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Review Article

The prognostic significance of vascular endothelial growth factor-D expression in colorectal cancer: a meta-analysis

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Abstract: Background: Vascular endothelial growth factor-D (VEGF-D) is a glycoprotein closely associated with lymphangiogenesis and angiogenesis. Although much research has been done on the relationship between VEGF-D and colorectal cancer, there is no agreed upon conclusion at present. We tried to summarize the reliable evidence on the use of the VEGF-D protein to estimate the prognostic and clinicopathological role of VEGF-D overexpression in colorectal cancer. Methods: Searching was performed in electronic databases to collect data without any language limits for original articles up through March 30, 2018. Furthermore, a meta-analysis was undertaken to evaluate the relationship between VEGF-D overexpression and the prognosis of patients with colorectal cancer, including disease-free survival (DFS), overall survival (OS), and clinicopathological characteristics. Results: 10 studies were included in the final analysis. 6 studies (n=730 patients) assessed the association between OS and VEGF-D overexpression. Statistics were calculated for OS (HR=0.91; 95% CI=0.33-1.49; P=0.002). Meanwhile, 3 studies (n=404 patients) evaluated the relationship between DFS and VEGF-D overexpression. Statistics were calculated for DFS (HR=1.28; 95% CI=0.95-1.60; P<0.001). When the studies were layered by the clinicopathological characteristics, including tumor stage (n=603; OR=2.19; 95% CI=1.54-3.12; P<0.001), T stage (n=263; OR=2.52; 95% CI=1.34-4.73; P=0.004); lymph node metastasis (n=655; OR=4.04; 95% CI=2.83-5.75; P<0.001), liver metastasis (n=298; OR=2.99; 95% CI=1.61-5.53; P=0.001), venous involvement (n=354; OR=0.93; 95% CI=0.60-1.45; P=0.758), lymphatic involvement (n=354; OR=1.38; 95% CI=0.81-2.36; P=0.242), and differentiation degree (n=655; OR=0.88; 95% CI=0.58-1.34; P=0.559), they provided important, objective, and extensive prognostic information. Conclusion: This study indicates that patients with VEGF-D overexpression have a shorter OS and DFS, higher levels of tumor stage and T stage, and easier lymph node and liver metastasis.

Keywords: Vascular endothelial growth factor D, colorectal cancer, overall survival, clinicopathological prognosis

Introduction

Colorectal cancer (CRC) is the third most common cause death from cancer in the world and its incidence in all parts of the world is rising [1-3]. Although the survival rate of CRC patients has slightly increased due to the improvement of treatment according to the size, stage, and grade of the tumor [4], these clinicopathological factors can't entirely predict individual prognosis. In order to improve situations in which patients with colorectal cancer can't be diagnosed and treated accurately, it is necessary for us to explore the valid, biological prognostic markers. Fortunately, there are many biomolecules in colorectal cancer, such as CEA, CA199 and CA724 [5, 6]. Although, these biomolecules have a certain significance in the diagnosis and prognosis of patients with colorectal cancer, their guiding role is not very helpful for treatment. Since the beginning of the 21st century, VEGF and its targeted drugs have proved a breakthrough in the treatment of colorectal cancer [7, 8]. In this meta-analysis, we mainly elaborate the relationship between VEGF-D and the prognosis of patients with colorectal cancer, so as to determine its guiding role.

VEGF was first discovered by Senger et al. [9] in 1983. It consists of 23 kD single chain proteins

with eight exons and seven introns. During the process of transcription, six kinds of VEGF isomers are formed by different kinds of splicing modes, including VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and PIGF. Many studies have found [10-15] that vascular endothelial growth factor can significantly promote the proliferation, migration, and chemotaxis of vascular and lymphatic endothelial cells in various tissues. Interestingly, by binding to the receptor-3 of vascular endothelial growth factor, VEGF-D is considered to be the only specific lymphocyte growth promoter in the VEGF family. Meanwhile, it plays an important role in lymph node metastasis [16].

The most common methods to detect VEGF-D are IHC, RT-PCR, and ELISA [17]. In this meta-analysis, we only included the articles that used the detective method by IHC, because VEGF-D in sections of tissue can be released only by tissue cells, while blood VEGF-D can be released by tumor cells as well as platelets and other cellular components [18].

The prognostic value of VEGF-D overexpression in patients with various cancers [19, 20] has been reported in many studies. Su et al. [21] found that CRC patients with VEGF-D positive tumors had a significantly shorter OS than CRC patients with VEGF-D negative tumors. On the other hand, Thomas et al. [22] found that the expression of VEGF-D in colorectal tumor tissues did not show a direct impact on the survival of patients with colorectal cancer.

