Clinical Research

Prognostic factors influencing recurrence in patients with endometrial cancer: a systematic review and meta-analysis

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pISSN: 0853-1773 • eISSN: 2252-8083
https://doi.org/10.13181/mji.oa.268139
Med J Indones. 2026;35:228–37

Received: March 24, 2025
Accepted: June 17, 2026

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ABSTRACT

BACKGROUND Endometrial cancer (EC) ranks as the 6th most common cancer among women worldwide. Despite early detection often yielding favorable outcomes, approximately 13% of early-stage EC patients still experience recurrence. This study aimed to identify prognostic factors for EC recurrence.

METHODS A systematic review and meta-analysis were conducted following preferred reporting items for systematic reviews and meta-analyses guidelines (International Prospective Register of Systematic Reviews ID: CRD42024501501). PubMed, Scopus, and Cochrane Library were searched for cohort and case-control studies published on January 1, 2018–January 1, 2024. The primary outcome was disease recurrence (any, locoregional, or distant). Inclusion criteria included adult women with histologically confirmed EC after primary surgery, ≥12-month follow-up, and sample size ≥100. Risk of bias was assessed using Quality in Prognosis Studies; certainty was rated using Grading of Recommendations Assessment, Development and Evaluation.

RESULTS 8 studies met inclusion criteria from 5,633 records screened. Significant prognostic factors included lymphovascular space invasion (LVSI) (relative risk [RR]: 4.83, 95% confidence interval [CI]: 3.49–6.69), cancer grade (RR: 2.15, 95% CI: 1.86–2.48), histology type (RR: 0.46, 95% CI: 0.34–0.61), cancer stage (RR: 2.58, 95% CI: 2.13–3.12), cervical stromal invasion (RR: 3.36, 95% CI: 1.30–8.73), myometrial invasion (RR: 2.60, 95% CI: 2.03–3.32), and chemotherapy history (RR: 1.81, 95% CI: 1.41–2.31). High heterogeneity was observed for chemotherapy history (I^2 = 92%) and cancer stage (I^2 = 77%).

CONCLUSIONS Various clinicopathological factors, particularly LVSI, grade, stage, histology, and myometrial invasion, significantly influence EC recurrence. These findings support the need for individualized risk stratification and treatment planning.

KEYWORDS endometrial cancer, meta-analysis, neoplasm recurrence, prognostic factors, systematic review

Endometrial cancer (EC) is the sixth most common cancer in women worldwide, with more than 417,000 new cases reported in 2020. In Indonesia, EC is among the top five most frequent gynecological cancers, with an increasing incidence found in urban populations. Postmenopausal bleeding is the primary presenting symptom of EC, allowing most patients to be diagnosed at an early stage and contributing to an overall favorable prognosis.[1] The 5-year survival rates for EC are approximately 80%, 60%, 30%, and 5% for stages I, II, III, and IV, respectively. However, recurrence remains a major clinical concern, affecting up to 13% of cases, including those detected early. Recurrence is defined as detection of new disease after complete primary treatment (surgery and adjuvant therapy), confirmed by biopsy or radiologic evidence, regardless of the anatomic site.[2] Site-specific recurrence is categorized as: (i) locoregional, involving

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the vaginal vault, parametrium, pelvic lymph nodes, or pelvic peritoneum; and (ii) distant, affecting the abdominal cavity (outside the pelvis), lungs, liver, bones, or supraclavicular lymph nodes. This anatomical dichotomy has prognostic significance, as locoregional recurrences may be amenable to curative salvage therapy, while distant recurrences are generally considered incurable, and are therefore treated with palliative intent. Temporal definitions further stratify recurrence risk: early recurrence occurs within <12 months of completing primary treatment, while late recurrence manifests ≥12 months post-treatment. Notably, EC recurrence is strongly associated with increased mortality, particularly in patients with early or rapid recurrence.[1,3–5]

Certain patient subgroups, such as those with high-grade tumors, advanced International Federation of Gynaecology and Obstetrics (FIGO) stage, or specific histological subtypes, such as serous carcinoma, have demonstrated higher recurrence risks in prior studies.[1,3–6] Existing systematic reviews and meta-analyses have primarily focused on narrow subpopulations, such as low-volume nodal metastasis, stage IC non-myoinvasive high-grade tumors, or specific molecular markers in serous carcinoma, often without any standardized recurrence definitions or stratification by the updated FIGO 2023 criteria.[7] This review addresses critical gaps by synthesizing the most recent evidence regarding recurrence risk factors across all histological subtypes and stages, applying explicit definitions of recurrence (distinguishing early [<12 months] *versus* late events), and emphasizing the relevance to Indonesia and Southeast Asia, where incidence is rising (3.5/100,000).[8] The ultimate goal is to improve risk stratification and support individualized treatment and surveillance strategies.[9] The present study aimed to explore and synthesize factors associated with recurrence risk in patients with EC. By focusing on recent studies from the past 5 years, it should provide updated and clinically relevant insights.

