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Original Article

Immune cell infiltration as a prognostic factor in endometrial cancer: a meta-analysis

Yibin Lin*, Qiaoming Lin*, Qi Guan, Danru Chen, Yan Zhou, Sang Li

*Department of Gynecology, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou 350014, Fujian, PR China. *Equal contributors and co-first authors.*

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Abstract: The immune system's role in cancer development and progression is receiving increasing attention. Endometrial cancer, common gynecological malignancy, has exhibited promising responses to immunotherapies. This study aims to assess the prognostic significance of various immune cell subsets in endometrial cancer, focusing on potential novel biomarkers and therapeutic targets. A systematic literature review and meta-analysis were conducted. Eleven eligible studies, comprising 2,319 patients with endometrial cancer, were included. The primary outcome was the association between levels of immune cell types, particularly CD8+ T cells, and overall prognosis. The meta-analysis found that high levels of tumor-infiltrating lymphocytes (TILs), particularly CD8+ T cells, were significantly associated with better overall prognosis in endometrial cancer patients. These findings suggest that the tumor immune microenvironment plays a crucial role in endometrial cancer prognosis. This meta-analysis indicates that higher levels of CD8+ T cells in the tumor microenvironment are linked to improved prognosis in endometrial cancer, underscoring the immune system's potential in prognostication and therapy.

Keywords: Immune cell infiltration, prognostic biomarkers, tumor microenvironment, personalized treatment, endometrial cancer

Introduction

Endometrial cancer (EC) is a common malignancy in women, with increasing incidence worldwide, posing a significant public health concern [1]. Originating from the uterine lining, EC is influenced by hormonal and metabolic changes typically associated with aging and obesity. The disease presents a complex challenge due to its multifactorial etiology, variable clinical manifestations, and diverse patient outcomes [2]. Despite advancements in treatment, traditional prognostic methods - mainly relying on clinical and histological parameters - often fail to accurately predict patient outcomes [3]. This underscores the need for additional prognostic factors to improve predictive models and guide personalized treatment plans.

In recent years, the role of the immune microenvironment in cancer progression and patient survival has gained significant attention in oncology [4]. The immune system plays a multifaceted role, with immune cells such as macrophages, dendritic cells, natural killer (NK) cells, and T cells either promoting or inhibiting tumor growth [5, 6]. The interaction among these immune populations is critical in determining cancer prognosis, and this complexity is particularly pronounced in EC [7, 8]. The advent of immunotherapy, including checkpoint inhibitors, has underscored the immune system's central role in cancer treatment, with the effectiveness of these therapies influenced by the tumor's immune landscape [9, 10]. Thus, understanding immune cell infiltration in EC is essential, not only for scientific insight but also for identifying novel prognostic biomarkers and therapeutic strategies.

This study aims to systematically evaluate the prognostic significance of immune cell infiltration in EC, with a particular focus on the role of CD8+ T cells. Through a meta-analysis, the study seeks to identify potential prognostic biomarkers and therapeutic targets.

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Methods

This study is registered with The International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY 202490006). The meta-analysis follows the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Literature search

Relevant articles were retrieved from PubMed, Medline, and Embase from the inception of these databases to May 31, 2024. The search strategy combined both free-text and subject headings, using keywords such as endometrial cancer, endometrial carcinoma, endometrial neoplasm, tumor-infiltrating lymphocytes (TILs), tumor-derived activated cells, prognosis, survival, and outcome.

Selection criteria

The inclusion criteria were as follows: 1) Patients diagnosed with endometrial cancer (stages I to IV) confirmed by postoperative pathology. 2) Patients who had not received chemotherapy or radiotherapy prior to surgery. 3) Patients without concurrent malignancies. 4) Studies that reported on the prognostic significance of total TILs or specific TIL subgroups (including CD3+ T cells, CD4+ T cells, CD8+ T cells, Forehead Box P3 (FoxP3) + lymphocytes, and others) in endometrial cancer. 5) Studies that provided complete data on hazard ratios (HRs) and 95% confidence intervals (CIs) for outcome measures.

Exclusion criteria included: 1) Non-clinical primary studies such as literature reviews, conference abstracts, case reports, animal studies, and editorials. 2) When multiple studies by the same author were available, only the most recent data were considered. 3) If a study presented both univariate and multivariate Cox regression analyses, the multivariate data were preferred due to higher precision.

The literature that met these criteria was reviewed by two independent researchers, who examined the titles, abstracts, full texts, and duplicates for inclusion or exclusion. Any discrepancies were resolved through discussion.

Data extraction

Data were independently extracted by two reviewers. The extracted information included: author details, nationality of study subjects, age, sample size, clinical stage, TIL subgroups, TIL data, tumor grade, cut-off values, median follow-up time, patient cohort, and outcome measures.

Overall Survival (OS) was defined as the time from surgery to death; Progression-Free Survival (PFS) was the time from treatment initiation to disease progression or death; Disease-Free Survival (DFS) was the time from surgery to recurrence or death; Disease-Specific Survival (DSS) excluded deaths due to causes unrelated to the tumor.

In cases of disagreement during data extraction, a third author was consulted, and consensus was achieved between the two reviewers.

Quality assessment

Two reviewers independently assessed the quality of the selected studies using predefined criteria. Disagreements were resolved through consensus. Observational studies, including case-control and cohort studies, were evaluated using an adapted version of the Newcastle-Ottawa Scale (NOS). This scale assigns scores across three domains: selection (four items), comparability (two items), and outcome ascertainment (three items), based on specific criteria. Studies with a total score of 7 or more were categorized as high quality, those scoring between 4 and 6 were deemed moderate quality, and studies with scores below 4 were considered low quality.

