Original Article

The relationship between vascular endothelial growth factor expression and the risk of childhood nephroblastoma: systematic review and meta-analysis

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Background: This study explores the correlation between vascular endothelial growth factor expression and the risk of childhood nephroblastoma.

Methods: PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang database were searched to collect independent study data published in China between 2010 and 2021 on the expression and significance of VEGF in childhood nephroblastoma, and literature heterogeneity was tested. The odds ratio (OR) value was used as the effect indicator. Meta-analysis software RevMan 4.2.2 was used, and the original data of each study were statistically processed to calculate the combined OR value and 95% confidence interval (CI).

Results: Twelve studies involving 1,226 cases of pediatric nephroblastoma were included for systematic evaluation. The 12 randomized controlled studies reported the expression of VEGF in childhood nephroblastoma (OR =9.06, 95% CI: 6.97–11.78, P<0.00001). There was a statistically significant difference in expression of VEGF between the unfavorable histology (UH) group and the favorable histology (FH) group (OR =1.17, 95% CI: 1.07–1.27, P=0.0006) and expression of VEGF in different clinical stages of nephroblastoma, including stage I–II and III–IV (OR =0.49, 95% CI: 0.42–0.58, P<0.00001). Positive expression of VEGF showed no significant statistical difference between cases with and without tumor metastasis (OR =1.08, 95% CI: 0.86–1.36, P=0.50).

Conclusions: The expression of VEGF may play an important role in the occurrence and development of childhood nephroblastoma and could help guide clinicians to judge disease and treatment.

Keywords: Vascular endothelial growth factor (VEGF); nephroblastoma; risk assessment; serum marker; meta-analysis

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Introduction

Blastomas are malignant solid tumors that most commonly occur in childhood. Nephroblastoma, also known as Wilms tumor (WT), is an embryonic tumor originating from undifferentiated mesodermal tissue (1). WT mainly occurs in infants, accounting for about 95% of childhood kidney tumors, and the incidence of nephroblastoma in infants is about 1/1,000,000 (2-4). Adult Wilms tumor (AWT) is a

clinically rare malignant kidney tumor, with an incidence of less than 3%. AWT has a high degree of malignancy, rapid growth, early metastasis, difficult preoperative diagnosis, and high misdiagnosis rate (5). Tumorigenesis may involve *WT1* (Wilms Tumor suppressor gene), *WT2*, *P53* and other genes, and may also be related to congenital genetic factors.

At present, the etiology of nephroblastoma is not clear and may be related to gene mutations that regulate normal embryonic development of the genitourinary tract (6). Most patients have palpable abdominal mass as the initial symptom, while some patients have hematuria, fever, urinary tract infection, varicocele, hypertension or hypotension, anemia, and other symptoms. At present, treatment of nephroblastoma involves multidisciplinary combination therapy, including surgery, chemotherapy, radiotherapy, and targeted therapy, with an overall cure rate of about 90%.

The growth and development of a tumor requires rapid angiogenesis, while the growth of blood vessels in nontumor sites is slow or even nonproliferating. Inhibition of angiogenesis can significantly prevent the development, spread, and metastasis of tumor tissue (7). Vascular endothelial growth factor (VEGF) is the most commonly used target for antiangiogenic therapy (8). VEGF is known to induce angiogenesis, and anti-angiogenesis therapy targeting VEGF receptor (VEGFR) is widely used in cancer treatment. VEGF is the most thoroughly studied factor inducing endothelial cell proliferation and angiogenesis. VEGF expression in serum and tissues of nephroblastoma is associated with poor prognosis, which lays a theoretical foundation for anti-angiogenic therapy (9). VEGF regulates angiogenesis and vascular permeability by activating 2 receptors, VEGFR-1, and VEGFR-2. Apatinib is a small molecule antiangiogenic agent that selectively binds to inhibit VEGFR-2 kinase activity, which reduces VEGF-mediated tumor endothelial cell migration and proliferation, thereby reducing tumor microtubule density and inhibiting the growth of nephroblastoma (10). Currently, bevacizumab, AZD2171, and other VEGF/VEGFR pathway inhibitors are being marketed or are in clinical trials (11,12).

