Cancer Control
Volume 28: 1–13

DOI: 10.1177/10732748211033743
journals.sagepub.com/home/ccx
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Prognostic Role of Matrix Metalloproteinases in Cervical Cancer: A Meta-Analysis

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Abstract

Objective: Studies have published the association between the expression of matrix metalloproteinases (MMPs) and the outcome of cervical cancer. However, the prognostic value in cervical cancer remains controversial. This meta-analysis was conducted to evaluate the prognostic functions of MMP expression in cervical cancer.

Methods: A comprehensive search of PubMed, Embase, and Web of Science databases was conducted to identify the eligible studies according to defined selection and excluding criteria and analyzed according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. Fixed and random effects models were evaluated through the hazard ratios (HRs) and 95% confidence intervals (CIs) to estimate the overall survival (OS), recurrence-free survival (RFS), and progress-free survival (PFS).

Results: A total of 18 eligible studies including 1967 patients were analyzed for prognostic value. Totally 16 selected studies including 21 tests were relevant to the cervical cancer OS, 4 studies focused on RFS, and 1 study on PFS. The combined pooled HRs and 95% CIs of OS were calculated with random-effects models (HR = 1.64, 95% CI = 1.01–2.65, $P = .000$). In the subgroup analysis for OS, there was no heterogeneity in MMP-2 ($I^2 = .0\%$, $P = .880$), MMP-1 ($I^2 = .0\%$, $P = .587$), and MMP-14 ($I^2 = 28.3\%$, $P = .248$). In MMP-7 and MMP-9, the heterogeneities were obvious ($I^2 = 99.2\%$ ($P = .000$) and $I^2 = 77.9\%$ ($P = .000$), respectively). The pooled HRs and 95% CIs of RFS were calculated with fixed-effects models (HR = 2.22, 95% CI = 1.38–3.58, $P = .001$) and PFS (HR = 2.29, 95% CI = 1.14–4.58, $P = .035$).

Conclusions: The results indicated that MMP overexpression was associated with shorter OS and RFS in cervical cancer patients. It suggested that MMP overexpression might be a poor prognostic marker in cervical cancer. Research Registry Registration Number: reviewregistry 1159.

Keywords

cervical cancer, matrix metalloproteinases, prognosis

Received September 2, 2020. Received revised May 24, 2021. Accepted for publication June 30, 2021.

Introduction

Cervical cancer is one of the leading causes of cancer death among women and the most common gynecological malignancy.[1,2] Every year, more than 2 million women worldwide are diagnosed with cervical or breast cancer.[3] Although the WHO is developing implementation of elimination strategy and 99% cervical cancer mortality would be reduced over the next century, the situation is still serious nowadays.[4] The primary etiologic risk factor is persistent

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infection with human papillomavirus (HPV).[5] The latest nine HPV valent vaccine could potentially prevent up to 90% of cervical cancer cases.[6] Nonetheless, the vaccination coverage is not optimal, especially for the developing countries, which encompass almost 90% of cervical cancer deaths.[7] In brief, new biomarkers which can estimate the prognosis of cervical cancer patients are urgently required.

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endoenzymes. Up to date, more than 25 closely related and evolutionarily conserved MMP enzymes have been discovered among which MMP-1 is the first identified subtype almost half a century ago.[8,9] MMPs are versatile proteases, displaying enzymic activity against a broad spectrum of substrates including cytoplasmic and nuclear proteins, such as extracellular matrix (ECM) degradation, loss of cellular adhesion, tumor angiogenesis, epithelial mesenchymal transitions (EMT), and cellular proliferation, and the role of MMPs as collagenolytic proteases remains one of their most critical physiological functions.[10,11] During the many years following their discovery, MMPs have been revealed to have many other functions in the pathophysiology of cancers by regulating the microenvironment and cell behaviors which include cancer cell proliferation, differentiation, apoptosis, migration and invasion, the regulation of tumor angiogenesis, and immune surveillance.[12] MMPs are upregulated in almost every type of human cancers. By cleaving a wide range of substrate, MMPs could promote cancer progression and were regarded to be relevant to the prognosis.

Previous systematic reviews have demonstrated that MMPs expression is associated with prognosis of osteosarcoma,[13,14] colorectal cancer,[15] gastric cancer,[16,17] renal cell carcinoma,[18] lung cancer,[19] and breast cancer.[20] In cervical cancer, a number of studies have revealed MMPs expression was extensively associated with survival. However, the results of these studies were not consistent due to pathological classification, genuine heterogeneity, or lower statistical veracity, such as MMP-2. Cornelis et al[21] and Maiko et al[22] reported that MMP-2 might be associated with worse prognosis of cervical cancer patients. Kim et al[23] and Branca et al[24] reported that MMP-2 was not predictive of recurrence and survival in cervical cancer patients. However, Wang et al reported that MMP-2 cooperated with RECK could function as a prognostic marker with long-term survival. Therefore, we carried out this meta-analysis to evaluate the correlation between MMPs and prognosis in cervical cancer.[25-41]

Methods

Search Strategies

Original literatures on MMPs expression and survival results in cervical cancers were searched in PubMed, Embase, Cochrane Library, and Web of Science databases update to May 24, 2021. The PRISMA guideline[42] was followed to carry out this systematic review. The study was registered with research Registry (Registration Number: reviewregistry 1159 (https://www.researchregistry.com). The search strategy was based on the combination of Medical Subject Headings (MeSH) and terms such as "cervical cancer" or "cervical carcinoma" or "uterine cervix cancer" or "uterine cervix carcinoma" and "MMP" or "Matrix metalloproteinase" and "prognostic" or "prognosis" or "survival" or "mortality" or "outcome" or "recurrence" or "relapse." In order to minimize the deviation caused during the search process, all references in retrieved articles were scanned to identify other potentially available reports.

Select Criteria and Data Extraction

Two independent reviewers selected the eligible candidate articles. Any disagreement on study selection and data collection was conversed and reached a final agreement via discussion with the third reviewer. Inclusion criteria were as follows: (1) the cervical cancer patients were confirmed by the department of pathology; (2) MMPs expression was measured in tumor tissue or serum; (3) MMPs expression model was identified by the immunohistochemistry (IHC) or enzyme linked immunosorbent assay (ELISA) instead of mRNA; (4) the HR value and 95% CI between MMPs expression and the survival status could be obtained from articles or calculated based on the information in articles; (5) articles in English and mentioned the association of MMPs with OS or RFS or PFS. Exclusion criteria were as follows: (1) studies use cell lines or animals; (2) studies without OS or RFS or PFS or in other language other than English; (3) reviews, letters to editors, or articles published in a book or not published.

Data table was designed to extract all available studies. All related data were extracted by 2 independent reviewers, and any disagreements were resolved by achieving consensus with the assistance of a third reviewer. The extracted data include following information: first author, year, case (N), country, medium/mean age, dominant ethnicity, stage, method, cut-off value, follow-up period, MMP type, prognosis type, HR statistics, univariate (HR and 95% CI, *P*-value), and multivariate (HR and 95 %CI, *P*-value). If HRs and 95% CIs were not available, we calculated them using the relevant data from the graphed survival plots in Kaplan–Meier curves, or emailed the authors for related information. Although we have tried to contact authors of original for missing data, some information above is still not accessible, which was marked as "not reported (NR)."

Sensitivity and Publication Bias

In order to assess the stability and reliability of the conclusions of the pooled HR and 95% CI in meta-analysis, we performed the sensitivity tests and publication bias tests for evaluating heterogeneity in meta-analysis. The sensitivity analyses were performed by omitting one study at a time to gauge the robustness of our study. The potential publication bias across the included studies was performed by the Deeks' funnel plot test whereas the prognostic studies analyzed with Begg's funnel plot and Egger's test.

Risk of Bias Assessment

To evaluate the risk of bias, two independent investigators performed the analysis with the Cochrane risk of bias tool. The risk of bias included selection bias (random sequence generation and allocation concealment), performance bias (binding of participants and personnel), detection bias (binding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other bias. Each item was rated as low, high, or unclear risk, and the overall risk of bias of a study was concluded by summarizing all the 6 aspects. Any disagreements were resolved through consensus with the third investigator.

