

Uncovering the Molecular Landscape of Secreted Phosphoprotein 1 and Its Expression Network in Kidney Renal Papillary Cell Carcinoma

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ABSTRACT

OBJECTIVE This study aims to investigate the expression pattern of Secreted Phosphoprotein 1 (SPP1), its prognostic relevance, and the associated co-expression gene network in kidney renal papillary cell carcinoma (KIRP).

METHODS Publicly available transcriptomic and clinical datasets were analyzed using GEPIA, UALCAN, and the GTEx Portal. SPP1 expression levels in KIRP versus normal kidney tissues were evaluated, followed by Kaplan–Meier survival analysis stratified by ethnicity, gender, and body weight. Co-expression analysis was performed to identify genes significantly correlated with SPP1 and to explore their potential biological functions.

RESULTS SPP1 expression was significantly upregulated in KIRP tissues compared with normal kidney tissues, consistent with GTEx data showing naturally high expression in kidney cortex and medulla. High SPP1 expression was associated with poorer overall survival, particularly among Caucasian patients, while no significant survival differences were observed by gender or body weight. Ten genes strongly co-expressed with SPP1, *MLLT3*, *AKIRIN2*, *YIPF1*, *SESTD1*, *LAMC1*, *FAS*, *ABCC3*, *MTHFD1L*, *ANXA2P2*, and *ARHGAP29* were identified, many of which are implicated in cell adhesion, migration, extracellular matrix remodeling, and apoptosis resistance.

CONCLUSIONS SPP1 is markedly overexpressed in KIRP and correlates with unfavorable prognosis, highlighting its potential as a diagnostic and prognostic biomarker. The identified SPP1-associated co-expression gene network may offer novel insights and therapeutic targets for improving molecular-based interventions in KIRP.

KEYWORDS kidney renal papillary cell carcinoma, Secreted Phosphoprotein 1, UALCAN, GEPIA

INTRODUCTION

Kidney cancer is one of the leading causes of urological cancer deaths worldwide, with kidney renal papillary cell carcinoma (KIRP) being the second major subtype after clear cell renal cell carcinoma (ccRCC) (1). Although KIRP exhibits a relatively less aggressive biological behavior

compared to ccRCC, its response to therapy remains variable and incompletely understood. Although KIRP is generally considered less aggressive than ccRCC, there remains a strong need for reliable biomarkers and more tailored therapeutic strategies. Epidemiological data indicate that KIRP accounts for approximately 10–15% of all renal cell

carcinoma (RCC) cases worldwide, representing the second most common subtype after ccRCC. Importantly, advanced-stage KIRP is associated with poor outcomes, with reported 5-year survival rates as low as 40–50%. Moreover, unlike ccRCC, KIRP often shows variable responses to standard systemic therapies, including tyrosine kinase inhibitors and immunotherapy, underscoring the heterogeneity of its biology. This clinical variability highlights the necessity of identifying molecular biomarkers that could improve risk stratification, guide therapeutic decision-making, and potentially enable the development of targeted treatments specifically for KIRP (2). Advances in omics approaches, especially transcriptomics, have opened up new opportunities to identify specific biomarkers that can be used for early diagnosis, risk stratification, and more targeted therapy. In this context, identifying genes that play a key role in the pathogenesis of KIRP is an urgent need to personalize therapy and improve patient prognosis (3). One candidate gene that has attracted attention in cancer research is Secreted Phosphoprotein 1 (SPP1), also known as osteopontin. SPP1 is a multifunctional glycoprotein involved in various biological processes such as cell adhesion, migration, angiogenesis, and regulation of immune responses (4, 5). Overexpression of SPP1 has been reported in various cancer types, including breast, lung, prostate, and liver cancers, and is often associated with poor prognosis and increased metastatic potential. However, the specific role of SPP1 in KIRP has not been comprehensively explored (6). Given the potential multifunctionality of SPP1 in the tumor microenvironment, further investigation of its expression in the context of KIRP may open new avenues for the development of molecular biomarkers (7).

Gene expression-based analytical approaches from bioinformatics databases allow for systematic analysis of SPP1 expression levels between tumor tissues and paired normal tissues (8, 9). In addition, gene expression correlation analysis provides information on other genes co-expressed with SPP1, which may reflect interrelated molecular pathways or transcriptional regulation (10). The identification of these genes may enhance our understanding of the molecular mechanisms underlying KIRP and may facilitate the develop-

ment of more accurate and sensitive biomarker panels. In this study, we evaluated SPP1 expression in KIRP tissues compared with normal kidney tissues and identified genes with the most similar expression patterns (co-expression) to SPP1 (11). The main objectives of this study were to explore the biological role of SPP1 in KIRP and to construct a gene expression network that may be clinically relevant (12). We hypothesize that increased expression of SPP1 and its co-expressed genes may reflect the activation of specific molecular pathways that support tumor growth and progression. It is anticipated that the results of this study will provide important contributions to the molecular understanding of KIRP and will support the development of new biomarkers and therapeutic targets in the future.

