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Expression and Prognostic Value of VEGF, VEGFR1, VEGFR2, VEGFR3, and E-Cadherin in Clear Cell Renal Cell Carcinoma

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Purpose: Clear cell renal cell carcinoma (ccRCC) is the most common histological subtype of renal carcinoma, accounting for 75%–80% of cases. Vascular endothelial growth factor (VEGF), which promotes angiogenesis via its membrane receptors (VEGFRs), and E-cadherin, which decreases in expression during invasion and metastasis, are both implicated in ccRCC pathogenesis. We analyzed the relationship between these proteins and ccRCC lesions to assess their usefulness as prognostic markers.

Materials and Methods: Renal tumor tissue samples from nephrectomies of 69 patients were analyzed using immunohistochemical techniques to evaluate the expression of the aforementioned proteins. These findings were then compared with established prognostic scales. Statistical analysis was performed using SPSS Statistics ver. 29.0.1.0.

Results: VEGF intensity was significantly correlated with tumor size (T; p=0.002), stage (p<0.001), and metastasis (M; p=0.049) according to the TNM classification. VEGFR3 expression correlated positively with tumor size (T; p=0.046) and stage (p=0.040). E-cadherin expression correlated negatively with tumor size (p=0.047). In relation to prognostic scales, VEGF expression correlated with the UCLA Integrated Staging System score (p=0.009), while E-cadherin correlated with the stage, size, grade and necrosis (SSIGN) score (p=0.044). For both overall and disease-free survival, significant differences were observed between the moderate (2++) and intense (3+++) VEGFR3 intensity groups (p=0.009 for both).

Conclusion: VEGF may have prognostic value due to its association with tumor size, stage, metastasis, and the UCLA Integrated Staging System score. Similarly, VEGFR3 shows prognostic potential based on its correlations with tumor size, stage, and its relation to overall and disease-free survival. E-cadherin also demonstrates prognostic significance through its association with tumor size and the SSIGN score.

Key Words: Clear cell renal cell carcinoma, Vascular endothelial growth factor, Vascular endothelial growth factor receptor 3, E-cadherin, Prognostic factor

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INTRODUCTION

In 2022, 434,840 new cases and 155,953 deaths due to kidney cancer were reported throughout the world, highlighting a serious threat to human health [1,2]. Renal cell carcinoma (RCC) is the most common type of kidney cancer, accounting for 90% of all cases and 2%–3% of malignant tumors in adults [3]. Clear cell RCC (ccRCC) is the predominant subtype and represents 70%–85% of all RCC cases [4]. It shows significant variability and is difficult to predict because of its early tendency to metastasize. Both sporadic (~90%) and hereditary forms are observed. Mutations in the Von Hippel-Lindau (VHL) tumor suppressor gene, located on chromosome 3, are an important cause of this malignancy [5]. Due to the loss of functionality of this gene, its product VHLp is not synthesized or is defective, leading to overexpression of hypoxia-inducible factor (HIF-1α), which increases the expression of genes that promote anomalous vascular neoformation, such as vascular endothelial growth factor (VEGF). In addition, HIF-1α induces the loss of E-cadherin [6].

ccRCC is a highly vascularized tumor and VEGF-A activity is important in its progression. This critical factor modulates endothelial cell growth, cell migration, vasodilation and vascular permeability. Among the other VEGF isoforms, VEGF-B is involved in embryonic angiogenesis, while VEGF-C and VEGF-D regulate lymphangiogenesis. These factors exert their effects by binding to their membrane receptors, VEGFRs: VEGF-A and VEGF-B bind to VEGFR1 located on blood vascular endothelial cells; VEGF-A and VEGF-C/VEGF-D bind to VEGFR2, which is expressed on growing blood and lymphatic vessels; and VEGF-C and VEGF-D bind to VEGFR3, which is expressed on blood vascular endothelial cells [7].

During epithelial–mesenchymal transition, epithelial cells lose their polarity and adhesion to other cells and acquire migratory and invasive capabilities. In this process of invasion and metastasis, the expression of the epithelial marker E-cadherin is reduced, and mesenchymal markers are overexpressed [8-10].

