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Review article

Prevalence of high-grade endometrioid endometrial cancer of no specific molecular profile (NSMP): A systematic review and *meta*-analysis

João Casanova [a,b], Ana Sofia Ramos [c], Alexandru Babiciu [d], Filipa Moutinho [d], Marta Tripepi [e], Ana Gomes da Costa [a,b], Sofia Silvério Serra [f], Teresa Costa [f], Nadeem R. Abu-Rustum [g,h], João Martins [i,j,1], Jorge Lima [b,k,*,1]

[a] Gynecologic Oncology Unit, Hospital da Luz Lisboa, Avenida Lusíada 100, 1500-650 Lisboa, Portugal
[b] Department of Obstetrics and Gynecology, Luz Saúde, Hospital da Luz Lisboa, Avenida Lusíada 100, 1500-650 Lisboa, Portugal
[c] Department of Obstetrics and Gynecology, Hospital de Cascais Dr. José de Almeida, Avenida Brigadeiro Victor Novais Gonçalves, 2755-009 Alcabideche, Portugal
[d] Unidade Local de Saúde do Algarve, Rua Leão Penedo, 8000-386 Faro, Portugal
[e] Unit of Gynecology and Obstetrics, Department of Women and Children, University of Padua 35122 Padua, Italy
[f] Library of NOVA Medical School (NMS), Universidade NOVA de Lisboa, Campo Mártires da Pátria, 130, 1169-056 Lisboa, Portugal
[g] Gynecology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, United States
[h] Department of Obstetrics and Gynecology, Weill Cornell Medical College, 1305 York Avenue, New York, NY 10021, United States
[i] School of Health, Polytechnic of Porto, Rua Dr. António Bernardino de Almeida, 400, 4200-072 Porto, Portugal
[j] Centre of Statistics and its Applications (CEAUL), Faculty of Sciences, University of Lisbon, Portugal
[k] Comprehensive Health Research Centre (CHRC), NOVA Medical School (NMS), Universidade NOVA de Lisboa, Campo Mártires da Pátria, 130 1169-056 Lisboa, Portugal

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ABSTRACT

Background: Endometrial cancer of no specific molecular profile (NSMP) represents the most prevalent molecular subtype of endometrial cancer, comprising over 50 % of all diagnoses. Although studies have explored the prevalence of the NSMP subtype, to our knowledge, no systematic review or *meta*-analysis has specifically targeted grade 3 (G3, high-grade) tumors.

Objectives: We aimed to determine the prevalence of G3 endometrioid endometrial cancer of NSMP and assess regional variations in this prevalence. We also sought to synthesize available data concerning oncologic outcomes, including overall survival, progression-free survival, and disease-specific survival.

Methods: We conducted a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (PROSPERO No: CRD42024544247). We searched the electronic databases: PubMed/Medline, Scopus, Web of Science, Cochrane Library, and EMBASE. To estimate the overall prevalence of the NSMP subtype, we performed a *meta*-analysis using the proportions method with the Freeman-Tukey (arcsine) transformation. For estimating oncologic outcomes, we conducted a *meta*-analysis using hazard ratios (HRs) when available. In the absence of HRs, we utilized Kaplan-Meier curves. All pooled estimates and their corresponding 95% confidence intervals (CIs) were calculated using a random-effects model with the inverse variance method and restricted maximum likelihood estimator.

Results: We analyzed 31 studies, encompassing 2,660 patients. The pooled prevalence of NSMP within G3 endometrioid endometrial cancer was 0.29 (95 %CI: 0.23–0.34, $I^2 = 80.8$ %). This prevalence was highest in North America (0.43, 95 %CI: 0.17–0.71) and lowest in Europe (0.23, 95 %CI: 0.19–0.28). The random-effects pooled estimate indicated that the NSMP subtype was associated with intermediate oncologic outcomes compared to other molecular subtypes.

* Corresponding author at: Department of Obstetrics and Gynecology, Hospital da Luz Lisboa, Avenida Lusíada 100, 1500-650 Lisboa, Portugal.
E-mail addresses: joaomiguelcasanova@gmail.com (J. Casanova), ana.sofia.pramos@gmail.com (A.S. Ramos), alexandrubabiciu@edu.ulisboa.pt (A. Babiciu), filipaisabm@gmail.com (F. Moutinho), marta.tripepi@studenti.unipd.it (M. Tripepi), ana.g.costa@hospitaldaluz.pt (A.G. da Costa), sofia.serra@nms.unl.pt (S.S. Serra), teresa.costa@nms.unl.pt (T. Costa), abu-rusn@mskcc.org (N.R. Abu-Rustum), jom@ess.ipp.pt (J. Martins), jorgeramoslima@sapo.pt (J. Lima).
[1] The authors share the last authorship.

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Conclusion: The pooled prevalence of G3 endometrioid endometrial cancer of NSMP is 29 %. The oncologic outcomes for this molecular subtype seem intermediate, though further refinement and research are needed for a more precise understanding.

Introduction

Endometrial cancer is the most prevalent gynecologic malignancy in Western countries [1]. The rising incidence and mortality rates of this cancer are closely linked to increasing obesity rates [2].

