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Immunohistochemical Expression of Vegf in Renal Cell Carcinoma and Its Correlation with Clinic morphological Features

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ABSTRACT

INTRODUCTION: Renal Cell Carcinoma (RCC) is the most common renal malignancy in adults, accounting for approximately 90% of kidney cancers. Prognostic and predictive biomarkers play a critical role in understanding RCC progression and guiding targeted therapy. Angiogenesis is a critical step in the growth, invasive progression and metastatic spread of solid tumors. Vascular endothelial growth factor (VEGF) is key regulator of angiogenesis, process of building new blood vessels, which is essential for tumor development and metastasis. Role of VEGF in RCC is not well established.

AIM: The aim of our study was to analyse VEGF expression in different histological variants of RCC and its relationship with histological type, tumor grade, pathological stage, necrosis, lymphovascular invasion, other clinicopathological parameters.

MATERILAS AND METHODS:A retrospective study was performed using paraffin blocks of Renal cell carcinoma reported between 2018 to 2024. For light microscopy screening, sections were initially stained with haematoxylin and eosin stains. In further sections, a primary antibody against VEGF was applied. The level of VEGF expression in renal cell carcinoma was evaluated using a scoring system.

RESULTS: Forty cases with renal cell carcinoma were included. In our study, immunohistochemical positivity showed no significant association with histological type, grade, pathological staging, or lymphovascular invasion ($p > 0.05$ for all). However, a statistically significant correlation was observed with tumor necrosis ($p = 0.015$), indicating a potential link between marker expression and necrotic changes in renal cell carcinoma.

CONCLUSION: In this study of renal cell carcinoma, VEGF expression did not significantly vary by histological type, grade, pathological stage, or lymphovascular invasion. However, a significant inverse association was observed between VEGF expression and tumor necrosis ($p = 0.015$), indicating that reduced VEGF expression is linked to increased tumor necrosis. These findings suggest that VEGF plays a critical role in maintaining vascular integrity within the tumor microenvironment and may have prognostic significance in RCC

Key Words: VEGF, Renal cell carcinoma, Immunohistochemistry

1. INTRODUCTION

Renal cancer is the 14th most commonly diagnosed cancer worldwide, 434,840 new cases reported annually. It ranks as the 16th cause of cancer related deaths, accounting for 155,953 fatalities. In India, renal cancer holds the 20th position in cancer

incidence, with 17,480 new cases (1.2% of all cancers) and ranks 21st in cancer mortality, contributing to 10,464 deaths (1.1% of all cancer-related deaths) according to 2022 data [1]. RCC is more prevalent in males than in women, and its prevalence rises sharply with age. Obesity, high blood. pressure, and smoking are major known risk factors for RCC. Additional related medical problems include acquired kidney cystic disease, hemo dialysis, kidney transplantation, chronic kidney disease, a prior diagnosis of RCC, perhaps diabetes mellitus [2]. The chances of RCC is also influenced by genetic factors; those with family history of disease are about twice as likely to develop it themselves [3]. Mutations in 11 genes (BAP1, FLCN, FH, MET, PTEN, SDHB, SDHC, SDHD, TSC1, TSC2, and VHL) have been found in research on familial RCC; several of these genes are also connected to the occurrence of sporadic RCC. VHL is a prime example; it is a gene mutation that causes Von Hippel-Lindau disease and raises the risk of ccRCC. For both familial and sporadic ccRCC cancers, inactivation of VHL protein results in the unchecked production oncogenic hypoxia-inducible factors (HIF-1 and HIF-2) [4]. The classical triad includes hematuria, flank pain and a mass in abdomen that is palpable is seen in < than 10% of patients and is typically indicates advanced disease. Other nonspecific symptoms include loss of weight, fever, and paraneoplastic syndromes like hypercalcemia and polycythemia[5]

