The clinicopathological characteristics of POLE-mutated/ultramutated endometrial carcinoma and prognostic value of POLE status: a meta-analysis based on 49 articles incorporating 12,120 patients

Qing Wu¹,², Nianhai Zhang¹,² and Xianhe Xie¹,²,³*

Abstract

Objective: This study was designed to investigate the frequency and clinicopathological characteristics of POLE-mutated/ultramutated (POLEmut) in endometrial carcinoma (EC) and assess the prognostic values of POLE status.

Methods: Electronic databases were screened to identify relevant studies. Meta-analysis was used to yield the pooled frequency of POLEmut and prognostic parameters by 95% confidence interval (CI), odd ratio (OR), and hazard ratio (HR).

Results: Totally, 12,120 EC patients from 49 studies were included. The pooled frequency of POLEmut was 7.95% (95% CI: 6.52–9.51%) in EC, 7.95% (95% CI: 6.55–9.46%) in endometrioid endometrial carcinoma, and 4.45% (95% CI: 2.63–6.61%) in nonendometrioid endometrial carcinoma. A higher expression occurred in grade 3 (OR = 0.51, 95% CI: 0.36–0.73, P = 0.0002), FIGO stage I-II (OR = 1.91, 95% CI: 1.29–2.83, P = 0.0013), and myometrial invasion < 50% (OR = 0.66, 95% CI: 0.50–0.86, P = 0.0025). Survival analyses revealed favorable OS (HR = 0.68, 95% CI: 0.55–0.85, P = 0.0008), PFS (HR = 0.74, 95% CI: 0.59–0.93, P = 0.0085), DSS (HR = 0.61, 95% CI: 0.44–0.83, P = 0.0016), and RFS (HR = 0.47, 95% CI: 0.35–0.61, P < 0.0001) for POLEmut ECs. Additionally, the clinical outcomes of POLEmut group were the best, but those of p53-abnormal/mutated (p53abn) group were the worst, while those of microsatellite-instable (MSI)/hypermutated group and p53-wild-type (p53wt) group were medium.

Conclusions: The POLEmut emerged higher expression in ECs with grade 3, FIGO stage I-II, and myometrial invasion < 50%; it might serve as a highly favorable prognostic marker in EC; the clinical outcomes of POLEmut group were the best one among the four molecular subtypes.

Keywords: POLE-mutated/ultramutated, Endometrial carcinoma, Overall survival, Progression free survival, Disease specific survival, Relapse free survival

Introduction

Endometrial carcinoma (EC) is one of the most prevalent among gynecological cancer with a steady increase in incidence worldwide [1, 2]. Histotype and other clinicopathological parameters such as Federation International of Gynecology and Obstetrics (FIGO) stage and
tumor grade] are associated with the prognosis of ECs [3, 4]. However, both histotype and grade assignment are relatively poor reproducible [5–7], which leads to inaccurate findings within clinical trials, and over- or under-treatment of ECs.

In order to improve the clinical/pathology-based risk stratification system, the updated classification of EC identifies four subtype [polymerase-ε-mutated/ultramutated (POLEmut), microsatellite-instable (MSI)/hypermutated or mismatch repair-deficient (MMRD), p53-wild-type (p53wt), and p53-abnormal/mutated (p53abn)] according to The Cancer Genome Atlas (TCGA) and Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) based on various genetic and molecular features possesses a potential promise, proving to be reproducible, and demonstrating the associations with clinical outcomes [8–11].

POLE is involved in DNA replication and has recently been recognized as hereditary cancer-predisposing genes. The alterations of POLE are associated with occurrence, development and prognosis of tumors, especially in EC [12]. The group of POLEmut, ECs with mutations in DNA POLE that is responsible for DNA replication and leads to exceedingly high somatic mutation frequencies ("ultramutated": > 100 mutations per megabase) [13, 14], was found to be associated with markedly favorable outcomes, even with poor clinicopathological features [15, 16]. Additionally, they were also candidates for therapy of immune checkpoint inhibitor (ICIs) [17, 18].

However, a consensus has not been reached, with some studies advocating non-superior survival in POLEmut ECs [19, 20]; additionally, the frequency and specific clinicopathological features of POLEmut ECs were various in different studies. Therefore, it remains to be fully illuminated the histopathological features and prognostic of POLEmut ECs. Previous study had preliminarily explored the POLEmut ECs through meta-analysis [21], but it was based on limited histopathological features and prognostic parameters. Consequently, we made a comprehensive survey based on a large scale (49 articles incorporating 12,120 EC patients), multi-level (including eight subgroup analyses), and diverse dimensions (incorporating overall survival (OS), progression free survival (PFS), disease specific survival (DSS), and relapse free survival (RFS)) to summarize the pooled frequency and clinicopathological characteristics of POLEmut ECs and to assess the prognostic value.

Materials and methods

Data sources and literature searches

Studies were screened by a systematic electronic literature retrieval for abstracts of relevant studies in the published literature. PubMed, Cochrane Library, and EMBASE were searched and the data were updated as of December 30th, 2021. The basic search terms were used as follows: “endometrial carcinoma”, “endometrial cancer”, “POLE”, “polymerase epsilon”, and “Polymerase ε”. Full-text papers were scrutinized if abstracts did not provide substantial information. Moreover, the references of relevant articles were reviewed for additional studies. Data retrieval was completed in English.

Selection of studies and definition

Initially, two investigators performed a screening of titles and abstracts respectively, then examined the full-text of articles to acquire eligible studies. For the duplicate studies based on the same study patients, only the latest or most comprehensive data were included.

OS was defined as time from surgery until death of any cause; PFS was defined as time from surgery until there is evidence of progressive disease or if they died of the disease prior to the censoring date; DSS was defined as time from surgery until death due to EC; RFS was defined as time from surgery until there is evidence of recurrent disease.

Inclusion criteria

(1) Prospective or retrospective studies to report the frequency and clinicopathological characteristics of POLEmut in EC; (2) the expression of POLE gene was reported using genetic testing (e.g. sequencing, sanger sequencing, next generation sequencing, and polymerase chain reaction); (3) a full paper had been published.

Data extraction

Data extraction was implemented conforming to the PRISMA guidance (Table S1). All eligible studies involved information as follows: the publication year and country, first author’s name, study type, and number of both ECs and POLEmut ECs.

Quality assessment

The quality of included studies was assessed independently by two reviewers using the Newcastle-Ottawa Scale (NOS) for case-control and cohort studies, which encompassed the three dimensions of selection, comparability, and exposure, with a full score of 9 points.