Endometrial cancer originates from the uterine lining and is generally categorized into two distinct types: endometrioid (type I) and non-endometrioid (type II). Endometrioid cancer accounts for approximately 80 % of cases, while non-endometrioid cancer makes up the remaining 20 % [1]. Typically, endometrioid endometrial cancer develops due to excess unopposed estrogen and often emerges from a background of atypical endometrial hyperplasia. In contrast, non-endometrioid endometrial carcinomas comprise several histologic subtypes, including serous, clear cell, carcinosarcoma, transitional cell carcinoma, squamous cell carcinoma, and undifferentiated carcinoma. These tumors are generally hormone-independent, and most lack well-defined precursor lesions [3,4]. However, recent evidence indicates that serous endometrial intraepithelial carcinoma represents an aggressive precursor to endometrial serous carcinoma [5].

Endometrioid endometrial carcinomas are classified using the three-tier system established by the International Federation of Gynecology and Obstetrics (FIGO) [6]. This system grades tumors from one to three based on the proportion of glandular versus solid components within the tumor. Grade 1 (G1) and Grade 2 (G2) tumors, collectively termed low-grade, are generally associated with a more favorable prognosis [6]. Conversely, Grade 3 (G3) tumors are considered high-grade malignancies. However, clinical outcomes for G3 tumors are variable; some exhibit aggressive behavior similar to non-endometrioid subtypes, while others may align with low-grade tumors and have a more favorable prognosis [7]. Additionally, the histopathological evaluation of these tumors is subject to interobserver variability, which limits diagnostic reproducibility [7].

In 2013, the Cancer Genome Atlas (TCGA) Network developed an integrated genomic characterization of endometrial cancer [8], which has gradually replaced the previous dualistic classification. This classification identifies four molecular subtypes of endometrial cancer: copy-number high, typically linked to *TP53* mutations; copy-number low, lacking distinct molecular markers or surrogates; polymerase epsilon (*POLE*) ultramutated, characterized by mutations within the exonuclease domains of the *POLE* gene; and microsatellite instability (MSI), resulting from deficiencies in one or more mismatch repair proteins (mismatch repair deficiency, MMRd) [8]. Within this molecular framework, G3 endometrioid endometrial carcinomas uniquely encompass all four TCGA-defined molecular subtypes [7]. The literature suggests that G3 endometrioid endometrial carcinomas exhibit biologically heterogeneous behavior based on their molecular profiles [7]. Notably, tumors with *POLE* mutations are associated with a significantly improved prognosis [9]. In contrast, G3 endometrioid endometrial cancers with abnormal p53 expression are consistently linked to poor oncologic outcomes [10].

Since the TCGA publication, research groups have concentrated on developing low-cost methods to widely characterize the four molecular subtypes of endometrial cancer in clinical settings [11,12]. Next-generation sequencing is used to determine *POLE* mutational status, while immunohistochemistry surrogates differentiate the copy-number high (p53 abnormal) and MSI (MMRd) subtypes [11]. However, no specific surrogates exist for the copy-number low subtype, also known as tumors of no specific molecular profile (NSMP) [11]. Diagnosis for this subtype is made by excluding other features: *POLE* wild-type, mismatch repair proficient, and *p53* wild-type [2,13].

NSMP tumors generally exhibit an intermediate to excellent prognosis; however, a subset of estrogen-receptor (ER) negative tumors is associated with poor outcomes. Most NSMP tumors are low-grade and driven by estrogen [13,14]. Due to the heterogeneity within the NSMP molecular subtype, substratification based on ER status is advisable. Patients with ER-positive tumors particularly benefit from endocrine therapy [2]. Additionally, NSMP endometrial tumors possess molecular heterogeneity with significant clinical implications [13].

Although numerous studies examine the prevalence of endometrioid endometrial cancer of the NSMP subtype, none, to our knowledge, have conducted systematic reviews or *meta*-analyses focused specifically on its prevalence in G3 (high-grade) tumors. In response to this gap, we conducted a systematic review and *meta*-analysis to ascertain the prevalence of the NSMP subtype within G3 endometrioid endometrial cancer and to evaluate regional variations in this prevalence. Additionally, we aimed to synthesize existing data on the oncologic outcomes for patients with NSMP G3 endometrioid endometrial cancer. This includes overall survival (OS), progression-free survival (PFS), and disease-specific survival (DSS), providing further insights into this biologically diverse cancer subtype.

Methods

Study protocol

This systematic review and *meta*-analysis followed the guidelines set forth by the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) [15] and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [16] statement (refer to Supplementary Material, Appendix A for the PRISMA 2020 checklist). The study was preregistered with PROSPERO (No: CRD42024544247) [17].

Information sources and search strategy

A comprehensive literature review was conducted on January 15, 2025. The literature search utilized major electronic databases: PubMed/Medline, Scopus, Web of Science, Cochrane Library, and EMBASE. The search strategy (Supplementary Material, Appendix B) employed Boolean operators combined with the following search terms: Endometrial Cancer, Endometrial Carcinoma, or EC; High-Grade Endometrioid Endometrial Cancer, G3 Endometrioid Endometrial Cancer, or G3 Endometrioid Endometrial Carcinoma; and Copy-number low, non-specific molecular profile, no specific molecular profile, or NSMP.

During the search process, we included only research involving human subjects, without limitations on language, publication year, or study design. We manually examined the references from the most relevant studies and reviews to identify any publications potentially overlooked in the electronic search. Additional searches were carried out to incorporate newly eligible publications that emerged during the review process. Artificial intelligence software was employed to store, organize, and manage all references obtained from the literature search [18].

