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ORIGINAL PAPER

Prognostic significance of vascular endothelial growth factor expression in gastric carcinoma: a meta-analysis

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Abstract
Purpose The purpose of this study was to comprehensively and quantitatively summarize available evidences for the use of VEGF protein to evaluate the clinicopathological and prognostic role of VEGF expression in Asian patients with gastric cancer.
Method Searches were applied to MEDLINE, EMBASE, and the Cochrane Library databases until June 2010, without language restrictions. A meta-analysis was performed to clarify the impact of VEGF expression on clinicopathological parameters or over survival (OS) in gastric cancer.
Results Our combined results showed that VEGF expression in Asian patients with gastric cancer was significantly higher in the case–control studies (1,194 patients and 1,618 controls) (odds ratio [OR] = 112.41, 95% confidence interval [CI] = 64.12–197.06). All the analyses estimated favored a stronger link between the high VEGF expression and the poor 5-year overall survival (1,236 patients) (risk ratio [RR] = 2.45, 95% CI = 2.11–2.83, $P = 0.000$). When stratifying the studies by the pathological variables, the depth of invasion (3,094 patients) (OR = 1.95, 95% CI = 1.40–2.71, $P = 0.000$), lymph node metastasis (3,240 patients) (OR = 1.82, 95% CI = 1.29–2.57, $P = 0.001$), distant metastasis (1,980 patients) (OR = 2.76, 95% CI = 1.22–6.25, $P = 0.015$), vascular invasion (1,803 patients) (OR = 2.61, 95% CI = 2.09–3.27, $P = 0.000$), and TNM stage (1,819 patients) (OR = 1.92, 95% CI = 1.57–2.36, $P = 0.000$) provided significant prognostic information.
Conclusion Our results indicate that VEGF can potently predict the overall survival in Asian patients with gastric cancer. Importantly, VEGF may be converted from candidate to the routine clinical setting for clinicians to predict the outcome of single patient with gastric carcinoma.

Keywords Gastric cancer · Vascular endothelial growth factor · Prognostic factor · Angiogenesis

Abbreviations

VEGF	Vascular endothelial growth factor
RR	Risk ratio
OR	Odds ratio
OS	Overall survival
VEGFR2	Vascular endothelial growth factor receptor 2

Introduction

Gastric cancer is the second leading cause of death among all cancers worldwide. Despite the decline in gastric cancer rates in most of the Western world (Parkin et al. 2005), a

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2005 analysis of the incidence and mortality showed that gastric cancer remains a serious fatal disease and the most common cancer in both sexes in Eastern Asia (Parkin et al. 2001). To improve clinical care, biological prognostic markers are highly desirable and must be identified in early stages of gastric cancer.

Angiogenesis is defined as the process of new capillary formation from preexisting vasculature (Folkman 1995). In regulating tumor angiogenesis, the vascular endothelial growth factor (VEGF) family plays a determinant role. VEGF induces cell proliferation, differentiation, and migration of vascular endothelial cells (Ferrara and Davis-Smyth 1997). VEGF is also required for the establishment of haematopoiesis in malignant tumors, which benefits primary tumor growth and metastasis (Kut et al. 2007). Recently, targeting constitutive VEGF and/or its receptors has been an attractive approach for cancer therapy (Jubb et al. 2006).

The prognostic potential of VEGF immunohistochemical expression has been reported by many literatures (Cheng et al. 2010; Wei et al. 2009; Li et al. 2008; Wang et al. 2008; Liu et al. 2007; Chen et al. 2007; Han et al. 2007; Ma et al. 2007; Gao et al. 2007; Lou et al. 2005; Du et al. 2003; Song et al. 2002; Jiao et al. 2005; Tang et al. 2008; Yu et al. 2003; Shi et al. 2003; Feng et al. 2002; Kolev et al. 2007; Mizokami et al. 2006; Urano et al. 2006; Aoyagi et al. 2005; Koga et al. 2004; Kaneko et al. 2003; Takahashi et al. 2003; Kawabe et al. 2002; Kimura et al. 2001; Ichikura et al. 2001; Kabashima et al. 2001; Maehara et al. 2000; Saito et al. 1999; Tomoda et al. 1999; Tanigawa et al. 1997; Baba et al. 1998; Maeda et al. 1998; Lee et al. 2009, 2010; Oh et al. 2008; Choi et al. 2006; Park et al. 2005; Joo et al. 2002, 2003). And, the most widely studied prognostic factors on VEGF refer to variables including tumor size, location, histo-differentiation, depth of invasion, lymph node status, distant metastasis, TNM stage, and vascular invasion. Although implicated in gastric cancer pathogenesis, the results on the correlation between VEGF and those factors are conflicting and inconclusive (Kyzas et al. 2005). It is unknown whether the differences in these investigations have been due to their limited sample size or genuine heterogeneity. It is estimated that almost two-thirds of gastric cancer occur in Asia (China and Japan) (Parkin et al. 2005). Therefore, in order to gain a full insight into the prognostic value of VEGF immunohistochemical expression in Asian patients with gastric cancer, we enrolled data only from cohorts of medical centers in Asia. The prognostic significance of our present analysis allows a better understanding of the natural history of gastric cancer; in addition, the use of VEGF may be converted from candidate to the routine clinical setting for clinicians to predict the outcome of single patient.

Materials and methods

Literature search

The meta-analysis was performed according to a predefined written protocol. Searches were applied to the following electronic databases: MEDLINE, EMBASE, and the Cochrane Library (last search update June 2010), without language restrictions. The search strategy was based on combinations [(VEGF or neovascularization) and "prognosis" and ("gastric" or "stomach"), "carcinoma" or "cancer" or "tumor"]. References of retrieved articles were cross-searched to identify any studies missed by the electronic search strategies. Our initial selection of all candidate articles was relied on careful screening of their abstracts by two independent reviewers. Primary studies that reported data required for meta-analysis were identified and categorized based on full-text review. Authors of eligible studies were contacted for the supplement of additional data relevant to meta-analysis.

Inclusion criteria for primary studies were as follows: (1) proven diagnosis of gastric cancer and normal gastric epithelial mucosa in humans; (2) VEGF evaluation with immunohistochemistry methods, and (3) data performed using cohorts from medical centers in Asian population.

Data extraction

Required information from all full publications was extracted carefully in duplicate by two of the authors (Chen and Li), using a prespecified data collection form with the following item: the first author, year of publication, nation, VEGF assessment method, cutoff value of VEGF positivity, number of readers, blinded reading, number of patients and controls included in the study, number of association between VEGF expression and overall 5-year survival, and number of events in each category of VEGF expression on clinicopathological factors including sex, age, tumor location, size, histo-differentiation, depth of invasion, lymph node status, distant metastasis, TNM stage, and vascular invasion of gastric cancer analyzed. Disagreement was resolved by consensus to all items.