However, so far, several studies have evaluated VEGF-D as an index to assess prognosis after surgery, but the results have been limited and controversial. Hence, in order to further investigate colorectal cancer, we conducted this study to summarize all of the available evidence.

Materials and methods

Literature search

This meta-analysis was based on the Preferred Reporting Items for Systematic Reviews and meta-analyses guidelines. The relevant literature was searched for items published up through March 30, 2018 in EMBASE, PubMed, and the Cochrane Library databases using the following key words: ("Colorectal Neoplasm" or "Colorectal Tumors" or "Colorectal Carcinoma" or "Colorectal Cancers" or "large bowel tumor" or "large bowel Carcinomas" or "large bowel tumor cancer" or "large intestine tumor" or "large intestine cancer" or "large intestine carcinoma" or "colon cancer" or "rectal cancer" or "CRC") [Title/Abstract] and ("Vascular Endothelial Growth Factor-D" or "VEGF-D" or "FIGF Protein") [Title/Abstract]. Moreover, lists of all relevant articles that meet the search parameters were screened for further studies by two authors (Chun-Lin Lin and Guang-Wei Zhu) respectively.

Selection criteria

The two authors screened the titles and abstracts of the original studies independently in the electronic database. Studies were included if they met the following criteria: 1. The test method for VEGF-D expression in colorectal cancer was immunohistochemistry (IHC); 2. Patients with colorectal cancer were diagnosed by histopathological examinations; 3. The data was collected from various medical centers of cohort studies.

Studies were excluded if they met the following criteria: 1. The test method for VEGF-D expression was tested only by RT-PCR or ELISA without IHC. 2. Patients with colorectal cancer accompanied by other types of tumors. 3. The article itself is a meta-analysis, a case report, a review, a letter, a poster, or a meeting abstract. 4. The research were not done on humans. 5. Preoperative neoadjuvant chemoradiotherapy was conducted for the patients with colorectal cancer.

Data synthesis and analysis

Finally, we divided the outcomes into three categories for analysis: the first part of meta-analysis was to evaluate the prognostic value of VEGF-D overexpression on OS with HR and 95% CI. The second part of this meta-analysis was to evaluate the prognostic value of VEGF-D overexpression on DFS with HR and 95% CI. If the data were provided in the article, we used the information directly. If the data were not provided, we calculated the available data from the survival curve using methods reported by Jayne F. Tierney [23]. The following information was collected and collated into a predesigned table: name of the first author, year of publication, patient source, study design, number of patients, stage, detection method, antibodies, cut-off value of VEGF-D positive, dilution, follow-up, hazard ratios and 95% CI (**Table 1**). The

Table 1. Main characteristics and results of the 6 articles evaluating the relationship between VEGF-D overexpression and overall survival

First author-year	Patient source	Study design	Number of patients Total (P/N)	Stage	Method	Antibody	Dilution	Cut-off	Follow-up (years)	HR estimation	HR (95%)
Jeff-2002	England	RC	84 (62/22)	I-IV	IHC	Santa Cruz	1:2000	Score 2	9	HR	3.811 (1.087-13.362)
Hiroshi-2003	Japan	RC	83 (26/57)	I-IV	IHC	Santa Cruz	1:2000	10%	10	Sur-curve	2.48 (0.68-9.01)
Seiji-2004	Japan	RC	139 (58/81)	I-IV	IHC	Santa Cruz	1:1000	10%	12.8	Sur-curve	3.05 (1.22-7.63)
Hu-2007	China	RC	69 (40/29)	I-IV	IHC	Santa Cruz	1:500	20%	9	Sur-curve	3.33 (0.86-12.84)
Markus-2008	Germany	RC	104 (70/34)	I-IV	IHC	Santa Cruz	1:50	25%	5	Sur-curve	0.61 (0.23-1.59)
Su-2016	China	RC	251 (180/71)	I-IV	IHC	Santa Cruz	1:150	10%	5	HR	3.634 (2.548-5.182)

VEGF-D vascular endothelial growth factor-D, RC retrospective cohort study, IHC immunohistochemistry, Sur-curve survival curve, HR hazard ratio, Score 1, 2, 3: different scores with the sum of staining intensity and extent. 10%: over 10% of the cancer cells were stained by VEGF-D antibody. 25%: over 25% of the cancer cells were stained by VEGF-D antibody.