METHODS

This study used a public data-based bioinformatics approach to evaluate gene expression of SPP1 in KIRP papillary renal cancer (13, 14). All analyses were performed *in silico* utilizing gene expression databases from the GEPIA (Gene Expression Profiling Interactive Analysis) platform (GEPIA2 v2021), UALCAN (update 2022), and Genotype-Tissue Expression (GTEx) Portal v8, which provide access to large-scale transcriptomic data from The Cancer Genome Atlas (TCGA) and GTEx projects, respectively.

Analysis of SPP1 expression and survival using GEPIA

Gene expression analysis and prognostics SPP1 on KIRP is carried out using GEPIA (Gene Expression Profiling Interactive Analysis, <http://gepia.cancer-pku.cn>), an R-based platform that uses RNA-seq data from The Cancer Genome Atlas (TCGA) and GTEx (15). To evaluate the differential expression of the SPP1 gene between KIRP tumor tissues and normal kidney tissues, the feature used was “Box Plot” on GEPIA. The analysis parameters were set as follows: log2 fold change (log2FC) cutoff of 1 and $p < 0.01$. The type of analysis selected was Differential Expression Analysis, with the data type selected as “KIRP vs Normal”. The resulting graph is a box-and-whisker plot that visually shows the distribution of SPP1 expression in the normal and tumor groups, as well as the statistical value of the t-test. Furthermore,

survival analysis was performed to determine the relationship between *SPP1* expression levels and the prognosis of KIRP patients. The feature “Survival Analysis” in GEPIA is used to generate Kaplan-Meier curves, which compare the probability of survival between patient groups by high expression and low expression from the *SPP1* gene. Group separation was performed automatically based on median gene expression. The survival types analyzed were overall survival (OS), with the median group cutoff data separation method and the log-rank test statistical method. The results are visualized in the form of a Kaplan-Meier plot, equipped with hazard ratio (HR), *p*-value, and number of patients in each group. A $p < 0.05$ was considered to indicate statistical significance. This analysis aims to assess the potential of *SPP1* as a prognostic biomarker in KIRP based on its transcriptomic expression and its effect on patient clinical outcomes (16).

Survival analysis based on SPP1 gene expression using UALCAN

To evaluate the effect of gene expression *SPP1* on the prognosis of patients with KIRP, survival analysis was performed using the platform UALCAN (<https://ualcan.path.uab.edu>). UALCAN is a web-based bioinformatics portal that provides access to clinical and transcriptomic data from TCGA, enabling analysis of gene expression and the relationship between gene expression and clinical outcomes, including patient survival (17). In this analysis, *SPP1* expression data in KIRP patients were grouped into two categories based on median expression: group high expression (high expression) and group low expression (low expression). Survival analysis was performed using the method Kaplan-Meier survival plot, provided by UALCAN, to compare the cumulative survival probabilities between the two groups over time. Differences between survival curves were tested using the χ^2 test log-rank test, which is automatically calculated by the platform. The value $p < 0.05$ was considered statistically significant. The resulting data were visualized in the form of Kaplan-Meier curves with information on the number of patients in each group, *p*-value, and median survival time when available (18).

SPP1 Normal Expression Analysis Using GTEx Portal

To obtain an overview of gene expression *SPP1* in normal kidney tissue, data from GTEx Portal

(<https://gtexportal.org>), a repository of RNA-seq gene expression data derived from healthy tissues of various human donors was used. The platform provides TPM (transcripts per million) based genetic expression information, enabling high-quality comparison of expression across normal tissues (19, 20). Using the feature gene expression browser on the GTEx portal, a search was carried out on the *SPP1* gene and its expression data was extracted from kidney tissue, specifically in two anatomical subtypes, namely kidney cortex and kidney medulla, if available. Expression data are visualized in the form of a boxplot, which shows the distribution of *SPP1* expression values from a number of normal kidney tissue samples. These results were used as physiological control references to compare with *SPP1* gene expression in KIRP tumor tissues from the TCGA database (21, 22).

Correlation analysis of gene expression against SPP1

To identify the genes that are most similar in expression to *SPP1* on KIRP, correlation analysis was carried out using the platform GEPIA (<http://gepia.cancer-pku.cn>). GEPIA offers features “Similar Gene Detection”, which allows searching for genes with the most similar expression patterns based on the entire RNA-seq dataset from TCGA and GTEx (23). In this analysis, *SPP1* was used as the query gene. GEPIA calculated the value of the Pearson Correlation Coefficient (PCC) between *SPP1* expression and each of the other genes in the KIRP dataset. Genes with the highest PCC values were selected for further analysis, focusing on strong positive correlations ($PCC > 0.5$). The results of the analysis are visualized in Table 1, which includes information on gene symbols, gene IDs, and correlation values.