Meta-Regression

To further investigate the heterogeneity, a meta-regression was performed to explore the variance in the association between MMPs expression and OS. We conducted the univariable and multivariable analyses on year, MMP subtype, country, age, method, follow, stage, and cell type (cancer, stroma, endothelial cell, and uncertain cells from ATCH data) covariate. The *P* values in the meta-regression revealed overall significance of the influence factors. *P* values were inversely proportional to the size of heterogeneity. $P < .05$ indicated the factors could present source of heterogeneity. Only subgroup analyses were used for the secondary outcomes with their merged effects.

Statistical Analysis

To assess the impact of MMPs expression on survival of cervical cancer patients, the pooled HRs and corresponding 95% CIs were used in combination as the effective value. A pooled HRs > 1 indicated a poor prognosis for patients with MMPs overexpression, and in contrast, a pooled HRs < 1 indicated an increased survival for patients with high MMPs expression. When the pooled HRs > 1 with corresponding 95% CIs was not overlapping 1, the influence of MMPs expression on prognosis of cervical cancer was statistically significant. Heterogeneity was determined by the Q test and I^2 statistic. A random-effects model was used if the heterogeneity was significant ($P < .05$ and/or $I^2 > 50\%$). Otherwise, a fixed-effects model was used. Potential publication bias was evaluated through visual inspection of the funnel plots and was further assessed by Egger's test ($P > .05$ indicated lack of publication bias). All analyses were performed using STATA 12.0 (StataCorp LP, College Station, Texas). All *P* values were two-sided, and $P < .05$ was considered statistically significant.

Results

Study Characteristics

A flow diagram of the process for inclusion and exclusion criteria with specific reasons is shown in Figure 1. A total of 596 studies were initially identified from PubMed, Embase, and Web of Science databases, including 1 study through other sources. After reviewing the titles and abstracts and full-text articles assessment, 18 studies were included meeting all the criteria, ultimately.

An overview of the main characteristics of 18 eligible studies is shown in Tables 1 and 2. Overall, all studies selected were published from 2002 to 2020. The total number of patients included was 1967, ranging from 24 to 304 per study, with 7 studies conducted in Caucasian population, which mainly came from European countries, and 11 studies were in Asian population, of which 9 from China, 1 from Japan, and 1 from Egypt. About the testing methods, 13 studies data were

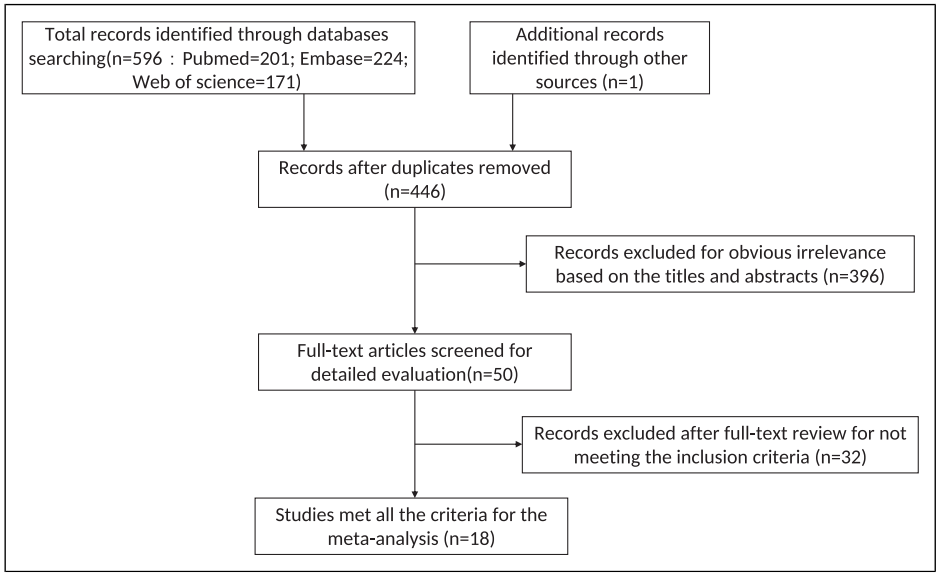

Figure 1. Flow chart of literature search and selection.

Table 1. Main Characteristics of Studies Included in the Meta-Analysis.

First author	Year	N	Country	Medium/Mean age	Dominant ethnicity	Stage		Method	Cut-off value	Follow-up period
						I/II	III/IV			
Talvensaari[25]	2005	24	Finland	40 (cut-off)	Caucasian	NR	NR	IHC	NR	5[a]
Cornelis[21]	2006	30	Netherland	NR	Caucasian	29	1	IHC	NR	10[a]
Tian[26]	2018	192	China	NR	Asian	NR	NR	TCGA	NR	NR
Wang[27]	2011	30	China	50 (cut-off)	Asian	30	0	IHC	≥1.5	8[b]
Masatsugu[28]	2002	52	Japan	50 (cut-off)	Asian	52	0	IHC	NR	NR
Rauvala[29]	2006	161	Sweden	58 (24–87)	Caucasian	125	36	IHC	<20%	20[a]
Ahmed[30]	2004	50	Egypt	51.8 ± 7.2	Asian	24	26	ELISA	16.9 ng/ml	36[b]
Wang[31]	2008	80	China	50 (cut-off)	Asian	80	0	IHC	<120.6	39[b]
Sier[32]	2008	30	Netherlands	45 (29–72)	Caucasian	28	2	IHC	4	10[a]
Xu[33]	2014	110	China	50 (cut-off)	Asian	110	0	IHC	<10%	7[a]
Wang[34]	2014	136	China	40 (cut-off)	Asian	107	29	IHC	<1	81[b]
Li[35]	2012	225	China	40 (cut-off)	Asian	107	118	IHC	<5%	8[b]
Zhao[36]	2020	257	China	NR	Asian	NR	NR	TCGA	NR	NR
Fan[37]	2016	66	China	NR	Asian	20	32	IHC	NR	NR
Roszik[38]	2018	28	America	NR	Caucasian	20	6	IHC	<10%	200[b]
Wang[39]	2020	304	China	57.5 (20–88)	Caucasian	231	65	TCGA	NR	15[a]
Yi[40]	2020	128	China	NR	Asian	NR	NR	TCGA	NR	6000[c]
Martins[41]	2020	64	Brazil	44 (22–94)	Caucasian	49	15	IHC	NR	12[a]

Abbreviations: TCGA, The Cancer Genome Atlas. NIH Gov.; NR, not reported; IHC, immunohistochemistry; ELISA, enzyme linked immunosorbent assay.
[a]Year.
[b]Month.
[c]Day.

obtained from IHC, 4 studies from TCGA, and 1 study result was based on ELISA test. The histologic type of cervical cancer in our analysis, 12 studies described in detail, includes squamous carcinoma, adenocarcinoma, and adenosquamous carcinoma, and 6 studies just presented only from cervical cancers. Among these included studies, 6 studies including 6 tests focused on associations between MMP-2 and cervical cancer, 5 studies including 6 tests on MMP-9, 4 studies on MMP-1, 2 studies including 3 tests on MMP-14, and 1 study with 2 distinct assessing methods on MMP-7. To sum up, 16 studies reported patient OS, 4 studies focused on RFS, and 1 study on PFS.

MMPs Expression on OS/RFS/PFS

Totally 16 selected studies including 21 tests were relevant to the cervical OS. A random-effects model was used to analyze the MMPs on OS since there existed heterogeneity (I^2 = 95.0%, P = .000), and MMPs overexpression was relevant to the worse OS and has significant difference (HR = 1.64, 95% CI = 1.01–2.65, P = .044) (Figure 2A). We categorized the 16 studies based on relevant MMPs family members, and there was no heterogeneity in MMP-2 (I^2 = .0%, P = .000), MMP-1 (I^2 = .0%, P = .587), and MMP-14 (I^2 = 28.3%, P = .248). In MMP-7, the heterogeneity was obvious (I^2 = 99.2%, P = .000), and MMP-9 also exhibited heterogeneity (I^2 = 77.9%, P = .000) (Figure 2B). All pooled MMP-2 (HR = 2.25, 95% CI = 1.58–3.22, P = .000), pooled MMP-9 (HR = 1.02, 95% CI = .53–1.96, P = .042), and pooled MMP-1 (HR = 1.35, 95% CI = 1.18–1.55, P = .000) overexpression and other subgroups with MMP-7 (P = .02) on endothelial cells had worse OS on cervical cancer. Pooled MMP-14 (HR = 2.05, 95% CI = .87–4.83, P = .102) overexpression had a tendency for worse OS, although no significant difference was reached.