Methodological assessment

There was no prespecified sample size or follow-up period for a study to be included in our meta-analysis. We did not weigh each study by a quality score, because no such score has received general agreement for use in a meta-analysis, especially of observational studies, making more difficult the evaluation of its quality (Altman 2001). Studies were not blinded to the readers, but exclusion was always decided without the knowledge of clinical outcome of each

study. We tried carefully to avoid duplication of data, by examining each publication the names of all authors and the different medical centers involved. When studies has same author, however, individuals came from different cohorts, we regarded as two independent data analyzed. Whenever reports pertained to overlapping patients, we selected the study where the most individuals were investigated.

Statistical analysis

Actually, we analyzed three categories of stratified models: the first stratified multivariate model was performed to confirm whether VEGF was highly expressed in gastric cancer patients in comparison with the normal gastric mucosa. The second outcome of meta-analysis was to measure the impact of VEGF expression on survival by estimating the risk ratio (RR) between the positive or negative VEGF groups. And the third interest was to examine the prognostic value of VEGF expression that was corrected for the clinical variables including age, sex, tumor size, location and histo-differentiation, depth of invasion, vascular invasion, lymph node status, distant metastasis, and TNM stage.

According to clinical characteristics, well and moderate differentiation were combined and poor and undifferentiation were combined; T_1 and T_2 were combined and T3 and T_4 were combined; Stage I and Stage II were combined and Stage III and Stage IV were combined; tumors larger than 5 cm in size were combined and tumors less than 5 cm were combined; also, patients who had greater than 60 years of age were combined and patients who had lesser than 60 years of age were combined.

All statistical analyses were performed using Statistical Analysis System software (STATA SE 9.0), and the P value for the summary effect <0.05 with two-tailed was considered statistically significant. The heterogeneity of all involved studies was assessed by a statistical value I^2. When I^2 was lower than 50%, the studies with an acceptable heterogeneity were considered, and then the fixed-effects model with Mantel–Haenszel method was used; otherwise, a random effect model with the DerSimonian and Laird (DL) method was adopted. The combined RRs or odd ratio (ORs) were initially estimated using Forrest plots graphically.

Assessment of publication bias was investigated for each of the pooled study groups mainly by the Egger's linear regression test. As supplement approach, the Begg's rank correlation also was applied to assess the potential publication bias, when $P > 0.05$ was considered that there was no publication bias in the study.

Result

Description of studies identified in meta-analysis

A total of 239 references were retrieved for initial review using search strategies as described. After exclusion of the articles that were out of the scope of our meta-analysis, we identified 99 potential studies for detail evaluation. Upon further review, 58 articles were eliminated due to the following reasons: 5 studies performed different cohorts outside Asian (1 report originated from Timisoara, 1 from Turkey, 1 from Italy, and 2 from Greece); 21 studies overlapped with others; 7 studies measured VEGF with other method rather than immunohistochemistry; and 25 studies lacked informative clinical data to create 2×2 tables for meta-analysis. Finally, 18 studies were performed on the association of VEGF expression between gastric cancer and normal gastric mucosa (Cheng et al. 2010; Li et al. 2008; Liu et al. 2007; Chen et al. 2007; Han et al. 2007; Du et al. 2003; Song et al. 2002; Jiao et al. 2005; Tang et al. 2008; Feng et al. 2002; Koga et al. 2004; Kawabe et al. 2002; Saito et al. 1999; Tomoda et al. 1999; Maeda et al. 1998; Lee et al. 2010; Joo et al. 2002, 2003); 11 studies dealt with the impact of VEGF expression on overall survival (Wei et al. 2009; Li et al. 2008; Ma et al. 2007; Kolev et al. 2007; Aoyagi et al. 2005; Kimura et al. 2001; Ichikura et al. 2001; Maehara et al. 2000; Saito et al. 1999; Maeda et al. 1998; Song et al. 2002); and 31 studies evaluated the prognostic value of VEGF expression and clinicopathological factors (Cheng et al. 2010; Li et al. 2008; Wang et al. 2008; Ma et al. 2007; Gao et al. 2007; Lou et al. 2005; Du et al. 2003; Song et al. 2002; Tang et al. 2008; Yu et al. 2003; Shi et al. 2003; Feng et al. 2002; Kolev et al. 2007; Mizokami et al. 2006; Urano et al. 2006; Kaneko et al. 2003; Takahashi et al. 2003; Kimura et al. 2001; Ichikura et al. 2001; Kabashima et al. 2001; Maehara et al. 2000; Saito et al. 1999; Tanigawa et al. 1997; Baba et al. 1998; Maeda et al. 1998; Lee et al. 2009, 2010; Oh et al. 2008; Choi et al. 2006; Park et al. 2005; Joo et al. 2002, 2003). After selection, a total of 41 literatures were finally enrolled in our meta-analysis including both English and non-English language articles, 5 for Chinese with English abstract (Wei et al. 2009; Wang et al. 2008; Chen et al. 2007; Du et al. 2003; Jiao et al. 2005), and 1 for Korean (Park et al. 2005). For all the patients, measurements had been taken in the primary tumor, and all specimens had been taken before chemotherapy or radiotherapy. The main features of eligible studies in our meta-analysis and the number of relation of VEGF expression with clinicopathological variables are summarized in Tables 1 and 2, respectively.

Table 1 Main characteristics of the 41 studies included in the final meta-analysis

