

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

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Background: Vascular endothelial growth factor (VEGF) is considered as a prime mediator of angiogenesis, and has been implicated in carcinogenesis and metastasis. Various studies examined the relationship between VEGF overexpression with the clinical outcome in patients with hepatocellular carcinoma (HCC), but yielded conflicting results.

Methods: Electronic databases updated to June 2013 were searched to find relevant studies. A meta-analysis was conducted with eligible studies which quantitatively evaluated the relationship between VEGF overexpression and survival of patients with HCC. Survival data were aggregated and quantitatively analyzed.

Results: We performed a meta-analysis of 14 studies that evaluated the correlation between VEGF overexpression and survival in patients with HCC. Combined hazard ratios suggested that VEGF overexpression had an unfavorable impact on overall survival (OS) [hazard ratio (HR) =1.42, 95% confidence interval (CI): 1.42-1.7], but not disease free survival (DFS) (HR=1.13, 95% CI: 0.89-1.38) in patients with HCC. No significant heterogeneity (P=0.949) was observed among 9 studies for OS, however significant heterogeneity (P=0.008) was observed among 11 studies for DFS.

Conclusions: VEGF overexpression indicates a poor prognosis for patients with HCC.

Key Words: Vascular endothelial growth factor (VEGF); hepatocellular carcinoma (HCC); prognosis; meta-analysis



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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third most common cause of death from cancer and the third largest cause of cancer-related deaths worldwide (1). Although liver resection is an effective treatment for patients with advanced HCC, the long-term postoperative prognosis remains poor because of the high recurrence rate and lack of effective systemic therapy for HCC patients with metastases. The main prognostic factors are clinicopathological characteristics of the disease, including tumor size, stage, and grade. However, the prognostic factors do not fully predict individual clinical outcome. There is the need for better markers to identify

patients with poor prognosis at the time of diagnosis. Researches have focused on the potential role of new biological factors involved in the carcinogenic process as prognostic markers in patients with HCC.

Angiogenesis, the formation of new blood vessels from existing vasculature, is an important process in many malignancies including HCC. It is the result of an intricate balance between pro-angiogenic and anti-angiogenic factors. VEGF (also referred to as VEGF-A, vascular permeability factor) is a critical pro-angiogenic factor in cancer. The role of VEGF in the regulation of angiogenesis is the object of intense investigation for more than a decade. The VEGF family is composed of several subtypes,

including VEGF-A, VEGF-B, VEGF-C and VEGF-D which exist as numerous splice variant isoforms (2,3). Many anti-angiogenic compounds are being developed, most of which target VEGF and/or its receptors. It is necessary to establish whether VEGF expression is a prognostic marker in HCC.

Many retrospective or prospective studies have evaluated whether VEGF overexpression may be a prognostic factor for survival in patients with HCC. However, the results of the studies are inconclusive and no consensus has been reached. It is unknown whether differences in these investigations have been mostly due to their limited sample size or genuine heterogeneity. Thus, we conducted a meta-analysis of all available studies relating VEGF with the clinical outcome in patients with HCC.

Materials and methods

Search strategy and study selection

The electronic databases PubMed and CNKI (China National Knowledge Infrastructure) were searched for studies to include in the present meta-analysis. An upper date limit of June 01, 2013 was applied; we used no lower date limit. Searches included the terms “hepatocellular or liver”, “cancer or carcinoma or tumour or neoplasm”, “VEGF”, “vascular endothelial growth factor”, and “prognosis”. We also reviewed the Cochrane Library for relevant articles. The references reported in the identified studies were also used to complete the search.

Studies eligible for inclusion in this meta-analysis met the following criteria: (I) measure VEGF expression in the primary hepatocellular carcinoma tissue with immunohistochemistry (IHC) or RT-PCR/ELISA (reverse transcription-polymerase chain reaction/enzyme linked immunosorbent assay); (II) provide information on survival [i.e., disease free survival (DFS) and/or overall survival (OS), studies investigating response rates only were excluded] and (III) When the same author reported results obtained from the same patient population in more than one publication, only the most recent report, or the most complete one, was included in the analysis. Two reviewers (P.Z. and Q.Q.) independently determined study eligibility. Disagreements were resolved by consensus.

