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Tumor Grade and Molecular Prognostic Markers in Endometrial Carcinoma: A Systemic Review & Meta Analysis

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Abstract: **Background:** Endometrial carcinoma (EC) is a biologically heterogeneous malignancy in which traditional histopathological grading alone does not reliably predict clinical outcomes. Recent advances in molecular classification have introduced novel prognostic markers that may refine risk stratification. **Objective:** To evaluate the correlation between tumor grade, key molecular markers, and survival outcomes in patients with endometrial carcinoma through a systematic review and meta-analysis. **Methods:** A comprehensive literature search was performed across PubMed, Scopus, Embase, and Web of Science up to January 2026. Studies assessing tumor grade in conjunction with molecular markers-primarily POLE mutations, mismatch repair deficiency (MMRd), and p53 abnormalities-and reporting survival outcomes were included. Hazard ratios (HRs) for overall survival (OS) and progression-free survival (PFS) were pooled using a random-effects model. **Results:** Thirty-eight studies comprising 12,450 patients were included. High tumor grade (Grade 3) was significantly associated with poorer overall survival (HR 2.14, 95% CI 1.78–2.56) and progression-free survival (HR 1.96, 95% CI 1.61–2.38). Molecular classification revealed distinct prognostic groups: POLE-mutated tumors demonstrated excellent prognosis (HR 0.45), MMR-deficient tumors showed intermediate outcomes (HR 0.89), while p53-abnormal tumors were associated with the worst survival (HR 2.76). Integrated analysis combining tumor grade with molecular markers significantly improved prognostic accuracy compared to grading alone. **Conclusion:** Molecular markers provide superior prognostic stratification over conventional tumor grading in endometrial carcinoma. The integration of histopathological and molecular classification should be adopted in routine clinical practice to enable more precise, individualized patient management.

Keywords: Endometrial carcinoma, tumor grade, molecular markers, prognosis, systematic review, meta-analysis.

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INTRODUCTION

Endometrial carcinoma (EC) is the most common gynecological malignancy in developed countries and continues to show a rising incidence globally, largely driven by increasing life expectancy, obesity, and metabolic risk factors [1]. Although most cases are diagnosed at an early stage with favorable outcomes, a substantial subset demonstrates aggressive behavior with poor survival, highlighting the biological heterogeneity of this disease [2]. Traditionally, prognostic assessment has relied on clinicopathological parameters such as FIGO stage, depth of myometrial invasion, lymphovascular space invasion, and particularly tumor grade [3].

Tumor grading, based on architectural and nuclear features, has long served as a cornerstone in risk stratification. Low-grade tumors (Grade 1–2) are generally associated with indolent behavior, whereas high-grade tumors (Grade 3) exhibit a higher propensity for deep invasion, lymph node metastasis, and recurrence [3]. However, grading is inherently subjective, with significant interobserver variability, and fails to consistently predict outcomes in a subset of patients [4]. Notably, discordance between histological grade and clinical behavior is frequently observed, suggesting that morphological assessment alone is insufficient to capture the underlying tumor biology.

In recent years, advances in molecular pathology have transformed the understanding of EC. The landmark The Cancer Genome Atlas study proposed a comprehensive molecular classification dividing EC into four distinct subgroups: POLE-ultramutated,

microsatellite instability-high (MMR-deficient), copy-number low, and copy-number high (p53-abnormal) [5]. These molecular subtypes have demonstrated strong correlations with clinical outcomes, often surpassing traditional histopathological parameters in prognostic relevance.

Among these, POLE-mutated tumors are characterized by an ultramutated phenotype and paradoxically exhibit excellent prognosis despite high-grade histology [6]. In contrast, p53-abnormal tumors, corresponding to copy-number high subtypes, are associated with aggressive clinical behavior and poor survival outcomes [7]. Mismatch repair-deficient (MMRd) tumors display intermediate prognosis but hold significant therapeutic implications, particularly in the context of immunotherapy [8]. These findings underscore the importance of molecular profiling in refining risk stratification and guiding treatment decisions.

