Microsatellite instability leads to poor prognosis in patients with early-stage endometrial cancer? a meta-analysis

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Abstract

Background

Poor prognosis of early-stage endometrial cancer (EC) is often accompanied by microsatellite instability (MSI). We hypothesized that MSI is an independent marker for poor prognosis of early-stage EC. To demonstrate this hypothesis, we evaluated the correlation between MSI and early-stage EC prognosis by meta-analysis.

Methods

Databases such as PubMed, EMBASE and the Cochrane Cooperative Library were searched from inception to October 2020, respectively. The disease-free survival (DFS), the overall survival (OS), and the progression-free survival (PFS) were pooled to analyze the correlation between MSI and prognosis in patients with early-stage EC. Besides, Egger's regression and Begg's test were used to detect Publication bias.

Results

There were 7 studies met the inclusion criteria and were enrolled in our meta-analysis with a sample size of 1150, and the included patients with early-stage EC were all endometrioid endometrial cancer (EEC). The pooled hazard ratios (HRs) in early-stage EC shows that MSI is significantly associated with lower DFS [HR = 3.90, 95%CI (2.81–6.99), $p = 0.000$], OS [HR = 1.48, 95%CI (1.12–1.96), $p = 0.006$], and PFS [HR = 2.41, 95%CI (1.05–5.52), $p = 0.038$]. There was no significant heterogeneity in the studies pooled analysis of DFS, OS, and PFS. There was also no statistical publication bias, the *P*-value of Egger`s test of OS and DFS is $p = 0.535$ and $p = 0.639$ respectively.

Conclusion

MSI is most likely an independent marker of poor prognosis in early-stage EC, and this correlation is even more significant in patients with EEC.

Background

Endometrial cancer (EC) is one of the most common cancers in the female reproductive tract, and the increase of incidence and mortality has an up-trend year by year [1, 2]. Assessment of prognosis is of great significance in the clinical management of EC, and prognostic assessment is key to identifying prognostic markers.[3, 4].

Mismatch repair (MMR) contains four proteins: MLH1, MSH2, MSH6 and PMS2. When one or more of these proteins are not expressed, it is called mismatch repair deficiency (MMRd). Due to MMRd, errors produced by DNA replication cannot be repaired in time, known as microsatellite instability (MSI) [5]. MSI is the most sensitive and specific marker of MMRd, and MMRd can be inferred by examining MSI [6, 7].

MSI accounts for 20–40% of patients with sporadic EC and has been associated with endometrioid histology [8, 9]. MSI is considered to be an important prognostic marker in the EC. Therefore, an increasing number of studies have focused on the correlation between MSI and prognosis of EC.

Some studies have shown MSI to be associated with better prognosis in EC [10, 11], some studies have shown the opposite [12–14], and others have shown no correlation with prognosis, including a meta-analysis [15–17]. The same contradiction also exists in studies with early-stage EC [18, 19]. Since patients with early-stage EC usually do not require adjuvant therapy after surgery, MSI is more strongly correlated with prognosis. However, none of the relevant meta-analyses have been reported.

To clarify the correlation between MSI and prognosis of EC, we performed a meta-analysis that included the disease-free survival (DFS), the overall survival (OS), and the progression-free survival (PFS) of early-stage EC.

Methods

Data sources and search strategy

This meta-analysis was rigorously evaluated by the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) guideline [20]. Database as PubMed, EMBASE, and the Cochrane Collaboration Library was searched from inception to October 2020, the language restriction was English.

We adjusted the MeSH terms combined with related text words to comply with the relevant rules for searching our interesting studies in each database. Our search strategy was that: (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 potential studies. The retrieved studies that met the inclusion criteria were evaluated in full text. Each of these discrepancies was resolved through discussion, and if conflicts remained, a third reviewer (Ji-sheng Wang) was involved.

Inclusion criteria

Studies containing the correlation between MSI or MMRd and prognosis of EC were included if they met the following criteria. (1) The stage of EC was early (stage I-II); (2) Reported DFS, OS, or PFS associated with MSI or MMRd; (3) Studies directly reported hazard ratios (HRs) with 95% confidence intervals (CIs) or have a Kaplan-Meier survival curves that can be used to extract HRs.