RESULTS

SPP1 expression in various types of cancer based on GEPIA analysis

To evaluate gene expression *SPP1* in various cancer types, expression analysis was performed using RNA-seq data available through GEPIA, which combines TCGA and GTEx datasets. This graph shows the comparison of median *SPP1* expression levels between tumor tissues (represented by pink bars) and normal tissues (represented by dark gray bars) across various cancer types. The results of the analysis show that *SPP1*

expression is consistently higher in tumor tissues than in normal tissues, especially in KIRP, Kidney Chromophobia (KICH), and Kidney Renal Clear Cell Carcinoma (KIRC). This marked increase in KIRP expression supports the hypothesis that *SPP1* plays a role in the pathogenesis of papillary renal cancer. In addition, the pattern of increased *SPP1* expression is also observed in several other cancer types, such as breast cancer (BRCA) and glioblastoma (GBM), although not as strong as that seen in renal cancer. These results can also be seen in Figure 1.

SPP1 expression in KIRP based on UALCAN analysis

UALCAN analysis revealed that *SPP1* expression was significantly elevated in KIRP tumor tissues compared with normal kidney tissues. These results are visualized in the form of a boxplot, where *SPP1* expression in tumor samples (red) appears much higher compared to normal samples (blue). This difference in expression is statistically significant, with a $p < 0.01$, indicating the involvement of *SPP1* in the pathogenesis of KIRP. The consistently higher *SPP1* expression in KIRP tissue supports the hypothesis that *SPP1* may play a role in the process of proliferation, migration, and remodeling of the tumor microenvironment. These findings strengthen the potential of *SPP1* as a molecular biomarker for diagnosis, prognosis, and as a therapeutic target in papillary kidney

cancer. The detailed statistical results are presented in Figure 2.

SPP1 expression analysis in KIRP based on GEPIA and UALCAN platforms

To further evaluate *SPP1* expression in KIRP cancer, gene expression analysis was performed using two major bioinformatics platforms, namely GEPIA and UALCAN. In GEPIA analysis (Figure 3A), *SPP1* expression in KIRP tumor tissue appeared significantly higher than in normal tissue. Visualization in the form of a scatter plot showed the distribution of transcripts per million (TPM) values, with the KIRP tumor group standing out significantly above normal tissue. This confirmed the strong upregulation of *SPP1* in KIRP tumor tissue. Meanwhile, analysis using UALCAN (Figure 3B) showed similar results through boxplot visualization. The level of *SPP1* expression in primary tumor tissue ($n = 290$) was significantly higher than in normal kidney tissue ($n = 32$), with a median expression more than twice that of normal tissue. Statistical analysis showed a significant difference ($p < 0.01$), strengthening the evidence that *SPP1* overexpression is an important molecular characteristic of KIRP. The consistency of findings from these two platforms suggests that *SPP1* may play a key role in KIRP pathogenesis and has potential as a diagnostic biomarker or molecular therapeutic target.

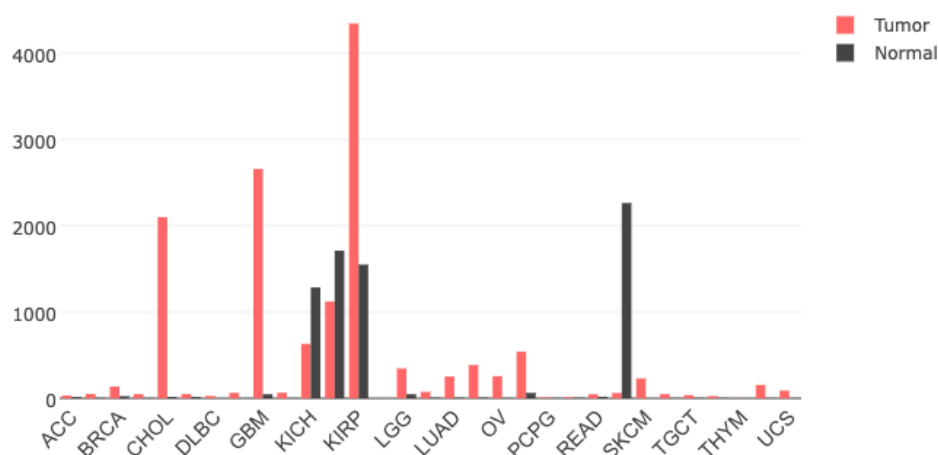


Figure 1. *SPP1* Gene expression in various types of cancer and normal tissues

ACC, adenocortical carcinoma; BRCA, breast invasive carcinoma; CHOL, cholangiocarcinoma; DLBC, diffuse large B-cell lymphoma; GMB, glioblastoma; KICH, kidney chromophobe; KIRP, kidney renal papillary cell carcinoma; LGG, low-grade glioma; LUAD, lung adenocarcinoma; OV, ovarian cancer; PCPG, pheochromocytoma and paraganglioma; READ, rectum adenocarcinoma; SKCM, skin cutaneous melanoma; TGCT, testicular germ cell tumors; THYM, thymoma, UCS, uterine carcinosarcoma