Data extraction and quality assessment

Data retrieved from the reports included author, publication

year, patient source, study design, test method, definition of positivity (cut-off value), VEGF positive ratio and survival data (Table 1). If data from any of the above categories were not reported in the primary study, items were treated as “not applicable”. We did not contact the author of the primary study to request the information. We did not use prespecified quality-related inclusion or exclusion criteria and did not weigh each study by a quality score, because the quality score has not received general agreement for use in a meta-analysis, especially observational studies (4). The data extraction and quality assessment could refer to our previous published meta-analysis (5-8).

Statistical methods

Included studies were divided into two groups for analysis: those with data regarding OS and those regarding DFS. For the quantitative aggregation of the survival results, we measured the impact of VEGF overexpression on survival by HR between the two survival distributions. HRs and 95% confidence intervals (CIs) were used to combine as the effective value. If the HRs and their 95% CIs were given explicitly in the articles, we used crude ones. When these variables were not given explicitly, they were calculated from the available numerical data using methods reported by Parmar *et al.* (9).

Heterogeneity of the individual HRs was calculated with χ^2 tests according to Peto's method (10). Heterogeneity test with inconsistency index (I^2) statistic and Q statistic was performed. If HRs were found to have fine homogeneity, a fixed effect model was used for secondary analysis; if not, a random-effect model was used. DerSimonian-Laird random effects analysis (11) was used to estimate the effect of VEGF overexpression on survival. By convention, an observed HR >1 implies worse survival for the group with VEGF overexpression. The impact of VEGF on survival was considered to be statistically significant if the 95% confidence interval (CI) did not overlap with 1. Horizontal lines represent 95% CIs. Each box represents the HR point estimate, and its area is proportional to the weight of the study. The diamond (and broken line) represents the overall summary estimate, with CI represented by its width. The unbroken vertical line is set at the null value (HR=1.0).

Evidence of publication bias was sought using the methods of Egger *et al.* (12) and of Begg *et al.* (13). Intercept significance was determined by the t test suggested by Egger ($P < 0.05$ was considered representative of statistically significant publication bias). All of the calculations were

Table 1 Main characteristics and results of the eligible studies

First author-year	Patients source	Study design	N pts	Method	Cut-off	Positive (%)	HR estimation	HR (95% CI)
Chow-1997	China	R	36	IHC	Any staining	50	Survival curves	OS 1.65 (0.41-6.55)
Jeng-2004	China	P	50	RT-PCR	NA	50	Survival curves	DFS 2.83 (1.06-7.54) OS 4.57 (1.04-20.11)
Deli-2005	China	P	105	IHC	≥60% stained	68.6	Survival curves	OS 1.89 (0.92-3.86)
Sheen-2005	China	P	60	RT-PCR	≥0.5	81.7	HR	DFS 2.29 (0.65-8.12) OS 2.38 (0.61-9.22)
Guo-2006	China	P	90	IHC	≥10% staining	76.7	HR	DFS 1.83 (1.18-2.83)
Wada-2006	Japan	R	60	IHC	Strong staining	20	Survival curves	DFS 1.67 (0.66-4.23)
Zhang-2006	China	R	82	IHC	≥10% staining	NA	HR	DFS 0.34 (0.10-1.16)
Ho-2007	China	P	71	IHC	Median	49.3	Survival curves	DFS 1.60 (0.56-4.55)
Tseng-2008	China	R	113	IHC	NA	17.7	HR	OS 1.95 (1.19-3.21)
Dai-2009	China	R	110	RT-PCR	NA	NA	HR	DFS 1.91 (1.10-3.13) OS 1.37 (0.76-2.48)
Hu-2009	China	P	162	IHC	NA	59.9	HR	DFS 1.62 (1.04-2.53) OS 1.51 (0.99-2.30)
Yang-2010	China	R	314	IHC	NA	NA	HR	DFS 0.99 (0.69-1.42) OS 1.27 (0.94-1.71)
Chen-2011	China	R	63	IHC	H-score ≥25	47.6	HR	DFS 1.16 (0.49-2.75) OS 1.49 (0.55- 4.10)
Minata-2013	Japan	R	133	IHC	NA	NA	HR	DFS 3.32 (1.93-5.41)

