Prognostic Significance of Clinicopathological Factors Influencing Overall Survival and Event-Free Survival of Patients with Cervical Cancer: A Systematic Review and Meta-Analysis

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Background: Cervical cancer (CC) is the most frequent type of cancer among women and its poor prognosis is a main concern, while the prognostic factors for CC have still remained controversial. We conducted this systematic review and meta-analysis to identify the prognostic significance of clinicopathological factors, influencing overall survival (OS), and event-free survival (EFS) of CC patients.

Material/Methods: The electronic databases of PubMed, Embase, and the Cochrane library were systematically searched for identification of eligible studies published until June 2021. The pooled hazard ratio (HR) with 95% confidence interval (CI) were calculated using the random-effects model. Sensitivity and subgroup analyses and assessment of publication bias were also conducted.

Results: We selected 140 studies that involved 47,965 patients for the meta-analysis. The results revealed that age, cell type, depth of tumor invasion, the International Federation of Gynecology and Obstetrics stage, hemoglobin level, histological grade, leukocytosis, lymph node involvement, lymph-vascular space invasion, neutrophil-to-lymphocyte ratio, parametrial invasion, platelet-to-lymphocyte ratio, resection margin, squamous cell carcinoma antigen level, thrombocytosis, tumor grade, tumor size, and tumor volume were clinicopathological factors influencing OS and EFS of CC patients (P<0.05).

Conclusions: This study comprehensively identified the prognostic significance of clinicopathological factors, influencing OS, and EFS of CC patients. However, further large-scale prospective studies should be conducted to verify our findings and develop more accurate prognostic models for CC.

Keywords: Pathological Conditions, Signs and Symptoms • Prognosis • Uterine Cervical Neoplasms

Abbreviations: CC – cervical cancer; CI – confidence interval; EFS – event-free survival; FIGO – International Federation of Gynecology and Obstetrics; HR – hazard ratio; LNI – lymph node involvement; LVS1 – lymph-vascular space invasion; NLR – neutrophil-to-lymphocyte ratio; NOS – Newcastle-Ottawa Scale; OS – overall survival; PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analysis; PLR – platelet-to-lymphocyte ratio; SCCA – squamous cell carcinoma antigen

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/934588
Background

Cervical cancer (CC) is a frequent gynecologic malignancy and is the primary cause of cancer-related deaths in women worldwide [1,2]. A total of 604,127 new cases and 341,831 CC-related deaths were reported in 2020, accounting for 7.7% of all cancer-related deaths in women [1]. The HPV infection rate is rising, particularly in developing countries, where the incidence and prevalence of CC are still high, which can be attributed to the lack of a universal and integrated vaccination program for CC [3,4]. The prognosis of CC could be improved by a variety of treatment strategies on the basis of the disease stage, metastasis, or recurrence [2,5]. The International Federation of Gynecology and Obstetrics (FIGO) staging system has been widely used for predicting the prognosis of CC patients, while the prognosis of CC patients with the same FIGO stage varies [6]. Several prognostic models have already been introduced to predict the prognosis of CC on the basis of tumor and demographic characteristics [7-10], but the practicality of these models is limited by uneven quality and various characteristics of clinical setting, outcomes, and predictors. Therefore, additional prognostic factors should be explored to improve the prognosis of CC patients.

We therefore attempted to construct a prognostic model using the previously defined factors to predict the prognosis of CC patients. Numerous systematic reviews and meta-analyses have been performed to identify the prognostic significance of other variables in estimating the rates of overall survival (OS) and event-free survival (EFS) [11-15]. However, the other clinicopathological characteristics influencing the prognosis of CC patients were not assessed. There is an urgent need to summarize the prognostic variables to establish more comprehensive prognostic models. We therefore conducted the present systematic review and meta-analysis to identify the prognostic factors for CC and we also investigated the prognostic significance of these factors for CC.

Material and Methods

Search Strategy and Selection Criteria

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement was utilized, as described previously [16]. Studies on the prognostic significance of clinicopathological factors, influencing OS, and EFS of CC patients were selected, and the language was restricted to English. No restriction was placed on publication status, including published, in press, or in progress. The electronic databases of PubMed, EmBase, and the Cochrane library were systematically searched for retrieving potential studies published until June 2021 using the following text word or Medical Subject Heading terms: (“cervical cancer” OR “cervical carcinoma” OR “cervical intraepithelial neoplasia” OR “uterine cervix cancer”) AND (“prognosis” OR “prognostic” OR “survival” OR “recurrence”). We also manually searched the reference lists of relevant reviews and original articles to identify eligible studies.

The literature search and study selection were independently performed by 2 reviewers, and the inconsistencies between reviewers were resolved by group discussion until a consensus could be reached. The following inclusion criteria were considered: (1) Study design: prospective or retrospective studies; (2) Patients: all patients who were diagnosed with CC; (3) Exposure: the clinicopathological factors reported ≥3 studies, including patients’ age, cell type, depth of tumor invasion, FIGO stage, hemoglobin level, histological grade, leukocytosis, lymph node involvement (LNI), lymph-vascular space invasion (LVS1), neutrophil-to-lymphocyte ratio (NLR), parametrical invasion, platelet-to-lymphocyte ratio (PLR), resection margin, squamous cell carcinoma antigen (SCCA), thrombocytosis, tumor grade, tumor size, and tumor volume; and (4) Clinical outcomes: OS or EFS. Reviews and abstracts were excluded because they contain no original data or have an unclear definition of prognostic factors.

Data Collection and Quality Assessment

Two reviewers independently abstracted the following items: characteristics of studies (the first author’s full name, year of publication, the first author’s country of residence, and study design), sample size, mean or median age, FIGO stage, follow-up duration, clinical outcomes, and prognostic factors. Then, these 2 reviewers assessed the quality of each study using the Newcastle-Ottawa Scale (NOS) score, which ranges from 0-9 stars for assessment of quality of each study [17]. Studies were classified into low quality (0-6 stars), medium quality (7-8 stars), and high quality (9 stars). Any disagreement between reviewers for data collection and quality assessment was resolved via reading the full-text of the included studies by the third reviewer.

Statistical Analysis

The prognostic factors, influencing OS and EFS of CC patients were presented as hazard ratio (HR) and 95% confidence interval (CI) for each individual study, and the pooled HRs and 95% CIs were calculated using the random-effects model, as described elsewhere [18,19]. Heterogeneity among the included studies was assessed using the Cochran’s Q-statistic and the I²-statistic, and a significant heterogeneity was defined as I² ≥50.0% or P<0.10 [20,21]. To determine sources of heterogeneity, we performed a leave-one-out sensitivity analysis via exclusion of individual studies one at a time, and the pooled estimates were recalculated for the remaining studies [22].

Indexed in:  [Current Contents/Clinical Medicine]  [SCI Expanded]  [ISI Alerting System]
[ISI Journals Master List]  [Index Medicus/MEDLINE]  [EMBASE/Excerpta Medica]
[Chemical Abstracts/CAS]
Subgroup analyses were undertaken on the basis of the first author’s country of residence, FIGO stage, cutoff value, and study quality, and the subgroups were calculated using the chi-square test to explore the differences in the estimates between subgroups [23]. The Eastern countries contained Asia, while Western countries including Europe, America, and Oceania. Assessment of publication bias was carried out by using Egger's and Begg's tests, which compared the summary estimate of each study to its precision for outcomes that were reported in more than 5 studies [24,25]. The trim and fill method was applied to adjust pooled results if significant publication bias was observed [26]. Two-sided \( P \leq 0.05 \) was regarded as statistically significant. The STATA 10.0 software was used to conduct the statistical analyses (Stata Corporation, College Station, TX, USA).

Results

Literature Search

The search strategy resulted in retrieving 18,912 articles, and 9,141 articles were retained after exclusion of 9,771 studies owning to duplicate publication. Then, 8,762 studies were excluded because of irrelevant titles, the review of the reference lists of potentially relevant studies indicated 21 studies, and a total of 380 studies were retrieved for further full-text evaluations. Next, 240 studies were removed because they investigated other interventions (n=169), had inadequate outcomes (n=46), and were review articles (n=25). The remaining 140 studies were selected for the final meta-analysis (Figure 1), and characteristics of the eligible studies are presented in Table 1 [27-166].

Characteristics of the Eligible Studies

Of 140 included studies, 7 were designed as prospective cohorts, 132 as retrospective cohorts, and the remaining 1 study had both prospective and retrospective design. The sample size of the included studies ranged from 38 to 3797, and a total of 47,965 patients were involved. Forty-seven studies were conducted in Western countries and the remaining 93 studies were performed in Eastern countries. In addition, 106 and 99 studies reported the prognostic significance of clinicopathological characteristics, influencing OS and EFS of CC patients, respectively. Moreover, 41 studies were of medium quality (7 stars), and a total of 99 studies were of low quality (6 stars (69 studies) versus 5 stars (30 studies)).

Overall Survival

The summary results for the prognostic factors on OS in CC patients are shown in Figure 2. The pooled results found older patients (HR: 1.10; 95% CI: 1.00-1.20; \( P=0.040 \)), cell types other than squamous type (HR: 1.64; 95% CI: 1.47-1.83; \( P<0.001 \)), deep depth of tumor invasion (HR: 1.92; 95% CI: 1.53-2.40; \( P<0.001 \)), high FIGO stage (HR: 2.00; 95% CI: 1.76-2.28; \( P<0.001 \)), low hemoglobin level (HR: 1.84; 95% CI: 1.36-2.50; \( P<0.001 \)), high histological grade (HR: 1.52; 95% CI: 1.27-1.83; \( P<0.001 \)), leukocytosis (HR: 2.21; 95% CI: 1.55-3.15; \( P<0.001 \)), LNI (HR: 2.59; 95% CI: 2.30-2.92; \( P<0.001 \)), LVSI (HR: 2.09; 95% CI: 1.75-2.49; \( P<0.001 \)), high NLR (HR: 1.69; 95% CI: 1.36-2.11; \( P<0.001 \)), parametrial invasion (HR: 2.18; 95% CI: 1.84-2.59; \( P<0.001 \)), high PLR (HR: 1.98; 95% CI: 1.45-2.71; \( P<0.001 \)), positive resection margin (HR: 1.97; 95% CI: 1.45-2.69; \( P<0.001 \)), high SCCA level (HR: 1.65; 95% CI: 1.28-2.15; \( P<0.001 \)), thrombocytosis (HR: 1.69; 95% CI: 1.32-2.17; \( P<0.001 \)), large tumor volume (HR: 2.87; 95% CI: 2.03-4.04; \( P<0.001 \)), high tumor grade (HR: 1.74; 95% CI: 1.24-2.43; \( P=0.001 \)), and large tumor size (HR: 1.81; 95% CI: 1.59-2.07; \( P<0.001 \)) were associated with shorter OS. There was significant heterogeneity for age, cell type, depth of tumor invasion, FIGO stage, hemoglobin, histological grade, leukocytosis, LNI, LVSI, NLR, parametrial invasion, resection margin, tumor grade, and tumor size. The pooled conclusions were stability for OS related to cell type, depth of tumor invasion, FIGO stage, hemoglobin level, histological grade, leukocytosis, LNI, LVSI, NLR, parametrial invasion, PLR, resection margin, SCCA level, tumor grade, and tumor size (data not shown).