METHODS

Protocol and registration

We registered the protocol prior to the conduct of this review and meta-analysis in the International Prospective Register of Systematic Reviews (registration number CRD42024501501, registered on January 26, 2024).

Study design

This systematic review and meta-analysis were conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2020 guidelines. The review question was framed using population, exposure, comparator, and outcome structures, defining the population as adult women aged ≥18 years with histologically confirmed endometrial carcinoma (endometrioid, serous, clear cell, or mixed subtypes; stages I–IV according to the FIGO 2009 or 2023 criteria) who had undergone primary surgical treatment, excluding those with carcinosarcoma, uterine sarcoma, or a history of prior pelvic malignancies. Exposure comprised demographic, clinical, pathological, or treatment-related prognostic factors, with comparators being the absence of the factor or the reference category, as reported in each study. The primary outcome was endometrial carcinoma recurrence (any recurrence, locoregional recurrence involving the vaginal vault, parametrium, pelvic nodes, or pelvic peritoneum, or distant recurrence involving extra-pelvic abdominal sites, lung, liver, bone, or supraclavicular nodes), confirmed by biopsy or radiological evidence, with a minimum follow-up period of 12 months. Adjusted effect estimates were prioritized where available. The meta-analysis focused primarily on cohort studies, with high-quality case-control studies included as supplementary evidence when cohort data were insufficient.

Eligibility criteria

Studies were eligible for inclusion if: (i) cohort or case-control in design; (ii) enrolled at least 100 participants; (iii) published in English between January 2018 and January 2024; (iv) provided full-text articles. Randomized controlled trials were excluded due to their intervention heterogeneity and differing prognostic factor profiles. Studies were also excluded if they were: (i) case reports, case series, reviews, editorials, or conference abstracts; (ii) included carcinosarcomas or uterine sarcomas; (iii) enrolled patients with prior pelvic malignancies; (iii) did not report recurrence-related outcomes; (iv) full-texts were inaccessible; (v) published in languages other than English.

Search strategy

A comprehensive literature search was conducted using three electronic databases: PubMed (via National

Library of Medicine interface), Scopus (Elsevier), and the Cochrane Library (Wiley). PubMed was searched from inception with coverage through January 1, 2024; Scopus indexed publications from 1996 onward; Cochrane Library included Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Database of Abstracts of Reviews of Effects databases. The search covered publications from January 1, 2018, to January 1, 2024, with no geographic restrictions.

The search strategy employed combinations of Medical Subject Headings and relevant keywords using Boolean operators (AND, OR, NOT). The search terms focused on three domains: (1) EC recurrence ("Endometrial Neoplasms," "Neoplasm Recurrence, Local," "Relapse"); (2) demographic and clinical characteristics (age, body mass index [BMI], and comorbidities); and (3) tumor features and treatment modalities (histology, FIGO stage, lymphovascular space invasion [LVSI], chemotherapy, and radiotherapy). The PubMed search was adapted for Scopus using Emtree terms where applicable, and for the Cochrane Library using controlled vocabulary.

Supplementary search methods included: (i) forward and backward citation chasing of included studies and relevant systematic reviews; (ii) handsearching of reference lists from 2018–2024 issues of Gynecologic Oncology, International Journal of Gynecological Cancer, and Journal of Clinical Oncology; (iii) grey literature search via OpenGrey and ProQuest Dissertations & Theses Global; and (iv) trial registry screening (ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform) for unpublished completed studies.