Table 2. Main research items of the 10 articles included in this meta-analysis

First author-year	Patient source	Study design	Number of patients Total (P/N)	Research items	NOS
Jeff-2002	England	RC	84 (62/22)	⑧⑨	7
Zhong-2003	China	RC	50 (20/30)	①②⑥	7
Hiroshi-2003	Japan	RC	83 (26/57)	①④⑤⑥⑦⑧	9
Seiji-2004	Japan	RC	139 (58/81)	①③④⑤⑥⑦⑧	9
Su-2016	China	RC	251 (180/71)	①②⑥⑧⑨	9
Masatoshi-2002	Japan	RC	76 (43/33)	①④⑤⑥⑦	7
Shinsuke-2007	Japan	RC	56 (31/25)	①④⑤⑥	7
Hu-2007	China	RC	69 (40/29)	⑧⑨	9
Markus-2008	Germany	RC	104 (70/34)	②⑧	7
Mark-2001	England	RC	59 (18/41)	③	6

①. Histological type. ②. TNM stage. ③. Duke stage. ④. Lymphatic involvement. ⑤. Venous involvement. ⑥. Lymph node metastasis. ⑦. Liver metastasis. ⑧. Overall survival. ⑨. Disease-free survival. NOS: Newcastle-Ottawa Scale.

last part of this meta-analysis was to measure the relationship between VEGF-D overexpression and the clinicopathological variables, including histological type, lymph node metastasis, liver metastasis, tumor stage, lymphatic involvement and venous involvement. Furthermore, for histological type, we compared undifferentiated (or poorly differentiated) with moderate (or well differentiated). In the tumor stage, we compered the advanced tumor stage (TNM stage I+II or Duke stage A+B) with the early tumor stage (TNM stage III+IV or Duke stage C+D). All the statistical analyses in this meta-analysis were conducted using Stata 14.0. We used the coefficients and generated forest plots to evaluate the relationship between VEGF-D overexpression and prognosis, including OS, DFS, and clinicopathological factors. The heterogeneity was evaluated by I^2 and Q tests across the studies. If the p value $\leq$ 0.1 for the Q test or the value of $I^2 \geq 50\%$ were considered to have substantial heterogeneity [24], the random effect was used, otherwise, the fixed-effect model was calculated for further analysis. Meanwhile, Egger's regression test and funnel plot were used (when the number of included studies ≥ 6) to evaluate the publication bias [25], and the Newcastle-Ottawa Scale was used for retrospective studies to assess the quality.

Results

Search results and clinicopathological characteristics

In this study, a total of 243 potentially relevant articles retrieved from the electronic database were included. After exclusion of duplicates by reading titles, 204 potentially relevant articles remained. Then we screened the titles and abstracts, and 30 articles belong to systematic reviews, meta-analyses, case reports, or meeting abstracts lacking available data were removed. After that, we read the full text, and 48 articles remained after excluding the papers

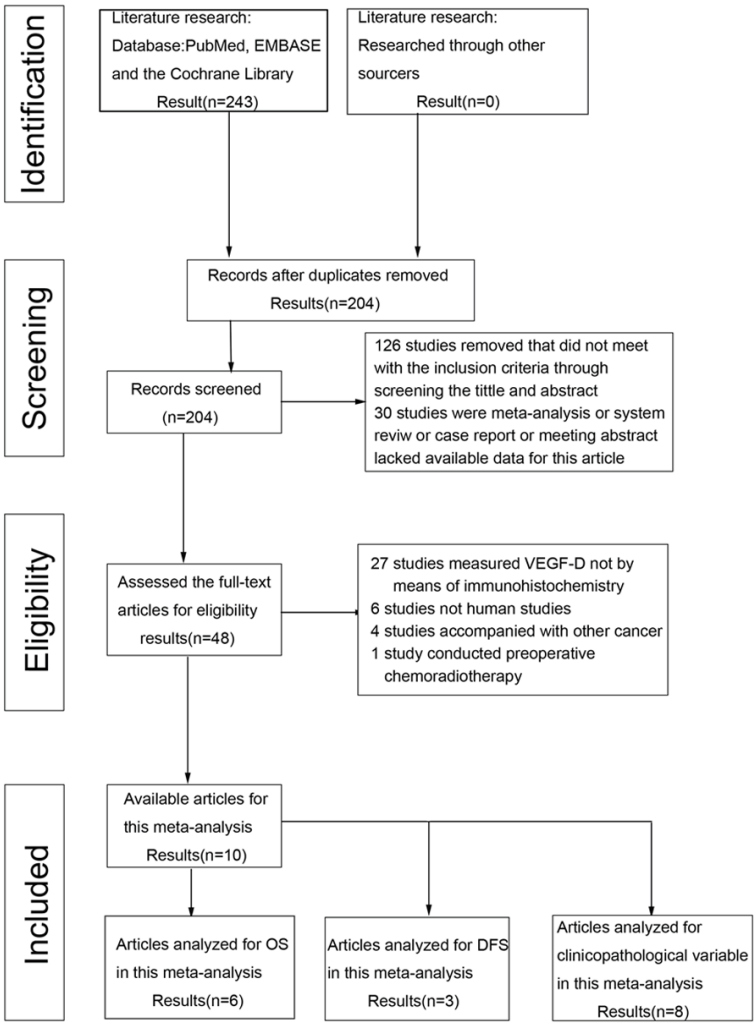

Figure 1. A flow chart of the activities in this screening process.

