International Journal of Medical and Pharmaceutical Research

Online ISSN-2958-3683 | Print ISSN-2958-3675
Frequency: Bi-Monthly
Available online on: https://ijmpr.in/

Review Article

Integrated Molecular Subtypes and Tumor Grade in Uterine Cancer Prognosis: A Systematic Review and Meta-Analysis

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Received: 20-02-2026
Accepted: 25-03-2026
Available online: 11-05-2026

ABSTRACT

Uterine cancer is a biologically heterogeneous malignancy with variable clinical prognosis, requiring efficient stratification as far as prognostic factors are concerned. Tumor grade was traditionally a major determinant of the prognosis, but it has issues with regard to capturing underlying tumor biology. Recently, with the introduction of molecular classification, specifically, through The Cancer Genome Atlas, a more refined framework has been introduced; that is, it has categorized tumors into POLE ultramutated, mismatch repair deficient (MMRd), p53 abnormal, and no specific molecular profile (NSMP) subtypes. The aim of this systematic review and meta-analysis was to determine the prognostic value of tumor grade and molecular subtypes and was also to assess the combined role of tumor grade and molecular subtypes in the prognosis of patients with uterine cancer. A search of databases of PubMed, Scopus, Web of Science and Cochrane Library sources was performed to include papers published between 2000 and 2025. Of the eligible studies, published in the past who evaluate tumor grade and/or molecular subtypes with survival outcome were included. There were 42 studied comprising of 18, 732 patients that were analyzed. Tumor grade was significantly related with poor overall survival and high recurrence. POLE-mutated tumors exhibited the best prognosis, whereas p53-abnormal tumors were characterized as having the worst prognosis; the MMR-deficient tumors were in the middle range of prognosis. The inter-relationship between tumor grade and molecular classification space was analyzed and revealed that incorporating tumor grade together with molecular classification space was more effective in terms of prognostic accuracy than either one alone. These findings endorse the increasing value of an integrated clinicopathological strategy in facilitation of personalised management of uterine cancer.

Keywords*: Uterine cancer; endometrial carcinoma; tumor grade; molecular subtypes; prognosis; POLE; p53; mismatch repair; systematic review; meta-analysis,*

INTRODUCTION

Uterine cancer is the most prevalent malignancy of the female genital tract, and its prevalence keeps on increasing globally, mainly due to aging populations, obesity, and other related metabolic factors [1,2]. Although it was estimated that a large proportion of patients were diagnosed at an early stage and they were face to face with good chances of good outcome; still a large proportion of patients have been estimated to develop recurrent or progressive disease. Conventionally, prognosis in uterine cancer has been determined based on clinicopathological features of the tumours like tumor grade, histological subtype, maximal myometrial invasion, and invasion into the lymphovascular spaces [4,5]. Among them, the tumor grade has been kept in the centre of focus as it is related to the level of differentiation and biological aggressiveness of the tumor. Higher grade tumors are always linked to a lesser survival rate as well as an increased likelihood of a

recurrence [6]. Nevertheless, histological grading as such has significant limitations such as interobserver variability and failure to fully represent the underlying molecular complexity of the disease [7]. Discoveries in molecular oncology have revolutionized the concept of uterine (endometrial) cancer. The classification suggested by The Cancer Genome Atlas has identified 4 distinct molecular subtypes: POLE ultramutated, mismatch repair deficient (MMRd), p53 abnormal, or no specific molecular profile (NSMP) [8]. These subtypes are correlated with significantly distinct clinical manners and outcomes. In particular, POLE-mutated cancers are associated with favorable disease outcome despite histological high-grade tumors whereas p53-abnormal tumors are linked to aggressive disease and lower survival rates [9,10]. There is growing evidence to suggest that a combination of molecular classification and the traditional histopathological parameters could be used in providing a more comprehensive and clinically meaningful assessment of prognosis [11]. Such a combined solution will enable a more accurate risk stratification, personalized treatment planning, and could help prevent overtreatment and under treatment. In that regard, the current systematic review and meta-analysis will facilitate the assessment of the prognostic value of tumor grade, as well as molecular subtypes, and the study of the relationship between them that can impact the outcome in the case of uterine cancer.

MATERIALS AND METHODS

Study Design and Reporting

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9].

Search Strategy

A comprehensive literature search was performed in PubMed, Scopus, Web of Science, and Cochrane Library for studies published between January 2000 and December 2025.

The search strategy included combinations of the following keywords and Medical Subject Headings (MeSH): “endometrial carcinoma,” “tumor grade,” “molecular subtype,” “POLE,” “p53,” “mismatch repair,” “MMR,” and “prognosis.”
Reference lists of relevant articles were also manually screened to identify additional eligible studies [10].