Subgroup analysis indicated the statistically significant prognostic significance of age in OS of patients with FIGO stages I-II CC or studies with low quality; cell type did not affect OS of patients with FIGO stages III-IV CC; depth of tumor invasion...
### Table 1. The baseline characteristics of included studies.

| Study                | Country | Study design | Sample size | Age (years) | FIGO stage | Follow-up (years) | Reported outcomes | Prognostic factors | NOS score |
|----------------------|---------|--------------|-------------|-------------|-------------|-------------------|-------------------|--------------------|-----------|
| Sevin 1995 [27]      | USA     | Retro        | 301         | 43.5        | I-II       | 5.0               | DFS               | CT, TS, LVSI, LNI, TV, FIGO, RM, CT, TG, age | 6         |
| Werner-Wasik 1995 [28] | USA  | Retro         | 125         | 55.0        | I-II       | 5.0               | DFS               | LNI, LVSI, PI, He, TS, FIGO, CT, TG | 5         |
| Tsai 1999 [29]       | China   | Retro        | 222         | 50.0        | I-II       | 5.0               | DFS               | FIGO, TS, age, CT, SCC, He, LNI, PI, LVSI, RM | 6         |
| Lai 1999 [30]        | China   | Retro        | 891         | NA          | I-II       | 5.0               | DFS               | TG, FIGO, TS, DI | 7         |
| Nakanishi 2000 [31]  | Japan   | Retro        | 509         | 49.3        | I           | 9.3               | OS, DFS           | CT, LNI, and TS | 6         |
| Hernandez 2000 [32]  | USA     | Retro        | 291         | 49.3        | II-IV      | 5.0               | DFS               | Th, LNI, TS, age, and FIGO | 7         |
| Alfsen 2001 [33]     | Norway  | Retro        | 505         | 53.0        | I-IV       | 5.0               | OS                | LNI, FIGO, and age | 7         |
| Flores-Luna 2001 [34] | Mexico | Retro      | 378         | 52.2        | I-IV       | 12.5              | OS                | FIGO, TG, TS, and age | 5         |
| Trattner 2001 [35]   | Austria | Retro        | 113         | 46.1        | I-II       | 4.7               | OS                | TV, LNI, LVSI, FIGO, PI, RM, CT, TG, and age | 5         |
| Yanoh 2001 [36]      | Japan   | Retro        | 751         | 45.0        | I           | > 5.0             | DFS               | LNI, PI, TS, DI, and LVS | 6         |
| Takeda 2002 [37]     | Japan   | Retro        | 187         | 48.2        | I-II       | 6.9               | OS                | FIGO, CT, LVSI, TS, DI, PI, and LNI | 6         |
| Gasinska 2002 [38]   | Poland  | Retro        | 152         | 55.0        | I-III      | 2.1               | OS                | Age, TG, and He | 6         |
| Martin-Loeches 2002 [39] | Spain  | Retro      | 114         | 49.1        | I-II       | 10.0              | OS                | TS, TV, DI | 5         |
| Brun 2003 [40]       | France  | Retro        | 308         | 53.0        | I-IV       | 7.8               | OS                | Age, TG, and PI | 6         |
| Morice 2003 [41]     | France  | Retro        | 193         | 37.0        | I-II       | 5.0               | OS                | FIGO, TS, LVSI, and LNI | 6         |
| Kodaira 2003 [42]    | Japan   | Retro        | 164         | 68.0        | II-III     | 1.9               | DFS               | TV, LNI, and FIGO | 6         |
| Grisaru 2003 [43]    | Canada  | Pro          | 871         | 42.1        | I           | 4.1               | DFS               | LNI, TG, LVSI, RM, and CT | 7         |
| Huang 2003 [44]      | China   | Pro          | 157         | 44.0        | I-II       | 5.0               | OS, DFS           | TS, age, CT | 6         |
| Shinohara 2004 [45]  | Japan   | Retro        | 130         | 49.0        | I-II       | 14.4              | DFS               | LVSI, LNI, and DI | 6         |
| Ho 2004 [46]         | China   | Retro        | 197         | 47.4        | I-II       | 5.8               | OS, DFS           | Age, FIGO, CT, TG, TS, DI, LVSI, LNI, PI | 5         |
| Ayhan 2004 [47]      | Turkey  | Retro        | 393         | 48.5        | I           | 2.6               | OS, DFS           | TS, LVSI, PI, and age | 6         |
| Choi 2006 [48]       | Korea   | Retro        | 85          | 50.0        | I-IV       | 3.0               | OS, DFS           | Age, CT, FIGO, TS, LNI, SCC, and He | 5         |
| Chittithaworn 2007 [49] | Thailand | Retro    | 205         | 44.2        | I           | 4.7               | DFS               | DI, LVSI, RM, and LNI | 5         |
| Grigiene 2007 [50]   | Lithuania | Retro  | 162         | 52.0        | II-III     | 2.7               | DFS               | FIGO, He | 7         |
| Horn 2007 [51]       | Germany | Retro        | 245         | 43.0        | II          | 4.5               | OS                | TS, LNI, FIGO | 6         |
| Atahan 2007 [52]     | Turkey  | Retro        | 183         | 54.0        | I-III      | 3.8               | OS, DFS           | Age, PI, FIGO, TS, CT, LNI | 7         |
| Garcia-Arias 2007 [53] | Mexico | Retro       | 294         | 49.4        | I-IV       | 2.3               | OS                | Le, He, age, CT, and FIGO | 7         |
| Choi 2008 [54]       | Korea   | Retro        | 143         | 58.0        | I-IV       | 2.2               | PFS               | FIGO, TS | 6         |
| Behnash 2009 [55]    | Iran    | Retro        | 203         | 49.8        | I-II       | 3.5               | OS, DFS           | Age, CT, FIGO, TS, LNI, PI, LVSI, DI | 6         |
Table 1 continued. The baseline characteristics of included studies.