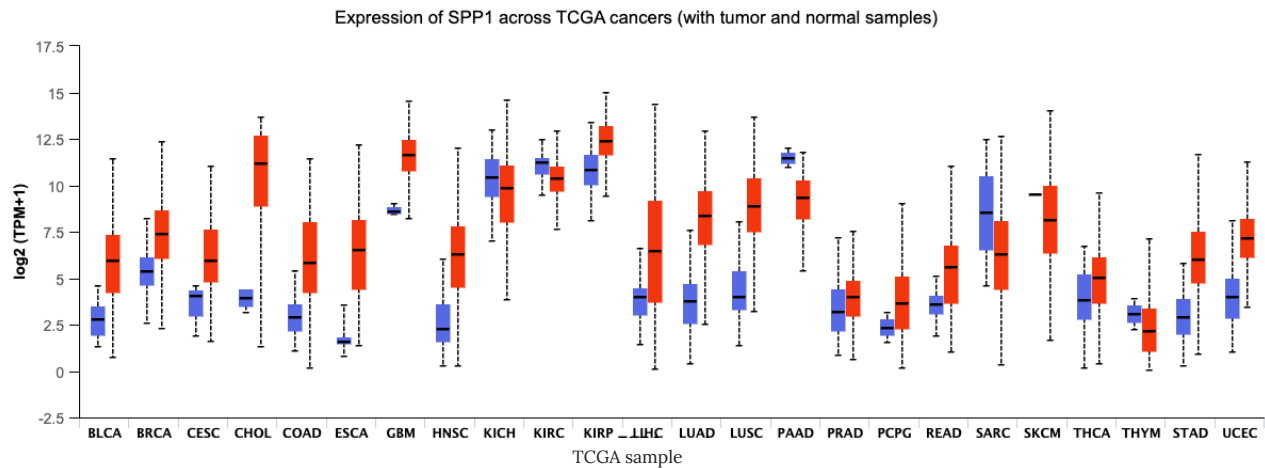


Figure 2. *SPP1* gene expression in KIRP tissue and normal kidney tissue based on UALCAN analysis, normal tissue (blue); tumor tissue (red)

BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; ESCA, esophageal cancer; GBM, glioblastoma; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; PAAD, pancreatic ductal adenocarcinoma; PRAD, prostate adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; READ, rectum adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma; THCA, thyroid carcinoma; THYM, thymoma; STAD, stomach adenocarcinoma UCEC, uterine corpus endometrial carcinoma

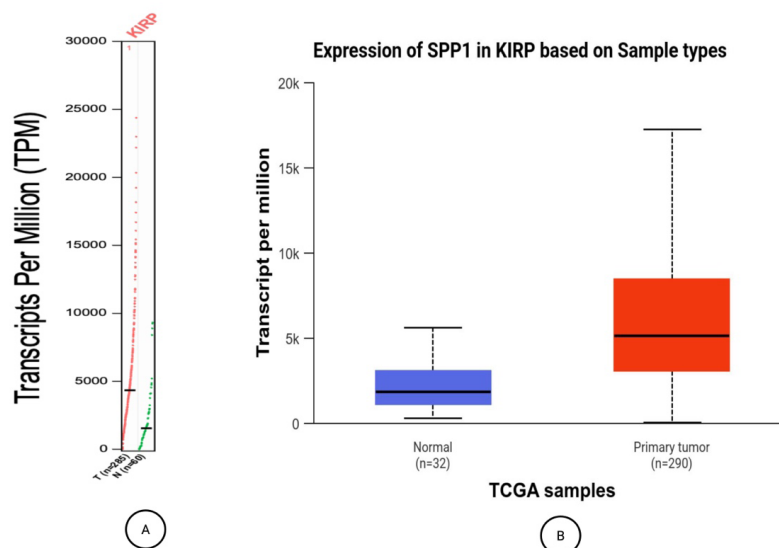


Figure 3. *SPP1* expression analysis in KIRP across two platforms. (A) Scatter plot from GEPIA showing significantly higher *SPP1* expression in KIRP tumor tissues compared with normal kidney tissues ($p < 0.01$). TPM values are displayed with median and interquartile ranges. (B) Boxplot from UALCAN showing *SPP1* expression levels in KIRP tumor samples ($n = 290$) versus normal kidney tissues ($n = 32$). Median tumor expression is more than twice that of normal tissues ($p < 0.01$).

Identification of highest co-expression genes against *SPP1* in KIRP

As part of the gene expression network exploration, expression correlation analysis was performed using datasets from GEPIA. The results of the analysis showed that several genes had the most similar expression patterns to *SPP1* in KIRP. The gene with the highest correlation was

SESTD1 (PCC = 0.65), followed by *AKIRIN2* (PCC = 0.59), *YIPF1* (PCC = 0.57), *SESTD1* (PCC = 0.55), and *LAMC1* (PCC = 0.54). Other genes such as *FAS*, *SESTD1*, *MTHFD1L*, *ANXA2P2*, and *ARHGAP29* also showed strong correlations with PCC values above 0.53. This co-expression suggests that these genes are likely involved in molecular pathways that are interconnected with *SPP1* function,

Table 1. List of genes with the highest co-expression with SPP1 in KIRP based on expression correlation analysis in GEPIA

Gene symbol	Gene ID	PCC
MLLT3	ENSG00000171843	0.65
ENDING2	ENSG00000135334	0.59
YIPF1	ENSG00000058799	0.57
SESTD1	ENSG00000187231	0.55
LAMC1	ENSG00000135862	0.54
FAS	ENSG00000026103	0.54
ABCC3	ENSG00000108846	0.54
MTHFD1L	ENSG00000120254	0.54
ANXA2P2	ENSG00000231991	0.54
ARHGAP29	ENSG00000137962	0.53

PCC, Pearson Correlation Coefficient

especially in processes such as cell migration, adhesion, tissue remodeling, and resistance to apoptosis. This finding opens up opportunities for further studies of these genes, both as part of a predictive biomarker network and as molecular therapeutic targets for KIRP as summarized in Table 1.