First author of issue (reference)	Year of publication	Language	Population	Study from PubMed	Number of patients (M/F)	Median age (years)	VEGF detection method	Cutoff for VEGF positivity (%)	Blinded reading	Reader (s) (n)	RR estimate	Survival analysis	Results
Cheng et al.	2010	English	China	Yes	57 (8)	56.8	Antibody	>25	?	2	Reported in text	OS	Positive
Wei et al.	2009	Chinese	China	Yes	49 (19)	56	Antibody	>10	?	?	Reported in text	OS	Positive
Li et al.	2008	English	China	Yes	79 (39)	57.8	Antibody	>25	?	2	Miss	OS	Positive
Wang et al.	2008	Chinese	China	Yes	82 (41)	65.5	Antibody	>25	?	2	Reported in text	OS	Positive
Liu et al.	2007	English	China	Yes	76 (32)	56	Antibody	>5	Yes	3	Miss	?	?
Chen et al.	2007	Chinese	China	Yes	78 (26)	62.5	Antibody	>25	?	?	Miss	?	?
Han et al.	2007	English	China	Yes	?	?	Antibody	>25	?	2	Miss	?	?
Ma et al.	2006	English	China	Yes	79 (39)	57.2	Antibody	>10	Yes	2	Miss	OS	Positive
Gao et al.	2006	English	China	Yes	26 (14)	55.2	Antibody	>10	?	?	Miss	?	?
Lou et al.	2005	English	China	Yes	?	41	Antibody	>5	?	?	Miss	?	?
Du et al.	2003	English	China	Yes	55 (25)	59	Antibody	>10	Yes	2	Miss	?	?
Song et al.	2002	English	China	Yes	35 (11)	56.7	Antibody	>10	?	?	Miss	OS	Positive
Jiao et al.	2005	Chinese	China	Yes	46 (34)	53.5	Antibody	>10	Yes	2	Miss	?	?
Tang et al.	2008	English	China	Yes	38 (15)	57	Antibody	>10	Yes	2	Miss	?	?
Yu et al.	2003	English	China	Yes	31 (14)	58.5	Antibody	>5	?	?	Miss	?	?
Shi et al.	2003	English	China	Yes	198 (83)	55.6	Antibody	>5	?	?	Reported in text	OS	Positive
Feng et al.	2002	English	China	Yes	?	61	Antibody	>10	Yes	2	Miss	?	?
Kolev et al.	2007	English	Japan	Yes	122 (47)	59.6	Antibody	>25	Yes	2	Miss	OS, DFS	Positive
Mizokami et al.	2006	English	Japan	Yes	85 (41)	65.2	Antibody	>5	Yes	2	Miss	?	?
Urano et al.	2006	English	Japan	Yes	?	?	Antibody	>10	?	?	Miss	OS	Negative
Aoyagi et al.	2005	English	Japan	Yes	24 (16)	59.7	Antibody	>25	?	?	Miss	OS	Positive
Kaga et al.	2003	English	Japan	Yes	74 (34)	62	Antibody	>5	Yes	2	Miss	?	?
Kaneko et al.	2003	English	Japan	Yes	72 (29)	60.8	Antibody	>50	Yes	2	Miss	OS	Negative
Takahashi et al.	2003	English	Japan	Yes	32 (21)	59.5	Antibody	>10	?	?	Reported in text	OS	Positive
Kawabe et al.	2002	English	Japan	Yes	75 (15)	66.1	Antibody	>10	Yes	2	Miss	?	?
Kimyra et al.	2001	English	Japan	Yes	66 (36)	61	Antibody	>5	Yes	2	Miss	OS	Positive
Ichikura et al.	2001	English	Japan	Yes	47 (29)	?	Antibody	>10	Yes	2	Miss	OS	Positive
Kabashima et al.	2001	English	Japan	Yes	68 (37)	58	Antibody	>10	?	?	Miss	?	?
Maehara et al.	2000	English	Japan	Yes	?	?	Antibody	>5	Yes	2	Reported in text	OS	Positive
Saito et al.	1999	English	Japan	Yes	61 (57)	61	Antibody	>10	?	2	Reported in text	OS	Positive
Tomoda et al.	1999	English	Japan	Yes	60 (34)	?	Antibody	>5	?	2	Miss	?	?
Tanigawa et al.	1997	English	Japan	Yes	?	?	Antibody	?	Yes	2	Miss	OS	Negative

Table 1 continued

First author of issue (reference)	Year of publication	Language	Population	Study from PubMed	Number of patients (M/F)	Median age (years)	VEGF detection method	Cutoff for VEGF positivity (%)	Blinded reading	Reader (s) (n)	RR estimate	Survival analysis	Results
Baba et al.	1998	English	Japan	Yes	26 (14)	56.9	Antibody	>30	Yes	2	Miss	?	?
Maeda et al.	1998	English	Japan	Yes	95 (34)	59.3	Antibody	>5	Yes	2	Reported in text	OS	Positive
Lee et a l	2009	English	Korea	Yes	71 (31)	62.3	Antibody	>30	?	2	Miss	?	?
Lee et al.	2009	English	Korea	Yes	177 (198)	60	Antibody	>10	Yes	2	Reported in text	OS, DFS	Negative
Oh et al.	2008	English	Korea	Yes	67 (47)	59	Antibody	>10	Yes	2	Miss	?	?
Choi et al.	2006	English	Korea	Yes	88 (49)	56	Antibody	>50	Yes	2	Miss	?	?
Park et al.	2005	Korean	Korea	Yes	?	?	Antibody	>10	?	2	Miss	?	?
Joo et al.	2003	English	Korea	Yes	64 (33)	59.7	Antibody	>10	Yes	2	Miss	?	?
Joo et al.	2002	English	Korea	Yes	99 (46)	59.2	Antibody	>10	Yes	2	Miss	OS	Negative

RR, risk ratio; OS, overall survival; RFS, relapse-free survival; Positive, inverse relationship between VEGF expression and survival; Negative, no relationship. "Reader" are readers of the histologic slides, "blinded reading" means that readers of the slides without knowledge of the clinical outcome, and "?" corresponds to missing data

Main results

Correlation of VEGF expression between gastric cancer and normal gastric mucosa

The combined results from all studies showed that VEGF expression in patients with gastric cancer was extremely higher in comparison with the normal gastric mucosa in 18 studies (1,194 patients and 1,618 controls) (OR = 112.41; 95% CI = 64.12–197.06; $P = 0.000$). When stratifying for race, results were similar among China, Japan, and Korea (Table 3).

Correlation between VEGF expression and overall survival in 5 years

In total, there were 11 studies including 1,236 patients to evaluate the relation of VEGF expression and overall 5-year survival. All studies favored a stronger link between high VEGF expression and poor survival. Mortality was much higher in VEGF-positive patients than VEGF-negative patients among Asians (RR = 2.45; 95% CI = 2.11–2.83; $P = 0.000$). When stratifying for race, results were also consistent with China and Japan (Figs. 1, 2, 8; Table 3).

Correlation between VEGF expression and clinicopathological characteristics

When stratifying for the different variables by the depth of invasion of gastric cancer, statistical significance was observed. Patients with T_3 and T_4 gastric cancer had a much higher VEGF expression in 25 studies (3,094 patients) (OR = 1.95; 95% CI = 1.40–2.71; $P = 0.000$) than those with T_1 and T_2 gastric cancer (Fig. 3; Table 3). When stratifying for lymph node status of gastric cancer, statistically significant results also appeared that VEGF expression was associated with lymph node metastasis in 28 studies (3,240 Asian patients) (OR = 1.82; 95% CI = 1.29–2.57, $P = 0.001$) (Fig. 4; Table 3), but not in Japanese in 11 studies (1,308 patients) (OR = 0.97; 95% CI = 0.61–1.57; $P = 0.915$). When stratifying for the distant metastasis of gastric cancer, there was a statistical significance that VEGF expression was associated with distant metastasis in 16 studies (1,980 patients) (OR = 2.76; 95% CI = 1.22–6.25; $P = 0.015$) (Fig. 5; Table 3), but negative in both Japanese in 6 studies (768 patients) (OR = 2.37; 95% CI = 0.85–6.57; $P = 0.097$) and Korean in 5 studies (813 patients) (OR = 0.89; 95% CI = 0.26–2.99; $P = 0.848$). When stratifying for vascular invasion, the overexpression of VEGF is significantly linked to the presence of vascular invasion in 14 studies (1,803 patients) (OR = 2.61; 95% CI = 2.09–3.27;