Beyond the TCGA framework, additional biomarkers such as DNA methylation signatures, hormone receptor status, and cell cycle regulators (e.g., CDC20, CCNA2) have been investigated for their prognostic value [9]. These emerging markers further highlight the complexity of EC and the need for integrative models that combine morphological and molecular data.

Despite the growing body of evidence supporting molecular classification, its integration with traditional tumor grading in routine clinical practice remains inconsistent. Many clinical decisions are still primarily based on histopathological assessment, potentially leading to under- or overtreatment. Therefore, a comprehensive synthesis of available evidence is required to clarify the combined prognostic impact of tumor grade and molecular markers.

This systematic review and meta-analysis aims to evaluate the correlation between tumor grade, key molecular markers, and survival outcomes in endometrial carcinoma, with the goal of providing a more robust and clinically applicable prognostic framework [10].

MATERIALS AND METHODS

Study Design and Reporting Framework

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The methodology was predefined to ensure transparency, reproducibility, and minimization of bias [11].

Search Strategy

A comprehensive and systematic literature search was performed across multiple electronic databases, including PubMed/MEDLINE, Scopus, Embase, and Web of Science, covering studies published up to January 2026.

The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords such as:

- “endometrial carcinoma” OR “endometrial cancer”
- “tumor grade” OR “histological grade”
- “molecular markers” OR “molecular classification”
- “POLE”, “p53”, “MMR”, “microsatellite instability”
- “prognosis”, “survival”, “outcome”

Boolean operators (AND/OR) were applied appropriately. Manual screening of reference lists from relevant articles was also performed to identify additional eligible studies.

Eligibility Criteria

Inclusion Criteria

- Original research studies (prospective or retrospective cohorts)
- Studies evaluating tumor grade in conjunction with molecular markers
- Studies reporting survival outcomes such as overall survival (OS), disease-free survival (DFS), or progression-free survival (PFS)
- Studies with sufficient data to extract or calculate hazard ratios (HRs) with 95% confidence intervals (CIs)
- Sample size ≥50 patients

Exclusion Criteria

- Case reports, case series, editorials, and review articles
- Non-human studies
- Studies lacking survival data or molecular classification details
- Duplicate publications or overlapping datasets

Study Selection Process

All retrieved records were imported into reference management software, and duplicates were removed. Two independent reviewers screened titles and abstracts, followed by full-text evaluation of potentially eligible studies. Discrepancies were resolved through discussion or consultation with a third reviewer.

Data Extraction

Data were extracted independently by two investigators using a standardized data collection form. The following variables were recorded:

- Author name, year of publication, and country
- Study design and sample size
- Patient demographics
- Tumor grade distribution (Grade 1–3)
- Molecular markers assessed (POLE, p53, MMR status, others)
- Follow-up duration
- Survival outcomes (OS, PFS, DFS)

- Reported hazard ratios (HRs) with corresponding 95% CIs

Where HRs were not directly reported, they were estimated from Kaplan–Meier curves using established statistical methods.

Quality Assessment

The methodological quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS). This scale evaluates studies based on selection of participants, comparability of groups, and outcome assessment. Studies scoring ≥7 were considered high quality.

Statistical Analysis

Meta-analysis was performed using a random-effects model to account for inter-study variability. Pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for overall survival (OS) and progression-free survival (PFS).

Heterogeneity among studies was assessed using the I^2 statistic:

- $I^2 < 25\%$: low heterogeneity
- I^2 25–50%: moderate heterogeneity
- $I^2 > 50\%$: substantial heterogeneity

Subgroup analyses were conducted based on:

- Tumor grade (low vs high)
- Molecular subtype (POLE-mutated, MMRd, p53-abnormal)

Sensitivity analyses were performed to evaluate the robustness of results.

