Original Article

Clinicopathological and prognostic role of MMP-9 in esophageal squamous cell carcinoma: a meta-analysis

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Objective: Many studies reported that matrix metalloproteinase-9 (MMP-9) participated in the development of esophageal squamous cell carcinoma (ESCC) and resulted in poor prognosis, however, they all included few patients and had inconsistent results. So we conducted a meta-analysis to explore the correlation between overexpression of MMP-9 and the clinicopathological characteristics and overall survival (OS) of ESCC.

Methods: PubMed, EMBASE, Web of Science, Chinese Biomedical Literature Database, Google Scholar and other databases were searched for relevant studies. The Newcastle-Ottawa quality assessment scale was used to assess the methodological quality of included study and RevMan 5.2 software was used to conduct meta-analysis.

Results: A total of 35 studies were included, and the results of meta-analysis showed that overexpression of MMP-9 was associated with grade of differentiation [well/moderate *vs.* poor: odds ratio (OR): 0.39, 95% confidence interval (CI): 0.29-0.52; P<0.00001], lymph node metastasis (negative *vs.* positive: OR: 0.24, 95% CI: 0.16-0.34; P<0.00001), TNM stage (T1/T2 *vs.* T3/T4: OR: 0.28, 95% CI: 0.14-0.54; P=0.0002), the depth of invasion (T1/T2 *vs.* T3/T4: OR: 0.29, 95% CI: 0.17-0.49; P<0.00001), and vascular invasion of ESCC (negative *vs.* positive: OR: 0.35, 95% CI: 0.21-0.58; P<0.0001), and also associated with poor overall survival of ESCC (HR: 2.17, 95% CI: 1.32-3.57; P=0.002). Subgroup analysis showed that more than 10% of carcinoma cell staining was associated with significant increase of mortality risk (HR: 2.44, 95% CI: 1.16-5.15; P=0.02), and sensitive analysis suggested that MMP-9 was an independent prognostic factor in ESCC (HR: 1.49, 95% CI: 1.16-1.91; P=0.002).

Conclusions: On the basis of limited evidence, overexpression of MMP-9 may be a potential independent prognosis factor of ESCC patients in Asia, and high-quality studies assessing the prognostic significance of MMP-9 for ESCC patients are still needed.

Keywords: Matrix metalloproteinase-9 (MMP-9); esophageal squamous cell carcinoma (ESCC); overall survival (OS); meta-analysis

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Introduction

Esophageal cancer is one of the most aggressive malignant tumors. The incidence of esophageal adenocarcinoma rose rapidly in the western country in the past two to three decades, esophageal squamous cell carcinoma (ESCC), however, was still much more common in Asian countries, especially in China and Japan (1-3). Despite recent advances in diagnosis and treatment, the overall prognosis for ESCC is still worse than other digestive tract cancers, with

5-year survival of 5-45% (4,5). The treatment failure of ESCC can be explained by the extensive local invasion and regional lymph node metastasis, which make it difficult to completely resect tumors (6).

The migration of tumor cells is associated with the degradation of the extracellular matrix, which could be induced by various proteolytic enzymes, including matrix metalloproteinases (MMPs) (7). There are at least 28 members in the MMP family, and studies had shown that overexpression of MMPs promoted tumor cell detachments and metastasis which resulted in malignant transformation and poor clinical outcome (8-10).

As a member of MMP family, MMP-9 works directly to degrade the extracellular matrix, and was reported to participate in the development of gastric cancer (11), breast cancer (12), colorectal cancer (13), and non-small cell lung cancer (14), and resulted in the poor prognosis of them. Many studies also researched the correlation between MMP-9 expression and ESCC, however, the numbers of patients they included were small, and the conclusions they drew were inconsistent. For example, Gu *et al*. (7) and Tanioka *et al*. (15) reported that MMP-9 was a negative, independent prognostic factor in ESCC and correlated with tumor cell differentiation, vessel permeation, and lymph node metastasis; Lu *et al*. (3) and Zhu *et al*. (16), however, reported that there was no correlation between MMP-9 expression and the clinicopathological characteristics of ESCC, and MMP-9 was not a prognostic factor. This made researchers and clinicians confused, and a meta-analysis was needed to explore the issue clearly. The present meta-analysis evaluated all the studies assessing the correlation between MMP-9 expression and ESCC to explore whether MMP-9 participated in the development of ESCC and whether MMP-9 could be a prognosis factor in ESCC.

