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Microsatellite instability as a marker of prognosis: a systematic review and meta-analysis of endometrioid endometrial cancer survival data

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Abstract

Introduction To investigate whether microsatellite instability (MSI) is an important prognostic biomarker for endometrioid endometrial cancer (EEC).

Methods The PubMed, EMBASE, and the Cochrane Cooperative Library databases were searched from inception to July 2021. Overall survival, disease-free survival, progression-free survival, EEC-specific survival, recurrence-free survival, and the recurrence rate were pooled to analyze the correlation between MSI and EEC. In addition, Egger's regression analysis and Begg's test were used to detect publication bias.

Results 17 studies met the inclusion criteria and were included in our meta-analysis with a sample size of 4723, and the included patients with endometrioid cancer (EC) all were EEC. The pooled hazard ratios (HR) in patients with EEC showed that MSI was significantly associated with shorter overall survival [HR = 1.37, 95% confidence interval (CI) (1.00–1.86), $p = 0.048$, $I^2 = 60.6\%$], shorter disease-free survival [HR = 1.99, 95% CI (1.31–3.01), $p = 0.000$, $I^2 = 67.2\%$], shorter EEC-specific survival [HR = 2.07, 95% CI (1.35–3.18), $p = 0.001$, $I^2 = 31.6\%$] and a higher recurrence rate [Odds ratios (OR) = 2.72, 95% CI (1.56–4.76), $p = 0.000$, $I^2 = 0.0\%$]. In the early-stage EEC subgroup, MSI was significantly associated with shorter overall survival [HR = 1.47, 95% CI (1.11–1.95), $p = 0.07$], shorter disease-free survival [HR = 4.17, 95% CI (2.37–7.41), $p = 0.000$], and shorter progression-free survival [HR = 2.41, 95% CI (1.05–5.54), $p = 0.039$]. No significant heterogeneity was observed in overall survival ($I^2 = 20.9\%$), disease-free survival ($I^2 = 0.0\%$), or progression-free survival ($I^2 = 0.0\%$) in patients with early-stage EEC. Meanwhile, publication bias was not observed, and the p-value for Egger's test of overall survival, disease-free survival, and EEC-specific survival were $p = 0.131$, $p = 0.068$, and $p = 0.987$, respectively.

Conclusion MSI is likely an important biomarker for poor prognosis in patients with EEC, and this correlation is even more certain in patients with early-stage EEC.

Keywords Endometrioid endometrial cancer · Early-stage endometrioid endometrial cancer · Microsatellite instability · Prognosis · Meta-analysis

Introduction

Endometrial cancer (EC) is one of the most common cancers of the female reproductive tract. Its incidence and mortality are increasing annually, and an increasing number of patients present with cancer progression and recurrence [1, 2].

EC is classified into two types, type I and type II, based on histological and clinicopathological features. Type I EC, known as endometrioid endometrial cancer (EEC), accounts for the majority of EC cases (approximately 70–80%) [3]. Therefore, an increasing number of studies are focusing on the treatment and prognostic assessment of EEC, and the key to the prognostic assessment is the ability to identify a prognostic biomarker.

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Microsatellite instability (MSI) is present in approximately 20–40% of patients with sporadic EEC [4, 5], so that many studies focused on correlation between MSI and prognosis in patients with EEC [6–11].

However, the studies on the correlation between MSI and EEC prognosis are currently divided, with some studies concluding that MSI has no significant correlation with the prognosis of EEC, some studies concluding that MSI is a biomarker for a good prognosis of EEC, and other studies concluding that MSI is a biomarker for a poor prognosis of EEC. However, a uniform conclusion has not been established and no relevant meta-analysis has been reported.

We conducted this systematic review and meta-analysis to clarify the correlation between MSI and the prognosis of EEC.

Methods

Data sources and search strategy

This meta-analysis was rigorously evaluated using the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) guidelines [12]. PubMed, EMBASE, and the Cochrane Collaboration Library databases were searched from inception to July 2021, and the language was restricted to English.