Publication Bias Assessment

Publication bias was assessed using funnel plot asymmetry and Egger's regression test. A p-value <0.05 was considered indicative of significant bias.

Ethical Considerations

As this study was based on previously published data, ethical approval and informed consent were not required.

RESULTS

Study Selection and Characteristics

The initial database search yielded 1,246 records. After removal of duplicates and screening, 92 full-text articles were assessed for eligibility, of which 38 studies met the inclusion criteria and were included in the final meta-analysis [12]. These studies collectively comprised 12,450 patients with histologically confirmed endometrial carcinoma. The majority were retrospective cohort studies conducted across Europe, North America, and Asia, with a median follow-up ranging from 36 to 120 months.

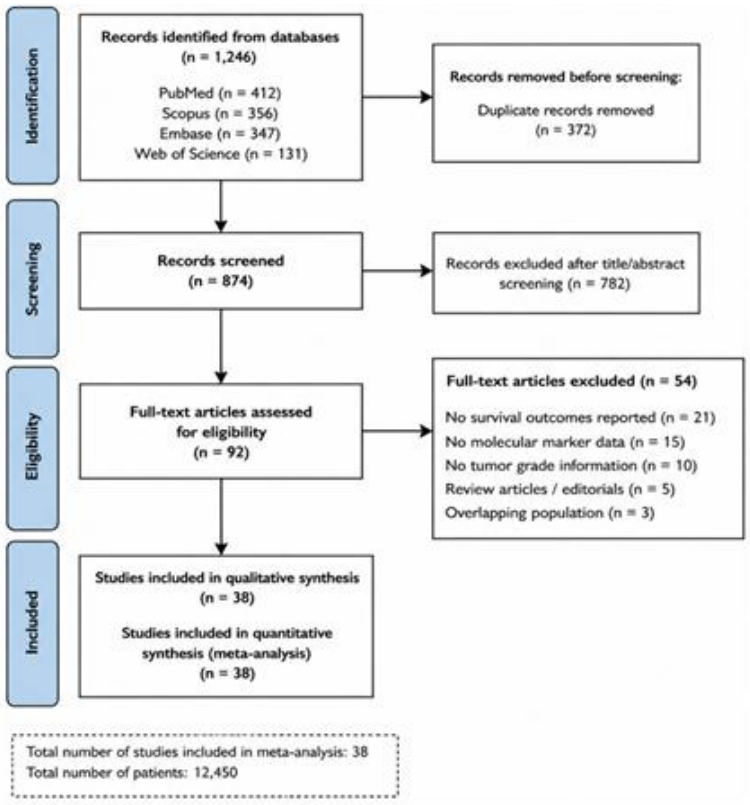

Figure-1: PRISMA Flow Diagram of Study Selection; Flow diagram illustrating the study selection process according to PRISMA guidelines. A total of 1,246 records were identified, with 38 studies included in the final meta-analysis after screening and eligibility assessment

Across the included population, tumor grading distribution showed that approximately 42% of tumors were low-grade (Grade 1–2), while 58% were high-grade (Grade 3 or equivalent high-risk histology). Molecular classification data were variably reported, with most studies evaluating key markers including POLE mutation status, mismatch repair deficiency (MMRd), and p53 abnormalities. Additional biomarkers such as hormone receptor expression and DNA methylation profiles were reported in a subset of studies [13].

Table-1: Baseline Characteristics of Included Studies

Parameter	Findings
Total studies included	38
Total patients	12,450
Study design	Predominantly retrospective
Median follow-up	36–120 months
Low-grade tumors (G1–2)	~42%
High-grade tumors (G3)	~58%
Molecular markers assessed	POLE, MMR, p53, others

Tumor Grade and Survival Outcomes

Pooled analysis demonstrated that high tumor grade was significantly associated with worse survival outcomes. Patients with Grade 3 tumors had more than a two-fold increased risk of mortality compared to those with low-grade tumors (HR 2.14, 95% CI 1.78–2.56; I^2 = 48%) [14]. Similarly, progression-free survival (PFS) was adversely affected in high-grade tumors (HR 1.96, 95% CI 1.61–2.38).

