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ORIGINAL ARTICLE

Integrative Analysis of *VEGFA* Gene Expression and Drug Targeting in Kidney Renal Clear Cell Carcinoma (KIRC)

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Abstract

Background/Aim: Vascular endothelial growth factor A (*VEGFA*) plays an important role in angiogenesis and is known to have a strong association with the development of various types of cancer, including kidney renal clear cell carcinoma (KIRC). The purpose of this study was to analyse *VEGFA* expression in KIRC tissue, identify genes that have high expression correlation and explore the therapeutic potential of *VEGFA* through the identification of drugs that target it.

Methods: This study used a public data-based bioinformatics approach to evaluate *VEGFA* gene expression, identify genes that have similar expression patterns (co-expression) with it and examine the potential of drugs targeting *VEGFA* in KIRC. Data and analysis were obtained from various trusted databases, namely *UALCAN, GEPIA, TCGA, TISIDB* and *DrugBank*.

Results: *VEGFA* was found to be significantly higher expressed in KIRC tissue compared to normal tissue. Ten genes showed high expression correlation with *VEGFA*, namely *RP1-261G23.7, FLT1, ZNF395, COL23A1, RP11-255M6.1, PLVAP, EXOC3L2, ESM1, EGLN3 and HIF1A-AS2*. In addition, *VEGFA* is known to be the target of various therapeutic agents such as ranibizumab, VEGF-AS, bevasiranib, gliclazide, SNS-032, denibulin, aflibercept, ABT-510, dalteparin and chondroitin sulphate, most of which have a mechanism of action in inhibiting angiogenesis.

Conclusion: *VEGFA* has the potential to be an important biomarker and therapeutic target in KIRC. The combination of gene expression analysis and drug data confirms the strategic value of *VEGFA* in the development of more effective antiangiogenic therapies.

Key words: *VEGFA*; Kidney; Carcinoma, renal cells; Drug discovery.

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Introduction

Kidney cancer is a significant global health problem, with a steadily increasing incidence over the past few decades.[1] Among the various histopathological subtypes of kidney cancer, *kidney renal clear cell carcinoma* (KIRC) is the most common subtype of kidney cancer, accounting for around 70–80 % of all cases.[2, 3] Kidney cancer ranks 14th in incidence globally and is the 10th leading cause of cancer death in men. According to *GLOBOCAN 2020* data, there were more than 430,000 new cases of kidney cancer and approximately 179,000 deaths worldwide.[4] Although advances in early detection and targeted therapy have improved clinical outcomes in some patients, the prognosis for advanced KIRC remains poor, with a 5-year survival rate of less than 10 % in metastatic patients.[5, 6] Therefore, a deeper understanding of the molecular mechanisms underlying the pathogenesis of KIRC is essential to find new therapeutic targets and improve the management of this disease.[7, 8]

One of the main molecular characteristics of KIRC is the activation of hypoxia and angiogenesis pathways, which are largely mediated by vascular endothelial growth factor A (*VEGFA*).[9, 10] *VEGFA* plays a key role in stimulating the formation of new blood vessels (angiogenesis), which is an important process in tumour development and progression.[9] Mutations in the gene *by Hippel–Lindau* (*VHL*), which is frequently found in KIRC, causes stabilisation of the transcription factor HIF-1α, which subsequently induces *VEGFA* expression. Increased *VEGFA* expression has been associated with higher tumour aggressiveness, invasion and metastasis, making it a promising potential therapeutic target in the treatment of KIRC.[11, 12] With the development of bioinformatics technology and the availability of public databases such as *UALCAN, TISIDB, GEPIA, DrugBank* and *TCGA*, an integrative approach can be used to analyse gene expression, identify genes closely related to key targets and explore the therapeutic potential of existing compounds.[13, 14] Genetic correlation analysis can reveal co-expression networks that may have similar or related biological functions, while pharmacological data exploration can help in mapping therapeutic agents that are known to target *VEGFA*.[9] By combining these approaches, studies can identify relevant drug candidates as well as biological pathways that can be modulated to inhibit KIRC progression.[15]

This study aimed to explore the expression of *VEGFA* in KIRC and identify genes that have a high correlation with *VEGFA,* as well as map drugs that directly target *VEGFA* based on data from *DrugBank*. With this approach, it is expected to find the functional relationship between *VEGFA* and relevant co-expression genes and identify potential therapeutic agents that can be used to target the *VEGFA* pathway more effectively.

