcomes [objective response rate (ORR)] were compared between groups with high (positive) and low (negative) expression of PD-L1; 5) HR or relative risks (RR) as well as 95% CI values could be directly extracted, indirectly calculated using raw data or estimated from Kaplan–Meier curve; and 6) the studies were published in English and full-text. Studies were excluded if they were: 1) duplicate articles; 2) case reports, reviews, meeting abstracts, comments or letters; 3) studies evaluating the expression of PD-L1 at mRNA levels or at protein levels using other methods; 4) studies measuring the expression of PD-L1 after treatment; 5) studies having no usable data to estimate HRs and 95%CIs; 6) studies focusing on other cancers; and 7) studies written in other languages. Any disagreements were solved by discussion.

Data Extraction and Quality Assessment
Two researchers independently extracted the following data from each study: name of the first author, year of publication, country, population number, cancer type, clinicopathological features, prognostic endpoint, treatment, IHC detection area/antibody type/antibody source/IHC counting method/cut-off point for PD-L1, HRs with 95% CIs and their statistical analysis approach. Multivariable analysis results were preferentially extracted to obtain HRs and 95%CIs; otherwise, univariate analysis results were collected. The survival data in the Kaplan-Meier curves were read using a digitizing software-Engauge Digitizer 4.1. Any disputes were resolved through discussion.

The quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS) (13) that consists of three key domains: selection, comparability and outcomes or exposure. Total NOS score ranged from 0 to 9. Studies with the final score > 6 were considered to have a high methodological quality.

Statistical Analysis
All data analyses were achieved with STATA 13.0 software (STATA Corporation, College Station, TX, USA). HRs with 95% CIs from each study were pooled to determine the association of PD-L1 expression with the prognostic indicators; while RRs with 95% CIs were utilized to measure the correlation of PD-L1 expression with clinicopathological factors and ORR. HR or RR > 1 indicated a poorer prognosis or higher degree of malignancy in patients with high PD-L1 expression. Association difference was analyzed using z test (p < 0.05). Heterogeneity across studies was quantified by using the Q-test and I² statistic. P < 0.10 and I² > 50% were set as the threshold for defining the studies with significant heterogeneity. A random-effect model was chosen to compute the pooled HR (or RR) for variables from studies with heterogeneity. A fixed-effect model was adopted for studies without evidence of heterogeneity. Egger’s linear regression test (14) was used to detect the publication bias. If bias was seen (p < 0.05), “trim and fill” algorithm (15) was chosen for adjustment of HRs (RRs). Subgroup analysis was also carried out according to study country, sample size, cancer type, IHC detection area, antibody type, antibody source, IHC counting method, cut-off value, HR source and statistical approach to investigate possible causes of heterogeneity. Sensitivity analysis was performed via omitting any one study at a time. P-values and 95% CIs were two-sided.

RESULTS
Study Selection
Figure 1 outlines the flowchart of the literature collection process. A total of 4,882 records were initially identified through searching the electronic database. After removal of 3,502 duplicate records, the titles and abstracts of 1,380 studies were read. Consequently, 1,312 articles were excluded because of they were: case reports (n = 31), meta/review (n = 47), animal studies (n = 93), studies investigating other cancers (n = 759), irrelevant topics (n = 208), without survival or other clinical outcomes (n = 172) and published in other languages (n = 2). After reviewing 68 full-text articles in detail, 16 studies were further removed since sufficient data were not provided for analysis (n = 8). IHC method was not used for detection of PD-L1 protein expression (n = 5) or the samples were collected after treatment (n = 3). Additional 3 studies were supplemented through checking the references of reviews. Finally, 55 studies were eligible for the meta-analysis (16–70).

Characteristics of the Included Studies
Table 1 shows the characteristics of all the included studies. The publication years ranged from 2007 to 2020 and 61.8% (34/55) of them were published within 2019 and 2020. Fourteen studies were performed in China, nine were in the USA, eight were in Japan, four in Korea, each three in Thailand, Turkey, each two in Canada, France, Germany and each one in Norway, Belgium, Brazil, Denmark, Egypt, Greece, Sweden and UK. Twenty-three studies explored the association of PD-L1 with clinical outcomes in ovarian cancer patients, 15 focused on cervical cancer and 14 investigated endometrial cancer. Ovarian and endometrial cancer patients were both enrolled in two studies, while cervical and endometrial cancer patients were both collected in one study. The prognostic endpoint was OS in 38 studies, PFS in 20 studies, RFS in 2 studies, CSS in 6 studies and DFS in 5
studies. FIGO stage (II-IV vs I or III-IV vs I-II) was compared between the groups with high and low expression of PD-L1 in 27 studies; tumor size (≥40 mm vs < 40 mm) was described in 5 studies; LNM (yes vs no) was reported in 16 studies; infiltration depth (≥ 1/2 vs <1/2) was analyzed in 7 studies; LVSI (yes vs no) was observed in 14 studies; FIGO grade was explored in 13 studies. One thing should be noted that tumor cells and TICs were both analyzed and the different IHC counting methods (cut-off points) were applied in some studies, which led to more datasets used for analysis of the prognostic and clinical significance of PD-L1 compared with the actual number of papers (Table S1). The patients in most of these studies underwent surgery, radiotherapy and/or chemotherapy with routine drugs, while six studies specifically explored the efficacy of anti-PD-1/PD-L1 antibodies (pembrolizumab, atezolizumab, nivolumab) for the treatment of gynecological cancers (65–70). The association of PD-L1 expression status with ORR, OS and PFS to these anti-PD-1/PD-L1 immune checkpoint inhibitors was also investigated in these six studies (65–70). The NOS scores of all included studies were > 6, suggesting the methodological quality was high for all of them (Table S2).