Some studies have applied whole-macrophage inhibitors, such as colony stimulating factor signaling pathway inhibitors, which has become a new direction of targeted therapy. Some drugs that specifically inhibit macrophages in tumor microenvironment have been used to enhance the anti-tumor effect. In this paper, the expression and correlation of VEGF in nephroblastoma were studied, hoping to provide theoretical basis for targeted therapy for refractory and recurrent pediatric nephroblastoma. To fully understand the relationship between VEGF expression and pediatric nephroblastoma, this study conducted a meta-analysis to systematically evaluate literature published in domestic journals on the use of immunohistochemistry to detect the relationship between VEGF expression and pediatric nephroblastoma. We present the following article in accordance with the PRISMA reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-21-593/rc).

Methods

Search strategy

Independent RCTs studies data on the expression and significance of VEGF in pediatric nephroblastoma were collected by searching PubMed, Cochrane Library, Web of Science, CNKI, CBM, *et al.* The search term was "corridor tube endothelial growth factor, VEGF, nephroblastoma" and there was no limit on language.

Inclusion criteria

The inclusion criteria were: independent RCTs studies on the expression and significance of VEGF in pediatric nephroblastoma; pediatric nephroblastoma case group confirmed by pathological examination and control group with normal renal tissue; studies with similar problems and methods; and studies providing odds ratio (OR) and 95% confidence interval (CI), or able to be converted into OR and 95% CI. Inclusion criteria for inclusion studies should be clarified using PICOS criteria. PICOS criterion was used to screen and include: P: Participant or Patient, study object; I: Intervention; C: Comparison; O: Outcome; S: Study design.

Exclusion criteria

Studies were excluded according to the following criteria: no control group, immunohistochemistry not used for detection, and literature with too little information to be useful.

Literature quality assessment

The methodological quality of each of the included randomized control trials (RCTs) was evaluated using