Statistical methods

The primary endpoint was to report the pooled frequency of POLEmut in ECs. Subgroup analyses were accomplished based on histotype, grade, FIGO stage, lymphovascular space invasion (LVSI), myometrial invasion, lymph node status, clinical risk stratification and adjuvant therapy. The measures to summarize them were odd ratios (ORs) and 95% confidence intervals (CIs).
second endpoint was to evaluate the prognostic value (including OS, PFS, DSS, and RFS) of POLE\text{mut} in ECs. The summary measures of survival analysis were hazard ratios (HRs) with corresponding 95% CIs. Funnel plots and Egger's test were implemented to evaluate publication bias. Statistical analysis was performed through R 4.0 statistical software. Heterogeneity was assessed by I-square tests and chi-square. If $P < 0.1$ or $I^2 > 40\%$, remarkable heterogeneity existed. A random effect model was adopted to analysis the pooled data when heterogeneity existed, otherwise, a fixed effect model was employed.

Results
Selection of study
Initially, 273 relevant articles were scrutinized intensively. Of them, 24 were filtered for duplication, and 104 were excluded for digression after screening the titles and abstracts. Then the full text of 145 articles was thoroughly reviewed, and 96 were filtered for: they were not human research, and not in English, commentaries, case reports, review articles, letters to the editor, and studies without enough data for calculation. Finally, a total of 49 articles (Table S2) incorporating 12,120 patients were included in this study. The elaborate procedure was displayed in Fig. 1.

Study traits
Totally, 12,120 individuals in the 49 articles (50 cohorts) published until December 30th, 2021 were included. Studies were published from 2013 to 2021. The sample size ranged from 14 to 982. Of these studies, 8 were prospective, and 41 were retrospective. ORs and 95% CIs were used to report the frequency and clinicopathological characteristics of POLE\text{mut} in ECs, and HRs with corresponding 95% CIs were utilized to assess the value

![Fig. 1 Flowchart on selection including trials in the meta-analysis](image-url)
of POLEmut in clinical prognosis. Of all the adopted studies, 16 cohorts contained data for OS, 10 for PFS, 8 for DSS, and 8 for RFS. The principal characteristics were listed in Table 1.

Data analyses

The frequency of POLEmut in EC

A total of 49 articles containing 12,120 patients were included in the investigation of frequency of POLEmut ECs. The pooled frequency of POLEmut in ECs was 7.95% (95% CI: 6.55–9.46%) with significant heterogeneity among the studies ($I^2 = 79.6, 95\%\text{ CI}: 71.8–85.2\%$, $P<0.0001$) (Fig. 2a). Furthermore, no publication bias was defined via Egger’s tests ($z=1.832, P=0.06695$) and funnel plot (Fig. 2b) in the pooled analysis.

Subgroup analyses

We explored subgroup analyses based on histotype, grade, FIGO stage, LVSI, myometrial invasion, lymph node status, clinical risk stratification, and adjuvant therapy. The outcomes of specific subgroup analysis were shown in Table 2. The pooled ORs with 95% CIs were also calculated for POLEmut ECs according to each subgroup variable (Table 1).

Subgroup analysis was performed based on histotype. A total of 8412 patients with EC from 32 cohorts were obtained for the meta-analysis. The pooled frequency of POLEmut in ECs was 5.35% (95% CI: 3.82–7.87%) in LVSI present and 6.96% (95% CI: 5.32–8.77%) in LVSI absent.

Subgroup analysis was carried out based on myometrial invasion. The pooled frequency of POLEmut ECs was 4.78% (95% CI: 3.47–6.28%) in myometrial invasion $\geq 50$ and 6.85% (95% CI: 5.04–8.89%) in myometrial invasion $<50$. The pooled OR of POLEmut ECs with myometrial invasion $\geq 50$ vs. myometrial invasion $<50$ was 0.66 (95% CI: 0.50–0.86, $P=0.0025$).

Subgroup analysis was performed based on lymph node status. The pooled frequency of POLEmut ECs was 4.97% (95% CI: 3.55–12.07%) in lymph node status present and 9.46% (95% CI: 7.77–11.28%) in lymph node status absent.

Subgroup analysis was accomplished based on clinical risk stratification. The pooled frequency of POLEmut ECs was 5.87% (95% CI: 3.01–8.63%) in low-risk stratification, 7.18% (95% CI: 1.07–16.78%) in intermediate-risk stratification, and 8.87% (95% CI: 6.07–12.09%) in high-risk stratification.

Subgroup analysis was conducted based on with or without adjuvant therapy. The pooled frequency of POLEmut ECs was 9.00% (95% CI: 6.78–11.46%) with adjuvant therapy, and 6.27% (95% CI: 4.11–8.75%) without adjuvant therapy.

The frequency of other molecular subtypes (MSI and p53abn) in ECs

The pooled frequency of MSI in ECs was 27.23% (95% CI: 23.66–30.95%) (Fig. S1a) with significant heterogeneity among studies ($I^2 = 91.1, 95\%\text{ CI}: 88.6–93.0\%, P<0.0001$) (Table S3); the pooled frequency of p53abn in ECs was 23.47% (95% CI: 19.70–27.46%) (Fig. S1b) with significant heterogeneity among studies ($I^2 = 56.0, 95\%\text{ CI}: 33.7–70.8\%, P<0.0001$). The pooled OR of POLEmut EEC vs. NEEC was 1.35 (95% CI: 0.88–2.08, $P=0.1719$) with heterogeneity ($I^2 = 49.6, 95\%\text{ CI}: 17.4–69.2\%, P=0.0047$).

Subgroup analysis was accomplished based on histotype. The pooled frequency of POLEmut ECs was 5.35% (95% CI: 4.16–6.67%) in grade 1–2 and 10.55% (95% CI: 8.35–12.94%) in grade 3. The pooled OR of POLEmut ECs with grade 1–2 vs. grade 3 was 0.51 (95% CI: 0.36–0.73, $P=0.0002$).

Subgroup analysis was executed based on FIGO stage. The pooled frequency of POLEmut ECs was 9.15% (95% CI: 7.06–11.46%) in FIGO stage I–II and 2.89% (95% CI: 1.43–4.67%) in FIGO stage III–IV. The pooled OR of POLEmut ECs with FIGO stage I–II vs. FIGO stage III–IV was 1.91 (95% CI: 1.29–2.83, $P=0.0013$).

Subgroup analysis was implemented based on LVSI. The pooled frequency of POLEmut ECs was 6.40% (95% CI: 3.82–9.48%) in LVSI present and 6.96% (95% CI: 5.32–8.77%) in LVSI absent.

Subgroup analysis was calculated via Egger’s tests (Table S3) and funnel plot (Fig. S2) in the pooled analyses.