that did not meet the inclusion criteria. Of these articles, 38 articles were excluded for the following reasons: 27 articles tested VEGF-D with another method instead of IHC. 6 articles presented research on animal rather than on humans, 4 articles studied patients who also had other types of cancer, 1 article studied patients with colorectal cancer who had undergone preoperative chemoradiotherapy. Finally, a total of 10 articles [21, 26-34] were included, and the main characteristics of the articles are shown in **Table 2**. Among these, 6 articles [21, 26, 28, 29, 32, 34] aimed to determine the influence of VEGF-D overexpression on OS, and 3 articles [21, 26, 32] aimed to determine the influence of VEGF-D overexpression on DFS. Meanwhile, 8 articles [21, 27-31, 33, 34] indicated the relationship between VEGF-D overexpression and clinicopathological characteristics (**Figure 1**).

Relationship between VEGF-D and OS, DFS

The findings of this meta-analysis are shown in **Figure 2**. The merged HR for all 6 feasible studies to assess VEGF-D overexpression on OS were 0.91 (95% CI=0.33-1.49; P= 0.002), and the merged HR for all 3 feasible studies to assess VEGF-D overexpression on DFS were 1.28 (95% CI=0.95-1.60; p<0.001). As for OS, the HR value showed no significant heterogeneity through the fixed effect model (I^2=57.6%, p=0.038). When grouped based on the postoperative target therapy setting of the individual studies, the combined HR of target therapy studies and non-target therapy studies were 1.25 (95% CI=0.95-1.55) and -0.49 (95% CI=-1.46-0.47), respectively (**Figure 3**), indicating VEGF-D was an indicator of the poor prognosis of OS in patients without postoperative target therapy. In addition, no significant heterogeneity was observed among the studies on the effect of VEGF-D overexpression on DFS (I^2=0.0%, P=0.902). The OS publication bias assessed was considered nonsignificant (Egger's test: p=0.415). The graphics are shown in **Figure 4A** and **4C**.

The relationship between VEGF-D overexpression and clinicopathological characteristics

The clinicopathologies were stratified into several variables by the character of the tumor stage, T stage, lymph node metastasis, liver metastasis, venous involvement, lymphatic involvement, and differentiation grade. For the tumor stage of colorectal cancer, the significant results indicated that VEGF-D overexpression was related to tumor stage in 5 articles (603 patients; OR=2.19; 95% CI=1.54-3.12; P<

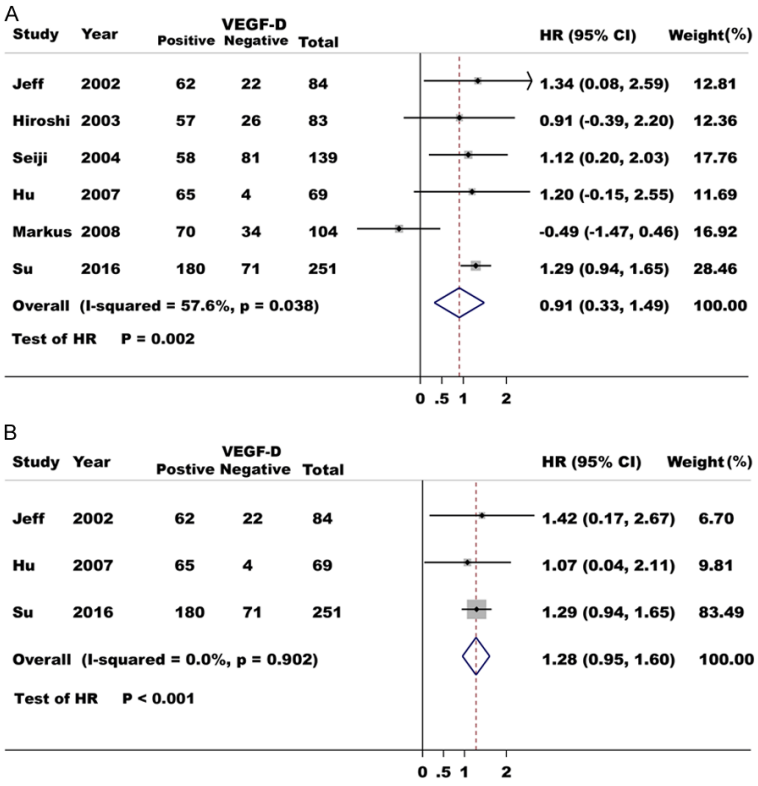

Figure 2. Meta-analysis of the relationship between VEGF-D overexpression and prognosis in CRC patients. A. Meta-analysis of the relationship between overall survival and VEGF-D in CRC patients. Each study is listed by the name of the first author, the publication year and the HR with 95% CI. B. Meta-analysis of the relationship between disease-free survival and VEGF-D in CRC patients. Each study is shown by the name of the first author, the publication year, and the HR with 95% CI.