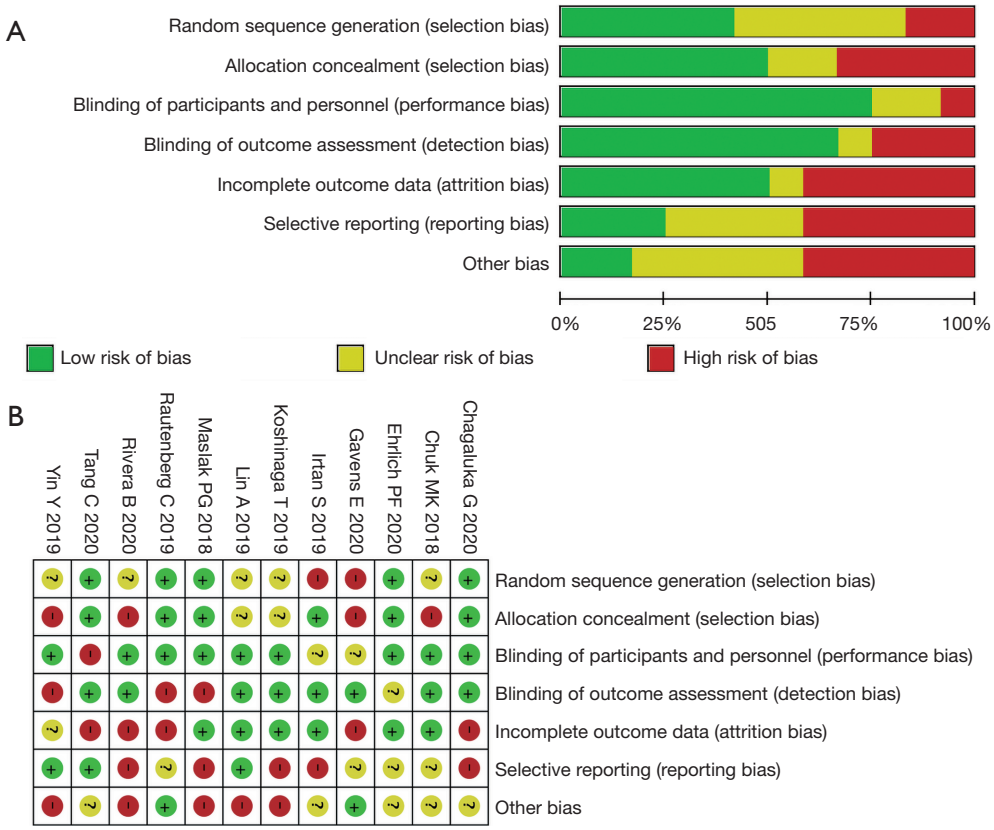

Figure 1 Literature quality evaluation chart. (A) Risk of bias graph; (B) risk of bias summary.

the method recommended by the Cochrane Handbook for Systematic Reviews of Interventions version 5.1. The evaluation considered whether: (I) randomization was adequate; (II) concealed allocation was used; (III) blinding was implemented; (IV) the loss of follow-up and withdrawal was reported; (V) the baseline was comparable. For concealed allocation, experiments were rated A (completely concealed), B (unclear if concealed), C (inadequate concealment), and D (no concealment used). All other indicators were rated A (yes), B (unclear), or C (no). If all evaluation items were graded A, the study had a low degree of bias, with the lowest possibility of the occurrence of all types of bias, and the quality was rated A. If 1 or more items were B, the test had a medium probability of corresponding bias, and the quality was rated as B. If 1 or more of the items was C, the test had a high probability of corresponding bias, and the quality was rated as C (*Figure 1*).

Bias analysis

The Cochrane Handbook's bias risk assessment tool was used by 2 independent researchers to assess the included studies for bias. The studies were assessed on the basis of random assignment, allocation concealment, blinded researchers and participants, blinded measurement results, data integrity, selective reports in 7 aspects, and other biases. Risk was evaluated as "low risk", "high risk", and "not clear". If there was ambiguity concerning the evaluation results, a third researcher was invited to discuss the decision. The literature publication bias of this study was analyzed by funnel plot, as shown in the figure below. Most of the included literatures were within the triangle area, suggesting that the publication bias of this study was not obvious. The literature included in this study was a randomized controlled study, which was analyzed according to the Cochrane RoB 2.0 principle (*Figure 2*).