Eligibility criteria and selection process

English-language manuscripts solely focusing on the molecular profiling of Grade 3 endometrial cancer were considered eligible. The additional inclusion criteria included:

- detailed data allowing for to calculation of the pooled prevalence of the NSMP subtype;
- the availability of comprehensive clinical and pathological data, particularly concerning tumor grading and histology (limited to G3 endometrioid endometrial cancer);
- a clear report of oncologic outcomes, including OS, PFS, and DSS; and
- sufficient data to extract the hazard ratio (HR) and to calculate the standard error (SE).

Abstracts lacking corresponding full-text manuscripts were excluded from the analysis. In addition, single case reports, commentaries, letters to editors, editorials, and review articles were omitted due to their publication type. Studies were further disregarded if they did not provide sufficient data for calculations or contained inconclusive information regarding histology, molecular subtype, or tumor grading. Duplicate studies were also removed. To minimize the risk of double counting, potential overlapping cohorts were identified by comparing study institutions, author lists, and recruitment periods. In cases of possible overlap, only the most comprehensive or recent dataset was included.

Two reviewers independently screened the titles and abstracts of all identified articles. Full-text selection was carried out separately by these reviewers. Any discrepancies during this process were resolved by a third, independent reviewer.

Data collection process and data items

Two reviewers independently analyzed each included study, resolving any disagreements with the assistance of a third reviewer. Two reviewers conducted data extraction, which was then verified by an additional reviewer. When necessary, corresponding authors were contacted to obtain or confirm data. Extracted data included study authors, year of publication, study design, country, sample size, mean age and body mass index (BMI) of patients, prevalence of NSMP in G3 endometrioid endometrial cancer, and the oncologic outcomes: OS, PFS, and DSS of patients with NSMP G3 endometrioid endometrial cancer.

Risk of bias assessment

One reviewer independently assessed the methodological quality and risk of bias for each study using the Joanna Briggs Institute critical appraisal checklist for studies reporting prevalence data (Supplementary Material, Appendix C) [19]. A second reviewer verified these assessments, and any disagreements were resolved by a third independent reviewer. This tool is specifically designed to evaluate studies reporting prevalence data and is recommended for systematic reviews of prevalence, regardless of the original study design, as long as only cross-sectional data are analyzed [19]. The checklist consists of nine items addressing key domains. Each domain was rated as "yes", "no", "unclear", or "not applicable", and the overall risk of bias along with methodological quality were determined based on these ratings [19].

Additionally, we assessed potential publication bias using visual inspection of funnel plots and the trim-and-fill method.

Statistical analyses

A *meta*-analysis was conducted to estimate the overall prevalence of an event utilizing the proportions method with the Freeman-Tukey (arcsine) transformation. To avoid extreme values of zero or those equal to the total sample size, a continuity correction of 0.5 was applied. Meta-analyses of OS, PFS, and DSS employed HRs. In instances where studies provided both unadjusted and adjusted HRs, the adjusted figure was used, as it is considered a less biased estimate. For studies lacking estimated HRs, Kaplan-Meier curves were used to reconstruct patient-level data, employing previously published algorithms [20]. WebPlotDigitizer software facilitated the digitization of the plots, and risk set data was used when available.

All pooled estimates and their 95 % confidence intervals (CIs) were calculated using a random-effects model, employing the inverse variance method and the restricted maximum likelihood estimator. The results were presented in forest plots. To evaluate heterogeneity, we calculated Cochran's Q statistic, the heterogeneity index (I^2), and τ^2 (tau-squared) values. We interpreted I^2 values as follows: 0–40 % indicated low heterogeneity, 30–60 % moderate, 50–90 % substantial, and 75–100 % considerable heterogeneity [21]. Subgroup analyses and *meta*-regression with study-level covariates were conducted to identify potential sources of heterogeneity. Specifically, subgroup analysis and *meta*-regression were used to assess the influence of continent and mean age on the prevalence of NSMP endometrioid endometrial cancer. For OS, PFS, and DSS, the subgroup analyses compared the HRs of the NSMP subtype to those of MMRd, p53-abnormal, and POLE subtypes.

Publication bias was evaluated through visual inspection of funnel plots, Egger's test, and the rank correlation test. An adjusted estimate accounting for publication bias was derived using the trim-and-fill method.

We considered statistical significance at $p < 0.05$ for all tests. We conducted all analyses using R statistical software (version 4.5.1), utilizing the 'meta' package for *meta*-analytic calculations.

Results

Study selection and characteristics of the included studies

The search yielded a total of 1,107 records. After removing 640 duplicates, 467 records were screened. Of these, 294 records were excluded, and the full texts of 173 articles were assessed for eligibility (Fig. 1). There were 31 studies that met all inclusion criteria, comprising a total of 2,660 patients with G3 endometrioid endometrial carcinoma (Table 1) [7,12,14,22–49]. The 31 studies included in the systematic review were further analyzed, and only data pertaining to G3 endometrioid carcinomas from each study were extracted and curated. The studies encompassed research from all five continents and employed both retrospective and prospective designs. They were conducted in diverse countries, including Canada, the USA, Brazil, Finland, France, Turkey, Spain, Japan, India, Thailand, Italy, the Netherlands, New Zealand, China, Korea, and the Czech Republic. Sample sizes ranged from 6 to 381 patients per study. The mean age of participants ranged from 54.5 to 70 years, and BMI ranged from 27.3 to 33.5 kg/m^2.

Risk of bias of included studies and publication bias

Almost all of the 31 studies received a "Yes" rating in every domain, with only two studies marked as "No" in the sample size criterion (Q3) [14,47]. Overall, the methodological quality was high (Appendix C).