Survival analyses

Survival analyses were displayed by pooled HRs with 95% CIs for OS, PFS, DSS, and RFS. Of all the adopted studies, 16 cohorts contained data for OS, 10 for PFS, 8 for DSS, and 8 for RFS. The pooled HRs of POLEmut vs. POLE-wild-type (POLEwt) ECs were 0.68 (95% CI: 0.55–0.85, $P=0.0008$) for OS (Fig. 3a), 0.74 (95% CI: 0.59–0.93, $P=0.0085$) for PFS (Fig. 3b), 0.61 (95% CI: 0.44–0.83, $P=0.0016$) for DSS (Fig. 3c), and 0.47 (95% CI: 0.35–0.61, $P=0.0001$) for RFS (Fig. 3d). These results indicated benefit survival and favorable prognosis in POLEmut EC patients. No publication bias was calculated via funnel plot (Fig. S2) in the pooled analyses.

Additionally, univariable and multivariable analyses were pooled to test the associations among the four molecular subtypes (POLEmut, MSI, p53wt and p53abn) with clinical outcomes (OS, PFS, DSS and RFS) in ECs
| Author          | Year | Country                | Study type   | EC size | POLEmut | MSI    | p53abn     | Sequencing method          | Histotype       | Location of exounuclease mutations | Outcomes |
|-----------------|------|------------------------|--------------|---------|---------|--------|------------|----------------------------|----------------|-----------------------------------|----------|
| Abdulfatah et al | 2019 | USA                    | retrospective | 60      | 2       | 20     | 9          | Sanger sequencing           | EEC(39); NEEC(21) | Exons 9 and 13                     | NA       |
| Beinse et al    | 2020 | France                 | prospective  | 125     | 4       | 35     | 30         | Sequencing                  | EEC(103); NEEC(22)  | NA                                 | NA       |
| Bellone et al   | 2017 | USA and Italy          | retrospective | 131     | 11      | NA     | NA         | Sequencing                  | EEC(96); NEEC(35)  | Exons 9–14                         | OS       |
| Billingsley et al | 2015 | USA                    | prospective  | 544     | 30      | NA     | NA         | Sanger sequencing           | EEC(544); NEEC(10) | Residues 268–471                  | OS, PFS  |
| Bosquet et al   | 2021 | USA                    | prospective  | 239     | 28      | 67     | 70         | Sequencing                  | EEC(1192); NEEC(47) | NA                                 | PFS      |
| Bosset et al    | 2018 | USA, Canada, and Europe| retrospective | 376     | 48      | 136    | 79         | Sanger or next-generation approaches | EEC(376); NEEC(0)  | Exons 9–14                         | OS, RFS  |
| Church et al    | 2014 | Europe                 | retrospective | 788     | 48      | NA     | NA         | Sanger sequencing           | EEC(770); NEEC(18) | Exons 9 and 13                     | OS, DSS, RFS |
| Church et al    | 2013 | Europe                 | retrospective | 173     | 14      | 24     | NA         | Sequencing                  | EEC(154); NEEC(19)  | residues 268–471                  | NA       |
| Conlon et al    | 2020 | USA                    | retrospective | 37      | 4       | 6      | NA         | Sanger sequencing           | EEC(0); NEEC(37)   | Exons 9, 13 and 14                 | NA       |
| Cosgrove et al  | 2018 | USA                    | prospective  | 982     | 39      | 379    | 84         | Sequencing                  | EEC(982); NEEC(0)   | Exons 9, 13 and 14                 | OS, PFS, DSS |
| Crumley et al   | 2019 | USA                    | retrospective | 132     | 1       | NA     | NA         | Next generation sequencing  | EEC(132); NEEC(0)   | Exons 9–14                         | NA       |
| Dai et al       | 2021 | NA                     | retrospective | 473     | 73      | 148    | 170        | Sequencing                  | EEC(363); NEEC(110) | NA                                 | NA       |
| DeLair et al    | 2017 | USA                    | retrospective | 30      | 2       | 4      | 8          | Sequencing                  | EEC(0); NEEC(30)   | Exons 9–14                         | NA       |
| Devereaux et al | 2021 | USA                    | prospective  | 310     | 15      | 79     | 81         | SNaPshot technique          | EEC(220); NEEC(90)  | Exons 9, 11, 13 and 14              | NA       |
| Eggink et al    | 2017 | Europe and Australia   | retrospective | 116     | 15      | 19     | 40         | Sanger sequencing           | EEC(86); NEEC(30)   | Exons 9, 13 and 14                 | NA       |
| Espinoza et al  | 2017 | Spain                  | retrospective | 21      | 9       | 5      | NA         | Sequencing                  | NA                 | Exons 9–14                         | NA       |
| Espinoza et al  | 2016 | Spain                  | retrospective | 40      | 1       | NA     | 4          | Sequencing                  | EEC(0); NEEC(20)   | Exons 13 and 14                    | NA       |
| van Esterik et al | 2017| Netherlands            | retrospective | 49      | 10      | 11     | 10         | Sanger sequencing           | EEC(42); NEEC(7)    | Exons 9 and 13                     | NA       |
| Falcone et al   | 2019 | Italy                  | retrospective | 15      | 3       | 4      | 1          | Sequencing                  | EEC(15); NEEC(0)   | NA                                 | NA       |
| Le Gallo et al  | 2017 | USA and Europe         | retrospective | 63      | 0       | 7      | 25         | Sanger sequencing           | EEC(0); NEEC(63)   | NA                                 | NA       |
| Haraldsdottir et al | 2014 | USA                    | retrospective | 14      | 3       | NA     | NA         | Next generation sequencing  | EEC(111); NEEC(3)   | NA                                 | NA       |
| Haruma et al    | 2018 | Japan                  | retrospective | 138     | 12      | 40     | NA         | Sanger sequencing           | EEC(123); NEEC(15)  | Exons 9 and 13                     | NA       |
| He et al        | 2020 | China                  | retrospective | 426     | 38      | 94     | 77         | Sanger sequencing           | EEC(364); NEEC(62)  | Exons 9, 13 and 14                 | OS, PFS  |
| Hoang et al     | 2015 | Canada                 | retrospective | 14      | 1       | NA     | 4          | Sanger sequencing           | EEC(0); NEEC(14)   | Exons 9–14                         | NA       |
| Imboden et al   | 2019 | Sweden                 | retrospective | 599     | 38      | NA     | NA         | Sanger sequencing           | EEC(499); NEEC(100) | Exons 9–14                         | OS, PFS, DSS, RFS |
| Joehlin-Price et al | 2021 | USA                    | retrospective | 95      | 10      | 35     | 18         | Next generation sequencing  | EEC(95); NEEC(0)   | Exons 9, 13 and 14                 | OS, RFS  |
| Jones et al     | 2020 | USA                    | retrospective | 621     | 28      | 203    | NA         | Next generation sequencing  | EEC(621); NEEC(0)   | NA                                 | NA       |
| Kim et al       | 2020 | Canada                 | retrospective | 52      | 1       | 5      | 18         | Sequencing                  | EEC(0); NEEC(52)   | NA                                 | OS, PFS, DSS |
| Kolehmainen et al | 2021 | Finland                | retrospective | 604     | 30      | 287    | 69         | Sequencing                  | EEC(535); NEEC(69)  | Exons 9, 13 and 14                 | NA       |
| León-Castillo et al | 2020 | UK, Italy, Canada, France, Australia, New Zealand | retrospective | 410     | 51      | 137    | 93         | Sequencing                  | EEC(274); NEEC(136) | Exons 9–14                         | OS, RFS  |
| Author          | Year | Country                     | Study type       | EC size | POLEmut | MSI | p53abn | Sequencing method          | Histotype       | Location of exonuclease mutations | Outcomes  |
|-----------------|------|-----------------------------|------------------|---------|---------|-----|--------|-----------------------------|----------------|----------------------------------|-----------|