Contrast enhanced Computed tomography(CECT) plays a major role in diagnosis. It is more sensitive than ultrasonography in identifying renal masses, ultrasonography can be used to differentiate solid tumors or more complicated cysts from simple benign cysts. [6]. According to the WHO 2022 classification of tumors of kidney 5th edition, Clear cell RCC (CRCC) is the most common type making up about 2% of all cancers [7]. RCC has a survival rate of less than 20% [8]. The present treatment strategies for RCC includes nephrectomy, either radical or partial for localized disease and targeted therapy or immunotherapy for advanced cases [9]. Several immunohistochemical markers have been identified to study RCC behaviour, progression, and prognosis[10]. The role of molecular markers to predict the outcome of the disease is an area of ongoing research, highlighting the need for this study. Despite extensive research on RCC worldwide, there is a deficit of comprehensive data regarding the immunohistochemical expression of VEGF in Indian population

Vascular Endothelial Growth Factor (VEGF) in Renal Cell Carcinoma:

Vascular Endothelial Growth Factor (VEGF) is a critical regulator of angiogenesis, facilitating new blood vessel formation essential for tumor development, progression, and metastasis. Renal cell carcinoma (RCC), particularly clear cell RCC (ccRCC), is among the most vascularized solid tumors. This is primarily attributed to frequent inactivation of the von Hippel-Lindau (VHL) gene, which leads to accumulation of hypoxia-inducible factor-1 alpha (HIF-1α) and subsequent upregulation of VEGF expression. The resulting aberrant angiogenesis promotes tumor growth and correlates with poor clinical outcomes. VEGF is overexpressed in more than 90% of ccRCC cases. The predominant mechanism driving this overexpression is VHL gene loss, which stabilizes HIF-1α and HIF-2α, enabling them to bind the VEGF gene promoter and enhance transcription. Additionally, VEGF expression is amplified by pro-inflammatory cytokines (e.g., IL-6, TNF-α), hypoxia, and activation of oncogenic pathways such as PI3K/Akt. Tumors with high VEGF expression typically show increased microvascular density (MVD), improved perfusion, and a greater capacity for metastasis. These features are strongly correlated with tumor aggressiveness and resistance to conventional therapies, making VEGF a key prognostic and predictive biomarker in RCC.

Beyond angiogenesis, VEGF contributes to metastasis by altering the tumor microenvironment and inducing epithelial-to-mesenchymal transition (EMT). [11,12]. Targeting the VEGF pathway has become a cornerstone of RCC treatment. Therapeutic strategies include:

- **Tyrosine kinase inhibitors (TKIs)** (e.g., sunitinib, pazopanib, axitinib, cabozantinib) that block VEGF receptor activation.
- **Monoclonal antibodies** (e.g., bevacizumab) that neutralize VEGF.
- **Combination therapies**, integrating VEGF inhibitors with immune checkpoint inhibitors (e.g., pembrolizumab + axitinib), have demonstrated improved clinical outcomes.

However, resistance to VEGF-targeted therapies frequently emerges due to activation of alternative angiogenic pathways (e.g., FGF, PDGF), tumor hypoxia-driven adaptations, and immune evasion mechanisms. Ongoing research focuses on identifying predictive biomarkers and optimizing combination regimens to enhance response durability. [13]

Hence, we propose to analyse VEGF expression in different histological types of renal cell carcinoma and their relationship with the patients' clinicopathological parameters. To the best of our knowledge less than five articles have been published based on analysis of VEGF expression in RCC in South Indian population.

2. MATERIALS AND METHODS

The present study was done over a period of one year between between October 2023 and September 2024. It is a hospital-based retrospective type of study design. The study comprised of forty patients who underwent nephrectomy between 2018 and 2024.