Materials and methods

Inclusion and exclusion criteria

Studies were included if they met the following criteria: (I) evaluated the correlation between MMP-9 expression and the clinicopathological parameters or overall survival (OS) of ESCC; (II) assessed MMP-9 expression in the primary ESCC tissues; and (III) were published as full texts. The exclusion criteria were as follow: (I) letters, reviews, case reports, conference abstracts, or editorials; (II) articles had no sufficient data to calculate odds ratio (OR) or hazard ratio (HR); and (III) studies had duplication data.

Search strategy

We conducted the meta-analysis following preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (17). PubMed, EMBASE, Web of Science and Chinese Biomedical Literature Database were searched from their start year up to Mar. 2013 using the terms of "MMP-9", "ESCC". The Mesh terms and their variations were used and no restriction on language was applied. In addition, Google Scholar and other databases were also searched.

Study screening and data extraction

Two reviewers screened each study independently to determine whether it met the inclusion criteria, and resolved disagreements by consensus. For each included study, Zeng R and Duan L independently extracted the following data using a standard form: first author, year of publication, study location, number of patients, test method, cut-off value for positive MMP-9 expression, treatments, clinicopathological parameters (differentiation, lymph node metastasis, TNM stage, the depth of invasion, vascular invasion) and patient survival results.

Methodological assessment

The Newcastle-Ottawa quality assessment scale (18) was used to assess the methodological quality of included studies. The scale assigned 0-9 stars to each study based on three categories (selection, comparability and outcome).

Statistical analysis

For clinicopathological parameters, ORs with 95% confidence intervals (CIs) were calculated. For the outcome of OS, HR with 95% CI was calculated. For studies had not reported HRs directly, we estimated them from available data using methods reported by Tierney *et al*. (19) and Zhang *et al*. (11). Heterogeneity of the studies was evaluated using the χ^2 test and the I^2 statistic. $P<0.1$ or $I^2>50\%$ was considered to be significant for heterogeneity, and a random effects model was used to pool the data, otherwise, a fixed effects model was used. All statistical analyses were conducted using Review Manager 5.2.

For the outcome of OS, subgroup analysis was conducted by different cut-off values for positive MMP-9 expression. We also conducted sensitive analysis only including HRs calculated by multivariate analysis to evaluate whether MMP-9 was an independent prognostic factor in ESCC.

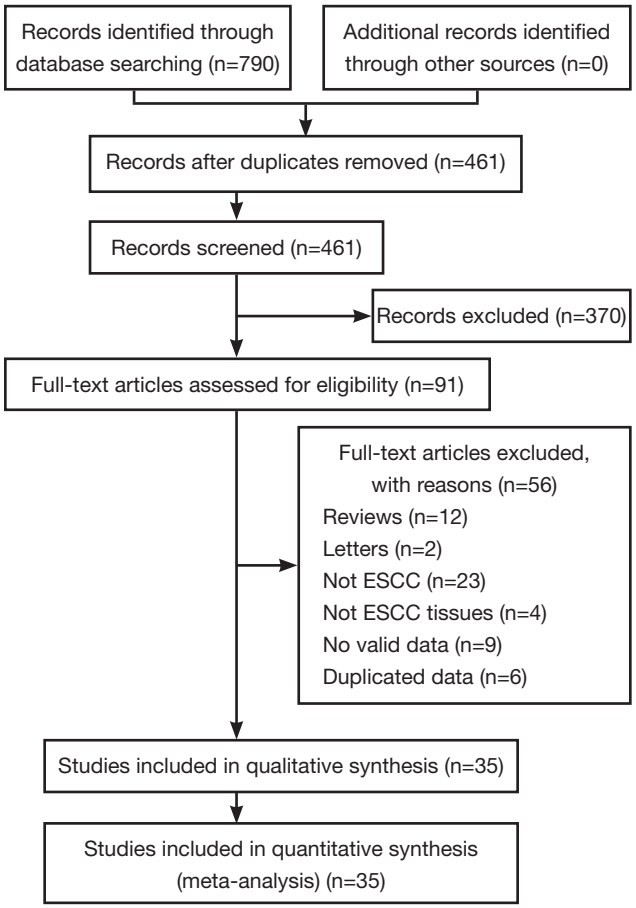

Figure 1 Flow chart of included studies.