The potential for publication bias was assessed using a funnel plot and Egger's regression test. The funnel plot appeared asymmetrical, indicating the possible presence of publication bias (Egger's test, $p = 0.002$). However, the trim-and-fill method did not impute any missing studies (Appendix D).

Prevalence of G3 endometrioid endometrial cancer of NSMP

The prevalence of NSMP within Grade 3 endometrioid endometrial cancer across individual studies varied from 0.13 (95 %CI 0.07–0.23) to 1.00 (95 %CI 0.63–1.00) (Fig. 2). The pooled prevalence was calculated to be 0.29 (95 %CI 0.23–0.34, $I^2 = 80.8$ %, based on 31 studies) (Fig. 2).

Subgroup analysis by continent revealed regional variations in the prevalence of NSMP within G3 endometrioid endometrial cancer (Appendix E). The pooled prevalence was highest in North America at 0.43 (95 %CI, 0.17–0.71), with substantial heterogeneity among the studies ($I^2 = 92.1$ %, $n = 7$). Conversely, Europe had the lowest prevalence at

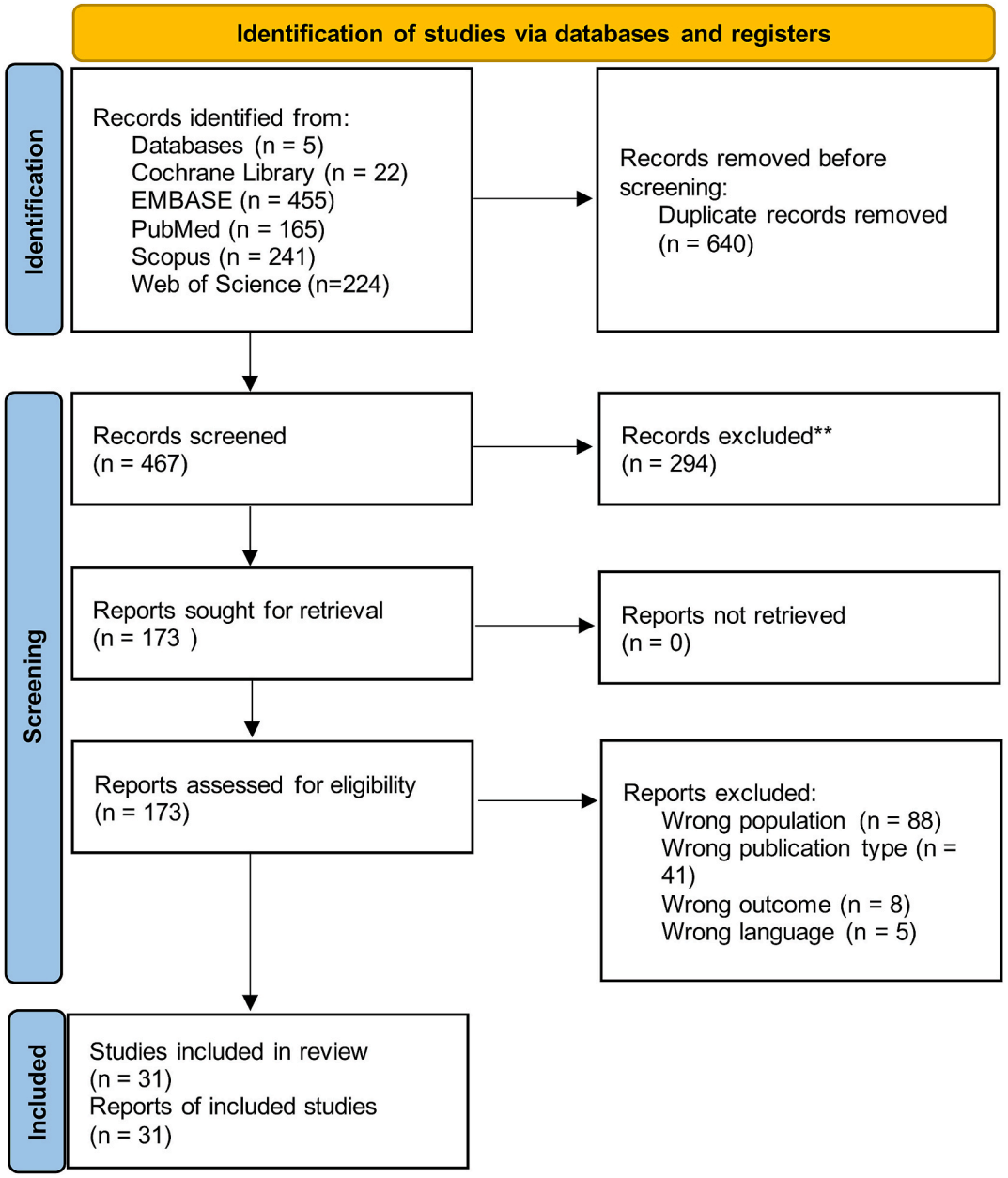

Fig. 1. PRISMA 2020 flow diagram of systematic review process and study selection.

0.23 (95 %CI, 0.19–0.28), with moderate heterogeneity ($I^2 = 63.6$ %, n = 14). However, these differences were not statistically significant (p = 0.102).

A *meta*-regression analysis was conducted to evaluate the effect of mean age on the prevalence of NSMP endometrioid endometrial cancer across various studies. The regression coefficient for mean age was not statistically significant (Slope = -0.0080, p = 0.25), suggesting that mean age is not associated with the prevalence of the NSMP subtype (Appendix F).