INCLUSION AND EXCLUSION CRITERIA

All nephrectomy cases including total, partial and cytoreductive nephrectomy were included. Inadequate or insufficient sample, Autolysed samples, Tissue blocks with insufficient material for immunohistochemistry and samples received post radiotherapy or chemotherapy will be excluded

STAINING TECHNIQUE

All radical and partial nephrectomy specimens will be received in 10% neutral buffered formalin. After adequate fixation, grossing and tissue processing will be done as per the standard grossing protocols. For histopathological examination (HPE), the sections were stained by haematoxylin and eosin (H&E). For old cases, patient details were collected from the case sheets. Tissue paraffin blocks and H&E-stained slides were obtained from the department archive. For VEGF IHC staining, additional sections were cut from the paraffin block of tissue and were taken on a glass slide coated with adhesive aminopropyltriethoxysilane (APTES). Primary antihuman antibody against VEGF (rabbit polyclonal antibody AR483 - 5R from Biogenex) was used.

SCORING METHOD

The positively stained tumour cells were scored at ×400 magnification. Semi-quantitative estimation of VEGF expression was done. Scoring for VEGF expression was based on the proportion of tumour cells exhibiting cytoplasmic immunopositivity. Capillary hemangioma was taken as positive control. The VEGF scoring results were calculated as follows: ≤ 10 % of tumor cells showing cytoplasmic staining was considered negative; whereas > 10 % of tumor cells showing cytoplasmic staining was considered positive. [14]

STATISTICAL ANALYSIS

Data was entered into Microsoft excel datasheet and was analysed using SPSS Statistics version 23.0. Pearson's Chi-square test was done to study the correlation of different parameters. A p-value less than 0.05 was considered statistically significant.

3. RESULTS

[Table/Fig 1] Clinicopathological parameters of Renal cell carcinoma patients (n=40 cases)

Parameter	Details
Gender	Male: 62.5% (25), Female: 37.5% (15)
Age Group	≤40 yrs: 15% (6), 40–60 yrs: 50% (20), >60 yrs: 35% (14)
Past Medical History	Hypertension: 67.5% (27) HTN + Diabetes: 22.5% (9) Smoking: 17.5% (7) CKD: 10.0% (4) No Comorbidity: 20.0% (8) Family History of CKD: 5.0% (2)
Clinical Presentation	Asymptomatic: 70.0% (28) Flank Pain: 12.5% (5) Abdominal Mass: 10.0% (4) Hematuria: 7.5% (3)
Kidney Involved	Left: 55.0% (22), Right: 45.0% (18)
Type of Surgery	Radical: 92.5% (37) Partial: 5.0% (2) Cytoreductive: 2.5% (1)
Tumor Site	Upper Pole: 35.0% (14) Lower Pole: 25.0% (10) Renal Pelvis: 12.5% (5) Other/Multiple sites: 27.5% (11)
Focality	Unifocal: 97.5% (39), Multifocal: 2.5% (1)

Lymph Node Evaluation	Evaluated (all negative): 22.5% (9) Not submitted: 77.5% (31)
Histological Subtypes	Clear Cell RCC: 72.5% (29) Papillary: 10.0% (4) Chromophobe: 5.0% (2) Other Oncocytic: 5.0% (2) Other Renal Tumors: 7.5% (3)
Histological Grading (n=37)	Grade 1: 48.6% (18) Grade 2: 27.0% (10) Grade 3: 5.5% (2) Grade 4: 18.9% (7) Not applicable (Chromophobe RCC): 3 cases
Tumor Stage (pT)	pT1a: 20.0% (8) pT1b: 32.5% (13) pT2a: 15.0% (6) pT2b: 7.5% (3) pT3a: 22.5% (9) pT3(m): 2.5% (1)
Sarcomatoid Features	Present: 5.0% (2), Absent: 95.0% (38)
Rhabdoid Features	Present: 12.5% (5), Absent: 87.5% (35)
Tumor Necrosis	Present: 42.5% (17), Absent: 57.5% (23)
Tumor Spread	Limited to Kidney: 65.0% (26), Beyond Kidney: 35.0% (14)
Lymphovascular Invasion	Present: 17.5% (7), Absent: 82.5% (33)
Additional Findings	None: 50.0% (20) Chronic Pyelonephritis: 40.0% (16) Benign Renal Cyst: 2.0% (1) Others: 8.0% (4 cases – includes abscess, xanthogranulomatous change, osseous metaplasia, calcification)