We adjusted the MeSH terms combined with related text words to comply with the relevant rules for searching for relevant studies in each database. Our search strategy was as follows: (Endometrial Neoplasm or Endometrial Neoplasms or Endometrial Carcinoma or Endometrial Carcinomas or Endometrial Cancer or Endometrial Cancers or Endometrium Cancer or Cancer of the Endometrium or Carcinoma of Endometrium or Endometrium Carcinoma or Endometrium Carcinomas or Cancer of Endometrium or Endometrium Cancers) AND (Mismatch repair or Microsatellite instability or Replication Error Phenotype or Replication Error Phenotypes) AND survival.

Study selection

Two independent researchers (Jing-ping Xiao and Yun-zi Wang) filtered all the titles and abstracts of the retrieved studies to identify potentially relevant studies. The full texts of the retrieved studies that met the inclusion criteria were evaluated. Each of these discrepancies was resolved through discussion, and if conflicts remained, a third reviewer (Ji-sheng Wang) was involved.

Inclusion and exclusion criteria

Studies describing the correlation between MSI and the prognosis of EEC were included if they met the following criteria: (1) patients with EEC or early-stage EEC (stage I-II); (2) reported overall survival, disease-free survival, progression-free survival, EEC-specific survival, or recurrence-free survival associated with MSI or mismatch repair deficiency; (3) directly reported HR or OR with 95% CI or generated Kaplan–Meier survival curves that could be used to extract HR.

Editorials, meeting reports, and letters to the editors were all excluded.

Data extraction

Two researchers (Jing-ping Xiao and Yun-zi Wang) independently screened studies based on the inclusion criteria, and any differences were resolved by consensus. From each study, we extracted the study characteristics, baseline characteristics, and pre-established outcomes for overall survival, disease-free survival, progression-free survival, EEC-specific survival, or recurrence-free survival.

Definition of MSI

MSI was defined as a lack of expression of at least 1 of the mismatch repair proteins (MLH1, MSH2, PMS2, and MSH6) detected using immunohistochemistry [11, 13, 14]; alternatively, microsatellite markers were identified by DNA isolation and molecular analysis, and tumors were considered to present MSI when they showed alterations in at least 2 of the 3–6 markers or in at least 1 of the 2 markers [7, 15–19].

Quality assessment

Two researchers (Jing-ping Xiao and Yun-zi Wang) separately applied the Newcastle–Ottawa Statement [20] to evaluate the quality of eligible studies, including selection, comparability, and exposure. Nine points were included in the scale, and a score greater than or equal to 7 was considered a high-quality study. A score of 4–6 was considered a good-quality study, a score of 3 or less was considered a low-quality study, and discrepancies were resolved through discussion, with the involvement of a third reviewer (Ji-sheng Wang) if a conflict remained.

Data synthesis and analysis

Stata (version 14) software was used to analyze all results. The HRs were extracted and calculated from Kaplan–Meier survival curves if HRs were not directly reported in the study. An I^2-value greater than or equal to 50% indicated significant heterogeneity, and then the HR were merged with the corresponding 95% CI using a random-effects model; otherwise, the fixed-effects model was used. Publication bias was statistically assessed using Egger's regression test and Begg's test, where a p-value < 0.05 was considered to indicate significant publication bias.

Results

Literature search

Figure 1 illustrates the flow chart for the selection of eligible studies. 720 studies were identified by searching PubMed, Cochrane, and EMBASE databases. 469 studies remained after removing duplicate files. After scanning the titles and abstracts, 50 studies were selected for full-text review. Finally, we included 17 studies that met the inclusion criteria for our meta-analysis [7, 8, 11, 13–19, 21–27].

Study characteristics

Table 1 shows the characteristics of the 17 studies included. Of these studies, 7 studies were conducted in Europe (Spain, Italy, Norway, and the European region) [8, 11, 13, 15, 21, 22, 24], and 9 studies were conducted in the Americas (United States, Canada, and North American region) [7, 14, 16–19, 23, 24, 27]. 1 study was conducted in Asia (Korea) [25], and 1 study was conducted in Oceania (Australia) [26]. 15 studies were retrospective cohort studies [8, 11, 13–19, 21, 23–27], and 2 studies were clinical trials [7, 22]. 8 studies assessed MSI using quasimonomorphic mononucleotide markers [7, 8, 15–19, 21], and 9 studies assessed MSI using immunohistochemistry [11, 13, 14, 22–27].

