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Clinicopathological and prognostic significance of the microcystic elongated and fragmented pattern in endometrial cancer: a systematic review and meta-analysis

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ABSTRACT

Objective The presence of the microcystic elongated and fragmented (MELF) pattern, distinguished by its microcystic, elongated and fragmented attributes, constitutes a common manifestation of myometrial invasion (MI) within endometrial carcinoma. However, the prognostic significance of this pattern has not been definitively established. Consequently, this research aimed to clarify the prognostic implications of the MELF pattern for individuals diagnosed with endometrial carcinoma.

Design Systematic review and meta-analysis of observational clinical studies.

Data sources An extensive review of the literature was conducted using reputable databases such as PubMed, Embase, Web of Science and the Cochrane Library, covering the period from January 2003 to October 2023. Search terms encompassed endometrial cancer and the MELF pattern.

Eligibility criteria for selecting studies The inclusion criteria were patients who had undergone hysterectomy and whose pathology confirmed endometrial endometrioid carcinoma, with or without MELF infiltration.

Data extraction and synthesis Two reviewers performed data extraction separately. The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS). Stata V.17.0 software was used for statistical analysis.

Results The meta-analysis incorporated 16 retrospective cohort studies. Employing a fixed-effects approach, the analysis demonstrated an association of the MELF pattern with reduced overall survival (HR 2.21, 95% CI 1.50–3.25, p=0.000) and lower disease-free survival rates among patients with endometrial cancer (HR 1.72, 95% CI 1.17 to 2.55, p=0.006). Furthermore, aggregated data revealed a linkage between the MELF pattern and significant MI, nodal metastasis, involvement of the lymphovascular space, penetration of the cervical stroma and progression to advanced stages of endometrial carcinoma.

Conclusion The MELF pattern serves as a significant adverse prognostic factor in endometrial cancer, warranting increased attention.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study is bolstered by a comprehensive search across four reputable databases and strict adherence to Preferred Reporting Items for Systematic Review and Meta-Analyses Protocols and Meta-analysis Of Observational Studies in Epidemiology guidelines, ensuring methodological integrity.
⇒ Studies defining the microcystic elongated and fragmented (MELF) pattern uniformly were included, focusing on high-quality research as assessed by the Newcastle-Ottawa Scale, for reliable results.
⇒ The observational nature of included studies requires a cautious interpretation of the MELF pattern's association with survival outcomes, considering potential unmeasured confounders, such as disparate adjuvant therapies.
⇒ The small number of studies eligible for survival outcome analysis and exclusion of non-English studies may limit the generalisability and introduce bias into our systematic review.

INTRODUCTION

Endometrial carcinoma is a common malignant tumour among women, with its prevalence rising worldwide. Endometrioid endometrial carcinoma (EEC) constitutes approximately 80% of all endometrial cancer cases and is the most common histological subtype.[1] The histological grade (HG) and tumour stage predominantly determine the prognosis and progression of EEC. Individuals diagnosed with low-grade EEC in its early stages typically exhibit a positive prognosis and might not necessitate further therapeutic intervention.[2] However, a subset of patients are at risk for recurrence and metastasis. Despite advancements in molecular research, over 20% of women with EEC eventually die from the disease, and mortality rates are expected to increase in the future.[3]

EEC manifests through multiple myometrial invasion (MI) patterns, notably the microcystic elongated and fragmented (MELF) pattern, characterised by microcystic, elongated and fragmented glandular structures.[4] The prognostic significance of the MELF pattern remains a topic of debate among researchers, with some viewing it as an adverse prognostic factor while others hold differing opinions.[5–9] The previous systematic review was limited in its capacity to conduct meta-analyses due to the dearth of comparable studies, which has hindered a comprehensive understanding of the MELF pattern's impact on EEC patients.[10] In this work, we aim to conduct a more exhaustive systematic review, thereby laying a robust foundation for meta-analysis. This approach will enable a clearer evaluation of the MELF pattern's association with critical clinical outcomes, such as lymphovascular space invasion (LVSI), lymph node metastasis (LNM), survival and recurrence, ultimately informing treatment strategies and clinical decision-making in EEC management.