| Li et al        | 2020 | USA                         | retrospective    | 529     | 55      | NA  | NA     | Sanger sequencing           | EEC(396); NEEC(133) | Exons 9, 13 and 14                | NA        |
|                 |      | China                       | retrospective    | 467     | 34      | NA  | NA     | Sanger sequencing           | EEC(398); NEEC(69) | Exons 9, 13 and 14                | NA        |
| López-Reig et al| 2019 | Spain                       | prospective      | 96      | 16      | NA  | NA     | Next generation sequencing  | EEC(83); NEEC(13) | NA                               | OS, RFS   |
| McConechy et al | 2016 | Canada                      | retrospective    | 406     | 39      | NA  | NA     | Sequencing                  | EEC(315); NEEC(91) | Exons 9–14                        | OS, DSS; PFS |
| Meng et al      | 2014 | Canada                      | retrospective    | 102     | 16      | NA  | NA     | Sanger sequencing           | EEC(102); NEEC(0) | Exons 9–14                        | OS, PFS; DSS |
| Monsur et al    | 2021 | Japan                       | retrospective    | 127     | 5       | NA  | NA     | Sequencing                  | EEC(109); NEEC(18) | NA                               | NA        |
| Da Cruz Paula A et al | 2021 | USA                         | retrospective    | 175     | 12      | 49  | 39     | Sequencing                  | EEC(116); NEEC(59) | NA                               | NA        |
| Prendergast et al | 2019 | USA                         | retrospective    | 74      | 1       | 13  | 32     | Sequencing                  | EEC(38); NEEC(36) | NA                               | NA        |
| Riggs et al     | 2020 | Caucasian, African American, Asian | prospective | 65      | 7       | NA  | NA     | Sequencing                  | EEC(37); NEEC(28) | NA                               | NA        |
| Rosa-Rosa et al | 2016 | USA and Europe              | retrospective    | 18      | 2       | 8   | 2      | Sequencing                  | EEC(0); NEEC(18) | Exons 9 and 13                    | NA        |
| Siraj et al     | 2019 | Riyadh, Saudi Arabia        | retrospective    | 414     | 2       | 52  | NA     | Capture sequencing and Sanger sequencing | EEC(370); NEEC(50) | NA                               | NA        |
| Stasenko et al  | 2020 | USA                         | prospective      | 451     | 23      | NA  | NA     | Sequencing                  | EEC(451); NEEC(0) | residues 268–471                 | NA        |
| Talhouk et al   | 2015 | Canada                      | retrospective    | 143     | 12      | 41  | 25     | Sequencing                  | EEC(119); NEEC(24) | Exons 9–14                        | OS, DSS; RFS |
| Talhouk et al   | 2017 | Canada                      | retrospective    | 319     | 30      | 64  | 86     | Sequencing                  | EEC(215); NEEC(104) | Exons 9–14                        | OS, PFS; DSS |
| Tessler-Cloutier et al | 2021 | Canada, USA, Australia       | retrospective    | 82      | 6       | 52  | NA     | Sequencing                  | EEC(0); NEEC(82) | Exons 9–14                        | NA        |
| Cancer Genome Atlas Research Network et al | 2013 | USA                         | retrospective    | 232     | 17      | 65  | 60     | Exome sequencing            | NA              | Pro286Arg and Val-411Leu          | PFS       |
| Timmerman et al | 2020 | Belgium                     | prospective      | 108     | 7       | 33  | 24     | Sanger sequencing           | EEC(87); NEEC(21) | Exons 9, 11, 13 and 14             | NA        |
| Wong et al      | 2016 | Singapore                   | retrospective    | 47      | 14      | 20  | NA     | Next generation sequencing  | EEC(47); NEEC(0) | Exons 9–14                        | OS, RFS   |
| ZHANG et al     | 2021 | China                       | retrospective    | 21      | 3       | 11  | 6      | Sanger sequencing           | NA              | Exons 9–14                        | NA        |
| Zong et al      | 2021 | China                       | retrospective    | 587     | 49      | 163 | 130    | Sequencing                  | EEC(594); NEEC(239) | Exons 9–14                        | NA        |
| Author                | FIGO stage | Grade | LVSI | Myometrial invasion | Lymph node status | Myometrial invasion | Lymph node status | Clinical risk stratification | Adjuvant therapy |
|-----------------------|------------|-------|------|---------------------|-------------------|---------------------|-------------------|---------------------------|-----------------|
| Abdulfatah et al      | 46         | 5     | 9    | 0                   | 19, 22, 10        | NA, NA             | NA, NA            | NA, NA                    | NA, NA          |
| Beinse et al          | 84         | 2     | 26   | 9                   | 61, 29, 13        | 29, 87             | NA, NA            | NA, NA                    | 40, 21, 40      |
| Bellone et al         | 62         | 23    | 34   | 12                  | 16, 42, 73        | NA, NA             | NA, NA            | NA, NA                    | 102, 29         |
| Billingsley et al     | NA         | NA    | NA   | NA                  | 267, NA, NA       | 181, 343           | 157, 336          | NA, NA                    | NA, NA          |
| Bosquet et al         | NA         | NA    | NA   | NA                  | 72, 73, 47        | NA, NA             | NA, NA            | NA, NA                    | NA, NA          |
| Bosse et al           | 291        | NA    | NA   | NA                  | 0, 0, 376         | NA, NA             | NA, NA            | NA, NA                    | NA, NA          |
| Church et al          | 742        | 46    | 0    | 0                   | 571, 108, 109     | 70, 718            | 560, 228          | NA, NA                    | 576, 212        |
| Church et al          | 114        | 18    | 15   | 8                   | 64, 59, 45        | NA, NA             | NA, NA            | NA, NA                    | NA, NA          |
| Conlon et al          | 19         | 1     | 11   | 6                   | NA, NA, NA        | NA, NA             | NA, NA            | NA, NA                    | NA, NA          |
| Cosgrove et al        | 732        | 91    | 141  | 18                  | 407, 423, 152     | 227, 737           | 260, 537          | NA, NA                    | NA, NA          |
| Crumley et al         | 112        | 5     | 13   | 2                   | NA, NA, NA        | 30, 102            | 30, 102           | 11, 77                    | NA, NA          |
| Dai et al             | NA         | NA    | NA   | NA                  | NA, NA, NA        | NA, NA             | NA, NA            | NA, NA                    | NA, NA          |
| DeLair et al          | 15         | 0     | 2    | 13                  | NA, NA, NA        | NA, NA             | NA, NA            | NA, NA                    | NA, NA          |
| Deveaux et al         | 177        | 12    | 66   | 24                  | NA, NA, 32        | 99, 167            | 115, 104          | NA, NA                    | NA, NA          |
| Eggink et al          | 42         | 21    | 41   | 11                  | 13, 5, 98         | 55, 40             | 87, 23            | NA, NA                    | 0, 0, 116       |
| Espinosa et al        | 10         | 1     | 5    | 5                   | NA, NA, NA        | NA, NA             | NA, NA            | NA, NA                    | NA, 12, 6       |
| Espinosa et al        | 11         | 2     | 2    | 5                   | NA, NA, NA        | 7, 13              | NA, NA            | NA, NA                    | NA, 16, 4       |
| van Esterik M et al   | NA         | NA    | NA   | NA                  | 7, 42, 22         | 27, 27             | 17, 19            | NA, NA                    | NA, NA          |
| Falcone et al         | 0          | 0     | 0    | 0                   | NA, NA, 0         | NA, NA             | NA, NA            | NA, NA                    | NA, NA          |
Table 1 (continued)