Abbreviations: VEGF, vascular endothelial growth factor; P, prospective; R, retrospective; IHC, immunohistochemistry; RT-PCR, reverse transcription-polymerase chain reaction; NA, not applicable; HR, hazard ratio

performed by STATA version 11.0 (Stata Corporation, College Station, TX).

Results

Study selection and characteristics

Fourteen studies (14-27) published between 1997 and 2013 were eligible for this meta-analysis. All reported the prognostic value of VEGF status for survival in HCC patients. The total number of patients included was 1,449, ranging from 36 to 314 patients per study (median 103). The major characteristics of the 14 eligible publications are reported in *Table 1*. The studies were conducted in 2 countries (China and Japan). Among the 14 studies, all studies were performed in Asian populations.

All of the studies reported the prognostic value of VEGF status for survival in patients with HCC tissue. Of the 14 studies, 9 directly reported HRs (multivariate analysis), while the other 5 studies provided survival curves.

Among them, the proportion of patients exhibiting VEGF overexpression in individual studies ranged from 17.7% to 81.7%. Estimation using survival curves were segregated according to either OS or DFS. A HR on DFS and OS could be extracted for 11 publications and 9 publications of studies, respectively. Seven of the 14 studies identified VEGF overexpression as an indicator of poor prognosis, and the other 7 studies showed no statistically significant impact of VEGF overexpression on survival.

Meta-analysis

The results of the meta-analysis were shown in *Table 2* and *Figures 1,2*. Overall, the combined HR for all 11 eligible studies evaluating VEGF overexpression on DFS was 1.13 (95% CI: 0.89-1.38), suggesting that VEGF overexpression in HCC tissue was not an indicator of poor prognosis for HCC. However, significant heterogeneity was observed among the studies ($Q=7.39$, $I^2=58.1\%$, $P=0.008$). When