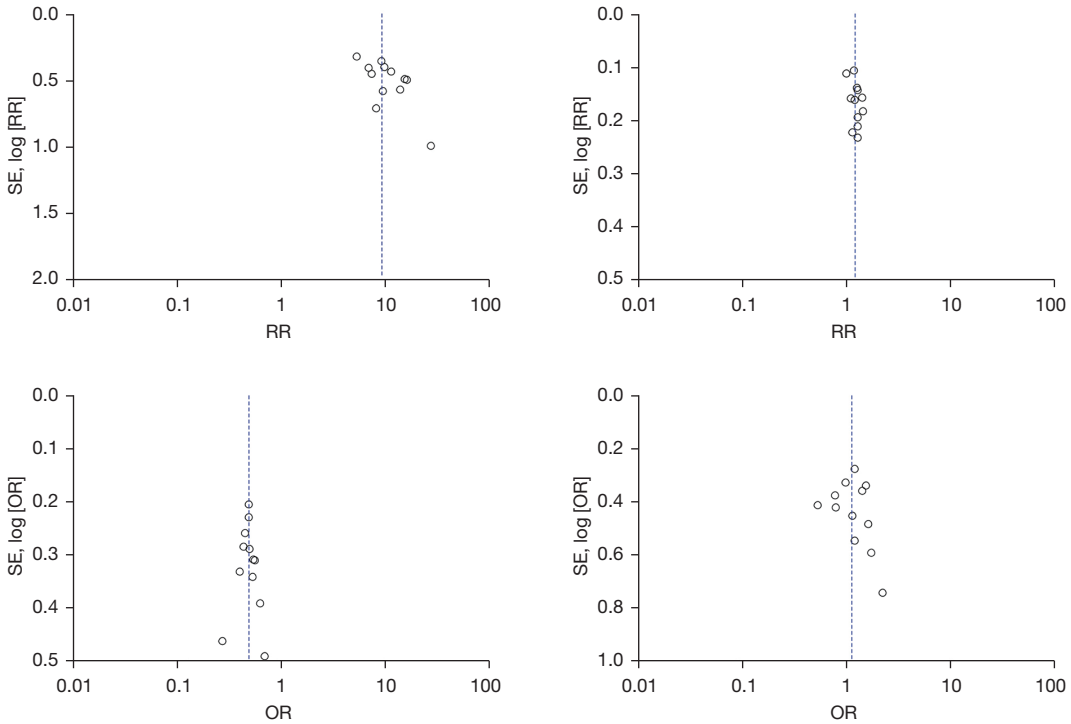

Figure 2 Funnel plot of literature publication bias. RR, relative risk; OR, odds ratio.

Statistical analysis

In accordance with meta-analysis requirements, the analysis process involved literature collection and evaluation, quantitative data merger, and results evaluation and interpretation. The index for measuring risk factors was OR value, and a consistency test of the data was conducted. The fixed effects model was used when the difference was not statistically significant, otherwise the random effect model was adopted. Statistical analyses were completed with RevMan 4.2.2 software. P<0.05 was considered a statistically significant difference.

Results

Basic information of the included literature

Based on the inclusion and exclusion criteria, 12 studies were included in the meta-analysis (13-24). The results of each study were tested for consistency (P=0.29) and a fixed effects model analysis was used (*Table 1*).

Results of literature screening

A total of 350 documents were initially retrieved using computer search databases PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang, and so on. After strict screening according to the inclusion and exclusion criteria, 12 documents with a total of 1,226 participants were finally included in the study (13-24). The literature screening flow chart is shown in *Figure 3*.

Meta-analysis of the included literature

The 12 literatures reported the expression of VEGF in childhood nephroblastoma. Positive expression of VEGF showed a statistically significant difference between the case group and the control group (OR =9.06, 95% CI: 6.97–11.76, P<0.00001). There was acceptable heterogeneity between studies (I^2=32%, Z=16.49; *Figure 4*).

VEGF expression in nephroblastoma of different tissue types

The 12 literatures reported the expression of VEGF in different tissue types of nephroblastoma, including favorable histology (FH) type and unfavorable histology (UH) type. There was a statistically significant difference in positive expression of VEGF between the FH group and the UH

Table 1 Basic clinical features of the 12 studies included in this meta-analysis

Study	Age (SD), years	Gender (male/female)	SOFA score (SD), 6.3–6.7	APACHE II (SD), 20.1–22.5	Outcome	
					Experimental group	Control group
Maslak *et al.*, 2018	4.2±1.02	40/45	NA	95.4–96.6	VEGF (+)	VEGF (–)
Chuk *et al.*, 2018	4.1±1.14	42/34	8.2–10.2	22.4–24.5	VEGF (+)	VEGF (–)
Rivera *et al.*, 2020	8.2±1.05	57/47	5.5–6.5	NA	VEGF (+)	VEGF (–)
Chagaluka *et al.*, 2020	5.2±1.50	73/38	NA	100.2–107.5	VEGF (+)	VEGF (–)
Tang *et al.*, 2020	3.5±1.18	24/20	NA	NA	VEGF (+)	VEGF (–)
Yin *et al.*, 2019	4.4±1.70	NA/NA	NA	NA	VEGF (+)	VEGF (–)
Ehrlich *et al.*, 2020	5.5±2.02	52/27	9.4–10.9	23.2–24.8	VEGF (+)	VEGF (–)
Lin *et al.*, 2019	8.6±1.45	62/25	10.8–11.2	NA	VEGF (+)	VEGF (–)
Rautenberg *et al.*, 2019	8.9±2.05	108/96	NA	NA	VEGF (+)	VEGF (–)
Gavens *et al.*, 2020	4.5±1.60	49/51	9.2–9.6	NA	VEGF (+)	VEGF (–)
Koshinaga *et al.*, 2019	5.2±1.55	59/68	7.1–8.5	23.5–24.9	VEGF (+)	VEGF (–)
Irtan *et al.*, 2019	3.2±1.25	74/88	NA	NA	VEGF (+)	VEGF (–)