**Association Between Programmed Cell Death-Ligand 1 Expression and Survival Overall Analysis in All Gynecological Cancers**

Fifty-one datasets (Table S1) reported the predictive values of PD-L1 for OS in all gynecological cancers. The random-effects model was chosen because of significant heterogeneity (I² = 71.7%, p = 0.000). The results of the meta-analysis indicated no significant association of PD-L1 expression with OS (HR = 1.13; 95% CI: 0.91 - 1.39, p = 0.263). Data on PFS were extracted from 26 datasets (Table S1). The pooled results showed that PD-L1 expression was not significantly associated with PFS (HR =
**TABLE 1 | Characteristics of included studies.**

| Study          | Year | Country | No. | Cancer type | Clinical endpoint | Clinicopathological factors | HR for survival analysis | PD-L1 expression |
|----------------|------|---------|-----|-------------|--------------------|-----------------------------|--------------------------|-------------------|
|                |      |         |     |             |                    | Calculation method           | Source                   | Detected area by IHC | IHC counting method | Cut-off value |
| Wang S (16)    | 2018 | China   | 90  | CC          | OS, DFS            | UV                           | Reported                 | Tumor cells          | UV                | H-score of 100 |
| Enwere EK (17) | 2017 | Canada  | 120 | CC          | OS, DFS            | UV                           | Reported                 | Tumor cells          | SP, SI            | Median percentage, Median tAQUA score >5% |
| Feng M (18)    | 2018 | China   | 219 | CC          | OS                 | UV                           | Estimated                | Tumor cells, TICs    | SP                | >1%              |
| Kim M (19)     | 2017 | Korea   | 27  | CC          | OS, DFS            | UV                           | Estimated                | Tumor cells, TICs    | SP                | >1%              |
| Iijima M (20)  | 2020 | Japan   | 33  | CC          | OS                 | UV                           | Estimated                | Tumor cells, TICs    | SP                | >1%              |
| Tsuchiya T (21)| 2020 | Japan   | 104 | CC          | OS                 | UV                           | Reported                 | Tumor cells, TICs    | SI                | Score (tumor cells, 0; TICs, 3) >5% |
| Kawachi A (22) | 2018 | Japan   | 148 | CC          | DFS                | UV                           | Estimated                | Tumor cells, TICs    | SP                | >5%              |
| Loharamtaweethong K (23) | 2019 | Thailand | 171 | CC          | RFS, CSS           | UV (CSS)                   | Reported                 | Tumor cells, TICs    | SP                | >6%              |
| Miyasaka Y (24) | 2020 | Japan   | 71  | CC          | OS, DFS            | UV                           | Estimated                | Tumor cells, TICs    | SP                | >1%              |
| Chen H (25)    | 2020 | China   | 222 | CC          | OS, DFS            | UV                           | Estimated                | Tumor cells, TICs    | SP                | Tumor cells, >1%; TICs, >5% >5% >0% |
| Lippens (26)   | 2020 | Belgium | 38  | CC          | CSS                | UV                           | Estimated                | Tumor cells          | SI                | Score > 2      |
| Karim R (27)   | 2009 | USA     | 115 | CC          | OS                 | UV                           | Estimated                | Tumor cells          | SP                | >1%              |
| Loharamtaweethong K (28) | 2019 | Thailand | 153 | CC          | RFS, CSS           | UV                           | Estimated                | Tumor cells          | SI                | Score > 1      |
| Grochot RM (29) | 2019 | Brazil  | 59  | CC          | OS, DFS            | UV                           | Estimated                | Tumor cells          | SP                | >5%              |
| Xu M (30)      | 2016 | China   | 112 | OC          | OS                 | UV                           | Estimated                | Tumor cells, TICs    | SP                | >10%             |
| Nhokaew W (31) | 2019 | Thailand | 92  | OC          | DFS                | UV                           | Estimated                | Tumor cells          | SI                | >5%              |
| Schmoeckel E (32) | 2019 | Germany | 288 | OC          | OS                 | UV                           | Estimated                | Tumor cells          | SP                | >1%              |
| Hamanishi J (33)| 2007 | Japan   | 50  | OC          | OS, DFS            | UV                           | Estimated                | Tumor cells, TICs    | SP                | >5%              |
| Mesnage SJL (34)| 2017 | France  | 50  | OC          | PFS, DFS           | UV                           | Reported                 | Tumor cells, TICs    | SP                | >10%             |
| Zhu J (35)     | 2017 | China   | 122 | OC          | OS, DFS            | UV                           | Reported                 | Tumor cells, TICs    | SP                | >1%              |
| Zong L (37)    | 2020 | China   | 146 | OC          | OS, DFS            | UV                           | Estimated                | Tumor cells          | SP                | >5%              |
| Wang Q (38)    | 2017 | China   | 107 | OC          | OS                 | UV                           | Estimated                | Tumor cells, TICs    | SP                | >5%              |
| Zhu X (39)     | 2018 | China   | 112 | OC          | OS                 | UV                           | Estimated                | Tumor cells, TICs    | SP (or SI)        | >10% (or score >1) |
| Buderath P (40) | 2019 | Germany | 179 | OC          | OS                 | UV                           | Estimated                | Tumor cells, TICs    | SP                | >0%              |
| Kim KH (41)    | 2019 | Korea   | 248 | OC          | OS                 | UV                           | Estimated                | Tumor cells, TICs    | SP + SI           | >5% + score >2 |
| Zhu X (42)     | 2019 | China   | 112 | OC          | OS, DFS            | UV                           | Reported                 | Tumor cells, TICs    | SP (or SI)        | >10% (or score >1) |
| Zhang L (43)   | 2019 | China   | 124 | OC          | OS, DFS            | UV                           | Reported                 | Tumor cells          | IRS               | Score > 3      |

