PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

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

Authors

Jia, Peng; Duan, Baofeng; Zhang, Yan

VERSION 1 - REVIEW

Reviewer	**1**
Name	**Alcázar, Juan**
Affiliation	**Clinica Universidad de Navarra**
Date	**28-Sep-2024**
COI	**None**

Dear authors

I have read with interest this manuscript.

The topic is interesting and deserves attention.

The paper is well-written and concise.

However, I have some concerns

1. Why you selected 16 studies and then present data about OS and DFS from 4 and 6 studies respectively? data for calculating HR present in the study was an inclusion criterion.

2. Please, explain or support the reason for considering a NOS scale of 7 or above to deem a study of high quality

3. I miss in the Discussion whether MELF shoud be consider as an indepedent prognostic factor

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Reviewer	**2**
Name	**Vitale, Salvatore Giovanni**

Affiliation	**University of Cagliari**
Date	**28-Sep-2024**
COI	**None**

I read with great interest the Manuscript titled “The Microcytic Elongated and Fragmented (MELF) Pattern as a Poor Prognostic Indicator in Endometrial Cancer: A Systematic Review and Meta-analysis” (ID bmjopen-2024-092006), which falls within the aim of BMJ Open. This paper aims to evaluate the prognostic significance of the MELF pattern in endometrial cancer and to clarify its potential role in patient management by analyzing its impact on clinical outcomes such as disease-free survival and overall survival.

I appreciated the overall quality of the discussion on the topic, and the conclusions are well supported by the reported data. However, I believe there are several points that could further improve the clarity and impact of the manuscript:

- The introduction touches upon the MELF pattern, but it would benefit from a more detailed explanation of the current controversies regarding its prognostic value. You should also discuss how the MELF pattern may influence clinical decision-making and treatment strategies, particularly in relation to adjuvant therapies.

- Please provide a clearer summary of the search strategy within the manuscript, including a brief description of the databases and search terms used, rather than only referencing the supplementary materials. This will improve the transparency and reproducibility of the study.

- The results section could benefit from further interpretation of the relationship between the MELF pattern and myometrial invasion or lymph node metastasis. The biological mechanisms linking MELF to these outcomes should be explored more deeply.

- The potential for publication bias, particularly given the retrospective nature of many studies, should be discussed in more detail.

- The discussion could be expanded to better compare the MELF pattern with molecular subtypes of endometrial cancer (e.g., p53 mutations or TCGA classifications) (PMID: 33806979) and how it might fit into future risk stratification models.

- The role of the MELF pattern in high-risk populations, such as breast cancer survivors who are at increased risk of endometrial malignancy, should be explored (PMID: 39023103). Including this could highlight the broader clinical relevance of the findings and propose MELF pattern analysis as a potential addition to existing monitoring protocols for these groups.

- Improve the clarity of Figures 2 and 3, particularly with regard to the scales and labeling. It would also help to improve their resolution for better readability.

- Add footnotes to Table 2 that clarify abbreviations and technical terms (e.g., LVSI, WMD) for readers who may not be familiar with them.

VERSION 1 - AUTHOR RESPONSE

Reviewer: 1

Dear Dr. Juan Alcázar,
Thank you for your insightful comments and interest in our manuscript. We appreciate the time and effort you have put into reviewing our work and addressing the concerns you raised. Here are our responses to your comments:

Q: Why you selected 16 studies and then present data about OS and DFS from 4 and 6 studies respectively? data for calculating HR present in the study was an inclusion criterion.
A: We apologize for any confusion caused by the initial description of our inclusion criteria. To clarify, our primary criterion for study selection was the inclusion of clinicopathological data ***OR*** survival data. The availability of survival data was not a mandatory requirement for inclusion. Therefore, while we initially included 16 studies that met our broader criteria, only six provided sufficient survival data amenable to meta-analysis, particularly regarding HR. We have revised the manuscript to enhance the clarity of our inclusion and exclusion criteria. We appreciate your attention to this detail and hope that our clarification addresses your concern. (line 111)

Q: Please, explain or support the reason for considering a NOS scale of 7 or above to deem a study of high quality
A: We appreciate your thoughtful feedback regarding our methodology. In response, we have revised the manuscript to enhance clarity on this point. Specifically, we have updated the description from "7 or above" to "greater than 6" to adopt a more universally accepted phrasing, while maintaining the same meaning. This threshold aligns with established benchmarks widely recognized in the field and has been consistently employed in numerous published meta-analyses to assess study quality. Additionally, we have included relevant references to support this choice. Thank you for bringing this to our attention. (line 128-129)

Q: I miss in the Discussion whether MELF should be consider as an independent prognostic factor
Response:
A: Thank you for your insightful comment. In the Discussion section, we have addressed the question of whether MELF should be considered an independent prognostic factor. Specifically, two studies included in our analysis demonstrated a significant association between MELF and poor prognosis in univariate analyses. However, in multivariate analyses, this association was notably weaker, indicating that MELF may not function as an independent prognostic factor. This finding is further supported by the observed correlations between MELF and established negative prognostic indicators such as lymph node metastasis (LNM), lymphovascular space invasion (LVSI), and FIGO stage. The potential influence of these factors on survival outcomes highlights the complexity of this relationship. We emphasize the need for prospective studies with larger cohorts to validate these observations and provide greater clarity. (line268-277)