A funnel plot recommended by the Cochrane Handbook (20) was made to explore whether publication bias existed in the meta-analysis or not.

Results

Study selection and characteristics

The literature search was performed in March 2013 and 790 potential relevant papers were identified, *Figure 1* details the selection process. Finally, 15 studies (1,3,7,15,16,21-30) and 20 other more (31-50) are included in the meta-analysis, with a total of 2,442 patients. These studies investigate the correlation between MMP-9 expression and ESCC were included in the meta-analysis. The studies were conducted between 2000 and 2012, and the numbers of ESCC patients they included ranged from 41 to 208. One study investigated ESCC patients from India (40), three from Japan (1,15,48), and the others from China. Almost all the studies used immunohistochemical analysis to examine the expression of MMP-9 in ESCC tissues except one study (49), which used indirect immunofluorescent analysis. Only one study had not reported the correlation between MMP-9 expression and ESCC clinicopathological parameters (48). Seven studies reported OS and had available data to calculate HRs (3,7,15,16,34,48,49). *Table 1* shows the main characteristics of all the included studies.

The Newcastle-Ottawa quality assessment scale was used

Table 1 Main characteristics of all studies included in the meta-analysis

First author (Ref.)	Year	Location	No. of patients	Method	Cut-off for MMP-9 positive	High expression (%)	Adjuvant treatment	Clinicopathological factors	Survival analysis	Hazard ratio	Quality score
Chan SM (21)	2009	China	90	IHC	Score ≥2	76 (84.8)	-	①	-	-	5
Chen JX (22)	2009	China	50	IHC	≥10%	45 (90.0)	-	②	-	-	4
Cui HC (23)	2011	China	69	IHC	≥20%, ≥50%	24 (34.8), 11 (15.9)	-	①②	-	-	4
Dong SA (24)	2007	China	55	IHC	≥20%	45 (81.8)	-	①②③④	-	-	5
Fan LR (25)	2010	China	73	IHC	Score ≥2	46 (63.0)	-	①②	-	-	5
Gao SH (26)	2005	China	78	IHC	≥10%	45 (57.7)	-	①②	-	-	4
Gu ZD (7)	2005	China	208	IHC	≥10%	102 (49.0)	-	①②③④⑤	OS	M	7
Guan YW (27)	2011	China	60	IHC	≥25%	45 (75.0)	-	②③④	-	-	4
Guo Y (28)	2011	China	67	IHC	Score ≥2, Score ≥3	45 (78.9), 35 (63.2)	-	①②④	-	-	4

Table 1 (*continued*)

Table 1 (continued)