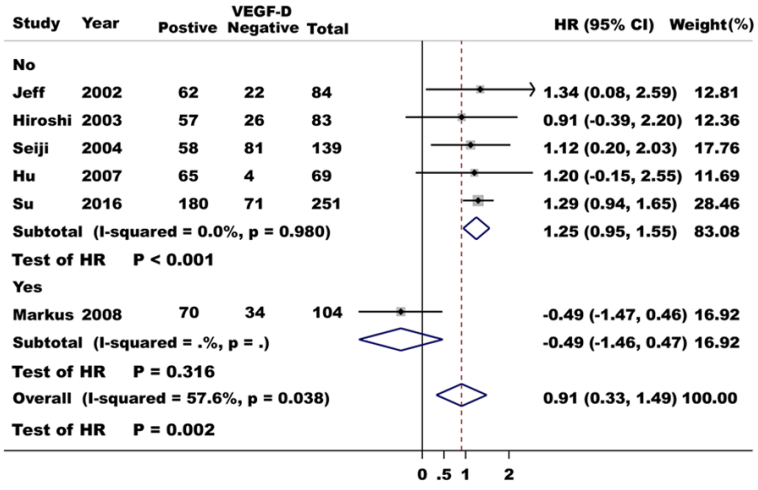

Figure 3. Meta-analysis (Forest plot) of the 6 evaluable studies assessing VEGF-D in colorectal cancer stratified by postoperative target therapy for overall survival.

0.001), patients at the advanced tumor stages had a higher VEGF-D expression than those at the early tumor stages. For the T stage of colorectal cancer, the significant results indicated that VEGF-D overexpression was related to T stage in 3 studies (263 patients; OR= 2.52; 95% CI=1.34-4.73; P= 0.004). For the lymph node metastasis of colorectal cancer, the significant results indicated that VEGF-D overexpression was relevant to lymph node metastasis in 6 articles (655 patients; OR=4.04; 95% CI=2.83-5.75; P<0.001). The publication bias was assessed and was considered nonsignificant (Egger's test: p= 0.565) (**Figure 4B** and **4D**). For the liver metastasis of colorectal cancer, the significant results indicated that VEGF-D overexpression was related to liver metastasis in 3 articles (298 patients; OR= 2.99; 95% CI=1.61-5.53; P= 0.001). For the venous involvement of colorectal cancer, no significant results indicated that VEGF-D overexpression was negatively correlated with it in 4 articles (354 patients; OR=0.93; 95% CI= 0.60-1.45; P=0.758). For the lymphatic involvement of colorectal cancer, nonsignificant results indicated that VEGF-D overexpression was negatively correlated with it in 4 articles (354 patients; OR=1.38; 95% CI=0.81-2.36; P=0.242). For the differentiation grade of colorectal cancer, the nonsignificant results indicated that VEGF-D overexpression was negatively correlated with it in 6 articles (655 patients; OR=0.88; 95% CI=0.58-1.34; P=0.559). The results of this meta-analysis are shown in **Figures 5**, **6**.

Discussion

The AJCC/UICC TNM system is currently regarded as the strongest prognostic indicator for