There were four selected studies for RFS and one study for PFS. A fixed-effects model was used to analyze the MMPs on RFS since there existed no heterogeneity (I^2 = 30.0%, P = .232), and MMPs overexpression was significantly relevant to the worse RFS (HR = 2.22, 95% CI = 1.38–43.58, P = .001) (Figure 2C). We categorized the four studies based on the relevant MMPs family members and there was no heterogeneity in MMP-2 (I^2 = 51.9%, P = .125). We did not assess the heterogeneity of MMP-9 because there was just one study. The pooled MMP-2 (HR = 2.04, 95% CI = 1.04–3.99, P = .038) and MMP-9 (HR = 2.42, 95% CI = 1.23–4.77, P = .038) had worse RFS on cervical cancer (Figure 2D). Since there was only one study on PFS, we did not test the heterogeneity on PFS. Besides, MMP-9 overexpression seemed to have no effect on PFS (HR = 1.44, 95% CI = .572–3.600, P = .035).

Sensitivity Analysis and Publication Bias

In order to assess the stability and reliability of the conclusions of the pooled HR and 95% CI in meta-analysis, we performed

Table 2. HRs and 95% CIs on Prognosis of the Included Studies in the Meta-Analysis.

				Univariate		Multivariate	
First author	MMP type	Prognosis type	HR statistics	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Talvensaari[25]	MMP-9	RFS	SC	2.42 (1.23–4.77)	.04	NR	NR
Cornelis[21]	MMP-2	OS	SC	2.71 (1.03–6.92)	.043	NR	NR
Tian[26]	MMP-1	OS	Reported	.74 (.5–1.09)	.001	1.699 (1.133–2.548)	.01
Wang[27]	MMP-2	RFS	SC	3.06 (0.89–10.08)	.034	NR	NR
		OS	SC	2.09 (0.91–4.77)	.057	NR	NR
Masatsugu[28]	MMP-2	OS	Reported	NR	NR	2.841 (1.000–8.076)	.0501
Rauvala[29]	MMP-2	OS	Reported	NR	NR	1.93 (1.10–3.37)	.022
Ahmed[30]	MMP-2	RFS	Reported	NR	NR	8.1 (1.3–49.1)	.04
Wang[31]	MMP-2	RFS	Reported	1.158 (.470–2.853)	.748	NR	NR
		OS	Reported	1.475 (.330–6.593)	.608	NR	NR
Sier[32]	MMP-7	OS[a]	SC	24.32 (11.04–53.50)	.02	NR	NR
		OS	SC	.28 (.17–.45)	.99	NR	NR
Xu[33]	MMP-9	PFS	SC	2.29 (1.14–4.58)	.035	NR	NR
		OS	SC	1.52 (.63–3.66)	.03	NR	NR
Wang[34]	MMP-14	OS	Reported	NR	<.001	1.448 (1.036–2.024)	.03
Li[35]	MMP-9	OS	Reported	3.12 (1.39–6.74)	.001	2.97 (1.23–6.19)	.002
Zhao[36]	MMP-1	OS	Reported	NR	NR	1.2974 (1.1069v1.5206)	.00131
Fan[37]	MMP-9	OS	SC	1.754 (1.278–2.230)	<.0001	NR	NR
Roszik[38]	MMP-1	OS	SC	2.12 (.57–7.88)	<.0001	NR	NR
Wang[39]	MMP-1	OS	SC	1.35 (.93–1.97)	.004	NR	NR
Yi[40]	MMP-9	OS	SC	.99 (.55–1.79)	.023	NR	NR
Martins[41]	MMP-2	OS[b]	Reported	3.91 (1.17–13.02)	.03	NR	NR
	MMP-9	OS[b]	Reported	.19 (.05–.65)	.01	NR	NR
	MMP-9	OS	Reported	.19 (.04–.90)	.04	NR	NR
	MMP-14	OS[b]	Reported	7.11 (.88–57.58)	.07	NR	NR
	MMP-14	OS	Reported	3.57 (.43–29.9)	.24	NR	NR

Abbreviations: SC, Kaplan–Meier survival curve; NR, not reported; OS, overall survival; MMP, matrix metalloproteinases; RFS, recurrence-free survival.
[a]Endothelial cells.
[b]Stroma cells.

the sensitivity tests and publication bias. For OS, sensitivity results indicated that the pooled HRs were significantly altered by excluding Sier et al[32] studies, indicating the MMP-7 might be the source of heterogeneity (Figure 3A). The Deeks' funnel plot of MMPs expression on OS was asymmetric (Figure 3B-a). Begg's funnel plot (Figure 3B-b) and Egger's test ($P = .020$) of publication bias showed there existed heterogeneity. For RFS, sensitivity results indicated that the pooled HRs were not significantly altered by excluding any studies (Figure 3C). Although the Deeks' funnel plot was not very symmetric (Figure 3D-a), Begg's funnel plot test (Figure 3D-b) and Egger's test ($P = .152$) of publication bias showed no significant heterogeneity. There was only one test for PFS, we did not perform tests on PFS.

Risk of Bias

The risk of bias assessment is shown in Figure 4. There were 2 trials at high risk in selection bias (allocation concealment) and 2 trials at high risk in other bias since the cell type detecting was different. There was 1 trial at high risk in selection bias (random sequence generation) and 1 trial at high risk in detection bias. There were 9 trials at unclear risk in attrition bias since the HR and 95% CI were calculated from the graphed survival plots in Kaplan–Meier curves. 7 trials were at unclear risk in selection bias (random sequence generation) since the trials did not state the selection bias clearly. There were 2 trials in selection bias (allocation concealment), 3 trials in performance bias, 4 trials in detection bias, and 3 trials in other bias at unclear risk.

Meta-Regression

We performed meta-regression analysis to identify the sources of the heterogeneity in OS meta-analysis. The strengths of the linear associations between the MMP effects on OS and each of the covariates (year, MMP subtype, country, age, method, follow, stage, and cell type) were analyzed with univariable and multivariable analyses. The results showed that cell type (regression coefficient: 1.809, 95% CI, .711–1.624, $P = .0089$) might be the source of heterogeneity. Among the 4 distinct cell types, the meta-regression results showed that endothelial