METHODS

Literature search

This systematic review was registered with PROSPERO (CRD42023488851), conforming to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Meta-analysis Of Observational Studies in Epidemiology guidelines.[11 12] A comprehensive search of the literature was conducted in electronic databases, including PubMed, Embase, Web of Science and the Cochrane Library, covering the period from January 2003 to October 2023. The search methodology employed keywords such as 'endometrial cancer,' 'endometrial carcinoma,' 'microcystic, elongated and fragmented' and 'MELF,' and was enhanced by examining the reference lists of pertinent studies. The complete search formula used to identify relevant studies included the following terms: ('endometrial cancer' OR 'endometrial carcinoma' OR 'uterine cancer' OR 'endometrial neoplasm') AND ('MELF pattern' OR 'microcystic elongated and fragmented pattern' OR 'MELF invasion' OR 'MELF infiltration'). Online supplemental materials 1 provides detailed search strategies in the four databases. In instances of duplicate publications, we prioritised the original article, particularly when a study was published in both abstract and full-text formats. Furthermore, for studies that were updated periodically, only the most current and comprehensive reports were considered for inclusion.

Selection criteria

Two reviewers meticulously screened titles and abstracts, then independently assessed the full texts of all the potential trials. In case of disagreements, a third reviewer was consulted to reach a consensus. Duplicate studies were systematically excluded. The inclusion criteria were: (1) endometrial carcinoma patients at any clinical stage; (2) reporting of MELF pattern status based on the criteria defined by Murray *et al*; (3) availability of comprehensive clinicopathological data or survival data, such as overall survival (OS), disease-free survival (DFS), International Federation of Gynaecologists and Obstetricians (FIGO) stage, tumour size, MI, cervical stroma involvement (CSI), LNM, LVSI and HG; (4) cohort studies comparing prognoses of patients with and without MELF infiltration; (5) studies published in English; (6) studies with accessible full-text publications.

Data extraction

Data were independently extracted by two researchers, noting specifics like the lead author, publication year, geographic location of the study, participant count, HR with 95% CI, CSI, FIGO stage, dimension of the tumour, presence of LNM, LVSI and the HG. A standardised data collection form, developed through collaborative consensus among the research team, was employed to systematically and comprehensively extract all pertinent information.

Methodological quality assessment

The quality of methodology in the studies was assessed through the Newcastle-Ottawa Scale (NOS), focusing on criteria such as selection, comparability and outcomes. Studies achieving a NOS score greater than 6 were deemed to be of high quality.[13 14]

Statistics

Risk ratios (RR) with 95% CI for dichotomous outcomes, weighted mean differences (WMD) with 95% CI for continuous variables and HR with 95% CI were computed in this meta-analysis using the generic inverse variance approach. The Q test and I^2 statistic evaluated heterogeneity. In cases of notable heterogeneity ($p<0.1$, $I^2>50\%$), a random-effects model was implemented; otherwise, a fixed-effects model was adopted. The presence of publication bias was investigated using the Egger test and the analysis of funnel plots. For the statistical analyses, Stata V.17.0 software was used.

Patient and public involvement

Patients and/or the public were not involved in this study.

RESULTS

Search results

From an initial pool of 313 studies, 130 duplicates were removed. Subsequent eligibility assessment excluded 163 studies for various reasons, resulting in 16 retrospective cohort studies being included in our meta-analysis (figure 1).[5 6 8 9 15–26] Two studies were excluded from the meta-analysis due to the absence of HR data, crucial for computing pooled HRs.[16 26] While HRs could potentially be derived from Kaplan-Meier plots, this approach is deemed less reliable; hence, data from these studies were not incorporated into the meta-analysis.