Study selection and data extraction

Study selection was conducted following a four-step process: title screening, abstract screening, full-text assessment, and final inclusion. The reasons for exclusion at the full-text stage are detailed in the PRISMA flow diagram. Six reviewers (FK, KAS, VNA, GSGB, MSM, and SBA) independently screened the articles using Rayyan (Qatar Computing Research Institute; Rayyan Systems Inc., USA), and discrepancies were resolved through consensus or third-party adjudication. Data extraction was conducted using a standardized pilot-tested form in Microsoft Excel version 16.0. (Microsoft Corporation, USA), capturing the following fields: author, year, country, study design, sample size, follow-up duration, demographic factors (age, BMI, and comorbidities), and prognostic variables, including histology, FIGO stage (2009 version prioritized during extraction, with 2023 updates noted where applicable), grade, LVSI, and treatment modalities. Recurrence was additionally recorded based on whether it was centrally verified (pathology and/or imaging) when reported. Studies with mixed or unclear verification methods were considered a potential source of heterogeneity. Given the inherent risk of confounding by indication, chemotherapy was recorded as a proxy prognostic factor. Recurrence verification methods varied across the included studies (e.g., biopsy-confirmed only *versus* imaging-inclusive criteria); central adjudication of recurrence was not performed, and this methodological variation was treated as a potential source of heterogeneity. Effect estimates, risk ratio (RR), hazard ratio (HR), and odds ratio (OR) with 95% confidence intervals (CIs) were extracted preferentially as adjusted estimates, unadjusted estimates were recorded when adjusted analyses were unavailable. In studies reporting multiple-effect measures, time-to-event estimates (HR) were prioritized over risk estimates (RR or OR). All data were double-extracted by paired reviewers, and discrepancies were resolved through discussion or reference to the original publication.

Risk of bias (RoB) and certainty assessment

Six reviewers independently screened articles using Quality in Prognosis Studies (QUIPS) for RoB assessment in prognostic factor studies; discrepancies were resolved through consensus.[10] Data were double-extracted into standardized Microsoft Excel for Microsoft 365 (Microsoft Corporation, USA) forms, capturing study characteristics, prognostic variables, and effect estimates (HR preferred over RR/OR and adjusted over unadjusted) with 95% CIs. The certainty of evidence was assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE), rating RoB, inconsistency, indirectness, imprecision, and publication bias, and the findings are summarized in GRADE tables.

Statistical analysis

A meta-analysis was conducted using the meta (version 6.5-0) and metafor (version 4.2-0) packages in Review Manager version 5.4.1 (Nordic Cochrane Centre, Cochrane Collaboration, Denmark) and R

software version 4.3.1 (R Foundation for Statistical Computing, Austria). A fixed-effects model was used with I^2 quantifying heterogeneity (25%, 50%, and 75% thresholds). Heterogeneity was assessed using subgroup (FIGO stage, histology, geography, and effect measure type) and sensitivity analyses (leave-one-out and exclusion of high RoB studies). Publication bias was assessed via funnel plots and Egger's test for $k \geq 10$ using STATA software version 17.0 (StataCorp LLC, College Station, USA); formal testing was not performed for $k < 10$ due to low power.

RESULTS

Study selection

A total of 5,633 records were identified from databases and registers. Of 22 studies assessed for eligibility, 14 were excluded. The final screening thus yielded eight studies which met the inclusion and exclusion criteria. A PRISMA 2020 flow diagram of the study selection process is presented in Figure 1.

Study characteristics and outcome

Among the eight included studies, seven were retrospective cohort studies and one was a prospective cohort study; all were published between 2021 and 2023. The sample sizes ranged from 96 to 2,974 participants (median 816), comprising a total of 10,009 women with histologically confirmed endometrial carcinoma who had undergone primary surgical treatment. The follow-up duration met or exceeded 12 months in all studies. Studies originated from high-income (n = 4; Sweden, Italy, United Kingdom, United States) and upper-middle-income countries (n = 4; Turkey, China). Detailed characteristics, including prognostic factors evaluated, adjustment variables, and effect estimates, are summarized in Table 1.

A meta-analysis was performed based on several factors as indicators of recurrence of EC. The meta-