Methods

VEGFA gene expression was analysed, genes that have similar expression patterns (co-expression) with it were identified and the potential of drugs targeting *VEGFA* in KIRC were analysed. Data and analysis were obtained from various trusted databases, namely *UALCAN, GEPIA, TCGA, TISIDB* and *DrugBank*. Each database was used for the following specific purposes:

VEGFA expression analysis and survival analysis using *UALCAN*

The mRNA expression data of *VEGFA* gene in KIRC cancer tissue compared with normal kidney tissue were obtained through the *UALCAN* platform, which is connected to *The Cancer Genome Atlas* (TCGA) data.[16] In addition, survival analysis was also performed based on *VEGFA* expression levels (low vs high), to assess the relationship of *VEGFA* expression to patient prognosis. The Student's t-test statistical test was used automatically by the system to compare expression between groups and the log-rank test was used in the survival analysis. A p value < 0.05 was considered statistically significant.[17]

Identification of co-expressed genes with *VEGFA* from *GEPIA*

The list of 10 genes most similar to *VEGFA* was determined based on the Pearson correlation coefficient (PCC) value from *GEPIA*.[18] *GEPIA* provides correlation analysis based on RNA-seq expression data from *TCGA* and *GTEx*. Genes with the highest PCC are considered to have a strong co-expression relationship with *VEGFA*. These data were used as the basis for selecting genes for further expression analysis in *UALCAN*. This analysis aimed to identify functional networks that may be co-controlled by *VEGFA* in the progression of KIRC.[18, 19]

Drug target genes exploration *VEGFA* using *TISIDB*

The *TISIDB* platform was used to explore the relationship between *VEGFA* expression and immunotherapy drug targets, based on target annotations from literature and clinical databases.[20, 21] Through the Drug Target Genes feature in *TISIDB*, it can be seen whether *VEGFA* expression correlates with target genes of immunotherapy drugs, both those being tested in clinical trials and those that have been approved. This information is important for identifying potential combination therapies between anti-VEGF and immunotherapy agents and supporting more precise treatment strategies based on the molecular expression of KIRC patients.[22]

Mapping of drugs targeting *VEGFA* using *DrugBank*

Drugs known to target *VEGFA* were identified through the *TISIDB* platform database and then continued with *DrugBank*.[15] The search was conducted by entering the keyword "Drugbank ID No" as the molecular target. The data collected included drug name, drug type (biologic or small molecule), number of targets and specific targets. This information was used to compile a list of drugs that could potentially be used or repositioned for *VEGFA*-targeted KIRC therapy.[23, 24]

Data visualisation

The results of the five stages above were then integrated to obtain a comprehensive picture of the role of *VEGFA* and co-expression genes in KIRC cancer, as well as its therapeutic potential. Data visualisation was performed in the form of gene expression bar graphs, as well as a table of *VEGFA*-targeted drugs. This analysis was designed to support the identification of molecular biomarkers and precision therapy approaches in KIRC patients.

Results

VEGFA expression in various types of cancer *TCGA*

VEGFA in various cancer types based on data from *TCGA*, including comparisons between tumour tissue and normal tissue is presented in Figure 1. The red box indicates expression in tumour tissue, while the blue box indicates normal tissue. It can be seen that the *VEGFA* expression was significantly increased in several types of cancer, including KIRC, compared to normal tissue.[25, 26]

Comparison of *VEGFA* expression between tumour and normal tissues in various cancers

Figure 2 shows a comparison of expression levels. *VEGFA* between tumour tissue (red colour) and normal tissue (black colour) in various cancer types based on RNA-seq data. It can be seen that in KIRC, *VEGFA* expression is very high in tumour tissue compared to normal tissue, indicating an important role of *VEGFA* in the tumori-

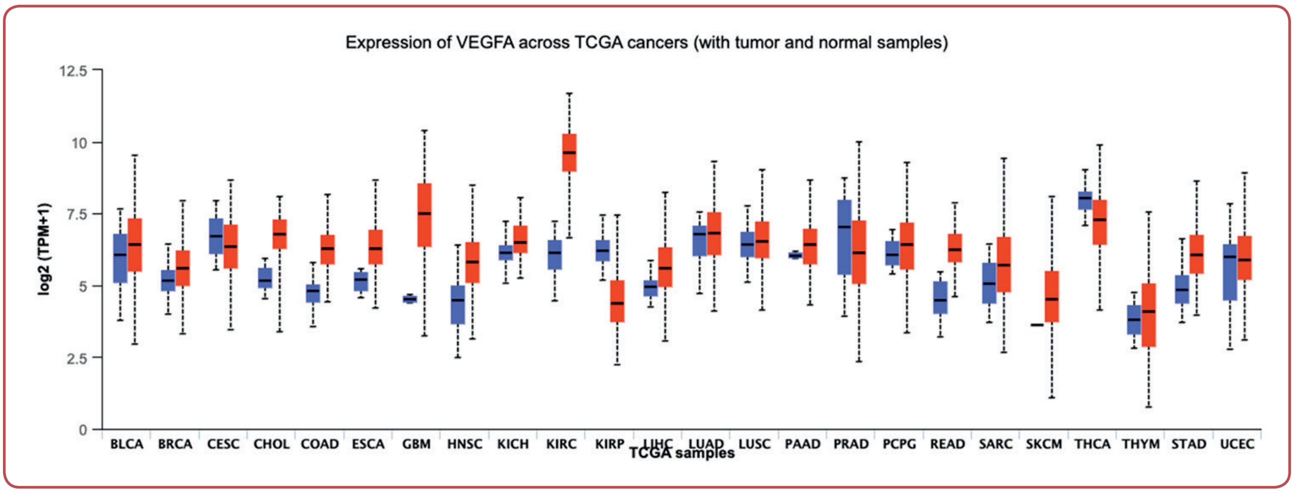

Figure 1: Vascular endothelial growth factor A (VEGFA) expression in various types of cancer based on TCGA data