As shown in Table 2, all studies scored 7 or higher and were high-quality studies.

Correlation between MSI and overall survival in the EEC or early-stage EEC

The pooled HR for patients with EEC showed that MSI was significantly associated with shorter overall survival [HR = 1.37, 95% CI (1.00–1.86), $p = 0.048$]. Meanwhile, significant heterogeneity was observed ($I^2 = 60.6\%$), as shown in Fig. 2a.

In the subgroup analysis of patients with early-stage EEC, patients with MSI had a shorter overall survival [HR = 1.47, 95% CI (1.11–1.95), $p = 0.07$], and no heterogeneity was observed ($I^2 = 20.9\%$), as shown in Fig. 3a.

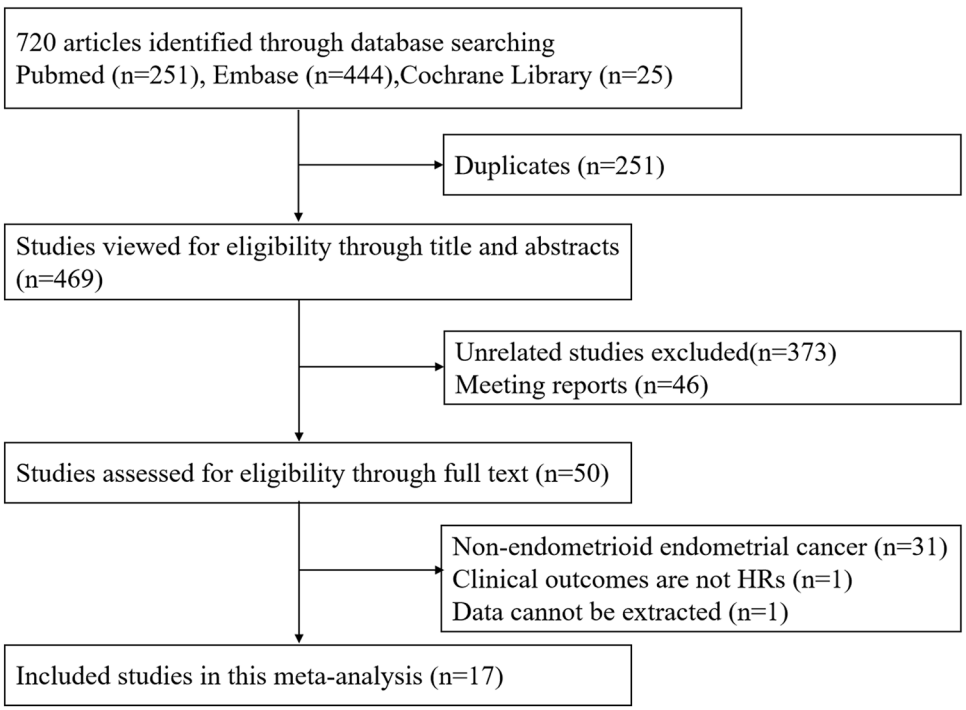

Fig. 1 The flow diagram of studies included in this meta-analysis

Table 1 Characteristics of studies included in the meta-analysis

Author	Year	Country or region	Number of patients	MSI, *n*	MSS, *n*	Stage distribution	Histology	Microsatellite markers	Microsatellte instability definition	Outcome assessment	Study design	Follow-up time
Fiumicino et al.	2001	Italy	65	11	54	I–II	EEC	D2S123, D2S119, D9S171, D9S157, D10S216, BAT26	≥2 of 6 markers with mutant alleles	DFS	Retrospective cohort study	76 ms (12 ms–139 ms)
Maxwell et al.	2001	United States	131	29	102	I–IV	EEC	BAT26, D14S65, D14S197	≥2 of 3 markers with mutant alleles	OS	Retrospective cohort study	75.6 ms (least 3 years)
Zighelboim et al.	2007	United States	446	147	299	I–IV	EEC	BAT26, BAT25, D2S123, D5S346, D17S250	≥2 of 5 markers with mutant alleles	OS/DFS	Retrospective cohort study	54.8 ms (0.7 ms–176 ms)
Bilbao et al.	2010	United States	93	20	73	I–III	EEC	BAT26, BAT25, NR–21, NR–24, NR-27	≥2 of 5 markers with mutant alleles	DFS	Retrospective cohort study	138 ms (16–232 ms)
Bilbao et al. (early-stage)	2010	United States	79	14	65	I–II	EEC	BAT26, BAT25, NR-21, NR-24, NR-27	≥2 of 5 markers with mutant alleles	DFS	Retrospective cohort study	138 ms (16–232 ms)
Mackey et al.	2010	Canada	84	23	61	I–II	EEC	BAT26, BAT25	≥1 of 2 markers with mutant alleles	DFS	Clinical trials	NR
Steinbakk et al.	2011	Norway	171	27	144	I	EEC	BAT26, BAT25, NR-21, NR-24, NR-27	≥2 of 5 markers withmutant alleles	OS	Retrospective cohort study	1–209 ms