| Author                  | FIGO stage | Grade | LVSI | Myometrial invasion | Lymph node status | Clinical risk stratification | Adjuvant therapy |
|-------------------------|------------|-------|------|---------------------|-------------------|-----------------------------|------------------|
|                         | I  II III IV |       |      | present absent      | ≥50% <50%         |                              |                  |
|                          |            |       |      |                     |                   | low intermediate high | Yes No           |
| Le Gallo et al          | NA NA NA NA | NA NA NA | NA NA NA NA | NA NA NA NA | NA NA NA NA | NA NA NA NA | NA NA NA NA |
| Haraldsdottir et al     | 12 0 2 0   | 6 3 5 | NA NA NA NA | NA NA NA NA | 40 98 49 89 | NA NA NA NA | 74 64           |
| Haruma et al            | 93 11 24 10 | 64 29 45 | 0 108 48 378 | 117 309 22 345 | NA NA NA NA | NA NA NA NA | NA NA NA NA |
| He et al                | NA NA NA NA | NA NA NA 108 | 48 378 117 309 | 22 345 22 345 | NA NA NA NA | NA NA NA NA | NA NA NA NA |
| Hoang et al             | 6 4 3 1   | NA NA NA | NA NA NA NA | NA NA NA NA | 63 237 238 70 | 203 84 258 | NA NA NA NA |
| Imboden et al           | 447 55 70 27 | NA NA 166 | 162 437 236 309 | 308 70 203 84 | 258 | 40 55 | NA NA NA NA |
| Joehlin-Price et al     | NA NA NA NA | 0 0 95 | NA NA NA NA | NA NA NA NA | 113 172 156 | NA NA NA NA | NA NA NA NA |
| Jones et al             | NA NA NA NA | 113 172 156 | NA NA NA NA | NA NA NA NA | NA NA NA NA | NA NA NA NA | NA NA NA NA |
| Kim et al               | 30 5 14 3   | NA NA NA | NA NA NA | NA NA NA | 35 16 13 31 | 9 25 25 25 | NA NA NA NA |
| Kolehmainen et al       | 440 47 97 20 | 293 155 87 | 160 444 249 355 | NA NA NA | NA NA NA NA | NA NA NA NA | NA NA NA NA |
| León-Castillo et al     | 127 105 178 0 | NA NA 113 | 255 155 223 187 | 0 0 410 410 | 0 | NA NA | NA NA NA NA |
| Li et al                | 330 51 121 27 | 96 116 295 | NA NA NA NA | NA NA NA | NA NA NA | NA NA | NA NA NA |
| López-Reig et al        | 388 37 38 4 | 321 58 63 | NA NA NA NA | NA NA NA | NA NA NA | NA NA | NA NA NA |
| McConechy et al         | 282 28 64 25 | 125 70 205 | NA NA NA NA | NA NA NA | NA NA NA | NA NA | 180 220 |
| Meng et al              | 29 6 23 12   | 0 0 102 | 25 53 25 53 | NA NA NA | NA NA NA | NA NA | NA NA NA |
| Monsur et al            | 81 22 21 3   | 70 23 16 | NA NA NA | NA NA NA | NA NA NA | NA NA | NA NA |
| Da Cruz Paula A et al   | 129 6 30 10  | 71 35 10 | NA NA NA | NA NA NA | NA NA NA | NA NA | NA NA |
| Prendergast et al       | 12 7 28 24   | 12 15 44 | NA NA NA | NA NA NA | NA NA NA | NA NA | NA NA NA |
| Author                     | FIGO stage | Grade | Myometrial invasion | Lymph node status | Clinical risk stratification | Adjuvant therapy |
|---------------------------|------------|-------|---------------------|-------------------|-------------------------------|------------------|
|                           | I  II  III IV | G1    | G2    | G3    | ≥50% | <50% | present | absent | present | absent | low | intermediate | high | Yes | No |
| Riggs et al               | 31 5 14 12 | 20 12 | 33    | NA    | NA   | NA   | NA      | NA    | NA      | NA    | NA  | NA          | NA   | NA  | NA |
| Rosa-Rosa et al           | 6 1 4 4   | NA    | NA    | NA    | NA   | NA   | NA      | NA    | NA      | NA    | NA  | NA          | NA   | NA  | NA |
| Siraj et al               | 267 66 34 | 140   | 138   | 123   | 88   | 233  | NA      | NA    | NA      | NA    | NA  | NA          | NA   | NA  | NA |
| Stasenko et al            | NA        | NA    | NA    | NA    | NA   | NA   | NA      | NA    | NA      | NA    | NA  | NA          | NA   | NA  | NA |
| Talhouk et al             | 102 39 53 | 51    | 39    | 53    | 58   | 79   | NA      | NA    | 19      | 120   | 56  | 23          | 64   | 63  | 79 |
| Talhouk et al             | 221 NA    | NA    | NA    | NA    | NA   | NA   | NA      | NA    | 195     | 190   | 95  | 49          | 173  | 147 | 163|
| Tessier-Cloutier et al    | 35 20     | NA    | NA    | NA    | NA   | NA   | NA      | NA    | NA      | NA    | NA  | NA          | NA   | NA  | NA |
| Cancer Genome Atlas Research Network et al | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Timmerman et al           | 76 18 6   | 61    | 17    | 30    | 28   | 79   | NA      | NA    | 11      | 66    | 44  | 17          | 14   | 37  | 71 |
| Wong et al                | 24 5     | 0 0   | 47    | 29    | 18   | NA   | NA      | NA    | NA      | NA    | NA  | NA          | NA   | NA  | NA |
| ZHANG et al               | 13 0 7    | NA    | NA    | NA    | NA   | NA   | NA      | NA    | NA      | NA    | NA  | NA          | NA   | NA  | NA |
| Zong et al                | 543 173 44 | NA    | NA    | 454   | 231  | 582  | 219    | 585   | 125     | 497   | NA  | NA          | NA   | NA  | NA |