| Study           | Country  | Study design | Sample size | Age (years) | FIGO stage | Follow-up (years) | Reported outcomes | Prognostic factors | NOS score |
|-----------------|----------|--------------|-------------|-------------|-------------|------------------|------------------|-------------------|-----------|
| Jacobson 2009   | USA      | Retro        | 436         | 52.3        | I-IV        | 8.0              | OS               | FIGO, CT          | 7         |
| Zusterzeel 2009 | Netherlands | Retro       | 167         | 42.0        | I-IV        | 2.8              | OS, DFS           | FIGO, CT, TG, LVS, DI, TS | 7         |
| Polterauer 2010 | Austria  | Retro        | 88          | 49.9        | I-IV        | 3.1              | OS, DFS           | FIGO, TG, CT      | 7         |
| Munagala 2010   | India    | Retro        | 89          | 46.0        | I-III       | 5.0-7.0          | OS, DFS/PFS       | Age, FIGO, LNI, PI, CT, TG, and TS | 6         |
| Huang 2010      | China    | Retro        | 960         | 45.0        | I-II        | 5.0              | OS               | FIGO, SCC, DI, PI | 6         |
| Touboul 2010    | France   | Retro        | 150         | 47.0        | I-IV        | 3.6              | OS               | FIGO, CT, RM, LNI | 7         |
| Horn 2010       | Germany  | Retro        | 194         | 44.0        | I-II        | 5.1              | OS               | LNI, TG, FIGO     | 6         |
| Kodama 2010     | Japan    | Retro        | 97          | 46.0        | I-IV        | 8.4              | OS, DFS           | Age, FIGO, DI, TS, PI, LVS, LNI | 5         |
| Lee 2010        | Korea    | Retro        | 134         | 58.0        | II-IV       | 3.2              | OS, PFS           | FIGO              | 5         |
| Tseng 2010      | China    | Pro          | 251         | 48.6        | II-IV       | 6.3              | OS               | SCC, TS, PI, LNI  | 6         |
| Nugent 2010     | USA      | Retro/Pro    | 111         | 51.0        | I-II        | 1.4              | OS, PFS           | FIGO              | 6         |
| Srisomboon 2011 | Thailand | Retro        | 680         | 44.5        | I           | 4.0              | DFS              | LNI, LVS, CT, DI, PI, TG, RM | 6         |
| Seamon 2011     | USA      | Retro        | 381         | 47.0        | I-IV        | 3.3              | OS, DFS           | FIGO, CT          | 7         |
| Polterauer 2011 | Austria  | Retro        | 178         | 49.2        | I-IV        | 3.8              | OS, DFS           | FIGO, LNI, TG, age, CT | 7         |
| Mabuchi 2011    | Japan    | Retro/Pro    | 536         | 57.5        | I-IV        | 6.4              | OS, PFS           | Age, FIGO, CT, TS | 6         |
| Min 2011        | China    | Retro        | 88          | NA          | I-II        | 5.0              | OS               | Age, TS, CT, TG, FIGO, LNI | 5         |
| Biewenga 2011   | Netherlands | Retro   | 710         | 41.0        | I-II        | 5.2              | DFS              | CT, TG, DI, PI, LNI, LVS, RM | 7         |
| Polterauer 2012 | Austria  | Retro        | 528         | 47.9        | I-IV        | 3.8              | OS               | Age, FIGO, TS, CT, LNI, PI | 7         |
| Kim 2012        | Korea    | Retro        | 174         | 50.0        | I-II        | 2.5              | OS, PFS           | FIGO, LNI, TS     | 6         |
| Lee 2012        | Korea    | Retro        | 1,061       | 50.0        | I-IV        | 4.4              | OS, PFS           | NLR, FIGO, CT     | 7         |
| Okazawa 2012    | Japan    | Retro        | 311         | 51.0        | I-II        | 5.2              | PFS              | Age, CT, LNI, PI, RM, DI, LVS, TS, He | 7         |
| Wang 2012       | China    | Retro        | 179         | 47.0        | I-IV        | 4.3              | OS, DFS           | FIGO, LNI, RM     | 6         |
| Yan 2012        | China    | Retro        | 148         | 42.0        | I           | 2.3              | OS               | Age, CT, TG, TS, DI, LVSI, LNI | 5         |
| Cibula 2012     | Czech Republic | Retro | 645         | 46.0        | I-II        | 3.3              | OS, DFS           | Age, FIGO, PI, LNI | 6         |
| Singh 2012      | Australia | Retro       | 196         | NA          | I-II        | 6.1              | OS, DFS           | Age, LVS, LNI, PI, TS, DI | 7         |
| Wang 2013       | China    | Retro        | 424         | NA          | I-II        | 7.0              | DFS              | Age, CT, TG, FIGO, LNI | 5         |
| Tsubamoto 2013  | Japan    | Retro        | 73          | 47.0        | I-II        | 5.9              | OS, DFS           | Age, FIGO, CT, TS, LNI | 6         |
| Song 2013       | Korea    | Retro        | 268         | 57.0        | I-IV        | 5.0              | OS, DFS           | FIGO, age, LNI, CT, He | 6         |
| Cho 2013        | Korea    | Retro        | 185         | 50.0        | I-II        | 5.9              | DFS              | Age, FIGO, LNI, RM, PI, TS, DI, LVS | 6         |
| Zhang 2014      | China    | Retro        | 460         | 44.0        | I-II        | 5.8              | OS, PFS           | FIGO, LNI, NLR    | 7         |
| Horn 2014       | Germany  | Retro        | 366         | 40.0        | I           | 7.8              | OS, DFS           | TS, LNI, TG       | 7         |
| Study                                      | Country | Study design | Sample size | Age (years) | FIGO stage | Follow-up (years) | Reported outcomes | Prognostic factors                                                                 |
|-------------------------------------------|---------|--------------|-------------|-------------|-------------|------------------|-------------------|-----------------------------------------------------------------------------------|
| Noh 2014 [87]                             | Korea   | Retro        | 1,323       | 50.0        | I-II       | 6.3              | OS, DFS           | CT, age, FIGO, TS, LNI, PI, LVSI, DI, RM                                       |
| Yu 2014 [88]                              | China   | Retro        | 153         | NA          | II         | 5.0              | DFS               | TS, LVSI, LNI                                                  |
| Liu 2014 [89]                             | China   | Retro        | 184         | 46.0        | I-II       | 5.8              | DFS               | Age, TS, CT, FIGO, DI, LVSI, LNI                                       |
| Kawano 2015 [90]                          | Japan   | Retro        | 286         | 63.6        | I-IV       | 6.7              | OS                | age, FIGO, PNI, CT, TS, He, Th                                  |
| Ruengkachorn 2015 [91]                    | Thailand| Retro        | 331         | 48.6        | I-II       | 7.0              | DFS               | He, CT, FIGO, PNI, CT, DI, LVSI                                      |
| Bradbury 2015 [92]                        | UK      | Retro        | 92          | 39.5        | I           | 4.8              | OS, DFS           | Age, TS, CT, TS, TG, LVSI, LNI, RM                                 |
| Yuan 2015 [93]                            | China   | Retro        | 38          | 40.4        | I-II       | 5.0              | DFS               | PI                                                                 |
| Mizunuma 2015 [94]                        | Japan   | Retro        | 56          | 65.1        | I-IV       | 6.7              | DFS               | FIGO, TS, He, LNI                                                |
| Endo 2015 [95]                            | Japan   | Retro        | 84          | 62.0        | I-II       | 6.7              | OS                | Age, CT, He, TS, LNI                                            |
| Zhao 2015 [96]                            | China   | Retro        | 220         | NA          | I-II       | 5.0              | DFS               | Age, FIGO, CT, TS, DI, LSNI                                       |
| Takatori 2015 [97]                        | Japan   | Retro        | 33          | 42.0        | I-II       | 2.8              | OS                | Age, FIGO, TS, SCC                                               |
| Huang 2016 [98]                           | China   | Retro        | 643         | NA          | I-II       | 3.1              | OS, DFS           | Age, CT, TS, FIGO, DI, LVSI, LNI, PI, RM                            |
| Li 2016 [99]                              | China   | Retro        | 347         | 51.6        | I-II       | 3.1              | OS, DFS           | Age, FIGO, CT, TS, LNI, He, Le, NLR                                 |
| Cho 2016 [100]                            | Korea   | Retro        | 2,456       | 56.0        | I-IV       | 5.4              | OS, DFS           | Age, FIGO, CT, TS, LNI, He, Le, NLR                                 |
| Matsumiya 2016 [101]                      | Japan   | Retro        | 54          | 55.0        | I-II       | 1.0              | OS                | CT                                                                 |
| Usami 2016 [102]                          | Japan   | Retro        | 111         | 51.0        | I-II       | 1.4              | OS                | Age, CT                                                          |
| Chen 2016 [103]                           | China   | Retro        | 407         | 44.0        | I-II       | 5.0              | OS, DFS           | Age, CT, TS, DI, LVSI, LNI, FIGO, PI, PLR, NLR                     |
| Oishi 2016 [104]                          | Japan   | Retro        | 85          | 55.0        | IV          | 0.8              | OS                | Age, CT, TS, TG, He, SCC                                      |
| Onal 2016 [105]                           | Turkey  | Retro        | 235         | 57.0        | I          | 5.8              | OS, DFS           | Age, FIGO, TS, LNI, NLR                                      |
| Wu 2016 [106]                             | USA     | Retro        | 71          | 49.0        | I-I        | 2.1              | OS, DFS           | FIGO, CT, TG                                                  |
| Xia 2016 [107]                            | China   | Retro        | 274         | 43.0        | I-II       | 2.4              | OS, DFS           | Age, FIGO, CT, TS, TG, DI, LVSI, RM, PI, LNI                      |
| Lee 2017 [108]                            | Korea   | Retro        | 231         | 58.0        | I-IV       | 2.3              | OS, DFS           | Age, LNI, FIGO, SCC, TV                                       |
| Barquet-Muñoz 2017 [109]                  | Mexico  | Retro        | 202         | 49.5        | I-II       | 5.0              | OS, DFS           | Age, CT, TS, DI, LVSI, RM, PI, LNI                                  |
| Jung 2017 [110]                           | Korea   | Retro        | 1,113       | 48.7        | I-II       | 7.6              | OS, DFS           | CT, FIGO, TS, DI, LNI, LVSI, PI, RM                                  |
| Chung 2017 [111]                          | Korea   | Retro        | 103         | 48.0        | I-II       | 2.4              | DFS               | FIGO, TS, LNI, PI, DI, LVSI                                      |
| Zheng 2017 [112]                          | China   | Retro        | 795         | 49.5        | I-II       | 5.2              | OS                | FIGO, He, TG, LVSI, LNI, TS, PI, RM                                 |
| Obrzut 2017 [113]                         | Poland  | Pro          | 102         | 48.0        | I-II       | 10.0             | OS, DFS           | FIGO, CT, TG, LNI, LVSI, RM                                      |
| Cho 2017 [114]                            | Korea   | Retro        | 105         | NA          | II         | 4.8              | PFS               | Age, CT, TS, LNI, NLR                                           |
Table 1 continued. The baseline characteristics of included studies.

| Study            | Country | Study design | Sample size | Age (years) | FIGO stage | Follow-up (years) | Reported outcomes | Prognostic factors                                                                 |
|------------------|---------|--------------|-------------|-------------|-------------|-------------------|-------------------|-----------------------------------------------------------------------------------|
| Chandeying 2017  | Thailand| Retro        | 626         | 45.0        | I           | 7.7               | OS, DFS           | CT, age, TS, FIGO, RM, PI, LNI, LVS, DI                                             |
| Yokoi 2017       | Japan   | Retro        | 249         | 61.5        | II-IV       | 5.0               | PFS               | Age, FIGO, LNI, CT, He                                                            |
| Lim 2017         | Korea   | Retro        | 180         | NA          | I-II        | 5.0               | OS, DFS           | PI, LNI                                                             |
| Xu 2018          | China   | Retro        | 40          | 45.5        | I-IV        | 5.0               | OS                | Age, FIGO, LNI, LVS, DI, TS                                                   |
| Wen 2018         | China   | Retro        | 99          | NA          | II-IV       | 4.0               | DFS               | Age, TS, CT, FIGO, SCC, PI                                                    |
| Joo 2018         | Korea   | Retro        | 397         | 45.0        | I-II        | 4.0               | OS, DFS           | CT, FIGO, LNI, PI, LVI, DI, TS                                                   |
| Dai 2018         | China   | Retro        | 302         | 45.1        | I-II        | 5.0               | OS                | FIGO, TS, TG, DI, LVS, PI, LNI                                                   |
| Zhu 2018         | China   | Retro        | 365         | 45.0        | I-II        | 3.7               | OS, DFS           | FIGO, TS, PI, LNI, LVI, PI                                                      |
| Zhou 2018        | China   | Retro        | 312         | 46.0        | I-II        | 4.7               | OS, DFS           | Age, FIGO, TS, TG, DI, LVS, LNI                                                  |
| Liu 2018         | China   | Retro        | 98          | 52.0        | I-III       | 3.1               | OS, DFS           | TS, LNI                                                             |
| Xie 2018         | China   | Retro        | 810         | 46.3        | I-II        | 5.0               | OS                | FIGO, LNI                                                             |
| Taarnhøj 2018    | Denmark | Retro        | 1,523       | NA          | I           | 5.0               | DFS               | FIGO, CT, age, DI, LVS, DI                                                   |
| Zhang 2018       | China   | Retro        | 235         | 46.0        | I-II        | 6.4               | OS, DFS           | Age, FIGO, TS, CT, LVS, LNI, DI, NLR                                           |
| Je 2018          | Korea   | Retro        | 1,069       | 49.0        | I-II        | 5.0               | DFS               | CT, PI, LVS, DI, TS, LNI                                                        |
| Ishimura 2018    | Japan   | Retro        | 103         | NA          | I-II        | 10.0              | DFS               | CT, TS, DI, LVS, PI, LNI, RM                                                   |
| Kwon 2018        | Korea   | Retro        | 259         | 47.0        | I-II        | 5.8               | DFS               | CT, LVS, I                                                                    |
| Zhu 2019         | China   | Retro        | 110         | 51.5        | I-II        | 4.0               | OS, DFS           | Age, TS, LNI, FIGO, TG, Ly                                                      |
| Yan 2019         | China   | Retro        | 347         | NA          | I-II        | 3.3               | OS, DFS           | Age, FIGO, LNI, TG, LVS, DI                                                    |
| Wang 2019        | China   | Retro        | 559         | 51.0        | I-IV        | 3.3               | DFS               | Age, SCC, FIGO, TS, LNI                                                        |
| Farzaneh 2019    | Iran    | Retro        | 307         | 40.4        | I-III       | 5.0               | DFS               | RM, NLR                                                                       |
| Sawada 2019      | Japan   | Retro        | 107         | 46.0        | I-II        | 4.8               | OS                | FIGO, CT, TS, LNI, PI                                                        |
| Khalkhali 2019   | Iran    | Retro        | 109         | 50.1        | I-IV        | 3.2               | OS                | Age, FIGO                                                                  |
| Yildirim 2019    | Turkey  | Retro        | 104         | 56.0        | I-IV        | 4.4               | DFS               | TS, FIGO, LNI                                                                |
| Gai 2019         | China   | Retro        | 79          | 51.0        | I-IV        | 5.0               | OS                | FIGO, LNI, LVS, DI                                                       |
| Chen 2019        | China   | Retro        | 88          | 48.0        | I-II        | 2.2               | DFS               | Age, CT, FIGO, TG, LVSI                                                      |
| Guani 2019       | France  | Pro          | 139         | NA          | I           | 3.0               | DFS               | LNI, CT, TS, FIGO, LVS, age                                                   |
| Huang 2019       | China   | Retro        | 458         | 45.0        | I-II        | 3.9               | OS                | Age, TG, TS, LNI, LVS, FIGO, NLR                                               |
| Queiroz 2019     | Brazil  | Retro        | 127         | 50.8        | II-IV       | 4.1               | OS, DFS           | Age, CT, TS, LNI                                                           |
| Gillani 2019     | Malaysia| Pro          | 3,797       | 57.3        | I-II        | 6.1               | OS                | Age, FIGO, TS, LNI, CT                                                       |
| de Foucher 2019  | France  | Retro        | 501         | 54.0        | I-II        | 3.0               | OS, DFS           | FIGO, LNI                                                                 |
| Yoshino 2019     | Japan   | Retro        | 128         | 65.0        | I-IV        | 2.5               | OS                | FIGO, CT                                                                 |
| Zhang 2019       | China   | Retro        | 89          | 40.5        | I-IV        | 4.8               | OS                | FIGO, TS, LNI, LVS, DI                                                        |
Table 1 continued. The baseline characteristics of included studies.