Tumors in other regions include tumors of both upper and lower pole (3 cases), upper pole and renal pelvis (4 cases), lower pole and renal pelvis (1 case), both upper and lower pole including renal pelvis (2 cases)

Other renal tumors (7.5%) which included histological subtypes of eosinophilic unclassified RCC (1 case), RCC with predominantly eosinophilic cells (1 case), Oncocytoma and eosinophilic variant of chromophobe RCC (1 case).

pT3(m) in which (m) suffix indicates multiple primary synchronous tumors in a single kidney.

Explanation of the [Table/Fig1]:

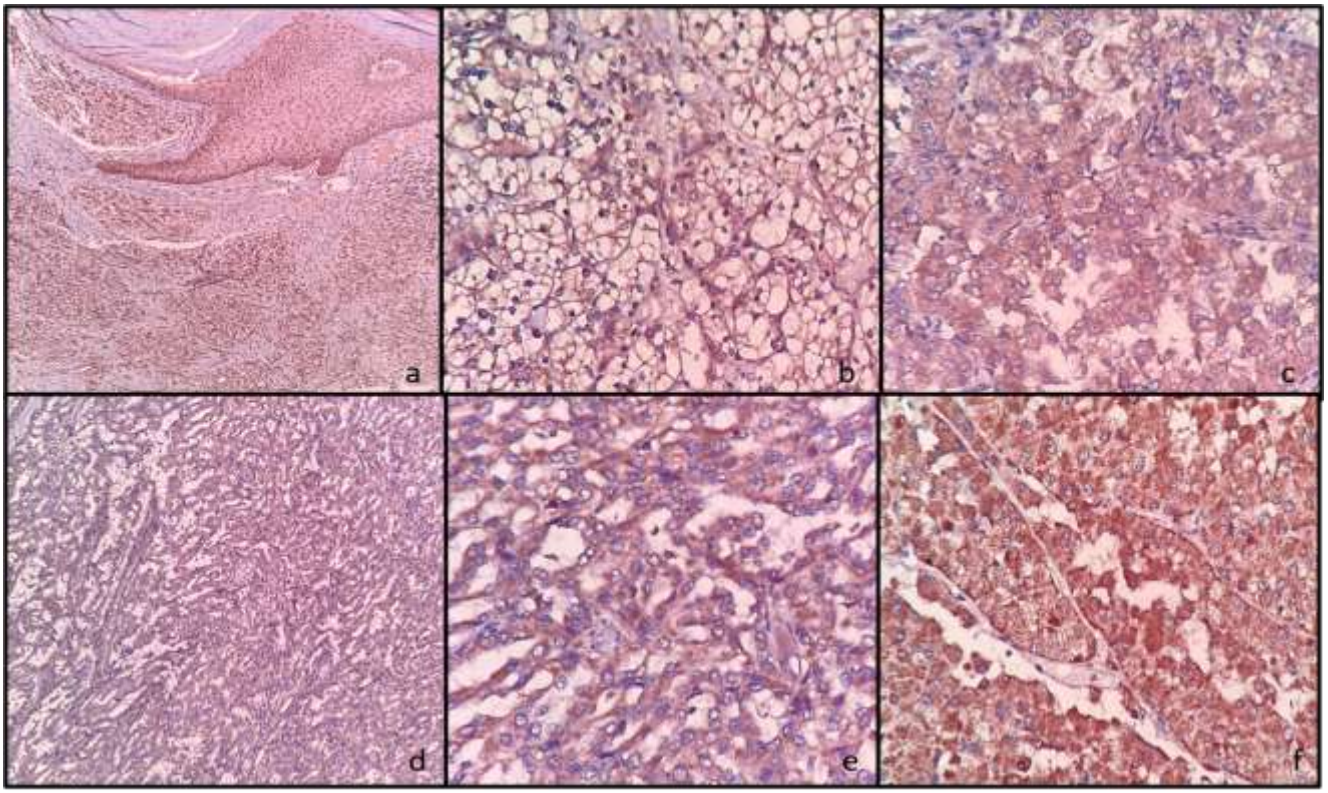
The research had more male subjects, which suggests that renal cell carcinoma (RCC) is more common in the male gender. The largest group of patients belonged to the age group 40–60 years, suggesting that middle-aged individuals are more and more affected. A high percentage (67.5%) had hypertension as a comorbid condition, which underlines its potential role as a common comorbidity in RCC patients.