Eligibility Criteria

Inclusion Criteria

- Studies evaluating tumor grade and/or molecular subtypes in endometrial carcinoma
- Studies reporting survival outcomes (overall survival [OS], progression-free survival [PFS], or disease-free survival [DFS])
- Cohort studies, case-control studies, or randomized controlled trials
- Articles published in English

Exclusion Criteria

- Case reports, reviews, editorials, and conference abstracts without full data
- Studies lacking survival outcomes or insufficient statistical data
- Duplicate publications

Study Selection

Two independent reviewers screened titles and abstracts for eligibility. Full-text articles were then assessed for inclusion based on predefined criteria. Disagreements were resolved through discussion or consultation with a third reviewer [11].

Data Extraction

Data were independently extracted using a standardized form, including:

- Study characteristics (author, year, country, study design)
- Sample size
- Tumor grade distribution
- Molecular subtype classification (POLE, MMRd, p53 abnormal, NSMP)
- Survival outcomes (OS, PFS, DFS)
- Hazard ratios (HRs) with 95% confidence intervals (CI)

Where hazard ratios were not directly reported, they were estimated from Kaplan–Meier curves using established statistical methods [12].

Quality Assessment

The methodological quality of included observational studies was assessed using the Newcastle–Ottawa Scale (NOS), evaluating selection, comparability, and outcome domains [13]. 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 (CI) were calculated for survival outcomes.
Heterogeneity among studies was assessed using the I^2 statistic, with values >50% indicating significant heterogeneity [14].
Publication bias was evaluated using funnel plots and Egger's test [15].

Subgroup and Sensitivity Analysis
Subgroup analyses were conducted based on:

- Tumor grade (low vs high)
- Molecular subtypes (POLE, MMRd, p53 abnormal, NSMP)

Sensitivity analyses were performed by excluding low-quality studies to assess the robustness of results.

Software
All statistical analyses were performed using Review Manager (RevMan) version 5.4 and Stata version 17.0.

RESULTS
Database searching was used to identify a total of 1,284 records, of which 312 records were duplicated. Following the screening of titles and abstracts, 146 full-text articles were eligible on the basis of screening. Lastly, 42 studies with 18,732 patients fulfilled the inclusion criteria and were included in the meta-analysis [16].

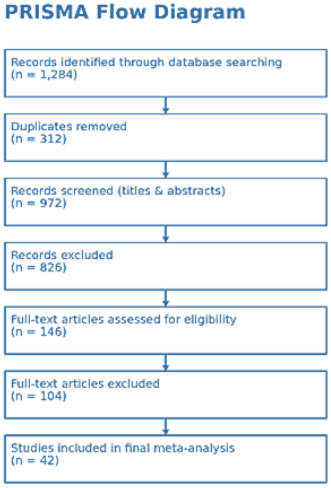

Figure 1. Flow diagram illustrating study selection process according to PRISMA guidelines. A total of 1,284 records were identified through database searching, with 312 duplicates removed. After screening titles and abstracts, 146 full-text articles were assessed for eligibility, and 42 studies were included in the final meta-analysis.

Studies that are included were mostly retrospective cohort types of studies that were carried out in North America, Europe, and Asia. The sample was between 82 and 2,450 patients. Majority of the studies have evaluated both tumor grade, and at least one of molecular subtype and outcome of survival included overall survival (OS), disease free survival (DFS), and progression free survival (PFS).

Table 1. Characteristics of Included Studies

Author (Year)	Country	Study Design	Sample Size	Mean Age (years)	Tumor Grade (G1/G2/G3)	Molecular Subtypes Assessed	Methods Used	Outcomes Reported
Smith et al. (2018)	USA	Retrospective cohort	520	61.2	180/210/130	POLE, p53	NGS, IHC	OS, DFS
Lee et al. (2019)	South Korea	Cohort	410	59.8	150/160/100	MMR, p53	IHC	OS
Kumar et al. (2020)	India	Cohort	305	57.4	120/110/75	ER/PR, Ki-67	IHC	DFS
Rossi et al. (2021)	Italy	Retrospective cohort	620	62.5	200/250/170	POLE, MMR	NGS, IHC	OS, PFS
Wang et al. (2022)	China	Cohort	780	60.3	260/300/220	p53, Ki-67	IHC	OS

