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Immunohistochemical expression of vascular endothelial growth factor-C in renal cell carcinoma subtypes

Omar F. Haider, Wahda M.T. Al-Nuaimy

Department of Pathology, College of Medicine, University of Mosul, Mosul, Iraq

Email: omarfarishaider.ib@gmail.com , wmt@uomosul.edu.iq

Abstract. Background: Vascular Endothelial Growth Factor-C is a glycoprotein encoded by the Vascular Endothelial Growth Factor-C gene, initially produced as an inactive precursor and activated through proteolytic processing. It belongs to the vascular endothelial growth factor family and plays a crucial role in angiogenesis (blood vessel formation) and lymphangiogenesis. Objectives of the study: To evaluate the immunohistochemical expression of Vascular Endothelial Growth Factor-C in renal cell carcinoma subtypes. To assess its association with some clinicopathological parameters. Methods: In this prospective and retrospective case series study, fifty cases of surgically excised kidney biopsies were included. The blocks of the cases were collected from Al-Jumhory teaching hospital and some private laboratories in Mosul city in a period from October 2023 to July 2024. Section slides from the blocks were stained by Vascular Endothelial Growth Factor-C. Interpretation of the slides and statistical analysis has been done. Results: The age of 50 renal cell carcinoma cases ranged from 21 to 77 years (mean± standard deviation= 55.6±13.5) with 56% of them ≥ 55 years, male to female ratio 2:3, 78% of cases were of clear cell renal cell carcinoma, regarding tumor grading 44% grade II, 34% with positive lymphovascular invasion, 48% were tumor stage T1. Among the fifty cases, 56% were with high level of expression of VEGF-C with 59% of them < 55 years old, 63% males, 56% were of clear cell renal cell carcinoma, 82.4% of them with positive lymphovascular invasion show high expression of VEGF-C. Conclusion: High VEGF-C expression was predominantly observed in cases with higher tumor grades (III and IV), also there is a high expression with advanced stages (T3 and T4), and lymphovascular invasion, suggesting that VEGF-C may serve as an important parameter for more aggressive and invasive forms of RCC.

Highlights:

1. High VEGF-C expression significantly correlates with advanced tumor grade (III–IV) and stage (T3–T4), indicating aggressive cancer behavior.
2. VEGF-C shows strong association with lymphovascular invasion, suggesting its role in tumor dissemination and poor prognosis.
3. VEGF-C expression may serve as a potential biomarker for identifying invasive renal cell carcinoma and guiding targeted therapy.

Keywords: Renal Cell Carcinoma, Vascular Endothelial Growth Factor-C, Clear Cell Carcinoma, Tumor Grade, Lymphovascular Invasion

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Introduction

Renal cell carcinoma (RCC) is a heterogeneous and complex disease with numerous pathophysiological variants, RCC incidence rates have been increasing and in higher-income settings, this may partially be due to an increase in the incidental detection of renal masses when abdominal imaging is performed for nonspecific musculoskeletal or gastrointestinal complaints, it accounts for more than 85% of all renal malignancies, with a steady increase of 4% in the incidence and 2.3% of the mortality, RCC has ranked thirdly most common urological cancer. Clear cell renal cell carcinoma (CCRCC), which comprises roughly 75%~80% of all RCC cases, is the most prevalent histological subtype, due to the absence of effective diagnostic methods(1), along with non-specific symptoms at early stage, nearly one-third of patients present with metastasis at the time of diagnosis, the prognosis of RCC patients with metastasis is unfavorable, with a fact that 5-year survival rate is less than 10% and the median survival time is 1.5 years while surgical removal is the gold standard treatment for localized kidney cancer, many targeted therapies have been recently introduced for the treatment of metastatic renal cell cancer, in recent years, multiple immunohistochemical markers have been studied and offered as tools to distinguish the various renal neoplasms from each other and from morphologically similar non-renal tumors no one marker has been found to be entirely specific for RCC in general or for any specific type of RCC(1).

The Vascular endothelial growth factor C (VEGF-C) is a protein that is a member of the platelet-derived growth factor / vascular endothelial growth factor (PDGF/VEGF) family. It is encoded in humans by the VEGFC gene, which is located on chromosome 4q34; the main function of VEGF-C is to promote the growth of lymphatic vessels (lymphangiogenesis). It acts on lymphatic endothelial cells (LECs) primarily via its receptor VEGFR-3 promoting survival, growth and migration. It was discovered in 1996 as a ligand for the orphan receptor VEGFR-3, Soon thereafter, it was shown to be a specific growth factor for lymphatic vessels in a variety of models. However, in addition to its effect on lymphatic vessels, it can also promote the growth of blood vessels and regulate their permeability (2).