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

Data extraction

Two researchers independently screened articles following inclusion criteria, and any differences were resolved by consensus. From each study, we extracted study characteristics, baseline characteristics, and pre-established outcomes for DFS, OS, and PFS.

Quality Assessment

Two researchers (Jing-ping Xiao and Yun-zi Wang) separately applied the Newcastle-Ottawa Statement 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 to be a high-quality study. A score of 4-6 was considered a good quality study and a score of 3 or less was considered a low-quality study [21], and discrepancies were resolved through discussion, with the involvement of a third reviewer (Ji-sheng Wang) if a conflict remained.

Data synthesis and analysis

A Stata (version 14) software was used to analyze all results. The hazard ratios (HRs) would be extracted and calculated by the Kaplan-Meier survival curves if there was not a directly available HRs in the study. If an I^2 greater than or equal to 50% indicated significant heterogeneity, the HRs were merged with the corresponding 95% CIs using a random-effects model; otherwise, the fixed-effects model was used. Publication bias was statistically assessed by Egger's regression and Begg's test, where a p-value < 0.05 was considered to be a significant publication bias.

Results

Literature search

Figure 1 illustrates the flow of the selection of eligible articles. A total of 720 articles were identified by searching PubMed, Cochrane, and EMBASE. 469 articles remained after removing duplicate files. Following the scanning of titles and abstracts, 50 articles were selected for full-text reading. Finally, we included seven studies [18, 19, 22-26] that met the inclusion criteria for our meta-analysis.

Study characteristics

Table 1 shows the characteristics of the seven studies included. Of these studies, four studies were conducted in Europe (Spain, Italy, and Norway) [18, 19, 22, 23], one study was conducted in Asia (Korea) [25], two studies was conducted in the Americas (Canada) [24, 26]. Five studies directly reported HRs for DFS, OS, or PFS, while HRs of the other two studies [18, 25] were extracted from Kaplan-Meier survival curves. Seven studies were cohort studies and one study was a clinical trial. Four studies assessed MSI by using five recommended quasimonomorphicmononucleotide markers, and three studies assessed MSI by immunohistochemistry testing. As shown in Table 2, all studies scored 7 or higher and were high-quality studies.

Correlation between MSI and DFS in early-stage EC

The pooled HRs in early-stage EC shows that MSI is significantly associated with lower DFS [HR=3.90, 95%CI (2.81-6.99), p=0.000], as shown in Figure 2a. Meanwhile, there was not a heterogeneity about DFS (I^2=0.0%, p=0.583).

Correlation between MSI and OS in early-stage EC

The pooled HRs in early-stage EC shows that MSI is significantly associated with lower OS [HR=1.48, 95%CI (1.12-1.96), p=0.006], as shown in Figure 2b. Meanwhile, there was not a significant heterogeneity about OS (I^2=25.9%, p=0.256).

Correlation between MSI and PFS in early-stage EC

As shown in Figure 2c, the pooled HRs in early-stage EC shows that MSI is significantly associated with lower PFS [HR=2.41, 95%CI (1.05-5.52), p=0.038]. Meanwhile, there was not a heterogeneity about PFS (I^2=0.0%, p=0.607).

Publication bias

No significant publication bias was detected by the funnel plot test (Figure 3). Additionally, there was also no statistical publication bias, the p-values of Egger`s test for DFS and OS are p=0.639 and p=0.535 respectively.

Sensitivity analysis

To explore the sensitivity of the pooled HRs of DFS, OS, and PFS in early EC, we omitted each study individually from the pooled analysis. The exclusion of any study had no significant influence on the results (Figure 4).

Discussion

The correlation between MSI and EC prognosis has been one of the hot topics of studies for more than two decades. Unfortunately, most of the current studies on the correlation between MSI and prognosis of EC have shown inconsistent results. For example, the meta-analysis by Diaz-Padilla et al. showed no correlation between MSI and prognosis in patients with EC [15], Nagle et al. reported that MSI was significantly associated with poor prognosis [27], while Black et al. showed that MSI was significantly associated with a good prognosis [10]. Therefore, the clinical prognostic significance of MSI in EC remains unclear.