| Study                      | Country     | Study design | Sample size | Age (years) | FIGO stage | Follow-up (years) | Reported outcomes | Prognostic factors | NOS score |
|----------------------------|-------------|--------------|-------------|-------------|-------------|-------------------|-------------------|--------------------|-----------|
| Seebacher 2019 [147]       | Austria     | Retro        | 116         | 52.1        | I-IV       | 1.7               | OS                | Age, FIGO, CT, SCC | 5         |
| Holub 2019 [148]           | Spain       | Retro        | 151         | 52.8        | I-IV       | 3.7               | OS                | TS, FIGO, age, NLR | 6         |
| Theplib 2020 [149]         | Thailand    | Retro        | 196         | 41.0        | I-IV       | 5.0               | OS, DFS           | LVSI, PI, LNI, DI  | 6         |
| Maulard 2020 [150]         | France      | Pro          | 238         | 45.9        | I-IV       | 4.4               | OS                | FIGO, CT, LNI      | 7         |
| An 2020 [151]              | China       | Retro        | 278         | 45.5        | I-II       | 5.0               | OS, DFS           | Age, CT, FIGO, TG, TS, LVSI, LNI, DI, RM, He | 6         |
| Casarin 2020 [152]         | Italy       | Retro        | 428         | 45.0        | I          | 4.7               | DFS               | TS, LVSI, TG, LNI  | 7         |
| Wang 2020 [153]            | China       | Retro        | 120         | 59.0        | I-III      | 3.2               | OS                | LNI, age, FIGO, TG, TS | 6         |
| Zyla 2020 [154]            | Canada      | Retro        | 285         | 41.0        | I          | 4.0               | OS, DFS           | TG, CT, LVSI      | 6         |
| He 2020 [155]              | China       | Retro        | 1,414       | NA          | I-II       | 3.6               | OS, DFS           | Age, FIGO, CT, TG, LNI, CT, RM, LNI, LVSI | 7         |
| Zeng 2020 [156]            | China       | Retro        | 251         | 46.0        | I-III      | 3.9               | OS, DFS           | FIGO, LNI         | 6         |
| Liu 2020 [157]             | China       | Retro        | 73          | NA          | I-II       | 5.7               | OS                | Age, CT, FIGO, TG, TS, SCC | 5         |
| Kim 2020 [158]             | Korea       | Retro        | 47          | 45.0        | I-II       | 2.4               | OS, DFS           | FIGO, SCC, DI, RM, PI, LNI, LVSI | 5         |
| Anfinan 2020 [159]         | Saudi Arabia| Retro        | 190         | 54.2        | I-IV       | 3.1               | OS                | FIGO, TG, PI      | 6         |
| Lee 2020 [160]             | Korea       | Retro        | 125         | 53.7        | II-III     | 4.2               | OS, DFS           | Age, CT, FIGO, LNI, SCC, NLR | 6         |
| Zong 2020 [161]            | China       | Retro        | 384         | 46.3        | I-II       | 3.6               | OS, DFS           | Age, FIGO, TG, TS, PI, LVI, DI, RM | 6         |
| Asian 2020 [162]           | Turkey      | Retro        | 185         | 50.0        | III        | 3.8               | OS, DFS           | Age, CT, DI, PI, TS, LVSI, RM, FIGO | 7         |
| Gülseren 2020 [163]        | Turkey      | Retro        | 194         | NA          | I-II       | 5.0               | DFS               | FIGO, TS, PI, LVI  | 6         |
| Kim 2021 [164]             | Korea       | Retro        | 55          | 52.6        | I-II       | 4.5               | DFS               | Age, FIGO, CT, LNI, RM | 7         |
| Okadome 2021 [165]         | Japan       | Retro        | 82          | NA          | II         | 5.8               | DFS               | CT, LNI, TS       | 6         |
| Buda 2021 [166]            | Italy       | Retro        | 573         | 45.5        | I-II       | 3.8               | DFS               | Age, CT, FIGO, LVI | 6         |

CT – cell type; DI – depth of invasion; He – hemoglobin; Retro – retrospective; Pro – prospective; PI – parametrial invasion; Le – leukocytosis; LVS – lymph vascular space invasion; LNI – lymph node involvement; Ly – lymphocyte; RM – resection margin; SCC – squamous cell carcinoma antigen; TG – tumor grade; Th – thrombocytosis; TS – tumor size; TV – tumor volume; NA – not available; NLR – neutrophil/lymphocyte ratio.

did not influence OS of patients with FIGO stages III-IV or I-IV CC; high FIGO stage did not influence OS of patients with FIGO stages III-IV CC; hemoglobin level did not influence OS of patients with FIGO stages I-II or III-IV CC; LVSI was not associated with OS in patients with FIGO stages III-IV CC; parametrial invasion did not affect OS of patients with FIGO stages III-IV CC; high PLR was not associated with OS of patients with FIGO stages III-IV CC; high FIGO stage did not influence OS of patients with FIGO stages III-IV CC; age, FIGO stage, CT, TG, PI, RM did not influence OS of patients with FIGO stages III-IV CC, according to the results of pooled analyses conducted in the Western countries, and cutoff value ≥10; high tumor grade was not associated with OS of patients with FIGO stages I-IV CC, according to the pooled analyses conducted in the Western countries, or studies with high quality; and tumor size did not influence OS of patients with FIGO stages III-IV CC (Table 2).

There was significant publication bias for the prognostic significance of FIGO stage (P (Egger’s test) <0.001; P (Begg’s test)=0.044; P (Begg’s test)=0.024); high SCCA level was not associated with OS of patients with FIGO stages III-IV CC; high SCCA level was not associated with OS of patients with FIGO stages III-IV CC; high SCCA level was not associated with OS of patients with FIGO stages III-IV CC, according to the results of pooled analyses conducted in the Western countries, and cutoff value ≥10; high tumor grade was not associated with OS of patients with FIGO stages I-IV CC, according to the pooled analyses conducted in the Western countries, or studies with high quality; and tumor size did not influence OS of patients with FIGO stages III-IV CC (Table 2).
### Event-Free Survival

The summary results for the prognostic factors on EFS in CC patients are shown in Figure 3. The pooled analyses indicated that older patients (HR: 1.22; 95% CI: 1.06-1.40; P=0.004), cell types other than squamous type (HR: 1.62; 95% CI: 1.42-1.86; P<0.001), deep depth of tumor invasion (HR: 1.72; 95% CI: 1.48-2.00; P<0.001), high FIGO stage (HR: 1.87; 95% CI: 1.67-2.08; P<0.001), low hemoglobin level (HR: 1.31; 95% CI: 1.12-1.53; P<0.001), high histological grade (HR: 1.43; 95% CI: 1.18-1.74; P<0.001), leukocytosis (HR: 2.08; 95% CI: 1.25-3.45; P=0.005), LNI (HR: 2.32; 95% CI: 2.03-2.64; P<0.001), LVSI (HR: 1.87; 95% CI: 1.60-2.18; P<0.001), high NLR (HR: 1.73; 95% CI: 1.33-2.25; P<0.001), parametrial invasion (HR: 1.91; 95% CI: 1.66-2.21; P<0.001), high PLR (HR: 2.05; 95% CI: 1.35-3.10; P=0.001), positive resection margin (HR: 1.99; 95% CI: 1.56-2.52; P<0.001), high SCCA level (HR: 1.80; 95% CI: 1.33-2.45; P<0.001), thrombocytosis (HR: 1.47; 95% CI: 1.08-1.98; P=0.013), large tumor volume (HR: 1.86; 95% CI: 1.40-2.47; P<0.001), high tumor grade (HR: 1.37; 95% CI: 1.14-1.66; P=0.001), and large tumor size (HR: 1.68; 95% CI: 1.48-1.90; P<0.001) were associated with shorter EFS. There was significant heterogeneity for age, cell type, depth of tumor invasion, FIGO stage, hemoglobin, histological grade, leukocytosis, LNI, LVSI, NLR, parametrial invasion, PLR, resection margin, SCCA level, and tumor size. The pooled conclusions were stability for EFS related to age, cell type, depth of tumor invasion, FIGO stage, hemoglobin level, histological grade, LNI, LVSI, NLR, parametrial invasion, PLR, resection margin, SCCA level, tumor grade, and tumor size (Data not shown).