Table 2 Main characteristics of 37 studies relating VEGF expression on clinicopathological factors

First author	Year of publication	Language	Nation	Number of case/control	Number of patients				
					T T3/T4 (T1/T2)	N (Positive/ Negative)	M (Positive/ Negative)	Vascular invasion (Positive/ Negative)	TNM TIII/IV (TI/TII)
Cheng et al.	2010	English	China	65 (30)	31 (34)	21 (44)	23 (42)	32 (33)	–
Li et al.	2008	English	China	118 (118)	71 (47)	84 (34)	55 (63)	89 (29)	–
Wang et al.	2008	Chinese	China	–	54 (69)	68 (55)	–	37 (86)	52 (71)
Liu et al.	2007	English	China	108 (6)	–	–	–	–	–
Chen et al.	2007	Chinese	China	104 (30)	–	–	–	–	–
Han et al.	2007	English	China	31 (15)	–	–	–	–	–
Ma et al.	2006	English	China	–	71 (47)	83 (35)	55 (63)	–	71 (47)
Gao et al.	2006	English	China	–	–	22 (18)	–	–	12 (28)
Du et al.	2003	English	China	80 (20)	41 (39)	28 (52)	–	–	–
Song et al.	2002	English	China	45 (20)	34 (12)	37 (9)	–	–	38 (8)
Jiao et al.	2005	Chinese	China	80 (20)	–		–	–	–
Tang et al.	2008	English	China	53 (40)	36 (17)	32 (21)	11 (42)	–	32 (31)
Yu et al.	2003	English	China	–	–	27 (18)	8 (37)	–	22 (23)
Shi et al.	2003	English	China	–	138 (94)	64 (168)	–	39 (193)	–
Feng et al.	2002	English	China	50 (10)	44 (11)	35 (20)	–	–	22 (33)
Kolev et al.	2007	English	Japan	–	80 (89)	73 (96)	–	83 (86)	50 (119)
Mizokami et al.	2006	English	Japan	–	45 (100)	51 (75)	–	27 (99)	–
Urano et al.	2006	English	Japan	–	45 (100)	78 (66)	9 (136)	24 (115)	75 (70)
Kaga et al.	2003	English	Japan	108 (108)	–	–	–	–	–
Kaneko et al.	2003	English	Japan	–	54 (47)	37 (64)	9 (92)	46 (55)	–
Takahashi et al.	2003	English	Japan	–	–	–	9 (44)	–	–
Kawabe et al.	2002	English	Japan	91 (91)	–		–	–	–
Kimyra et al.	2001	English	Japan	–	11 (91)	91 (11)	–	19 (83)	–
Ichikura et al.	2001	English	Japan	–	36 (40)	52 (24)	–	43 (33)	–
Maehara et al.	2001	English	Japan	–	–	70 (35)	–	10 (95)	–
Saito et al.	1999	English	Japan	118 (118)	85 (55)	48 (70)	6 (134)	81 (37)	53 (65)
Tomoda et al.	1999	English	Japan	94 (94)	–	–	–	–	–
Tanigawa et al.	1997	English	Japan	–	100 (100)	100 (100)	100 (100)	100 (100)	–
Baba et al.	1998	English	Japan	–	31 (9)	29 (9)	–	–	–
Maeda et al.	1998	English	Japan	129 (129)	73 (56)	80 (49)	14 (115)	71 (58)	79 (50)
Lee et a l.	2009	English	Korea	102 (102)	–	–	–	–	–
Lee et al.	2009	English	Korea	–	74 (300)	203 (171)	8 (336)	–	–
Oh et al.	2008	English	Korea	–	37 (77)	73 (41)	–	–	47 (67)
Choi et al.	2006	English	Korea	–	92 (45)	58 (79)	12 (125)	–	90 (47)
Park et al.	2005	Korean	Korea	–	60 (30)	50 (40)	14 (76)	–	49 (41)
Joo et al.	2003	English	Korea	97 (97)	64 (33)	54 (43)	12 (85)	–	52 (45)
Joo et al.	2002	English	Korea	145 (145)	89 (56)	75 (70)	20 (125)	–	72 (73)

Case, gastric cancer; Control, normal gastric mucosa; T, the depth of invasion; N, lymph node status; M, distant metastasis; Positive, patients have VEGF expression; Negative, patients have no VEGF expression. "–" corresponds to missing data and do not be analyzed in meta-analysis

$P = 0.000$) (Fig. 6; Table 3). When further stratifying for TNM stage, VEGF expression of patients with stages III and IV gastric cancer was much higher than those with stage I and II gastric cancer in 17 studies (1,819 patients) (OR = 1.92; 95% CI = 1.57–2.36; $P = 0.000$) (Figs. 7, 8; Table 3).

We also observed trends toward a correlation of VEGF positivity with age older than 60 years ($P = 0.005$), but not for sex ($P = 0.331$), size ($P = 0.551$), location ($P = 0.837$), and degree of differentiation ($P = 0.396$) in the whole Asians, except for those patients with poor differentiation in Chinese who had a significantly higher