Statistical analyses

This study assessed the prognostic significance of TILs in EC by examining HRs and their corresponding 95% CIs. The heterogeneity across studies was assessed using the χ^2 test and the I^2 statistic. If the I^2 value was less than 50% ($I^2 < 50\%$) and the *P* value was greater than 0.1 ($P > 0.1$), indicating low heterogeneity, a fixed-effect model was applied for statistical analysis. In contrast, if heterogeneity was high, a random-effects model was used. Publication bias was evaluated using Egger's and Begg's tests. The data included in the final analysis

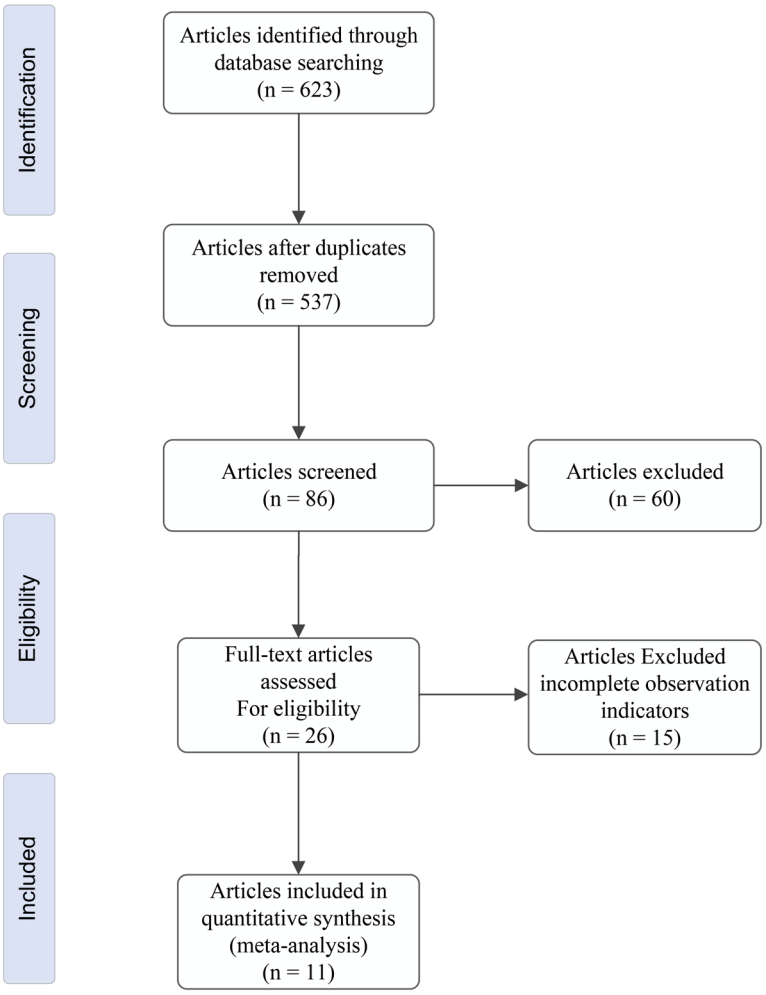

Figure 1. Flow chart of literature screening.

were processed and visualized using Stata software, version 14.0. Trial sequential analysis (TSA) was performed using TSA Viewer software, version 0.9, to account for cumulative heterogeneity, reduce the type I error rate, and estimate the potential effect of incomplete registered studies. The information size was determined based on an alpha risk of 5% and a beta risk of 20%. Statistical significance was determined by examining the 95% CI; values not encompassing the null value (less than 1.00 or greater than 1.00) were considered significant.

Results

Search results

The literature search across the databases yielded a total of 623 articles. After excluding duplicate publications, 351 non-qualifying documents, and an additional 100 articles for various reasons, 86 articles remained. A review of the titles and abstracts led to the exclusion of 60 articles. Furthermore, 15 articles with incomplete observation data were excluded, leaving 11 articles that were ultimately selected for the meta-analysis (**Figure 1**).

Study description

Table 1 summarizes the characteristics of the studies included in this review. A total of 2,319 patients from various countries, including Greece, the United States, the Netherlands, the Czech Republic, Japan, Canada, and Spain, were included. Of the 11 studies, 10 focused on the prognostic value of CD8+ T cells (8 studies examined their correlation with OS, 3 with DSS, and 2 with DFS), while 1 study investigated the prognostic implications of TILs in relation to DSS. Additionally, 3 studies explored the prognostic importance of CD4+ T cells, with 3 analyzing their association with OS, 1 with DSS, and 1 with DFS.

Quality assessment

The details of the quality assessment are provided in **Table 2**. Five studies were classified as high quality, with NOS scores of 7 or higher. Overall, the quality of the included studies was deemed acceptable.

Meta-analysis of the impact of TILs and TIL subgroups on the prognosis of EC

The meta-analysis indicated that the levels of TILs and their subgroups in EC were positively associated with prognosis (HR = 0.484, 95% CI = 0.411-0.556, $P < 0.05$, **Figure 2**), with significant heterogeneity across the studies ($P = 0.003$; $I^2 = 91.7\%$). These results suggest that higher levels of TILs and TIL subgroups in EC may significantly prolong survival rates. This conclusion was further validated through trial sequential analysis (TSA), which confirmed that

Table 1. Summary of the key characteristics of the included studies

Study	Area	TILs/TIL subgroups	Sample size	Age, mean (SD) or Median (range)	Follow up (months)	Tumor staging (I/II/III/VI)	Tumor grading (G1/G2/G3)	Cut of value	Survival outcomes
Vagios et al. [23]	Greece	CD8+	101	64.43 (10.20)	12-178	52/10/30/9	NA	Median	OS
Zhang et al. [24]	Japan	CD4+/CD8+	221	57 (26-84)	132 (3-209)	144/17/36/24	115/56/25	Median	OS
Čermáková et al. [25]	Czech Republic	CD8+	124	66 (9)	102 (64-145)	90/19/13/2	44/63/17	Median	OS
de Jong et al. [26]	Netherlands	CD8+	368	65 (32-89)	52.8 (0-258)	201/60/80/26	16/96/10 7	Median	OS
Kim et al. [27]	Korea	CD8+	183	53.0 (10.4)	30.3	NA	NA	K-Adaptive partitioning method	OS
Ikeda et al. [28]	USA	CD8+	32	56.5 (35-78)	NA	6/10/10/7	15/11/6	Median	OS
Workel et al. [29]	Netherlands	CD8+	305	NA	29	158/53/72/22	132/82/86	Median	DSS/DFS
Suemori et al. [30]	Japan	CD8+	123	57.8 (38-80)	85.3 (1.1-149.2)	58/6/36/9	55/38/31	Median	DSS
Versluis et al. [31]	Netherlands	Total CTLs	355	64 (56-73)	74.4	169/54/69/21	22/91	The lowest quartile (2.5)	DSS/DFS
Talhouk et al. [32]	Canada	CD8+/CD4+	460	NA	NA	NA	NA	Median	DSS/DFS/OS
Palomero et al. [1]	Spain	CD8+/CD4+	47	70.36 (10.28)	45.6	35/9/3	15/6/26	Median	OS

Notes: TILs: tumor-infiltrating lymphocytes; NK cells: Natural Killer cells; CTLs: Cytotoxic T cells; DSS: disease-specific survival; DFS: disease-free survival; OS: overall survival.