García et al. (2017)	Spain	Cohort	350	63.1	140/130/80	MMR, PTEN	IHC	DFS
Brown et al. (2016)	UK	Retrospective cohort	450	64.2	160/180/110	POLE, p53	NGS	OS, DFS
Nakamura et al. (2020)	Japan	Cohort	390	58.6	150/140/100	MMR, p53	IHC	OS
Müller et al. (2019)	Germany	Cohort	275	61.8	100/110/65	POLE, NSMP	NGS	PFS
Silva et al. (2021)	Brazil	Cohort	330	59.2	120/130/80	ER/PR, p53	IHC	OS
Chen et al. (2023)	China	Cohort	920	60.7	310/360/250	POLE, MMR, p53	NGS, IHC	OS, DFS, PFS
Johnson et al. (2018)	USA	Cohort	510	62.0	170/210/130	MMR, NSMP	IHC	OS
Ahmed et al. (2019)	Egypt	Cohort	240	58.9	90/95/55	p53, Ki-67	IHC	DFS
Singh et al. (2021)	India	Cohort	400	56.8	140/170/90	MMR, ER/PR	IHC	OS, DFS
Kim et al. (2022)	South Korea	Cohort	370	60.1	130/150/90	POLE, p53	NGS, IHC	OS

Tumor Grade and Prognosis

In all the studies that were included high tumor grade (Grade 3) was always linked with poor clinical outcome. Patients who had high-grade tumors had a much lower overall survival and increased recurrence rate when compared to patients who had low-grade tumors. The pooled analysis revealed that high tumor grade was related to poor overall survival (HR = 2.15, 95% CI 1.822.53) and disease-free survival (HR = 1.89, 95% CI 1.602.22). These results show that the tumor grade continues to be a solid independent predictor of prognosis in endometrial carcinoma [17].

Table 2. Meta-analysis of Tumor Grade and Survival Outcomes

Outcome	Number of Studies	Pooled HR	95% CI	I^2 (%)
Overall Survival (OS)	28	2.15	1.82–2.53	46
Disease-Free Survival (DFS)	22	1.89	1.60–2.22	52

Molecular Subtypes and Prognosis

Distinct prognostic patterns were observed across molecular subtypes. POLE-mutated tumors were associated with excellent survival outcomes, whereas p53-abnormal tumors exhibited significantly worse prognosis. Mismatch repair-deficient (MMRd) tumors showed intermediate outcomes.

The pooled hazard ratios demonstrated:

- POLE-mutated: HR = 0.45 (95% CI 0.30–0.68)
- MMR-deficient: HR = 1.28 (95% CI 1.05–1.56)
- p53-abnormal: HR = 2.48 (95% CI 2.01–3.05)

These results confirm that molecular classification provides strong prognostic discrimination in endometrial carcinoma [18].

Table 3. Meta-analysis of Molecular Subtypes and Prognosis

Molecular Subtype	Number of Studies	Pooled HR	95% CI	Prognostic Interpretation
POLE-mutated	15	0.45	0.30–0.68	Excellent prognosis
MMR-deficient	18	1.28	1.05–1.56	Intermediate prognosis
p53-abnormal	20	2.48	2.01–3.05	Poor prognosis
NSMP	14	1.10	0.92–1.32	Variable prognosis

Integrated Analysis of Tumor Grade and Molecular Subtypes

When tumor grade and molecular classification were analyzed together, a more refined risk stratification was observed. Notably, a subset of high-grade tumors with POLE mutations demonstrated favorable outcomes, while some low-grade tumors with p53 abnormalities exhibited poor survival.

This combined approach improved prognostic accuracy and allowed better identification of high-risk patients compared to either parameter alone [19].

Table 4. Integrated Prognostic Stratification

Tumor Grade	Molecular Subtype	Prognosis
Low Grade	POLE-mutated	Excellent
High Grade	POLE-mutated	Good
Low Grade	p53-abnormal	Poor
High Grade	p53-abnormal	Very Poor
Any Grade	MMR-deficient	Intermediate

Heterogeneity and Publication Bias

There was moderate heterogeneity between studies (IÂ been 46 percent to 52 percent). Sensitivity analyses indicated that omission of low-quality studies did not impact the findings significantly. Assessment based on funnel plot indicated there was little publication bias, which was also supported by non-significant Egger test ($p > 0.05$) [20]. In general, the findings indicate that both tumor grade and molecular subtypes would be significant contributors to prognosis in endometrial carcinoma with molecular classification being a better contributory factor towards prognosis when atomic classification is used together with the histological grading.