There are numerous anatomical, histological, clinical and molecular prognostic factors for RCC. Different prognostic scales have been published that combine these factors to predict postnephrectomy results, facilitate the management and adjuvant therapeutic guidance of RCC, define RCC subtypes, stratify patients according to risk, and predict response to targeted therapies. The UCLA Integrated Staging System (UISS) and stage, size, grade and necrosis (SSIGN) scores are recognized for stratifying cases of localized RCC. On the other hand, the UISS MI and Memorial Sloan-Kettering Cancer Center (MSKCC) [11] scores are used for metastatic RCC cases. Despite the availability of these scales, there is a lack of specific markers that are useful for early diagnosis and for detecting recurrence after nephrectomy [7].

The objective of this study was to assess the relationship between the expression of VEGF, VEGFR1, VEGFR2, VEGFR3 and E-cadherin; characteristics of ccRCC lesions, including tumor size, stage and metastasis; and prognostic scales. Additionally, the potential of these proteins as markers of mortality and relapse risk and their utility as prognostic markers for ccRCC was evaluated.

MATERIALS AND METHODS

1. Patients

The patients included in the study were adults diagnosed with ccRCC who underwent nephrectomy at the Lozano Blesa University Clinical Hospital in Zaragoza, Spain, after signing the informed consent form approved by the Clinical Research Ethics Committee of Aragón. They could not have received previous RCC treatment with chemotherapy or radiotherapy.

2. Sample and Data Collection

Tumor tissue from nephrectomies performed between April 2008 and December 2011 on patients with RCC was used. Data were collected preoperatively, intraoperatively, from the pathology results, as well as from patient and disease progression. The patients were staged based on the 8th edition of the TNM classification of the American Joint Committee on Cancer [12]. The SSIGN and UISS scores were used for localized disease, and the UISS M1 and MSKCC scores were used for metastatic disease [11].

3. Sample Processing

The tissue was processed after surgical extraction using a scalpel, 4% paraformaldehyde, graded alcohols and paraffin. First, the samples were deparaffinized and rehydrated in a graded alcohol series (100% to 70%) and then rinsed in tap water for 5 minutes. Antigen retrieval was performed using PT-Link (Dako, Denmark) by heating the sections at 92°C in buffer, with an acidic or basic pH depending on the antibody (Target Retrieval Solution, high pH or low pH, Dako) for 20 minutes. The samples were washed in washing buffer (Dako), and the Dako EnVision FLEX+ Mouse Kit was used for immunohistochemistry. Subsequently, endogenous peroxidase blocking (Peroxidase-Blocking Reagent, Dako) was performed, followed by addition of primary antibodies against VEGF (Ref. RB-9031, Thermo Scientific, USA), VEGFR1 (Ref. PA1-37710, Thermo Scientific), VEGFR2 (Ref. RB-1526, Thermo Scientific), VEGFR3 (Ref. PA1-37712, Thermo Scientific) and E-cadherin (Ref. M3612, Dako). The sections were incubated with EnVision FLEX + Mouse LINKER followed by Dako EnVision/HRP reagent. A brown reaction product was developed using a diaminobenzidine solution and substrate buffer (Dako) containing hydrogen peroxide. The sections were counterstained with Mayer's hematoxylin, dehydrated using a series of increasing alcohol concentrations, rinsed with xylene and mounted for microscopic observation.

The VEGF, VEGFR1, VEGFR2, VEGFR3 and E-cadherin staining patterns were established based on 69 cases of ccRCC. A pathologist analyzed the samples using a microscope (Leica, Switzerland). The immunohistochemical expression of the proteins of interest was evaluated using the following scale: 0, negative or absent staining; +1, weakly positive staining; ++2, moderately positive staining; and +++3, intensely positive staining.