Table 2. Risk bias assessment of included literature (NOS scale)

Study	Selection of objects				Group comparability	Outcome assessment			Total score
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	
Vagios et al. [23]	1	0	1	0	1	1	1	1	66
Zhang et al. [24]	1	1	1	0	1	1	1	1	7
Čermáková et al. [25]	1	0	1	1	0	1	1	1	6
de Jong et al. [26]	1	0	1	0	1	1	1	1	6
Kim et al. [27]	1	1	0	1	1	1	1	1	7
Ikeda et al. [28]	1	1	1	1	0	1	0	1	6
Workel et al. [29]	1	1	0	1	1	1	1	0	6
Suemori et al. [30]	1	1	1	1	1	1	0	1	7
Versluis et al. [31]	1	1	1	1	1	0	1	1	7
Talhouk et al. [32]	1	1	0	1	1	1	0	1	6
Palomero et al. [1]	1	0	1	1	1	1	1	1	7

Notes: Q: question; NOS: Newcastle-Ottawa Scale.

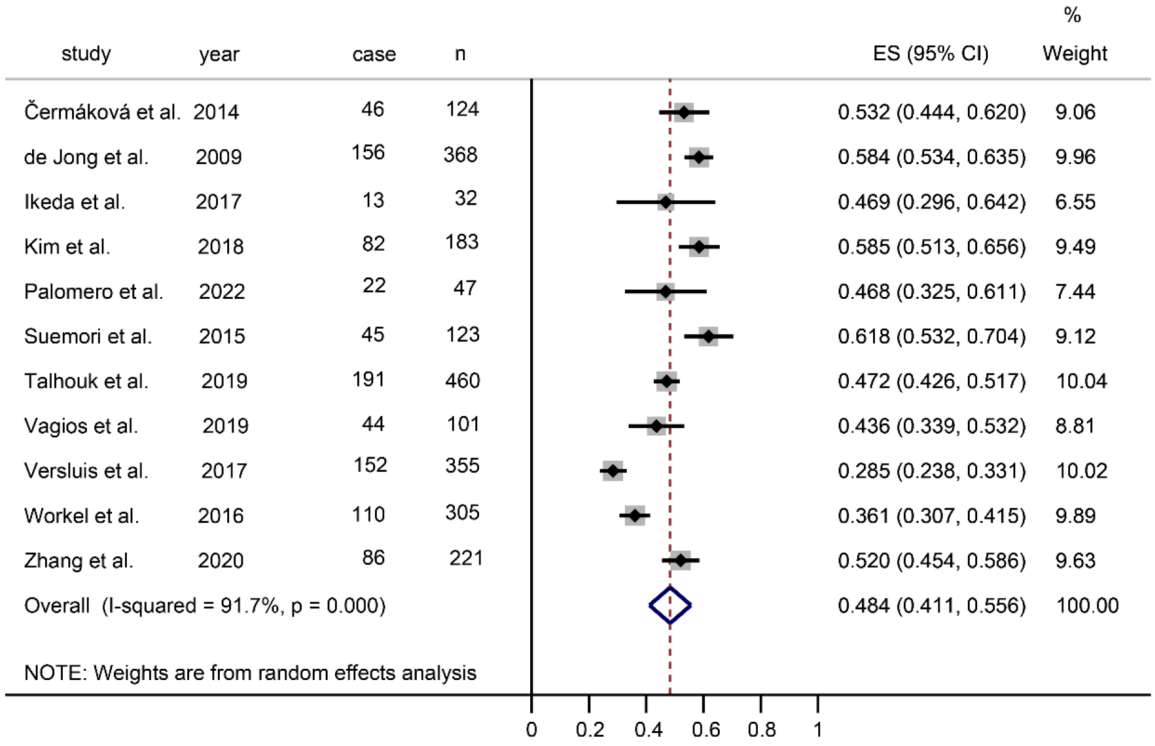

Figure 2. The forest plot of the impact of TILs and TIL subgroups on the prognosis of EC. TILs, tumor-infiltrating lymphocytes; EC, endometrial cancer.

the required information size had been reached (**Figure 3**).

Subgroup analyses

Subgroup analyses were performed on intratumoral CD8+ T cells and CD4+ T cells in EC to assess their prognostic significance. As shown in **Figure 4**, there was no heterogeneity within the CD8+ T cell group (P = 0.0001, HR = 0.507, 95% CI = 0.450-0.563), indicating a statistically significant association between CD8+ T cell infiltration and survival outcomes in EC patients. Similarly, no heterogeneity was observed within the CD4+ T cell group (P = 0.45, HR = 0.568, 95% CI = 0.390-0.745), suggesting that CD4+ T cells do not significantly affect survival rates in EC patients (**Figure 5**).