Note: The details of included studies can be found in the Table S2.
Abbreviations: EC endometrial carcinoma, POLE Polymerase ε, POLEmut POLE-mutated/ultramutated, MSI microsatellite-instable/hypermutated, p53abn p53-abnormal/mutated, NA not available, EEC endometrioid endometrial carcinoma, NEEC nonendometrioid endometrial carcinoma, OS overall survival, PFS progression free survival, DSS disease specific survival, RFS relapse free survival, FIGO Federation International of Gynecology and Obstetrics, LVSI lymphovascular space invasion.
Table 3). The results revealed that the clinical outcomes of POLEmut group were the best, but those of p53abn group were the worst, while those of MSI group and p53wt group were medium.

Assessment of study quality
All the studies were highly qualified (quality assessment of 49 included articles is summarized in Table S4) with relatively satisfying results for bias risk assessment.

Discussion
Worldwide, EC is one of the most common cancers of women with survival rate not improving. TCGA research network firstly identified the molecular cohort of POLEmut EC that features a favorable prognostic potential, despite with bad clinicopathological parameters [22]. Accumulating studies were conducted on the POLEmut, but the frequency and prognostic value of POLEmut in EC patients were variable among previous researches [3, 23–25]. Therefore, this study aimed to estimate the frequency and clinicopathological characteristics of POLEmut and the overall effect on prognosis of EC patients.

Our study revealed that 7.95% (95% CI: 6.52–9.51%) of EC patients harbored POLEmut. The results exhibited that there were no significant differences in histotype (EEC vs. NEEC) of POLEmut ECs; and no significant relations were observed between POLEmut and LVSI, lymph node status, clinical risk stratification, or adjuvant therapy. However, it should be noted that histotype and LVSI are features that generally subjective with interobserver variability and may not be reproducible between series [6, 26]. The vast majority of it presented higher expression at earlier stage and less myometrial invasion, both of which were “traditional” identified as an important marker of low-risk stratification; meanwhile, the POLEmut ECs presented at the highest grade (grade 3), which were generally considered to be associated with a higher risk of recurrence and death [27].

Studies have confirmed that POLEmut ECs had better clinical outcomes with survival analysis, even those at high grade [28–30]. Paradoxically, some investigators advocated that superior survival was not found in POLEmut ECs [19, 20]. Based on our study, EC patients with POLEmut possessed better clinical survivals (including
### Table 2 The pooled frequency of POLEmut ECs according to clinicopathology characteristics

| Clinicopathological characteristics in EC | Pooled frequency of POLEmut (95% CI), (%) | No. of studies | I² (95% CI), (%) | P for I² | Model | Egger's test |
|------------------------------------------|------------------------------------------|----------------|----------------|---------|-------|-------------|
| Overall POLEmut                          | 7.95 (6.52–9.51)                         | 50             | 86.3 (82.7–89.1) | < 0.0001 | Random effect | z = 1.832, P = 0.06695 |
| EEC                                      | 7.95 (6.55–9.46)                         | 32             | 79.6 (71.8–85.2) | < 0.0001 | Random effect | z = 2.562, P = 0.0104 |
| NEEC                                     | 4.45 (2.63–6.61)                         | 30             | 56.0 (33.7–70.8) | 0.0001   | Random effect | z = 1.018, P = 0.3087 |
| Grade 1–2                                | 5.35 (4.16–6.67)                         | 23             | 57.2 (31.9–73.1) | 0.0004   | Random effect | z = 1.0836, P = 0.2785 |
| Grade 3                                  | 10.55 (8.35–12.94)                       | 27             | 66.6 (50.0–77.7) | < 0.0001 | Random effect | z = 0.50043, P = 0.6168 |
| FIGO stage I–II                          | 9.15 (7.06–11.46)                        | 29             | 80.8 (73.2–86.3) | < 0.0001 | Random effect | z = 2.7772, P = 0.005483 |
| FIGO stage II–IV                         | 3.08 (1.72–4.71)                         | 30             | 51.9 (26.9–68.3) | 0.0006   | Random effect | z = 0.66061, P = 0.5089 |
| FIGO stage III–IV                        | 2.89 (1.43–4.67)                         | 28             | 39.4 (4.6–61.6) | 0.0180   | Random effect | z = 0.25724, P = 0.797 |
| LVS1 absent                               | 6.96 (5.32–8.77)                         | 17             | 68.3 (47.6–80.8) | < 0.0001 | Random effect | z = 1.7728, P = 0.07626 |
| LVS1 present                             | 6.40 (3.82–9.48)                         | 17             | 75.1 (60.0–84.5) | < 0.0001 | Random effect | z = 0.24716, P = 0.8048 |
| Myometrial invasion ≥ 50%                | 4.78 (3.47–6.28)                         | 11             | 39.6 (0.0–70.3) | 0.0846   | Random effect | z = 0.70065, P = 0.4835 |
| Myometrial invasion < 50%                | 6.85 (5.04–8.89)                         | 11             | 65.5 (34.5–81.8) | 0.0013   | Random effect | z = 0.93704, P = 0.3487 |
| Lymph node status absent                 | 9.46 (7.77–11.28)                        | 7              | 0.0 (0.0–45.4)   | 0.7823   | Fixed effect  | z = 0.75094, P = 0.4527 |
| Lymph node status present                | 4.97 (0.55–12.07)                        | 7              | 66.0 (23.9–84.8) | 0.0072   | Random effect | z = 0.30722, P = 0.7587 |
| Risk stratification-low                  | 5.87 (3.81–8.30)                         | 5              | 0.0 (0.0–0.0)    | 0.9660   | Fixed effect  | z = 0, P = 1          |
| Risk stratification-intermediate         | 7.18 (1.07–16.78)                        | 5              | 69.4 (21.5–88.0) | 0.0110   | Random effect | z = 0, P = 1          |
| Risk stratification-high                 | 8.87 (6.07–12.09)                        | 7              | 52.1 (0.0–79.6)  | 0.0512   | Random effect | z = -0.15019, P = 0.8806 |
| With adjuvant therapy                    | 9.00 (6.78–11.46)                        | 15             | 60.5 (30.6–77.6) | 0.0012   | Random effect | z = 0.14846, P = 0.8820 |
| Without adjuvant therapy                 | 6.27 (4.11–8.75)                         | 14             | 47.0 (1.4–71.5)  | 0.0266   | Random effect | z = 0.4927, P = 0.6222 |

Abbreviations: EC Endometrial Carcinoma, POLE Polymerase ε, POLEmut POLE-Mutated/Ultramutated, EEC Endometrioid Endometrial Carcinoma, NEEC Nonendometrioid Endometrial Carcinoma, FIGO Federation International of Gynecology and Obstetrics, LVS1 Lymphovascular Space Invasion, CI Confidence Interval.