Materials and methods

In this prospective and retrospective case series study, fifty cases of surgically excised renal cell carcinoma biopsies were included. The blocks of the cases were collected from the 1st of October 2023 till the 1st of July 2024 from Al-Jumhory teaching hospital and

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some private laboratories in Mosul city, and the period of study was conducted from 1st of January 2024 till the 1st of September 2024.

Sections from paraffin embedded tissue were taken on clean slides and stained with H and E, then examined under the light microscope, to confirm the diagnosis of RCC subtypes, grad of the tumor and lymphovascular invasion. The most appropriate block of each case was chosen for immune-histochemical staining with VEGF-C and other information regarding the age of the patient, gender, laterality and, tumor size, were collected from surgical pathology reports.The inclusion criteria Patients who undergo total nephrectomy for RCC and confirm them by H&E staining, while the exclusion criteria included tumors other than RCC and RCC cases received neoadjuvant therapy. This study was performed by using the primary antibody VEGF-C, isotype IgG1, Mouse monoclonal antibody, supplied by Santa Cruz Biotechnology.

Interpretation of immunohistochemistry staining: By using light microscope of Nikon:

Cytoplasmic and membranous immunoreactivity for VEGF-C was evaluated and scored manually. Both the quantity and quality of the staining of the tumor cells in an average of 10 microscopic fields (magnification x400) were demonstrated and pictures were taken by light microscope of Leica. The brown pigmentation of the cytoplasm and membranous was detected in the tumor cells and the VEGF-C staining was evaluated as following:

The proportional score (PS)

The percentage of Cytoplasmic and membranous staining of VEGF-C graded as:

P.S.0 = less than 10%

P.S.1 = 10–25%

P.S.2 = 26–50%

P.S.3 = >50%

The intensity score (IS) scaled from 0 to 3, where:

I.S. 0 = Negative

I.S. 1 = Weak staining

I.S. 2 = Moderate staining

I.S. 3 = Strong staining

The total score (TS) calculated by summation of proportional score and intensity sore:

T.S. 1

T.S. 0 = 0

T.S. 1 = 1 –2

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T.S.2 = 3–4

T.S.3 = 5-6

For the purpose of statistical analysis:

Low expression=T.S. 0 less than 10% (PS) T.S. 1(Negative)

High expression = T.S.2 or T.S.3. (3,4) (positive)

Statistical analysis: Statistical analysis was done by using of Chi-square and Fisher exact test, when indicated using SPSS for statistical analysis.A "P value of ≤ 0.05" was considered statistically significant with confidence interval of 95%.

Results

The descriptive analysis of clinicopathological characteristics from this cohort of 50 renal cell carcinoma patients reveals several important demographic and pathological patterns. Regarding anatomical distribution, the left kidney was more frequently affected than the right, accounting for 60% of cases compared to 40% on the right side. The histopathological examination demonstrated that clear cell renal cell carcinoma was the predominant variant, comprising 78% of all cases, while papillary cell RCC represented 16% of the cohort and chromophobe RCC was the least common subtype at only 6%. The tumor grading distribution showed a concentration in the intermediate grades, with Grade 2 tumors being most prevalent at 44% of cases, followed by Grade 3 at 28%, while Grade 4 high-grade tumors constituted 20% and the well-differentiated Grade 1 tumors were least common at 8%. The staging analysis revealed considerable heterogeneity in tumor extent, with T1a tumors representing the largest single category at 26% of cases, followed by T3a tumors at 24%. Early-stage disease (T1 and T2 combined) accounted for approximately 60% of the cohort, while locally advanced disease (T3 and T4) comprised the remaining 40%. Notably, lymphovascular invasion was absent in the majority of patients, occurring in 66% of cases, while 34% demonstrated evidence of vascular or lymphatic invasion. This distribution pattern suggests a cohort with predominantly clear cell histology and a mixture of early and intermediate-stage disease, with a substantial minority showing aggressive features such as high-grade morphology and lymphovascular invasion (Table 1).

Table 1. The descriptive analysis of clinicopathological data of this study.