Online supplemental table S1 presents the clinical characteristics and methodological quality of the included studies, which collectively involved 3438 patients. Of

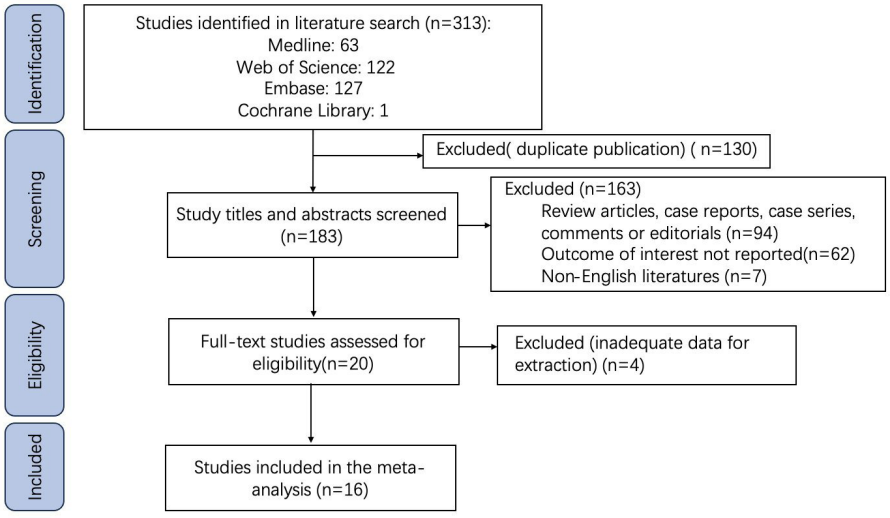

Figure 1 Flow chart of the study search and selection.

these, 638 (18.56%) were MELF-positive. All studies were retrospective cohort analyses, categorising tumours using the WHO classification system. Tumour grading and staging followed the FIGO guidelines and the 2009 FIGO staging system. Most patients had EEC, with one study including 24 non-EEC cases.

MELF pattern correlates with decreased OS

Four studies, encompassing 868 patients, investigated OS differences between patients with and without MELF invasion.[5 6 8 17] The fixed-effects model analysis disclosed a significant correlation between the MELF pattern and a decrease in OS among patients with endometrial cancer (HR=2.21, 95% CI:1.50 to 3.25, p=0.000; figure 2). There was negligible heterogeneity (I^2=0.0%<50%, p=0.634 >0.1) and no signs of publication bias were detected (Egger test, p=0.536).

MELF pattern correlates with reduced DFS

In six studies encompassing 2123 patients, the MELF pattern was significantly associated with poorer DFS (HR=1.72, 95% CI:1.17 to 2.55, p=0.006; figure 3).[5 6 8 9 17 26] There was minimal heterogeneity among the studies (I^2=24.8%<50%, p=0.248>0.1), with no signs of publication bias (p=0.562).

Association between the MELF pattern and clinicopathological features

An analysis of three studies,[6 17 23] including 681 patients, revealed no significant relationship between the MELF pattern and tumour size (WMD =0.80, 95% CI: −0.71–2.32, p=0.30), using a random-effects model (I^2=90.8%, p=0.000). Outcomes from the Egger test indicated an absence of publication bias (p=0.880). Detailed in online