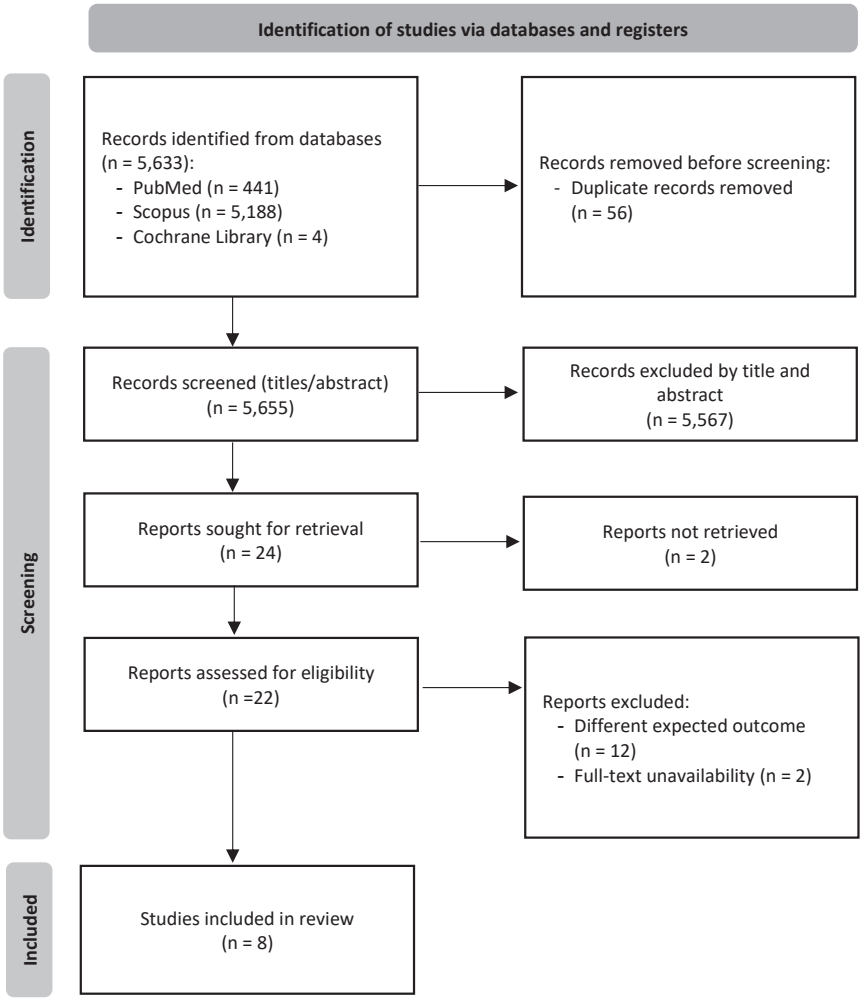


Figure 1. Study selection for prognostic factors of EC recurrence with PRISMA model. EC=endometrial cancer; PRISMA=preferred reporting items for systematic reviews and meta-analyses

Table 1. Characteristics of included studies on prognostic factors for EC recurrence

First author, year	Study design	Country (income level)	Study population	Risk exposure vs. control	Adjusted (yes/no)	Key covariates	Measurement	Effect estimate (95% CI)	Results summary
Åkesson et al,[11] 2023	Prospective cohort	Sweden (high-income)	1,630 women with endometrioid EC	Age (continuous per year)	Yes	Age, FIGO stage, and adjuvant treatment	HR	1.29 (1.11–1.51)	Older age independently increased recurrence risk
				FIGO stage III–IV vs. I–II				2.78 (1.80–4.29)	Advanced stage independently increased recurrence risk
				Adjuvant treatment vs. none				1.84 (1.22–2.78)	Adjuvant treatment independently increased recurrence risk
Buda et al,[13] 2023	Retrospective cohort	Italy (high-income)	1,428 women with EC undergoing surgical staging with SLN mapping	Micrometastases vs. low-volume metastases	Yes	Not fully specified	HR	2.61 (CI not reported)	Micrometastases associated with higher recurrence than low-volume metastases (p = 0.01)
Altın et al,[15] 2023	Retrospective cohort	Turkey (upper-middle income)	289 patients with LVSI-negative early-stage endometrioid EC; median follow-up 45 months	Grade 3 vs. 1–2	Yes	Grade	HR	4.79 (1.50–15.32)	Grade 3 was sole independent predictor of recurrence
Zouridis et al,[14] 2023	Retrospective cohort	United Kingdom (high-income)	863 patients with EC (96 women with high-grade endometrioid EC)	Cervical stromal involvement vs. none	Yes	Cervical stromal involvement, other pathological, and treatment variables	HR	25.67 (2.95–223.30)	Cervical stromal involvement independently increased recurrence risk (p = 0.003)
Liu et al,[16] 2023	Retrospective cohort	China (upper-middle income)	665 patients with EC (196 MIS vs. 469 OS)	MIS vs. OS	No	None - unadjusted comparison	RR*	Not calculated	MIS group had higher recurrence rate: 17.3% vs. 6.6% (p<0.001)
Dou et al,[2] 2022	Retrospective cohort	China (upper-middle income)	2,974 women with EC classified by FIGO stage	Grade 3 vs. 1–2	Yes	Grade, LVSI, myometrial infiltration, and bilateral ovariectomy	OR	1.55 (1.17–2.05)	Grade 3 independently increased recurrence risk
				LVSI present vs. absent				3.36 (1.50–7.54)	LVSI independently increased recurrence risk
				Myometrial infiltration present vs. absent				2.07 (1.17–3.65)	Myometrial infiltration independently increased recurrence risk
				Bilateral ovariectomy vs. none				0.26 (0.14–0.51)	Bilateral ovariectomy reduced recurrence risk
Merritt et al,[12] 2021	Retrospective cohort	USA (high-income)	816 patients with stage II–IV endometrioid adenocarcinoma	ER positive vs. negative	Yes	Not fully specified	HR	0.67 (CI not reported)	ER positivity reduced recurrence risk
				IR positive vs. negative				0.53 (CI not reported)	IR positivity reduced recurrence risk
				Circulating estradiol positive vs. negative				1.55 (CI not reported)	Circulating estradiol positivity increased recurrence risk