Overall survival

Regarding OS, the random-effects pooled estimate indicated that the NSMP subtype is associated with an intermediate outcome relative to other molecular subtypes. However, these differences were not statistically significant (p = 0.0705). Specifically, we observed a tendency for a lower risk of death among patients with the NSMP subtype compared to those with the p53 abnormal subtype (HR = 0.73, 95 %CI = 0.48–1.11), and a tendency for a higher risk of death compared to patients with the *POLE* ultramutated subtype (HR = 1.79, 95 %CI 0.87–3.69) (Fig. 3).

Progression-free survival and disease-specific survival

For PFS, the random-effects pooled estimate indicated an intermediate outcome for patients with the NSMP subtype. We found that patients with the NSMP subtype had a lower risk of disease progression compared to those with the p53 abnormal subtype (HR = 0.47, 95 %CI 0.01–29.23). Conversely, there was a significantly higher risk of disease progression for NSMP patients compared to those with the *POLE* ultramutated subtype (HR = 4.35, 95 %CI 1.31–14.42), according to the random-effects model (p = 0.0006) (Fig. 4).

For the outcome of DSS, the pattern remained consistent: patients with the NSMP subtype showed a tendency for a lower risk of disease-related death compared to those with the p53 abnormal subtype (HR = 0.33, 95 %CI 0.03–3.17) (Fig. 5).

Table 1
The characteristics of the included studies.

Author (year of publication)	Study design	Country	Sample size	Age[a] (years)	BMI[a] (kg/m^2)	NSMP prevalence
Alafraidi *et al.* (2024)	Retrospective cohort study	Canada	8			1.00
Alvarez *et al.* (2012)	Retrospective cohort study	USA	25	61 (37–88)		0.68
Andrade *et al.* (2024)	Retrospective cohort study	Brazil	68	63.1 ± 9.8	30.7 ± 7.2	0.18
Aro *et al.* (2024)	Prospective + Retrospective sample	Finland	158	70	28.2	0.15
Asami *et al.* (2023)	Retrospective cohort study	Japan	76	60		0.22
Beinse *et al.* (2019)	Retrospective cohort study	France	6	66.2		0.5
Bilir *et al.* (2023)	Retrospective cohort study	Turkey	30	59 ± 9.1	33 ± 5.6	0.33
Bosse *et al.* (2018)	Retrospective cohort study	USA	381	67 (36–96)		0.3
Cabrera *et al.* (2024)	Retrospective cohort study	Spain	248	65 (56–73)	30 (26–35)	0.24
Dahiya *et al.* (2024)	Retrospective cohort study	India	45	58.6 ± 11.5	29.2 ± 7.2	0.42
Dankai *et al.* (2023)	Retrospective cohort study	Thailand	39	57.2 (25–81)		0.44
de Biase *et al.* (2025)	Retrospective cohort study	Italy	39	62.5 ± 10.5	28 ± 7.2	0.18
Hammer *et al.* (2024)	Retrospective cohort study	Netherlands	17	67 (25–91)		0.29
Hattori *et al.* (2025)	Prospective	Japan	80	57 (29–78)		0.46
Henry *et al.* (2021)	Retrospective cohort study	New Zealand	13	57		0.38
Hussein *et al.* (2016)	Retrospective cohort study	USA	75	64		0.13
Huvila *et al.* (2023)	Retrospective cohort study	Canada	78			0.18
Joe *et al.* (2023)	Retrospective cohort study	Korea	37	55.9 (30–83)		0.27
Kolehmainen *et al.* (2020)	Retrospective cohort study	Finland	87			0.15
Leon-Castillo *et al.* (2022)	Retrospective cohort study	Netherlands	159			0.19
Li *et al.* (2022)	Retrospective cohort study	China	70	54.5		0.19
Loukovaara *et al.* (2021)	Retrospective cohort study	Finland	54	68 (60–75)	27.3 (23.7–32.4)	0.24
Michalova *et al.* (2024)	Retrospective cohort study	Czech Republic	36			0.31
Soylemez *et al.* (2024)	Retrospective cohort study	Turkey	42	59.9 ± 9.2	33.5 ± 6.2	0.45
Pasanen *et al.* (2021)	Retrospective cohort study	Finland	67			0.19
Smith *et al.* (2024)	Retrospective cohort study	Canada	26	65 (35–90)	33.2	0.46
Stelloo *et al.* (2016)	Cohort study	Netherlands	110	68 (41–90)		0.32
Thompson *et al.* (2022)	Retrospective cohort study	Canada	143	63.4		0.19
Travaglino *et al.* (2023)	Observation study	Italy	6	57.5 (29–74)		0.17
Vermij *et al.* (2023)	Retrospective cohort study	Netherlands	260			0.17
Zong *et al.* (2023)	Retrospective cohort study	China	177	59 (30–85)		0.25

BMI, body mass index; NSMP, no specific molecular profile.
[a] Data is presented as mean, mean ± standard deviation, or mean (minimum–maximum), as applicable.

Discussion

To the best of our knowledge, this is the first systematic review and *meta*-analysis to determine the prevalence of G3 (high-grade) endometrioid endometrial cancer of the NSMP subtype and to assess regional variations in this prevalence. Our data indicate that the NSMP subtype constitutes 29 % of all G3 endometrioid endometrial carcinomas. Additionally, we found that this molecular subtype is more prevalent in North America, accounting for 43 % of all G3 endometrioid endometrial carcinomas in the region. We can speculate that regional differences in the prevalence of NSMP tumors may be related to variations in patient risk profiles and demographic characteristics among study populations.