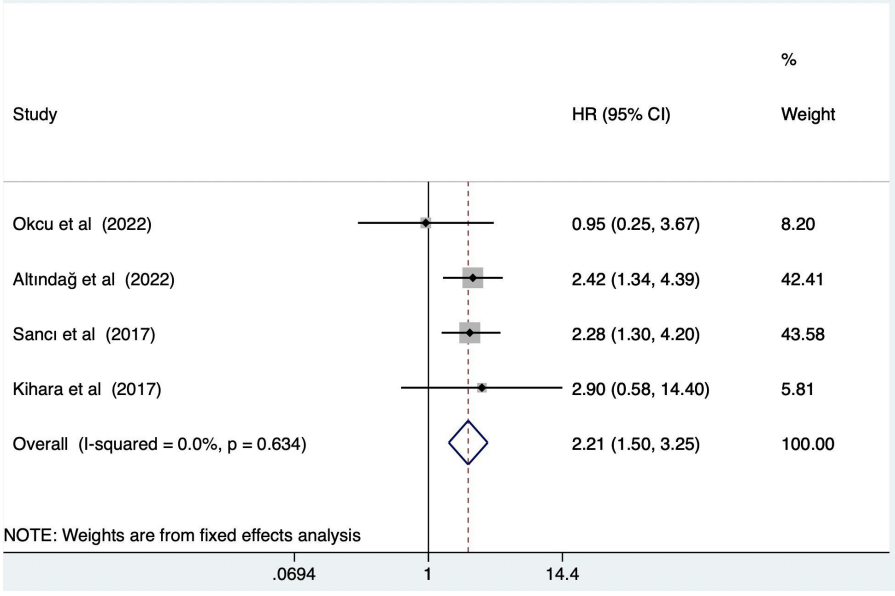

Figure 2 Forest map illustrates the relationship between the MELF pattern and OS.

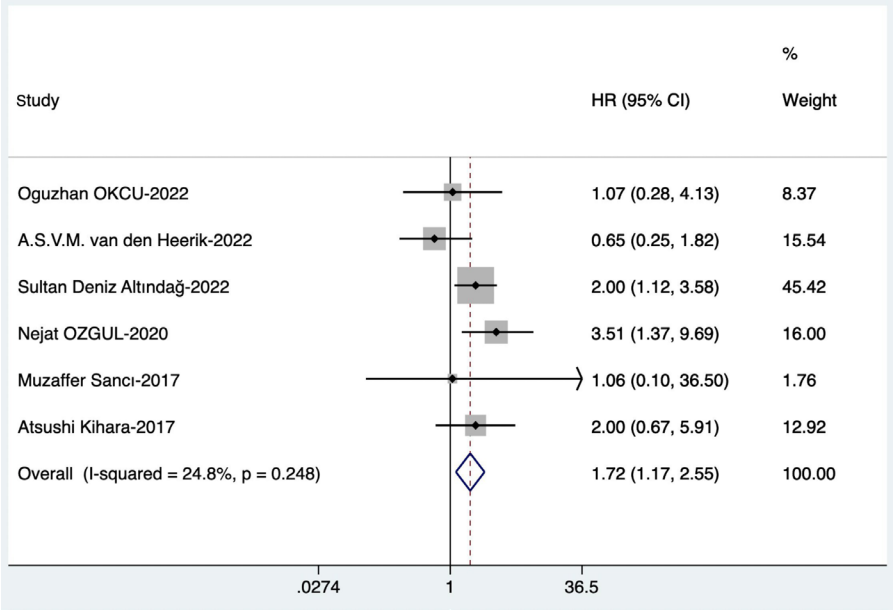

Figure 3 Forest map illustrates the relationship between the MELF pattern and DFS.

supplemental table S2 are the relationships between the MELF pattern and various prognostic indicators. A significant link was established between the presence of the MELF pattern and factors such as extensive myometrial penetration, nodal metastasis, invasion of the lymphovascular space, involvement of the cervical stroma and elevated FIGO stages. Deep MI was observed in 69.3% of MELF-positive patients compared with 41.0% of MELF-negative patients (RR: 2.37, 95% CI: 1.69 to 3.34, p<0.001), while LNM occurred in 27.9% and 11.8% of these groups, respectively (RR: 3.06, 95% CI: 1.73 to 5.41, p<0.001). These findings highlight the MELF pattern as a marker of tumour aggressiveness, though substantial heterogeneity (I^2 = 91.2% for MI; I^2 = 81.6% for LNM) underscores the need for further investigation into its biological and clinical significance. Notably, the incidence of the MELF pattern in grade 2 EEC was significantly higher compared with grades 1 and 3 (grade 2 31.4% vs grade 1 15.7%, grade 3 18.1%). The findings were considered reliable, with a minimal likelihood of publication bias, as corroborated by funnel plot analysis.