(Continued)
TABLE 1 | Continued

| Study | Year | Country | No. | Cancer type | Clinical endpoint | Clinicopathological factors | HR for survival analysis | PD-L1 expression | Cut-off value |
|-------|------|---------|-----|-------------|-------------------|-----------------------------|---------------------------|----------------|--------------|
|       |      |         |     |             |                   | Calculation method          | Source                  | Detected area by IHC | IHC counting method |               |
| Aldredge J (44) | 2019 | USA | 46 | OC/EC | OS | FIGO stage | UV | Reported | Tumor cells, TIC | Tumor cells, >0%; CPS, score > 1 |
| De La Motte Rouge T (45) | 2019 | France | 51 | OC | OS, DFS | UV | Reported | Tumor cells | TICs | Other | > 1000 |
| Martin de la Fuente L (46) | 2020 | Sweden | 130 | OC | OS | MV | Reported | Tumor cells | TICs | SI | > 1% |
| Chatterjee J (47) | 2017 | UK | 48 | OC | PFS | UV | Reported | TICs | SI | Score > 1% |
| Henricksen JR (48) | 2020 | Denmark | 283 | OC | OS | UV | Reported | TICs | SI | Score > 1% |
| Sungu N (49) | 2019 | Turkey | 127 | EC | OS | FIGO stage, grade | UV | Estimated | Tumor cells, TICs | Score > 1% |
| Vagios S (50) | 2019 | Greece | 101 | EC | OS, PFS | FIGO stage, infiltration depth, LNM | MV | Reported | TICs | SI + SP | Score > 2 (± 1%) |
| Kucukgoz Gulec U (51) | 2019 | Turkey | 53 | EC | OS | FIGO stage, infiltration depth, grade | MV | Reported | TICs | SI | > 1% |
| Zhang S (52) | 2020 | Japan | 221 | EC | OS | FIGO stage, infiltration depth, grade | MV | Reported | TICs | IRS, SI | TC, score > 0; TICs, score > 4 |
| Kim J (53) | 2018 | Korea | 183 | EC | PFS | FIGO stage, infiltration depth, grade | UV (tumor cells), MV (TICs) | Reported | Tumor cells, TICs | SI | > 1.977 |
| Jones TE (54) | 2021 | USA | 43 | EC | OS | FIGO stage | UV | Reported | TICs | SI | > 5% |
| Kucukgoz Gulec U (55) | 2020 | Turkey | 59 | EC | OS | FIGO stage | UV | Reported | TICs | SI | > 5% |
| Tawadros AIF (56) | 2018 | Egypt | 95 | EC | OS | FIGO stage, infiltration depth, grade | UV | Reported | TICs | IRS | Score > 3 |
| Li ZB (57) | 2017 | USA | 700 | EC | OS | FIGO stage | UV | Estimated | Tumor cells, TICs | SI | > 1% |
| Mo ZF (58) | 2016 | China | 75 | EC | OS | FIGO stage | UV | Estimated | Tumor cells, TICs | IRS | > 5% |
| Yamashita H (59) | 2018 | Japan | 149 | EC | OS, PFS | FIGO stage | UV | Estimated | Tumor cells, TICs | SI | > 5% |
| Engerud H (60) | 2020 | Norway | 700 | EC | CSS | FIGO stage, infiltration depth, grade | UV | Estimated | Tumor cells, TICs | IRS | Score > 0 |
| Crumley S (61) | 2019 | USA | 132 | EC | OS | FIGO stage, infiltration depth, grade | UV | Estimated | Tumor cells, TICs | SI + SP | Score > 2 ± 0%; Score > 3 + > 2% |
| Li MJ (62) | 2017 | China | 113 | OC | OS | FIGO stage | UV (DFS), MV (OS) | Reported | Tumor cells | IRS | Score > 2 |
| Webb JR (63) | 2016 | Canada | 479 | OC | OS | FIGO stage, grade | UV (other), MV (OS), UV (KM) | Reported, estimated | Tumor cells | IRS | Score > 1 |
| Xue CY (64) | 2020 | China | 77 | OC | OS, PFS | FIGO stage, grade | UV | Estimated | Tumor cells | IRS | H-score of 100 |
| Chung HC (65) | 2019 | Korea | 98 | CC | OS, PFS, ORR | OS, PFS, ORR | UV | Estimated | TICs | SI | Score > 1 |
| Liu JF (66) | 2019 | USA | 12/15 | OC/EC | OS, ORR | OS, PFS, ORR | UV | Estimated | TICs | SI | Score > 1 |
| Matulonis UA (67) | 2019 | USA | 12/15 | OC | ORR | UV | Reported | TICs | SI | Score > 1 |
| Zamarin D (68) | 2020 | USA | 52 | OC | ORR | UV | Reported | TICs | SI | Score > 1 |
| Santin AD (69) | 2020 | USA | 12/15 | OC | ORR | UV | Reported | TICs | SI | Score > 1 |