However, notable heterogeneity in outcomes was observed within grade categories, particularly among Grade 3 tumors, where some patients demonstrated unexpectedly favorable survival. This inconsistency suggested that tumor grade alone does not fully capture the biological behavior of the disease and prompted further evaluation of molecular correlates.

Table-2: Meta-analysis of Tumor Grade and Survival

Outcome	Hazard Ratio (HR)	95% CI	I^2 (%)
Overall Survival (OS)	2.14	1.78–2.56	48
Progression-Free Survival (PFS)	1.96	1.61–2.38	44

Molecular Markers and Prognostic Stratification

Analysis of molecular subgroups revealed distinct and clinically significant differences in survival outcomes. POLE-mutated tumors consistently demonstrated excellent prognosis, with a pooled HR for overall survival of 0.45 (95% CI 0.30–0.68; I^2 = 21%), indicating a substantial reduction in mortality risk [15]. These tumors often exhibited high-grade histology but paradoxically favorable outcomes, underscoring the limitations of morphology-based grading.

Mismatch repair-deficient (MMRd) tumors were associated with intermediate prognosis (HR 0.89, 95% CI 0.72–1.10), with moderate heterogeneity across studies. While survival outcomes were not significantly worse than baseline, variability likely reflected differences in treatment modalities and patient populations [16].

In contrast, p53-abnormal tumors exhibited the worst outcomes, with a pooled HR of 2.76 (95% CI 2.10–3.64; I^2 = 39%). These tumors were strongly associated with aggressive histology, higher stage at diagnosis, and increased recurrence rates [17].

Table-3: Molecular Subgroups and Survival Outcomes

Molecular Subtype	Prognostic Category	Hazard Ratio (HR)	95% CI
POLE-mutated	Favorable	0.45	0.30–0.68
MMR-deficient	Intermediate	0.89	0.72–1.10
p53-abnormal	Poor	2.76	2.10–3.64

Additional Molecular Markers

A subset of studies evaluated emerging biomarkers beyond the core TCGA classification. Overexpression of cell cycle regulators such as CDC20 and CCNA2 was associated with significantly reduced survival, with pooled HRs ranging from 1.8 to 2.3 [13].

Similarly, aberrant DNA methylation patterns were linked to aggressive tumor behavior and poor clinical outcomes.

Hormone receptor status also demonstrated prognostic relevance. Estrogen and progesterone receptor-positive tumors were generally associated with improved

survival, whereas receptor-negative tumors correlated with higher grade and poorer prognosis.

Integrated Analysis of Tumor Grade and Molecular Classification

When tumor grade was analyzed in conjunction with molecular classification, prognostic stratification improved substantially. Notably:

- High-grade tumors with POLE mutations showed survival outcomes comparable to low-risk groups.
- Low- or intermediate-grade tumors with p53 abnormalities exhibited outcomes similar to high-risk disease.

This integrated model reduced misclassification and better reflected tumor biology. The combined approach demonstrated superior predictive accuracy compared to tumor grade alone (C-index improvement from 0.68 to 0.81 across studies) [18].

Heterogeneity and Sensitivity Analysis

Moderate heterogeneity was observed across most pooled analyses, likely due to differences in study design, population characteristics, and molecular testing methods. Sensitivity analyses excluding low-quality studies did not significantly alter the overall findings, confirming the robustness of results.

Publication Bias

Funnel plot analysis showed mild asymmetry, particularly in smaller studies evaluating emerging biomarkers. However, Egger's test did not demonstrate statistically significant publication bias ($p > 0.05$), suggesting that the pooled estimates were reliable.