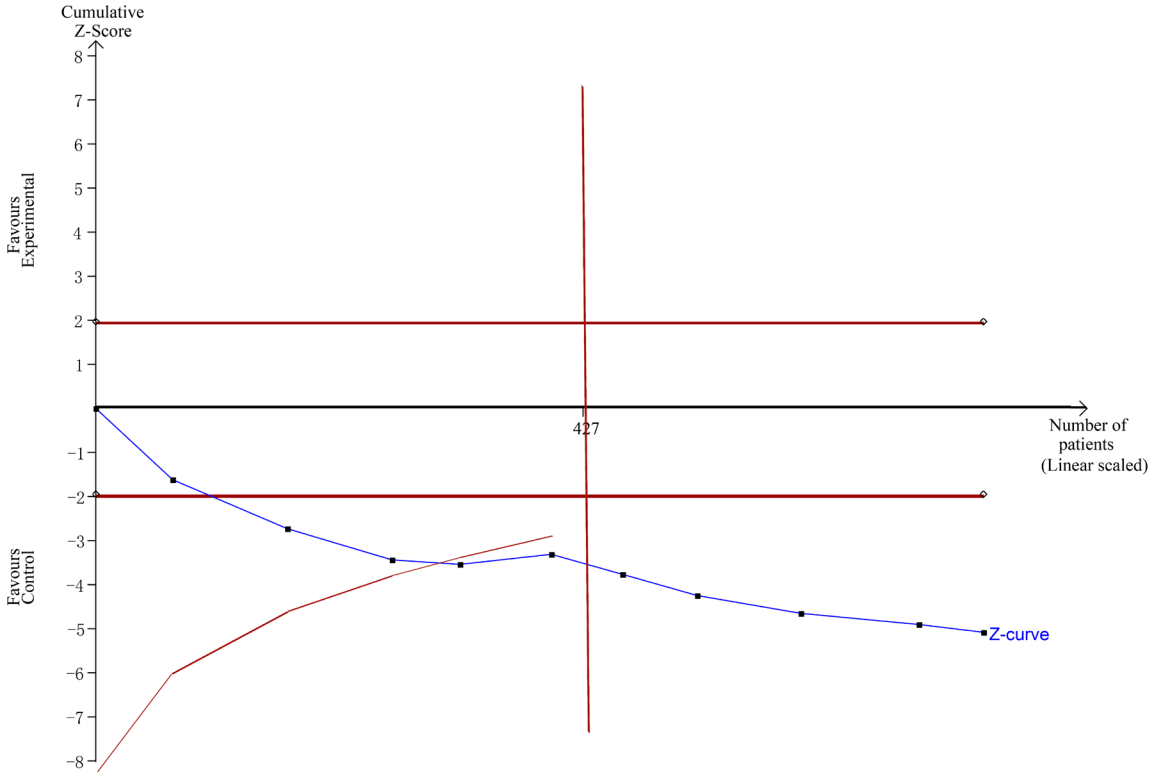

Figure 3. Trial sequential analysis of the impact of TILs and TIL subgroups on the prognosis of EC. TILs, tumor-infiltrating lymphocytes; EC, endometrial cancer.

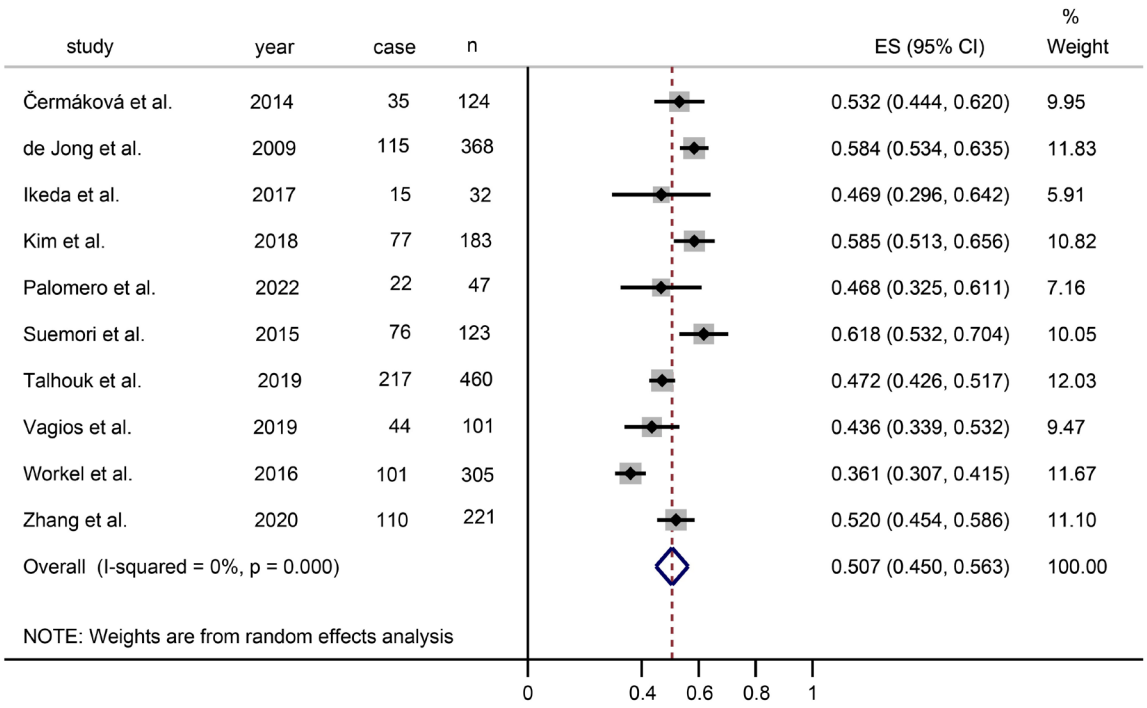

Figure 4. Subgroup analysis of the impact of CD8+ T cell infiltration on the prognosis of EC. EC, endometrial cancer.