NA, not applicable; SOFA, sequential organ failure assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II; SD, standard deviation.

group (OR =1.17, 95% CI: 1.07–1.27, P=0.0006), and there was acceptable heterogeneity between studies (I^2=0%, Z=3.45; *Figure 5*).

VEGF expression in nephroblastoma at different clinical stages

The 12 literatures reported the expression of VEGF at different clinical stages of nephroblastoma (including stage I–II and III–IV). Positive expression of VEGF showed a statistically significant difference between the stage I–II group and the stage III–IV group (OR =0.49, 95% CI: 0.42–0.58, P<0.00001). There was acceptable heterogeneity between studies (I^2=0%, Z=8.25; *Figure 6*).

VEGF expression in nephroblastoma with or without tumor metastasis

The 12 literatures reported the expression of VEGF in nephroblastoma with and without tumor metastasis. Positive expression of VEGF showed no statistically significant difference between the group with and without tumor metastasis (OR =1.08, 95% CI: 0.86–1.36, P=0.50). There was acceptable heterogeneity between studies (I^2=0%, Z=0.68; *Figure 7*).

Discussion

At present, VEGF is the most effective angiogenesis-stimulating factor known (25). VECF is an important factor for stimulating the proliferation and migration of vascular endothelial cells and can affect vascular permeability. Normal tissues can also produce a small amount of VEGF to regulate the proliferation of endodermal cells in their tissues. However, the expression of VEGF in cancer cells is significantly higher than that in adjacent tissues, resulting in vascular injury and invasion during cancer metastasis, often accompanied by platelet activation and aggregation (26). VEGF changes the formation process of gene activation in endothelial cells, upregulates the expression of urokinase plasminogen activator (uPA), tissue plasminogen activator (tPA), and plasminogen activator inhibitor 1 (PAI-1), and induces the expression of proteolytic enzyme, interstitial collagenase, and tissue factor in endothelial cells, that is, induces vascular formation. High expression of VEGF messenger RNA (mRNA) and protein has been found in malignant tumor tissues and *in vitro* cultured tumor cell lines, including gastric cancer, colon cancer, liver cancer, lung cancer, breast cancer, glioma, bladder cancer, and kidney cancer (27). The correlation between VEGF and malignant tumor has been reported in adults but rarely