4. Statistical Analysis

IBM SPSS Statistics ver. 29.0.1.0 (IBM Co., USA) was used for descriptive and inferential analysis. The data were subjected to the Shapiro-Wilk test to determine whether it followed a normal distribution. The clinicopathological parameters are presented as proportions, and the quantitative variables are presented as the median and interquartile range (IQR). The non-parametric Mann-Whitney U and Kruskal-Wallis tests were performed to identify significant differences between 2 and more than 2 groups, respectively. Spearman correlation analysis was used to assess correlations. A p-value ≤ 0.05 was considered statistically significant.

In addition, considering the follow-up from 2008 to 2018 (median, 83.17 months), the probability of survival was estimated using the Kaplan-Meier method. The log-rank test was used to compare 2 or more survival functions ($p \leq 0.05$). Multiple comparisons (pairwise) were performed using Bonferroni correction, with $p \leq 0.0125$ considered to indicate a statistically significant difference.

RESULTS

1. Descriptive Analysis

Table 1 presents the analyzed clinicopathological parameters. Postnephrectomy samples were obtained from 88 patients. Histological analysis revealed that 78.4% of the patients (n=69) presented the ccRCC subtype, comprising 48 men and 21 women, with ages ranging from 35 to 90 years and a median age of 66.12 years (IQR, 56.05–77.11 years). The tumor size ranged from 2.5 to 20 cm with a median of 6.5 cm (IQR, 5–8 cm).

2. Inferential Analysis

1) VEGF

There was a significant positive correlation between VEGF and tumor size (T; r_s=0.386, p=0.002) and stage (r_s=0.443, p<0.001) (Table 2). There was no correlation between VEGF intensity and T>10 cm and regional lymph node metastasis (N). However, there was a significant relationship between VEGF and metastasis (M; p=0.049).

2) VEGFR1, VEGFR2, and VEGFR3

There were no correlations between the intensity of VEGFR1 and VEGFR2 and the studied variables. However, VEGFR3 intensity correlated positively with T (r_s=0.251, p=0.046) and tumor stage (r_s=0.257, p=0.040), but not with T>10 cm, N and M (Table 2).

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Table 1. Clinicopathological parameters and descriptive statistics

Parameter	Value
Sex	
Male	48 (69.6)
Female	21 (30.4)
Age (yr), median (range)	68 (35–90)
Fuhrman grade (n=69)	
G1	7 (10.1)
G2	19 (27.5)
G3	11 (15.9)
G4	5 (7.3)
NC	27 (39.1)
TNM pathological classification (n=69)	
Primary tumor (T)	
T1	26 (37.7)
T2	12 (17.4)
T3	29 (42)
T4	2 (2.9)
Regional lymph nodes (N)	
N0	15 (21.7)
N1	3 (4.4)
Nx	51 (73.9)
Metastasis (M)	
M0	62 (89.9)
M1	7 (10.1)
Tumor stage (n=69)	
Stage I	26 (37.7)
Stage II	16 (23.2)
Stage III	17 (24.6)
Stage IV	10 (14.5)
Necrosis (n=46)	
Yes	28 (60.87)
No	18 (39.13)
Progression (n=69)	
Yes	24 (34.8)
No	45 (65.2)
Death (n=67)	
Yes	21 (31.3)
No	46 (68.7)

Values are presented as number (%).

Table 2. Results of the inferential analysis of the study variables

Variable	Test	No.	r_s	p-value
VEGF				
Stage	Spearman correlation analysis	64	0.443	<0.001
T		64	0.386	0.002
N	Kruskal-Wallis	16	-	0.283
M	Mann-Whitney U	64	-	0.049
VEGFR1				
Stage	Spearman correlation analysis	67	-0.149	0.230
T		67	-0.081	0.515
N	Kruskal-Wallis	17	-	0.406
M	Mann-Whitney U	67	-	0.583
VEGFR2				
Stage	Spearman correlation analysis	66	0.069	0.583
T		66	0.063	0.615
N	Kruskal-Wallis	16	-	0.585
M	Mann-Whitney U	66	-	0.405
VEGFR3				
Stage	Spearman correlation analysis	64	0.257	0.040
T		64	0.251	0.046
N	Kruskal-Wallis	16	-	0.578
M	Mann-Whitney U	64	-	0.215
E-cadherin				
Stage	Spearman correlation analysis	47	-0.240	0.104
T		47	-0.291	0.047
N	Kruskal-Wallis	16	-	0.559
M	Mann-Whitney U	47	-	0.605

VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

3) E-cadherin

There was a significant negative correlation between E-cadherin intensity and T (r_s=-0.291, p=0.047); it did not correlate with tumor stage, T>10 cm, N and M (Table 2).