Red: tumour tissue, blue: normal tissue;

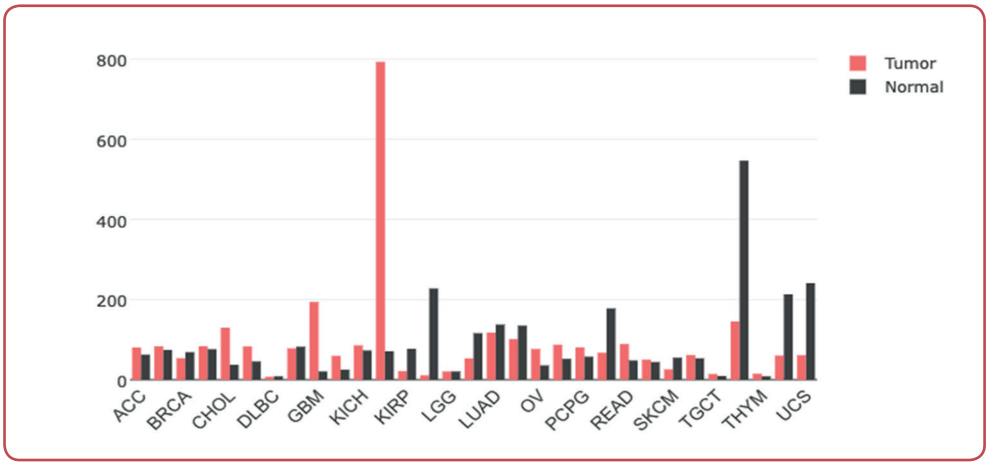

Figure 2: Comparison of vascular endothelial growth factor A (VEGFA) expression between tumour and normal tissues in various cancer types

genesis of this cancer. A similar pattern can also be observed in *GBM* and *BRCA*, although at a level not as high as KIRC.

Analysis of *VEGFA* promoter expression and methylation in KIRC

To understand the regulatory mechanism of *VEGFA* expression, promoter methylation analysis was performed (Figure 3). The results showed that *VEGFA* expression in primary KIRC tumour tissue (n = 533) was much higher than normal tissue (n = 72), with a significantly increased transcript per million (TPM) value. This further strengthens the role of *VEGFA* in the development of clear cell subtype kidney cancer. The level of *VEGFA* promoter methylation between normal tissue (n = 160) and primary tumour (n = 324). It was seen that *VEGFA* promoter methylation was much lower in tumour tissue than in normal tissue. This decrease in methylation has the potential to cause increased *VEGFA* gene expression in cancer tissue, considering that promoter hypomethylation is often associated with activation of gene transcription.

Relationship of *VEGFA* expression to KIRC patient prognosis

To assess the clinical impact of *VEGFA* expression in KIRC patients, survival analysis was performed using Kaplan-Meier curves (Figure 4). Patients were grouped based on *VEGFA* expression levels into two categories: high expression (n = 133) and low/moderate expression (n = 398). The results showed that there was no significant difference between the high and low expression groups in terms of survival probability (p = 0.96). Although *VEGFA* was expressed higher in tumour tissues, its expression was not directly related to prognosis or risk of death in this dataset statistically.