DISCUSSION

Summary of main results

This investigation constitutes the first meta-analysis to explore the correlation between the MELF pattern and prognostic outcomes in patients with endometrial cancer. Incorporating data from 3438 instances, our findings demonstrate a significant association of the MELF pattern with decreased OS (HR 2.21, 95% CI 1.50 to 3.25) and diminished DFS (HR 1.72, 95% CI 1.17 to 2.55) among these individuals. Furthermore, this pattern is linked to unfavourable clinical and pathological prognostic factors.

Results in the context of published literature

EEC is the predominant histological subtype of endometrial carcinoma. Current risk assessment and treatment planning for this cancer typically consider factors such as tumour stage, grade, lymph node status and LVSI. While early-stage, low-grade endometrioid carcinomas generally have a favourable prognosis, recurrences do occur in some cases. Thus, there is a pressing need for more reliable biomarkers to accurately stratify risk in these patients. The occurrence of the MELF pattern in low-grade EECs at an early FIGO stage poses a dilemma for gynaecological oncologists regarding the need for post-operative adjuvant therapy in such cases.

First introduced by Murray in 2003, the MELF pattern has been recognised for over two decades.[4] Characterised by tumour glands exhibiting a microcystic or slit-like appearance with flattened cells within oedematous or myxoid stroma, the MELF pattern is identified at the invasive front of MI. It is one of five distinct histological features of MI in endometrial cancer: invasive infiltration, pushover infiltration, adenomyosis-like infiltration, malignant adenomatous infiltration and MELF infiltration.[6 27] Initially thought to represent degenerative changes in tumour glands, later studies revealed that MELF is predominantly observed in zones of tumour activity. Research suggests that MELF infiltration is associated with reduced expression of markers such as β-catenin, ER and PR, as determined by immunohistochemical staining, potentially indicative of epithelial-mesenchymal transition. Additionally, increased nicotinamide N-methyltransferase levels have been linked to the MELF pattern, suggesting that it may reflect not merely degenerative changes but aggressive tumour behaviour.[28 29]

Numerous studies have investigated the association between the MELF pattern and clinical factors in

endometrial cancer, with many findings indicating a link between MELF infiltration, LVSI and LNM. Despite ongoing debates regarding its impact on the prognosis of EEC patients, our meta-analysis demonstrated that EECs with MELF infiltration exhibit increased rates of regional LNM and LVSI compared with those without MELF. Among 12 analysed studies, 11 identified a significant relationship between MELF infiltration and lymph node involvement.[5 6 15 17–19 21 23–26] Two studies even suggested that the MELF pattern could independently forecast LNM.[5 24] The pooled data revealed a 27.9% incidence rate of LNM in patients with MELF infiltration. Furthermore, several studies linked the MELF pattern with isolated tumour cell lymph node metastases,[2 23 30] highlighting a greater risk of occult micrometastasis in patients with MELF, which may signify a worse prognosis.[23] It has also been found that in grade 1 EEC, LNM occurs in up to 18.3% of patients if accompanied by the MELF pattern, and most of them are not small and subtle, so lymphatic dissection should be routinely performed.[31] Consequently, immunohistochemical analysis is advocated for detecting such micrometastases in MELF cases, and, for patients who have not received lymphadenectomy, a secondary surgical intervention for lymph node removal may be considered. Our comprehensive review consistently found a significant association between the MELF pattern and LVSI, a recognised prognostic factor in endometrial cancer guidelines[32] and FIGO staging.[33] LVSI presence could lead to upgrading patients from a low-intermediate to a high-intermediate risk category, affecting adjuvant treatment decisions. However, further studies are essential to determine whether MELF status should influence adjuvant therapy choices.