Two patients also came from families that had a history of CKD, though since this is a fairly small percentage of instances, it would appear that genetic predisposition plays relatively little part in the overall incidence of RCC. Interestingly, both patients were under the age of 30, so familial factors could be more important in early-onset disease.

At diagnosis, most participants (70.0%) were asymptomatic, highlighting the pivotal role of incidental discovery by imaging studies. The sarcomatoid and rhabdoid features—recognized as predictors of aggressive tumor behavior—were noted in a minority of patients. Tumor necrosis, a histopathological feature of adverse prognosis, was noted in 42.5% of cases.

[Table/Fig 2]:Immunohistochemical studies a-VEGF control tissue of capillary hemangioma showing cytoplasmic

positivity(VEGF stain,100x); b- Clear cell RCC showing Negative in tumor cells (VEGF stain 400x view); c- Clear cell RCC showing cytoplasmic positivity in tumor cells (VEGF stain 400x view);d & e- Papillary RCC showing cytoplasmic positivity in tumor cells (d - VEGF stain 100x view, e- 400x); f- RCC with oncocytic features showing cytoplasmic positivity in tumor cells (VEGF stain 400x)



Table/Fig 3: Correlation of immunohistochemical expression of VEGF marker with pathological parameters

S.NO	VARIABLE	HISTOLOGICAL TYPE		Chi square	p value
		CLEAR CELL RCC (n = 29)	OTHER TYPE RCC (n = 11)		
1	Positive	21 (67.7%)	10 (32.3%)	1.564	0.211
	Negative	8 (88.9%)	1 (11.1%)		
2		**HISTOLOGICAL GRADE**			
		GRADE 1 -2 (n = 28)	**GRADE 3 -4 (n = 9)**		
	Positive	21 (75.0%)	7 (25.0%)	0.028	0.865
	Negative	7 (77.8%)	2 (22.2%)		
3		**PATHOLOGICAL STAGING**			
		pT1 -2 (n = 30)	**pT3 (n = 10)**		
	Positive	24 (77.4%)	7 (22.6%)	0.430	0.511
	Negative	6 (66.7%)	3 (33.3%)		
4		**TUMOR NECROSIS**			
		PRESENT (n = 17)	**ABSENT (n = 23)**		
	Positive	10 (32.3%)	21 (67.7%)	**5.914**	**0.015***
	Negative	7 (77.8%)	2 (22.2%)		
5		**LYMPHOVASCULAR INVASION**			
		PRESENT (n = 7)	**ABSENT (n = 33)**		

	Positive	6 (19.4%)	25 (80.6%)	0.328	0.566
	Negative	1 (11.1%)	8 (88.9%)		

VEGF Expression in Context with Clinicopathological Parameters in RCC:

The expression of Vascular Endothelial Growth Factor (VEGF) was studied in 40 renal cell carcinoma (RCC) cases and its correlation with different clinicopathological features such as histological type, grade, stage, tumor necrosis, and lymphovascular invasion. The expression of VEGF was immunohistochemically evaluated and computed for analysis through the Chi-square test.