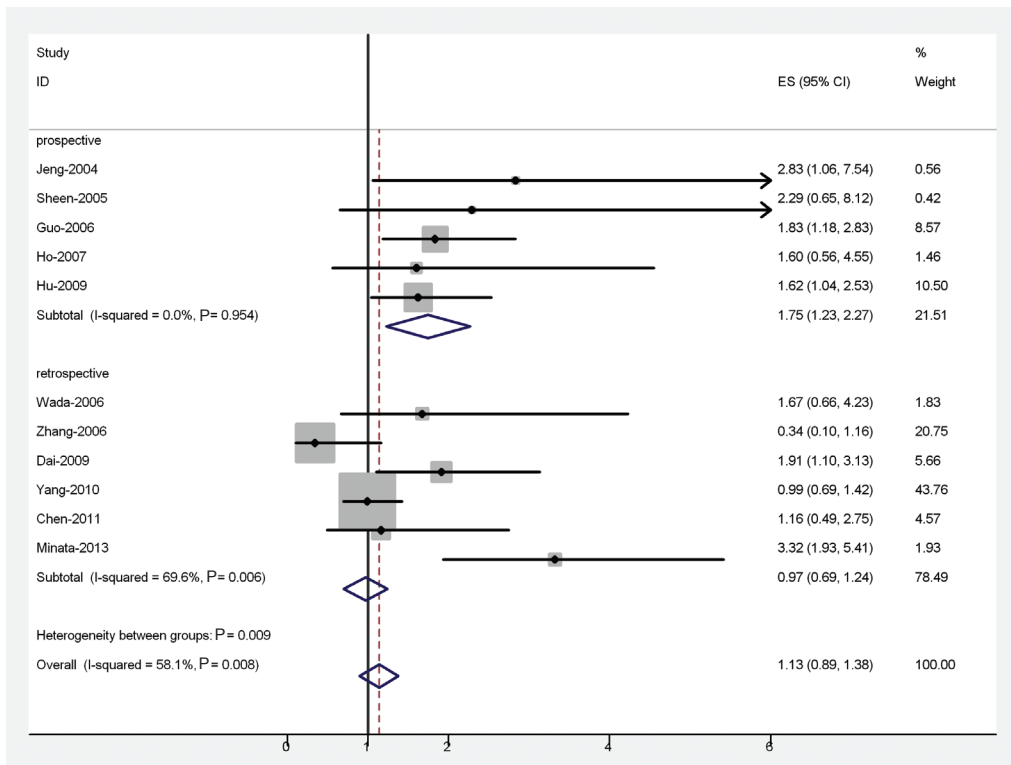


Figure 1 Meta-analysis (Forest plot) of the 11 evaluable studies assessing VEGF in hepatocellular carcinoma stratified by study design for disease-free survival

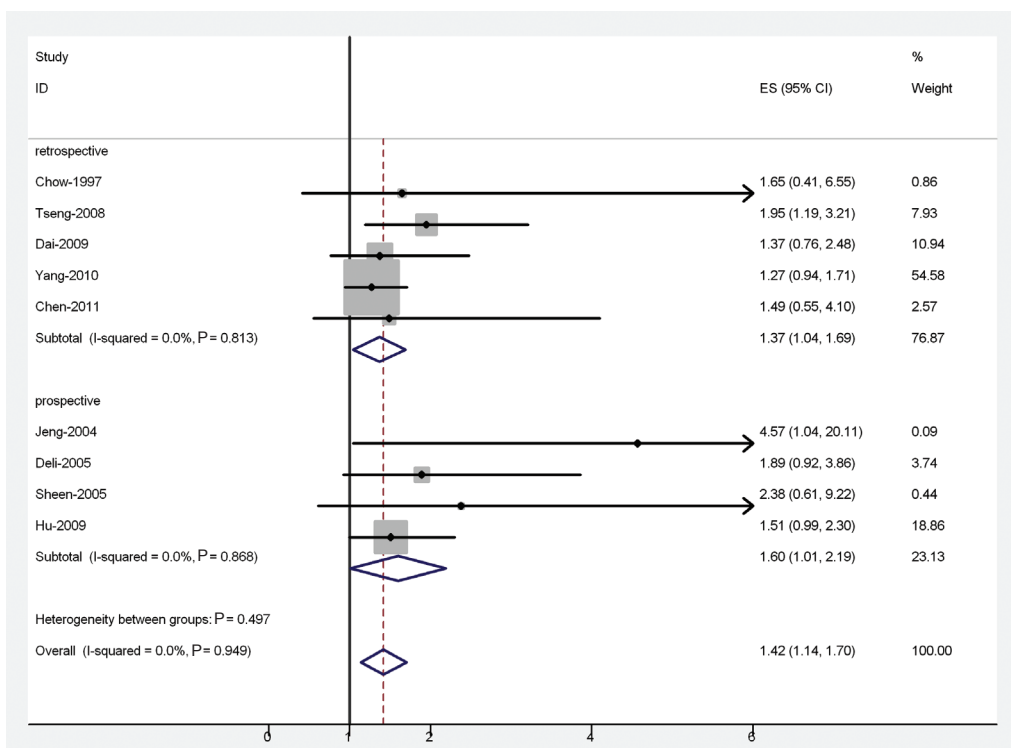
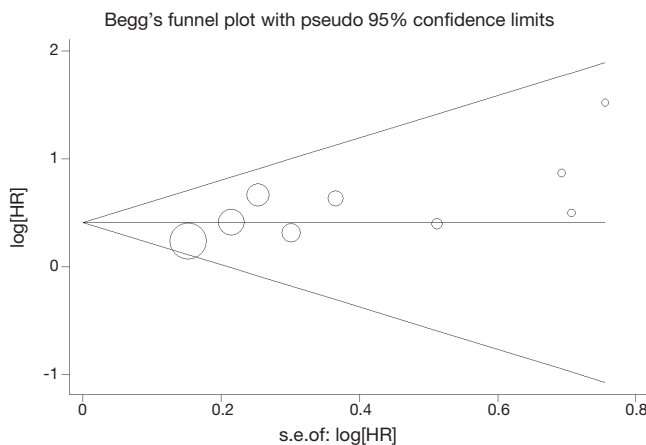