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Table 1. (Continued)

First author, year	Study design	Country (income level)	Study population	Risk exposure vs. control	Adjusted (yes/no)	Key covariates	Measurement	Effect estimate (95% CI)	Results summary
Li et al,[17] 2021	Retrospective cohort	China (upper-middle income)	111 women with atypical endometrial hyperplasia or early EC	BMI ≥25 vs. <25 kg/m²	Yes	BMI, IR, MetS, histological type, and maintenance treatment	OR	2.70 (CI not reported)	BMI ≥25 increased recurrence risk
				Insulin resistance positive vs. negative				9.50 (CI not reported)	IR independently increased recurrence risk
				MetS positive vs. negative				4.90 (CI not reported)	MetS independently increased recurrence risk
				Maintenance treatment vs. none				0.30 (CI not reported)	Maintenance treatment significantly reduced recurrence risk

BMI=body mass index; CI=confidence interval; EC=endometrial cancer; ER=estrogen receptor; FIGO=International Federation of Gynaecology and Obstetrics; HR=hazard ratio; IR=insulin resistance; LVSI=lymphovascular space invasion; MetS=metabolic syndrome; MIS=minimally invasive surgery; OR=odds ratio; OS=open surgery; RR=relative risk; SLN=sentinel lymph node
*RR was not reported in the original study; only crude recurrence proportions were available, so an effect estimate could not be calculated

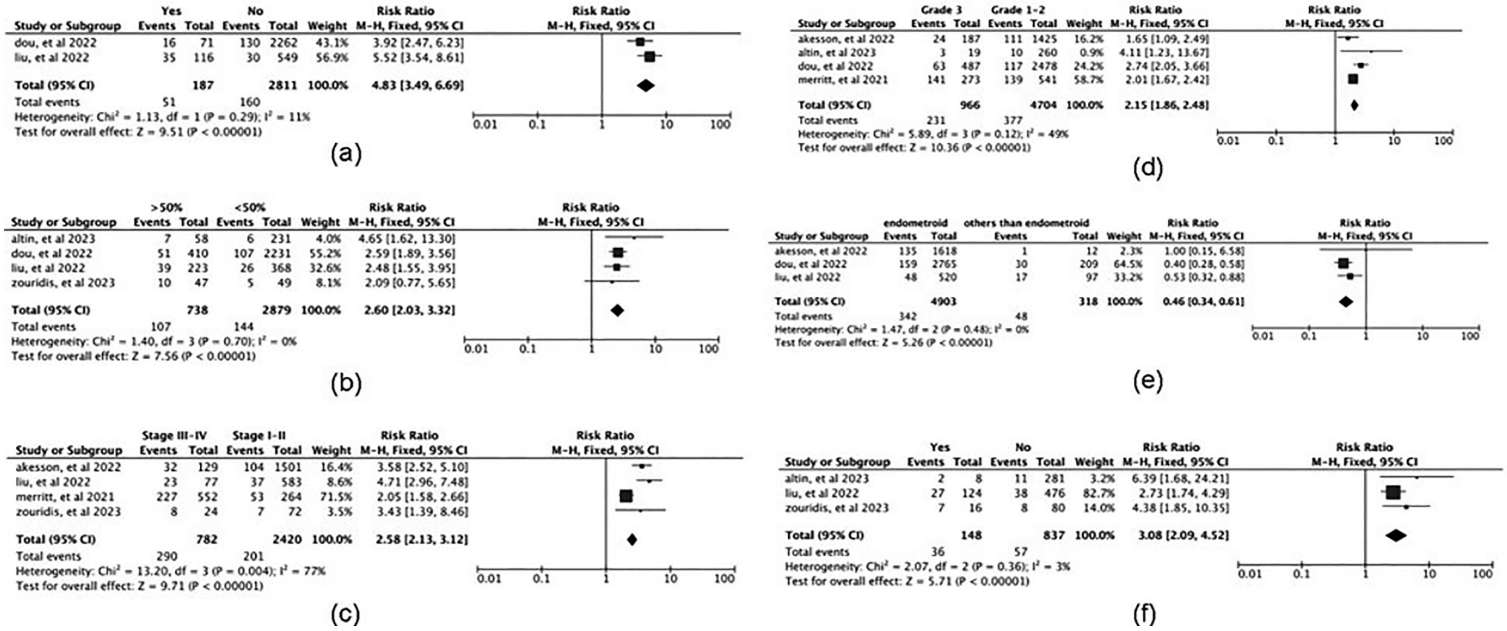


Figure 2. Forest plots of the demographic and patients characteristics with order of: (a) LVSI; (b) myometrial invasion; (c) FIGO stage; (d) cancer grade; (e) histology; (f) cervical stromal invasion. CI=confidence interval; FIGO=International Federation of Gynaecology and Obstetrics; LVSI=lymphovascular space invasion