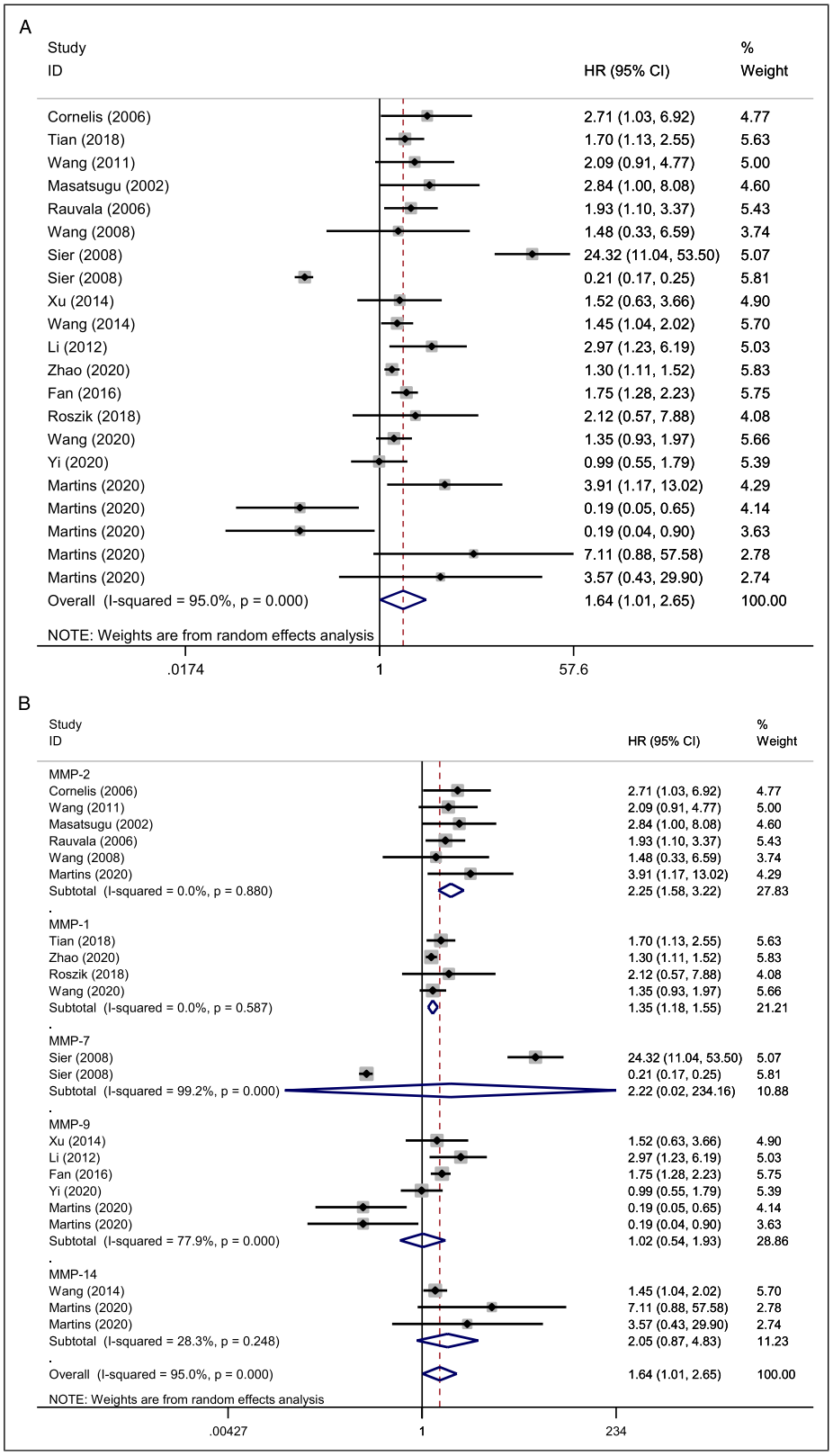

Figure 2. Forest plots of merged analyses of MMPs overexpression included 18 trials. (A) MMPs overexpression on OS; (B) subgroup of MMPs overexpression on OS; (C) MMPs overexpression on RFS; (D) subgroup of MMPs overexpression on RFS. The size of the gray markers corresponds to the weight of the study. Combined hazard ratio was calculated using a random-effects model. The dotted lines are used to represent the merged HR value. HR, hazard ratio; CI, confidence interval; MMPs, matrix metalloproteinases; OS, overall survival; RFS, recurrence-free survival.

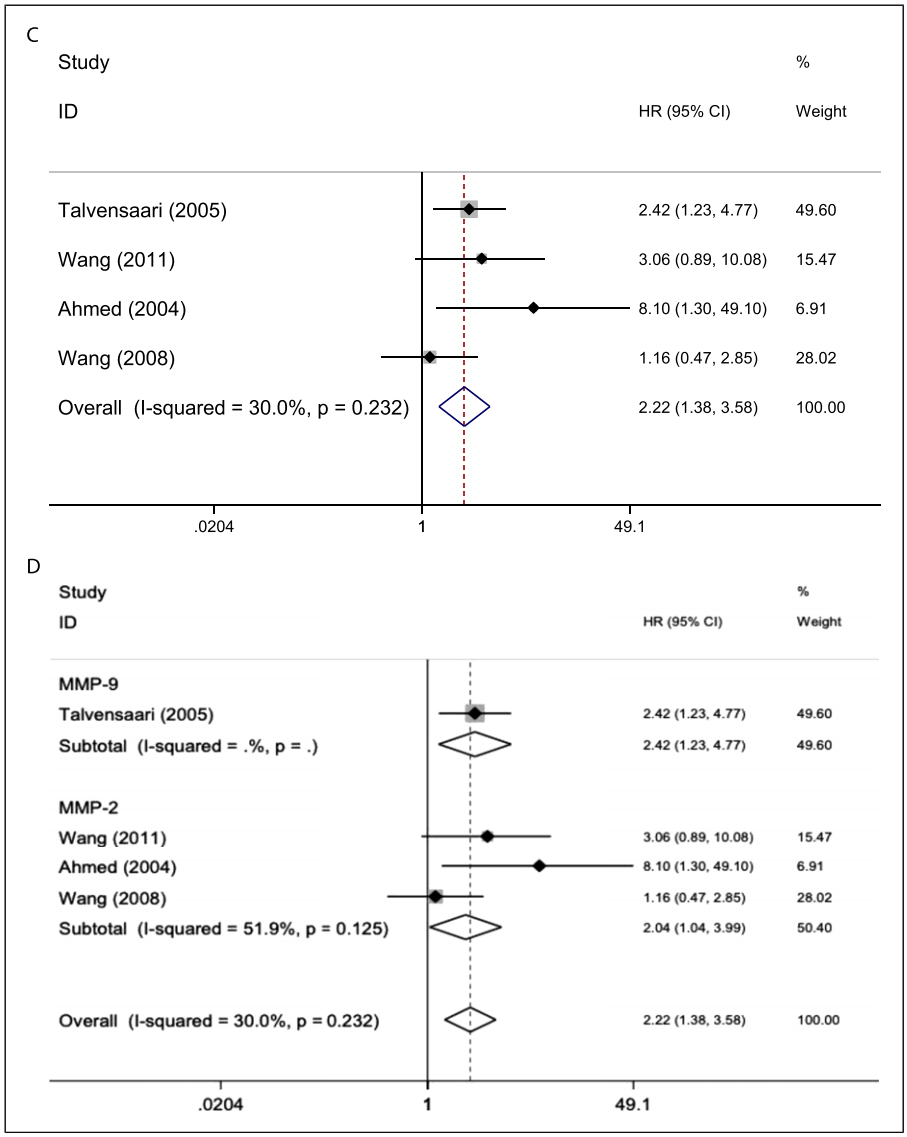

Figure 2. Continued.

cells from MMP-7 testing were the source which affected the heterogeneity significantly (P = .005) (Figure 5). The year, MMP subtype, country, age, method, follow, and stage had no significant difference on heterogeneity (P > .05).

Discussion

Cervical cancer is the predominant female malignancy all over the world. With the rapid development and remarkable advance in treatment, the conventional histological and cytological techniques are insufficient to follow the cancer progression and also could not offer intervention in time.[43] It has been proposed that upregulated expression of MMPs to degrade and remodel the ECM was essential for cancer cells to initiate disseminating environments.[44] The description of MMPs catalytic activities was first put forward in 1962.[8] Since then, the functions of MMPs were extensively explored. Besides their physiological role such as tissue remodeling and wounding healing,[45,46] the pathophysiological functions in cancers, aging, arthritis, and cardiovascular diseases make these enzymes as an attractive field of study. In human cancers, MMPs regulated the microenvironment and cell behaviors.[11] Up to now, MMPs are reported to be expressed aberrant and associated with prognosis in a considerable number of cancers.[47] In osteosarcoma, lung cancer, and renal cell carcinoma, MMP-2 and MMP-9 were analyzed as prognostic biomarkers with