Reviewer: 2

Dear Dr. Salvatore Giovanni Vitale,
Thank you very much for your detailed review and constructive comments on our manuscript. We have carefully considered your suggestions and have made the following revisions to enhance the clarity and impact of our manuscript:

Q: The introduction touches upon the MELF pattern, but it would benefit from a more detailed explanation of the current controversies regarding its prognostic value. You should also discuss how the MELF pattern may influence clinical decision-making and treatment strategies, particularly in relation to adjuvant therapies.
A: We have expanded the introduction to include a more detailed discussion of the current controversies surrounding the prognostic value of the MELF pattern. We have also added a section discussing how the MELF pattern may influence clinical decision-making and treatment strategies, with a specific focus on adjuvant therapies. (line 74-79,290-294)

Q: Please provide a clearer summary of the search strategy within the manuscript, including a brief description of the databases and search terms used, rather than only referencing the supplementary materials. This will improve the transparency and reproducibility of the study.
A: We have provided a clearer summary of the search strategy within the main text of the manuscript, including a description of the databases and search terms used, to improve transparency and reproducibility. Furthermore, Supplementary Material 1 has been updated to include more detailed search strategies for the four databases. (line 95-104)

Q: The results section could benefit from further interpretation of the relationship between the MELF pattern and myometrial invasion or lymph node metastasis. The biological mechanisms linking MELF to these outcomes should be explored more deeply.
A: We have expanded the Results section to provide a more detailed interpretation of the relationship between the MELF pattern and lymph node metastasis. Additionally, we have delved deeper into the potential biological mechanisms that may link MELF to these outcomes, enriching the discussion to address this important aspect. (line180-187,234-237)

Q: The potential for publication bias, particularly given the retrospective nature of many studies, should be discussed in more detail.
A: Thank you for highlighting this important point. While all the studies included in our analysis were of high quality based on NOS scale, we acknowledge that they were all retrospective in nature, which inherently introduces the potential for publication bias. For example, studies that fail to identify an association between MELF and prognosis may be less likely to be published. We have expanded the Discussion section to address this issue in greater detail and to emphasize the need for prospective studies to mitigate such biases and validate our findings. Thank you for your valuable suggestion. (line 286-289)

Q: The discussion could be expanded to better compare the MELF pattern with molecular subtypes of endometrial cancer (e.g., p53 mutations or TCGA classifications) (PMID: 33806979) and how it might fit into future risk stratification models.
A: Thank you for your valuable suggestion. We have expanded the Discussion to further explore the potential prognostic implications of the MELF pattern in relation to molecular subtypes of endometrial cancer. Additionally, we have cited the recommended reference (PMID: 33806979) to support this comparison and to discuss how MELF might contribute to future risk stratification models. (line 263-267)

Q: The role of the MELF pattern in high-risk populations, such as breast cancer survivors who are at increased risk of endometrial malignancy, should be explored (PMID: 39023103). Including this could highlight the broader clinical relevance of the findings and propose MELF pattern analysis as a potential addition to existing monitoring protocols for these groups.
A: Thank you for this insightful suggestion. The MELF pattern is predominantly observed in endometrioid carcinoma, a subtype of endometrial cancer that is estrogen-dependent. This raises the possibility of a connection between MELF and endometrial cancer secondary to breast cancer, particularly in survivors of hormone receptor-positive breast cancer. We agree that this area warrants further investigation to elucidate the potential role of MELF in this high-risk population. To address this, we have incorporated the recommended reference (PMID: 39023103) and expanded our discussion to highlight the potential broader clinical relevance of MELF pattern analysis, including its possible integration into monitoring protocols for breast cancer survivors. (line 301-304)

Q: Improve the clarity of Figures 2 and 3, particularly with regard to the scales and labeling. It would also help to improve their resolution for better readability.
A: We have improved the clarity of Figures 2 and 3, with particular attention to scales, labeling, and resolution for better readability.

Q: Add footnotes to Table 2 that clarify abbreviations and technical terms (e.g., LVSI, WMD) for readers who may not be familiar with them.
A: Footnotes have been added to Table 2 to clarify abbreviations and technical terms for readers who may not be familiar with them. (173-174, 179, Table 2)

VERSION 2 - REVIEW

Reviewer	**1**
Name	**Alcázar, Juan**
Affiliation	**Clinica Universidad de Navarra**
Date	**12-Dec-2024**
COI	

The authors have address correctly my comments and questions

Reviewer	**2**
Name	**Vitale, Salvatore Giovanni**
Affiliation	**University of Cagliari**
Date	**26-Nov-2024**
COI	

The authors have revised the manuscript according to the reviewers' recommendations. The paper is clear, well-structured, and free of inconsistencies. It deserves to be published without further modifications in its current version.

VERSION 1 - AUTHOR RESPONSE

The author provided a marked copy with additional comments. Please contact the publisher for full details.