Endometrial cancer of the NSMP subtype is the most prevalent molecular form, representing over 50 % of all diagnosed endometrial carcinomas [50]. Unlike the favorable prognosis associated with G3 *POLE* ultramutated tumors and the generally poor prognosis of G3 p53 abnormal tumors, G3 endometrioid carcinomas of the NSMP subtype display heterogeneous clinical outcomes [13,50]. NSMP endometrial carcinomas have been shown to exhibit considerable morphologic and clinical heterogeneity. Compared with copy number-high or *POLE* ultramutated subtypes, patients with the NSMP subtype tend to have an intermediate prognosis, comparable to that observed in women with MSI-high endometrial carcinomas [13]. These tumors are characterized by diverse clinical, demographic, molecular, and genomic features [7,13,51]. Endometrioid endometrial carcinomas of NSMP can occur in young women, often with low-grade tumors linked to excess estrogen or obesity, typically resulting in a favorable prognosis [50,51]. However, these tumors can also lead to poor clinical outcomes, particularly when they are ER-negative and exhibit specific genomic alterations, such as those in the Kirsten rat sarcoma viral oncogene homolog (*KRAS*), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*), or when there is positivity for L1 cell adhesion molecule (L1CAM) [13,50,52,53]. Although statistical significance was reached only for the comparison between *POLE* ultramutated and NSMP subtypes for PFS, the direction of the HRs across outcomes consistently placed NSMP between the favorable *POLE* ultramutated and the poor p53 abnormal prognosis, suggesting an overall intermediate trend.

Despite significant progress, further refinement in the characterization of these tumors is essential to guide adjuvant therapy based on the distinct features of NSMP tumors [54]. It is important to emphasize that staging plays a crucial role in the prognosis of this patient subset and must always be considered [55]. Given the well-documented heterogeneity of G3 endometrioid endometrial cancer and the previously observed mixed behavior of endometrioid carcinomas of NSMP, data from studies such as PORTEC 4a are urgently needed. This data will help integrate the molecular profiling of these tumors into clinical practice [56,57].

This study exhibits several strengths. First, it includes a large number of studies and participants, drawing on data from diverse populations, which enhances the external validity of the findings. Second, most studies demonstrated high methodological quality, with all meeting key criteria for sample representativeness, appropriate recruitment, and adequate data analysis. Only two studies were identified as having a moderate risk of bias due to insufficient sample size. Therefore, the overall quality of the included studies was generally high, further reinforcing the reliability of this *meta*-analysis.

Despite the study's valuable insights, it contains several limitations. First, only retrospective studies were included, without any randomized controlled trials. In terms of oncologic outcomes, our systematic review and *meta*-analysis have limited statistical power. This limitation arises from the inclusion of only two studies comprehensive enough to robustly determine OS, PFS, and DSS [7,32]. It is important to note that while the TCGA classification has significantly advanced the diagnosis and management of endometrial cancer, FIGO staging remains essential for