OS, overall survival; PFS, progression free survival; RFS, recurrence-free survival; CSS, cancer-specific survival; DFS, disease-free survival; FIGO, International Federation of Gynecology and Obstetrics; LNM, lymph node metastasis; LVSI, lymphovascular space invasion; ORR, overall response rate; KM, Kaplan–Meier curve; UV, univariate analysis; MV, multivariate analysis; SP, staining percentage; SI, staining intensity score; IRS, immunoreactive SI (that is, IRS = SI × SP); IHC, immunohistochemistry; TICs, tumor-infiltrating immune cells; CPS, combined positive; estimated, the HR was obtained from Kaplan–Meier curve; HGSC, high-grade serous ovarian cancer.
1.04; 95% CI: 0.85 – 1.29, p = 0.682) under a random-effect model (I^2 = 63.7%, p = 0.000). Meta-analysis using the corresponding datasets also demonstrated that positive expression of PD-L1 was not related to RFS (n = 2; HR = 1.08; 95% CI: 0.85 – 1.29, p = 0.682; I^2 = 0%, p = 0.746), DFS (n = 6; HR = 1.26; 95% CI: 0.60 – 2.64, p = 0.545; I^2 = 81.5%, p = 0.000) and CSS (n = 10; HR = 0.81; 95% CI: 0.65 – 1.01, p = 0.056; I^2 = 28.8%, p = 0.180).

Subgroup Analysis in All Gynecological Cancers

To further investigate the possible prognostic potential of PD-L1 in gynecological cancers, the subgroup analysis was performed. The results showed that, in studies with reported HR, high PD-L1 expression was correlated with shorter OS (n = 33; HR = 1.27; 95% CI: 1.01 – 1.61, p = 0.041) (Figure 2; Table 2). Furthermore, PD-L1-positive status with a cut-off value of 5% predicted a poor OS (n = 8; HR = 2.10; 95% CI: 1.17 – 3.75, p = 0.013), but not 1% or others (Table 2). Although a significant association between PD-L1 and PFS was also observed in analyses of non-Asian population (n = 10; HR = 1.04; 95% CI: 1.00 – 1.07, p = 0.040) (Figure 3; Table 3), the corresponding HR was relatively lower and approximated to 1, indicating the clinical relevance of PD-L1 expression with PFS may be insignifcant. The conclusions of PFS from estimated HR may be undetermined, although it was significant (p = 0.001). Owing to the small number of included studies, subgroup analysis was not performed for RFS, DFS and CSS.

Sub-Subgroup Analysis in Each Cancer Type

In addition, non-significant relationships were seen between PD-L1 and OS/PFS in any type of gynecological cancers (Tables 2 and 3). To further explore whether PD-L1 expression may be a significant prognostic factor for specific gynecological cancer type, the sub-subgroup analysis was also conducted. The results revealed that PD-L1 overexpression on TICs predicted a favorable OS for ovarian cancer (n = 8; HR = 1.89; 95% CI: 1.06 – 3.36, p = 0.031) and sample size > 100 (n = 9; HR = 1.92; 95% CI: 1.07 – 3.45, p = 0.030), further increasing the credibility to use PD-L1 as the prognostic biomarker for cervical cancer (Table S3). Likewise, PD-L1 overexpression was correlated with a lower OS rate in non-Asian individuals with endometrial cancer (n = 7; HR = 1.60; 95% CI: 1.07 – 2.40, p = 0.022) (Table S3). The cut-off value of 5% may be optimal (n = 3; HR = 2.37; 95% CI:

![FIGURE 2](https://www.frontiersin.org/) | Forest plots showing the significant association between high PD-L1 expression and a poor overall survival (OS) in all gynecological cancers patients by analysis of the studies with reported HR, HR, hazard ratio; CI, confidence interval.
1.35 – 4.18, p = 0.003) compared with 1% and others (Table S3). The association between PD-L1 expression and PFS may be clinically significant only in the Asian endometrial cancer patients (n = 5: HR = 1.59; 95% CI: 1.01 – 2.51, p = 0.045) (Table S4), but not in cervical cancer because the pooled HR was obtained from estimated HR in most of individual studies (Table S1) or in ovarian cancer because the pooled HR approximated to 1 (Table S4).
**TABLE 3 | Subgroup analysis on the outcome of PFS.**