Variables		No. [total = 50]	Percent %
Site (laterality)	Left	30	60.0
	Right	20	40.0

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Histopathological variant	Clear cell RCC	39	78.0
	Papillary cell RCC	8	16.0
	Chromophobe RCC	3	6.0
Tumor grade (G)	1	4	8.0
	2	22	44.0
	3	14	28.0
	4	10	20.0
Tumor Stage (T)	T1	1	2.0
	T1a	13	26.0
	T1b	10	20.0
	T2a	5	10.0
	T2b	1	2.0
	T3	3	6.0
	T3a	12	24.0
	T3b	1	2.0
	T4	3	6.0
Lymphovascular invasion	Absent	33	66.0
	Present	17	34.0

The analysis of VEGF-C expression patterns across various clinicopathological parameters in this cohort of 50 renal cell carcinoma patients revealed several significant associations that underscore the protein's role in tumor progression and aggressiveness (Table 2). Age-related patterns showed a notable trend, with patients under 55 years demonstrating predominantly low VEGF-C expression (59.1%) compared to high expression (40.9%), while those 55 years and older exhibited a reversed pattern with high expression predominating at 67.8% versus 32.1% low expression, though this difference did not reach statistical significance (p=0.085). Gender distribution showed males having a higher proportion of high VEGF-C expression (63.6%) compared to females (41.2%), but this association was not statistically significant (p=0.147).

The most striking and statistically significant associations emerged when examining tumor grade, where a clear progressive relationship was observed between increasing histological grade and VEGF-C expression intensity (p=0.001). Grade 1 tumors showed balanced expression with 50% exhibiting low and 50% high VEGF-C levels, while Grade 2 tumors demonstrated predominantly low expression at 81.8%. In stark contrast, high-

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grade tumors showed dramatically elevated VEGF-C expression, with Grade 3 tumors exhibiting 92.8% high expression and Grade 4 tumors showing 90% high expression, indicating a strong correlation between tumor dedifferentiation and VEGF-C upregulation.

Lymphovascular invasion status revealed another significant association (p=0.008), where tumors without vascular invasion predominantly showed low VEGF-C expression (57.6%), while those with lymphovascular invasion demonstrated high expression in 82.4% of cases, suggesting VEGF-C's role in promoting tumor cell dissemination. Tumor staging analysis provided equally compelling evidence (p=0.001), with early-stage tumors (T1, T2) showing predominantly low VEGF-C expression (63.3%), while advanced-stage tumors (T3, T4) exhibited high expression in 85% of cases, reinforcing the protein's association with tumor progression and local invasion.

Interestingly, neither tumor laterality nor histopathological variant showed significant associations with VEGF-C expression patterns. Right-sided tumors demonstrated 65% high expression compared to 50% in left-sided tumors (p=0.386), while the three histological variants showed relatively similar expression patterns, with clear cell RCC exhibiting 56.4% high expression, papillary cell RCC showing 50% high expression, and chromophobe RCC demonstrating 66.7% high expression (p=0.789). These findings collectively suggest that VEGF-C expression serves as a robust biomarker for tumor aggressiveness, correlating strongly with high histological grade, advanced stage, and the presence of lymphovascular invasion, while being independent of tumor location and histological subtype.

Table 2. The results of VEGF-C expression and its association with the studied clinicopathological variables in this study.

Parameters	Data	No.	VEGF-C expression				P value
			Low		High		
			No.	%	No.	%	
Age in years	< 55	22	13	59.1	9	40.9	0.085
	≥ 55	28	9	32.1	19	67.8	
Sex	Male	33	12	36.4	21	63.6	0.147
	Female	17	10	58.8	7	41.2	
Grade	G1	4	2	50.0	2	50.0	**0.001**
	G2	22	18	81.8	4	18.1	
	G3	14	1	7.1	13	92.8	

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	G4	10	1	10.0	9	90.0	
Lymphovascular invasion	Present	33	19	57.6	14	42.4	**0.008**
	Absent	17	3	17.7	14	82.4	
Tumor Size	T1, T2	30	19	63.3	11	36.7	**0.001**
	T3, T4	20	3	15.0	17	85.0	
Tumor Site	Right	20	7	35.0	13	65.0	0.386
	Left	30	15	50.0	15	50.0	
Histopathological Variant	Clear cell RCC	39	17	43.6	22	56.4	0.789
	Papillary cell RCC	8	4	50.0	4	50.0	
	Chromophobe RCC	3	1	33.3	2	66.7	
P value ≤ 0.05 is significant							