First author (Ref.)	Year	Location	No. of patients	Method	Cut-off for MMP-9 positive	High expression (%)	Adjuvant treatment	Clinicopathological factors	Survival analysis	Hazard ratio	Quality score
Li Y (29)	2009	China	58	IHC	≥10%	24 (41.4)	-	①②	-	-	5
Li C (30)	2004	China	45	IHC	-	8 (17.8)	-	①②④	-	-	4
Li N (31)	2009	China	50	IHC	≥10%	36 (72.3)	-	②	-	-	4
Li SL (32)	2007	China	62	IHC	Score ≥2	50 (80.6)	-	①②④	-	-	5
Li XL (33)	2009	China	71	IHC	Score ≥3	58 (81.7)	-	①②④	-	-	4
Lin JQ (34)	2003	China	86	IHC	Score ≥3	56 (65.1)	-	①②③	OS	U	6
Liu EN (35)	2009	China	51	IHC	Score ≥3	42 (82.4)	-	①②③④	-	-	4
Lu CL (3)	2011	China	127	IHC	≥50%	74 (58.3)	Chemotherapy (64 patients)	①②③④	OS	M	7
Ma H (36)	2012	China	80	IHC	Score ≥2	65 (81.3)	-	②④	-	-	5
Ohashi K (1)	2000	Japan	77	IHC	-	40 (51.9)	-	①②⑤	-	-	5
Pang X (37)	2011	China	59	IHC	Score ≥2	48 (81.4)	-	①②④	-	-	5
Pu JT (38)	2010	China	60	IHC	Score ≥2	42 (70.0)	-	①②④	-	-	5
Qi B (39)	2008	China	52	IHC	≥50%	38 (73.0)	-	②	-	-	4
Samantaray S (40)	2004	India	58	IHC	-	32 (55.0)	-	①②④	-	-	5
Tanioka Y (15)	2003	Japan	55	IHC	≥10%	26 (47.3)	-	①②⑤	OS	M	7
Tao SB (41)	2010	China	64	IHC	Score ≥2	45 (70.3)	-	①②	-	-	5
Wang XL (42)	2009	China	56	IHC	Score ≥3	34 (60.7)	-	②④	-	-	4
Wang YX (43)	2011	China	49	IHC	≥10%	35 (71.4)	-	①②	-	-	5
Wang YZ (44)	2005	China	75	IHC	≥10%	62 (82.7)	-	②④	-	-	5
Wen HT (45)	2006	China	41	IHC	≥25%	26 (63.4)	-	②④	-	-	4
Wu TT (46)	2009	China	80	IHC	≥20%	65 (81.3)	-	②	-	-	4
Xiong SB (47)	2007	China	57	IHC	≥50%	47 (82.5)	-	①②	-	-	5
Yamamoto H (48)	2004	Japan	100	IHC	≥10%	56 (56.0)	-	–	OS	U	6
Yu JL (49)	2010	China	45	IIF	-	28 (62.2)	-	①②③	OS	U	6
Zhao WP (50)	2005	China	75	IHC	≥25%	56 (74.7)	-	①②	-	-	5
Zhu SC (16)	2008	China	59	IHC	Score ≥2	50 (84.7)	Radiotherapy alone	④	OS	M	5

IHC, immunohistochemistry; IIF, indirect immunofluorescent; OS, overall survival; M, hazard ratio come from multivariate analysis; U, hazard ratio come from univariate analysis; ①, differentiation; ②, lymph node metastasis; ③, TNM stage; ④, depth of invasion; ⑤, vascular invasion.

to assess the methodological quality of included studies. The numbers of stars achieved by them ranged from 4 to 7: 13 studies achieved 4 stars, 16 studies achieved 5, 3 studies achieved 6, and 3 studies achieved 7.

Meta-analysis results

There were 34 studies reported the correlation between MMP-9 expression and clinicopathological characteristics of ESCC. As shown in *Table 2*, the results of meta-analysis showed that overexpression of MMP-9 was associated with grade of differentiation (well/moderate *vs.* poor: OR: 0.39, 95% CI: 0.29-0.52; P<0.00001), lymph node metastasis (negative *vs.* positive: OR: 0.24, 95% CI: 0.16-0.34; P<0.00001), TNM stage (T1/T2 *vs.* T3/T4: OR: 0.28, 95% CI: 0.14-0.54; P=0.0002), the depth of invasion (T1/T2

Table 2 Main meta-analysis results

Clinicopathological parameter	No. of studies	No. of patients	Heterogeneity	Statistical model used	OR (95% CI), P
Grade of differentiation (well/moderate *vs.* poor)	25	1,807	P=0.07; I^2=32%	Random	0.39 (0.29-0.52), P<0.00001
Lymph node metastasis (negative *vs.* positive)	33	2,258	P<0.0001; I^2=58%	Random	0.24 (0.16-0.34), P<0.00001
TNM stage (T1/T2 *vs.* T3/T4)	8	722	P=0.007; I^2=64%	Random	0.28 (0.14-0.54), P=0.0002
The depth of invasion (T1/T2 *vs.* T3/T4)	16	1,150	P=0.0003; I^2=64%	Random	0.29 (0.17-0.49), P<0.00001
Vascular invasion (negative *vs.* positive)	4	381	P=0.45; I^2=0%	Fixed	0.35 (0.21-0.58), P<0.0001