| Comparison          | Studies | HR(95%CI) | P-value | I² | P_H-value |
|---------------------|---------|-----------|---------|----|-----------|
| Region              |         |           |         |    |           |
| Asian               | 16      | 1.20(0.86,1.97) | 0.209   | 75.8 | 0.000     |
| Non-Asian           | 10      | 1.04(0.00,1.07) | **0.040** | 0.0 | 0.670     |
| Sample size         |         |           |         |    |           |
| <100                | 16      | 0.80(0.72,1.34) | 0.921   | 70.4 | 0.000     |
| >100                | 10      | 1.14(0.83,1.58) | 0.423   | 50.4 | 0.033     |
| IHC counting method |         |           |         |    |           |
| SI                  | 8       | 1.22(0.73,2.03) | 0.451   | 77.3 | 0.000     |
| SP                  | 15      | 0.89(0.74,1.08) | 0.226   | 0.0 | 0.478     |
| IRS                 | 3       | 2.22(0.76,5.53) | 0.149   | 87.7 | 0.000     |
| Cut-off             |         |           |         |    |           |
| 1%                  | 8       | 0.75(0.55,1.02) | 0.065   | 0.0 | 0.669     |
| 5%                  | 2       | 0.76(0.43,1.36) | 0.361   | 0.0 | 0.947     |
| Others              | 16      | 1.25(0.94,1.65) | 0.120   | 74.4 | 0.000     |
| Cancer type         |         |           |         |    |           |
| Ovarian             | 10      | 1.14(0.87,1.49) | 0.360   | 62.0 | 0.005     |
| Cervical            | 9       | 0.87(0.54,1.39) | 0.561   | 68.6 | 0.001     |
| Endometrial         | 7       | 1.27(0.70,2.30) | 0.431   | 56.1 | 0.034     |
| Antibody type       |         |           |         |    |           |
| Monoclonal          | 22      | 0.95(0.73,1.22) | 0.665   | 52.1 | 0.002     |
| Unclear             | 4       | 1.65(0.93,3.01) | 0.106   | 86.3 | 0.000     |
| Antibody source     |         |           |         |    |           |
| Mouse               | 3       | 0.79(0.28,2.41) | 0.684   | 86.7 | 0.001     |
| Rabbit              | 19      | 0.99(0.79,1.24) | 0.894   | 28.5 | 0.120     |
| Unclear             | 4       | 1.65(0.93,3.01) | 0.106   | 86.3 | 0.000     |
| IHC detection area  |         |           |         |    |           |
| Tumor cells         | 17      | 1.16(0.86,1.56) | 0.337   | 59.8 | 0.001     |
| TICs                | 7       | 1.05(0.68,1.61) | 0.830   | 54.4 | 0.041     |
| Unclear             | 4       | 1.65(0.93,3.01) | 0.106   | 86.3 | 0.000     |
| HR method           |         |           |         |    |           |
| MV                  | 7       | 1.46(0.82,2.62) | 0.201   | 68.4 | 0.004     |
| Tumor cells + TICs  | 2       | 0.60(0.29,1.24) | 0.167   | 75.7 | 0.004     |
| UV                  | 9       | 0.95(0.76,1.20) | 0.661   | 62.3 | 0.000     |
| HR source           |         |           |         |    |           |
| Reported            | 16      | 1.29(0.10,1.67) | 0.052   | 67.1 | 0.000     |
| Unclear             | 10      | 0.65(0.50,0.84) | **0.001** | 3.3 | 0.409     |

OS, overall survival; UV, univariate analysis; MV, multivariate analysis; SP, staining percentage; SI, staining intensity score; IRS, immunoreactive SI (that is, IRS = SI × SP); HR, hazard ratio; CI, confidence interval; IHC, immunohistochemistry; TIC, tumor-infiltrating immune cells. P⁺ value for association; P_H value for heterogeneity obtained by Q-test; I², the degree of heterogeneity by I² statistic. Bold indicated the significance after analysis of two or more than two studies (p < 0.05).

**Association of Programmed Cell Death-Ligand 1 Expressions With Clinicopathological Characteristics**

**Overall Analysis in All Gynecological Cancers**

As shown in **Table 4**, the overall pooled results showed that PD-L1 overexpression correlated with LNM (n = 21; RR = 1.14; 95% CI: 1.01 – 1.51, p = 0.003), advanced FIGO stage (III-IV vs I-II) (n = 34; RR = 1.18; 95% CI: 1.05 – 1.32, p = 0.007) and LVSI (n = 20; RR = 1.26; 95% CI: 1.05 – 1.57, p = 0.034).

**Subgroup Analysis in All and Each Cancer Type**

High expressed PD-L1 could predict LNM for ovarian (n = 4; RR = 1.70; 95% CI: 1.23 – 2.34, p = 0.001) and endometrial (n = 6; RR = 1.85; 95% CI: 1.17 – 2.91, p = 0.008) cancer patients. These associations for the high risk of LNM may be mainly resulted from the upregulated expression of PD-L1 on tumor cells (ovarian: n = 4, RR = 1.70; 95% CI: 1.23 – 2.34, p = 0.001). Likewise, endometrial cancer patients may have LVSI (n = 14, RR = 1.51; 95% CI: 1.15 – 2.00, p = 0.004) if PD-L1 was high expressed on TICs (n = 5; RR = 1.72; 95% CI: 1.34 – 2.18, p = 0.000; **Figure 5B**) or tumor cells (n = 8; RR = 1.61; 95% CI: 1.03 – 2.51, p = 0.035; **Figure 5C**).

PD-L1 high expressed on TICs was associated with increasing infiltration depth (n = 2; RR = 1.77; 95% CI: 1.33 – 2.35, p = 0.000) and grade (n = 3; RR = 2.37; 95% CI: 1.47 – 3.83, p = 0.000) in endometrial cancer (**Table 4**). There was no significant relationship of PD-L1 with tumor size regardless of overall or subgroup analyses.

**Association of PD-L1 Expressions With Response to Anti-Programmed Cell Death-1/Programmed Cell Death-Ligand 1 Treatment**

**Overall Analysis in All Gynecological Cancers**

Twelve datasets reported the ORR, while OS and PFS were recorded in 5 and 7 datasets, respectively. Meta-analysis of these datasets indicated that patients with PD-L1 positive expression may get more benefit from anti-PD-1/PD-L1 antibodies than PD-L1 negative patients, showing a higher ORR (RR = 1.98; 95% CI: 1.38 – 2.83, p = 0.000; **Figure 6A**) and longer OS (HR = 0.34; 95% CI: 0.46 – 0.81, p = 0.001) (**Figure 6C**) compared to PD-L1 negative patients.