3. Relationship Between Immunohistochemical Variables and Prognostic Scores

VEGFR1, VEGFR2, and VEGFR3 intensity did not correlate with the prognostic scores. In contrast, VEGF intensity correlated positively with the UISS score (r_s=0.341, p=0.009) (Table 3) and E-cadherin correlated negatively with the SSIGN score (r_s=-0.312, p= 0.044) (Table 3). There was no significant association between E-cadherin intensity and the UISS, UISS M1, and MSKCC scores. Of note, the association between VEGF intensity and the metastatic disease scores could not be calculated.

4. Survival Analysis

1) Overall survival

There were no significant differences in overall survival (OS) based on VEGF, VEGFR1, VEGFR2, and E-cadherin intensity. However, OS did differ significantly based on VEGFR3 intensity (p=0.047). Pairwise comparisons revealed a significant difference between the moderate 2++ and intense 3+++ intensity groups (p=0.009) (Fig. 1).

2) Disease-free survival

There were no significant differences between disease-free survival (DFS) and VEGF, VEGFR1, VEGFR2, and E-cadherin intensity. However, it did differ based on VEGFR3 intensity (p=0.046). Specifically, there was a significant difference between the moderate 2++ and intense

Table 3. Spearman correlation analysis for immunohistochemical protein expression and prognostic scores

Variable	No.	r_s	p-value
VEGF			
SSIGN score	56	0.252	0.061
UISS score	57	0.341	0.009
UISS M1 score	-	-	-
MSKCC score	-	-	-
VEGFR1			
SSIGN score	58	-0.1	0.456
UISS score	60	-0.088	0.505
UISS M1 score	5	0	1.000
MSKCC score	5	-0.167	0.789
VEGFR2			
SSIGN score	57	0.204	0.128
UISS score	59	0.025	0.848
UISS M1 score	5	0.860	0.061
MSKCC score	5	-0.148	0.812
VEGFR3			
SSIGN score	56	0.159	0.243
UISS score	58	0.094	0.483
UISS M1 score	5	0.631	0.254
MSKCC score	5	0	1.000
E-cadherin			
SSIGN score	42	-0.312	0.044
UISS score	44	-0.236	0.123
UISS M1 score	3	0.5	0.667
MSKCC score	3	0.5	0.667

VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; SSIGN, stage, size, grade and necrosis; UISS, UCLA Integrated Staging System; MSKCC, Memorial Sloan-Kettering Cancer Center.

3+++ groups (p=0.009) (Fig. 2).

DISCUSSION

The search for biomarkers to non-invasively diagnose, predict, and monitor RCC is highly valuable [13]. Therefore, our objective was to elucidate potential relationships between some of the factors related to ccRCC that have been studied and known prognostic factors, as well as their association with OS and DFS over a 10-year period. For this purpose, and given the lack of consensus and variability in interpretation, we measured the expression of various proteins with immunohistochemistry in the same patient based on an intensity scale. This approach yielded results that are easy to interpret and reproducible.

