

Significance of sex-determining region Y box family members (SOX6 and SOX9) in clear cell renal cell carcinoma: immunohistochemical study

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Background

Renal cell carcinoma (RCC) ranks as the third most common urological malignancy worldwide, comprising ~2.2% of all cancers. The clear cell subtype, which accounts for 80–90% of RCC cases, is characterized by a wide spectrum of survival outcomes. The sex-determining region Y box (SOX) family of proteins, expressed in multiple cell types, plays a crucial role in regulating cell differentiation and fate in various physiological contexts. Among them, SOX6 and SOX9 have been implicated in the regulation of carcinogenesis in several human cancers.

Aim

The primary objective of this study is to investigate the immunohistochemical expression of SOX6 and SOX9 in clear cell RCC, with a focus on their potential role in tumor progression and as predictors of patient prognosis and survival.

This retrospective analysis included 50 cases of clear cell RCC. Immunostaining for SOX6 and SOX9 was performed, and the results were correlated with clinicopathological features.

Results

SOX6 and SOX9 expression was significantly altered in RCC compared with normal renal tissue ($P < 0.001$). SOX9 expression showed a strong positive association with key clinicopathological factors such as tumor size, Fuhrman grade, tumor, nodal, metastasis (TNM) stage, and lymphovascular invasion ($P < 0.05$). Conversely, SOX6 expression exhibited a significant negative correlation with these same parameters ($P < 0.05$).

Conclusion

SOX9 and SOX6 are potentially involved in the progression of clear cell RCC and may serve as useful biomarkers for this malignancy.

Keywords:

immunohistochemistry, renal cell carcinoma, sex-determining region Y box factor 6, sex-determining region Y box factor 9

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Introduction

The most prevalent malignant tumor of the kidney, accounting for 70% of cases, is renal cell carcinoma, clear cell type (ccRCC), and its incidence is increasing yearly. It accounts for about 1% of all cases of cancer, worldwide. In Egypt, the median age is 55 years old and there is 2: 1 male preponderance (El-Bolkainy *et al.*, 2016). The disease has a high recurrence incidence of over 30% even with locally circumscribed tumors, and over one-third of patients present with metastasizing disease. Even with major breakthroughs in cancer therapy, the prognosis of advanced cases is still bleak. The main risk factors for renal cell carcinoma are older age, male sex, obesity, smoking, hypertension, and a few medical disorders such as kidney transplantation, hemodialysis, and chronic kidney disease. Environmental, nutritional, occupational, and lifestyle factors have also been linked to an increased risk of RCC (Aguilar-Medina *et al.*, 2019).

The SOX family is a newly recognized, significant class of transcription factors implicated in carcinogenesis. It consists of around 20 transcriptional regulators with a highly conserved high-mobility group domain that mediates DNA binding (Yazdi *et al.*, 2021). In brief, SOX transcription factors could control the fate and differentiation of cancer cells. Many members of the SOX family are thought to play a role in the growth, invasion, and metastasis of malignancies (Chen *et al.*, 2020).

SOX6 is expressed in the central nervous system during embryonic development in mice denoting possible involvement in regulating embryogenesis and cell fate

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determination. Evidence suggests that SOX6 may influence stem cell characteristics. Recent research has shown that SOX6 can function as either an oncogene in various human cancers, or a tumor suppressor (Jiang *et al.*, 2018).

SOX9 is essential for controlling several developmental processes, such as male sex determination, chondrogenesis, neurogenesis, and neural crest formation (Jo *et al.*, 2014). SOX9 knockdown has been associated with decreased cellular proliferation, cell cycle arrest at the G0/G1 phase, and increased susceptibility to apoptosis (Grimm *et al.*, 2020). Prostatic adenocarcinoma, lung cancer, gastric cancer, and breast cancer have all been associated with elevated SOX9 expression (Dang *et al.*, 2020; Yamada *et al.*, 2023; