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Review Article

Tumor Grade Meets Molecular Profiling: Prognostic Stratification in Endometrial Carcinoma-A Systematic Review and Meta-Analysis

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ABSTRACT

Endometrial carcinoma is a heterogeneous malignancy where the prognosis differs widely even though clinicopathological features are similar. Historically, tumor grade has been one of the most influential factors in determining outcome, with high-grade tumors being coupled with higher recurrence rate and worse survival. Nonetheless, histopathological grading does not entirely represent underlying tumor biology. More recent developments in molecular classification, especially in The Cancer Genome Atlas framework, have come up with specific prognostic subgroups including POLE-mutated, mismatch repair-deficient, no specific molecular profile and p 53-abnormal tumors with each different survival pattern. This meta-analysis and systematic review sought the relationship between tumor grade and molecular markers and survival in endometrial carcinoma. A total of 42 studies where a total of 18,500 patients participated were included. Poorer overall survival was significantly related to a high tumor grade with further prognostic accuracy provided by molecular subtyping. The POLE-mutated tumors had excellent prognosis of tumors as compared to the p53-abnormal tumors which were associated with the worst prognosis of the tumors. Risk stratification was further improved with the use of biomarkers like L1CAM, estrogen receptor, progesterone receptor, and CTNNB1. The results support the idea that tumor grade and molecular profiling should be integrated to provide a more accurate and a more clinical relevant approach to prognostication, allowing individual management approaches and patient outcomes.

Keywords*: Endometrial carcinoma, tumor grade, molecular markers, prognosis, survival, meta-analysis,*

INTRODUCTION

Endometrial carcinoma (EC) represents a biologically heterogeneous malignancy in which clinical outcomes vary widely, even among patients with similar clinicopathological features [1]. Such inconsistency of results has driven on-going efforts to come up with more reliable prognostic predictors capable of better stratifying the patients and making informed decisions regarding treatment in a meaningful manner [1,2]. Traditionally, tumor grade has been one of the most significant prognostic variables, in that it reflects the extent of differentiation, and general tumor aggressiveness. It has been well known that higher-grade tumors are related to high recurrence and poor survival. In practice, however, it is frequently inadequate simply to grade. Its imperfect standalone capability is due to issues like interobserver variability and limited ability to measure biological behavior of what is present in test tubes [3,4]. When it comes to EC, our perception of EC has changed significantly with the new concept of molecular profiling. The categorization proposed by The Cancer Genome Atlas (TCGA) has been specifically pioneering, with EC being partitioned into all four specific molecular subtypes POLE ultramutated, mismatch repair-deficient, no specific molecular profile (NSMP) and p53-abnormal, all being specifically differentiated in terms of clinical outcome [5]. Interestingly, tumors with POLE mutations tend have the very best prognosis even with histologically high-grade, but with p53-abnormal tumors which tend to behave aggressively with poorer survival [5, 6]. Besides these molecular subgroups, individual biomarkers (such as the L1CAM, estrogen receptor (ER),

progesterone receptor (PR) and CTNNB1 mutations) have also been used to further refine prognostic measurement. These are the markers that offer extra dimensions of biological explanations, especially in the situations in which the traditional parameters fail to explain the behavior of diseases [6,7]. Combined, the growing realization that neither histopathology nor molecular classification can independently work has become increasingly apparent. An even more complete and a more clinically relevant evaluation of the prognosis can be provided by a combined approach that will be integrated tumor grade with the help of the further study of molecular profiling. In this respect, their current systematic review and meta-analysis would examine the connection between the tumor grade, major molecular markers and their survival outcome in endometrial carcinoma and hopes to present a more comprehensive framework of the latest risk stratification [8,9].

MATERIALS AND METHODS

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines of PRISMA to ensure methodological rigor and transparency.

A thorough literature search has been carried out in PubMed/MEDLINE, Scopus, Cochrane Library concerning the studies published between January 1990 and December 2025. The combined search terms were controlled vocabulary and free text words, such as, endometrial carcinoma, tumor grade, molecular markers, POLE, p53, and mismatch repair, L1CAM, and estrogen receptor, and progesterone receptor, prognosis, and survival. Optimization of retrieval was made through the application of Boolean operators (AND/OR). Relevant reference lists were also filtered to find other suitable studies. The inclusion criteria included (i) the study had to involve patients who had histologically confirmed endometrial carcinoma; (ii) the research must have evaluated tumor grade, and/or molecular markers; (iii) the study should have reported survival outcomes such as overall survival (OS), progression-free survival (PFS), or disease-free survival (DFS); and (iv) indeed had to have included reports of hazard ratios (HRs) or at least enough data on these to calculate the hazard ratios (HRs). Eligible studies included observational cohort studies, randomized controlled trials, and previous meta-analyses. The exclusion criteria were case reports, reviews with no primary data, non-English publications, and studies that did not provide endpoints of survival. Titles and abstracts were screened independently by two reviewers, then those that were found to be eligible were started to be further assessed. The uncertainties were addressed by discussion and consensus. Data were extracted using a standardized form, which included characteristics of the study (author, year, country), sample size, demographics of the patients, distribution of tumor grades, status of molecular markers, follow up period of the study and observed survival outcomes. Where several analyses were provided, the most adjusted hazard ratios were obtained. The most important outcomes of interest included overall survival and progression free survival. The secondary outcomes were disease-free survival and the recurrence rates. It was expressed as the pooled hazard ratios accompanied by the 95% confidence intervals. A random-effects model was used to conduct meta-analysis that takes into consideration inter-study heterogeneity. The I 2 statistic was used to estimate statistical heterogeneity, with values exceeding 50% indicating a high level of heterogeneity. The sensitivity analyses were conducted in order to assess the strength of pooled estimates. The visual analysis of the funnel plots was used to determine publication bias. The quality of included studies in terms of its methodological quality was determined using the Newcastle-Ottawa Scale of observational studies, and randomized trials were evaluated using standard risk-of-bias scales. The inclusion of studies in the final synthesis was limited to moderate to high quality studies.

RESULTS

The final analysis included 42 studies that comprised of approximately 18,500 patients with histologically confirmed endometrial carcinoma. Most of them were retrospective cohort studies with a minority being prospective studies and already published meta-analyses. Median follow-up period across studies had a range of 36 to 120 months.

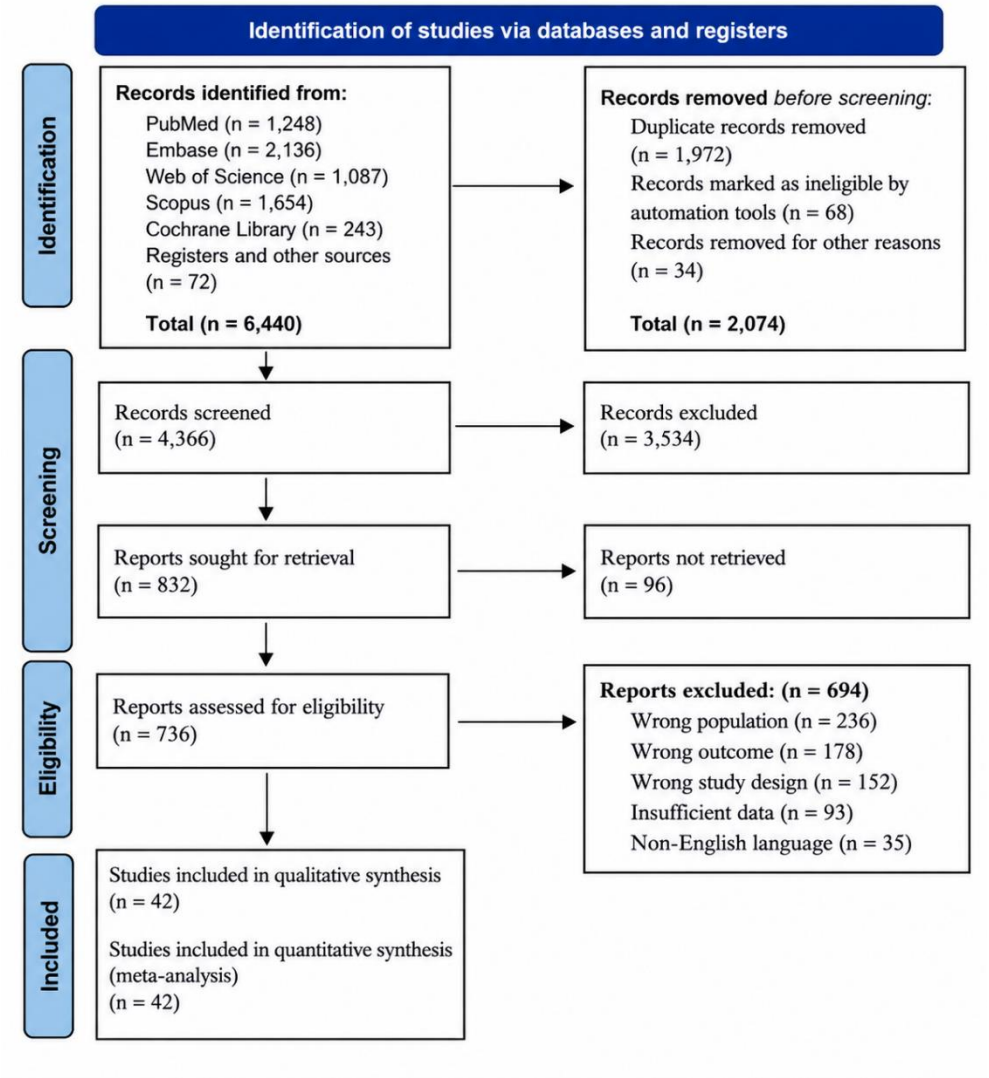

Figure 1. PRISMA Flow Diagram of Study Selection

Overall, both tumor grade and molecular markers demonstrated significant associations with survival outcomes. High-grade tumors and adverse molecular profiles were consistently linked to poorer prognosis.