The most frequent histological subtype was ccRCC (78.4%). A similar frequency was described in the European Association of Urology guidelines [14]. Additionally, according to the demographic data, there was a higher prevalence in males, with a male-to-female ratio of 2.28:1, and a median age of 66.12 years, consistent with the literature [14]. Early-stage diagnoses accounted for 37.7% of cases, while 14.5% of cases were diagnosed at stage IV, and 10.1% of cases presented with metastasis. These data contrast with the findings published by Gupta and Kanwar [15]: approximately 30% of those patients showed metastasis

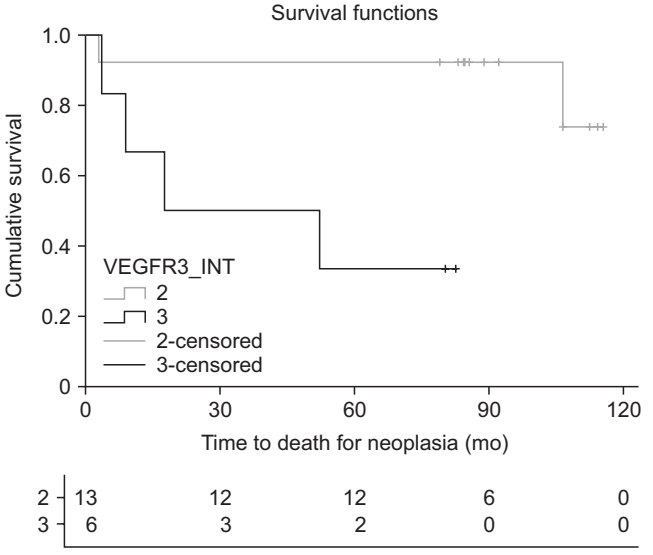

Fig. 1. Overall survival for the VEGFR3 moderate (2++) and intense (3+++) groups. Based on the Kaplan-Meier survival curve, there was lower survival in the intense (3+++) group (log-rank test, p=0.009). VEGFR3, vascular endothelial growth factor receptor 3.

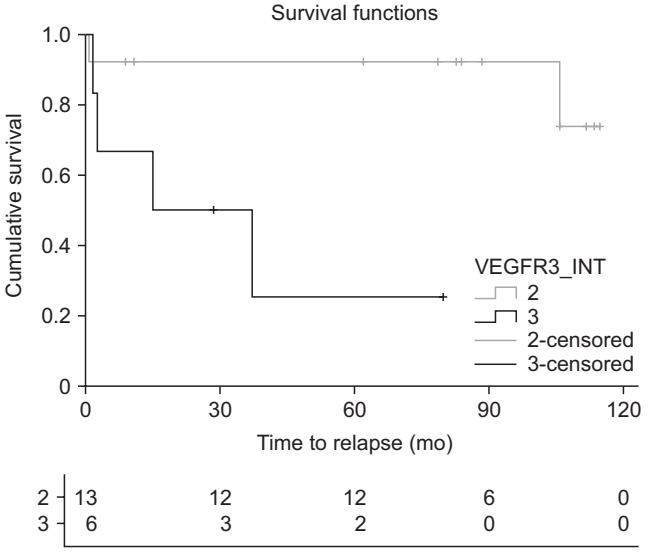

Fig. 2. Disease-free survival for the VEGFR3 moderate (2++) and intense (3+++) groups. Based on the Kaplan-Meier survival curve, there was lower survival in the intense (3+++) group (log-rank test, p=0.009). VEGFR3, vascular endothelial growth factor receptor 3.

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at diagnosis, contributing to a poor prognosis. On the other hand, 61% of the cases presented metastasis, in line with the findings described by Minervini et al. [16] and Klatte et al. [17]. Necrosis was not mentioned in 33.33% of cases; however, some pathologists consider that the lack of mention implies its absence. Thus, we could consider that there was necrosis in 40% of the cases, consistent with the findings reported by Cano-García and Chablé-Montero [18]. The large number of staff members in the Department of Pathology at the hospital and the different methods used to collect information resulted in a limitation in patient staging due to the lack of unified criteria when describing the tumor.

There was a significant relationship between VEGF and tumor size, stage and metastasis: higher VEGF intensity correlated with an increase in tumor size and stage, and there was higher intensity in patients with metastasis. These findings are consistent with those reported by Minardi et al. [19] and confirm that higher VEGF expression is associated with an advanced TNM stage.