In this research, the occurrence rate of the MELF pattern was established at 18.6%, aligning with previous investigations that reported frequencies between 5.8% and 48%.[7 21] Intriguingly, the majority of MELF infiltrations were detected in individuals diagnosed with FIGO grade 2 neoplasms, accounting for 55.5% of these instances. Furthermore, a greater prevalence of MELF positivity was observed in patients harbouring grade 2 tumours compared with those with grade 1 or grade 3 tumours. Although low-grade (grade 1 and grade 2) EEC is typically considered less invasive, molecular diversity within this category has been observed. Specifically, about 5% of patients with low-grade EEC exhibit a p53 abnormal expression (p53abn), associated with increased invasiveness and poorer outcome.[34–36] Additionally, 61.0% of patients present a non-specific molecular profile (NSMP), highlighting the need for further risk differentiation. While earlier studies linked the MELF pattern with deficient mismatch repair, recent findings indicate a higher prevalence of NSMP in patients positive for MELF.[37] Furthermore, the NSMP and p53abn groups show worse prognoses compared with those with mismatch repair deficiency and DNA polymerase epsilon (POLE) mutations. Another study found that endometrial cancer patients with POLE mutations and MELF infiltration had a 15.1-fold increased risk of disease recurrence and progression.[38] Recognising the enhanced precision that molecular typing offers for risk stratification and the guidance of adjunctive therapeutic strategies, these insights underscore the importance of integrating MELF pattern analysis with molecular typing in the evaluation of low-invasive EEC.[39]

Previous studies have debated the prognostic significance of the MELF pattern in endometrial cancer. Our research substantiates that the MELF pattern adversely affects both OS and DFS. Two studies within our analysis demonstrated a significant link between MELF and poor prognosis in univariate analyses.[8 9] However, in multivariate analyses, the strength of this association diminishes, suggesting that MELF may not be an independent prognostic factor. Given the identified connections between MELF and known negative prognostic indicators such as LNM, LVSI and FIGO stage, the influence of these factors on survival outcomes cannot be disregarded. Therefore, it is crucial to undertake prospective studies with larger cohorts to corroborate these findings.[40 41] Additionally, research indicating that combining MELF with tumour budding acts as an independent prognostic element for EEC underscores the potential of examining MELF alongside other morphological parameters in future investigations.

Strengths and weaknesses

This systematic review possesses several strengths, including a registered protocol and adherence to a standardised guideline. It is the first meta-analysis to assess the prognostic relevance of the MELF pattern in endometrial cancer patients, identifying an association with poor prognosis.

However, the study acknowledges key limitations. While the included studies were deemed high quality based on the NOS scale, their retrospective nature inherently raises the possibility of publication bias. Notably, studies reporting a lack of association between the MELF pattern and prognosis may be underrepresented in the literature. Additionally, critical gaps remain in understanding the interplay between the MELF pattern, molecular subtypes and the response to adjuvant therapies in endometrial cancer, as no comprehensive analyses have been conducted to address these aspects. Future research should prioritise these unexplored dimensions to deepen our understanding and refine clinical management strategies.

Implications for practice and future research

EEC, particularly low-grade EEC, necessitates additional biomarkers to refine treatment guidance. Our study indicates that 29.5% of patients with low-grade EEC exhibit the MELF pattern, which is associated with a poor prognosis. Extensive research is essential to validate these observations. It is crucial to determine whether patients with low-grade EEC exhibiting the MELF pattern benefit from adjuvant therapy. Moreover, as an oestrogen-dependent feature, the MELF pattern may also be relevant in endometrial cancer arising in breast cancer survivors, particularly those with hormone receptor-positive disease. Investigating its role in this high-risk group could enhance clinical management strategies.[42]

Conclusion

To summarise, a significant correlation exists between the MELF pattern and lower survival outcomes, as well as negative clinicopathological prognostic markers such as nodal metastasis, LVSI, extensive myometrial penetration, cervical stroma infiltration and advanced FIGO stages. Nevertheless, there is a pressing need for further prospective randomised studies to assess the impact of adjuvant therapy in this context.

Contributors YZ was responsible for the study's conception and design, while PJ and BD handled the data assembly, analysis, interpretation and manuscript writing. YZ acted as guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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