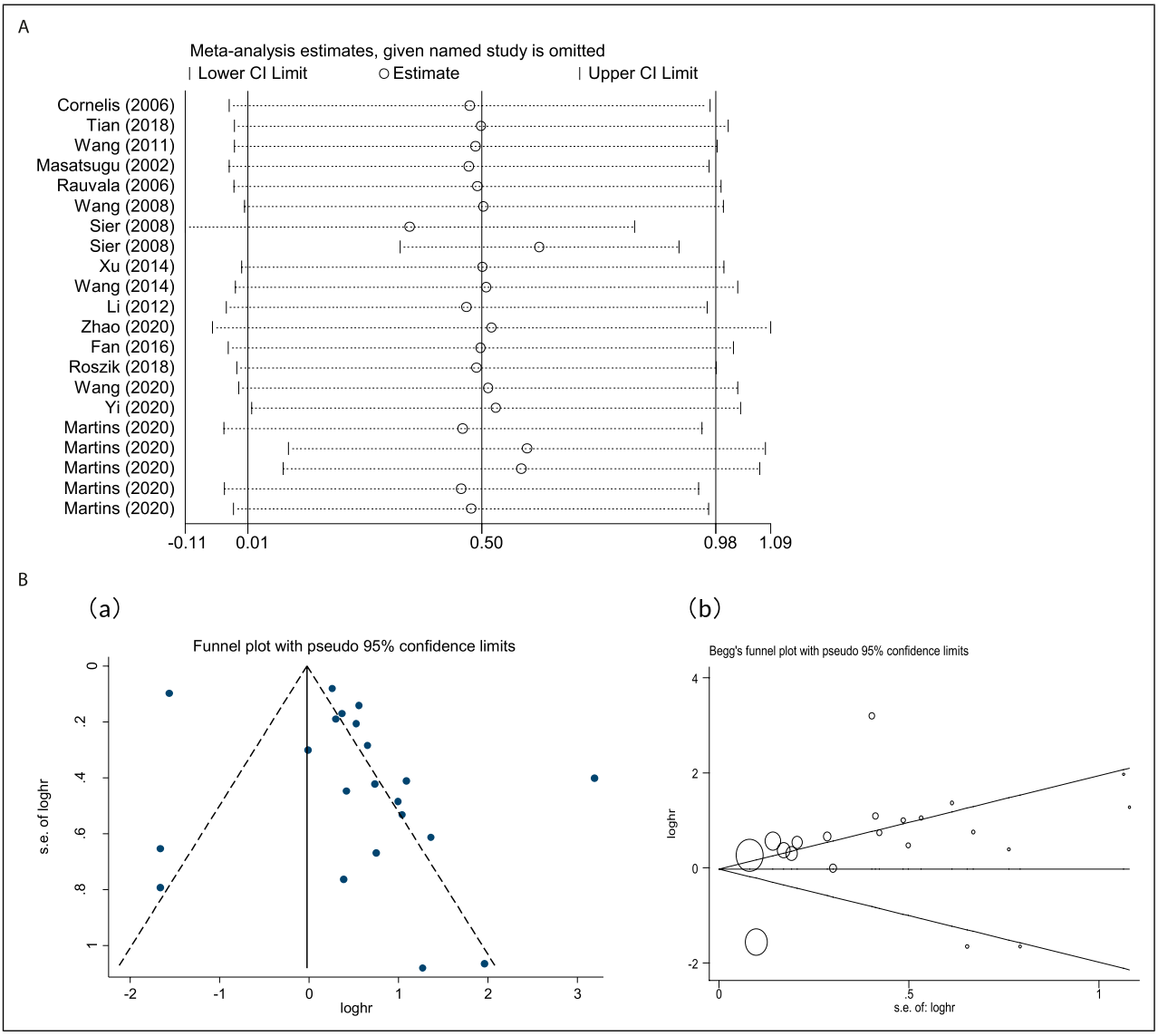

Figure 3. Sensitivity analysis and funnel graph on OS and RFS. (A) Effect of each eligible MMP overexpression on OS; (B) Deeks' funnel plot (a) and Begg's funnel plot (b) graph of OS; (C) effect of each eligible MMP overexpression on RFS; (D) Deeks' funnel plot (a) and Begg's funnel plot (b) graph of RFS. In sensitivity analysis, dotted squares indicate mean sensitivity or specificity for each study; horizontal lines indicate the 95% CIs of sensitivity or specificity for each study. In funnel plot, each dot of the plot represents a separate study; the two dotted lines at either side represent the pseudo 95% confidence intervals. The middle solid line indicates the overall effect from the meta-analysis. CI, confidence interval; MMP, matrix metalloproteinases; OS, overall survival; RFS, recurrence-free survival.

meta-analysis. In digestive system carcinoma, MMP-7, MMP-14, MMP-1, MMP-9, and MMP-2 were analyzed as prognostic biomarkers. In breast cancer, MMPs family was analyzed with meta-analysis and recognized as prognostic biomarkers. Our study also indicated MMPs family had prognostic significance in cervical cancer.

In our study, there were six studies showing that MMP-2 overexpression was related with OS in general. But Wang et al[31] published the results that there was no relation between MMP-2 overexpression and OS. We reviewed each study and found the prognostic value of MMP-2 was limited for the stage, histological type, observe method, and so on. Because there was no exact definition of IHC expression grade and calculating method for H-score, different diagnostic expression grades may have different or even contradicting results.[48] Besides, the function of MMPs is also controlled by their inhibitors.[49] Therefore, the contrasting activities of MMP-2 seem to depend on the extracellular environment, the stage of the cervical cancer, and so on.

Concerning MMP-9 personality which could degrade gelatin and type IV collagen, it plays an irreplaceable role in cell invasion. There were 5 studies including 6 selected tests which were eligible for MMP-9 analysis. The pooled MMP-9 overexpression was proposed to be related with

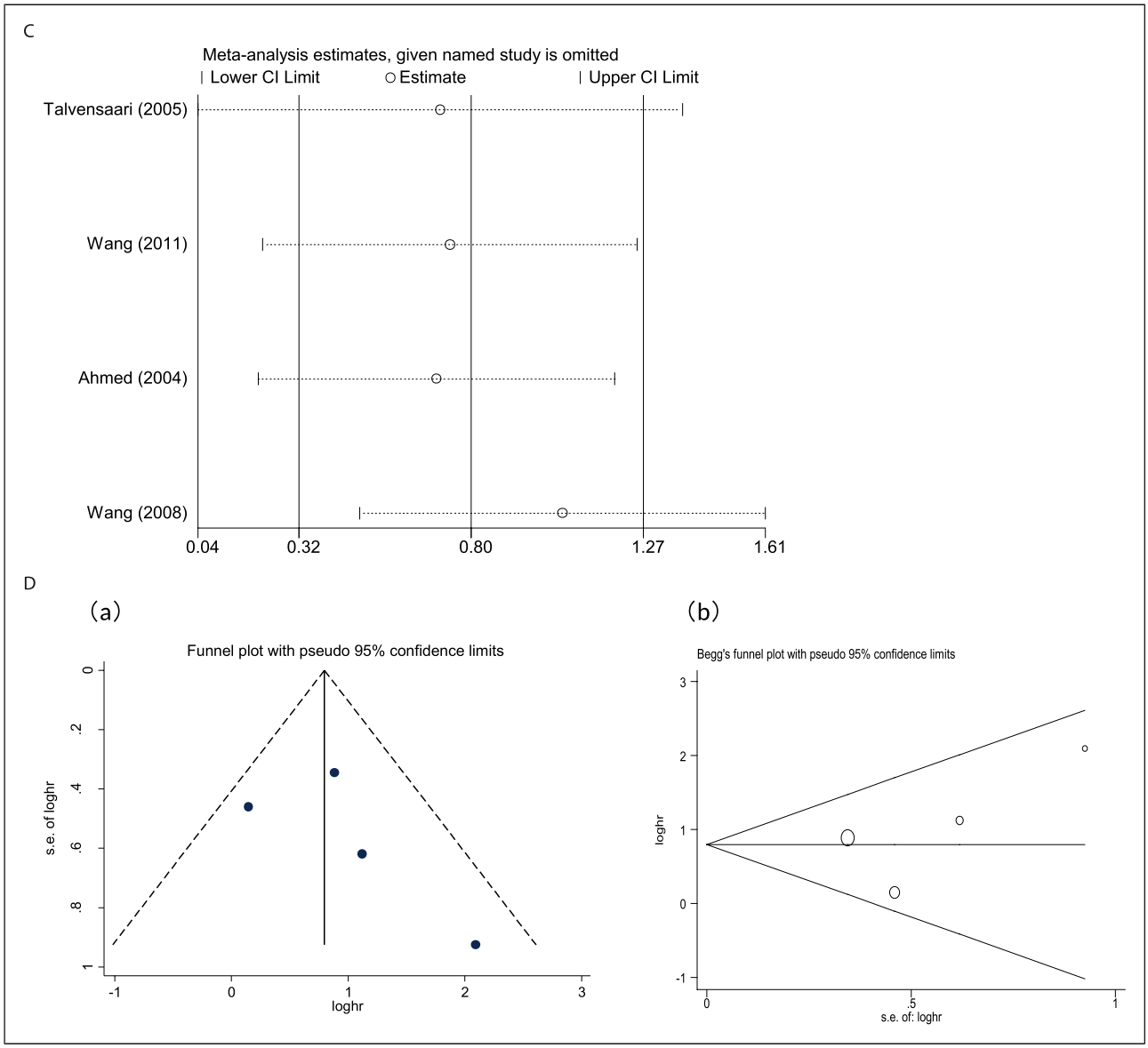

Figure 3. Continued.

worse OS. But Davidson et al[50] reported, the presence of MMP-9 mRNA or protein did not predict the prognosis.[44] The contradicting results may originate from the mRNA detecting method, cervical cancer stage, and histological types. When more data of advanced cervical cancer were available, the results seemed to be related with poor prognosis. The other MMPs in our analysis seemed to be related with OS. But the sample number was too small for each individuality, we need more additional studies to evaluate.