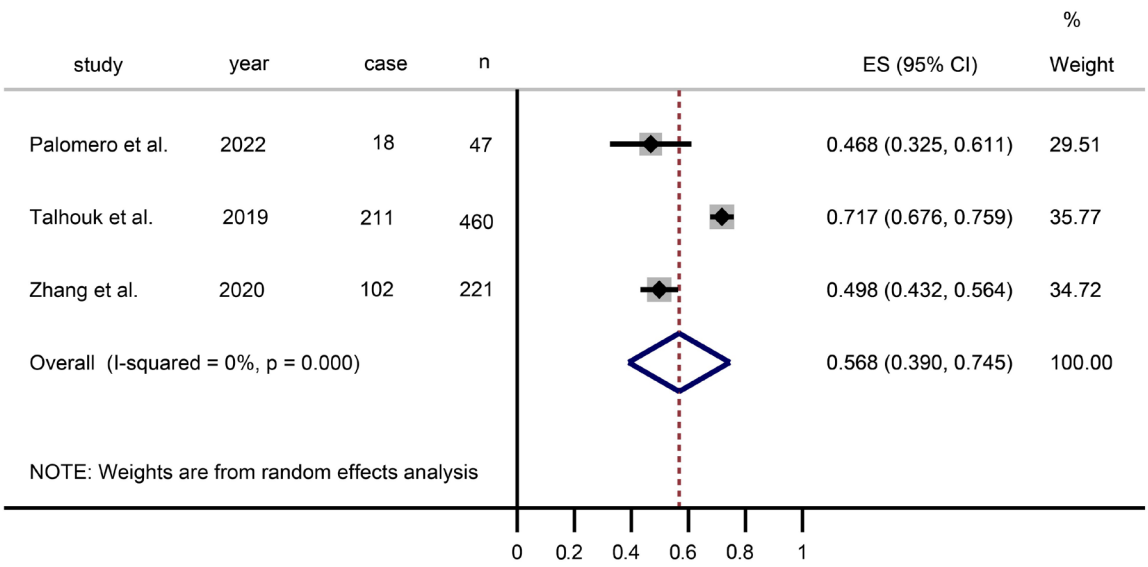

Figure 5. Subgroup analysis of the impact of CD4+ T cell infiltration on the prognosis of EC. EC, endometrial cancer.

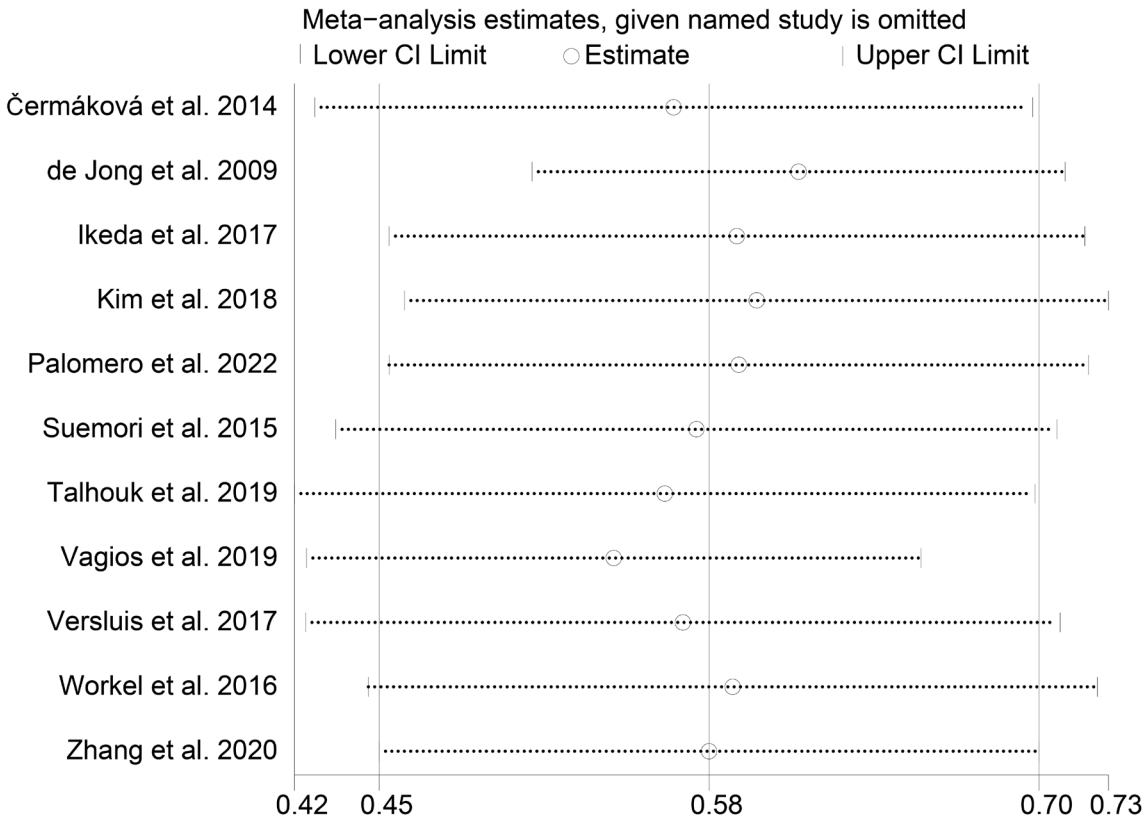

Figure 6. Sensitivity analysis for the impact of TILs and TIL subgroups on the prognosis of EC. TILs, tumor-infiltrating lymphocytes; EC, endometrial cancer.

Sensitivity analysis

Given the notable heterogeneity in the effects of TILs and TIL subgroups on EC prognosis, a sensitivity analysis was conducted (**Figure 6**). No significant changes were observed when individual studies were removed and the remaining studies were pooled, suggesting that

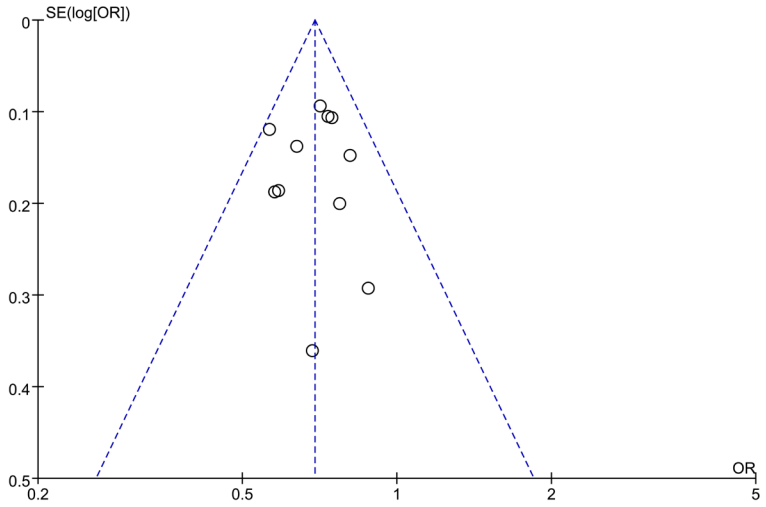

Figure 7. The funnel plot for assessing publication bias for the impact of TILs and TIL subgroups on the prognosis of EC. TILs, tumor-infiltrating lymphocytes; EC, endometrial cancer.

the primary findings of this meta-analysis are stable and reliable.

Publication bias

A funnel plot was used to assess potential publication bias (**Figure 7**). No significant publication bias was detected, as confirmed by Egger's regression test (t = 0.33, P = 0.71).