Subgroup analysis indicated the statistically significant prognostic significance of age in EFS was observed for studies performed in Eastern countries, patients with FIGO stages I-II CC, the cutoff value of age was ≥50.0, and studies with low quality; depth of tumor invasion did not influence EFS of patients with FIGO stages III-IV or I-IV CC; high FIGO stage did not influence EFS of patients with FIGO stages III-IV CC; EFS were not affected by hemoglobin when pooled studies with high quality; histological grade did not influence EFS of patients with FIGO stages I-II CC; leukocytosis did not impact EFS of patients with FIGO stages I-II CC, and cutoff value ≥10 000, or studies with low quality; LVSI was not associated with EFS in patients with FIGO stages III-IV or I-IV CC; PLR did not influence EFS of patients with FIGO stages I-IV CC, studies conducted in...
Table 2. Subgroup analysis for overall survival and event-free survival based on countries, FIGO stage, and cutoff value.

| Prognostic factors | Outcome | Variables | Subgroups | HR and 95% CI | P value | I² (%) | Q statistic | P value between subgroups |
|--------------------|---------|-----------|-----------|---------------|---------|---------|-------------|----------------------------|
| Age                | OS      | Countries | Eastern   | 1.11 (1.00-1.23) | 0.052   | 61.8    | <0.001      | 0.703                       |
|                    |         |           | Western   | 1.08 (0.86-1.36) | 0.489   | 72.0    | <0.001      |                             |
| FIGO stage         |         |           | I-II     | 1.23 (1.10-1.38) | <0.001  | 56.2    | <0.001      |                             |
|                    |         |           | III-IV   | 1.13 (0.76-1.69) | 0.539   | 0.0     | 0.719       | 0.070                       |
|                    |         |           | Both     | 0.94 (0.79-1.13) | 0.524   | 72.7    | <0.001      |                             |
| Cutoff value       |         |           | ≥50.0    | 1.09 (0.97-1.23) | 0.162   | 68.2    | <0.001      | 0.592                       |
|                    |         |           | <50.0    | 1.13 (0.96-1.33) | 0.140   | 58.4    | <0.001      |                             |
| Study quality      |         |           | High     | 1.03 (0.86-1.24) | 0.723   | 71.9    | <0.001      | 0.206                       |
|                    |         |           | Low      | 1.15 (1.03-1.28) | 0.016   | 59.8    | <0.001      |                             |
| EFS                |         | Countries | Eastern   | 1.19 (1.02-1.38) | 0.024   | 67.4    | <0.001      | 0.082                       |
|                    |         |           | Western   | 1.40 (0.99-1.98) | 0.061   | 67.5    | 0.002       |                             |
| FIGO stage         |         |           | I-II     | 1.31 (1.13-1.52) | <0.001  | 56.3    | <0.001      |                             |
|                    |         |           | III-IV   | 0.91 (0.59-1.40) | 0.666   | –       | –           | <0.001                      |
|                    |         |           | Both     | 1.03 (0.76-1.39) | 0.864   | 77.7    | <0.001      |                             |
| Cutoff value       |         |           | ≥50.0    | 1.23 (1.04-1.46) | 0.016   | 70.1    | <0.001      | 0.022                       |
|                    |         |           | <50.0    | 1.20 (0.96-1.51) | 0.116   | 59.0    | 0.001       |                             |
| Study quality      |         |           | High     | 0.90 (0.76-1.08) | 0.251   | 65.2    | <0.001      |                             |
|                    |         |           | Low      | 1.49 (1.29-1.73) | <0.001  | 37.6    | 0.019       | <0.001                      |
| Cell type          | OS      | Countries | Eastern   | 1.74 (1.52-1.98) | <0.001  | 39.9    | 0.007       | 0.047                       |
|                    |         |           | Western   | 1.44 (1.20-1.73) | <0.001  | 18.6    | 0.231       |                             |
| FIGO stage         |         |           | I-II     | 1.65 (1.43-1.91) | <0.001  | 24.2    | 0.120       |                             |
|                    |         |           | III-IV   | 1.58 (0.89-2.78) | 0.115   | 0.0     | 0.521       | 0.963                       |
|                    |         |           | Both     | 1.63 (1.36-1.95) | <0.001  | 51.3    | 0.002       |                             |
| Study quality      |         |           | High     | 1.79 (1.53-2.09) | <0.001  | 42.6    | 0.015       | 0.049                       |
|                    |         |           | Low      | 1.50 (1.29-1.74) | <0.001  | 26.5    | 0.090       |                             |
| EFS                |         | Countries | Eastern   | 1.68 (1.43-1.97) | <0.001  | 62.9    | <0.001      | 0.008                       |
|                    |         |           | Western   | 1.50 (1.18-1.91) | 0.001   | 58.8    | 0.001       |                             |
| FIGO stage         |         |           | I-II     | 1.56 (1.31-1.86) | <0.001  | 65.2    | <0.001      |                             |
|                    |         |           | III-IV   | 2.33 (1.38-3.94) | 0.002   | –       | –           | 0.490                       |
|                    |         |           | Both     | 1.71 (1.37-2.13) | <0.001  | 59.8    | 0.001       |                             |
| Study quality      |         |           | High     | 1.88 (1.57-2.24) | <0.001  | 67.4    | <0.001      | 0.004                       |
|                    |         |           | Low      | 1.43 (1.17-1.74) | <0.001  | 56.7    | <0.001      |                             |
Table 2 continued. Subgroup analysis for overall survival and event-free survival based on countries, FIGO stage, and cutoff value.

| Prognostic factors | Outcome | Variables | Subgroups | HR and 95% CI | P value | I² (%) | Q statistic | P value between subgroups |
|--------------------|---------|-----------|-----------|---------------|---------|--------|-------------|--------------------------|
| Depth of invasion  | OS      | Countries | Eastern   | 2.09 (1.66-2.63) | <0.001 | 59.1   | <0.001     | 0.024                    |
|                    |         |           | Western   | 1.11 (0.52-2.38) | 0.790   | 75.3   | 0.003      |                          |
|                    | FIGO    | stage     | I-II      | 2.09 (1.65-2.63) | <0.001 | 62.1   | <0.001     |                          |
|                    |         |           | III-IV    | 0.89 (0.42-1.89) | 0.761   | -      | -          |                          |
|                    |         |           | Both      | 1.01 (0.43-2.37) | 0.979   | 58.9   | 0.088      |                          |
|                    | Cutoff  | value     | ≥1/2      | 2.02 (1.59-2.57) | <0.001 | 37.2   | 0.053      | 0.782                    |
|                    |         |           | <1/2      | 1.73 (1.15-2.61) | 0.009   | 77.1   | <0.001     |                          |
|                    | Study   | quality   | Low       | 2.02 (1.51-2.40) | <0.001 | 62.6   | <0.001     |                          |
|                    |         |           | High      | 1.75 (1.20-2.55) | 0.004   | -      | -          |                          |
|                    | EFS     | Countries | Eastern   | 1.83 (1.60-2.09) | <0.001 | 28.1   | 0.070      | 0.010                    |
|                    |         |           | Western   | 1.29 (0.75-2.22) | 0.359   | 80.7   | <0.001     |                          |
|                    | FIGO    | stage     | I-II      | 1.77 (1.52-2.06) | <0.001 | 51.6   | <0.001     |                          |
|                    |         |           | III-IV    | 0.93 (0.51-1.71) | 0.815   | -      | -          |                          |
|                    |         |           | Both      | 0.86 (0.32-2.31) | 0.765   | -      | -          |                          |
|                    | Cutoff  | value     | ≥1/2      | 1.67 (1.39-2.00) | <0.001 | 43.8   | 0.019      | 0.549                    |
|                    |         |           | <1/2      | 1.77 (1.37-2.29) | <0.001 | 60.5   | <0.001     |                          |
|                    | Study   | quality   | Low       | 1.77 (1.49-2.09) | <0.001 | 34.6   | 0.047      |                          |
|                    |         |           | High      | 1.64 (1.23-2.16) | 0.001   | -      | -          |                          |
|                    | FIGO    | stage     | OS        | Western   | 2.36 (1.73-3.21) | <0.001 | 85.9   | <0.001     | <0.001                   |
|                    |         |           | I-II      | 1.60 (1.41-1.82) | <0.001 | 73.4   | <0.001     |                          |
|                    |         |           | III-IV    | 1.47 (0.85-2.54) | 0.168   | -      | -          |                          |
|                    |         |           | Both      | 2.51 (2.04-3.09) | <0.001 | 81.7   | <0.001     |                          |
|                    | Cutoff  | value     | IA or IB  | 1.92 (1.65-2.23) | <0.001 | 87.6   | <0.001     | <0.001                   |
|                    |         |           | II-III    | 2.24 (1.78-2.81) | <0.001 | 64.9   | <0.001     |                          |
|                    | Study   | quality   | High      | 2.40 (1.87-3.07) | <0.001 | 86.9   | <0.001     | <0.001                   |
|                    |         |           | Low       | 1.80 (1.57-2.06) | <0.001 | 78.9   | <0.001     |                          |
|                    | EFS     | Countries | Eastern   | 1.83 (1.60-2.08) | <0.001 | 69.1   | <0.001     | 0.355                    |
|                    |         |           | Western   | 1.97 (1.61-2.41) | <0.001 | 62.4   | <0.001     |                          |
|                    | FIGO    | stage     | I-II      | 1.70 (1.50-1.93) | <0.001 | 52.6   | <0.001     |                          |
|                    |         |           | III-IV    | 1.01 (0.55-1.83) | 0.984   | -      | -          |                          |
|                    |         |           | Both      | 2.11 (1.75-2.54) | <0.001 | 75.5   | <0.001     |                          |
|                    | Cutoff  | value     | IA or IB  | 1.80 (1.59-2.04) | <0.001 | 68.1   | <0.001     | 0.021                    |
|                    |         |           | II-III    | 2.04 (1.65-2.52) | <0.001 | 62.5   | <0.001     |                          |
|                    | Study   | quality   | High      | 1.70 (1.45-2.00) | <0.001 | 73.9   | <0.001     | 0.023                    |
|                    |         |           | Low       | 1.99 (1.72-2.31) | <0.001 | 61.3   | <0.001     |                          |
Table 2 continued. Subgroup analysis for overall survival and event-free survival based on countries, FIGO stage, and cutoff value.