1. Histological Type

Out of 29 clear cell RCC cases, 21 (67.7%) were VEGF positive, and out of 11 non-clear cell cases, 10 (32.3%) were VEGF positive. In contrast, 8 (88.9%) were VEGF negative in clear cell RCC, and only 1 (11.1%) in others. Association was not statistically significant ($\chi^2 = 1.564$, $p = 0.211$), meaning that the expression of VEGF does not differ significantly between clear cell and others among these histological subtypes of RCC.

2. Histological Grade

VEGF positivity occurred slightly more often in low-grade tumors (75.0% in grades 1–2) than in high-grade tumors (25.0% in grades 3–4). VEGF negativity had a similar distribution, with 77.8% in low-grade and 22.2% in high-grade tumors. This was not statistically significant ($\chi^2 = 0.028$, $p = 0.865$), indicating a lack of any significant association between VEGF expression and histological grade.

3. Pathological Staging

Of the 30 pT1–2 staged cases, 24 (77.4%) were VEGF-positive and 6 (66.7%) were negative. Of the 10 pT3 cases, 7 (22.6%) were VEGF-positive and 3 (33.3%) were negative. Though VEGF was expressed more in the early-stage tumors, the correlation failed to reach statistical significance ($\chi^2 = 0.430$, $p = 0.511$).

4. Tumor Necrosis

There was a significant association between VEGF expression and tumor necrosis ($\chi^2 = 5.914$, $p = 0.015$). Tumors that were non-necrotic had a greater percentage of VEGF positivity (67.7%) compared to necrotic tumors (32.3%). The opposite was seen with VEGF-negative tumors, which were predominantly necrotic (77.8%) compared to non-necrotic (22.2%). These findings suggest that VEGF has a protective role in maintaining vascular integrity, reducing hypoxia-induced necrosis.

5. Lymphovascular Invasion

VEGF expression was noted in 6 of 7 (19.4%) cases with lymphovascular invasion, and in 25 of 33 (80.6%) without it. VEGF negativity was greater in tumors lacking invasion (88.9%) than in invaded ones (11.1%). The difference was not significant statistically ($\chi^2 = 0.328$, $p = 0.566$), signifying the lack of much utility for VEGF expression as a marker for lymphovascular invasion in RCC.

Summary of Results:

In general, VEGF expression in RCC did not correlate significantly with tumor grade, stage, type, or lymphovascular invasion. Yet, VEGF expression was inversely correlated significantly with tumor necrosis, which is consistent with its recognized function of inducing angiogenesis and supporting perfusion of tumor tissue. These data are in favor of the use of VEGF as a functional marker in RCC biology, especially with respect to hypoxia and necrosis, but its prognostic value in other parameters seems limited in this population.

4. DISCUSSION

VEGF Expression and Histological Type:

Findings from this study shows that VEGF positivity was 67.7% in Clear Cell RCC and 32.3% in Other RCC types, but the p-value (0.211) was not significant, indicating no strong association between VEGF and RCC histology. However, VEGF negativity was higher in Other RCC types (11.1%) than in Clear Cell RCC (8.9%). Study by Escudier et al. (2012) [15] confirmed that VEGF inhibitors (e.g., sunitinib, bevacizumab) work best in Clear Cell RCC, suggesting a stronger biological link in this subtype. Research by Hakimi AA et al. (2013) [16] reported that VEGF-targeted therapies are less effective in non-Clear Cell RCC subtypes, explaining why VEGF expression may not be as strongly associated in Other RCC types.

Although VEGF expression is more prevalent in Clear Cell RCC, the lack of statistical significance suggests it may still play a role in Other RCC types. Since VEGF inhibitors are already widely used in Clear Cell RCC treatment, additional studies should explore how VEGF expression varies in other subtypes and whether alternative anti-angiogenic therapies could be effective in those cases.