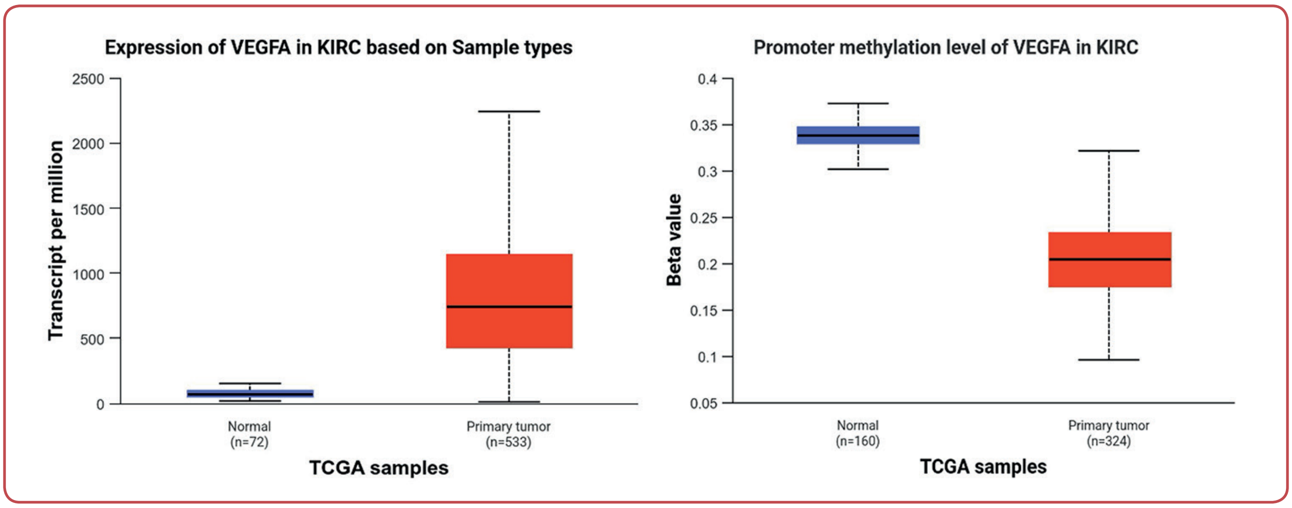

Figure 3: Expression and methylation of vascular endothelial growth factor A (VEGFA) promoter in kidney renal clear cell carcinoma (KIRC) based on TCGA-UALCAN

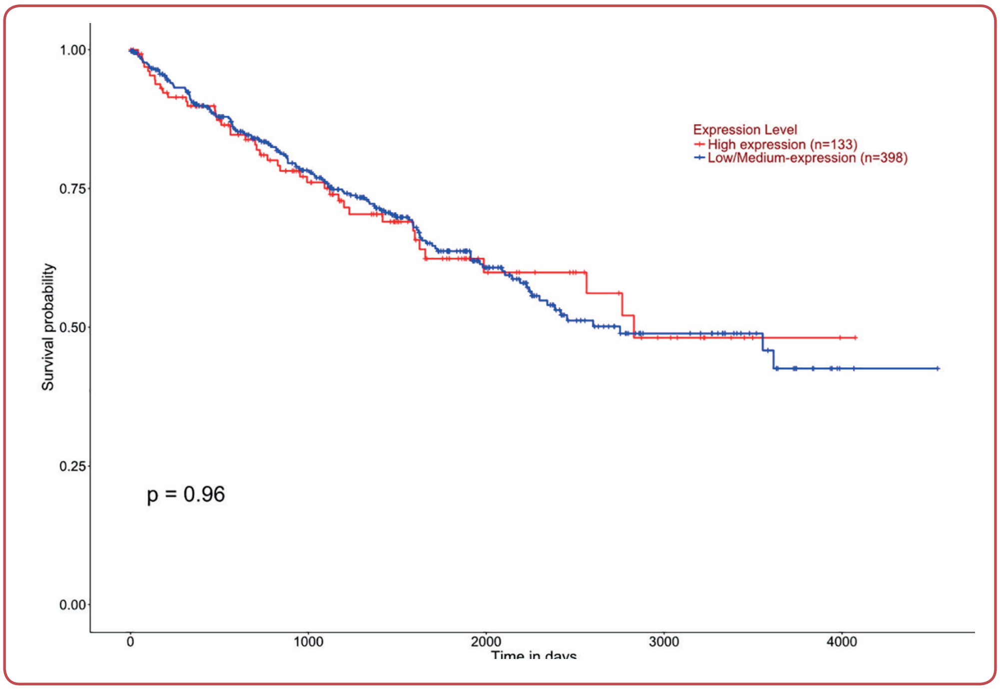

Figure 4: Kaplan-Meier curve showing the relationship between vascular endothelial growth factor A (VEGFA) expression levels and survival of kidney renal clear cell carcinoma (KIRC) patients

The effect of *VEGFA* expression and tumour grade on survival

Kaplan-Meier results showed that when *VEGFA* expression was combined with tumour differentiation level (grade), there was a highly significant difference in survival ($p < 0.0001$). Patients with high *VEGFA* expression and high grade (Grade 3–4) had a significantly worse prognosis than patients with low expression and low grade. These findings suggest that *VEGFA* expression worsens outcome when combined with more aggressive tumour characteristics (Figure 5).