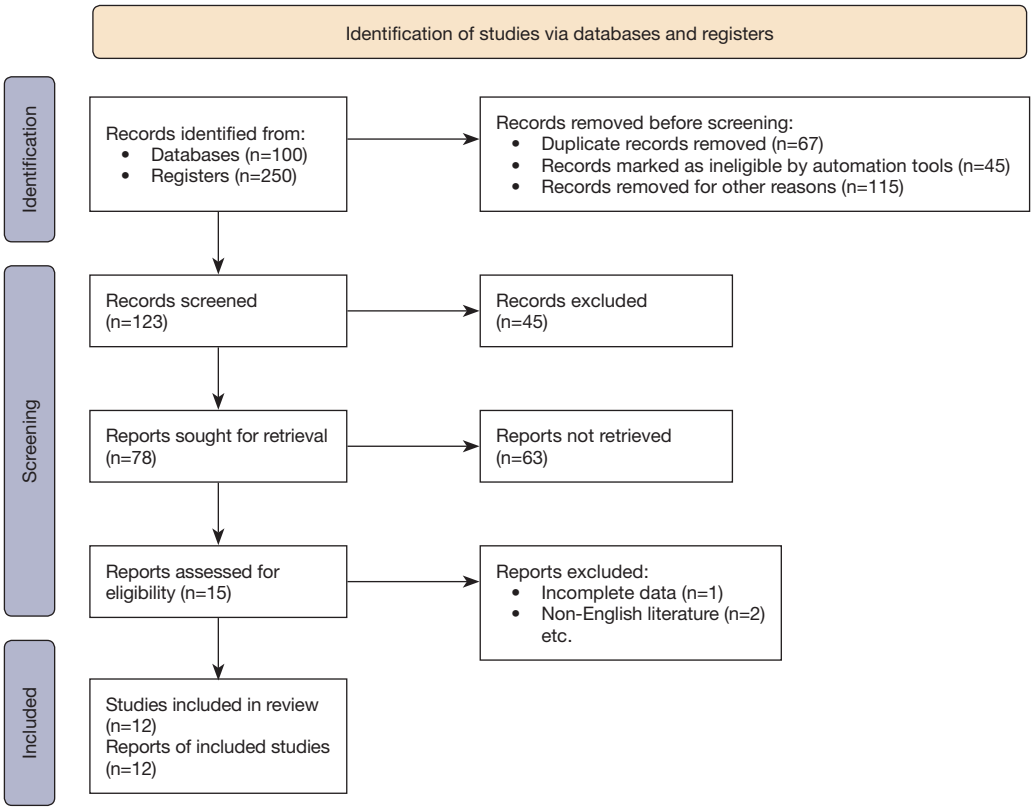

Figure 3 Flow chart of the literature screening.

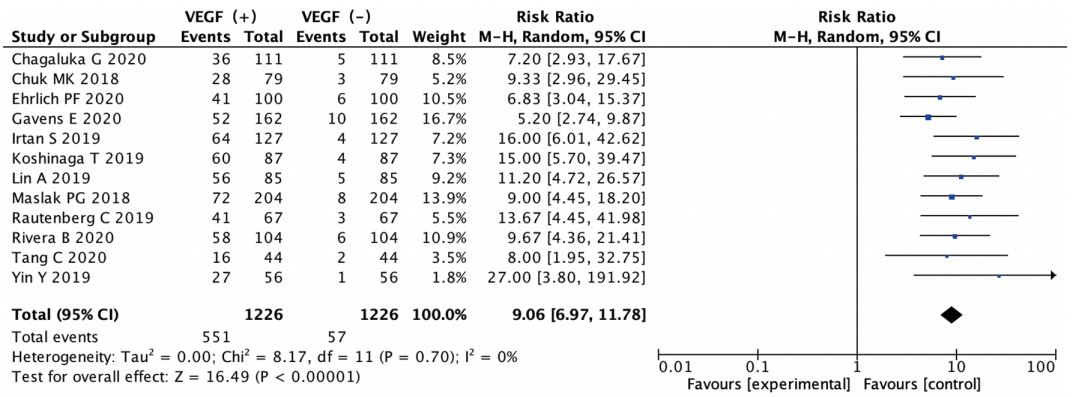

Figure 4 Expression of VEGF in childhood nephroblastoma. VEGF, vascular endothelial growth factor; CI, confidence interval.

in children (28). Nephroblastoma is the most common malignant tumor of the urinary system, accounting for 8% of solid tumors in children, and is still an important disease threatening children's health (29).