By this meta-analysis, we found that a significant association between MSI and poorer prognosis in early-stage EC. We analyzed the correlation between MSI and prognosis of early-stage EC by DFS, OS, and PFS, then found that the DFS, OS, and PFS of early-stage EC patients with MSS (microsatellite stability) were significantly higher than patients with MSI, which is consistent with the cancer-specific survival of early-stage EC reported in the study by Bilbao et al. [23]. Also, none of the three pooled forest plots were heterogeneous, so we used a fixed-effects model, which proved the high reliability of the results we obtained.

Furthermore, in the study by Black et al. [10], MSI was associated with a good prognosis for EC, which is the opposite of our findings. The reason for the analysis maybe that 20% of the patients included in Black's study were non-endometrioid endometrial cancer (EEC). In contrast, in our meta-analysis, the included patients with early-stage EC were all EEC, which may indicate that MSI can be significantly associated with worse prognosis only in EEC patients, which is also consistent with the study by Nagle et al. [27].

Usually, the majority of patients with EC in all clinical stages (stages I-IV) received one or more adjuvant therapies, which increase the uncertainty as to whether MSI has a prognostic predictive role. Whereas, in our study, women with early-stage EC generally did not receive adjuvant therapy after surgery. Thus, our study is better able to exclude the confounding effects of adjuvant therapy and illustrate the correlation between MSI and EC.

There are still some deficiencies in our study. First, some of the data came from the extraction of survival curves, which may produce some deviations compared with the real data. Second, the number of studies included in the pooled PFS was small, and more studies are needed to support our conclusions. Third, the vast majority of the studies we included were retrospective case studies, which carries the risk of selective reporting. Fourth, the four studies used genotyping for MSI detection, and other three of the included studies used immunohistochemistry for MSI detection, but so far, the concordance between the two detection methods has not been ascertained in EC.

Conclusions

The results of our meta-analysis showed that MSI is most likely an independent marker of poor prognosis in early-stage EC,and this correlation is even more significant in patients with EEC. This correlation requires more large-scale, well-designed prospective studies as well as randomized controlled trials to illustrate the mechanisms of the relationship between MSI and early EC.

Abbreviations

EC
Endometrial cancer
MSI
Microsatellite instability
DFS
Disease-free survival
OS
Overall survival
PFS
Progression-free survival
DFS
Disease-free survival
MMR
Mismatch repair
MMRd
Mismatch repair deficiency
PRISMA
Preferred Reporting Items for Systemic Reviews and Meta-Analyses
CIs
confidence intervals

Declarations

Acknowledgments

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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 and MQH developed the inclusion and exclusion criteria for the eligible studies. JPX, YZW, and JSW reviewed the eligible studies and extracted the data. JPX, YYZ, and MQH 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. All authors have read and approved the manuscript.

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Availability of data and materials

Meta-analysis is a secondary analysis, which the data are all fully available without restriction, and all the material can be found in the included original studies.

Consent for publication

Not applicable.

Conflict of interest

The authors declare that they have no conflict of interest.

Compliance with ethical standards

No ethical approval or formal consent is required for this type of study.

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Tables

Table 1 Characteristics of studies included in the meta-analysis.

author	Year	Number of patients	Stage distribution	histology	Microsatellite markers	Microsatellte instability definition	Outcome assessment	Study design
Kim et al.	2020	475	IA	EEC	MLH1,MSH2,MSH6,PMS2	≥1 of 4 MMR protein was lost	OS/PFS	Cohort study
Kim et al	2018	151	I-I I	EEC	MLH1,MSH2,MSH6,PMS2	≥1 of 4 MMR protein was lost	OS/PFS	Cohort study
Ruiz et al.	2014	163	I-I I	EEC	MLH1,MSH2,MSH6,PMS2	≥1 of 4 MMR protein was lost	OS/DFS	Cohort study
Steinbakk et al	2011	171	I	EEC	BAT26,BAT25, NR-21,NR-24,NR-27	≥2 of 5 markers with mutant alleles	OS	Cohort study
Bilbao et al.	2010	93	I-I I	EEC	BAT26,BAT25, NR-21,NR-24,NR-27	≥2 of 5 markers with mutant alleles	DFS	Cohort study
Mackey et al.	2010	97	I-I I	EEC	BAT26,BAT25	≥1 of 2 markers with mutant alleles	DFS	Clinical Trials
Fiumicino et al.	2001	65	I-I I	EEC	D2S123,D2S119,D9S171,D9S157,D10S216,BAT26	≥2 of 6 markers with mutant alleles	DFS	Cohort study