Nout et al.	2012	Italy	64	22	42	I	EEC	MLH1, MSH2, MSH6, PMS2	≥1 of 4 MMR protein was lost	DFS	Retrospective cohort study	88 ms (4–106 ms)
Ruiz et al.	2014	Spain	163	50	113	I–II	EEC	MLH1, MSH2, MSH6, PMS2	≥1 of 4 MMR protein was lost	OS/DFS	Clinical trials	NR
Bilbao-Sieyro et al.	2014	Spain	155	32	123	I–III	EEC	BAT26, BAT25, NR21, NR24, NR27	≥2 of 5 markers with mutant alleles	DFS/ESS	Retrospective cohort study	112 ms (6–227 ms)
Zighelboim et al.	2015	United States	475	368	107	I–IV	EEC	BAT26, BAT25, D2S123, D5S346, D17S250	≥2 of 5 markers with mutant alleles	OS/DFS	Retrospective cohort study	79 ms (0.2 ms–122.5 ms)

Table 1 (continued)

Author	Year	Country or region	Number of patients	MSI, *n*	MSS, *n*	Stage distribution	Histology	Microsatellite markers	Microsatellte instability definition	Outcome assessment	Study design	Follow-up time
McMeekin et al.	2016	United States	1024	639	385	I–IV	EEC	MLH1, MSH2, MSH6, PMS2	≥1 of 4 MMR protein was lost	PFS	Retrospective cohort study	NR
Kim et al.	2018	Korea	151	34	117	I–II	EEC	MLH1, MSH2, MSH6, PMS2	≥1 of 4 MMR protein was lost	OS/PFS	Retrospective cohort study	27 ms (1–123 ms)
Nagle et al.	2018	Australia	581	458	123	I–IV	EEC	MLH1, MSH2, MSH6, PMS2	≥1 of 4 MMR protein was lost	OS/ESS	Retrospective cohort study	36–102 ms
Bosse et al.	2018	Europe and North America	249	136	113	I–IV	EEC	MLH1, MSH2, MSH6, PMS2	≥1 of 4 MMR protein was lost	OS/RFS/Recurrence	Retrospective cohort study	73.2 ms (2.4–204 ms)
Backes et al.	2018	United States	197	64	133	I–II	EEC	MLH1, MSH2, MSH6, PMS2	≥1 of 4 MMR protein was lost	RFS/Recurrence	Retrospective cohort study	54 ms (0–120 ms)
Ruz-Caracuel et al.	2019	Spain	199	31	168	I–II	EEC	MLH1, MSH2, MSH6, PMS2	≥1 of 4 MMR protein was lost	OS/DFS	Retrospective cohort study	83.96 ms (0–174 ms)
Kim et al.	2020	Canada	475	131	344	IA	EEC	MLH1, MSH2, MSH6, PMS2	≥1 of 4 MMR protein was lost	OS/PFS	Retrospective cohort study	23.4 ms (14–39 ms)

EEC endometrioid endometrial cancers, *MMR* mismatch repair, *OS* overall survival, *PFS* progression-free survival, *DFS* disease-free survival, *ESS* EEC-specific survival, *ms* months, *NR* not reported