| Prognostic factors | Outcome | Variables | Subgroups | HR and 95% CI | P value | I² (%) | Q statistic | P value between subgroups |
|--------------------|---------|-----------|-----------|---------------|---------|--------|-------------|--------------------------|
| Hemoglobin         | OS      | Countries | Eastern   | 1.56 (1.15-2.10) | 0.004   | 58.1   | 0.019       | 0.001                    |
|                    |         |           | Western   | 3.05 (2.01-4.64) | <0.001 | 0.0    | 0.608       |                          |
| FIGO stage         |         | III       | 1.39 (0.99-1.95) | 0.061      |         |        |             |                          |
|                    |         | I-IV      | 1.81 (0.90-3.64) | 0.097      |         | 75.7   | 0.001       | 0.720                    |
|                    |         | Both      | 2.07 (1.00-1.99) | 0.001      |         |        |             |                          |
| Cutoff value       |         | 10        | 1.94 (1.13-3.36) | 0.017      |         | 80.2   | <0.001      | 0.156                    |
|                    |         | >10       | 1.77 (1.39-2.27) | <0.001     |         |        |             |                          |
| Study quality      |         | High      | 2.01 (1.00-4.04) | 0.050      |         | 88.0   | <0.001      | 0.337                    |
|                    |         | Low       | 1.70 (1.33-2.17) | <0.001     |         | 0.0    | 0.740       |                          |
| EFS                |         | Countries | Eastern   | 1.20 (1.07-1.34) | 0.002   | 4.3    | 0.401       | 0.004                    |
|                    |         | Western   | 2.25 (1.48-3.41) | <0.001     |         | 0.0    | 0.580       |                          |
| FIGO stage         |         | I-II      | 1.58 (1.19-2.09) | 0.001      |         | 0.0    | 0.778       |                          |
|                    |         | III-IV    | –         | –            | –       | –      |             |                          |
|                    |         | Both      | 1.24 (1.03-1.50) | 0.022      |         | 53.6   | 0.044       | 0.071                    |
| Cutoff value       |         | 10        | 1.50 (1.11-2.04) | 0.009      |         | 58.9   | 0.023       | 0.248                    |
|                    |         | >10       | 1.19 (1.04-1.35) | 0.010      |         | 0.0    | 0.733       |                          |
| Study quality      |         | High      | 1.30 (0.86-1.96) | 0.216      |         | 67.5   | 0.026       | 0.718                    |
|                    |         | Low       | 1.70 (1.33-2.17) | <0.001     |         | 0.0    | 0.740       |                          |
| Histological grade | OS      | Countries | Eastern   | 1.56 (1.24-1.96) | <0.001 | 56.3   | 0.004       | 0.460                    |
|                    |         | Western   | 1.48 (1.08-2.02) | 0.014      |         | 55.0   | 0.011       |                          |
| FIGO stage         |         | I-II      | 1.44 (1.19-1.74) | <0.001     |         | 41.6   | 0.030       |                          |
|                    |         | III-IV    | –         | –            | –       | –      |             |                          |
|                    |         | Both      | 1.75 (1.13-2.72) | 0.012      |         | 72.6   | 0.001       | 0.414                    |
| Cutoff value       |         | 1         | 1.52 (1.20-1.92) | 0.001      |         | 61.8   | <0.001      | 0.424                    |
|                    |         | 2         | 1.56 (1.17-2.07) | 0.002      |         | 32.6   | 0.157       |                          |
| Study quality      |         | High      | 1.43 (1.16-1.76) | 0.001      |         | 29.1   | 0.160       | 0.839                    |
|                    |         | Low       | 1.62 (1.20-2.19) | 0.001      |         | 66.2   | <0.001      |                          |
| EFS                |         | Countries | Eastern   | 1.47 (1.09-1.97) | 0.011   | 73.4   | <0.001      | 0.377                    |
|                    |         | Western   | 1.38 (1.07-1.78) | 0.013      |         | 44.0   | 0.051       |                          |
| FIGO stage         |         | I-II      | 1.49 (1.17-1.89) | 0.001      |         | 66.7   | <0.001      |                          |
|                    |         | III-IV    | –         | –            | –       | –      |             |                          |
|                    |         | Both      | 1.24 (0.99-1.57) | 0.066      |         | 0.0    | 0.517       | 0.340                    |
| Cutoff value       |         | 1         | 1.47 (1.13-1.90) | 0.004      |         | 72.5   | <0.001      | 0.746                    |
|                    |         | 2         | 1.41 (1.15-1.73) | 0.001      |         | 0.0    | 0.447       |                          |
| Study quality      |         | High      | 1.43 (1.12-1.84) | 0.005      |         | 64.5   | 0.001       | 0.308                    |
|                    |         | Low       | 1.45 (1.05-2.01) | 0.025      |         | 58.7   | 0.013       |                          |
Table 2 continued. Subgroup analysis for overall survival and event-free survival based on countries, FIGO stage, and cutoff value.

| Prognostic factors | Outcome | Variables | Subgroups | HR and 95% CI | P value | I² (%) | Q statistic | P value between subgroups |
|--------------------|---------|-----------|-----------|---------------|---------|--------|-------------|--------------------------|
| Leukocytosis | OS | Countries | Eastern | 2.20 (1.48-3.26) | <0.001 | 75.2 | 0.001 | 0.726 |
| | | | Western | 2.46 (1.15-5.26) | 0.020 | - | - | - |
| | FIGO stage | I-II | 1.55 (1.16-2.05) | 0.003 | 0.0 | 0.623 | 0.013 |
| | | III-IV | 3.04 (1.52-6.07) | 0.002 | - | - | - |
| | | Both | 2.66 (1.53-4.64) | 0.001 | 73.7 | 0.010 | - |
| | Cutoff value | ≥10000 | 2.05 (1.25-3.35) | 0.004 | 50.6 | 0.132 | 0.242 |
| | | <10000 | 2.35 (1.39-4.00) | 0.002 | 79.8 | 0.002 | - |
| | Study quality | High | 1.74 (1.18-2.56) | 0.005 | 9.6 | 0.293 | 0.148 |
| | | Low | 2.41 (1.51-3.85) | <0.001 | 76.6 | 0.002 | - |
| EFS | Countries | Eastern | 2.08 (1.25-3.45) | 0.005 | 69.6 | 0.011 | - |
| | | Western | - | - | - | - | - |
| | FIGO stage | I-II | 1.66 (0.52-5.26) | 0.389 | - | - | - |
| | | III-IV | - | - | - | - | - |
| | Both | 2.14 (1.20-3.81) | 0.010 | 76.8 | 0.005 | - |
| | Cutoff value | ≥10000 | 1.63 (0.66-4.05) | 0.290 | 0.0 | 0.964 | 0.526 |
| | | <10000 | 2.22 (1.16-4.24) | 0.016 | 84.3 | 0.002 | - |
| | Study quality | High | 2.10 (1.62-2.74) | <0.001 | - | - | 0.685 |
| | | Low | 2.00 (0.86-4.65) | 0.109 | 76.9 | 0.005 | - |
| LNI | OS | Countries | Eastern | 2.49 (2.17-2.85) | <0.001 | 71.4 | <0.001 | 0.007 |
| | | Western | 2.90 (2.29-3.67) | <0.001 | 60.5 | <0.001 | - |
| | FIGO stage | I-II | 2.97 (2.57-3.43) | <0.001 | 65.8 | <0.001 | - |
| | | III-IV | - | - | - | - | - |
| | Both | 2.04 (1.66-2.51) | <0.001 | 72.3 | <0.001 | - |
| | Study quality | High | 2.52 (2.08-3.04) | <0.001 | 68.5 | <0.001 | 0.639 |
| | | Low | 2.64 (2.26-3.09) | <0.001 | 70.7 | <0.001 | - |
| EFS | Countries | Eastern | 2.37 (2.03-2.77) | <0.001 | 81.0 | <0.001 | 0.001 |
| | | Western | 2.18 (1.75-2.72) | <0.001 | 61.6 | <0.001 | - |
| | FIGO stage | I-II | 2.54 (2.14-3.01) | <0.001 | 81.8 | <0.001 | - |
| | | III-IV | - | - | - | - | - |
| | Both | 1.89 (1.57-2.26) | <0.001 | 61.5 | <0.001 | 0.998 |
| | Study quality | High | 2.16 (1.73-2.70) | <0.001 | 87.0 | <0.001 | <0.001 |
| | | Low | 2.40 (2.10-2.75) | <0.001 | 51.3 | <0.001 | - |
Table 2 continued. Subgroup analysis for overall survival and event-free survival based on countries, FIGO stage, and cutoff value.

| Prognostic factors | Outcome | Variables | Subgroups | HR and 95% CI | P value | I² (%) | Q statistic | P value between subgroups |
|--------------------|---------|-----------|-----------|---------------|---------|--------|-------------|--------------------------|
| LVSI               | OS      | Countries | Eastern   | 1.99 (1.64-2.43) | <0.001  | 63.2   | <0.001      | 0.036                    |
|                    |         |           | Western   | 2.49 (1.72-3.60) | <0.001  | 36.3   | 0.100       |                          |
| FIGO stage         |         |           | I-II      | 2.08 (1.70-2.55) | <0.001  | 64.6   | <0.001      |                          |
|                    |         |           | III-IV    | 2.10 (0.32-13.68) | 0.438   | –      | –           | 0.539                    |
|                    |         |           | Both      | 2.20 (1.66-2.90) | <0.001  | 0.0    | 0.976       |                          |
| Study quality      |         |           | High      | 1.78 (1.41-2.24) | <0.001  | 47.4   | 0.029       | 0.046                    |
|                    |         |           | Low       | 2.30 (1.80-2.94) | <0.001  | 62.0   | <0.001      |                          |
| EFS                |         |           | Eastern   | 1.87 (1.62-2.16) | <0.001  | 48.0   | 0.001       | <0.001                   |
|                    |         |           | Western   | 1.80 (1.33-2.46) | <0.001  | 80.5   | <0.001      |                          |
| FIGO stage         |         |           | I-II      | 1.92 (1.68-2.18) | <0.001  | 51.1   | <0.001      |                          |
|                    |         |           | III-IV    | 0.94 (0.36-2.44) | 0.899   | –      | –           | <0.001                   |
|                    |         |           | Both      | 1.02 (0.95-1.09) | 0.572   | –      | –           |                          |
| Study quality      |         |           | High      | 1.77 (1.34-2.32) | <0.001  | 85.6   | <0.001      | <0.001                   |
|                    |         |           | Low       | 1.91 (1.63-2.23) | <0.001  | 43.0   | 0.004       |                          |
| NLR                | OS      | Countries | Eastern   | 1.48 (1.23-1.79) | <0.001  | 52.9   | 0.038       | 0.001                    |
|                    |         |           | Western   | 2.50 (1.39-4.50) | 0.002   | 50.5   | 0.155       |                          |
| FIGO stage         |         |           | I-II      | 1.78 (1.37-2.31) | <0.001  | 0.0    | 0.476       | 0.004                    |
|                    |         |           | III-IV    | –           | –      | –      | –           |                          |
|                    |         |           | Both      | 1.62 (1.22-2.14) | 0.001   | 72.7   | 0.003       |                          |
| Cutoff value       |         |           | ≥3.0      | 2.40 (1.75-3.28) | <0.001  | 0.0    | 0.494       | <0.001                   |
|                    |         |           | <3.0      | 1.35 (1.15-1.59) | <0.001  | 41.1   | 0.131       |                          |
| Study quality      |         |           | High      | 1.58 (1.23-2.03) | <0.001  | 75.7   | 0.001       | 0.005                    |
|                    |         |           | Low       | 2.04 (1.43-2.92) | <0.001  | 0.0    | 0.926       |                          |
| EFS                |         |           | Eastern   | 1.56 (1.23-1.98) | <0.001  | 76.6   | <0.001      | <0.001                   |
|                    |         |           | Western   | 3.58 (2.11-6.08) | <0.001  | –      | –           |                          |
| FIGO stage         |         |           | I-II      | 1.99 (1.51-2.63) | <0.001  | 0.0    | 0.816       | <0.001                   |
|                    |         |           | III-IV    | –           | –      | –      | –           |                          |
|                    |         |           | Both      | 1.61 (1.17-2.21) | 0.003   | 86.1   | <0.001      |                          |
| Cutoff value       |         |           | ≥3.0      | 2.12 (1.28-3.52) | 0.004   | 58.4   | 0.065       | <0.001                   |
|                    |         |           | <3.0      | 1.51 (1.16-1.98) | 0.002   | 81.7   | <0.001      |                          |
| Study quality      |         |           | High      | 1.65 (1.16-2.36) | 0.006   | 85.8   | <0.001      | <0.001                   |
|                    |         |           | Low       | 1.85 (1.24-2.78) | 0.003   | 60.6   | 0.038       |                          |
Table 2 continued. Subgroup analysis for overall survival and event-free survival based on countries, FIGO stage, and cutoff value.