Table 3 Meta-analysis of VEGF expression and gastric cancer

Stratification of gastric cancer	Nation	Number of studies	Total patients	Model	OR (RR) (95% CI)	*P* value	I^2 for heterogeneity	
Gastric cancer–normal gastric mucosa	China	10	734	Fixed	81.761 (37.887–176.441)	0.000	0	0.117
	Japan	5	540	Fixed	116.215 (39.830–339.085)	0.000	0	
	Korea	3	344	Fixed	201.529 (55.567–730.901)	0.000	29	
	All	18	1,618	Fixed	112.411 (64.123–197.063)	0.000	0	
Overall 5-year survival	China	4	350	Fixed	3.439 (2.624–4.509)	0.000	0	0.436
	Japan	7	886	Fixed	2.158 (1.811–2.571)	0.000	40	
	All	11	1,236	Random	2.445 (2.111–2.831)	0.000	51	
The depth of invasion	China	9	890	Random	2.947 (1.498–5.796)	0.002	78	0.523
	Japan	10	1,247	Random	1.707 (1.068–2.727)	0.025	69	
	Korea	6	957	Fixed	1.420 (0.999–2.018)	0.051	0	
	All	25	3,094	Random	1.949 (1.400–2.713)	0.000	72	
Lymph node status	China	11	975	Random	4.032 (2.328–6.983)	0.000	63	0.184
	Japan	11	1,308	Random	0.974 (0.607–1.565)	0.915	72	
	Korea	6	957	Fixed	1.660 (1.167–2.362)	0.005	14	
	All	28	3,240	Random	1.823 (1.291–2.573)	0.001	75	
Distant metastasis	China	5	399	Random	11.777 (2.450–56.604)	0.002	81	0.617
	Japan	6	768	Random	2.369 (0.854–6.570)	0.097	72	
	Korea	5	813	Random	0.888 (0.263–2.993)	0.848	74	
	All	16	1,980	Random	2.764 (1.222–6.252)	0.015	83	
TNM stage	China	7	480	Random	3.895 (2.575–5.892)	0.000	52	0.121
	Japan	5	657	Fixed	1.395 (1.008–1.931)	0.045	0	
	Korea	5	583	Fixed	1.630 (1.135–2.340)	0.008	0	
	All	17	1,819	Fixed	1.923 (1.565–2.363)	0.000	47	
Vascular invasion	China	4	538	Random	5.378 (3.296–8.775)	0.000	67	0.183
	Japan	10	1,265	Fixed	2.059 (1.589–2.668)	0.000	0	
	All	14	1,803	Fixed	2.613 (2.086–3.272)	0.000	45	
Age	China	1	43	Fixed	0.731 (0.254–2.104)	0.561	–	0.849
	Japan	3	340	Fixed	0.993 (0.643–1.534)	0.974	0	
	Korea	5	820	Fixed	2.052 (1.434–2.937)	0.000	19	
	All	9	1,236	Fixed	1.463 (1.122–1.906)	0.005	40	
Sex	China	4	395	Fixed	0.891 (0.550–1.443)	0.639	0	0.212
	Japan	5	506	Fixed	0.914 (0.625–1.337)	0.644	0	
	Korea	6	957	Fixed	1.434 (1.035–1.987)	0.030	0	
	All	15	1,858	Fixed	1.115 (0.895–1.389)	0.331	0	
Size	China	5	441	Fixed	1.001 (0.657–1.524)	0.998	32	0.727
	Japan	1	169	Fixed	1.129 (0.616–2.069)	0.694	–	
	Korea	1	145	Fixed	1.385 (0.678–2.827)	0.372	–	
	All	7	755	Fixed	1.099 (0.806–1.500)	0.551	8	
Location	China	3	163	Fixed	0.578 (0.244–1.369)	0.213	0	0.310
	Japan	1	169	Fixed	1.124 (0.612–2.065)	0.705	–	
	All	4	332	Fixed	0.897 (0.548–1.466)	0.664	0	
Histological differentiation	China	12	1,013	Fixed	1.823 (1.252–2.655)	0.002	37	0.033
	Japan	9	1,160	Random	0.693 (0.432–1.111)	0.128	71	
	Korea	4	413	Fixed	0.972 (0.516–1.832)	0.930	43	
	All	25	2,586	Random	1.126 (0.824–1.539)	0.396	67	

OR, odd ratio; RR, risk ratio; CI, confidence interval

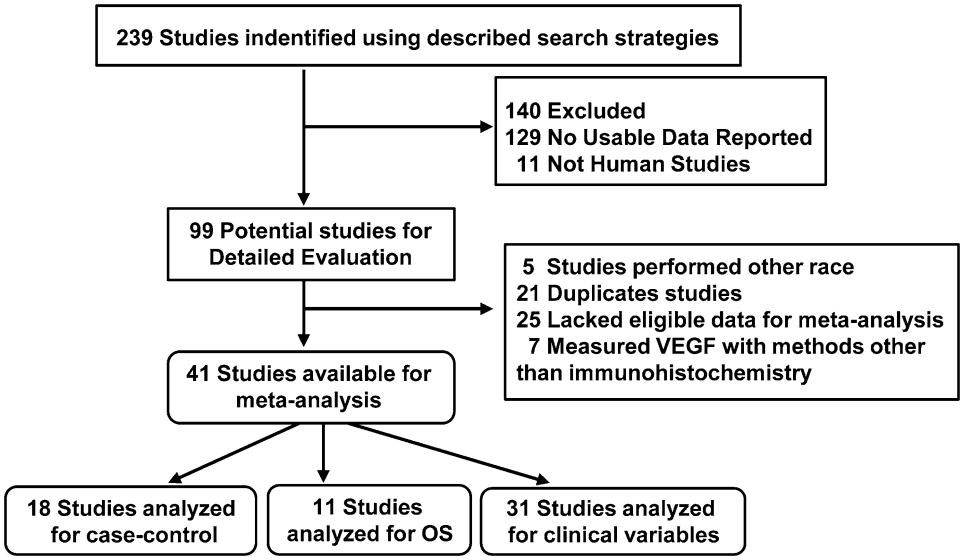

Fig. 1 Flow chart of the meta-analysis

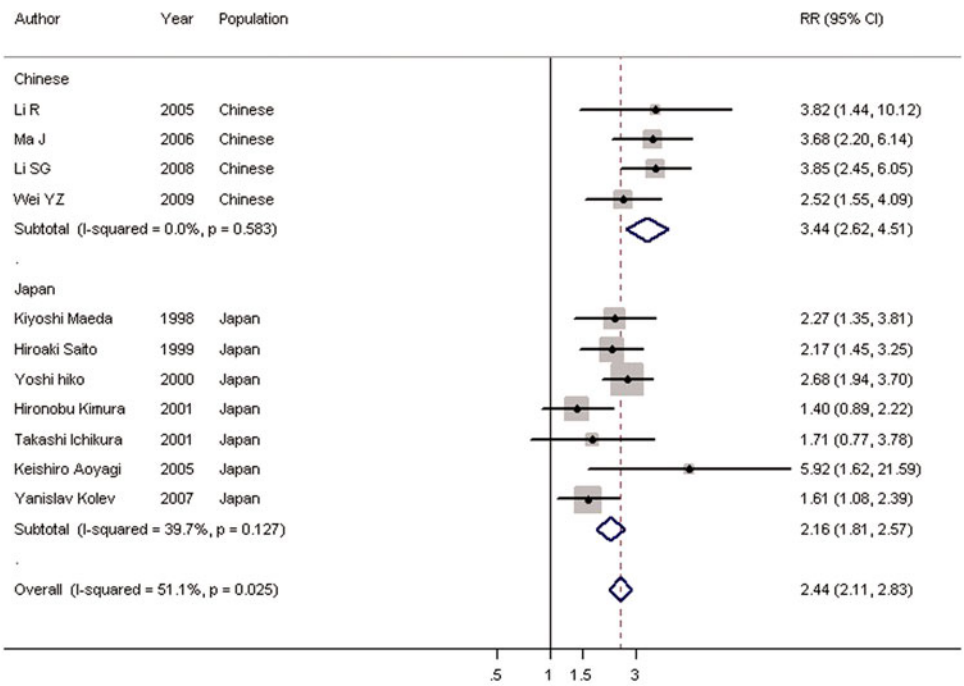

Fig. 2 Meta-analysis on the relation between VEGF expression and 5-year overall survival (OS)

VEGF expression than those with well differentiation (1,028 patients) (OR = 1.82; 95% CI = 1.25–2.66; $P = 0.002$). Men tended to have a higher VEGF expression than women in Korea including 9 studies (1,213 patients), but the effect was modest (OR = 1.43; 95% CI = 1.04–1.99, $P = 0.03$) (Table 3).