Relationship between SPP1 expression and prognosis of KIRP patients

Survival analysis using the GEPIA platform showed that SPP1 expression levels were associated with the prognosis of KIRP patients. The Kaplan-Meier survival plot (Figure 4) showed

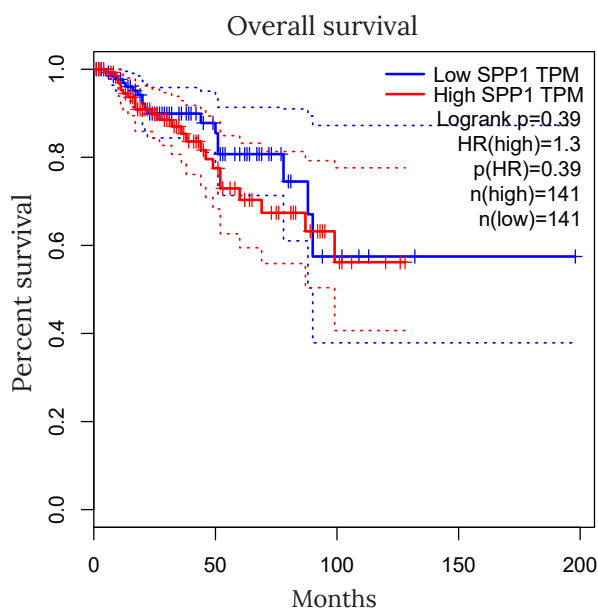


Figure 4. Kaplan-Meier analysis of the relationship between SPP1 expression and overall survival of KIRP patients using GEPIA

that patients with high SPP1 expression (high expression) had a lower overall probability of survival compared to patients with low expression (low expression). Statistically, this difference was significant with a $p < 0.05$, indicating that SPP1 overexpression may be associated with worse clinical outcomes in KIRP patients. These findings strengthen the potential role of SPP1 as a negative prognostic biomarker, where increased expression of this gene may reflect greater tumor aggressiveness and a worse prognosis.

Relationship between SPP1 Expression and Prognosis of KIRP Patients Based on Survival Analysis

Survival analysis of KIRP patients based on SPP1 expression was performed using data from the UALCAN platform. The results of the survival analysis (Figure 5A) Kaplan-Meier survival plot showed patients with high SPP1 expression tended to have a lower probability of survival than patients with low or moderate expression. However, this difference did not reach statistical significance ($p = 0.36$). This finding suggests that although there was a trend of decreased survival in the high expression group, SPP1 expression alone may not be strong enough to independently predict the prognosis of KIRP patients. When stratification was performed based on patient race (Figure 5B), it was found that the combination of SPP1 expression and race factors gave significant results ($p = 0.045$). In particular, Caucasian patients with high SPP1 expression showed lower survival rates than other groups. These results indicate that the effect of SPP1 expression on prognosis may also depend on the genetic or racial background of the patient. Further analysis based on patient gender (Figure 5C) showed that there was no significant difference in survival rate based on SPP1 expression between male and female patients ($p = 0.42$). This suggests that gender does not modify the relationship between SPP1 expression and clinical outcome in KIRP. Survival analysis based on weight category (Figure 5D) similarly showed no significant difference ($p = 0.69$) in the prognosis of KIRP patients based on SPP1 expression. Thus, weight status does not appear to influence the impact of SPP1 expression on patient survival.