| Prognostic factors | Outcome | Variables | Subgroups | HR and 95% CI | P value | I² (%) | Q statistic | P value between subgroups |
|-------------------|---------|-----------|-----------|---------------|---------|--------|-------------|--------------------------|
| Parametrical invasion | OS      | Countries | Eastern   | 2.16 (1.81-2.58) | <0.001 | 31.7   | 0.060 | 0.828 |
|                   |         | Western   | 2.26 (1.44-3.55) | <0.001 | 67.5 | 0.001 |
|                   | FIGO stage | I-II    | 2.15 (1.81-2.55) | <0.001 | 31.4 | 0.053 |
|                   |         | III-IV   | 1.11 (0.53-2.32) | 0.782 |       |       |       |
|                   |         | Both     | 2.26 (1.31-3.89) | 0.003 | 68.9 | 0.007 |
|                   | Study quality | High | 1.90 (1.36-2.66) | <0.001 | 66.1 | 0.001 |
|                   |         | Low      | 2.36 (1.96-2.64) | <0.001 | 22.9 | 0.146 |
| EFS               | Countries | Eastern | 1.89 (1.63-2.21) | <0.001 | 37.6 | 0.019 |
|                   | Western   | 2.03 (1.66-2.21) | <0.001 | 58.0 | 0.015 |
|                   | FIGO stage | I-II    | 1.96 (1.68-2.28) | <0.001 | 42.7 | 0.005 |
|                   |         | III-IV   | 3.70 (1.14-11.96) | 0.029 |       |       |       |
|                   |         | Both     | 1.48 (1.01-2.15) | 0.044 | 24.9 | 0.262 |
|                   | Study quality | High | 1.54 (1.32-1.80) | <0.001 | 12.1 | 0.321 |
|                   |         | Low      | 2.23 (1.86-2.69) | <0.001 | 32.7 | 0.056 |
| PLR               | OS      | Countries | Eastern | 2.20 (1.62-3.00) | <0.001 | 0.0 | 0.531 |
|                   | Western   | 1.54 (0.73-3.25) | 0.260 | 69.8 | 0.069 |
|                   | FIGO stage | I-II    | 2.10 (1.51-2.91) | <0.001 | 0.0 | 0.486 |
|                   |         | III-IV   |           |           |       |       |       |
|                   |         | Both     | 1.86 (0.97-3.59) | 0.062 | 65.6 | 0.055 |
|                   | Cutoff value | ≥150 | 2.59 (1.68-3.99) | <0.001 | 0.0 | 0.862 |
|                   |         | <150     | 1.72 (1.12-2.65) | 0.014 | 48.4 | 0.121 |
|                   | Study quality | High | 1.55 (0.98-2.43) | 0.059 | 45.1 | 0.162 |
|                   |         | Low      | 2.54 (1.76-3.66) | <0.001 | 0.0 | 0.805 |
| EFS               | Countries | Eastern | 2.47 (1.80-3.38) | <0.001 | 0.0 | 0.914 |
|                   | Western   | 1.01 (0.60-1.70) | 0.973 |       |       |
|                   | FIGO stage | I-II    | 2.44 (1.71-3.48) | <0.001 | 0.0 | 0.779 |
|                   |         | III-IV   |           |           |       |       |       |
|                   |         | Both     | 1.58 (0.63-3.95) | 0.333 | 78.8 | 0.030 |
|                   | Cutoff value | ≥150 | 2.59 (1.58-4.23) | <0.001 | 0.0 | 0.992 |
|                   |         | <150     | 1.82 (0.96-3.46) | 0.069 | 71.3 | 0.030 |
|                   | Study quality | High | 1.56 (0.62-3.93) | 0.343 | 76.7 | 0.038 |
|                   |         | Low      | 2.44 (1.72-3.46) | <0.001 | 0.0 | 0.779 |

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Table 2 continued. Subgroup analysis for overall survival and event-free survival based on countries, FIGO stage, and cutoff value.

| Prognostic factors | Outcome | Variables | Subgroups | HR and 95% CI | \( P \) value | \( I^2 \) (%) | Q statistic | \( P \) value between subgroups |
|--------------------|---------|-----------|-----------|---------------|--------------|--------------|-------------|-----------------------------|
| Resection margin   | OS      | Countries | Eastern   | 1.88 (1.29-2.75) | 0.001        | 65.7         | 0.002       | 0.268                      |
|                    |         |           | Western   | 2.22 (1.25-3.95) | 0.006        | 44.1         | 0.111       |                             |
| FIGO stage         | I-II    | Countries | Eastern   | 1.89 (1.36-2.62) | <0.001       | 57.3         | 0.004       |                             |
|                    |         |           | Western   | 2.26 (1.20-2.37) | 0.003        | 39.3         | 0.106       |                             |
|                    | III-IV  |           | Eastern   | 1.55 (0.86-2.81) | 0.148        |              |             |                             |
|                    |         |           | Western   | 1.69 (1.20-2.37) | 0.003        | 39.3         | 0.106       |                             |
| Study quality      | High    |           | Eastern   | 2.13 (1.24-3.66) | 0.006        | 74.6         | <0.001      | 0.569                      |
|                    |         |           | Western   | 1.75 (1.27-2.40) | 0.001        | 18.3         | 0.285       |                             |
| EFS                | Countries | Eastern   | 2.16 (1.56-2.99) | <0.001       | 52.2         | 0.006       | 0.129       |                             |
|                    |         |           | Western   | 1.67 (1.20-2.37) | 0.003        | 39.3         | 0.106       |                             |
| FIGO stage         | I-II    | Countries | Eastern   | 1.86 (1.43-2.43) | <0.001       | 45.2         | 0.012       |                             |
|                    |         |           | Western   | 1.71 (1.20-2.43) | 0.003        | 0.0          | 0.925       |                             |
|                    | III-IV  |           | Eastern   | 1.80 (1.33-2.45) | <0.001       | 53.3         | 0.015       | 0.218                      |
| Study quality      | Low     |           | Eastern   | 2.26 (1.53-3.33) | <0.001       | 45.7         | 0.032       |                             |
| SCC                | OS      | Countries | Eastern   | 1.72 (1.26-2.35) | 0.001        | 42.0         | 0.078       | 0.884                      |
|                    |         |           | Western   | 1.50 (0.92-2.45) | 0.105        |              |             |                             |
| FIGO stage         | I-II    | Countries | Eastern   | 1.81 (1.22-2.68) | 0.003        | 0.0          | 0.737       |                             |
|                    |         |           | Western   | 1.00 (0.55-1.82) | 0.992        |              |             |                             |
|                    | III-IV  |           | Eastern   | 1.97 (1.25-3.10) | 0.003        | 63.1         | 0.028       |                             |
| Cutoff value       | ≥10     |           | Eastern   | 1.39 (0.76-2.53) | 0.288        | 20.4         | 0.285       | 0.654                      |
|                    | <10     |           | Western   | 1.77 (1.29-2.42) | <0.001       | 45.4         | 0.076       |                             |
| Study quality      | High    |           | Eastern   | 2.61 (1.42-4.83) | 0.002        | 37.0         | 0.204       | 0.019                      |
|                    |         |           | Western   | 1.36 (1.15-1.60) | <0.001       | 0.0          | 0.440       |                             |
| EFS                | Countries | Eastern   | 1.80 (1.33-2.45) | <0.001       | 43.7         | 0.087       |              |                             |
|                    |         |           | Western   | –               | –            | –            | –           |                             |
| FIGO stage         | I-II    | Countries | Eastern   | 1.17 (0.61-2.22) | 0.637        | 34.4         | 0.218       |                             |
|                    |         |           | Western   | –               | –            | –            | –           |                             |
|                    | III-IV  |           | Eastern   | 2.08 (1.51-2.87) | <0.001       | 36.6         | 0.177       |                             |
| Cutoff value       | ≥10     |           | Eastern   | 1.63 (0.56-4.76) | 0.370        | 77.4         | 0.035       | 0.954                      |
|                    | <10     |           | Western   | 1.83 (1.33-2.53) | <0.001       | 37.6         | 0.156       |                             |
| Study quality      | High    |           | Eastern   | 1.70 (1.14-2.56) | 0.010        | 52.4         | 0.122       | 0.469                      |
|                    |         |           | Western   | –               | –            | –            | –           |                             |