Wiles *et al.* (30) first found that there was a special vascular distribution phenomenon in the tumor tissues of a mouse model of nephroblastoma, including vascular structure disorder, vascular plexus, microaneurysm formation, and local hemorrhage, which was significantly different from the orderly vascular distribution in normal tissues. Since then, Hisada *et al.* (31) confirmed that this pathological vascular structure in childhood nephroblastoma was related to the upregulation of VEGF expression level. Zhang *et al.* (32) found that the expression level of VEGF in

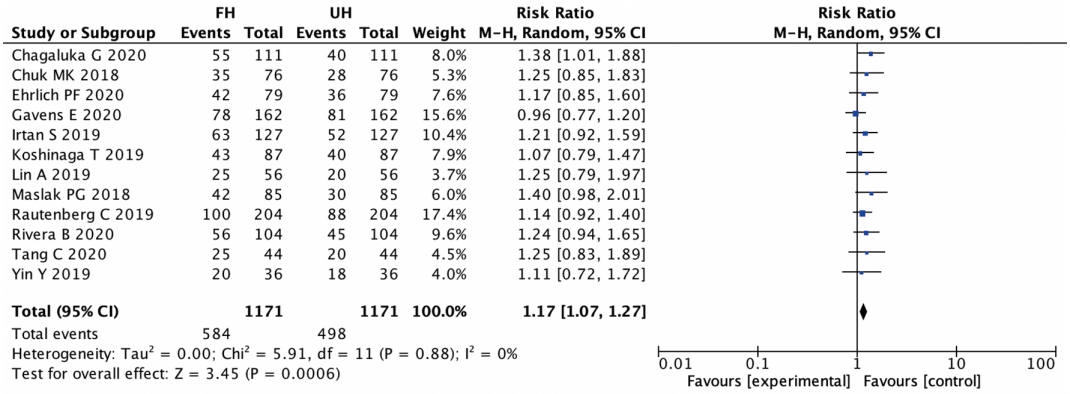

Figure 5 VEGF expression in nephroblastoma of different tissue types (FH and UH). VEGF, vascular endothelial growth factor; UH, unfavorable histology; FH, favorable histology; CI, confidence interval.

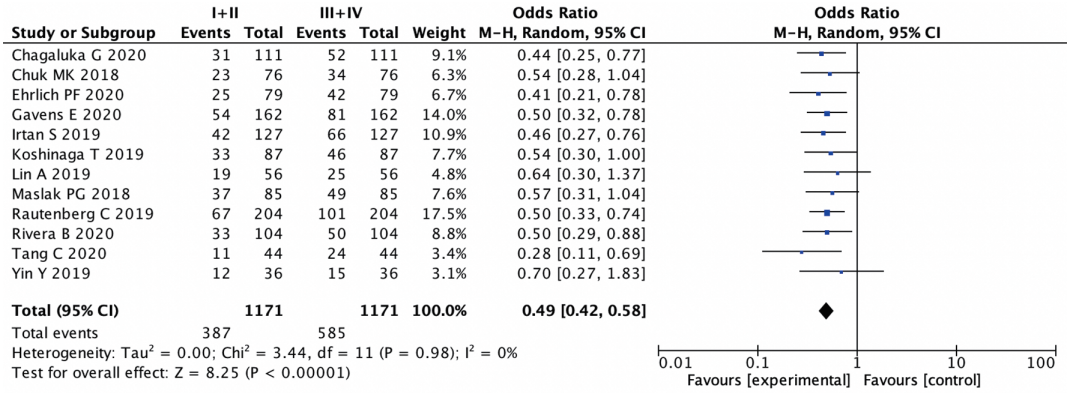

Figure 6 VEGF expression in nephroblastoma at different clinical stages (I–II and III–IV). VEGF, vascular endothelial growth factor; CI, confidence interval.