Assessment of publication bias

Egger′s linear regression test and Begg's test were used to examine publication bias. The potential for publication bias could not be ruled out except assessment of the relation between VEGF expression and histo-differentiation; however, the effect of bias was slight ($P = 0.033$) (Table 3).

Discussion

To our best knowledge, it is the first time that a comprehensive and detailed meta-analysis has assessed the prognostic role of VEGF for gastric cancer clinical outcome. High VEGF expression, as detected by immunohistochemistry, was confirmed in patients with gastric cancer according to the evidence-based medicine in our study. The

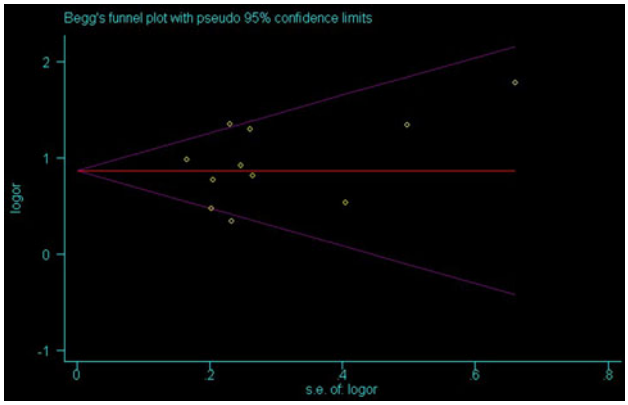

Fig. 3 Begg's funnel plot analysis to detect publication bias for 5-year overall survival (OS)

pooled statistical data showed that VEGF protein, an independent marker of angiogenesis, can potently predict the 5-year survival. Further, when stratifying for baseline characteristics of patients, including sex, age, tumor size, location, histo-differentiation, depth of invasion, lymph node status, distant metastasis, vascular invasion, and TNM stage, our results showed that VEGF expression provided significant prognostic value, which increased the predictive accuracy of prognosis in patients with gastric cancer.

Our current finding was in agreement with the recent meta-analysis reports on VEGF expression in hepatocellular cancer (Schoenleber et al. 2009), colorectal cancer (Des Guetz et al. 2006), and head and neck squamous cell carcinoma (Kyzas et al. 2005). As a rule of the thumb, a prognostic factor with RR > 2 is considered as useful practical value (Hayes et al. 2001). In the present study, we found the global RR is 2.45, indicating that the statistical link between VEGF expression and survival in gastric cancer was rather strong. Although there was heterogeneity between studies, the effect was modest ($I^2 = 51\%$), and all of the studies were in the same direction. During analysis, we strictly considered the most important variables that might confound the impact of high VEGF expression on survival. Our results showed that VEGF expression was significantly correlated with the depth of invasion, lymph node status, distant metastasis, vascular invasion, and poor TNM staging (Table 3), which collectively contribute to the survival of patients with gastric cancer. Although VEGF initially had no association with lymphangiogenesis (Jubb et al. 2006), recent experimental studies showed that

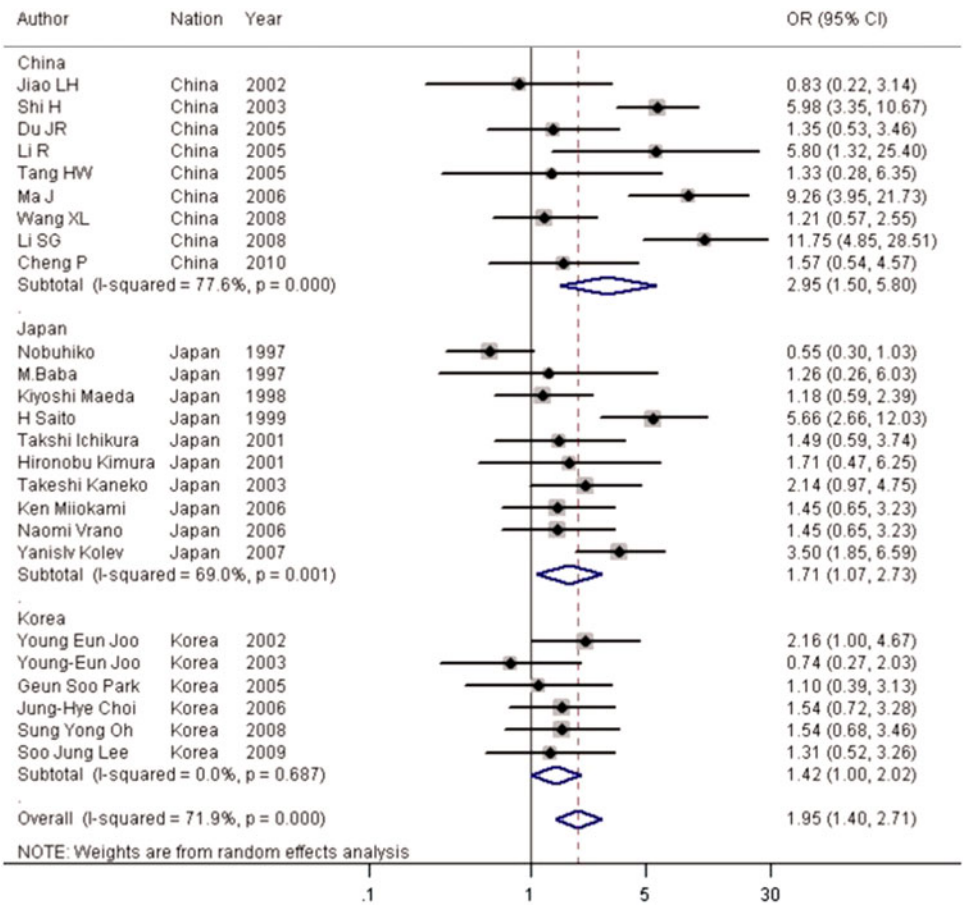

Fig. 4 Meta-analysis on the relation between VEGF expression and the depth of invasion