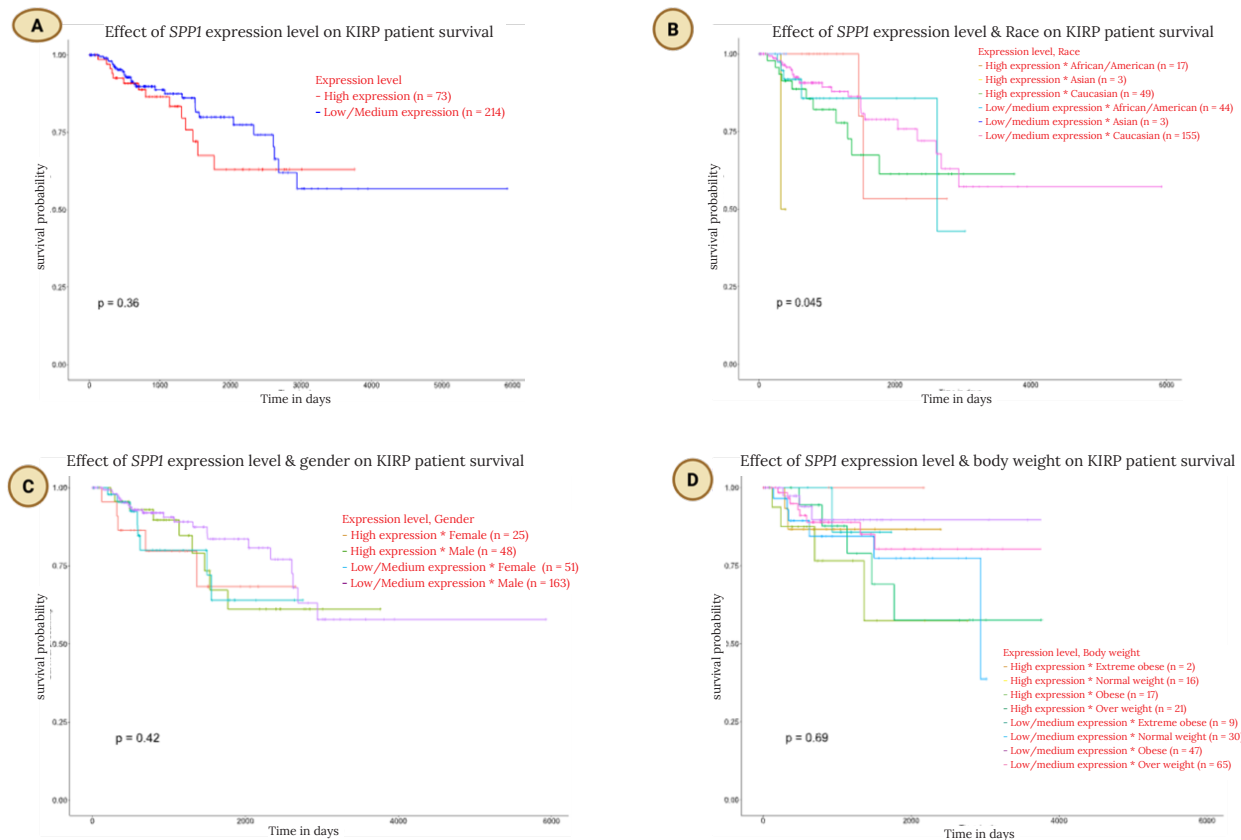


Figure 5. Kaplan-Meier survival plot of KIRP patients based on *SPP1* expression. (A) Overall survival stratified by high versus low *SPP1* expression ($p = 0.36$, not significant). (B) Survival stratified by race, showing significantly worse prognosis in Caucasian patients with high *SPP1* expression ($p = 0.045$). (C) Survival stratified by gender, showing no significant difference between male and female patients ($p = 0.42$). (D) Survival stratified by patient weight category, showing no significant difference ($p = 0.69$).

Normal expression of *SPP1* gene based on GTEx data

Physiological expression analysis of the *SPP1* gene in various normal human tissues was performed using data from GTEx Portal. The visualization resulted in the form of violin plots showed that *SPP1* expression varied among various tissues. The highest expression was detected in kidney cortex and kidney medulla tissues. These data strengthen the finding that increased *SPP1* expression was observed in KIRP tissues. Thus, *SPP1* has potential as an important molecular indicator in detecting abnormal biological changes in KIRP as can be seen in Figure 6.

DISCUSSION

In this study, *SPP1* gene expression was found to be significantly increased in KIRP tissues compared with normal kidney tissues. Data from the GEPIA and UALCAN platforms showed consistent results, with *SPP1* expression in KIRP tumors more

than double that in normal tissues, a statistically significant difference ($p < 0.01$) (18, 23). Additional analysis from the GTEx Portal showed that *SPP1* had relatively high expression levels in both kidney cortex and kidney medulla tissues (24). This confirms that the increase in *SPP1* in KIRP is not simply a result of physiological variability but rather reflects specific molecular deregulation in tumor tissues. *SPP1*, as a multifunctional glycoprotein, is known to be involved in a number of important biological processes, including cell adhesion, migration, extracellular matrix remodeling, and modulation of the immune response in the tumor microenvironment (25). Overexpression of *SPP1* in KIRP can be assumed to enhance tumor aggressiveness through activation of pro-inflammatory and pro-metastatic pathways, accelerate local tissue invasion, and support the formation of distant metastases (26). This is in line with data on various other cancers, such as breast, lung, and liver cancer, where *SPP1* functions as a major