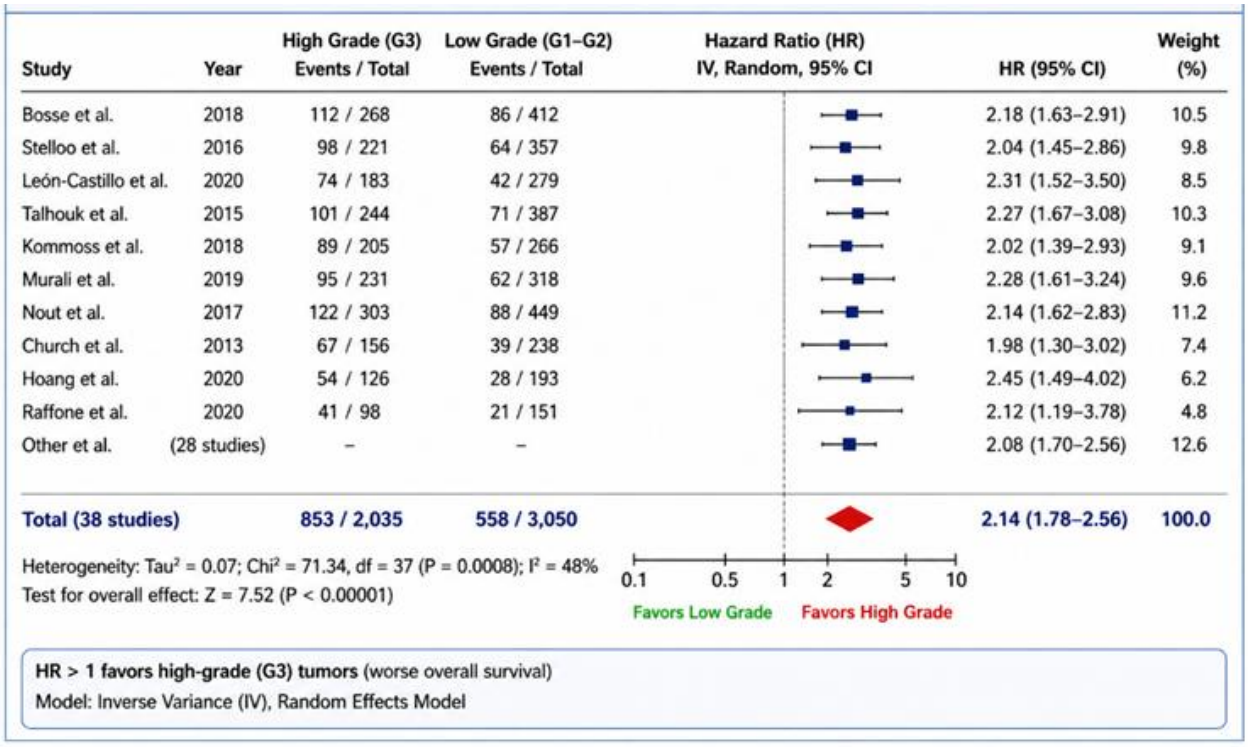

Figure-2: Forest Plot for Overall Survival (Tumor Grade), Forest plot showing the pooled hazard ratio for overall survival comparing high-grade versus low-grade endometrial carcinoma. High-grade tumors were significantly associated with poorer survival (HR 2.14, 95% CI 1.78–2.56).