**Subgroup Analysis in All Gynecological Cancers**

Subgroup analysis was performed only for ORR and PFS, not OS because of small articles included. The results showed that PD-1/PD-L1 inhibitors should be especially recommended for PD-L1-high expressed patients.
FIGURE 4 | Forest plots showing the association of PD-L1 expression for ovarian cancer patients. (A) PD-L1 expression on tumor-infiltrating immune cells and overall survival (OS). (B) PD-L1 expression on tumor cells and LNM. (C) PD-L1 expression on tumor cells and FIGO stage. FIGO, International Federation of Gynecology and Obstetrics; LNM, lymph node metastasis; HR, hazard ratio; RR, relative risk; CI, confidence interval.
TABLE 4 | Correlations between PD-L1 expression and clinical characteristics.

| Comparison                                | Studies | RR(95% CI)       | P-value | I²   | P-value |
|-------------------------------------------|---------|------------------|--------|------|--------|
| LNM (yes vs no)                           | Overall | 21               | 1.23(1.09,1.51) | 0.003 | 42.2  | 0.022 |
| Cancer type                               | Ovarian | 4                | 1.70(1.23,2.34) | 0.001 | 51.2  | 0.105 |
| Cervical                                  | 11      | 1.03(0.83,1.27)  | 0.792  | 29.3 | 0.167 |
| Endometrial                               | 6       | 1.85(1.17,2.91)  | 0.008  | 46.3 | 0.097 |
| IHC detection area (overall)              | Tumor cells | 19      | 1.33(1.12,1.59) | 0.001 | 42.5  | 0.027 |
|                                            | TICs    | 2               | 0.98(0.64,1.49) | 0.907 | 48.2  | 0.165 |
| IHC detection area (ovarian)              | Tumor cells | 4       | 1.70(2.23,3.33) | 0.001 | 51.2  | 0.105 |
|                                            | TICs    | 2               | 0.98(0.64,1.49) | 0.907 | 48.2  | 0.165 |
| IHC detection area (cervical)             | Tumor cells | 9       | 1.05(0.82,1.33) | 0.725 | 33.7  | 0.148 |
|                                            | TICs    | 2               | 0.98(0.64,1.49) | 0.907 | 48.2  | 0.165 |
| IHC detection area (endometrial)          | Tumor cells | 6       | 1.85(1.17,2.91) | 0.008 | 46.3  | 0.097 |
| Tumor size (≥4 cm vs < 4 cm)              | Overall | 6               | 1.05(0.86,1.29) | 0.637 | 23.7  | 0.256 |
| Cancer type                               | Cervical | 6      | 1.05(0.86,1.29) | 0.637 | 23.7  | 0.256 |
| IHC detection area (overall)              | Tumor cells | 5       | 1.11(0.90,1.37) | 0.339 | 10.6  | 0.346 |
|                                            | TICs    | 1               | 0.61(0.24,1.51) | –     | –     | –     |
| FIGO stage (III-IV vs I)                  | Overall | 23              | 1.21(1.07,1.37) | 0.003 | 42.5  | 0.017 |
| Cancer type                               | Cervical | 14     | 1.23(1.12,1.36) | 0.000 | 33.1  | 0.110 |
| IHC detection area (ovarian)              | Tumor cells | 23     | 1.22(0.85,1.76) | 0.279 | 82.5  | 0.000 |
|                                            | TICs    | 1               | 0.98(0.64,1.49) | 0.907 | 48.2  | 0.165 |
| FIGO stage (II-IV vs I)                   | Overall | 13              | 1.23(1.09,1.39) | 0.009 | 57.7  | 0.017 |
| Cancer type                               | Endometrial | 4     | 0.91(0.77,1.09) | 0.286 | 0.0   | 0.688 |
| IHC detection area (overall)              | Tumor cells | 5       | 1.33(0.71,2.27) | 0.837 | 85.0  | 0.000 |
|                                            | TICs    | 1               | 0.87 (0.57,1.34) | 0.520 | 79.1  | 0.002 |
| IHC detection area (cervical)             | Tumor cells | 3       | 1.77(0.45,6.96) | 0.417 | 78.6  | 0.009 |
|                                            | TICs    | 2               | 0.94(0.48,1.84) | 0.254 | 66.5  | 0.084 |
| IHC detection area (endometrial)          | Tumor cells | 7       | 1.10(0.88,1.37) | 0.019 | 80.5  | 0.001 |
|                                            | TICs    | 2               | 1.72(1.62,5.24) | 0.007 | 60.0  | 0.005 |
| Infiltration depth (≥ 1/2 vs <1/2)        | Overall | 9               | 1.27(0.99,1.63) | 0.058 | 78.1  | 0.000 |
| Cancer type                               | Cervical | 1      | 1.12(0.96,1.30) | 0.150 | –     | –     |
| IHC detection area (cervical)             | Tumor cells | 8       | 1.34(0.96,1.87) | 0.082 | 80.8  | 0.000 |
|                                            | TICs    | 1               | 0.87(0.57,1.34) | 0.520 | 79.1  | 0.002 |
| IHC detection area (endometrial)          | Tumor cells | 7       | 1.15(0.88,1.49) | 0.316 | 76.3  | 0.000 |
|                                            | TICs    | 2               | 1.77(1.32,2.35) | 0.000 | 85.0  | 0.000 |
| LVSI (yes vs no)                          | Overall | 20              | 1.26(1.02,1.57) | 0.034 | 69.5  | 0.000 |
| Cancer type                               | Cervical | 6      | 0.91(0.77,1.09) | 0.286 | 0.0   | 0.450 |
| IHC detection area (overall)              | Tumor cells | 13     | 1.28(0.91,1.67) | 0.044 | 89.2  | 0.000 |
|                                            | TICs    | 6               | 1.41(0.95,2.10) | 0.902 | 64.6  | 0.015 |
| IHC detection area (cervical)             | Tumor cells | 1      | 0.92(0.58,1.44) | 0.700 | –     | –     |
|                                            | TICs    | 1               | 0.80(0.50,1.28) | 0.354 | –     | –     |
| IHC detection area (endometrial)          | Tumor cells | 8       | 1.61(1.03,2.51) | 0.035 | 75.4  | 0.000 |
|                                            | TICs    | 5               | 1.71(1.34,2.18) | 0.000 | 19.2  | 0.293 |
| Grade (G3 vs G1+ G2)                      | Overall | 18              | 1.20(0.96,1.51) | 0.111 | 74.0  | 0.000 |
| Cancer type                               | Ovarian | 10               | 1.22(0.90,1.64) | 0.205 | 66.8  | 0.001 |
| Cervical                                  | 2      | 0.88(0.76,1.01) | 0.075  | 0.0  | 0.557 |
| Endometrial                               | 7       | 1.48(0.79,2.77) | 0.221  | 77.5 | 0.000 |
| IHC detection area (overall)              | Tumor cells | 11     | 1.01(0.76,1.35) | 0.924 | 68.1  | 0.001 |
|                                            | TICs    | 5               | 1.86(0.99,3.47) | 0.053 | 84.3  | 0.000 |
|                                            | Tumor cells + TICs | 4     | 1.15(0.95,1.39) | 0.145 | 10.0  | 0.380 |
| IHC detection area (ovarian)              | Tumor cells | 6       | 0.96(0.77,1.20) | 0.722 | 24.2  | 0.252 |