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META-ANALYSIS

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| Prognostic factors | Outcome | Variables | Subgroups | HR and 95% CI | P value | I² (%) | Q statistic | P value between subgroups |
|--------------------|---------|-----------|-----------|---------------|---------|--------|-------------|--------------------------|
| Tumor grade        | OS      | Countries | Eastern   | 2.00 (1.37-2.93) | <0.001 | 61.5   | 0.016       | 0.007                    |
|                    |         |           | Western   | 1.07 (0.78-1.45) | 0.678 | 0.0    | 0.899       |                          |
| FIGO stage         |         | I-II      | Eastern   | 2.00 (1.37-2.93) | <0.001 | 61.5   | 0.016       | 0.007                    |
|                    |         | III-IV    | Western   | --              | --     | --     | --          |                          |
|                    |         | Both      | Eastern   | 1.07 (0.78-1.45) | 0.678 | 0.0    | 0.899       |                          |
| Study quality      |         | High      | Western   | 1.67 (0.90-3.10) | 0.101 | --     | --          | 0.721                    |
|                    |         | Low       | Western   | 1.76 (1.21-2.57) | 0.003 | 69.4   | 0.002       |                          |
| EFS                |         | Countries | Eastern   | 1.39 (1.14-1.71) | 0.001 | 39.2   | 0.130       | 0.480                    |
|                    |         | Western   | 1.16 (0.60-2.26) | 0.661 | 11.6   | 0.288       |                          |
| FIGO stage         |         | I-II      | Eastern   | 1.41 (1.17-1.70) | <0.001 | 30.3   | 0.186       | 0.226                    |
|                    |         | III-IV    | Western   | --              | --     | --     | --          |                          |
|                    |         | Both      | Eastern   | 0.89 (0.41-1.94) | 0.769 | --     | --          |                          |
| Study quality      |         | High      | Western   | 1.35 (0.96-1.89) | 0.084 | 54.1   | 0.113       | 0.754                    |
|                    |         | Low       | Western   | 1.38 (1.05-1.82) | 0.021 | 29.1   | 0.217       |                          |
| Tumor size         | OS      | Countries | Eastern   | 1.76 (1.52-2.05) | <0.001 | 71.7   | <0.001      | 0.004                    |
|                    |         | Western   | 1.95 (1.51-2.53) | <0.001 | 59.9   | 0.001       |                          |
| FIGO stage         |         | I-II      | Eastern   | 1.66 (1.41-1.97) | <0.001 | 70.6   | <0.001      |                          |
|                    |         | III-IV    | Western   | 1.09 (0.55-2.15) | 0.811 | 45.3   | 0.176       | <0.001                   |
|                    |         | Both      | Eastern   | 2.17 (1.78-2.65) | <0.001 | 59.1   | <0.001      |                          |
| Cutoff value       | ≥4.0 cm | Western   | 1.72 (1.48-2.00) | <0.001 | 69.6   | <0.001      | <0.001                   |
|                    | <4.0 cm | Western   | 2.09 (1.61-2.70) | <0.001 | 64.8   | <0.001      |                          |
| Study quality      |         | High      | Western   | 1.87 (1.52-2.31) | <0.001 | 66.1   | <0.001      | 0.010                    |
|                    |         | Low       | Western   | 1.78 (1.51-2.11) | <0.001 | 70.7   | <0.001      |                          |
| EFS                |         | Countries | Eastern   | 1.70 (1.46-1.98) | <0.001 | 77.8   | <0.001      | <0.001                   |
|                    |         | Western   | 1.67 (1.25-2.22) | 0.001 | 74.4   | <0.001      |                          |
| FIGO stage         |         | I-II      | Eastern   | 1.67 (1.45-1.93) | <0.001 | 66.9   | <0.001      |                          |
|                    |         | III-IV    | Western   | 1.59 (0.89-2.83) | 0.115 | --     | --          | <0.001                   |
|                    |         | Both      | Eastern   | 1.75 (1.34-2.28) | <0.001 | 86.1   | <0.001      |                          |
| Cutoff value       | ≥4.0 cm | Western   | 1.66 (1.39-1.98) | <0.001 | 78.5   | <0.001      | 0.062                    |
|                    | <4.0 cm | Western   | 1.76 (1.43-2.17) | <0.001 | 77.1   | <0.001      |                          |
| Study quality      |         | High      | Western   | 1.48 (1.28-1.72) | <0.001 | 68.3   | <0.001      | 0.053                    |
|                    |         | Low       | Western   | 1.90 (1.54-2.35) | <0.001 | 81.3   | <0.001      |                          |
Figure 3. The results of the meta-analysis of the prognostic factors influencing EFS.

Table 3. Publication bias for clinicopathological factors.
the Western countries, cutoff value <150, or studies with high quality; high SCCA level did not affect EFS of patients with FIGO stages I-II CC, or cutoff value ≥10; high tumor grade was not associated with EFS of patients with FIGO stages I-IV CC, according to the pooled analyses conducted in the Western countries, or studies with high quality; and tumor size did not influence EFS of patients with FIGO stages III-IV CC (Table 2).

There was significant publication bias for the prognostic significance of age (P (Egger’s test) <0.001; P (Begg’s test)=0.010), FIGO stage (P (Egger’s test)=0.016; P (Begg’s test)=0.061), hemoglobin level (P (Egger’s test)=0.026; P (Begg’s test)=0.024), LNI (P (Egger’s test) <0.001; P (Begg’s test)=0.460), LVSI (P (Egger’s test) <0.001; P (Begg’s test)=0.273), NLR (P (Egger’s test)=0.006; P (Begg’s test)=0.210), and tumor size (P (Egger’s test) <0.001; P (Begg’s test)=0.082) in EFS (Table 3). The pooled conclusions for EFS were not altered after adjusting for potential publication bias.

**Discussion**

The results of this study showed that the potential risk factors for OS and EFS were age, cell type, depth of tumor invasion, FIGO stage, hemoglobin level, histological grade, leukocytosis, LNI, LVSI, NLR, parametrial invasion, PLR, resection margin, SCCA level, thrombocytosis, tumor grade, tumor size, and tumor volume. Moreover, we noted that the first author’s country of residence could affect the prognostic significance of cell type, depth of tumor invasion, FIGO stage, hemoglobin level, LNI, LVSI, NLR, tumor stage, and tumor size in OS, and the prognostic significance of cell type, depth of tumor invasion, hemoglobin level, LNI, LVSI, NLR, PLR, and tumor size in EFS was influenced by the first author’s country of residence. Furthermore, FIGO stage could affect the prognostic significance of age, FIGO stage, hemoglobin level, LNI, LVSI, NLR, parametrial invasion, resection margin, SCCA level, thrombocytosis, tumor grade, and tumor volume in EFS. Therefore, we conducted the present systematic review and meta-analysis to identify the prognostic significance of clinicopathological factors influencing OS and EFS of patients with CC.

Compared with previous studies, this study revealed that FIGO stage, tumor size, parametrial invasion, resection margin, LNI, LVSI, and depth of tumor invasion could affect the prognosis of CC patients, which may be related to the fact that these factors could directly reflect distant metastasis and are associated with a poor prognosis of CC patients [168-170]. Furthermore, we studied additional prognostic factors, such as age, cell type, hemoglobin level, histological grade, leukocytosis, NLR, PLR, SCCA level, thrombocytosis, tumor grade, and tumor volume. The above-mentioned results could be explained as follows: (1) The incidence of CC varies among different age-based groups, and the FIGO stage of CC also significantly differs among various age-based groups [2]; (2) Compared with squamous cell carcinoma, patients with adenocarcinoma may tend to have other extracervical spread, associating with a poor prognosis of CC patients [171]; (3) The hemoglobin level is significantly correlated to the tumor size and infiltrative phenotypes of tumors [172,173]; Moreover, the hemoglobin level may act as a surrogate marker of tumor hypoxia, which is significantly associated with resistance to radiotherapy [174]; (4) Histological grade, tumor grade, and tumor volume are significantly correlated to tumor extension and invasion, which may influence the prognosis of CC patients; (5) Leukocytosis in CC patients is associated with a poor prognosis, which may be related to a poor response to radiation therapy [100]; (6) Increased NLR is markedly associated with a large tumor size, advanced clinical stage, and positive LNI, resulting in shorter OS and EFS [15]; (7) Elevated PLR can induce inflammatory cytokines and chemokines, promoting the progression of cancer cells [175]; (8) Increased SCCA concentration can reflect the degree of cell proliferation for patients with CC [176]; and (9) Cancer treatment can induce thrombocytosis, cytokines or growth factors, receptors, and downstream effectors, playing an important role in the prognosis of CC [177].

The current meta-analysis indicated the prognostic significance of cell type, depth of tumor invasion, FIGO stage, hemoglobin level, LNI, LVSI, NLR, PLR, tumor stage, and tumor size, which significantly differed in patients studied in the Eastern and...
Western countries. The results were based on the diagnosis of CC patients at various FIGO stages in different countries. Moreover, the vaccination rate in the Eastern and Western countries is different, influencing the incidence and prognosis of CC. Moreover, the effects of age, depth of tumor invasion, leukocytosis, LNI, LVSI, NLR, parametrial invasion, resection margin, tumor grade, and tumor size on the prognosis of CC patients could be influenced by FIGO stage. Additionally, the effects of age, FIGO stage, NLR, and tumor size on the prognosis of CC patients could be affected by the cutoff value.

The strengths of our study include: (1) our study contained 18 clinicopathological factors, which provide relatively comprehensive prognostic factors for CC; (2) the analysis was based on a large number of included studies, and the pooled conclusions are potentially more robust than are those of any individual study; and (3) subgroup analyses were performed for prognostic factors reported by more than 5 studies, which could assess the prognostic role of clinicopathological factors on OS and EFS according to studies’ characteristics. Several shortcomings of this study should be pointed out: (1) the majority of the included studies had a retrospective design, and selection or confounder biases were therefore inevitable; (2) the noticeable changes of the cutoff values partly expanded the range of the results of subgroup analyses; (3) the heterogeneity among the included studies was not fully explained by the results of the sensitivity and subgroup analyses; (4) the treatment strategies for CC significantly differed among the included studies, which could influence the prognosis of CC patients; (5) several other outcomes should be addressed in further large-scale prospective studies, including response to chemotherapy, remission rates, hospitalization rates, and complication rates; (6) the transparency of our study was restricted because it was not registered in PROSPERO; and (7) inherent limitations of meta-analysis of previously published articles are noteworthy.

Conclusions

This study comprehensively identified the prognostic significance of clinicopathological factors and influencing OS and EFS of patients with CC, including age, cell type, depth of tumor invasion, FIGO stage, hemoglobin level, histological grade, leukocytosis, LNI, LVSI, NLR, parametrial invasion, PLR, resection margin, SCCA level, thrombocytosis, tumor grade, tumor size, and tumor volume. However, further large-scale prospective studies should be conducted to verify our findings and develop more accurate prognostic models for CC.

Declaration of Figures’ Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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