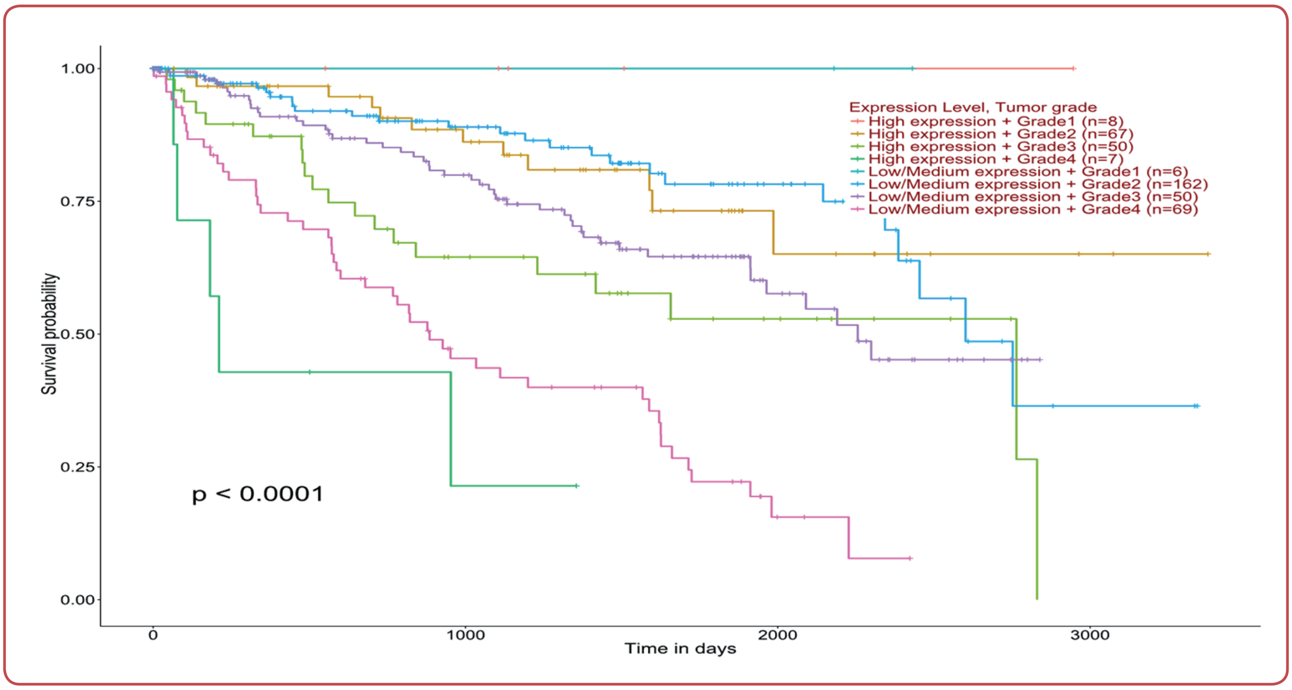

Figure 5: Survival analysis based on the combination of vascular endothelial growth factor A (VEGFA) expression and tumour grade in kidney renal clear cell carcinoma (KIRC) patients

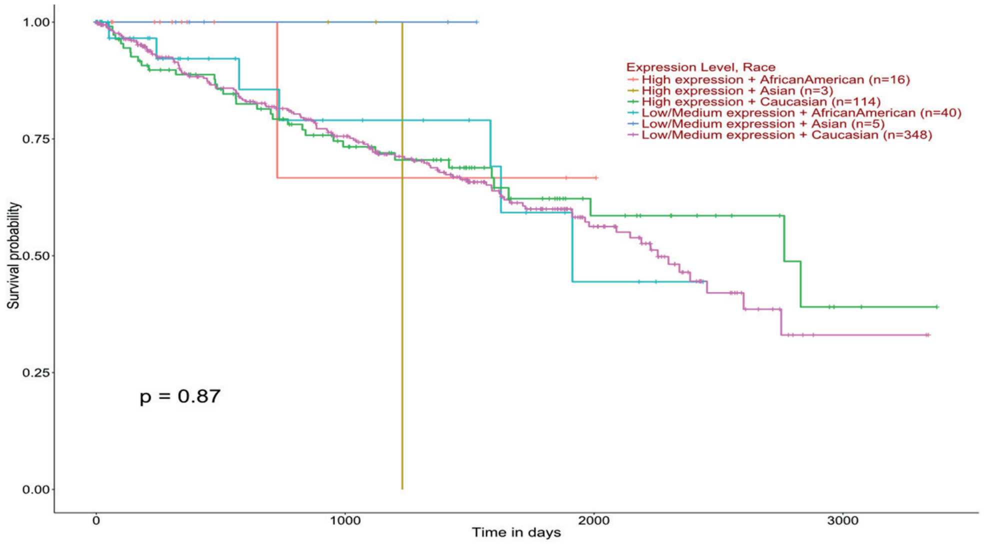

Figure 6: Survival analysis based on the combination of vascular endothelial growth factor A (VEGFA) expression and race of kidney renal clear cell carcinoma (KIRC) patients

The effect of *VEGFA* expression and race on survival

Kaplan-Meier results showed that based on race, there was no significant difference in survival between high and low *VEGFA* expression groups in patients from Caucasian, Asian, or African-American racial groups (p = 0.87) (Figure 6). These results indicate that race does not significantly modulate the effect of *VEGFA* expression on the prognosis of KIRC patients in this dataset.

Effect of *VEGFA* expression and gender on survival

Kaplan-Meier results showed that based on gender, there was no significant difference in survival between men and women with different levels of *VEGFA* expression (p = 0.89) (Figure 7). These results indicate that gender does not provide a modifying effect on the relationship between *VEGFA* expression and outcome of KIRC patients.