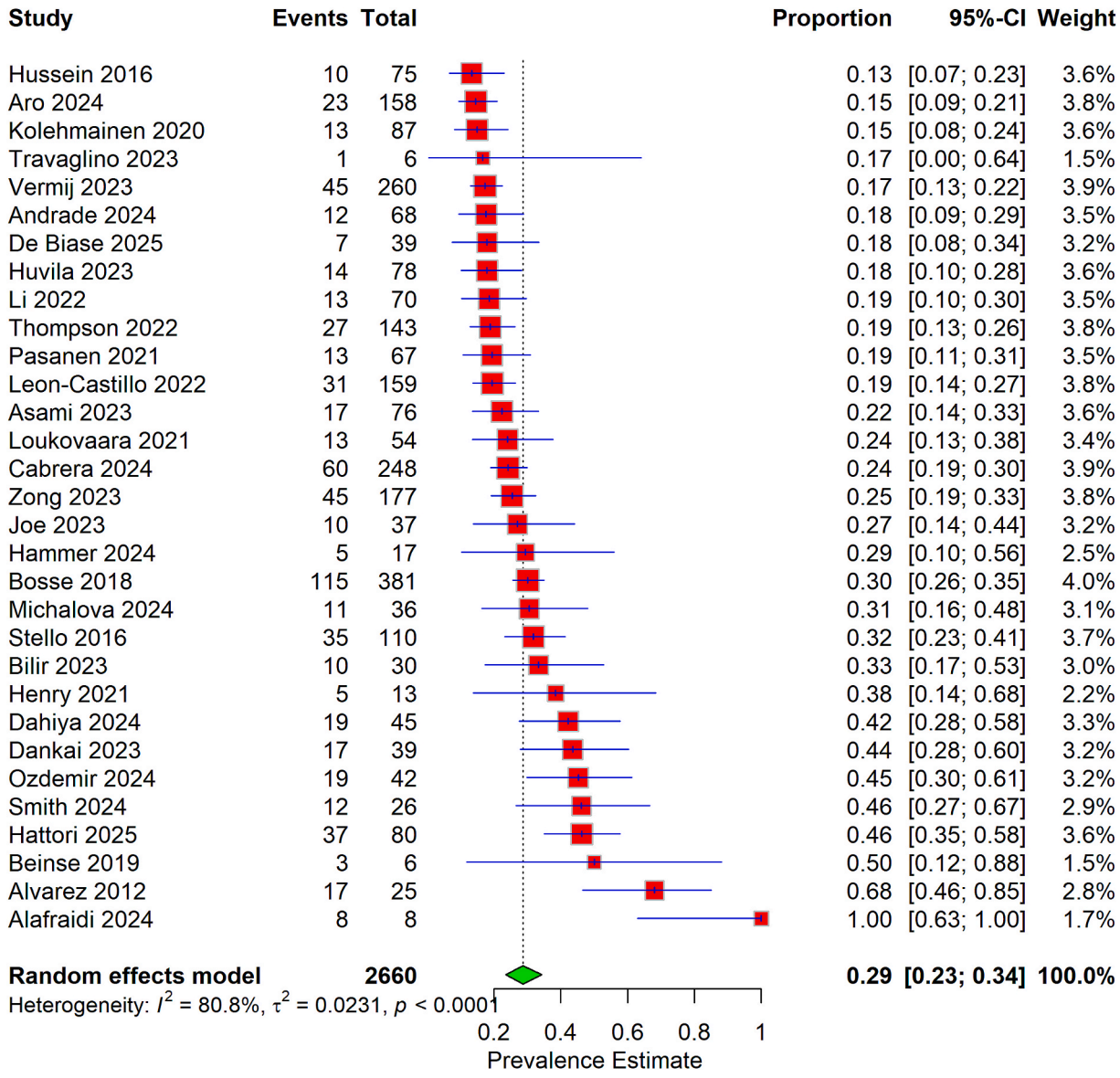

Fig. 2. Forest plot showing individual and pooled NSMP prevalence estimates with 95% confidence intervals (CI) in G3 endometrioid endometrial cancer.

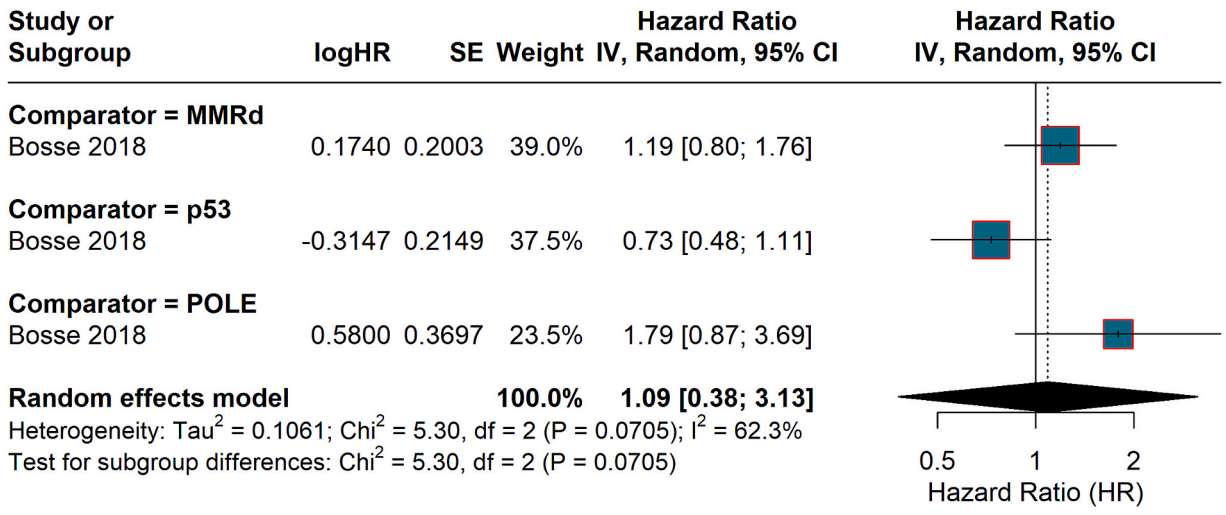

Fig. 3. Forest plot for overall survival of patients with NSMP G3 endometrioid endometrial cancer compared to patients with MMRd, p53-abnormal, and POLE subtypes. CI, confidence interval; HR, hazard ratio; IV, inverse variance; MMRd, mismatch repair deficiency; POLE, polymerase epsilon; SE, standard error.