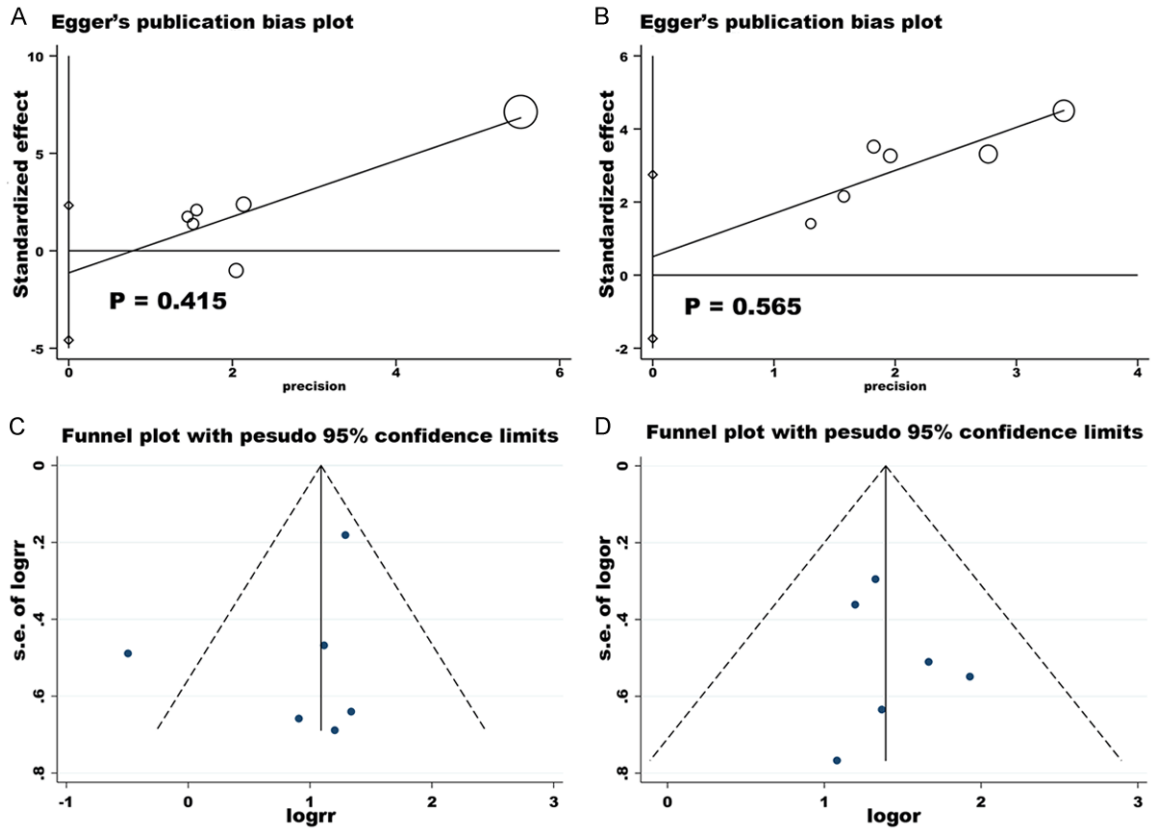

Figure 4. Egger's funnel plot analysis to detect publication bias for overall survival and lymph node metastasis. A. Egger's funnel plot analysis to detect publication bias for overall survival. B. Egger's funnel plot analysis to detect publication bias for lymph. node metastasis. C. Funnel plot analysis to detect publication bias for overall survival. D. Funnel plot analysis to detect publication bias for lymph node metastasis.

patients with colorectal cancer, but further treatment decisions are mainly based on lymph node metastasis [35]. Among the various available biomarkers, VEGF-D is considered to be a lymphocyte growth promoter [36] by binding with the Vascular endothelial growth factor receptor-2 (VEGFR-2) and VEGFR-3. As we all know, VEGFR-2 is necessary for the promotion of blood vessels, and in view of that, it is expressed in normal vascular endothelial cells and in tumor cells [37]. Although VEGFR3 can provide two vital processes in vivo, including lymphangiogenesis and angiogenesis, it is largely restricted to inducing the growth of lymphatic vessels [38, 39].

In this meta-analysis, VEGF-D overexpression significantly predicts a poorer survival and a lower quality of life for patients with colorectal cancer. Therefore, it is feasible to invent VEGF-D target drugs, for instance, Sorafenib [40, 41]. These drugs block a particular signaling pathway and strike the target precisely, so that they can improve the cure rate of cancer and reduce the drugs' side effects. As the study shows, [34] comparing the OS between low and high VEGF-D expressions of patients who use cetuximab after surgery leads to the opposite result found in other studies, so there is a significant heterogeneity among the OS studies. This may indicate that cetuximab is one of the targeted therapy drugs that can promote anti-angiogenesis, effectively inhibit tumor growth, and improve the OS of patients with higher VEGF-D expressions. Accordingly, VEGF-D as a potential target is worthy of further research.

In addition, when the studies were layered by the clinicopathological variables, including tumor stage, lymph node metastasis, and liver metastasis, which were shown to predict the prognosis of patients with colorectal cancer, the results revealed that VEGF-D overexpression was significantly related to these factors