### Table 3 The pooled OR of POLEmut ECs according to clinicopathology characteristics

| Clinicopathological characteristics in EC | Pooled OR (95% CI) | P for pooled OR | No. of studies | I² (95% CI), (%) | P for I² | Model | Egger's test |
|------------------------------------------|--------------------|----------------|----------------|----------------|---------|-------|-------------|
| EEC vs. NEEC                             | 1.35 (0.88–2.08)   | 0.1719         | 22             | 49.6 (17.4–69.2) | 0.0047  | Random effects | z = 0.98693, P = 0.3237 |
| Grade 1–2 vs. 3                          | 0.51 (0.3–0.73)    | 0.0002         | 22             | 53.5 (24.6–71.3) | 0.0016  | Random effects | z = -0.14099, P = 0.8879 |
| FIGO stage I–II vs. III–IV               | 1.91 (1.29–2.83)   | 0.0013         | 28             | 41.4 (8.0–62.7)  | 0.0125  | Random effects | z = 0.19757, P = 0.8434 |
| LVS1 present vs. absent                  | 0.98 (0.77–1.25)   | 0.8644         | 17             | 15.4 (0.0–51.8)  | 0.2727  | Fixed effect  | z = -1.647, P = 0.09941 |
| Myometrial invasion ≥ 50% vs. < 50%      | 0.66 (0.50–0.86)   | 0.0025         | 10             | 0.0 (0.0–42.7)   | 0.7489  | Fixed effect  | z = -0.98387, P = 0.3252 |
| Lymph node status present vs. absent     | 1.01 (0.65–1.57)   | 0.9641         | 7              | 23.0 (0.0–65.8)  | 0.2537  | Fixed effect  | z = -1.0513, P = 0.2931 |
| Clinical risk stratification: high vs. low| 1.21 (0.73–2.01)   | 0.4678         | 5              | 0.0 (0.0–75.4)   | 0.4966  | Fixed effect  | z = 0, P = 1          |
| Adjuvant therapy: yes vs. no             | 1.16 (0.88–1.54)   | 0.2939         | 14             | 0.0 (0.0–41.7)   | 0.6918  | Fixed effect  | z = -0.27372, P = 0.7843 |

Abbreviations: EC Endometrial Carcinoma; POLE Polymerase ε; POLEmut POLE-Mutated/Ultramutated; EEC Endometrioid Endometrial Carcinoma; NEEC Nonendometrioid Endometrial Carcinoma; FIGO Federation International of Gynecology and Obstetrics; LVS1 Lymphovascular Space Invasion; OR Odds Ratio; vs. Versus.

OS, PFS, DSS, and RFS) than those with POLEwt. Additionally, according to both pooled univariable and multivariable analyses, the POLEmut cohort showed the best clinical prognosis among the four molecular subtypes, with a death risk of any cause lower than that of other three molecular subtypes, and a risk of recurrent/progressive disease lower; while the p53abn group, as expected, showed the worst prognosis. The reason why POLEmut correlates favorable outcomes in the patients remains unclear. Meng et al. [31] had speculated that this
might due to the high mutation burden and the increase in base substitution; Howitt et al. [32] showed that POL-Emut ECs were associated with high neoantigens and elevated CD8+ tumor infiltrating lymphocytes, which was counterbalanced by overexpression of program death-ligand. POLE proofreading mutations might elicit an anti-tumor response [33].

There is now an emerging link between high mutation burden in tumors and improved prognosis in cancer patients. Indeed, POLEmut tumors have been shown to feature higher immune infiltrations and programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) expression [34], which may offset the survival risk caused by higher tumor grades in ultramutated POLE and thus generate a favorable prognosis. Consequently, POLEmut in EC patients was a promising therapeutical target [35].

Talhouk et al. [4] found that half of POLEmut ECs were identified as with “high risk” based on stage, histology, and grade. It is clear that there may be both overtreatment and undertreatment of women based solely on application of the previous risk-assessment tool. In 2020, the European Society of Gynaecological Oncology (ESGO)/European Society for Radiotherapy and Oncology (ESTRO)/European Society of Pathology (ESP) published their joint guidelines for the management of EC, for the first time incorporating the TCGA findings [including groups of POLEmut, MMRd, p53abn and NSMP (surrogate of the copy number low/endometrioid group)] to assess the prognosis of EC in association with classic and distinct clinicopathologic prognostic factors (such as stage, grade, histotype, myometrial invasion or LVSI) in the risk stratification of EC [36]. However, several points remain to be clarified, as the prognostic value of the TCGA molecular group may vary among diverse histotypes of EC [37]. It has been recorded that POLEmut served as the molecular signature least affected by other prognostic clinicopathological factors [38]. Furthermore, based on our study, there was no significant difference in frequency of POLEmut between EC patients with and without adjuvant therapy. For this reason, the clinical practice that many of the patients currently undergo adjuvant treatment may constitute an overtreatment. It is reasonable to identify POLEmut status at the moment of diagnosis and to mete out less intensive treatment for EC patients with POLEmut.

It remains obscure whether the favorable clinical outcomes observed in patients with POLEmut ECs were independent of the receipt of adjuvant therapy. Furthermore, other molecular factors and clinicopathological might have an independent prognostic value in the context of the TCGA classification [38], such as the LVSI [39]. Therefore, novel initiatives stratifying ECs for clinical trials according to molecular subtype are recommended, since they will provide a key step toward precision medicine for ECs.
Table 3  The pooled HRs of OS, PFS, DSS, RFS for four molecular subtypes at univariable and multivariable analyses