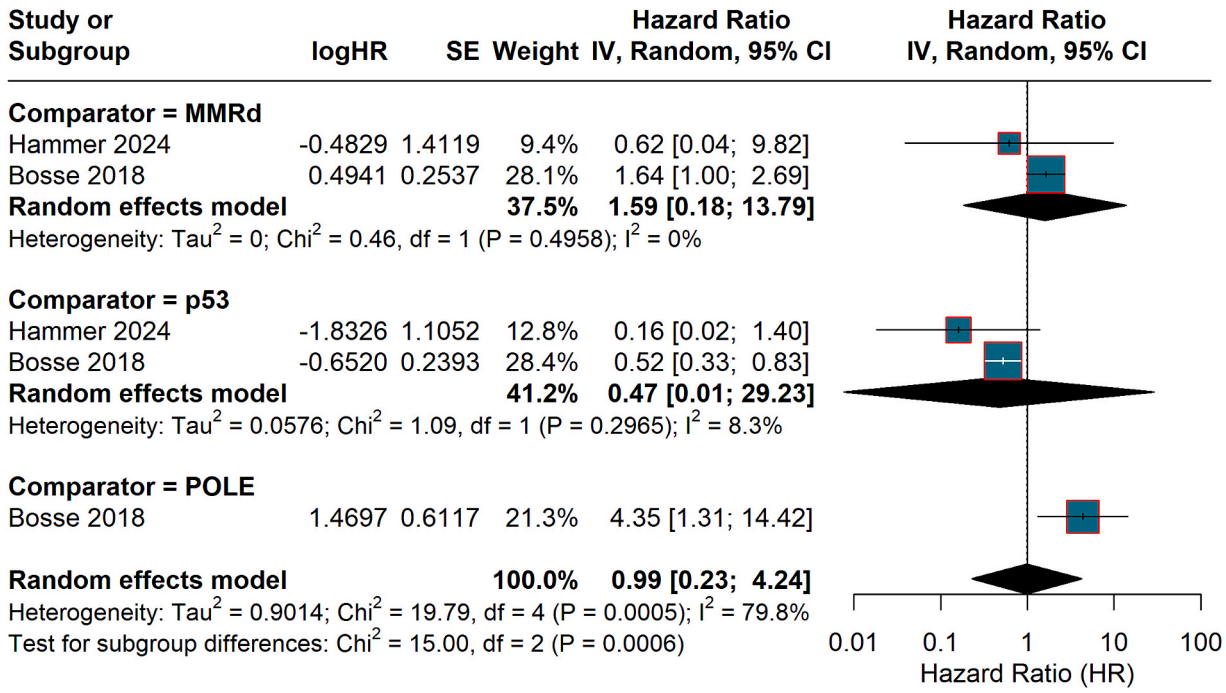

Fig. 4. Forest plot for progression-free survival of patients with NSMP G3 endometrioid endometrial cancer compared to patients with MMRd, p53-abn, and POLE subtypes. CI, confidence interval; HR, hazard ratio; IV, inverse variance; MMRd, mismatch repair deficiency; POLE, polymerase epsilon; SE, standard error.

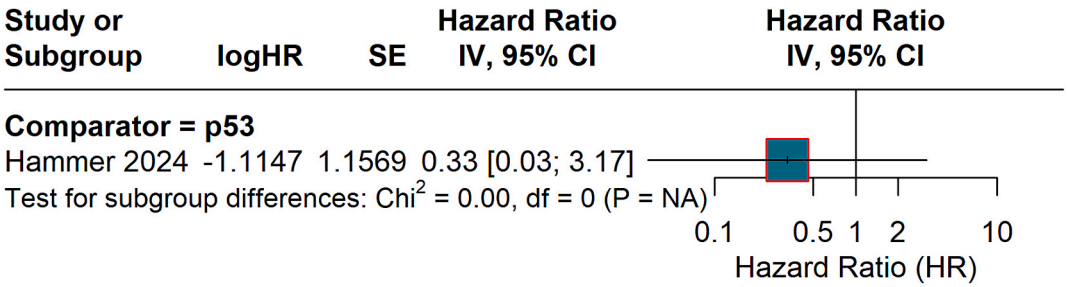

Fig. 5. Forest plot for disease-specific survival of patients with NSMP G3 endometrioid endometrial cancer compared to patients with p53-abnormal subtype. CI, confidence interval; HR, hazard ratio; IV, inverse variance; SE, standard error.

prognostication [55,56].

A further limitation is that our analysis of G3 endometrioid endometrial carcinomas focused solely on the molecular subtype (NSMP), excluding FIGO stage considerations. This exclusion was due to incomplete FIGO staging data for G3 endometrioid carcinoma cases in the included studies. Moreover, although the funnel plot exhibited asymmetry, suggesting potential publication bias, the trim-and-fill method did not indicate any missing studies.

Despite these limitations, our findings support existing literature by suggesting that G3 (high-grade) endometrioid endometrial carcinomas of the NSMP subtype have an intermediate prognosis [7]. This emphasizes the necessity of refining the NSMP subtype to better delineate oncologic outcomes [48]. Looking ahead, we hope this review will prompt researchers to conduct further studies, advancing beyond molecular classification toward a more personalized approach for this subset of tumors.

Informed consent statement

Not applicable.

Consent for publication

Not applicable.

Availability of data

All data relevant to the study are included in the article. Further information can be obtained from the corresponding author.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT 4o PLUS in order to improve readability and language. After using this tool/service, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

CRediT authorship contribution statement

João Casanova: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Data curation, Conceptualization. **Ana Sofia Ramos:** . **Alexandru Babiciu:** Validation, Methodology, Investigation, Data curation. **Filipa Moutinho:** Validation,

Methodology, Investigation, Data curation. **Marta Tripepi:** Validation, Methodology, Investigation, Data curation. **Ana Gomes da Costa:** Validation, Methodology, Investigation, Data curation. **Sofia Silvério Serra:** . **Teresa Costa:** Validation, Software, Methodology, Investigation, Formal analysis, Data curation. **Nadeem R. Abu-Rustum:** Writing – review & editing, Validation, Investigation, Data curation. **João Martins:** Writing – review & editing, Validation, Software, Methodology, Investigation, Formal analysis, Data curation. **Jorge Lima:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization.

Ethics approval

No ethics committee approval was required because the study analyzed only published data.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Abu-Rustum received research funding paid to the institution from GRAIL. Memorial Sloan Kettering Cancer Center also has equity in GRAIL. Dr. Abu-Rustum also held a leadership or fiduciary role in the National Comprehensive Cancer Network (NCCN) and the International Gynecologic Cancer Society (IGCS). All the other authors declare no conflicts of interest.

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Appendix A. Supplementary data

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