There were 4 studies revealing MMP-1 overexpression was related with poor prognosis and may function as a biomarker of patients with cervical cancer. Tian et al[26] pointed out that MMP-1 was an independent prognostic biomarker of cervical cancer and involved in the lymph node metastasis. However, the molecular mechanisms remain unclear. Zhao et al[36] investigated the immune and gene expression profile, revealing the underlying relationship between MMP-1 and immune infiltrating cells and also identifying MMP-1 as an essential prognostic factor. Roszik et al[38] revealed MMP-1 was overexpressed in cervical cancer, and knockdown of MMP-1 reduced the proliferation and migration of cervical cancers. Wang et al[39] proposed MMP-1 as a risk factor in cervical cancer.

Some researchers found MMP-14 overexpression associated with tumor progression due its role in MMP-2 activation.[51] But others found it independently related with lower overall survival.[52] Our results showed MMP-14 overexpression in cancer tissues and stroma cells and showed its relation with prognosis of cervical cancer, but not in the

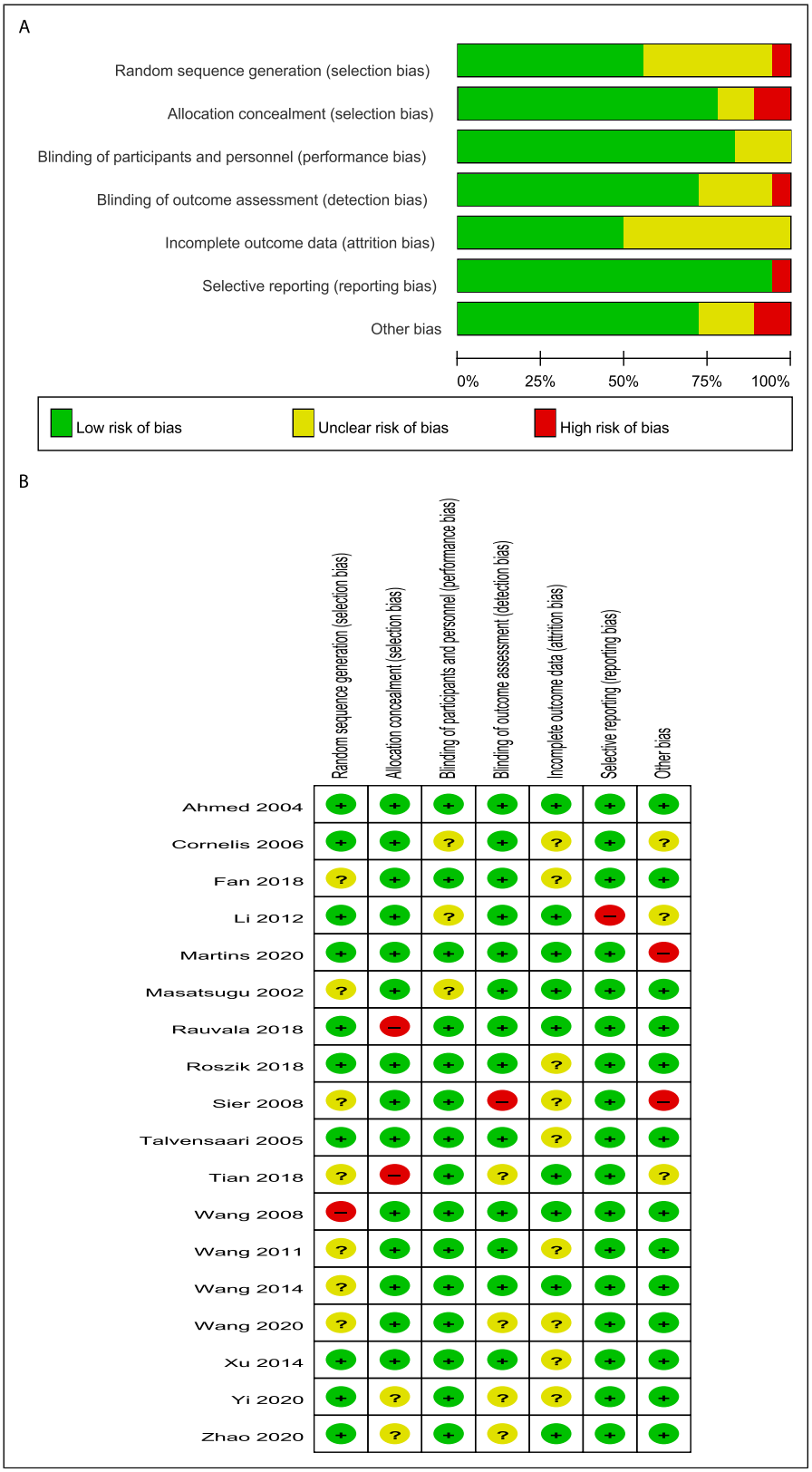

Figure 4. (A) Bias risk as a percentage: authors' judgments about percentage of each risk of bias item in all included studies; (B) bias risk summary for each element: authors' judgments about each risk of bias item for each included study.

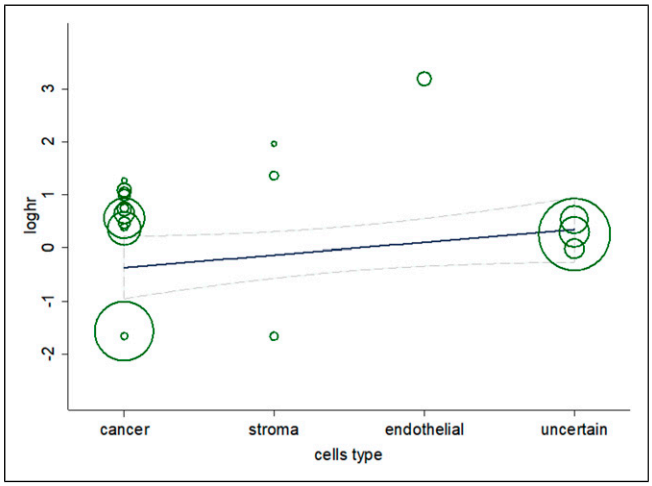

Figure 5. Meta-regression of effect size in terms of cell types of included studies on OS. Circles are sized according to the precision of each estimate with larger bubbles for more precise estimates. CI, confidence interval; HR, hazard ratio; OS, overall survival.

cancer cells, suggesting that MMP-2 activation may be a peri-fibroblastic event.[53]

MMP-7 expression in endothelial cells showed that overexpression had obvious relation with prognosis of cervical cancer, but not in cancer cells. We reviewed the study in which Cornelis et al[32] found the contradictory effects of MMP-7 on the pooled HRs and 95% CIs of OS based on the expression location. When we evaluated the relation of MMP-7 expression with cervical cancer in endothelial cells, its expression was related to decreased survival. When evaluated in tumor cells, the result was contrary. Compared with other MMPs subtypes, the MMP-7 may function through distinct mechanism, possibly involved in the angiogenesis.[32]

We also analyzed MMPs on RFS, and the pooled HR and 95% CI proposed that MMP overexpression was related with RFS. Wang et al[31] reported that MMP-2 was not related with RFS because RFS was related with cell differentiation, uterine parametrium invasion, and lymph node metastasis, but MMP-2 was not correlated with cancer cell differentiation. Another limitation we should consider was the activation of MMPs during the cancer cells metastasis. Mostly, the MMPs were activated by themselves or other substrates to active forms. MMPs overexpression usually could not equate to the prognostic values at all.