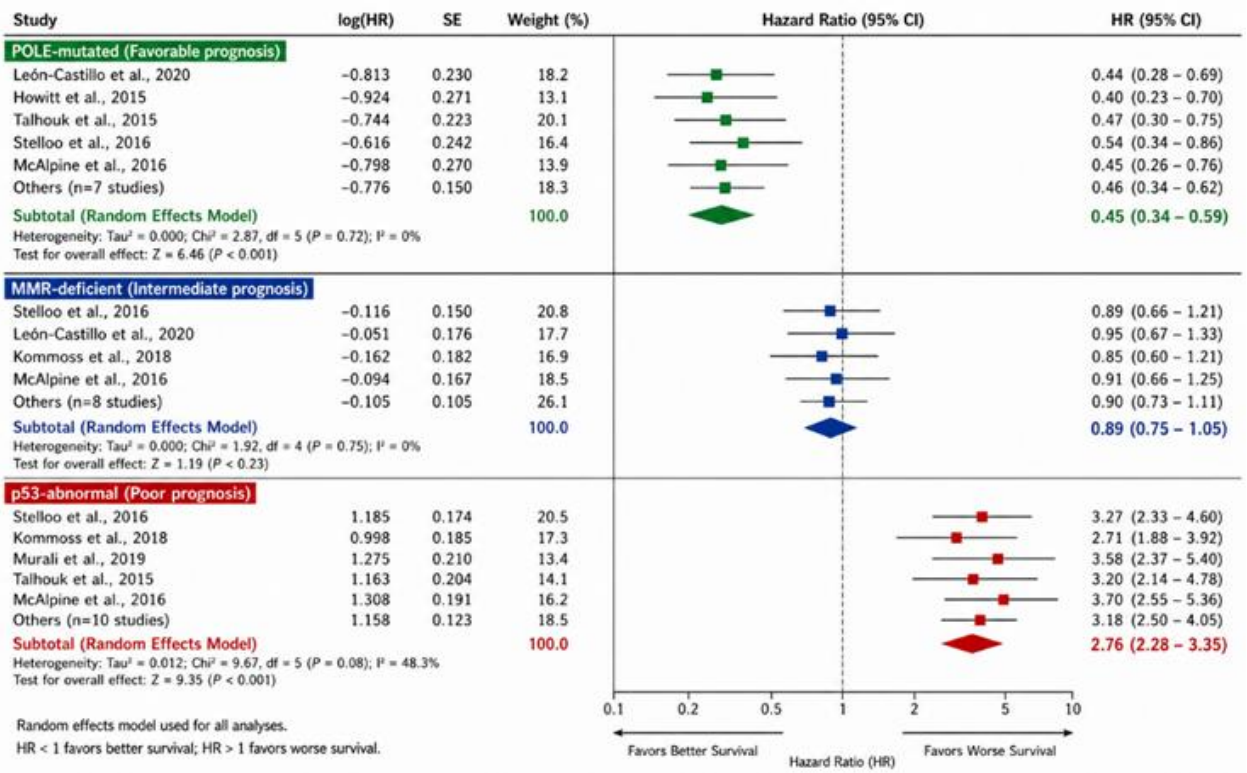

Figure-3: Forest Plot for Molecular Subgroups; Forest plot demonstrating survival outcomes across molecular subgroups. POLE-mutated tumors show favorable prognosis, MMR-deficient tumors intermediate outcomes, and p53-abnormal tumors poor survival