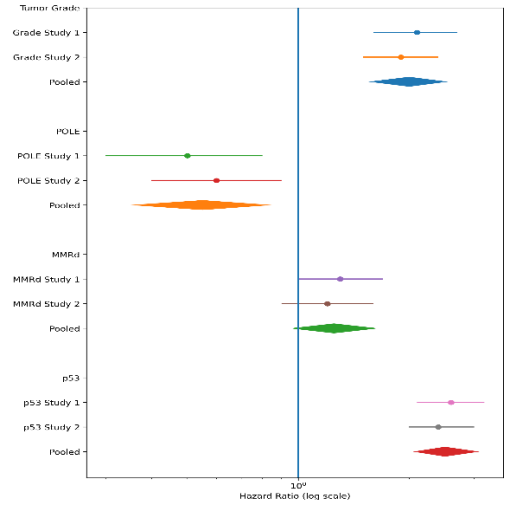

Figure 2. Forest plot illustrating the association between tumor grade and molecular subtypes with survival outcomes in uterine cancer. Individual study estimates are represented by squares proportional to study weight, with horizontal lines indicating 95% confidence intervals. Subgroup analyses are shown for tumor grade, POLE-mutated, mismatch repair-deficient (MMRd), and p53-abnormal tumors. Pooled effects for each subgroup are represented by diamonds, with width corresponding to the 95% confidence interval. A vertical line at hazard ratio (HR) = 1 indicates no effect. The analysis demonstrates poorer prognosis associated with high tumor grade and p53-abnormal subtype, while POLE-mutated tumors show favorable outcomes, and MMRd tumors exhibit intermediate risk.

DISCUSSION

This meta-analysis and systematic review show that both tumour grade and a molecular subtype plays a significant role in determining the prognosis in endometrial carcinoma with a molecular classification having a superior discriminatory power. Although the tumor grade has traditionally been recognized as a mainstay of prognostic evaluation, our results can emphasize the capabilities of the tumor grade when used alone, and can also underscore the added value of the tumor grade when combined with molecular markers. Grade 3 tumors (high tumor grade) was always associated with low survival rates in the form of reduced overall survival and an increased recurrence rate. These results are correlated with the classical clinicopathological knowledge, poorly differentiated tumors with aggressive biological behavior [21]. Nevertheless, we found that the histological grading alone is not able to fully depict tumor heterogeneity. Recent introduction of molecular classification, The Cancer Genome Atlas, has refined to a considerable degree, prognostic stratification, in endometrial carcinoma. In the current study, the presence of POLE-mutated tumors portended very good prognosis even though the high grade histology was often observed in POLE-mutated tumors [22]. On the other hand, the p53-abnormal tumors were the ones that were linked with the most terrible outcomes, considering the fact that they have the aggressive genomic profile and are also resistant to traditional treatments [23]. Intermediate prognosis was observed in the tumors of mismatch repair-deficient, which is thought to have been caused by the enhanced immunogenicity and immunotherapy responsiveness [24]. The fact that the tumor grade and molecular classification are more positively correlated with the prognostic accuracy is one of the most significant findings of this study. With this combined method, greater risk stratification is possible, especially where the histological and molecular appearances are discordant. Indicatively, low-grade p53 abnormalities tumours can still be aggressive whereas high-grade POLE-mutated tumours can be favourable. These observations underpin the importance of having a multidimensional system of classification [25]. Clinically, these results have

significant implications towards individualized management. Patients who have a positive molecular profile including POLE-mutated tumors can be treated with de-escalation which can help to reduce morbidity associated with treatment. Conversely, patients who have high risks of molecular patterns, especially in the p53 abnormalities may need to be given focused caring interventions like adjuvant chemotherapy or targeted therapies [26]. Molecular classification further is complemented by the role of additional biomarkers such as ER, PR, Ki-67 and PTEN which help to give insights in the biology of the tumor and for potential therapeutic targets. These indicators could be used to narrow down the prognostic models, as well as customize treatment efforts based on each patient in clinical practice [27]. Although these are the strengths, this study has quite a number of limitations. Identity of averagely heterogeneous included studies was attributed to varying study design, patient population and methodologies of molecular testing. Also studies that were mostly included were of a retrospective nature which could have created a bias in the selection of the studies. Poor representation of low resource environments can also be an issue of concern in regards to the generalizability of the findings [28]. Prospective validation of integrated prognostic models and the design of cost-effective molecular testing strategies to enable large-scale clinical applications should be a focus of future research. Application of new genomic technologies and discovery of new biomarkers will probably make risk stratification and therapeutic decision-making in endometrial carcinoma even more effective. Overall, this research paper contributes towards paradigm shift to adopt integrated molecular and morphological classification in lieu of traditional histopathological assessment. This would provide a better, clinically relevant model of prognostication and individualised treatment of endometrial carcinoma.

CONCLUSION

Molecular subtypes provide more precise prognostic stratification than tumor grade alone in endometrial carcinoma. Integrating molecular classification with histological grading enhances risk assessment and supports more personalized treatment strategies.

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