Because the angiogenic action of VEGF primarily occurs through interaction with the membrane receptors VEGFR1 and VEGFR2, we examined the relationship between their expression and the anatomopathological variables. Neither receptor correlated with the analyzed variables. Although there are limited data available, it has been established that the immunohistochemical expression of VEGFR1 and VEGFR2 is higher in tumor tissues from patients with poor prognostic anatomopathological factors [20]. On the other hand, we found that VEGFR3 correlated positively with tumor size and stage, indicating higher VEGFR3 intensity as tumor size and stage increase, consistent with findings from a previous study [21]. There are studies in which a relationship seems to be found between the expression of VEGFR3 and the presence of tumor lymphoid proliferation, which could indirectly affect the survival rate of patients with elevations in this marker [22].

There was a significant correlation between E-cadherin and the tumor size. Other research groups have associated low E-cadherin expression with larger tumors, a higher tumor stage and metastasis [23,24].

Considering that high VEGF expression is associated with known poor prognostic factors, we analyzed the correlation between VEGF and prognostic scores. There was a significant correlation with the UISS score. Patients with the highest VEGF intensity (3+++) had higher scores than those with a moderate (2++) or weak (1+) intensity, in agreement with Fujita et al. [24]. There was a trend for a significant correlation between VEGF and the SSIGN score (r_s=0.252, p=0.061); increasing the sample size might result in a significant correlation. Of note, this scale considers T>10 cm, and we did not find a correlation between VEGF and T>10 cm because the median tumor size was 6.5 cm. There was a similar situation with necrosis: it was absent in 59% of the nephrectomy specimens classified as stage III, while it was present in 80% of those classified as stage IV. The association between VEGF and metastatic disease scores could not be calculated, as all metastatic data corresponded to intense VEGF expression (3+++) and there was a small sample size (n=5). E-cadherin was found to decrease as the tumor progresses, and its relationship with the SSIGN score showed a significant negative correlation, indicating that lower E-cadherin expression corresponds to a higher SSIGN score.

OS did not show significant relationships with VEGF, VEGFR1, VEGFR2, and E-cadherin intensity or time until death due to neoplasia. Lkhagvadorj et al. [25] also reported no correlation between VEGFR1 and OS. However, other studies have shown prolonged OS in patients with lower VEGF expression [19] and reduced OS in patients with aberrant E-cadherin expression [22]. On the other hand, increased VEGFR3 intensity was associated with decreased survival, with a significant difference between the moderate 2++ and intense 3+++ groups.

Regarding DFS, there were no significant relationships between VEGF intensity and the time to relapse. In contrast, Fujita et al. [24] reported that patients with positive VEGF expression had a shorter time to disease recurrence. We found that increased VEGFR3 intensity was associated with decreased DFS, with a significant difference between the moderate 2++ and intense 3+++ groups. In other words, patients with the most intense VEGFR3 expression have a higher risk of disease recurrence.

CONCLUSIONS

Given the established utility of tumor biomarkers in the

study of ccRCC and therapeutic decision-making, this research highlights VEGF as a valuable prognostic marker due to its association with tumor size, disease stage, metastasis and the UISS score. VEGF may complement this score and other prognostic methods. VEGFR1 and VEGFR2 did not yield promising results, in contrast to VEGFR3, which demonstrated associations with tumor size and stage as well as OS and DFS, thus enabling risk assessments for mortality and recurrence. Additionally, E-cadherin is a candidate prognostic marker due to its association with tumor size and the SSIGN score. However, discrepancies among various clinical studies persist, leaving these potential prognostic markers still limited to the research context.

NOTES

- **Author Contribution:**

  Conceptualization: JGP, BSG, JMSZ, MSdP, ABF; Data curation: JGP, MSdP, VCP, JMSZ; Formal analysis: JGP, MSdP, NRM, DUB, JBH, ALdV, MGB, JAR, VCP; Methodology: JGP, MSdP, MGB, ABF, JMSZ, BSG; Project administration: MGB, ABF, JMSZ, BSG; Visualization: MGB, ABF, JMSZ, BSG; Writing - original draft: JGP, MSdP, NRM, DUB, JBH, ALdV; Writing - review & editing: JGP, MSdP, JMSZ, BSG, NRM, DUB, JBH, ALdV.

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