VEGF Expression and Tumor Grade:

VEGF positivity was observed in 75.0% of Grade 1-2 tumors and 25.0% of Grade 3-4 tumors, but the p-value (0.865) was not statistically significant; suggesting that VEGF expression does not strongly correlate with tumor grade. Study by Escudier B et al. (2012) [17] found that VEGF expression is highly variable across tumor grades, but its inhibition remains effective regardless of grade. Study by Hakimi AA et al. (2013) [16] suggested that while VEGF is critical in Clear Cell RCC, its role in tumor grading remains inconsistent. Since VEGF expression does not significantly differ between tumor grades, it may not be a useful prognostic marker for grading RCC. However, VEGF-targeted therapies remain the standard treatment for both low-grade and high-grade RCC

VEGF Expression and Pathological Stage:

VEGF positivity was observed in 77.4% of pT1-2 tumors and 22.6% of pT3 tumors, but the p-value (0.511) was not statistically significant, suggesting VEGF expression does not strongly correlate with pathological stage. Study by Escudier B et al. (2012) [17] found that VEGF expression is highly variable across tumor stages, but VEGF-targeted therapy remains effective regardless of stage. Study by Hakimi AA et al. (2013) [16] suggested that VEGF expression fluctuates in RCC due to VHL gene mutations but does not necessarily predict tumor stage. Since VEGF expression does not significantly differ between tumor stages, it may not be a strong prognostic marker for RCC staging. However, VEGF inhibitors remain the mainstay of treatment for both early-stage and advanced RCC.

VEGF Expression and Tumor Necrosis:

VEGF positivity was observed in 32.3% of necrotic tumors and 67.7% of non-necrotic tumors, with a p-value of 0.015 (statistically significant). VEGF negativity was more common in necrotic tumors (77.8%) compared to non-necrotic tumors (22.2%), suggesting VEGF expression is lower in necrotic RCC tumors. Study by Escudier B et al. (2012) [17] found that VEGF expression is essential for tumor angiogenesis but may decrease in necrotic areas due to vascular collapse. Study by Hakimi AA et al. (2013) [16] suggested that VEGF expression is often lost in necrotic RCC tumors due to excessive hypoxia and loss of vascular integrity. Since VEGF expression is lower in necrotic tumors, it may indicate that tumor necrosis reduces VEGF-driven angiogenesis. VEGF inhibitors may be less effective in highly necrotic tumors, which may require alternative treatments such as immunotherapy or metabolic targeting.

5. LIMITATIONS

This study is based on single centre, retrospective type with small sample size number which may limit its applicability to other regions or patient groups. Deeper understanding of prognostic or therapeutic implications is limited by the lack of genetic profiling or survival data, and the simple VEGF scoring method may miss subtle expression patterns. Additionally, its therapeutic application is limited by the lack of treatment response and follow-up.

6. CONCLUSION:

VEGF is highly inversely related to tumor necrosis in RCC, which points to its potential functional implication in guaranteeing tumor vascularity.The expression of VEGF has no appreciable correlation with tumor type, grade, stage, or lymphovascular invasion, which places a limitation on its role as an overall prognostic biomarker for RCC. The research indicates that VEGF could be more useful as a functional or predictive marker (e.g., for anti-angiogenic therapy) rather than being a general prognostic marker. Large multicentric studies and genetic correlation are required to further elucidate the contribution of VEGF to RCC biology and therapeutic implications.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Govardhani V, Kalaivani Amitkumar.

Acquisition, analysis, or interpretation of data: Govardhani V, Kalaivani Amitkumar..

Drafting of the manuscript: Govardhani V, Kalaivani Amitkumar.

Critical review of the manuscript for important intellectual content: Govardhani V, Kalaivani Amitkumar.

Supervision: Govardhani V, Kalaivani Amitkumar.

7. DISCLOSURES

Human subjects: Consent was obtained or waived by all participants in this study. Department of Pathology, Sri Ramaswamy Memorial (SRM) Medical College Hospital and Research Centre- Institutional Ethics Committee issued approval SRMIEC-ST0523-1051. Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work

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