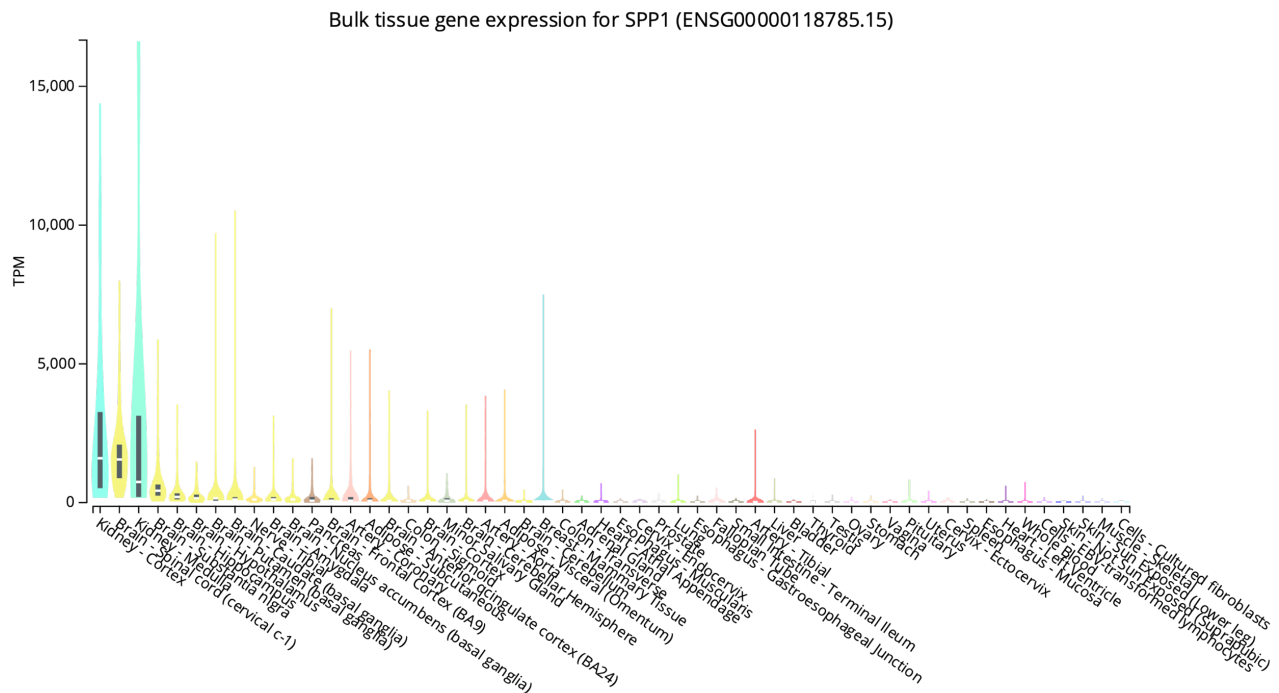


Figure 6. Distribution of *SPP1* gene expression in various normal human tissues based on data from the GTEx portal

mediator of tumor phenotype changes towards a more invasive direction. Clinically, KIRP demonstrates variable outcomes. While early-stage KIRP is often associated with favorable prognosis, advanced-stage disease suggests a markedly worse outcome, with reported 5-year survival rates as low as 40–50%. Population-based data also indicate that KIRP contributes significantly to renal cancer-related mortality, particularly in patients with metastatic or treatment-resistant disease. Moreover, the relatively poor response of KIRP to conventional targeted therapy and immunotherapy further underscores its clinical aggressiveness in advanced settings. In this context, the identification of prognostic biomarkers such as *SPP1* may be particularly valuable, as they could help refine risk stratification, better predict therapeutic response, and ultimately improve clinical decision-making in patients with KIRP (27).

Interestingly, we observed a discrepancy between the results obtained from GEPIA and UALCAN. While GEPIA analysis indicated that high *SPP1* expression was significantly associated with worse OS, the UALCAN platform showed a similar trend but without statistical significance in the overall cohort. Several factors may underlie this inconsistency. First, cohort composition and sample size differ between the two platforms: GEPIA integrates TCGA and GTEx datasets, resulting in a broader and more heterogeneous

cohort, whereas UALCAN relies solely on TCGA-KIRP data, which may reduce statistical power. Second, differences in statistical methods are likely contributors: GEPIA applies log-rank tests with median cutoffs for survival group stratification, while UALCAN employs χ^2 -based log-rank statistics with automatic subgrouping, which can influence outcome significance. Third, data normalization and processing pipelines vary between platforms. GEPIA uses an integrated normalization strategy across TCGA and GTEx, while UALCAN utilizes level 3 TCGA RNA-seq data processed by its own pipeline. These differences may lead to subtle variations in expression quantification and survival estimates. Acknowledging these platform-specific discrepancies is important, as it emphasizes the need for multi-cohort validation and highlights that survival associations should be interpreted with caution unless replicated across independent datasets. Next, the relationship between *SPP1* expression levels and clinical prognosis of KIRP patients was explored through GEPIA and UALCAN-based Kaplan-Meier analysis. The results of GEPIA showed that patients with high *SPP1* expression had worse OS than those with low expression, with a $p < 0.05$. This indicates that *SPP1* may serve as a negative prognostic biomarker. However, the results of UALCAN, although showing a similar trend, did not reach statistical significance overall ($p = 0.36$). Interestingly, when strati-