Figure 2 Meta-analysis (Forest plot) of the 9 evaluable studies assessing VEGF in hepatocellular carcinoma for overall survival

Table 2 Meta-analysis: HR value of OS and DFS in hepatocellular carcinoma subgroups according to study design

	Nb	Random effects HR (95% CI)	χ^2 heterogeneity test (P)
Overall for DFS	11	1.13 (0.89-1.38)	0.008
Prospective	5	1.75 (1.23-2.27)	0.954
Retrospective	6	0.97 (0.69-1.24)	0.006
Overall for OS	9	1.42 (1.14-1.70)	0.949
Prospective	5	1.60 (1.01-2.19)	0.868
Retrospective	4	1.37 (1.04-1.69)	0.813

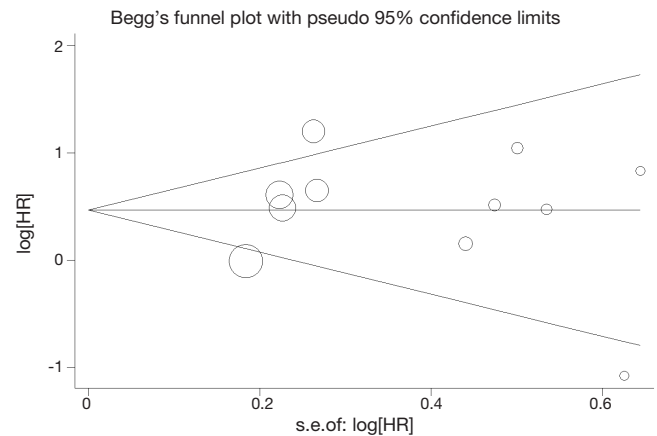
Abbreviations: HR, hazard ratio; Nb, number of studies; OS, Overall survival; DFS, Disease-free survival

**Figure 4** Funnel plot of the 9 evaluable studies assessing VEGF in oral cancer for overall survival

grouped according to study design, the combined HRs of prospective studies and retrospective studies were 1.75 (95% CI: 1.23-2.27) and 0.97 (95% CI: 0.69-1.24), respectively, indicating VEGF is an indicator of poor prognosis of DFS in prospective studies. Interesting, for OS analysis, statistically significant effect of VEGF overexpression (HR=1.42, 95% CI: 1.14-1.70) in patients with HCC was also observed. ($Q=2.48$, $I^2=0.0\%$, $P=0.949$). When grouped according to study design, the combined HR was 1.60 (1.01-2.19) for prospective studies and 1.37 (1.04-1.69) for retrospective studies, suggesting that VEGF overexpression is associated with low survival rates.

Publication bias

Begg's funnel plot and Egger's test were performed to

**Figure 3** Funnel plot of the 11 evaluable studies assessing VEGF in hepatocellular carcinoma for disease-free survival

assess the publication bias in the literature. All 11 eligible studies investigating VEGF overexpression on DFS yielded a Begg's test score of $P=0.938$ and an Egger's test score of $P=0.928$, meanwhile according to the funnel plot (Figure 3), the absence of publication bias was found. However, publication biases were found for investigating VEGF overexpression on OS (a Begg's test score of $P=0.095$ and an Egger's test score of $P=0.037$) (Figure 4).