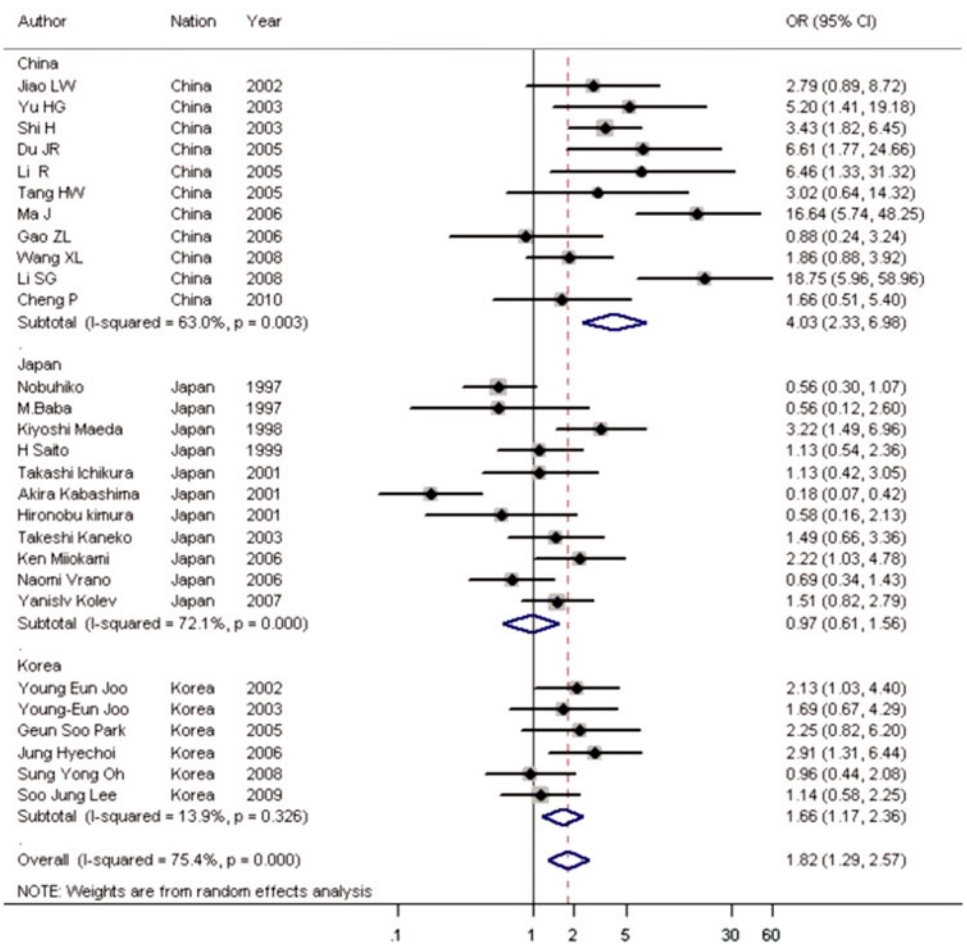

Fig. 5 Meta-analysis on the relation between VEGF expression and lymph node status

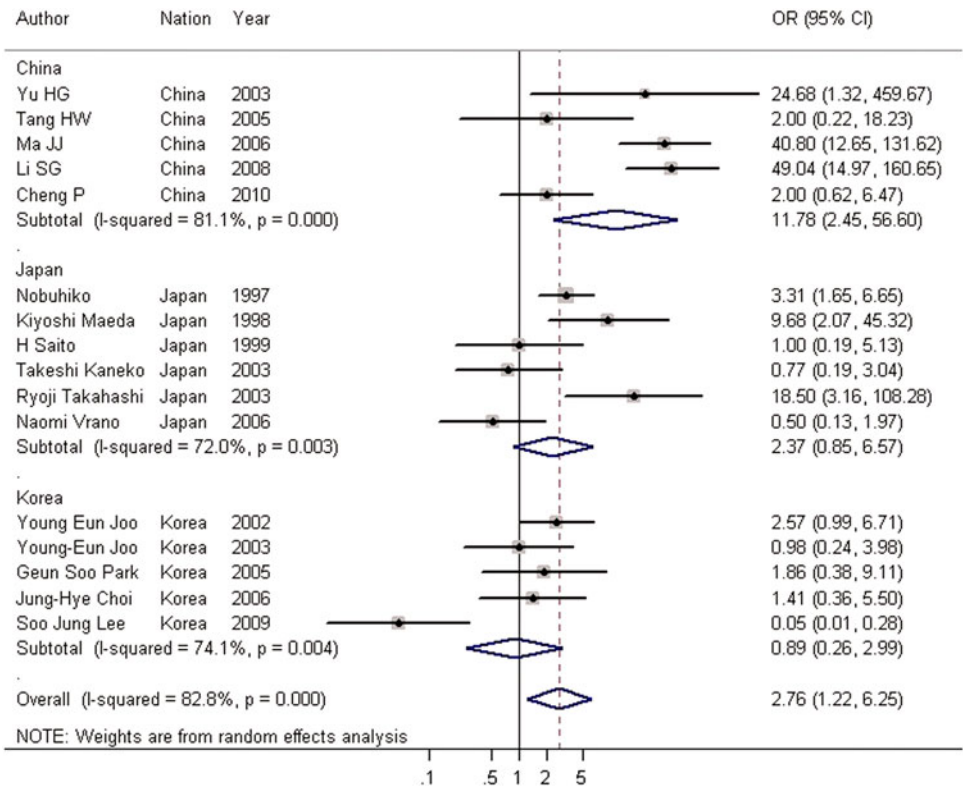

Fig. 6 Meta-analysis on the relation between VEGF expression and distant metastasis

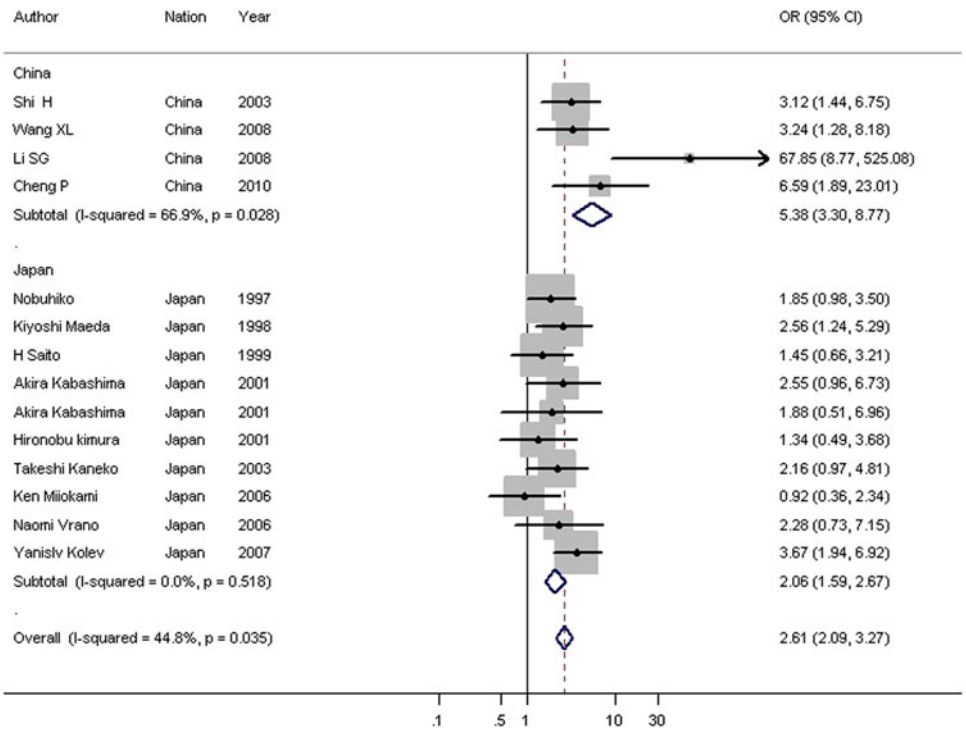

Fig. 7 Meta-analysis on the relation between VEGF expression and vascular invasion