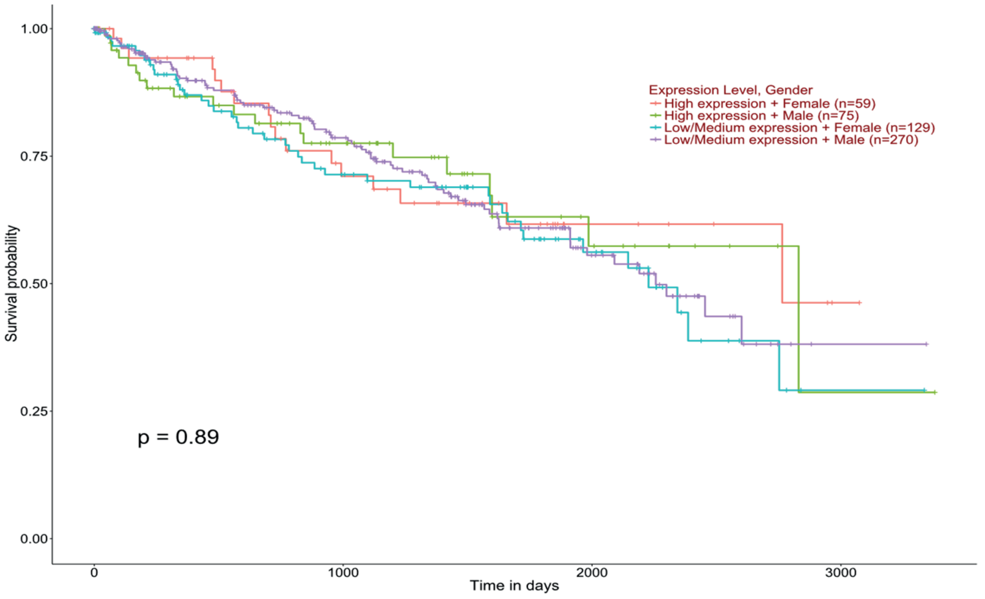

Figure 7: Survival analysis based on the combination of vascular endothelial growth factor A (VEGFA) expression and gender of kidney renal clear cell carcinoma (KIRC) patients

Genes with the highest expression correlation to *VEGFA* in KIRC

To identify genes that have similar expression patterns to *VEGFA*, co-expression analysis was performed using *GEPIA*. The results of the analysis showed the top 10 genes with the highest PCC values to *VEGFA*, which are potentially involved in the same biological pathways such as angiogenesis and hypoxia (Table 1). The *FLT1* gene, which is a *VEGFA* receptor, emerged as one of the genes with high correlation, strengthening the biological validity of this finding.

Table 1: Ten genes with the highest expression correlation to vascular endothelial growth factor A (VEGFA) in kidney renal clear cell carcinoma (KIRC) based on GEPIA

Gene	ID	PCC
RP1-261G23.7	ENSG00000272114.1	0.93
FLT1	ENSG00000102755.10	0.73
ZNF395	ENSG00000186918.13	0.67
COL23A1	ENSG00000050767.15	0.66
RP11-255M6.1	ENSG00000271044.1	0.65
PLVAP	ENSG00000130300.8	0.64
EXOC3L2	ENSG00000130201.7	0.64
ESM1	ENSG00000164283.12	0.61
EGLN3	ENSG00000129521.13	0.61
HIF1A-AS2	ENSG00000258667.1	0.61

PCC: Pearson correaltion coefficient;

Mapping of *VEGFA* targeting drugs based on *DrugBank*

In an effort to explore the potential of targeted therapy against *VEGFA*, a search was conducted for drugs known to directly interact with this gene through the *DrugBank* database (Table 2). The mapping results showed that there are various types of drugs that target *VEGFA*, both from the biotechnology (biological drugs) and small molecule groups. The visualisation of the relationship between *VEGFA* and drug candidates is depicted in the form of a network in Figure 8, which shows the direct relationship between *VEGFA* (in red) and 16 drug candidates (in dark blue).