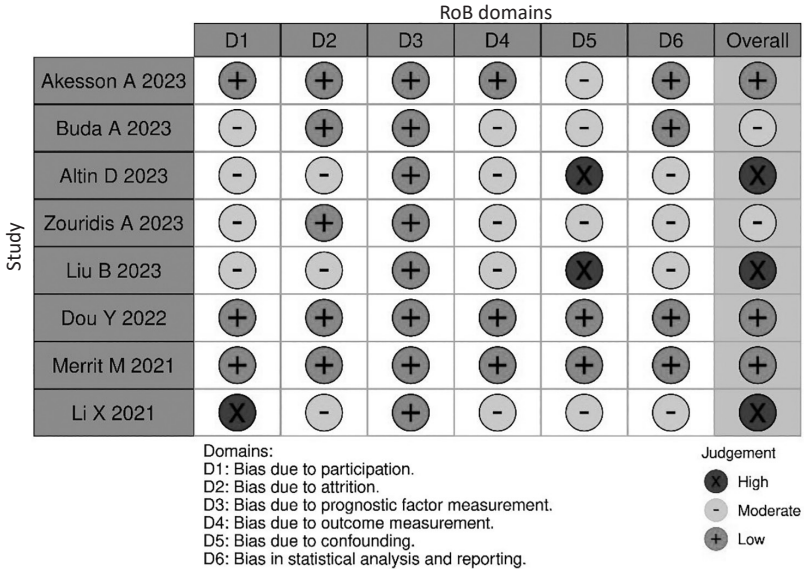


Figure 3. Risk of bias (RoB) of included studies

Table 2. Results of GRADE criteria

Outcomes	Impact	Number of studies	Certainty of the evidence (GRADE)
Cancer grade (grade 3 vs. grade 1–2)	2.15-fold increased risk of recurrence (RR: 2.15, 95% CI: 1.86–2.48)	3	LOW ⨁⨁◯◯
Histology type (non-endometrioid vs. endometrioid)	54% reduced risk with endometrioid (RR: 0.46, 95% CI: 0.34–0.61)	3	LOW ⨁⨁◯◯
Cancer stage (stage III–IV vs. stage I–II)	2.58-fold increased risk of recurrence (RR: 2.58, 95% CI: 2.13–3.12)	3	VERY LOW ⨁◯◯◯
Cervical stromal invasion (present vs. absent)	3.36-fold increased risk of recurrence (RR: 3.36, 95% CI: 1.30–8.73)	2	VERY LOW ⨁◯◯◯
History of chemotherapy (yes vs. no)	1.81-fold increased risk of recurrence (RR: 1.81, 95% CI: 1.41–2.31)	2	VERY LOW ⨁◯◯◯
Myometrial invasion (>50% vs. <50%)	2.60-fold increased risk of recurrence (RR: 2.60, 95% CI: 2.03–3.32)	3	LOW ⨁⨁◯◯
LVSI (present vs. absent)	4.83-fold increased risk of recurrence (RR: 4.83, 95% CI: 3.49–6.69)	3	MODERATE ⨁⨁⨁◯
Surgical approach (laparoscopy vs. laparotomy)	31% reduced risk with laparoscopy (RR: 0.69, 95% CI: 0.51–0.95)	2	VERY LOW ⨁◯◯◯
Age at enrollment (per year increase)	1.88 years older on average in recurrence group (95% CI: 0.98–2.79)	2	VERY LOW ⨁◯◯◯
Adjuvant treatment (yes vs. no)	Increased recurrence risk (p = 0.015, no effect estimate reported)	2	VERY LOW ⨁◯◯◯

CI=confidence interval; GRADE=Grading of Recommendations Assessment, Development and Evaluation; LVSI=lymphovascular space invasion; RR=relative risk

analysis of this study was divided into two main categories: forest plots of the demographic and patient characteristics and forest plots of the clinical factors and treatments, which can be seen in Figure 2 and Supplementary Figure 1.