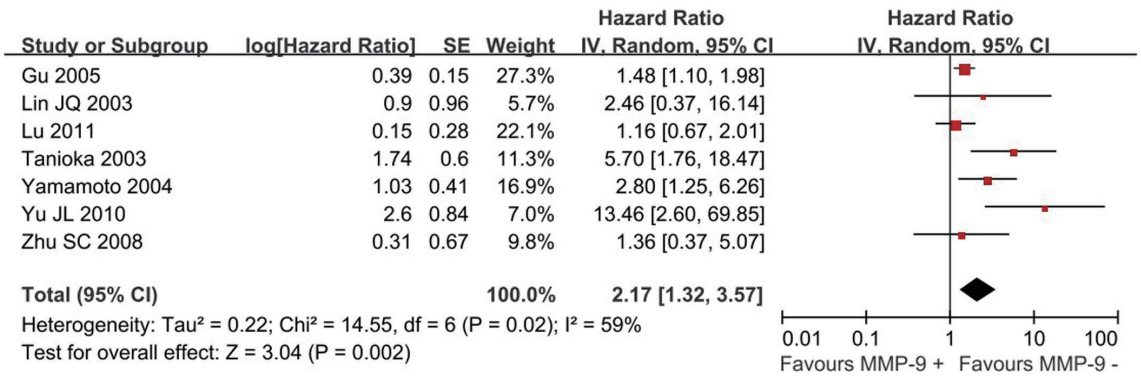

Figure 2 Meta-analysis of effects of MMP-9 on OS of patients with ESCC.

Table 3 Subgroup analysis and sensitive analysis on the outcome of OS

	No. of studies	No. of patients	Heterogeneity	Statistical model used	HR (95% CI), P
More than 10% staining as cut-off value for MMP-9 positive	3	363	P=0.04; I^2=69%	Random	2.44 (1.16-5.15), P=0.02
HR calculated by multivariate analysis	4	449	P=0.12; I^2=48%	Fixed	1.49 (1.16-1.91), P=0.002

vs. T3/T4: OR: 0.29, 95% CI: 0.17-0.49; P<0.00001), and vascular invasion (negative *vs.* positive: OR: 0.35, 95% CI: 0.21-0.58; P<0.0001).

Seven studies reported the outcome of OS and had available data to calculate HRs. However, significant heterogeneity existed among them (I^2=59%, P=0.02), so, a random-effects model was used to pool the data, and the results showed that overexpression of MMP-9 was associated with significant increase of mortality risk (HR: 2.17, 95% CI: 1.32-3.57; P=0.002), as shown in *Figure 2*. Subgroup analysis showed that more than 10% of carcinoma cell staining (i.e., chose ≥10% as cut-off value for MMP-9 positive) was associated with significant increase of mortality risk (HR: 2.44, 95% CI: 1.16-5.15; P=0.02), as shown in *Table 3*. Sensitive analysis only including HRs calculated by multivariate analysis also showed that MMP-9 overexpression was correlated with poor survival (HR: 1.49, 95% CI: 1.16-1.91; P=0.002), as shown in *Table 3*.

Figure 3 shows the funnel plot for the outcome of the correlation between MMP-9 expression and the grade of ESCC differentiation, and it showed no asymmetry exhibiting, demonstrating that there was probably no

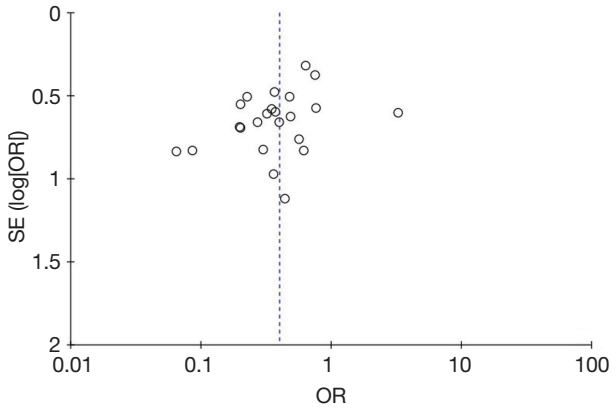

Figure 3 Funnel plot for the assessment of potential publication bias in studies of MMP-9 expression in patients with ESCC.

publication bias.

Discussion

The present study is the first meta-analysis exploring the correlation between MMP-9 expression and the clinicopathological characteristics and prognosis of ESCC. We analyzed the data of 2,442 ESCC patients from 35 individual studies, and showed that overexpression of MMP-9 was significantly associated with the depth of invasion, lymph node metastasis, distant metastasis, vascular invasion and grade of differentiation. The most important finding of the present study was that overexpression of MMP-9 was associated with poor OS of ESCC patients.