Based on our study, the MMPs were associated with OS, RFS, and PFS of cervical cancer. How MMPs' overexpression associate with prognosis of cervical cancer has been the research hotpoint for a long time. A persistent infection with HPV is considered as the main risk factor for cervical carcinogenesis.[54] Human papillomavirus infects epithelial cells through pathological changes[55] of epithelial cells. After that, virus particles enter epithelial cells and diffuse to the basal layer. The infected cells start to produce virus particles which lead to the development of low-grade and high-grade lesions or cervical intraepithelial neoplasia, thus evolving into invasive cancer.[56,57] There is no doubt that MMPs are involved in the carcinogenesis and progression of cervical cancer. A series of MMPs expression and HPV detection were analyzed to assess the association between HPV and MMPs. Although early studies showed there was no relation between MMPs and HPV,[24,58,59] recent studies have shown that HPV-16 or HPV-18 oncoproteins control transcription of MMPs (MMP-1, MMP-2, MMP-9, MMP-7, MMP-13, and MMP-14) and promote the migration of cervical cancer cells with their oncoproteins.[55,60-64] But, whether HPV oncoproteins affect the prognostic value of MMPs expression in cervical cancer is rarely studied. We will try to collect more data to catalyze the association between HPV oncoproteins and prognostic value of MMPs expression in cervical cancer in the future.

In conclusion, our meta-analysis indicated the poor prognostic significance of MMPs overexpression in cervical cancer patients. MMP-2, MMP-9, and MMP-1 on endothelial cells overexpression had worse prognosis on OS. However, not all the subtypes function as predictors for worse prognosis, and the mechanism maybe distinct among the different predictors, like MMP-7 and MMP-14. Our analysis also showed that MMP-2 and MMP-9 were relevant to worse RFS. About the PFS, we need further study to continue. Considering the MMPs overexpression values were involved in cervical cancer stage, histological type, and many other issues, further high quality studies with large data size are needed to confirm our findings.

Author Contributions

Dr. Weiwei Chen designed and wrote this paper; Dr. Kun Shi and Dr. Lisha Yi were responsible collecting the data and checking the paper; Dr. Yaqiong Liu resolved the disagreements when any disparity in data collecting was conversed; Dr. Wenjie Liu analyzed the final results.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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References

1. 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.
2. Lea JS, Lin KY. Cervical cancer. *Obstet Gynecol Clin N Am*. 2012;39(2):233-253.

3. Ginsburg O, Bray F, Coleman MP, et al. The global burden of women's cancers: A grand challenge in global health. *Lancet*. 2017;389(10071):847-860.
4. Canfell K, Kim JJ, Brisson M, et al. Mortality impact of achieving WHO cervical cancer elimination targets: A comparative modelling analysis in 78 low-income and lower-middle-income countries. *Lancet*. 2020;395(10224):591-603.
5. Siegel RL, Miller KD, Jemal A. Cancer statistics. *CA Cancer J Clin*. 2018;68(1):7-30.
6. Serrano B, Alemany L, Tous S, et al. Potential impact of a nine-valent vaccine in human papillomavirus related cervical disease. *Infect Agents Canc*. 2012;7(1):38.
7. Torre LA, Islami F, Siegel RL, Ward EM, Jemal A. *Global Cancer in Women: Burden and Trends*. Cancer Epidemiology Biomarkers & Prevention; 2017:26, 444-457.
8. Gross J, Lapiere CM. Collagenolytic activity in amphibian tissues: A tissue culture assay. *Proc Natl Acad Sci Unit States Am*. 1962;48(6):1014-1022.
9. Fonseca FLA, da Costa Aguiar Alves B, Azzalis LA, Belardo TMG. Matrix metalloproteases as biomarkers of disease. *Methods Mol Biol*. 2017:299-311.
10. Fridman R. Preface – matrix metalloproteinases. *Biochim Biophys Acta Mol Cell Res*. 2017;1864(11 Pt):1925-1926.
11. Egeblad M, Werb Z. New functions for the matrix metalloproteinases in cancer progression. *Nat Rev Canc*. 2002;2(3): 161-174.
12. Kessenbrock K, Plaks V, Werb Z. Matrix metalloproteinases: Regulators of the tumor microenvironment. *Cell*. 2010;141(1): 52-67.
13. Wen X, Liu H, Yu K, Liu Y. Matrix metalloproteinase 2 expression and survival of patients with osteosarcoma: A meta-analysis. *Tumor Biol*. 2014;35(1):845-848.
14. Li H, Zhang K, Liu LH, et al. A systematic review of matrix metalloproteinase 9 as a biomarker of survival in patients with osteosarcoma. *Tumor Biol*. 2014;35(6):5487-5491.
15. LicY Y. Matrix metalloproteinase 9 expression and prognosis in colorectal cancer: A meta-analysis. *Tumour Biol*. 2013; 34(2):735.
16. Shen W, Xi H, Wei B, Chen L. The prognostic role of matrix metalloproteinase 2 in gastric cancer: A systematic review with meta-analysis. *J Canc Res Clin Oncol*. 2014;140(6):1003-1009.
17. Duan F, Peng Z, Yin J, Yang Z, Shang J. Expression of MMP-14 and prognosis in digestive system carcinoma: A meta-analysis and databases validation. *J Canc*. 2020;11(5):1141-1150.
18. Cheng HP, Duan YR, Li Y, Li XD, Zhu CY, Chen BP. Clinicopathological significance of matrix metalloproteinase-2 protein expression in renal cell carcinoma patients. *Anal Quant Cytopathol Histopathol*. 2015;37:353-363.
19. Qian Q, Wang Q, Zhan P, et al. The role of matrix metalloproteinase 2 on the survival of patients with non-small cell lung cancer: A systematic review with meta-analysis. *Canc Invest*. 2010;28(6):661-669.
20. Ren F, Tang R, Zhang X, et al. Overexpression of MMP family members functions as prognostic biomarker for breast cancer patients: A systematic review and meta-analysis. *PLoS One*. 2015;10(8):e0135544.
21. Sier Cornelis F.M., Zuidwijk K, Zijlmans HJMAA, et al. EMMPRIN-induced MMP-2 activation cascade in human cervical squamous cell carcinoma. *Int J Canc* 2006;118(12): 2991-2998.
22. Noriyuki M, Sumi T, Zhi X, et al. Vascular endothelial growth factor, matrix metalloproteinases, and cyclooxygenase-2 influence prognosis of uterine cervical cancer in young women. *Int J Oncol*. 2007;31(3):531-536.
23. Kim K, Cho SY, Kim BJ, Kim MH, Choi SC, Ryu SY. The type of metastasis is a prognostic factor in disseminated cervical cancer. *J Gynecol Oncol*. 2010;21(3):186-190.
24. Branca M, Ciotti M, Giorgi C, et al. Matrix metalloproteinase-2 (MMP-2) and its tissue inhibitor (TIMP-2) are prognostic factors in cervical cancer, related to invasive disease but not to high-risk human papillomavirus (HPV) or virus persistence after treatment of CIN. *Anticancer Res*. 2006;26(2B):1543-1556.
25. Talvensaari-Mattila A, Turpeenniemi-Hujanen T, Puistola U. Matrix metalloproteinase 9 and relapse in patients with early stage squamous cervical carcinoma. *Int J Gynecol Obstet*. 2005; 91(1):75-76.
26. Tian R, Li X, Gao Y, Li Y, Yang P, Wang K. Identification and validation of the role of matrix metalloproteinase-1 in cervical cancer. *Int J Oncol*. 2018;52(4):1198-1208.
27. Wang PH, Ko JL, Yang SF, et al. Significant relation of tissue inhibitor of matrix metalloproteinase-2 and its combination with matrix metalloproteinase-2 to survival of patients with cancer of uterine cervix. *Reprod Sci*. 2011;18(8):798-808.
28. Ueda M, Terai Y, Yamashita Y, et al. Correlation between vascular endothelial growth factor-C expression and invasion phenotype in cervical carcinomas. *Int J Canc*. 2002;98(3): 335-343.
29. Rauvala M, Aglund K, Puistola U, et al. Matrix metalloproteinases-2 and -9 in cervical cancer: Different roles in tumor progression. *Int J Gynecol Canc*. 2006;16(3):1297-1302.
30. Ahmed MI, Salahy EE, Tawfiq H, Khalifa A, Hassan MM. Matrix metalloproteinase-2, squamous cell carcinoma antigen, and tissue polypeptide-specific antigen expression in Egyptian patients with cervical carcinoma: Relationship with prognosis. *Dis Markers*. 2004;20(6):333-343.
31. Wang PH, Ko JL, Tsai HT, et al. Clinical significance of matrix metalloproteinase-2 in cancer of uterine cervix: A semiquantitative study of immunoreactivities using tissue array. *Gynecol Oncol*. 2008;108(3):533-542.
32. Sier CF, Hawinkels LJ, Zijlmans HJ, et al. Endothelium specific matrilysin (MMP-7) expression in human cancers. *Matrix Biol*. 2008;27(3):267-271.
33. Xu Q, Ying M, Chen G, et al. ADAM17 is associated with EMMPRIN and predicts poor prognosis in patients with uterine cervical carcinoma. *Tumor Biol*. 2014;35(8):7575-7586.
34. Wang H, Zhang X, Huang L, Li J, Qu S, Pan F. Matrix metalloproteinase-14 expression and its prognostic value in cervical carcinoma. *Cell Biochem Biophys*. 2014;70(2): 729-734.