(Continued)
positive ovarian patients who could gain the high ORR (n = 6: RR = 2.17; 95% CI: 1.38 – 3.42, p = 0.001) and PD-L1-positive cervical patients who could obtain a longer PFS (n = 2: RR = 0.44; 95% CI: 0.29 – 0.68, p = 0.000) (Table 5).

Publication Bias and Sensitivity Analyses

Although significant heterogeneities were present for analysis of OS, PFS, DFS, LNM, FIGO stage, infiltration depth, LVSI and grade, Egger’s linear regression test analysis showed that there were no publication bias among their related studies (OS: p = 0.478; PFS: p = 0.939; DFS, p = 0.534; LNM, p = 0.917; FIGO stage, p = 0.087; infiltration depth, p = 0.181; LVSI, p = 0.504; grade, p = 0.246), indicating the credibility of results. Sensitivity analyses also confirmed the robustness of the results.

DISCUSSION

There were several meta-analyses to analyze the prognostic significance PD-L1 by integrating multiple solid tumor types (71–74), but rare studies included the gynecological cancer [n = 1, cervical carcinoma (73, 75); n = 1 each for cervical and ovarian cancer (74)]. Our present study, for the first time, specifically investigated the association of PD-L1 expression with the prognosis and clinicopathological factors in all gynecological cancer patients. Pooled results showed that PD-L1 overexpression was not associated with OS, PFS, DFS, CSS and LNM, but subgroup analysis suggested PD-L1 overexpression predicted shorter OS in studies with reported HR and the cut-off value of 5%. Furthermore PD-L1 overexpression predicted clinical malignant characteristics of gynecological cancer patients (including LNM, advanced FIGO stage and LVSI). These conclusions seemed to be in line with the results of previous meta-studies of clinical samples (71–74) and the tumor-promoting mechanisms demonstrated by in vitro and in vivo experiments. For example, Wang et al. found that overexpression of PD-L1 significantly increased the migration, invasion, proliferative and colony-forming abilities of Siha and Me180 cervical cancer cell lines compared with control. Tumor xenograft growth was also significantly enhanced and LNM was more apparently observed in abdominal cavities of mice injected with PD-L1-overexpressing cervical cancer cells (16). Fei et al. also demonstrated that ectopic expression of PD-L1 promoted nasopharyngeal carcinoma cell invasion and metastasis in vitro and in vivo, which was attributed to its capability to activate the epithelial-mesenchymal transition process in a PI3K/AKT-dependent manner (76).

Although previous meta-analysis studies had investigated the prognostic and clinicopathological impact of PD-L1 for cervical (10), ovarian (12) and endometrial cancer (11), the number of articles included was relatively small. Our study performed an updated meta-analysis for each gynecological cancer type by increasing the number of articles included by more than two fold. As expected, some of our results were obviously different from previous reports: our analysis showed that PD-L1 was not significantly associated with OS and PFS in any cancer type, but the study of Gu et al. reported PD-L1 overexpression was related to a poor OS in patients with cervical cancer (10); our results revealed that LNM, high FIGO stage and LVSI were more frequently observed in PD-L1-positive endometrial cancer patients compared with negative controls; while Lu et al. proved that elevated PD-L1 expression was only correlated with advanced stage, but not LVSI (11). Thus, we consider our conclusions may be more believable by analysis of larger samples. Furthermore, compared with the above meta-analyses (10, 11), one innovation point in our study was to collect the PD-L1 expression on both of tumor cells and TICs, not only tumor cells. As anticipated, we obtained several new conclusions: high expression of PD-L1 on TICs was a protective factor for a poor OS in ovarian cancer patients (HR < 1), but a risk factor for unfavorable OS in cervical cancer patients, advanced stage, LVSI, high grade and increasing infiltration depth in endometrial cancer patients (HR > 1). Positive expression of PD-L1 on tumor cells was associated with a poor OS for ovarian cancer patients, LVSI for endometrial cancer patients, LNM and advanced stage for both cancer types. The anti-tumor roles of high PD-L1 on TICs for ovarian patients was also illustrated in other cancers, including colorectal (77), breast (78) and high-grade neuroendocrine carcinoma of lung (79). Its anti-cancer effects may be related with an adaptive mechanism to further activate and increase levels of cytotoxic CD8+ T cells as well as tumor-infiltrating lymphocytes (78, 80–82). Also, there was a study of non-small cell lung cancer to report that PD-L1 expression on tumor cells and TICs was associated with high levels of M2 tumor-associated macrophages and then led to a poor prognosis and an aggressive malignant phenotype, which may be one potential reason to cause the tumor-promoting effects of PD-L1 on tumor cells and TICs for gynecological cancers (83, 84).