Table 2 Methodological quality of cohort studies included in the meta-analysis

Authors	Year	Representativeness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Control for important factor or additional factor	Outcome assessment	Follow up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total quality scores
Fiumicino et al.	2001	+*	+	+	+	+	+	+	+	8
Maxwell et al.	2001	+	+	+	+	++	+	+	+	9
Zighelboim et al.	2007	+	+	+	+	++	+	+	+	9
Bilbao et al.	2010	+	+	+	+	++	+	−**	+	8
Mackey et al.	2010	+	+	+	+	++	+	−	−	7
Steinbakk et al.	2011	+	+	+	+	−	+	+	+	7
Nout et al.	2012	−	−	+	+	++	+	+	+	7
Ruiz et al.	2014	+	+	+	+	++	+	−	+	8
Bilbao-Sieyro et al.	2014	−	−	+	+	++	+	+	+	7
Zighelboim et al.	2015	+	+	+	+	+	+	−	−	6
McMeekin et al.	2016	−	−	+	+	++	+	+	+	7
Kim et al.	2018	+	+	+	+	++	+	+	+	9
Nagle et al.	2018	+	+	+	+	++	+	+	+	9
Bosse et al.	2018	+	+	+	+	++	+	+	+	9
Backes et al.	2018	+	+	+	+	++	+	+	+	9
Ruz-Caracuel et al.	2019	+	+	+	+	++	+	+	+	9
Kim et al.	2020	+	+	+	+	+	+	−	+	7