In the immunohistochemical analysis of VEGF-C expression across renal tissues, distinct patterns emerged that illuminated the protein's distribution and intensity in both normal and pathological contexts. The positive control specimen revealed robust VEGF-C expression within the glomerular epithelial cells of normal renal tissue, where the protein appeared as distinct brown chromogenic deposits distributed throughout the cytoplasm of podocytes and parietal epithelial cells, serving as a baseline reference for optimal staining conditions at 400X magnification. In contrast, the clear cell renal cell carcinoma (ccRCC) specimens demonstrated a heterogeneous expression pattern that varied significantly between tumor samples. Low-grade ccRCC tissue exhibited markedly diminished VEGF-C immunoreactivity, with sparse, weakly positive staining scattered throughout the neoplastic cells, suggesting downregulated lymphangiogenic signaling in these less aggressive tumors. Conversely, high-grade ccRCC specimens displayed intense, diffuse VEGF-C positivity throughout the malignant epithelial cells, with strong cytoplasmic staining that often extended to the cell membrane regions, indicating upregulated expression that likely correlates with enhanced lymphangiogenic potential and metastatic capacity. This differential expression pattern between normal glomerular epithelium, low-grade ccRCC, and high-grade ccRCC underscores VEGF-C's potential role as both a diagnostic marker and prognostic indicator in renal cell carcinoma progression (Figure 1).

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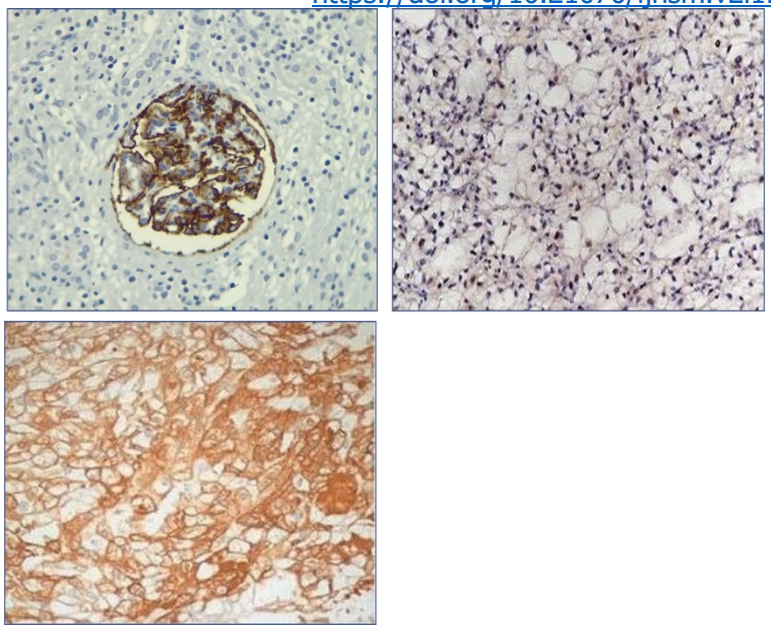

Figure 1. Immunohistochemical staining of VEGF-C expression in CRCC and normal renal tissue(VEGF-C expression in glomerular epithelial cells positive control A:400X, Low positive expression of VEGF-C in ccRCC B:400X, Hight positive expression of VEGF-C in ccRCC C:400X)

Discussion

VEGF-C is an indispensable mediator in the processes of lymphangiogenesis and angiogenesis, playing a critical role in tumor biology, particularly in facilitating metastasis through lymphatic dissemination. Its expression has been widely studied in various cancers, including RCC, where it is believed to contribute to the aggressive nature of the disease. Immunohistochemistry is a vital tool in assessing the expression of VEGF-C within tumor tissues, providing insights into its relation with key clinicopathological features such as tumor grade, stage, lymphovascular invasion, patient prognosis and treatment mode.(5)

In the current research, the high expression of VEGF-C was noticed in 56% of the cases, this was consistent with the results obtained by Zhao in china (6) & Moselhy et al (7), in Egypt where the frequency of expression of VEGF-C was (50%, 56%) respectively. However, this finding was inconsistent with Voss et al (3) in Germany because the frequency of expression of VEGF-C was higher (84%) and inconsistent with Bierer et al (8) in Germany where the frequency of expression was lower (24.1 %). This variability in results could be due to the use different anti-VEGF-C antibody clones, using different cut off points for immunostaining scoring and other factors that differ among these studies which include: sample size, time of fixation (under or over fixation) and the techniques

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used.

Regarding the age, (67.5%) of the cases aged <55 years were found to have high VEGF-C expression this was consistent with the results obtained by Shi et al (4) in China, Zhao et al (6) in china, but inconsistent with the findings and Moselhy et al (7) in Egypt, where the high frequency of expression found in the age group 55> years. No explanation found to this variability in these results.