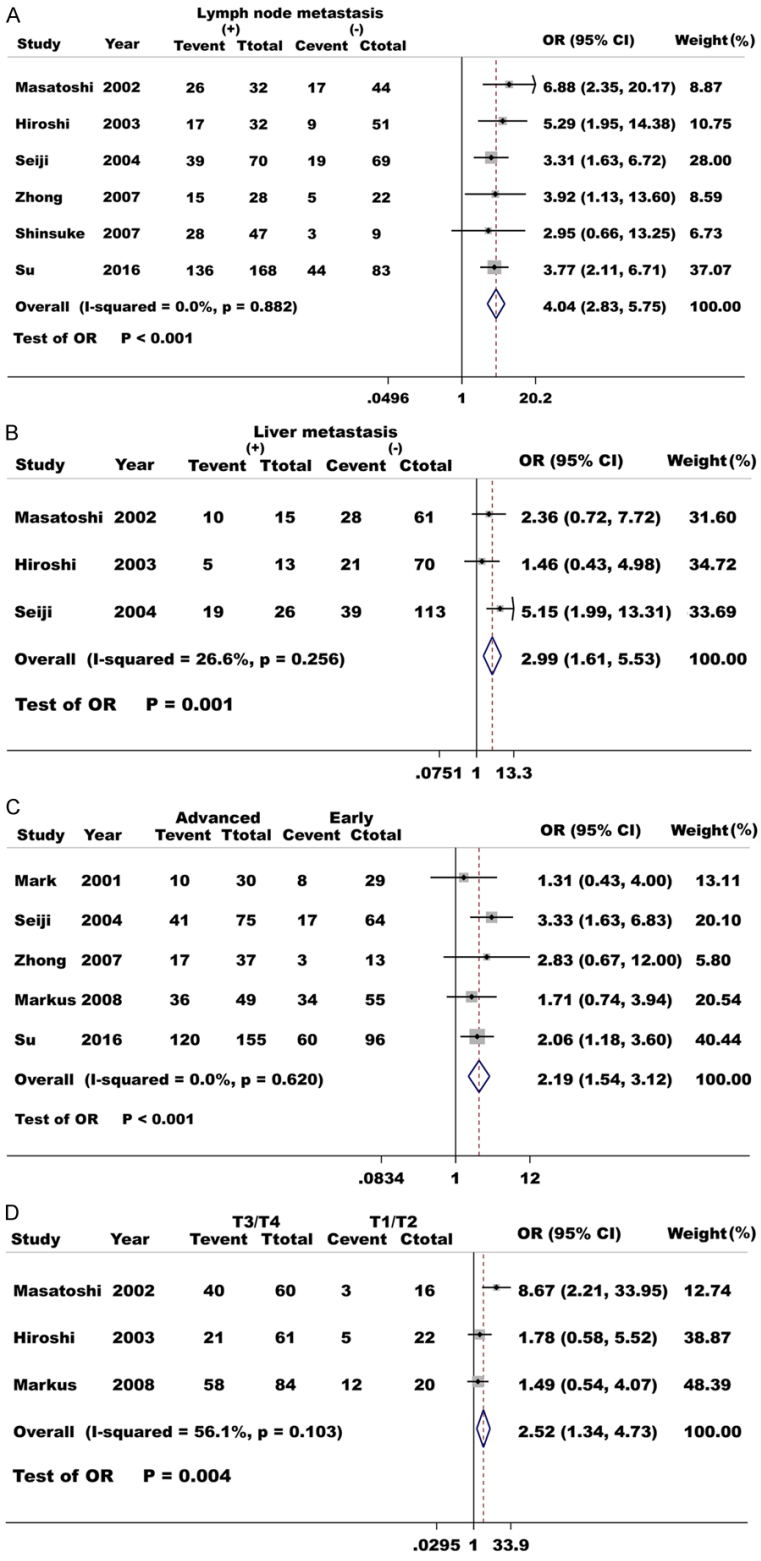

Figure 5. Meta-analysis of the relationship between VEGF-D overexpression and clinicopathological variables in CRC patients, including lymph node metastasis, tumor stage, and liver metastasis. Each study is shown by the name of first author, the publication year, and the OR with 95% CI. A. Meta-analysis of the relationship between lymph node metastasis and VEGF-D; B. Meta-analysis of the relationship between liver metastasis and VEGF-D; C. Meta-analysis of the relationship between tumor stage and VEGF-D; D. Meta-analysis of the relationship between T stage and VEGF-D.

[28]. Furthermore, this provides sufficient evidence for VEGF-D as a biomolecule prognosis factor for colorectal cancer. However, other clinicopathological variables, including venous involvement, lymphatic involvement, and differentiation grade showed that they lack an evident connection with VEGF-D expression. Obviously, this conclusion is totally consistent with the unique function of VEGF-D largely working at VEGFR3 or VEGFR2 [38], so it has little effect on venous involvement, lymphatic involvement, or differentiation grade. Although we have tried our best to retrieve relevant research in many databases through a rigorous retrieval strategy, there are still some limitations in this meta-analysis. Firstly, all enrolled studies are case-control trials and belong to retrospective cohort studies, which inevitably provide a lower level of evidence than randomized controlled trials. Secondly, only 10 studies were included in this meta-analysis, and what's more, the total sample size of colorectal cancer was 971 cases, meaning we lacked a larger sample to better demonstrate the correlation between vascular endothelial growth factor-D and colorectal cancer. Third, "negative" results may be easily ignored by the editors than published results.