*If there is a positive symbol that means score one point

**A negative symbol means no point

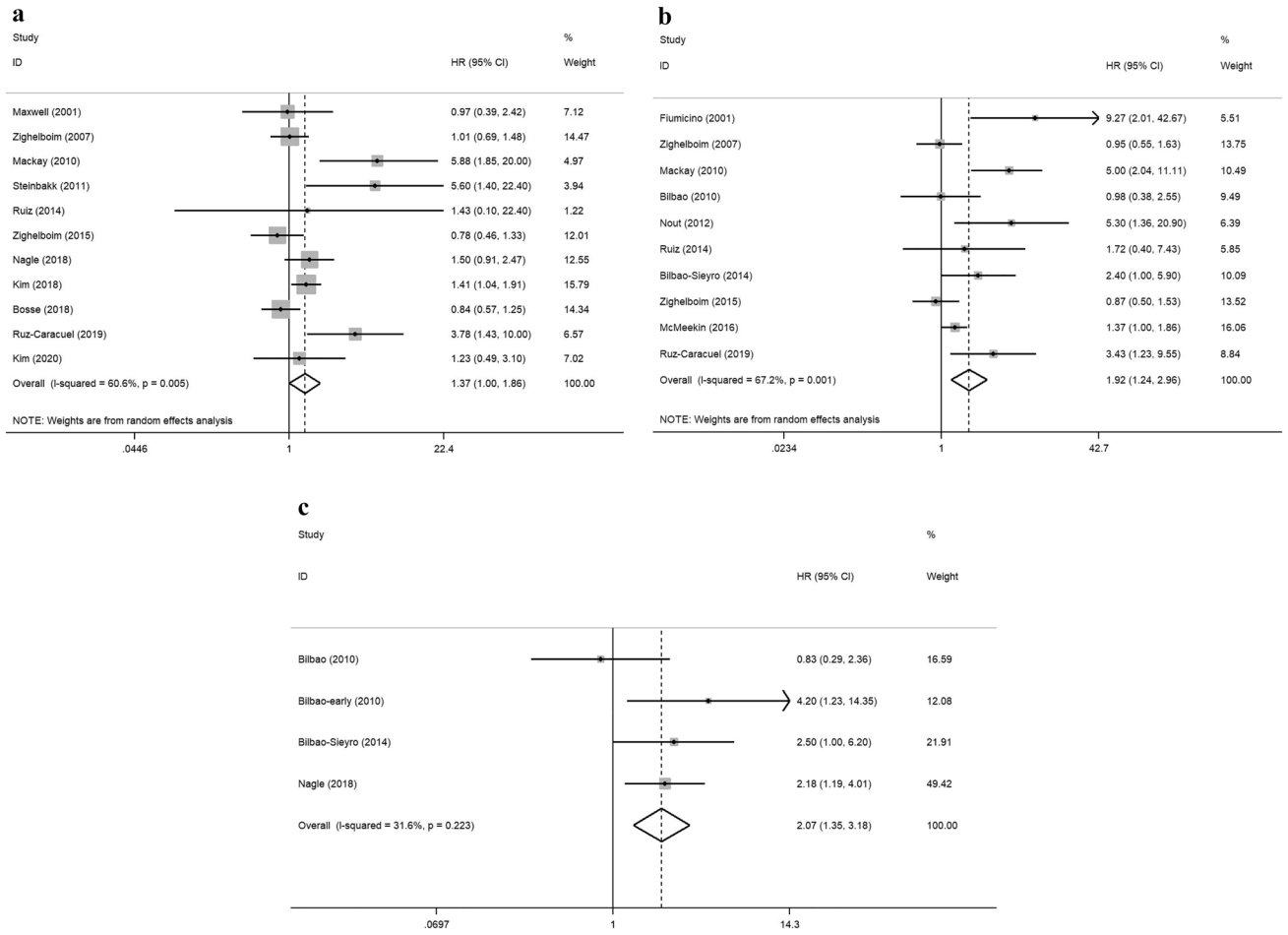

Fig. 2 Forest plot of HR for the correlation between MSI and the prognosis of EEC. the overall survival (**a**), the disease-free survival (**b**), and the EEC-special survival (**c**)

Correlation between MSI and disease-free survival in the EEC or early-stage EEC

The pooled HR for patients with EEC showed that MSI was associated with shorter disease-free survival [HR = 1.99, 95% CI (1.31–3.01), $p = 0.000$]. Meanwhile, heterogeneity was observed ($I^2 = 65.7\%$, $p = 0.001$), as shown in Fig. 2b.

In the subgroup analysis of early-stage EEC, patients with MSI had a shorter disease-free survival [HR = 4.17, 95% CI (2.37–7.41), $p = 0.000$], and no heterogeneity was identified ($I^2 = 0.0\%$), as shown in Fig. 3b.

Correlation between MSI and EEC-specific survival in patients with EEC

As shown in Fig. 2c, the pooled HR for patients with EEC showed a significant association between MSI with shorter EEC-specific survival [HR = 2.07, 95% CI (1.35–3.18), $p = 0.001$]. Meanwhile, no significant heterogeneity was observed ($I^2 = 31.6\%$).

Correlation between MSI and progression-free survival in patients with early-stage EEC

As shown in Fig. 3c, the pooled HR for the early-stage EEC subgroup showed that MSI was significantly associated with shorter progression-free survival [HR = 2.41, 95% CI (1.05–5.54), $p = 0.039$]. Meanwhile, no heterogeneity was detected ($I^2 = 0.0\%$).

Correlation between MSI and recurrence-free survival in patients with EEC

The pooled HR for patients with EEC showed that MSI was not significantly associated with shorter recurrence-free survival [HR = 1.35, 95% CI (0.27–6.60), $p = 0.714$]. Meanwhile, significant heterogeneity was observed ($I^2 = 92.7\%$) (Supplemental Fig. 1).