Zhao et al (6) in China and Moselhy et al (7) in Egypt found that VEGF-C was highly expressed in male cases affected with RCC, in agreement with this study, where VEGF-C was highly expressed in male cases (63.6%) but inconsistent with Shi et al (4) in China who found that VEGF-C highly expressed in both male and female cases, this might be referred to the effect of sex-hormone levels, genetic and epigenetic modification of steroid receptors (9).

Regarding the tumor Laterality, most tumors were located in the left kidney (60%), with the remaining 40% in the right kidney, High VEGF-C expression was seen in 50% of tumors located in the left kidney and 65% in the right kidney. The association between VEGF-C expression and tumor laterality was not statistically significant.

Clear cell RCC was the predominant variant, accounting for 78% of cases. Papillary RCC accounted for 16% of cases, and Chromophobe RCC for 6%.

Clear cell RCC had a high VEGF-C expression in 56.4% of cases, papillary RCC in 50%, and chromophobe RCC in 66.7%, Similar findings were observed in Voss et al (3) in Germany, with clear cell RCC showing varying levels of VEGF-C expression based on tumor size. Papillary RCC showed strong VEGF-C expression, while chromophobe RCC had moderate staining intensity in another study Bierer et al(8) in Germany, found (ccRCC): VEGF-C expression was positive in (11.1%) of cases, (pRCC): VEGF-C expression was significantly higher, positive in (35.5%) of cases.

In this study, VEGF-C had the highest expression among the high grade cases, Grade III-IV: showing (92.8% & 90%) of cases respectively had high VEGF-C expression, while the low Grade I and II: showing (8 and 44%) of cases respectively show high VEGF-C expression, this results in agreement with Zhao et al (65) in China, in another studies that show no association with tumor grade of RCC as in Bierer et al (8) in Germany and Voss et al (3) in Germany another study Shi L, (4) in China they show opposite expression in association with the grade parameter they show high frequency of VEGF-C expression in low grade tumor Grade I-II and high tumor Grade III-IV low frequency of VEGF-C expression, this variable relation may be due to tumor heterogeneity. Renal cell carcinoma

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is a heterogeneous disease with significant variability in tumor biology across patients. This heterogeneity can lead to differences in VEGF-C expression even within the same tumor grades across different studies. Tumors of the same grade in different cases may have varying levels of VEGF-C expression due to genetic and molecular differences (10), and also a combination of others factors, like differences in study design, patient populations, tumor biology, and technical methodologies can all contribute to the observed discrepancies.

Regarding the lymphovascular invasion (82.4%) of cases of RCC with positive lymphovascular invasion in the current study showed high expression of VEGF-C, this finding consistent with Zhao et al (6) in China and Shi et al (4) in China too.

Voss et al (3) study show that there is no direct association between VEGF-C expression and lymphovascular invasion within the tumor itself, though it suggested a possible indirect role through peritumoral lymphangiogenesis (11) .

Regarding the T tumor size and spread in surrounding tissue, the high expression of VEGF-C was in T3-T4 category (80%) in agreement with Zhao et al (6) in China who showed a similar results, Voss et al (3) in Germany and Bierer et al (8) in USA who showed that VEGF-C was highly expressed in T3-T4 category. These findings may reinforce the poor clinicopathological role played by VEGF-C since its roles in promoting lymphangiogenesis, responding to hypoxia, enhancing tumor invasiveness, and interacting with the tumor microenvironment. This makes VEGF-C a key factor in the progression and aggressiveness of RCC, particularly in advanced stages where the tumor’s need for additional blood and lymphatic support is greatest. Understanding this relation helps in targeting therapies that may inhibit VEGF-C and reduce the tumor's ability to spread (12).

High stage RCC is often treated with targeted therapies that inhibit the VEGF pathway, mainly through VEGF receptor (VEGFR) inhibitors such as sunitinib, sorafenib, and axitinib. While these therapies primarily aim VEGF-A and VEGFR-2, there is new attract in understanding how VEGF-C expression might influence treatment reaction, this recent study focus on the VEGF-C IHC indicates high expression in a patient’s tumor, there may be a rationale for combining VEGFR-2 inhibitors with agents that specifically target VEGF-C or VEGFR-3 (its receptor), may be enhancing treatment efficacy. This is an area of ongoing research, with the aim of tailoring therapy more precisely based on individual tumor biology (13).

Conclusion

High VEGF-C expression was predominantly observed in cases with higher tumor grades

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(III and IV), also there is a high expression with advanced stages (T3 and T4), and lymphovascular invasion, suggesting that VEGF-C may serve as an important parameter for more aggressive and invasive forms of RCC.

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