35. Li Y, Wu T, Zhang B, Yao Y, Yin G. Matrix metalloproteinase-9 is a prognostic marker for patients with cervical cancer. *Med Oncol*. 2012;29(5):3394-3399.
36. Zhao S, Yu M. Identification ofMMP1as a potential prognostic biomarker and correlating with immune infiltrates in cervical squamous cell carcinoma. *DNA Cell Biol*. 2020;39(2):255-272.
37. Fan D, Wang Y, Qi P, et al. MicroRNA-183 functions as the tumor suppressor via inhibiting cellular invasion and metastasis by targeting MMP-9 in cervical cancer. *Gynecol Oncol*. 2016; 141(1):166-174.
38. Roszik J, Ring KL, Wani KM, et al. Gene expression analysis identifies novel targets for cervical cancer therapy. *Front Immunol*. 2018;9:2102.
39. Wang J, Zheng H, Han Y, Wang G, Li Y. A novel four-gene prognostic signature as a risk biomarker in cervical cancer. *Int J Genomics*. 2020;2020:4535820.
40. Yi Y, Fang Y, Wu K, Liu Y, Zhang W. Comprehensive gene and pathway analysis of cervical cancer progression. *Oncol Letters*. 2020;19(4):3316-3332.
41. Azevedo Martins JM, Rabelo-Santos SH, do Amaral Westin MC, Zeferino LC. Tumoral and stromal expression of MMP-2, MMP-9, MMP-14, TIMP-1, TIMP-2, and VEGF-A in cervical cancer patient survival: a competing risk analysis. *BMC Canc* 2020;20(1):660.
42. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.
43. Asha Nair S, Karunagaran D, Nair MB, Sudhakaran PR. Changes in matrix metalloproteinases and their endogenous inhibitors during tumor progression in the uterine cervix. *J Canc Res Clin Oncol*. 2003;129(2):123-131.
44. Liotta LA, Kohn EC. The microenvironment of the tumour-host interface. *Nature*. 2001;411(6835):375-379.
45. Caley MP, Martins VLC, O'Toole EA. Metalloproteinases and wound healing. *Adv Wound Care*. 2015;4(4):225-234.
46. Paiva KBS, Granjeiro JM. Bone tissue remodeling and development: Focus on matrix metalloproteinase functions. *Arch Biochem Biophys*. 2014;561:74-87.
47. Itoh Y, Nagase H, Nagase H. Matrix metalloproteinases in cancer. *Essays Biochem*. 2002;38:21-36.
48. Wiegand S, Dünne AA, Müller HH, et al. Meta analysis of the significance of matrix metalloproteinases for lymph node disease in patients with head and neck squamous cell carcinoma. *Cancer*. 2005;104(1):94-100.
49. Brew K, Nagase H. The tissue inhibitors of metalloproteinases (TIMPs): An ancient family with structural and functional diversity. *Biochim Biophys Acta Mol Cell Res*. 2010;1803(1): 55-71.
50. Davidson B, Goldberg I, Kopolovic J, et al. Expression of matrix metalloproteinase-9 in squamous cell carcinoma of the uterine cervix-clinicopathologic study using immunohistochemistry and mRNA in situ Hybridization. *Gynecol Oncol*. 1999;72(3):380-386.
51. Mitra A, Chakrabarti J, Banerji A, Chatterjee A. Cell membrane-associated MT1-MMP dependent activation of MMP-2 in SiHa (human cervical cancer) cells. *J Environ Pathol Toxicol Oncol*. 2006;25(4):655-666.
52. Têtu B, Brisson J, Wang CS, et al. The influence of MMP-14, TIMP-2 and MMP-2 expression on breast cancer prognosis. *Breast Cancer Res*. 2006;8(3):R28-R29.
53. Chenard MP, Lutz Y, Mechine-Neuville A, et al. Presence of high levels of MT1-MMP protein in fibroblastic cells of human invasive carcinomas. *Int J Canc*. 1999;82(2):208-212.
54. Walboomers JMM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol*. 1999;189(1):12-19.
55. Zhu D, Ye M, Zhang W. E6/E7 oncoproteins of high risk HPV-16 upregulate MT1-MMP, MMP-2 and MMP-9 and promote the migration of cervical cancer cells. *Int J Clin Exp Pathol*. 2015; 8(5):4981-4989.
56. Muñoz N, Bosch FX, de Sanjosé S, Shah KV. The role of HPV in the etiology of cervical cancer. *Mutat Res Fund Mol Mech Mutagen*. 1994;305(2):293-301.
57. Syrjänen KJ, Syrjänen SM. Human papilloma virus (HPV) infections related to cervical intraepithelial neoplasia (CIN) and squamous cell carcinoma of the uterine cervix. *Ann Clin Res*. 1985;17(2):45-56.
58. Nuovo GJ, MacConnell PB, Simsir A, Valea F, French DL. Correlation of the in situ detection of polymerase chain reaction-amplified metalloproteinase complementary DNAs and their inhibitors with prognosis in cervical carcinoma. *Canc Res*. 1995; 55(2):267-275.
59. Garzetti GG, Ciavattini A, Lucarini G, et al. The role of human papillomavirus DNAs in cervical carcinoma and risk of lymph node metastasis: Association with 72-kilodalton metalloproteinase immunostaining. *Cancer*. 1998;82(5):886-892.
60. Lu J, Chua HH, Chen SY, Chen JY, Tsai CH. Regulation of matrix metalloproteinase-1 by Epstein-Barr virus proteins. *Canc Res*. 2003;63(1):256-262.
61. Fu Y, Liang GY, Chi QJ, Jin XM. Analysis on the correlation between HPV infection and the expression of MMP-2, MMP-7 and MMP-9 in cervical cancer. *J Harbin Med Univ* 2014;48(6): 444-448.
62. Kaewprag J, Umnajvijit W, Ngamkham J, Ponglikitmongkol M. HPV16 oncoproteins promote cervical cancer invasiveness by upregulating specific matrix metalloproteinases. *PLoS One*. 2013;8(8):e71611.
63. Ryzhakova OS, Solovyeva NI. Matrix metalloproteinases (MMP)–MMP-1,-2,-9 and its endogenous activity regulators in transformed by E7 oncogene HPV16 and HPV18 cervical carcinoma cell lines. *Biomed Khim*. 2013;59(5):530-540.
64. Basukala O, Mittal S, Massimi P, Bestagno M, Banks L. The HPV-18 E7 CKII phospho acceptor site is required for maintaining the transformed phenotype of cervical tumour-derived cells. *PLoS Pathog*. 2019;15(5):e1007769.