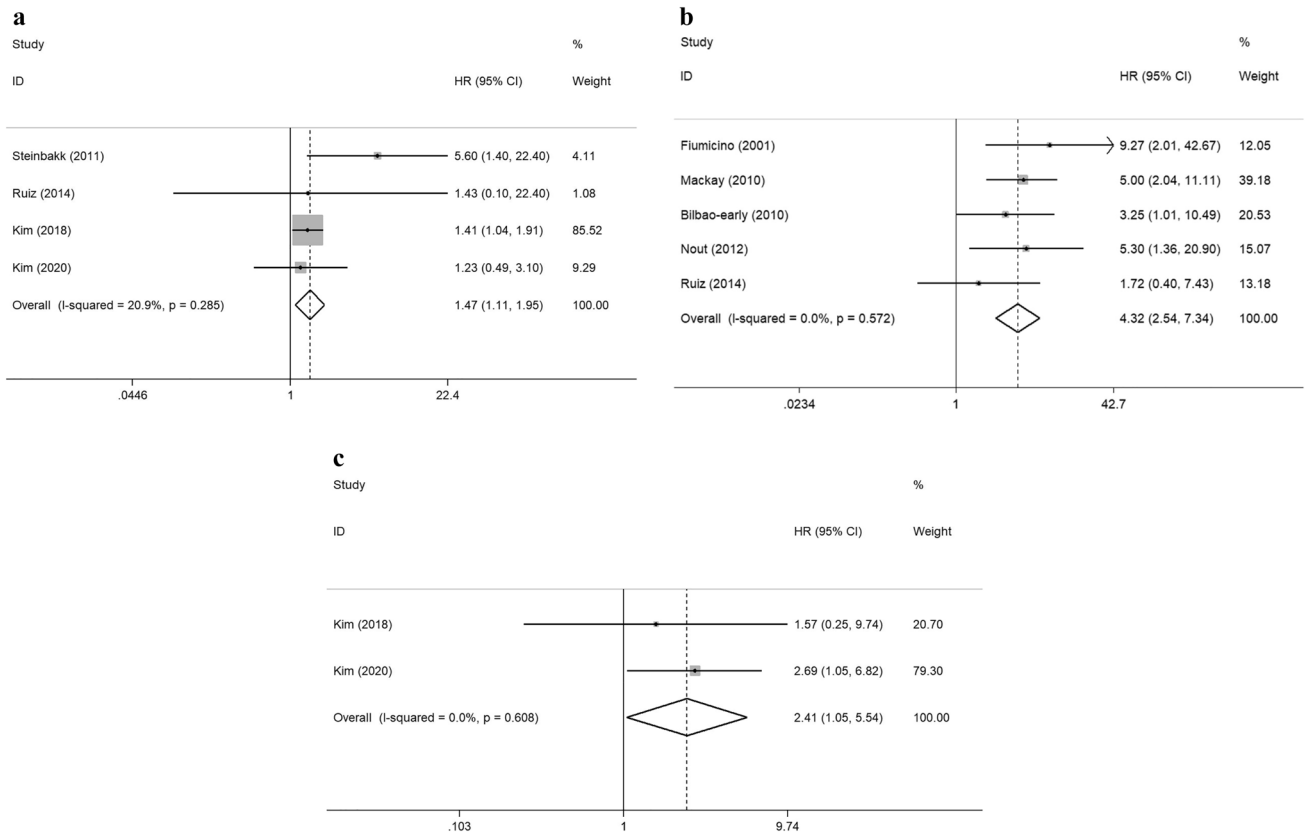

Fig. 3 Forest plot of HR for the correlation between MSI and the prognosis of early-stage EEC (stage I-II). the overall survival (**a**), the disease-free survival (**b**), and the EEC-special survival (**c**)

Correlation between MSI and recurrence rate in patients with EEC

The pooled OR for EEC showed that MSI was significantly associated with a higher recurrence rate [OR = 2.72, 95% CI (1.56–4.76), $p = 0.000$]. Heterogeneity in the recurrence rate was not observed ($I^2 = 0.0\%$) (Supplemental Fig. 2).

Publication bias

No significant publication bias was detected in the funnel plot (Supplemental Fig. 3). Additionally, significant publication bias was not observed, and the *p*-values of Egger's test for overall survival, disease-free survival, and EEC-specific survival were significant ($p = 0.131$, $p = 0.068$, and $p = 0.987$, respectively).

Sensitivity analysis

We omitted each study individually from the pooled analysis to explore the sensitivity of the pooled HR for overall survival, disease-free survival, and progression-free survival in EEC. The exclusion of any study did not have a significant effect on the results (Supplemental Fig. 4).

Discussion

Classical parameters associated with a high risk of EC recurrence include FIGO stage, age, histological tumor type and grade, depth of myometrial infiltration, and presence of lymphovascular infiltration, however they do not accurately predict the prognosis of EC [28].