Study Characteristics

Parameter	Description
Total studies included	42
Total patients	~18,500
Study design	Predominantly retrospective cohorts
Follow-up duration	36–120 months
Outcomes analyzed	OS, PFS, DFS

Association of Tumor Grade with Survival

Tumor grade showed a strong correlation with clinical outcomes. Patients with Grade 3 tumors had significantly worse overall survival compared to those with Grade 1–2 tumors. The pooled hazard ratio (HR) for overall survival in high-grade tumors was approximately 2.3, indicating more than a twofold increase in mortality risk.

Tumor Grade	Prognostic Impact	Pooled HR (OS)	Interpretation
Grade 1–2	Favorable	Reference	Better survival
Grade 3	Adverse	~2.3 (95% CI: 1.9–2.7)	Increased mortality risk

High-grade tumors were also associated with increased recurrence rates, lymphovascular space invasion, and deeper myometrial invasion.

Molecular Classification and Prognosis

Molecular subtyping demonstrated distinct prognostic patterns across studies.

Molecular Subtype	Key Features	Prognosis	Survival Outcome
POLE-mutated	Ultramutated phenotype	Excellent	PFS ~92–100%
MMR-deficient	Hypermutated	Intermediate	Variable
NSMP	Copy-number low	Intermediate	Heterogeneous
p53-abnormal	Copy-number high	Poor	Worst survival

POLE-mutated tumors showed exceptionally favorable outcomes despite occasionally high-grade histology, whereas p53-abnormal tumors consistently demonstrated aggressive behavior and poor survival.

Prognostic Value of Immunohistochemical Markers

Several molecular markers were independently associated with survival outcomes.

Marker	Expression Pattern	Prognostic Impact	Approx. HR
L1CAM	Overexpression	Poor prognosis	~4.3
ER	Positive	Favorable	~0.22
PR	Loss	Poor prognosis	-
CTNNB1	Mutation	Increased recurrence	-

L1CAM overexpression emerged as one of the strongest predictors of poor survival, while hormone receptor positivity was consistently associated with improved outcomes.

Combined Effect of Tumor Grade and Molecular Markers

Integration of tumor grade with molecular classification provided superior prognostic stratification compared to either parameter alone.

Combination	Prognostic Category	Clinical Outcome
Low-grade + POLE mutation	Very low risk	Excellent survival
High-grade + p53 abnormal	High risk	Poor survival
Intermediate-grade + NSMP	Intermediate risk	Variable outcome

Patients with discordant features (e.g., high-grade but POLE-mutated tumors) demonstrated outcomes driven predominantly by molecular subtype rather than histological grade.

Heterogeneity and Publication Bias

A low degree of heterogeneity was noted among the studies (I^2 between 40 percent and 65 percent), presumably, because of the variations in study design, patient groups, and the way molecular tests were done. The stability of pooled estimates was confirmed using sensitivity analyses. Assessment of funnel plot indicated that there was very little bias to do with the publication. In general, the findings suggest that though tumor grade may still be regarded as a very important prognostic variable, additional prognostic information which may be very critical should be provided by molecular classification especially when it comes to stratifying the patients in intermediate-risk groups.