Discussion

Members of the VEGF family promote two very important processes *in vivo*, angiogenesis and lymphangiogenesis, which involve growth of new blood and lymphatic vessels from pre-existing vasculature, respectively. VEGF-A exists as a homodimer or can heterodimerize with either VEGF-B or non-VEGF factors such as PlGF (placenta growth factor) (28-30). VEGF-A and VEGF-B promote vascular angiogenesis primarily through activation of vascular endothelial cell associated VEGFR-1 (Flt1) and VEGFR-2 (Flk1/KDR). On the other hand, VEGF-C and VEGF-D which are ligands for VEGFR-2 and VEGFR-3, promote angiogenesis and lymphangiogenesis (31,32).

The present meta-analysis has combined 14 publications including 1,449 patients to yield statistics, indicating a statistically significant role of VEGF on overall survival, but not on disease-free survival in HCC. In subgroup analysis according to the different study designs, statistically significant detrimental effect of VEGF was found in prospective studies for OS and DFS, however for DFS in retrospective studies the statistically significant detrimental

effect of VEGF was not found.

Our data were consistent with the results of a previous meta-analysis (33) published in 2009 that showed an association between VEGF overexpression and poor survival of patients with HCC. This analysis included only 8 studies, and the data were insufficient to determine the prognostic value of VEGF in different study designs. We have improved upon that previous meta-analysis by including more recent related studies and by generally using a more comprehensive search strategy. Screening, study selection and quality assessment were performed independently and reproducibly by two reviewers. We also explored heterogeneity and potential publication bias in accordance with published guidelines.

There were several meta-analyses studying the prognostic value of VEGF in other cancer types, such as head and neck squamous cancer (34), lung cancer (35), colon cancer (36), gastric cancer (37), and hepatocellular carcinoma (38). Association of VEGF overexpression with poor outcomes provides a rationale for anti-angiogenics use in the treatment of cancer. VEGF has become a leading therapeutic target for the treatment of cancer. Potentially therapeutic strategies to inhibit VEGF pathway include monoclonal antibodies directed against VEGF, tyrosine kinase inhibitors (TKIs), and antisense strategies (39). Bevacizumab (Avastin) is a humanized monoclonal antibody directed against VEGF (40). It binds to all isoforms of VEGF-A, thus blocking its binding to VEGFR, but it does not bind to other VEGF molecules, such as VEGF-B or VEGF-C.

The heterogeneity issue was complicated in the systematic review and meta-analysis was. We found no significant heterogeneity among all studies included and subgroup analysis. Another potential source of bias is related to the method of HR and 95% CI, extrapolation. If these statistics were not reported by the authors, we calculated them from the data available in the article. If this was not possible, we extrapolated them from the survival curves, necessarily making assumptions about the censoring process. Data for multivariate survival analysis reported in the article were included in the present systematic review and meta-analysis; if these data were not available, data calculated from survival curves by univariate analysis were included. These results should be confirmed by an adequately designed prospective study. Furthermore, the exact value of VEGF overexpression status needs to be determined by appropriate multivariate analysis.

Publication bias (41) is a major concern for all forms

of meta-analysis; positive results tend to be accepted by journals, while negative results are often rejected or not even submitted. The present analysis does not support publication bias; the obtained summary statistics likely approximate the actual average. However, it should be noted that our meta-analysis could not completely exclude biases. For example, the study was restricted to papers published in English and Chinese, which probably introduced bias.

In conclusion, our meta-analysis estimated the association between prognostic significance of VEGF positivity and patients with HCC. As determined in our meta-analysis, we concluded that VEGF expression was associated with poor overall survival, but not in disease-free survival, and there is significant heterogeneity among DFS studies. To strengthen our findings, well-designed prospective studies with better standardized assessment of prognostic markers should help to explore the relation between VEGF overexpression and survival of HCC.

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