Therefore, The Cancer Genome Atlas (TCGA) classified EC into 4 types [29], POLE mutant, MSI, low-copy, and high-copy types, according to their molecular characteristics to better identify patients at high risk of recurrence and to allow appropriate treatment or follow-up of patients and to avoid overtreatment of patients with good prognosis.

MSI, as one of the TCGA strains of endometrial cancer, is mostly found in EEC, and its correlation with EEC prognosis has been a recent research hotspot. It has been hypothesized that MSI can lead to altered immune surveillance in endometrial cancer as well as lead to altered host

cell-cancer cell interactions, which may determine the prognosis of EEC patients with MSI [30], and it has also been found that EEC patients with MSI have higher tumor grade and are more prone to retroperitoneal lymph node recurrence [31]. Although some studies [9] showed that there was no significant correlation between MSI and the prognosis of EEC patients. However, our combined analysis of studies related to MSI and EEC patients found that there was indeed a strong association between MSI and EEC.

In our meta-analysis, Patients with MSI had a significantly poorer prognosis in terms of overall survival, disease-free survival, EEC-specific survival, and the recurrence rate. However, there was significant heterogeneity in the pooled data for overall survival and disease-free survival. And we performed sensitivity analyses and did not detect studies that caused heterogeneity.

Due to patients with early-stage EEC rarely receive adjuvant therapy, we performed a subgroup analysis of the prognostic value of MSI in patients with early-stage EEC. The pooled analysis showed that Patients with MSI had a significantly poor prognosis in terms of overall survival, disease-free survival, and progression-free survival, and the heterogeneity disappeared in all pooled data.

In addition, in our meta-analysis, there was no significant correlation was observed between MSI and recurrence-free survival. The pooled analysis showed that MSI was associated with better recurrence-free survival in the study by Bosse et al. [24]. We found that EEC was FIGO grade 3 only in this study, the most patients received adjuvant therapy. In contrast, in the study by Backes et al. [27], MSI was associated with a significantly worse recurrence-free survival, in which EEC was FIGO grade1-3, and patients receive adjuvant at a much lower rate. Therefore, We assume that more adjuvant therapy is an important influencing factor on the prognostic value of MSI.

To more accurately predict the prognosis of EC patients, currently, the ESTRO/ESGO/ESP guidelines recommend a risk stratification system using a combination of TCGA molecular typing and classical clinicopathological factors for the management of EC patient [32]. And the accuracy of prediction would be enhanced if the TCGA molecular typing and classical clinicopathological factors were independent from each other.

There were some studies had demonstrated that, in EC patients, some classical clinicopathological factors, such as LVSI, have prognostic value independent of TCGA markers, age, and adjuvant treatment [33, 34]. And the effect of deep myometrial invasion (DMI) on the risk of recurrence is independent from the TCGA group [35]. The additional study suggested that, in EC patients, some TCGA molecular typings, such as MSI, may predict independently lower disease-specific survival [36]. And our findings also suggest that MSI may be an independent prognostic factor for EEC. Of course, as previously discussed, more studies to confirm whether other TCGA molecular typing and classical clinicopathological factors are independent of each other are necessary.

Our study has some limitations. First, some data were extracted from survival curves, which may produce some bias compared with the real data. Second, the number of studies on recurrence-free survival was small, and more studies are needed to support our conclusions. Third, the vast majority of studies we included were retrospective case studies, which carries the risk of selective reporting. However, the heterogeneity of the combined data for our meta-analysis was not significant generally, and no significant publication bias was detected in the included studies, so our general results were reliable.

Conclusion

In summary, MSI has a significant prognostic value in EEC, and this prognostic value is more definite in patients with early-stage EEC.

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Author contributions JPX and YZW designed the study and wrote the manuscript. YYZ and JD developed the search strategy and completed the literature search. JSW developed the inclusion and exclusion criteria for the eligible studies. JPX, YZW, and JSW reviewed the eligible studies and extracted the data. JPX and YYZ did the methodological judgement. YYZ and JD performed the statistical analysis methods. JPX, YZW, and JD summarized the original data. Contributions to the interpretation of the data and review of the manuscript were made by all authors.

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Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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