fied by race, high *SPP1* expression in Caucasian patients showed a significant association with worse outcomes ($p = 0.045$). Collectively, these observations indicate that our race-specific findings from UALCAN align with known epidemiologic and outcome disparities in RCC, reinforcing the need for race-aware validation of *SPP1* as a prognostic biomarker in KIRP. Population heterogeneity in KIRP outcomes may partly reflect genetic differences. For example, *MET* alterations and *FH* mutations, which drive papillary RCC subtypes, occur with variable frequency across populations, while *APOL1* risk variants—common in individuals of African ancestry—have been associated with poorer renal outcomes. These findings highlight the importance of validating prognostic biomarkers such as *SPP1* in multi-ethnic cohorts. Further analysis based on patient gender (Figure 5C) found no significant difference in survival. Taken together, these findings suggest that high *SPP1* expression may serve as a negative prognostic marker in KIRP. The GEPIA results demonstrated statistical significance for overall survival, likely reflecting the larger integrated cohort and higher statistical power achieved by combining TCGA and GTEx data. By contrast, UALCAN did not show significance in the overall analysis, but its subgroup stratification (e.g., by race) revealed clinically meaningful differences, particularly in Caucasian patients. This indicates that while GEPIA may provide stronger statistical evidence of association, UALCAN highlights population-specific heterogeneity that could be clinically relevant. Therefore, both platforms are complementary: GEPIA supports the general prognostic role of *SPP1* in KIRP, whereas UALCAN underscores the importance of considering patient demographics and molecular diversity when interpreting prognostic biomarkers. These insights strengthen the significance of *SPP1* expression, not only as a potential universal biomarker but also as a candidate for personalized prognostic evaluation in specific subgroups of KIRP patients.

These results underscore the importance of considering genetic or ethnic background variables in the interpretation of molecular biomarkers. Genetic factors underlying population heterogeneity may modulate tumor responses to *SPP1* expression or affect its downstream signaling

pathways. Meanwhile, analysis based on patient gender and weight showed no significant association, indicating that the influence of *SPP1* on prognosis seems to be more intrinsic to the tumor rather than modified by external factors such as hormonal or metabolic (28). Overall, these findings place *SPP1* as a potential prognostic biomarker candidate in KIRP, although further validation with a larger cohort and multivariate analysis is needed to strengthen its application in clinical practice (29).

Furthermore, gene co-expression analysis showed that *SPP1* forms a close molecular expression network with several other genes that have relevant biological functions in cancer progression. *SESTD1*, *AKIRIN2*, *LAMC1*, *FAS*, and *SESTD1* genes showed high PCC with *SPP1*, indicating involvement in similar biological pathways. *SESTD1* is associated with transcriptional regulation and hematopoiesis, which may contribute to the dynamics of tumor cell proliferation. *LAMC1*, as part of the laminin gamma chain, plays a role in cell interaction with the extracellular matrix and has been associated with increased migration and cancer invasion in various tumor types. Co-expression of *SPP1* with *FAS*, a master regulator of apoptosis, suggests potential involvement in evasion of programmed cell death, a critical mechanism in the development of therapy-resistant tumors (30). Furthermore, co-expression with *AKIRIN2* and *SESTD1* extends the indication that *SPP1* may be involved in the regulation of inflammatory signals and remodeling of the cell cytoskeleton. The integration of these data makes it clear that *SPP1* does not act alone, but rather is part of a complex molecular network that regulates the aggressive phenotype of KIRP. These findings open up opportunities to develop combination-based therapeutic strategies, targeting not only *SPP1*, but also critical co-expression pathways that may enhance the efficacy of molecular interventions against papillary renal cancer.

CONCLUSIONS

This study showed that *SPP1* was significantly more highly expressed in KIRP tissues compared to normal kidney tissues, based on GEPIA and UALCAN analysis, and supported by GTEx data showing low *SPP1* expression in healthy kidneys.

SPP1 overexpression was associated with worse clinical prognosis, especially in Caucasian patients, while there was no significant difference based on gender or body weight. Gene expression correlation analysis identified ten genes with the highest co-expression with SPP1, namely, *SESTD1*, *AKIRIN2*, *YIPF1*, *SESTD1*, *LAMC1*, *FAS*, *SESTD1*, *MTHFD1L*, *ANXA2P2*, and *ARHGAP29*, which may possibly play a role in cell adhesion, migration, extracellular matrix remodeling, and resistance to apoptosis pathways. Overall, these findings confirm that SPP1 has strong potential as a diagnostic biomarker, prognostic biomarker, and molecular therapeutic target in the management of KIRP.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest regarding the publication of this paper.

AUTHOR CONTRIBUTIONS

D.P.A.: conceptualization, methodology, writing – review & editing; R.I.P.: data curation, writing – original draft preparation; M.S.B.: formal analysis, software, validation, resources; D.E.: formal analysis; R.I.P.: visualization, investigation; D.E.: Visualization, Investigation; D.P.A.: supervision, project administration, funding acquisition;

All authors have read and agreed to the published version of the manuscript.

DATA AVAILABILITY STATEMENT

All datasets analyzed in this study are publicly available from GEPIA (<http://gepia.cancer-pku.cn>), UALCAN (<https://ualcan.path.uab.edu>), and the GTEx Portal (<https://gtexportal.org>).

INSTITUTIONAL REVIEW BOARD STATEMENT

This study used publicly available datasets containing de-identified patient information. Therefore, ethical approval was not required. The study complies with the Declaration of Helsinki principles for ethical research.

INFORMED CONSENT STATEMENT

Patient consent was waived because the study used publicly available de-identified datasets.

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