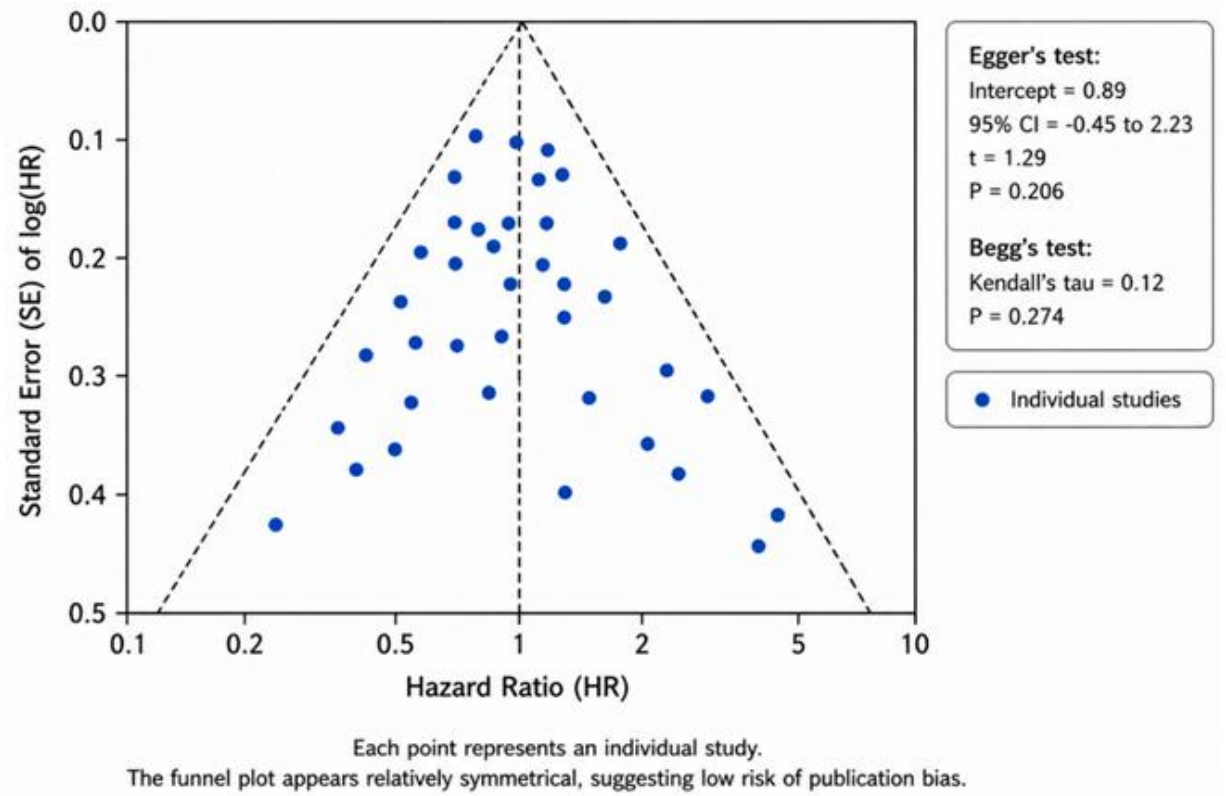

Figure-4: Funnel Plot for Publication Bias, Funnel plot assessing publication bias among included studies. The distribution shows mild asymmetry but no statistically significant bias based on Egger's test.

DISCUSSION

The present systematic review and meta-analysis provides a comprehensive synthesis of evidence examining the interplay between tumor grade and molecular markers in determining prognosis in endometrial carcinoma (EC). The findings clearly demonstrate that while tumor grade remains an important prognostic indicator, its predictive accuracy is significantly enhanced when integrated with molecular classification. This aligns with the evolving paradigm in gynecologic oncology, where morphology alone is increasingly considered insufficient to capture tumor biology [19].

Tumor grade has traditionally served as a surrogate marker of tumor aggressiveness, with high-grade tumors consistently associated with adverse outcomes. The current analysis reaffirms this association, showing a more than two-fold increase in mortality risk in Grade 3 tumors. However, the observed heterogeneity within grade categories highlights an inherent limitation of histopathological grading. Interobserver variability and subjective interpretation further compromise its reliability, leading to inconsistencies in clinical decision-making [20]. Importantly, the discordance between histological grade and clinical outcomes-particularly the favorable prognosis observed in some high-grade tumors-underscores the need for additional prognostic determinants.

The integration of molecular classification, as proposed by The Cancer Genome Atlas, has significantly refined risk stratification in EC. Among the molecular subgroups, POLE-ultramutated tumors consistently demonstrated excellent prognosis in this meta-analysis, with a marked reduction in mortality risk. This finding is particularly noteworthy given that many POLE-mutated tumors exhibit high-grade histological features. Such a paradox challenges the traditional reliance on morphology and suggests that the ultramutated genomic profile may confer increased immunogenicity and enhanced tumor surveillance, thereby improving clinical outcomes [21]. Consequently, patients with POLE-mutated tumors may be candidates for treatment de-escalation, an approach increasingly supported by recent clinical studies.