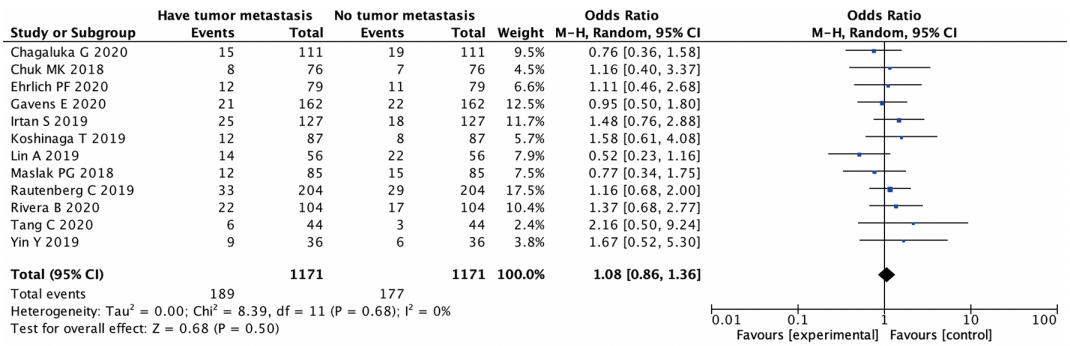

Figure 7 VEGF expression in nephroblastoma tumor metastasis. VEGF, vascular endothelial growth factor; CI, confidence interval.

children with nephroblastoma was significantly higher than that in children without nephroblastoma. Lin *et al.* (33) also found that serum VEGF expression was high in children with nephroblastoma, but VEGF level decreased sharply after radical tumor resection. These results suggested that preoperative VEGF level was pathological rather than

physiological, indicating that the tumor itself was the most likely source of VEGF high expression, although it may not be the only source (34). Serum VEGF level was higher in children who died within 6 months after surgery, suggesting that postoperative VEGF expression level may be an important indicator for predicting the metastasis and prognosis of nephroblastoma (35).

This study had some limitations: (I) among the 12 included studies, each index standard was different, and there were a large number of them, which inevitably leads to errors in data statistics; (II) differences in treatment regimens and corresponding methodologies between studies may have contributed to heterogeneity; (III) many of the projects included in this study were open trials, which may also have increased the risk of literature bias. Heterogeneity may result from differences and diversity in the inclusion criteria of patients in the studies, interventions, and measures across a range of studies, or from variations in the inherent authenticity of those studies. Statistical heterogeneity is used specifically to describe the degree of variation in effect sizes across a series of studies and to indicate variability between studies except for foreseeable chance.

In this study, meta-analysis was conducted to compare pediatric nephroblastoma tissues with normal adjacent renal tissues. The results (OR =9.06, 95% CI: 6.97–11.76, P<0.00001) and acceptable heterogeneity between studies (I^2=0%, Z=16.49) suggested that VEGF was highly expressed in Wilms tumor tissues compared with normal tissues. This is consistent with the findings of the studies discussed above. There were significant differences in the expression of CDl63 and VEGF in the adjacent tissues and the nephroblastoma tissues (P<0.05), suggesting that TAM aggregation was highly expressed in the tumor cell region and presented a consistent trend with vascular proliferation. Many studies have shown that M2 TAM is positively correlated with tumor angiogenesis. TAM can regulate tumor vascular proliferation, thereby promoting blood vessel growth, as well as tumor cell growth and metastasis. Tumor metastasis and growth require blood supply, blood vessels.

Neovascularization is required, which also indicates the correlation between VEGF expression and the survival and prognosis of nephroblastoma.

Meta-analysis of VEGF expression and clinical stage of nephroblastoma showed a significant correlation (P<0.01), indicating that clinical stage of nephroblastoma affected the expression of VEGF. There was no significant correlation between VEGF expression and tumor metastasis (P>0.05). In conclusion, we found that there was a high expression of VEGF in childhood nephroblastoma, which was affected by clinical stage, but there was no significant correlation with tumor metastasis. The expression of VEGF plays an important role in the occurrence and development of childhood nephroblastoma and could help guide clinicians to evaluate the disease and treatment in children.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-21-593/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-21-593/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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