Therefore, some data with "negative" results may be lost,

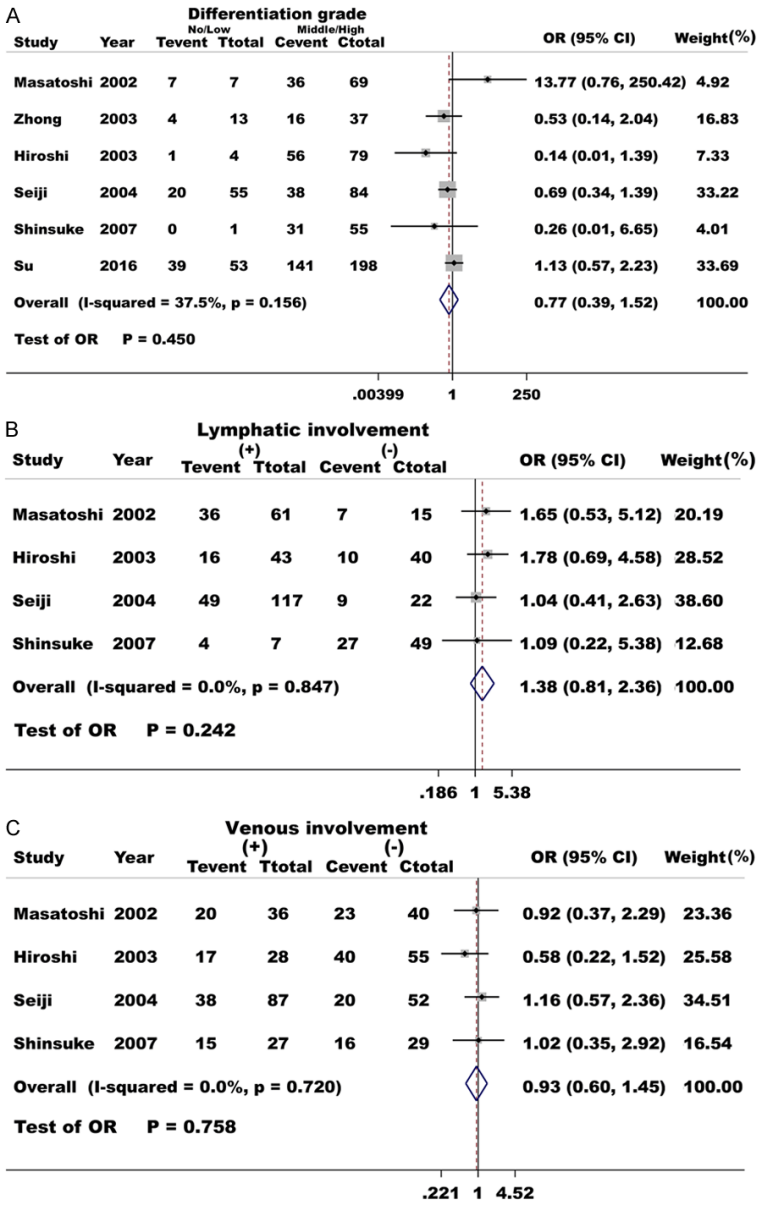

Figure 6. Meta-analysis of the relationship between VEGF-D overexpression and clinicopathological variables in CRC patients, including lymphatic involvement, histological differentiation grade, and venous involvement. A. Meta-analysis of the relationship between histological differentiation grade and VEGF-D; B. Meta-analysis of the relationship between lymphatic involvement and VEGF-D; C. Meta-analysis of the relationship between venous involvement and VEGF-D.

leading to errors in the final conclusion. But it is gratifying to note that there was no publication bias in this meta-analysis. Fourth, the majority of the cases involved in the studies were in Asia and Europe, and the languages of this study were mainly English and Chinese, so caution should be taken in applying the results to other ethnic groups.

Publication bias means researchers and editors tend to publish works with positive results. Studies with "positive" results and a large sample are more likely to be published than those with "negative" results. Thus, researchers whose studies have "negative" results should be encouraged to publish them. Although there is no clear evidence of publication bias in this meta-analysis, the impact of bias cannot be avoided completely. For instance, 2 studies in Korean [42, 43] were removed, which may produce bias.

To conclude, this meta-analysis indicates that a higher level of VEGF-D, the biomarker of lymphangiogenesis, indeed predicts poorer survival and a lower quality of life in patients with colorectal cancer. However, the accurate value of VEGF-D overexpression in patients with colorectal cancer needs to be confirmed by conducting prospective investigations with large cohorts.

The consequences of this meta-analysis demonstrate that VEGF-D overexpression is significantly associated with OS, DFS, tumor stage, lymph node metastasis, and liver metastasis, respectively, in patients with colorectal cancer.

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Disclosure of conflict of interest

None.

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