Discussion

Predicting clinical outcomes in EC typically involves histopathological evaluation of tissue samples obtained after surgical resection of the primary tumor [11]. However, it is recognized that even within the same disease stage, significant variability exists in the prognosis of different EC patients. For example, patients with identical histological stages of EC can have vastly different outcomes, highlighting the limitations of conventional tumor staging in providing precise prognostic information and guiding treatment decisions [12]. In recent years, studies have demonstrated that immune cell infiltration within the tumor stroma is associated with prognosis in various cancers, including breast, gastric, colorectal, lung, and ovarian cancers [13, 14]. Additionally, growing evidence suggests that the immune score could serve as a predictive tool for cancer prognosis and treatment response, supplementing traditional tumor staging methods to enhance the accuracy of disease prediction [15].

Despite these advancements, inconsistencies remain regarding the prognostic value of specific subsets of TILs in EC [16]. Therefore, we conducted a comprehensive analysis and integration of existing literature to clarify the prognostic significance of TILs through a larger sample size, thus enhancing the reliability of its predictive value.

The findings of this study indicate that the presence and activity of immune cells in the tumor microenvironment significantly influence the prognosis of EC patients. This highlights the potential role of immune-based biomarkers and therapeutic interventions in managing this disease. The positive correlation between the level of TILs and improved prognosis in EC patients is consistent with previous studies, suggesting that T cell infiltration into the tumor microenvironment may represent an effective anti-tumor immune response [17]. Of particular interest is the strong association between the level of CD8+ T cells and improved survival in EC patients. CD8+ T cells, known for their cytotoxic potential, are essential in eliminating tumor cells [17]. Numerous studies have emphasized the critical role of these cells in the body's immune response to cancer [18, 19]. For instance, CD8+ T cells can secrete cytotoxic molecules such as perforin and granzymes, inducing apoptosis in tumor cells [20]. They can also activate other immune cells, such as macrophages, to further enhance the anti-tumor response. Furthermore, the suppression of CD8+ T cells has been shown to promote tumor growth and metastasis in animal models [21]. These findings underscore the importance of CD8+ T cells in monitoring and controlling tumor progression, making them promising biomarkers for predicting patient outcomes in cancer therapy. Our meta-analysis suggests that higher CD8+ T cell infiltration is associated with a reduced risk of mortality in EC, reinforcing the prognostic relevance of this immune cell subset.

In contrast to the findings for CD8+ T cells, we did not observe a significant association be-

tween CD4+ T cell infiltration and EC prognosis. This discrepancy may be due to the diverse functions of CD4+ T cells, which can either promote or inhibit tumor progression depending on the context. The functional diversity of CD4+ T cells could offset their prognostic impact in EC [22]. Moreover, differences in study populations, methodologies, and the classification of immune cell subgroups may contribute to the inconsistent results across studies.

One of the primary limitations of this meta-analysis is the notable heterogeneity observed across the included studies. Potential sources of this heterogeneity include variations in study design, patient characteristics, methodologies for assessing immune cell infiltration, and the criteria used to define outcome measures. This heterogeneity complicates the interpretation of the pooled results and requires caution when extrapolating the findings to clinical settings. Additionally, publication bias, a common concern in meta-analyses, represents another potential limitation. Although the funnel plot and Egger's regression test did not reveal significant publication bias in this analysis, they cannot entirely exclude its possibility, particularly given the limited number of studies in this field.

Another limitation is the reliance on retrospective data, which may not fully capture the complexity of tumor-immune interactions over time. Furthermore, the retrospective nature of the data may overlook confounding variables that could influence the relationship between TILs and patient prognosis.

Despite these limitations, the meta-analysis has several strengths. By including studies from diverse geographical locations and patient cohorts, this analysis offers a comprehensive evaluation of the prognostic significance of immune cells in EC. The systematic search strategy and strict selection criteria ensured the inclusion of high-quality studies with reliable data. Moreover, the rigorous quality assessment and comprehensive data extraction process contribute to the validity of the findings.

The findings of this meta-analysis have important clinical and research implications for EC. The positive prognostic role of TILs, especially CD8+ T cells, suggests that immune-based biomarkers could be used to predict the prognosis of EC patients. This could, in turn, inform tailored treatment strategies that consider individual immune cell profiles.

In conclusion, this meta-analysis has clarified the prognostic role of TILs in EC, confirming that the presence and activity of immune cells within the tumor microenvironment significantly impact patient prognosis. The study highlights the potential predictive value of immune cell infiltration, particularly CD8+ T cells, which are associated with improved survival outcomes in EC patients.

Future research should focus on rigorous validation of the prognostic significance of immune cell subsets across diverse patient populations, considering the heterogeneity of EC. Establishing uniform criteria for sample collection, processing, and immune cell quantification will be crucial to ensure the reliability and comparability of results across studies. Additionally, investigating potential interactions between immune cells and other molecular factors in the tumor microenvironment will be essential for a more comprehensive understanding of EC pathogenesis and progression.

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Disclosure of conflict of interest

None.

Address correspondence to: Sang Li, Department of Gynecology, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital (Fujian Branch of Fudan University Shanghai Cancer Center), No. 420 Fuma Road, Fuzhou 350014, Fujian, PR China. Tel: +86-059187113828; E-mail: lisang123@fjmu.edu.cn