We conducted a meta-analysis using several factors as indicators of EC recurrence. The meta-analysis was divided into two main categories: forest plots of demographic/patient characteristics and clinical factors/treatments. Factors influencing EC recurrence based on patient characteristics and demographics included cancer grade (grade 3 *versus* grade 1–2) (RR: 2.15; 95% CI: 1.86–2.48), histological type (endometrioid *versus* non-endometrioid) (RR: 0.46; 95% CI: 0.34–0.61), and cancer stage (stage III–IV *versus* stage I–II) (RR: 2.58; 95% CI: 2.13–3.12).

Age at enrollment has also emerged as a significant prognostic factor. Patients with recurrent disease were, on average, 1.88 years older at enrollment (95% CI: 0.98–2.79).

Furthermore, the factors influencing recurrence related to clinical conditions and management included cervical stromal invasion (yes *versus* no) (RR: 3.36; 95% CI: 1.30–8.73), history of chemotherapy treatment (yes *versus* no) (RR: 1.81; 95% CI: 1.41–2.31), myometrial invasion (>50% *versus* <50%) (RR: 2.60; 95% CI: 2.03–3.32), surgical approach (laparoscopy *versus* laparotomy) (RR: 0.69; 95% CI: 0.51–0.95), and LVSI (yes *versus* no) (RR: 4.83; 95% CI: 3.49–6.69) (Table 2).

Risk of bias (RoB)

Based on the RoB assessment using the QUIPS tool, the certainty of evidence was rated using GRADE. Åkesson et al[11] demonstrated a low RoB across all six domains, and was rated with moderate certainty. Dou et al[2] and Merritt et al[12] further showed a predominantly low RoB, although, as retrospective studies, they started with low certainty and were rated as having low certainty overall. The studies by Buda et al,[13] Zouridis et al,[14] and Altın et al[15] all exhibited a moderate RoB in multiple domains, particularly regarding study participation and confounding factors, resulting in low-to-very low certainty ratings. Liu et al[16] and Li et al[17] further demonstrated a high RoB in critical domains, including study participation and confounding factors, leading to very low certainty ratings. Overall, only three of the eight studies achieved a low RoB in all QUIPS domains, with the majority showing moderate to serious limitations that substantially reduced the certainty of evidence for prognostic factor identification in EC recurrence. Figure 3 presents the domain-specific assessments.

Assessment of certainty

The certainty of evidence was assessed using the GRADE approach for prognostic factor studies. Among the eight included studies, only one prospective cohort study provided evidence of moderate certainty, while the remaining seven retrospective cohort studies were rated as having low or very low certainty due to the inherent risks of selection bias and confounding. LVSI demonstrated moderate certainty evidence, with an RR of 4.83 and narrow CI, supported by a large magnitude of effect and low heterogeneity across the three studies. Cancer grade, histological type, and myometrial invasion were all rated with low certainty owing to serious limitations in RoB and imprecision from the small study numbers. Cancer stage, cervical stromal invasion, chemotherapy history, surgical approach, age at enrollment, and adjuvant treatment all received very low certainty ratings owing to critical issues, including high heterogeneity, extremely wide CIs, confounding by indication, and the absence of any reported effect estimates. The unexpected association between chemotherapy history and increased recurrence risk was interpreted as confounding by indication, rather than as a causal prognostic factor. Overall, only one of the 10 evaluated prognostic factors achieved a moderate certainty, highlighting the substantial methodological limitations of the current evidence base for predicting EC recurrence.

DISCUSSION

Overall, this meta-analysis demonstrated that LVSI was the strongest predictor of recurrence (pooled RR: 4.83), followed by deep myometrial invasion (2.6-fold increased risk). High tumor grade and advanced FIGO stage were significant risk factors, while endometrioid histology exerted a clear protective effect. Clinically, these pooled findings indicate that patients with LVSI or deep myometrial invasion, even in early stage disease, should be considered for adjuvant therapy, while those with endometrioid histology may be candidates for de-escalated surveillance or treatment.[18,19]

These results are largely consistent with those of previous systematic reviews and current guidelines. The European Society of Gynaecological Oncology 2020 guidelines already identify LVSI, deep myometrial invasion, and high grade as key risk factors for adjuvant therapy decisions, factors that our quantitative synthesis confirms with high precision. The 4.83-fold increase in risk with LVSI firmly supports its classification as a high-risk feature warranting adjuvant treatment. Similarly, the 2.6-fold risk associated with deep myometrial invasion validated the FIGO staging distinction between <50% and ≥50% invasion. Finally, the protective effect of endometrioid histology aligns with contemporary molecular classification systems (The Cancer Genome Atlas and Proactive Molecular Risk