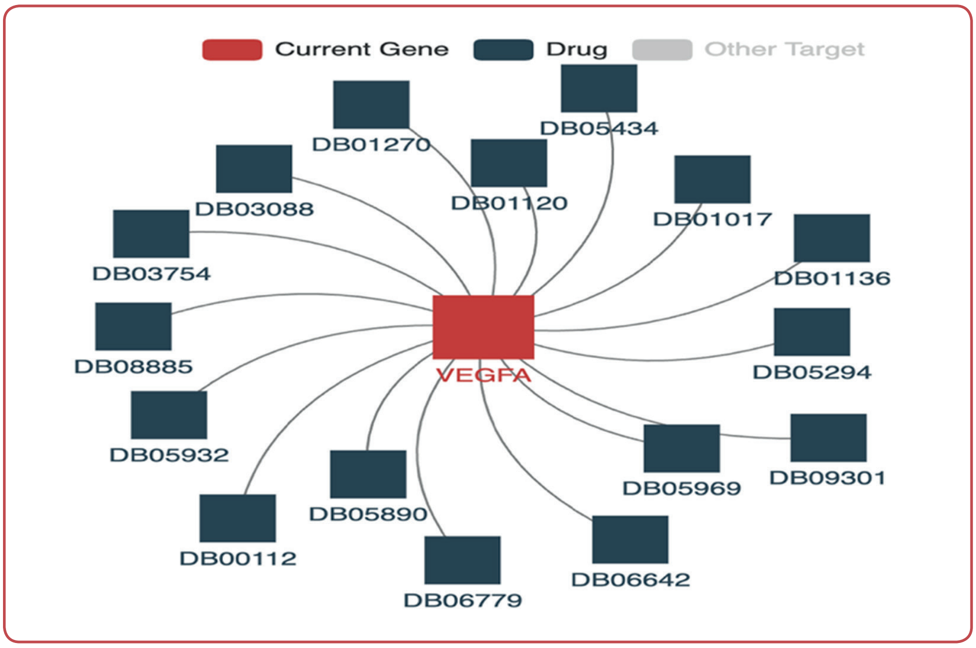

Figure 8: Visualisation of the interaction network between vascular endothelial growth factor A (VEGFA) and drugs targeting it based on DrugBank data

Red colour indicates the target gene (VEGFA), while dark blue represents the interacting drugs.

Table 2: List of drugs targeting vascular endothelial growth factor A (VEGFA) based on DrugBank

ID	Name	Drug type	Targets	Specific function
DB01270	Ranibizumab	Biotech	*VEGFA*	Chemoattractant activity
DB05890	VEGF-AS	Small molecules	*VEGFA*	Chemoattractant activity
DB06642	Bevasiranib	Biotech	*VEGFA*	Chemoattractant activity

DB01120	Gliclazide	Small molecules	*VEGFA*	Chemoattractant activity
DB05969	SNS-032	Small molecules	*VEGFA*	Chemoattractant activity
DB05932	Denibulin	Small molecules	*VEGFA*	Chemoattractant activity
DB08885	Aflibercept	Biotech	*VEGFA*	Chemoattractant activity
DB05434	ABT-510	Small molecules	*VEGFA*	Chemoattractant activity
DB06779	Dalteparin	Small molecules	*VEGFA*	Chemoattractant activity
DB09301	Chondroitin sulphate	Small molecules	*VEGFA*	Chemoattractant activity
DB05932	Denibulin	Small molecules	*VEGFA*	Chemoattractant activity
DB05969	SNS-032	Small molecules	*VEGFA*	Chemoattractant activity
DB01120	Gliclazide	Small molecules	*VEGFA*	Chemoattractant activity
DB06642	Bevasiranib	Biotech	*VEGFA*	Chemoattractant activity
DB05890	VEGF-AS	Small molecules	*VEGFA*	Chemoattractant activity
DB01270	Ranibizumab	Biotech	*VEGFA*	Chemoattractant activity

Discussion

This study showed that the *VEGFA* gene was expressed significantly higher in KIRC type kidney cancer tissue compared to normal kidney tissue.[27, 28] This increased expression reflects the important role of *VEGFA* in supporting angiogenesis, which is the process of forming new blood vessels that is vital in supporting the growth and development of cancer cells.[29] Angiogenesis allows sufficient oxygen and nutrient supply to tumour tissue and facilitates invasion and metastasis, making *VEGFA* a potential therapeutic target in cancer, including KIRC.[28]

Genetic correlation analysis using data from *GEPIA* identified ten genes that had the most similar expression relationships with *VEGFA*, as indicated by high PCC values.[30] The gene that had the strongest correlation with *VEGFA* was *RP1-261G23.7* with a PCC value of 0.93. In addition, the *FLT1* gene, also known as the *VEGFR-1* receptor of *VEGFA*, had a correlation of 0.73, indicating a direct involvement in the mechanism of angiogenesis.[31] Other genes that also showed high correlations included *ZNF395 (PCC: 0.67), COL23A1 (PCC: 0.66), RP11-255M6.1 (PCC: 0.65), PLVAP (PCC: 0.64), EXOC3L2 (PCC: 0.64), ESM1 (PCC: 0.61), EGLN3 (PCC: 0.61)* and *HIF1A-AS2 (PCC: 0.61).* These genes are generally involved in vascularisation, signal transduction, transcriptional regulation and cellular response to hypoxia, all of which are crucial components in tumour progression. Notably, *EGLN3* acts as an oxygen sensor that regulates the stability of *HIF-1α*, which in turn controls *VEGFA* transcription. *ZNF395* is a hypoxia-inducible transcription factor that may enhance *VEGFA* expression under tumour microenvironment conditions. *ESM1* is known to be induced by *VEGFA* and contributes to endothelial cell activation, suggesting a feedback mechanism. In physiological states, these genes function in maintaining vascular homeostasis, whereas in pathological conditions such as KIRC, they may become dysregulated and collectively promote angiogenesis via *VEGFA* upregulation.[31, 32]