EEC: endometrioid endometrial cancers; MMR: mismatch repair; OS: overall survival; PFS: progression-free survival; DFS: disease-free survival; 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
Kim et al.	2020	+*	+	+	+	+	+	+	+	8
Kim et al	2018	+	+	+	+	++	+	+	+	9
Ruiz et al.	2014	+	+	+	+	++	+	-**	+	8
Steinbakk et al	2011	+	+	+	+	-	+	+	+	7
Bilbao et al.	2010	+	+	+	+	++	+	-	+	8
Mackey et al	2010	+	+	+	+	++	+	+	+	8
Fiumicino et al.	2001	+	+	+	+	+	+	+	+	9

* If there is a positive symbol that means score one point; ** A negative symbol means no point.

Figures

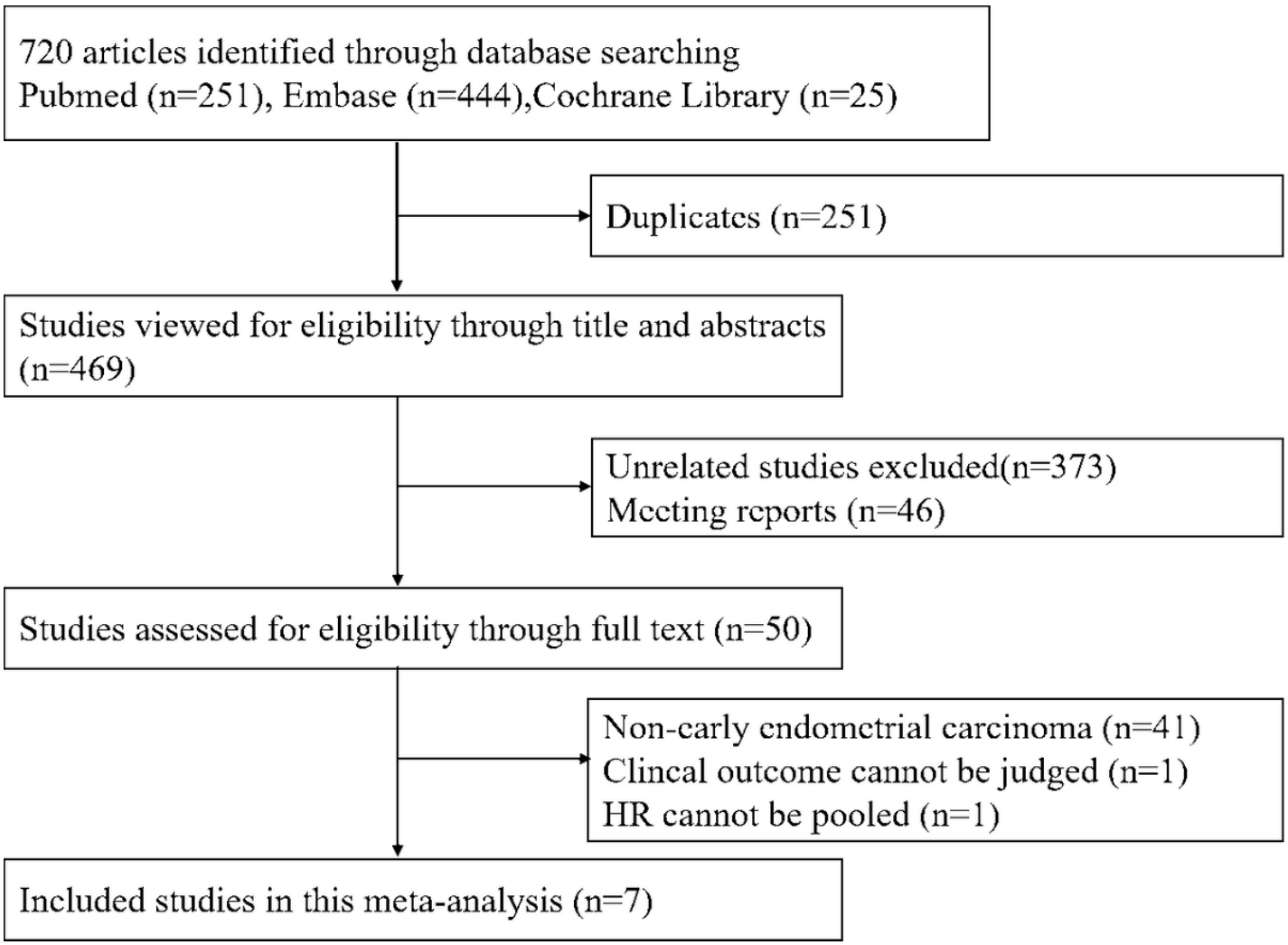

Figure 1

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

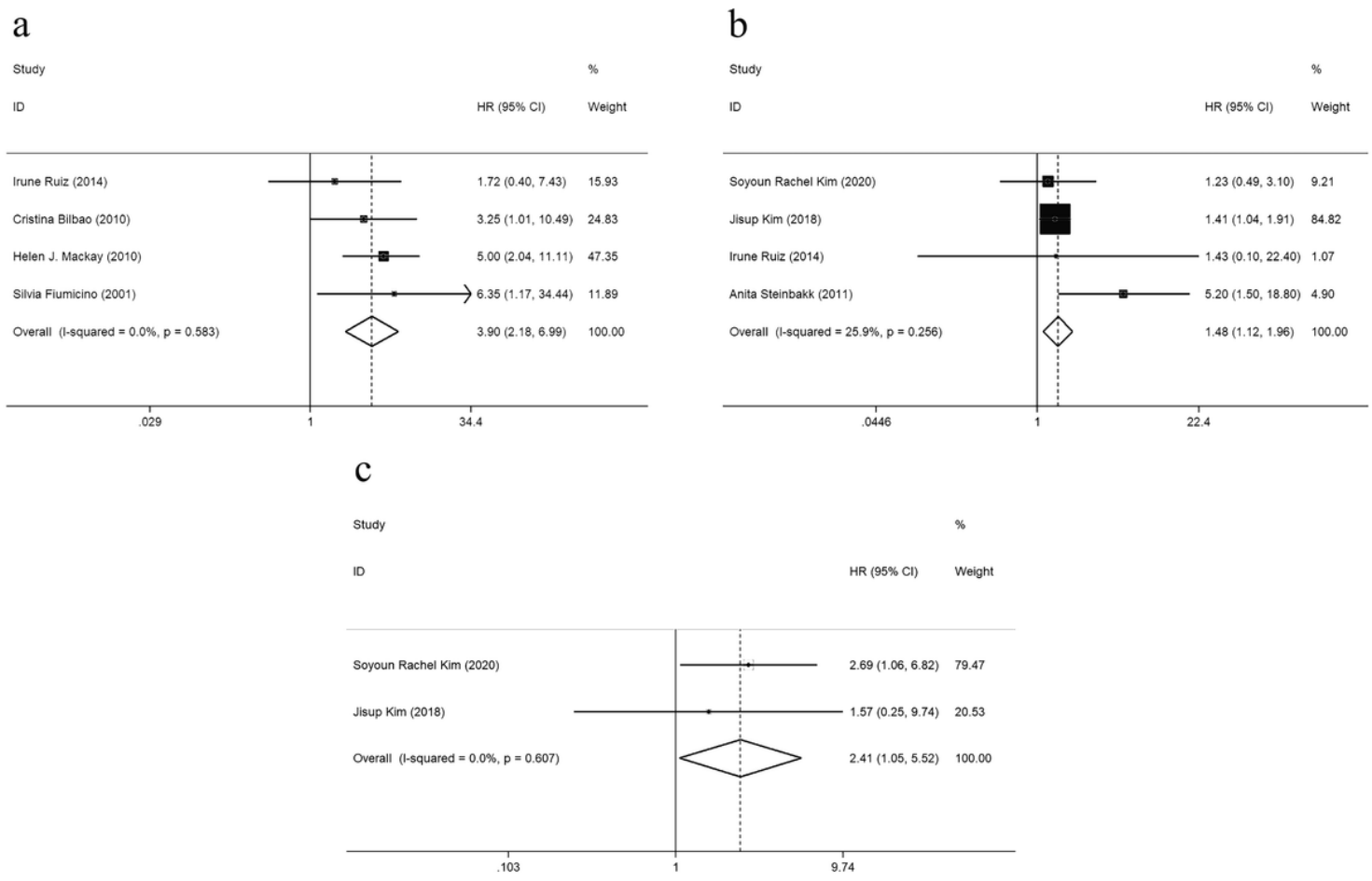

Figure 2

Forest plot of hazard ratios for the correlation between microsatellite instability and the prognosis of early-stage endometrial cancer. the disease-free survival(a), the overall survival (b), and the progression-free survival (c).