Classifier for Endometrial Cancer), which consistently place endometrioid tumors in a more favorable prognostic category than serous, clear-cell, or p53-aberrant subtypes.[20,21]

One unexpected finding was the association between a history of chemotherapy and an increased risk of recurrence (RR: 1.81, 95% CI: 1.41–2.31). However, this likely reflects confounding by indication; patients receiving chemotherapy were selected based on high-risk features (advanced stage, high grade, or residual disease) that independently predicted recurrence. The high heterogeneity (I^2 = 92%) supports this interpretation, as the effect estimates vary substantially across studies with different case mixes. Similarly, the high heterogeneity in cancer stage (I^2 = 77%) likely stems from varying staging versions (FIGO 2009 *versus* 2023), with the 2023 revision reclassifying some stage IIC cases into stage IIIC1, potentially affecting risk stratification.[19] These findings underscore that chemotherapy is a marker of aggressive disease biology, rather than a causative factor for recurrence.

Several discrepancies with the prior literature warrant further study. While individual studies identified age, diabetes, BMI, and menopausal status as predictors of recurrence, our pooled analyses revealed no significant associations. These null findings likely reflect case-mix differences across studies; some studies included predominantly early stage endometrioid cancers, where metabolic factors may have limited prognostic impact, while others focused on high-grade or advanced-stage disease, where tumor biology dominates. Additionally, the varying definitions of metabolic syndrome and diabetes across studies may have introduced measurement heterogeneity. The lack of any association between minimally invasive surgery (MIS) and recurrence in our pooled estimate (RR: 0.69, 95% CI: 0.51–0.95, favoring laparoscopy) contrasts with concerns raised by the Laparoscopic Approach to Cervical Cancer trials in cervical cancer; however, our finding aligns with Cochrane reviews showing equivalent oncologic outcomes for MIS in EC when performed by experienced surgeons using appropriate surgical techniques.[22,23]

The moderate heterogeneity observed in cancer grade (I^2 = 49%) may reflect variations in grading systems (architectural *versus* nuclear grade) and interobserver variability, particularly for grade 2 tumors. The low heterogeneity of LVSI, myometrial invasion, and histology (I^2 = 0–37%) supports the reliability of these factors in diverse clinical settings. The present findings regarding metabolic factors, specifically the association between insulin resistance and recurrence reported in two studies, indicate that metabolic dysregulation may represent a modifiable risk pathway, although the limited number of studies precluded pooled analysis.[18] Future research should evaluate whether metformin or lifestyle interventions targeting insulin resistance can reduce the risk of recurrence, particularly in obese and diabetic populations.[24]

Limitations of this study include the retrospective design of most of the included studies, which would have introduced potential selection and confounding biases. Furthermore, restriction to English-language publications may have excluded relevant studies from non-English-speaking regions, including Southeast Asia, where its incidence is increasing. Additionally, the small number of studies on several variables (chemotherapy, radiotherapy, and surgical approach) limited the statistical power and generalizability. Finally, due to the heterogeneity in recurrence definitions, some studies requiring biopsy confirmation, while others accepted radiologic evidence, may have affected the effect estimates, particularly for early recurrence detection, where imaging sensitivity varies.

Nevertheless, this meta-analysis provides robust, quantitative evidence confirming that LVSI, deep myometrial invasion, advanced stage, high grade, and cervical stromal invasion are key prognostic factors for EC recurrence. Overall, these findings support the current guideline recommendations for risk stratification and adjuvant therapy. The unexpected association between chemotherapy and recurrence highlights the importance of interpreting treatment variables as markers of disease severity rather than as causal factors. Future prospective studies should standardize recurrence definitions, incorporate molecular classifications (p53-abnormal, polymerase epsilon-mutated, and mismatch repair-deficient subtypes), and evaluate whether metabolic interventions can modify recurrence risk in high-risk populations.

In conclusion, the present meta-analysis confirmed that LVSI, deep myometrial invasion, advanced stage, high tumor grade, and cervical stromal invasion were the strongest predictors of EC recurrence, with RRs ranging from 2.15 to 4.83. These findings provide quantitative support for current risk stratification systems and underscore the need for the intensive surveillance of

patients with multiple risk factors. The prognostic impact of metabolic factors and optimal follow-up protocols for different molecular subtypes remain uncertain. By synthesizing contemporary evidence and highlighting methodological inconsistencies across studies, this review identifies priorities for future research, including standardized recurrence definitions and evaluation of metabolic interventions to reduce recurrence risk.

Conflict of Interest

The authors affirm no conflict of interest in this study.

Acknowledgment

None.

Funding Source

None.

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