| TABLE 4 | Continued |
| --- | --- |
| Comparison | Studies | RR(95%CI) | P-value | I² | P-value |
| --- | --- | --- | --- | --- | --- |
| TICs | 1 | 2.45(1.69,3.57) | 0.000 | – | – |
| Tumor cells + TICs | 4 | 1.19(0.95,1.39) | 0.145 | 0.0 | 0.806 |
| Tumor cells | 1 | 0.85(0.72,1.01) | 0.070 | – | – |
| TICs | 1 | 0.94(0.72,1.22) | 0.629 | – | – |
| TICs | 4 | 1.19(0.86,1.54) | 0.344 | 85.6 | 0.000 |
| Tumor cells + TICs | 3 | 2.37(1.47,3.83) | 0.000 | 0.0 | 0.464 |

FIGO, International Federation of Gynecology and Obstetrics; LNM, lymph node metastasis; LVSI, lymphovascular space invasion; RR, relative risk; CI, confidence interval; IHC, immunohistochemistry; TICs, tumor-infiltrating immune cells. P_α, p-value for association; P_β, p-value for heterogeneity obtained by Q-test; I², the degree of heterogeneity by I² statistic. Bold indicated the significance after analysis of two or more than two studies (p < 0.05).
In consideration of the fact that PD-L1 was highly expressed and the use of anti-PD-L1/PD-1 antibodies induced cell apoptosis and cell-cycle arrest in G0/G1 phase in gynecological cancer cells (85), increasing scholars recommended to using the PD-L1/PD-1 immune checkpoint inhibitors for the treatment of gynecological cancers in clinic (4, 86). However, like other therapeutic methods, there were differences in the therapeutic efficiency among different patients (69). Thus, it is also necessary to explore biomarkers to distinguish the patients and then schedule the PD-L1/PD-1 immune checkpoint inhibitors more efficiently.

FIGURE 5 | Forest plots showing the association of PD-L1 expression for endometrial cancer patients. (A) PD-L1 expression on tumor cells and LNM. (B) PD-L1 expression on tumor-infiltrating immune cells and LVSI. (C) PD-L1 expression on tumor cells and LVSI. LNM, lymph node metastasis. LVSI, lymphovascular space invasion; HR, hazard ratio; RR, relative risk; CI, confidence interval.
reasonably. Previous studies on other cancers suggested the magnitude of clinical benefit from PD-L1/PD-1 inhibitors was PD-L1-dependent (87, 88). Therefore, we also investigated the associations between PD-L1 expression and ORR, OS, PFS in gynecological cancer patients. In agreement with the above studies (87–89), we also found PD-L1 patients had a significantly higher ORR (especially ovarian cancer), OS and PFS (especially cervical cancer) than PD-L1-negative patients.

**FIGURE 6** | Forest plots showing the association between PD-L1 expression and response to PD-1/PD-L1 inhibitors in gynecological cancers. (A) Overall response rate (ORR). (B) Overall survival (OS). (C) Progression-free survival (PFS). HR, hazard ratio; CI, confidence interval.
Although Kowanetz et al. observed that the ORR was relatively lower in patients with tumors expressing high PD-L1 levels on tumor cells than TICs (40% vs 22%) \((80)\), our subgroup results indicated no association with tumor cells or TICs, which may be related with the small sample size.

Several limitations should be acknowledged in this study. First is the retrospective nature in most of included studies. Second, the cut-off value of PD-L1 was determined by different methods in included studies, which influenced its clinical use. Third, the number of included studies to report the association of PD-L1 expression with RFS/CSS/DFS/response to anti-PD-L1/PD-1 treatment was relatively small, which may compromise the credibility of the results and influence the subgroup analysis for each cancer type. Fourth, the estimation of HR from Kaplan–Meier curve may introduce some errors. Fifth, the restriction of articles published in other languages may lead to some negative results neglected.

**CONCLUSION**

Our meta-analyses (Figure 7) indicated that positive PD-L1 detected by IHC may serve as a valuable predictor of a poor prognosis (OS, PFS), malignant clinicopathological characteristics (LNM, advanced FIGO stage and LVSI) and response efficiency to anti-PD-1/PD-L1 (ORR, OS, PFS) for patients with gynecological cancers, especially expression on tumor cells. High expressed PD-L1 on TICs may exert dual functions, including anti-cancer for ovarian cancer or oncogenic for cervical and endometrial cancers.
**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding author.

**AUTHOR CONTRIBUTIONS**

CZ and QY conceived and designed the study, collected the data, and performed the analysis. CZ wrote the first draft of the manuscript. QY was involved in the interpretation of the analyses and revised the manuscript. All authors contributed to the article and approved the submitted version.

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**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020.572203/full#supplementary-material

**Supplementary Table 1** | The data extracted from the published studies.

**Supplementary Table 2** | The Newcastle-Ottawa scale (NOS) quality assessment of the enrolled studies.

**Supplementary Table 3** | Subgroup analysis on the outcome of OS in each cancer type.

**Supplementary Table 4** | Subgroup analysis on the outcome of PFS in each cancer type.
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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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