Some of the drugs identified in this study such as SNS-032 and gliclazide may exert indirect effects on *VEGFA* by modulating these upstream regulators. For example, inhibition of *EGLN3* or related hypoxia-inducible elements may suppress *VEGFA*-driven angiogenic signalling. Therefore, the impact of these drugs is potentially twofold directly inhibiting *VEGFA* function and modulating gene expression networks that converge on *VEGFA* regulation. This dual mechanism could have significant implications for enhancing treatment precision and improving prognosis in KIRC patients.

In addition to the identification of correlative genes, exploration data from *DrugBank* revealed that *VEGFA* is a target of various drugs that have been developed, both in the form of small molecules and biotechnology products.[33] In this study, it was found that the *VEGFA* gene is a target of various drugs that have been registered in the *DrugBank* database. Some of these drugs include ranibizumab, VEG-FAS, bevasiranib, gliclazide, SNS-032, denibulin, aflibercept, ABT-510, dalteparin and chondroitin sulphate. These drugs consist of small molecules and biotechnology agents that have a primary mechanism of action in inhibiting *VEGFA* activity, especially in the chemotaxis and angiogenesis processes that are important in cancer development.[34] Some of these drugs, such as ranibizumab, bevasiranib and aflibercept, have been used clinically for antiangiogenic therapy, while others are still in development or used in the context of additional therapy.[35]

The presence of these diverse therapeutic agents further emphasises the importance of *VEGFA* as a potential target in cancer treatment, especially KIRC type kidney cancer.[9, 27] Furthermore, understanding the interaction pathways between *VEGFA* and its co-expressed genes is crucial to optimise targeted therapy. Many of the genes found to be highly correlated with *VEGFA*, such as *FLT1, ZNF395* and *EGLN3*, are involved in angiogenesis, hypoxic response, or endothelial function. For instance, *FLT1* acts as a receptor for *VEGFA*, mediating angiogenic signalling, while *EGLN3* participates in the regulation of hypoxia-inducible factors that can indirectly affect *VEGFA* levels.[9]

The interplay between these genes and *VEGFA* suggests the presence of a coordinated network in both physiological and pathological angiogenesis. Selected drugs such as ranibizumab, bevasiranib and aflibercept are known to inhibit *VEGFA* directly at the protein level; however, some agents may also modulate upstream gene expression or signalling pathways. For example, gliclazide and SNS-032 may influence hypoxia-related pathways or transcription factors that regulate *VEGFA* and its correlated genes. This multi-level regulation might enhance treatment efficacy and provide insights for personalised therapy, especially in advanced-stage KIRC where angiogenesis plays a dominant role.[9]

Other drugs are still under development or used in additional therapy with mechanisms that focus on inhibiting *VEGFA* activity, especially in the process of chemotaxis and blood vessel formation. The existence of these various pharmacological agents further emphasises the strategic potential of *VEGFA* as a molecular target in KIRC type kidney cancer therapy and opens up opportunities for the development of more personalised and targeted therapeutic approaches in the future.[9] This study is based on publicly available databases and *in silico* bioinformatics analysis, which may not capture post-transcriptional modifications or *in vivo* protein dynamics. Functional validation through experimental models is necessary to confirm the precise molecular interactions between *VEGFA*, its co-expressed genes and the effects of the identified drugs. Furthermore, the current study does not consider tumour heterogeneity or individual genetic variability, which may influence therapeutic response.

Conclusion

This study showed that *VEGFA* was significantly higher expressed in KIRC type renal cancer compared to normal kidney tissue, indicating its central role in tumour angiogenesis. Ten genes that were highly correlated with *VEGFA* were identified, most of which are involved in vascular regulation and hypoxic response. In addition, *VEGFA* is known to be the target of various drugs such as ranibizumab, VEGF-AS, bevasiranib, gliclazide, SNS-032, denibulin, aflibercept, ABT-510, dalteparin and chondroitin sulphate, which work by inhibiting the angiogenic function of *VEGFA*. These findings confirm that *VEGFA* is a promising therapeutic target and potential biomarker in KIRC. The strong correlation of *VEGFA* with genes involved in angiogenesis and hypoxia indicates an integrated signalling network that may be disrupted by targeted therapies. Understanding these molecular interactions provides a foundation for more precise drug selection and therapeutic prediction. However, future experimental validation is required to explore how these drugs influence *VEGFA*-related gene networks in both pathological and normal conditions.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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Validation: RIP
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Investigation: RIP
Data curation: DPA
Writing - original draft: DPA, RIP
Writing - review and editing: DPA
Visualisation: DPA, RIP.

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