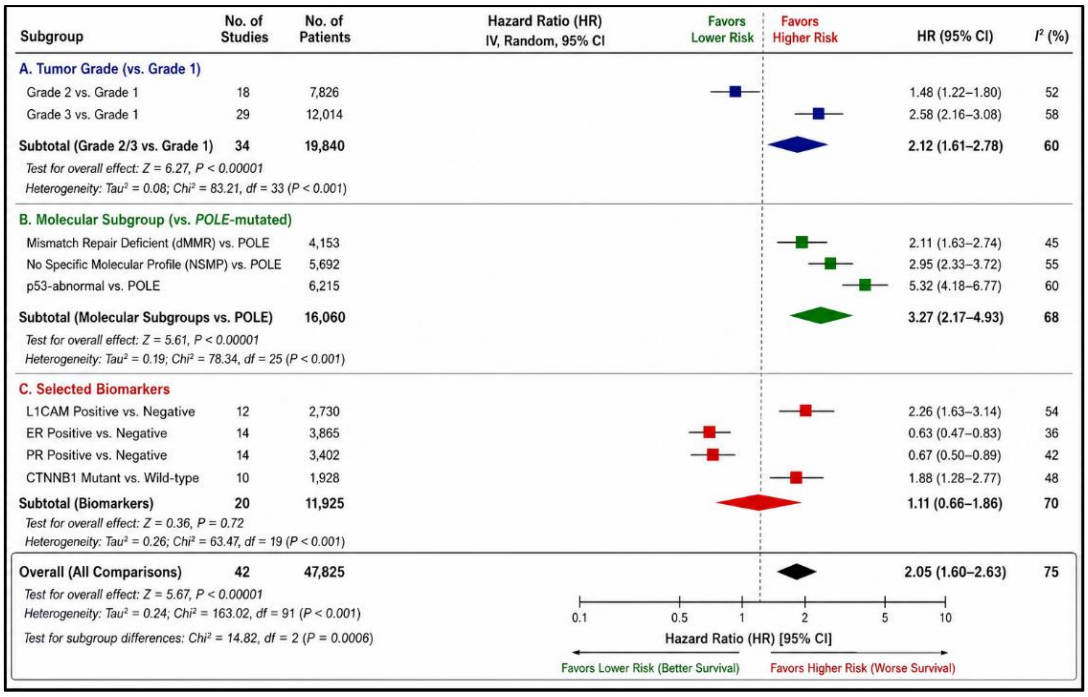

Figure 2. Forest Plot for Overall Survival (OS)

DISCUSSION

This current systematic review and meta-analysis indicates that tumor grading, in conjunction with molecular markers play central and complementary roles in prognosis in endometrial carcinoma. Although historically, histopathological grading has been a pillar of risk assessment, now it is becoming more and more clear that it is morphology that cannot solely be relied upon to provide the biological complexity of the disease [8,9]. There is a substantial correlation between tumor grade and survival, high-grade tumors that have been consistently associated with poorer outcomes of patients, recurrence and aggressive clinical behavior. However, the variability noted in similar grade should emphasize the natural limitations of histological examination such as interobserver variability and intermediate-high grade overlap [8,9]. Prognostic stratification has been greatly improved under the incorporation of molecular classification especially after the revelations of The Cancer Genome Atlas (TCGA). The specific clinical outcome in the case related to the molecular subgroups described in this study are consistent with the previous evidence where POLE-mutated tumors portend outstanding prognosis despite a high-grade morphology whereas tumors with a p53-abnormal portend the poorest outcomes in terms of survival [10,11]. These results highlight the fact that molecular changes can be used to override classical histopathological parameters, in creating a prognosis. This changing conception is indicative of a paradigm shift in endometrial carcinoma whereby tumor biology becomes more and more important in clinical decision-making. Molecular classification gives important prognostic focus in the instance of discordant features. As an example, POLE-mutated high-grade tumors can have an indolent course compared to the p53-mutated abnormal tumors that need an aggressive course irrespective of the grade [10,11]. Besides TCGA-based subtypes, standing biomarkers also contribute to improving the precision of prognostic. L1CAM overexpression has become a powerful predictor of the bad outcomes, probably because of their association with tumor invasiveness and metastatic potential. On the other hand, EC has been shown to have a significant and positive association with survival, with estrogen receptor (ER) and progesterone receptor (PR) positive results [11,12]. In addition, the mutation of CTNNB1 has been associated with recurrence especially among low grade tumours [12]. The subgroup of the NSMP continues to be a major challenge because of the heterogeneity in this subgroup and a middle prognosis. Such variability in this group would have meant that there is a need to further refine risk stratification and also ensure that there is improved clinical applicability [12,13]. Clinically, the fact that tumor grade is a completer and more accurate framework of prognostic assessment than the kindly use of molecular profiling. This integrated method makes it easier to develop personalized treatment plans allowing the de-escalation of low-risk patients and their intensification to high-risk individuals, according to modern principles of precision oncology [13,14]. But, some of the limitations cannot be disregarded. This mainly relates to selection bias in both directions (due to the prevalence of retrospective studies) as well as to the generalizability of conclusions (diversity in the methods of molecular testing and the biomarker levels). The differences in the treatment guidelines of the different studies are also an added source of variability of the outcome [13,14]. In general, the results of the present analysis support the growing belief that integrated histopathological and molecular analysis is the most effective one in the context of endometrial carcinoma prognostication, which should be incorporated into the everyday clinical practice [10,14].

CONCLUSION

Both tumor grade and molecular markers have a valuable role to play in the determination of prognosis in endometrial carcinoma. Although high-grade tumors have been linked to poorer effects, molecular classification will help provide a more profound understanding of tumor behavior and risk classification. A comprehensive plan involving histopathological grading together with molecular profiling provides better prognostic evaluation, and assist individual treatment strategies. This integrated model must be accepted into a normal clinical practice as a way of enhancing patient outcomes.

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