References

[1] Palomero J, Panisello C, Lozano-Rabella M, Tirtakasuma R, Díaz-Gómez J, Grases D, Pasamar H, Arregui L, Dorca Duch E, Guerra Fernández E, Vivancos A, de Andrea CE, Melero I, Ponce J, Vidal A, Piulats JM, Matias-Guiu X and Gros A. Biomarkers of tumor-reactive CD4(+)

and CD8(+) TILs associate with improved prognosis in endometrial cancer. J Immunother Cancer 2022; 10: e005443.
[2] McCluggage WG, Bosse T, Gilks CB, Howitt BE, McAlpine JN, Nucci MR, Rabban JT, Singh N, Talia KL and Parra-Herran C. FIGO 2023 endometrial cancer staging: too much, too soon? Int J Gynecol Cancer 2024; 34: 138-143.
[3] Žalytė E. Ferroptosis, metabolic rewiring, and endometrial cancer. Int J Mol Sci 2023; 25: 75.
[4] Nawrocki ST, Olea J, Villa Celi C, Dadrastoussi H, Wu K, Tsao-Wei D, Colombo A, Coffey M, Fernandez Hernandez E, Chen X, Nuovo GJ, Carew JS, Mohrbacher AF, Fields P, Kuhn P, Siddiqi I, Merchant A and Kelly KR. Comprehensive single-cell immune profiling defines the patient multiple myeloma microenvironment following oncolytic virus therapy in a phase Ib trial. Clin Cancer Res 2023; 29: 5087-5103.
[5] de Vries-Brilland M, Rioux-Leclercq N, Meylan M, Dauvé J, Passot C, Spirina-Menand E, Flippot R, Fromont G, Gravis G, Geoffrois L, Chevreau C, Rolland F, Blanc E, Lefort F, Ravaud A, Gross-Goupil M, Escudier B, Negrier S and Albiges L. Comprehensive analyses of immune tumor microenvironment in papillary renal cell carcinoma. J Immunother Cancer 2023; 11: e006885.
[6] Tang F, Li J, Qi L, Liu D, Bo Y, Qin S, Miao Y, Yu K, Hou W, Li J, Peng J, Tian Z, Zhu L, Peng H, Wang D and Zhang Z. A pan-cancer single-cell panorama of human natural killer cells. Cell 2023; 186: 4235-4251, e4220.
[7] Sharma P, Stecklein SR, Yoder R, Staley JM, Schwensen K, O'Dea A, Nye L, Satelli D, Crane G, Madan R, O'Neil MF, Wagner J, Larson KE, Balanoff C, Kilgore L, Phadnis MA, Godwin AK, Salgado R, Khan QJ and O'Shaughnessy J. Clinical and biomarker findings of neoadjuvant pembrolizumab and carboplatin plus docetaxel in triple-negative breast cancer: NeoPACT phase 2 clinical trial. JAMA Oncol 2024; 10: 227-235.
[8] Xin Z, Lin M, Hao Z, Chen D, Chen Y, Chen X, Xu X, Li J, Wu D, Chai Y and Wu P. The immune landscape of human thymic epithelial tumors. Nat Commun 2022; 13: 5463.
[9] Baumgartner CK, Ebrahimi-Nik H, Iracheta-Vellve A, Hamel KM, Olander KE, Davis TGR, McGuire KA, Halvorsen GT, Avila OI, Patel CH, Kim SY, Kammula AV, Muscato AJ, Halliwill K, Geda P, Klinge KL, Xiong Z, Duggan R, Mu L, Yeary MD, Patti JC, Balon TM, Mathew R, Backus C, Kennedy DE, Chen A, Longenecker K, Klahn JT, Hrusch CL, Krishnan N, Hutchins CW, Dunning JP, Bulic M, Tiwari P, Colvin KJ, Chuong CL, Kohnle IC, Rees MG, Boghossian A, Ronan M, Roth JA, Wu MJ, Suermondt JSMT, Knudsen NH, Cheruiyot CK, Sen DR, Griffin GK, Golub TR, El-Bardeesy N, Decker JH, Yang Y, Guffroy M, Fossey S, Trusk P, Sun IM, Liu Y, Qiu W, Sun Q, Paddock MN, Farney EP, Matulenko MA, Beauregard C, Frost JM, Yates KB, Kym PR and Manguso RT. The PTPN2/PTPN1 inhibitor ABBV-CLS-484 unleashes potent anti-tumour immunity. Nature 2023; 622: 850-862.
[10] van Weverwijk A and de Visser KE. Mechanisms driving the immunoregulatory function of cancer cells. Nat Rev Cancer 2023; 23: 193-215.
[11] Vrede SW, Donkers H, Reijnen C, Smits A, Visser NCM, Geomini PM, Ngo H, van Hamont D, Pijlman BM, Vos MC, Snijders MPLM, Kruitwagen R, Bekkers RLM, Galaal K and Pijnenborg JMA. Abnormal preoperative haematological parameters in endometrial cancer; reflecting tumour aggressiveness or reduced response to radiotherapy? J Obstet Gynaecol 2024; 44: 2294332.
[12] Li L, Yue P, Zhu J, Li L, Wang K, Yuan G and Song Y. TTN mutation in endometrial endometrioid carcinoma is associated with poor clinical outcomes and high tumor mutation burden. Cancer Invest 2024; 42: 297-308.
[13] Duan J, Zhang Y, Chen R, Liang L, Huo Y, Lu S, Zhao J, Hu C, Sun Y, Yang K, Chen M, Yu Y, Ying J, Huang R, Ma X, Leaw S, Bai F, Shen Z, Cai S, Gao D, Wang J and Wang Z. Tumor-immune microenvironment and NRF2 associate with clinical efficacy of PD-1 blockade combined with chemotherapy in lung squamous cell carcinoma. Cell Rep Med 2023; 4: 101302.
[14] Davidson G, Helleux A, Vano YA, Lindner V, Fattori A, Cerciat M, Elaidi RT, Verkarre V, Sun CM, Chevreau C, Bennamoun M, Lang H, Tricard T, Fridman WH, Sautes-Fridman C, Su X, Plassard D, Keime C, Thibault-Carpentier C, Barthelemy P, Oudard SM, Davidson I and Malouf GG. Mesenchymal-like tumor cells and myofibroblastic cancer-associated fibroblasts are associated with progression and immunotherapy response of clear cell renal cell carcinoma. Cancer Res 2023; 83: 2952-2969.
[15] Ling AL, Solomon IH, Landivar AM, Nakashima H, Woods JK, Santos A, Masud N, Fell G, Mo X, Yilmaz AS, Grant J, Zhang A, Bernstock JD, Torio E, Ito H, Liu J, Shono N, Nowicki MO, Triggs D, Halloran P, Piranlioglu R, Soni H, Stopa B, Bi WL, Peruzzi P, Chen E, Malinowski SW, Prabhu MC, Zeng Y, Carlisle A, Rodig SJ, Wen PY, Lee EQ, Nayak L, Chukwueke U, Gonzalez Castro LN, Dumont SD, Batchelor T, Kittelberger K, Tikhonova E, Miheecheva N, Tabakov D, Shin N, Gorbacheva A, Shumskiy A, Frenkel F, Aguilar-Cordova E, Aguilar LK, Krisky D, Wechuck J, Manzanera A, Matheny C, Tak PP, Barone F, Kovarsky D, Tirosh I, Suvà ML, Wucherpfennig