| Subtype | Event | HR (95% CI) | P of HR | I^2 (95% CI) | P of I^2 | Number of studies |
|---------|-------|-------------|---------|--------------|----------|------------------|
| **OS** | POLEmut vs. p53wt | 0.69 (0.55–0.87) | 0.0016 | 0.0% (0.0–62.5%) | 0.6952 | 5 |
| MSI vs. p53wt | 1.15 (0.97–1.37) | 0.1054 | 59.9% (1.6–83.7%) | 0.0288 | 6 |
| p53mt vs p53 wt | 1.40 (1.15–1.71) | 0.0007 | 66.0% (11.3–87.0%) | 0.0192 | 5 |
| **PFS** | POLEmut vs. p53wt | 0.66 (0.42–1.04) | 0.0743 | 0.0% (0.0–76.3%) | 0.6447 | 3 |
| MSI vs. p53wt | 1.29 (0.92–1.82) | 0.1421 | 59.9% (0.0–88.6%) | 0.0828 | 3 |
| p53mt vs p53 wt | 1.81 (1.24–2.36) | 0.0023 | 79.2% (33.7–93.5%) | 0.0082 | 3 |
| **DSS** | POLEmut vs. p53wt | 0.81 (0.52–1.26) | 0.3392 | 0.0% (0.0–13.3%) | 0.9123 | 4 |
| MSI vs. p53wt | 1.04 (0.69–1.57) | 0.8534 | 74.8% (30.1–90.9%) | 0.0076 | 4 |
| p53mt vs p53 wt | 1.77 (1.51–2.09) | < 0.0001 | 16.5% (0.0–87.2%) | 0.3087 | 4 |
| **RFS** | POLEmut vs. p53wt | 0.46 (0.29–0.74) | 0.0015 | 0.00% | 0.9695 | 2 |
| MSI vs. p53wt | 0.92 (0.81–1.06) | 0.2449 | 0.0% (0.0–86.9%) | 0.4521 | 3 |
| p53mt vs p53 wt | 1.47 (1.14–1.89) | 0.0030 | 50.9% (0.0–85.8%) | 0.1306 | 3 |

**Abbreviations:** POLEmut: POLE-Mutated/Ultramutated; MSI: Microsatellite-Instable/Hypermutated; p53abn: p53 Abnormal/Mutated; p53wt: p53 Wild-Type; OS: Overall Survival; PFS: Progression Free Survival; DSS: Disease Specific Survival; RFS: Relapse Free Survival; CI: Confidence Interval; HR: Hazard Ratio
Limitations
This study came across three drawbacks: firstly, there were only 8 prospective studies despite containing 49 articles involving 12,120 patients, for analyzing the clinicopathological characteristics of POLEmut ECs and prognostic value of POLE status; secondly, bias might exist to some extent for excluding relevant studies published in non-English language; the last was that the heterogeneity of included studies was high to some degree.

Conclusions
The POLEmut emerged higher expression in ECs with grade 3, FIGO stage I-II, and myometrial invasion<50%; it might serve as a highly favorable prognostic marker in EC; the clinical outcomes of POLEmut group were the best one among the four molecular subtypes.

Abbreviations
EC: Endometrial Carcinoma; POLE: Polymerase ε; POLEmut: POLE-Mutated/Ultramutated; MSI: Microsatellite-Instable/Hypermutated; p53abn: p53-Abnormal; p53wt: p53-Wild-Type; ICIs: Immune Checkpoint Inhibitor; NA: Not Available; EEC: Endometrioid Endometrial Carcinoma; NEEC: Nonendometrioid Endometrial Carcinoma; OS: Overall Survival; DFS: Disease Specific Survival; RFS: Relapse Free Survival; FIGO: Federation International of Gynecology and Obstetrics; ProMisE: Proactive Molecular Risk Classifier for Endometrial Cancer; LVSI: Lymphovascular Space Invasion; CI: Confidence Interval; HR: Hazard Ratio; OR: Odd Ratio; NOS: Newcastle-Ottawa Scale; ESGO: Gynaecological Oncology; ESTRO: European Society for Radiotherapy and Oncology; ESP: European Society of Pathology.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12885-022-10267-2.

Additional file 1: Table S1. PRISMA
Additional file 2: Table S2. The list of the included studies.
Additional file 3: Figure S1. Forest plot for the pooled frequency of (a) microsatellite-instable/MSI/Hypermutated and (b) p53-abnormal/mutated (p53abn) in endometrial carcinoma (EC); funnel plot for the pooled frequency of (c) MSI and (d) p53abn in EC.
Additional file 4: Table S3. The proportion of MSI and p53abn molecular subtypes in ECs.
Additional file 5: Figure S2. Funnel plot of (a) overall survival (OS), (b) progression-free survival (PFS), (c) disease specific survival (DSS), and (d) relapse free survival (RFS) for POLEmut compared with POLEwt EC patients.
Additional file 6: Table S4. The Newcastle-Ottawa scale for quality assessment of the studies.

Acknowledgments
None.

Code availability
Not applicable.

Registration and protocol
The review was not registered and the protocol was not prepared.

Authors’ contributions
Qing Wu: Conceptualization, Methodology, Software, Data curation, Formal analysis, Writing-Original Draft; Nianhai Zhang: Visualization, Investigation. Xianhe Xie: Conceptualization, Validation, Writing- Review & Editing. The author(s) read and approved the final manuscript.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors have no conflicts of interest to declare that are relevant to the content of this article.

Author details
1Department of Oncology, Molecular Oncology Research Institute, The First Affiliated Hospital, Fujian Medical University, Chazhong Road No, 20, Fujian 350005 Fuzhou, China. 2Department of Oncology, National Regional Medical Center, Binhai Campus of the First Affiliated Hospital, Fujian Medical University, Fuzhou 350212, China. 3Fujian Key Laboratory of Precision Medicine for Cancer, The First Affiliated Hospital, Fujian Medical University, Fuzhou 350005, China.

Received: 8 August 2022 Accepted: 2 November 2022
Published online: 10 November 2022

References
1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA Cancer J Clin. 2021;71(1):7–33. https://doi.org/10.3322/caac.21654.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424. https://doi.org/10.3322/caac.21492.
3. He D, Wang H, Dong Y, Zhang Y, Zhao J, Lv C, et al. POLE mutation combined with microcytotic, elongated and fragmented (MEFL) pattern invasion in endometrial carcinomas might be associated with poor survival in Chinese women. Gynecol Oncol. 2020;159(1):36–42. https://doi.org/10.1016/j.ygyno.2020.07.102.
4. Talhouk A, McConkey MK, Leung S, Li-Chang HH, Kwon JS, Melnyk N, et al. A clinically applicable molecular-based classification for endometrial cancers. Br J Cancer. 2015;113(2):299–310. https://doi.org/10.1038/bjc.2015.190.
5. Murali R, Soslow RA, Wiegelt B. Classification of endometrial carcinoma: more than two types. Lancet Oncol. 2014;15(7):e268–78. https://doi.org/10.1016/S1470-2045(13)70591-6.
6. Gills CB, Oliva E, Soslow RA. Poor interobserver reproducibility in the diagnosis of high-grade endometrial carcinoma. Am J Surg Pathol. 2013;37(6):874–81. https://doi.org/10.1097/PAS.0b013e318275776a.
7. Han G, Sidhu D, Duggan MA, Arsineau J, Cesari M, Clement PB, et al. Reproductive history of histological cell type in high-grade endometrial carcinoma. Mod Pathol. 2013;26(12):1594–604. https://doi.org/10.1038/modpathol.2013.102.
8. Cancer Genome Atlas Research Network, Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497(7447):67–73. https://doi.org/10.1038/nature12113.