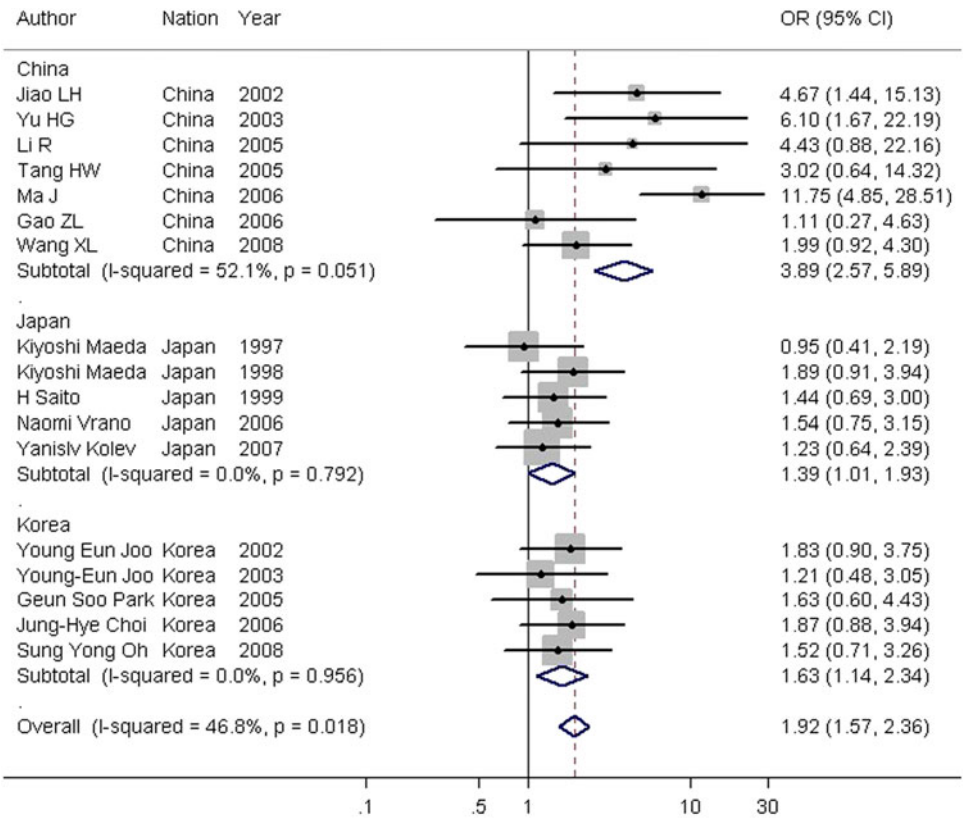

Fig. 8 Meta-analysis on the relation between VEGF expression and TNM staging

VEGF overexpression could induce the formation of new lymph vessels (Nagy et al. 2002; Kunstfeld et al. 2004) by targeting VEGF receptor 2 (VEGFR2) signaling pathway. Furthermore, VEGF overexpression was correlated with larger metastatic deposits, which has been found in malignant lymphoma (Kadowaki et al. 2005), lung cancer

(Niki et al. 2000), and breast cancer (Mohammed et al. 2007). All of these reports were consistent with our finding in gastric cancer. High VEGF expression induces the formation of a rich vascular network and nutritious environment (Breslin et al. 2003), which is an active process that requires the degradation of the extracellular matrix and the increase in vascular permeability both in blood and lymphatic vessels, favoring the progression of tumor cells into the vascular space and lymphatics. This may offer a possible explanation for the observed strong statistical association between VEGF overexpression and tumor invasion and metastasis. Our present study is the first to reinforce the relationship between tumor angiogenesis and the spread of metastases in gastric cancer.

Interestingly, in the meta-analysis of subgroups, we also observed the correlation of VEGF positivity with older patients ($P = 0.005$) and poor differentiation in Chinese ($P = 0.002$), which may explain its prognostic effect to some extent. Similar findings were also reported by other studies both on age (Lee et al. 2009; Oh et al. 2008; Park et al. 2005; Joo et al. 2002, 2003) and histo-differentiation (Kyzas et al. 2005). We did not detect significant heterogeneity for the above two independent factors; however, further studies are intended to assess the relation of VEGF on histo-differentiation and sex.

Several limitations of the current studies could not be ignored. First, although we did not detect significant publication bias between studies, it is uncertain whether the cases are comparably representative in Asia. All the patients and references enrolled in our meta-analysis came from main cancer centers, and they are observational studies, more prone to many biases than prospective randomized controlled studies. Obviously, we could not account for unpublished studies, and it is unavoidable that some data could still be missing. Missing information may reflect "negative" or more conservative association of VEGF with overall survival, which could reduce the significance of VEGF expression as a predictor of mortality (Uzzan et al. 2004). The discrepancies in the conclusion of various studies encouraged researchers to publish their data whatever the results mean, thus limiting the publication bias. Secondly, studies included in our meta-analysis used immunohistochemistry to assess VEGF expression status, which represented potential selection bias. The choice of the cutoff value for VEGF positivity varied from 5 to 50% among studies, whereas 19 studies used 10%. The most commonly used VEGF antibody was A20 (Santa Cruz Biotechnology, Santa Cruz, CA). And 7 studies had evaluated the correlation between VEGF and clinical outcome using reverse transcription-PCR, ELISA, or western blotting. Although results obtained from different methods are fixed, these findings are consistent with our meta-analysis. And finally, it should be noted that several potential sources of heterogeneity were identified to investigate the variables, including "the depth of invasion," "lymph node status," and "distant metastasis." This may contribute to the variability in assessment of these variables between different studies. However, the DerSimonian and Laird method (random effect model) we used took them together into account.

In conclusion, our meta-analysis showed that VEGF overexpression has a detrimental effect on survival in Asian patients with gastric cancer. VEGF protein might be a powerful prognostic marker, which can help to identify high-risk patients earlier and guide clinical decision-making regarding therapy and outcome. However, this conclusion should be interpreted cautiously since this analysis would ideally be performed on individual patient data. Further investigation into this subset of patients from other cohorts should assess the generalization of results before VEGF is implemented in the routine clinical management of gastric cancer.

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Conflict of interest The authors have no conflict of interest.

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