KW, Ligon K, Reardon DA and Chiocca EA. Clinical trial links oncolytic immunoactivation to survival in glioblastoma. Nature 2023; 623: 157-166.
[16] Guo C, Tang Y, Zhang Y and Li G. Mining TCGA data for key biomarkers related to immune microenvironment in endometrial cancer by immune score and weighted correlation network analysis. Front Mol Biosci 2021; 8: 645388.
[17] Liu X, Liu C, Liu J, Song Y, Wang S, Wu M, Yu S and Cai L. Identification of tumor microenvironment-related alternative splicing events to predict the prognosis of endometrial cancer. Front Oncol 2021; 11: 645912.
[18] Kersten K, Hu KH, Combes AJ, Samad B, Harwin T, Ray A, Rao AA, Cai E, Marchuk K, Artichoker J, Courau T, Shi Q, Belk J, Satpathy AT and Krummel MF. Spatiotemporal co-dependency between macrophages and exhausted CD8(+) T cells in cancer. Cancer Cell 2022; 40: 624-638, e629.
[19] Kristensen NP, Heeke C, Tvingsholm SA, Borch A, Draghi A, Crowther MD, Carri I, Munk KK, Holm JS, Bjerregaard AM, Bentzen AK, Marquard AM, Szallasi Z, McGranahan N, Andersen R, Nielsen M, Jönsson GB, Donia M, Svane IM and Hadrup SR. Neoantigen-reactive CD8+ T cells affect clinical outcome of adoptive cell therapy with tumor-infiltrating lymphocytes in melanoma. J Clin Invest 2022; 132: e150535.
[20] Wu J, Xiao Y, Lu W, Zhang Z, Yang H, Cui X, Wu D and Chen Y. Correlation between tumor microenvironment and immune subtypes based on CD8 T Cells Enhancing Personalized Therapy of Gastric Cancer. J Oncol 2022; 2022: 8933167.
[21] Mahdi HS, Woodall-Jappe M, Singh P and Czuczman MS. Targeting regulatory T cells by E7777 enhances CD8 T-cell-mediated anti-tumor activity and extends survival benefit of anti-PD-1 in solid tumor models. Front Immunol 2023; 14: 1268979.
[22] Gi T, Yamashita A, Aman M, Kuwahara A, Asada Y, Kawagoe Y, Onishi J, Sameshima H and Sato Y. Tissue factor expression and tumor-infiltrating T lymphocytes in ovarian carcinomas and their association with venous thromboembolism. Pathol Int 2021; 71: 261-266.
[23] Vagios S, Yiannou P, Giannikaki E, Doulgeraki T, Papadimitriou C, Rodolakis A, Nonni A, Vlachos A and Pavlakis K. The impact of programmed cell death-ligand 1 (PD-L1) and CD8 expression in grade 3 endometrial carcinomas. Int J Clin Oncol 2019; 24: 1419-1428.
[24] Zhang S, Minaguchi T, Xu C, Qi N, Itagaki H, Shikama A, Tasaka N, Akiyama A, Sakurai M, Ochi H and Satoh T. PD-L1 and CD4 are independent prognostic factors for overall survival in endometrial carcinomas. BMC Cancer 2020; 20: 127.
[25] Čermáková P, Melichar B, Tomšová M, Zoul Z, Kalábová H, Spaček J and Doležel M. Prognostic significance of CD3+ tumor-infiltrating lymphocytes in patients with endometrial carcinoma. Anticancer Res 2014; 34: 5555-5561.
[26] de Jong RA, Leffers N, Boezen HM, ten Hoor KA, van der Zee AG, Hollema H and Nijman HW. Presence of tumor-infiltrating lymphocytes is an independent prognostic factor in type I and II endometrial cancer. Gynecol Oncol 2009; 114: 105-110.
[27] Kim J, Kim S, Lee HS, Yang W, Cho H, Chay DB, Cho SJ, Hong S and Kim JH. Prognostic implication of programmed cell death 1 protein and its ligand expressions in endometrial cancer. Gynecol Oncol 2018; 149: 381-387.
[28] Ikeda Y, Kiyotani K, Yew PY, Sato S, Imai Y, Yamaguchi R, Miyano S, Fujiwara K, Hasegawa K and Nakamura Y. Clinical significance of T cell clonality and expression levels of immune-related genes in endometrial cancer. Oncol Rep 2017; 37: 2603-2610.
[29] Workel HH, Komdeur FL, Wouters MC, Plat A, Klip HG, Eggink FA, Wisman GB, Arts HJ, Oonk MH, Mourits MJ, Yigit R, Versluis M, Duiker EW, Hollema H, de Bruyn M and Nijman HW. CD103 defines intraepithelial CD8+ PD1+ tumour-infiltrating lymphocytes of prognostic significance in endometrial adenocarcinoma. Eur J Cancer 2016; 60: 1-11.
[30] Suemori T, Susumu N, Iwata T, Banno K, Yamagami W, Hirasawa A, Sugano K, Matsumoto E and Aoki D. Intratumoral CD8+ lymphocyte infiltration as a prognostic factor and its relationship with cyclooxygenase 2 expression and microsatellite instability in endometrial cancer. Int J Gynecol Cancer 2015; 25: 1165-1172.
[31] Versluis MAC, Marchal S, Plat A, de Bock GH, van Hall T, de Bruyn M, Hollema H and Nijman HW. The prognostic benefit of tumour-infiltrating Natural Killer cells in endometrial cancer is dependent on concurrent overexpression of Human Leucocyte Antigen-E in the tumour microenvironment. Eur J Cancer 2017; 86: 285-295.
[32] Talhouk A, Derocher H, Schmidt P, Leung S, Milne K, Gilks CB, Anglesio MS, Nelson BH and McAlpine JN. Molecular subtype not immune response drives outcomes in endometrial carcinoma. Clin Cancer Res 2019; 25: 2537-2548.