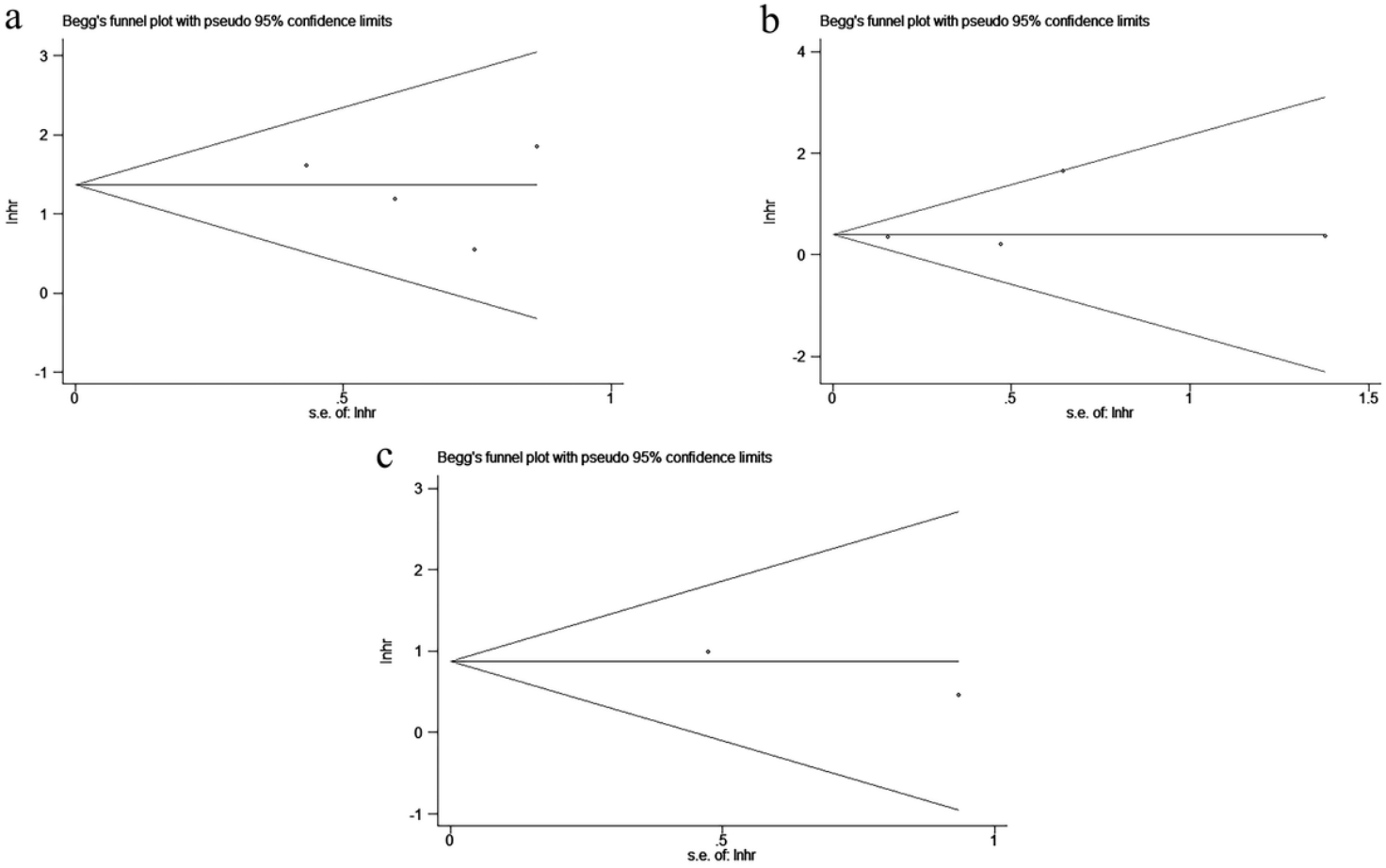

Figure 3

Results of publication bias for the disease-free survival (a), the overall survival (b), and the progression-free survival (c).