MMPs are multi-domain, zinc-dependent endopeptidases, and all of them share homologous amino acid (AA) sequences (9,48). The structure of most MMPs (except MMP-7, -23 and -26) includes a propeptide containing about 80 AA, a catalytic domain with about 170 AA, followed by a linker peptide called the 'hinge region', of variable length, and a hemopexin domain of about 200 AA (10). There are six categories in the MMP family: collagenases, gelatinases, stromelysins, matrilysins, membrane-type MMPs, and other MMPs (10).

As proteolytic enzymes, MMPs play important roles in the degradation of the extracellular matrix, leading to the proteolysis of microvessel basement membranes and invasion of endothelium, which contribute highly to the first step of tumor development and metastasis (8,9,48).

MMP-9, categorized in the subgroup of gelatinases, works directly to degrade the extracellular matrix (10). Many systematic reviews reported MMP-9 participated in the development of cancers, and resulted in poor prognosis. Zhang *et al*. (11) conducted a meta-analysis including 11 studies (covering 1,700 patients with gastric cancer), and reported that positive MMP-9 expression had an adverse impact on OS in gastric cancer patients (HR: 1.25, 95% CI: 1.11-1.40). A meta-analysis conducted by Song *et al*. (12) analyzed 15 studies (including 2,344 breast cancer patients), and the results suggested that MMP-9 overexpression had an unfavorable impact on both OS (HR: 1.70, 95% CI: 1.41-2.04) and relapse free survival (RFS) (HR: 1.54, 95% CI: 1.17-2.01) in breast cancer patients. The results of the meta-analysis conducted by Li *et al*. (13) (including 1,379 colorectal cancer patients) also found that MMP-9 overexpression was associated with poorer OS (HR: 1.78, 95% CI: 1.31-2.41) as well as RFS (HR: 1.92, 95% CI: 1.46-2.53) in patients with colorectal cancer. Seventeen studies covering 2,029 non-small cell lung cancer cases were analyzed by the study of Peng *et al*. (14), and the combined HR of 1.84 (95% CI: 1.62-2.09) suggested that MMP-9 overexpression was associated with a poor prognosis in patients with NSCLC.

The correlation between MMP-9 expression and ESCC was also explored by many studies, however, the patients they included were too few to draw a firm conclusion. Moreover, the studies had different cut-off values for positive MMP-9 expression and different adjuvant treatments, which made them had inconsistent conclusions (3,7,15,16). The present study conducted a comprehensive search for related studies, and finally included 35 studies (including 2,442 patients) to investigate whether MMP-9 was correlated with clinicopathological characteristics of ESCC and whether MMP-9 could be a prognostic factor in ESCC. The results of meta-analysis showed that overexpression of MMP-9 was associated with poor cell differentiation, poor TNM stage, lymph node metastasis, vascular invasion as well as poor prognosis of ESCC, which suggested that MMP-9 participated in the development of ESCC and could be a prognostic factor in ESCC. We also conducted sensitive analysis only including HRs calculated by multivariate analysis (Cox proportional hazards model), and found that MMP-9 was an independent prognostic factor in ESCC (HR: 1.49, 95% CI: 1.16-1.91; P=0.002). Given the included studies were limited, we only conducted subgroup analysis on studies choosing 10% staining as cut-off value, but we failed to conducted subgroup analysis by different adjuvant treatments. Future studies should focus on what cut-off value is optimal, and whether different treatments affect the prognostic power of MMP-9.

Our study had several limitations. Firstly, only seven studies (including 680 ESCC patients) had available data to calculate HRs, which made it difficult to draw a firm conclusion on the prognostic value of MMP-9 for ESCC. Secondly, given all the included studies investigated ESCC patients from Asia, especially from China and Japan, the results may just represent the correlation between MMP-9 expression and ESCC patients from Asia. Thirdly, most included studies had poor methodological quality, which just achieved four to five stars assessed by the Newcastle-Ottawa quality assessment scale, and most of them did not had follow-up period long enough.

In conclusion, the meta-analysis suggested that MMP-9 participated in the development of ESCC, and may be a potential independent prognostic factor in ESCC patients in Asia. High-quality studies assessing the prognostic significance of MMP-9 for ESCC patients are still needed.

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