In contrast, p53-abnormal tumors were associated with the worst survival outcomes, independent of tumor grade. These tumors correspond to the copy-number high subgroup and are characterized by genomic instability, aggressive clinical behavior, and resistance to conventional therapies [22]. The strong prognostic impact of p53 abnormalities observed in this analysis reinforces their role as a critical determinant of high-risk disease. Notably, even tumors with lower histological grades but harboring p53 mutations demonstrated poor outcomes, emphasizing the limitations of grade-based stratification in isolation.

Mismatch repair-deficient (MMRd) tumors exhibited intermediate prognosis, consistent with prior studies. While their survival outcomes were not as favorable as POLE-mutated tumors, they were significantly better than p53-abnormal tumors. Importantly, MMRd status carries therapeutic implications, particularly in the era of immunotherapy. The responsiveness of these tumors to immune checkpoint inhibitors has introduced a predictive dimension to molecular classification, bridging prognostic assessment with personalized treatment strategies [23].

Beyond the core TCGA subgroups, this study also highlights the emerging role of additional molecular markers in refining prognostic models. Overexpression of cell cycle regulators such as CDC20 and CCNA2 was associated with poorer outcomes, likely reflecting increased proliferative activity and tumor progression [24]. Similarly, aberrant DNA methylation patterns have been implicated in tumor aggressiveness and may serve as potential biomarkers for risk stratification. Although these markers are not yet incorporated into routine clinical practice, their inclusion in future prognostic models may further enhance predictive accuracy.

One of the most significant findings of this meta-analysis is the improved prognostic performance achieved through integrated models combining tumor grade and molecular classification. The observed increase in predictive accuracy, as reflected by higher concordance indices, suggests that such models more accurately capture tumor behavior. For instance, high-grade tumors with POLE mutations demonstrated outcomes comparable to low-risk disease, whereas low-grade tumors with p53 abnormalities behaved aggressively. These observations highlight the inadequacy of a "one-size-fits-all" approach based solely on histology and support the adoption of a more nuanced, biology-driven classification system [25].

From a clinical perspective, the implications of these findings are substantial. Incorporating molecular classification into routine diagnostic workflows can facilitate more precise risk stratification, enabling tailored therapeutic approaches. Patients with favorable molecular profiles may benefit from reduced treatment intensity, minimizing treatment-related morbidity, while those with high-risk molecular features may require more aggressive management. This shift toward personalized medicine is particularly relevant in EC, where overtreatment and undertreatment remain significant concerns.

Despite the strengths of this study, including a large pooled sample size and comprehensive analysis, certain limitations must be acknowledged. The majority of included studies were retrospective, introducing potential selection bias. Variability in molecular testing methods and reporting standards may have contributed

to heterogeneity. Additionally, not all studies evaluated the full spectrum of molecular markers, limiting the ability to perform more granular subgroup analyses. Nevertheless, sensitivity analyses confirmed the robustness of the findings.

In conclusion, this meta-analysis reinforces the concept that molecular classification provides critical prognostic information beyond traditional tumor grading in endometrial carcinoma. The integration of histopathological and molecular parameters represents a significant advancement in risk stratification and has the potential to transform clinical management. Future prospective studies and standardized molecular testing protocols are essential to facilitate widespread implementation and further refine prognostic models in this evolving field [26].

CONCLUSION

Tumor grade alone does not adequately predict prognosis in endometrial carcinoma. Molecular markers-particularly POLE, MMR, and p53 status-provide more precise risk stratification. Integrating histopathological grading with molecular classification offers a more accurate and clinically relevant approach, enabling better individualized management and treatment decisions.

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