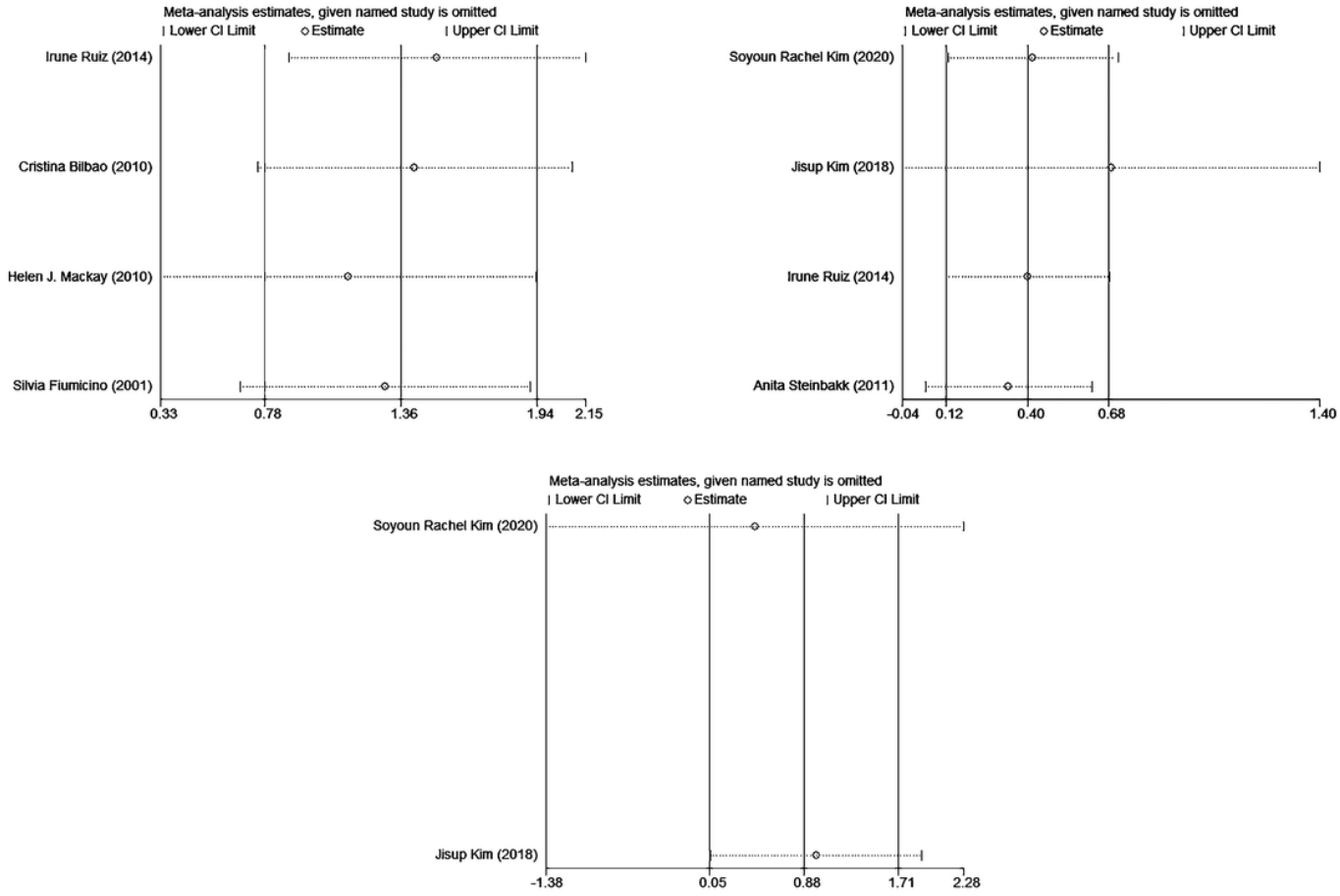

Figure 4

Sensitivity analyses of studies regarding the disease-free survival (a), the overall survival (b), and the progression-free survival (c).

Supplementary Files

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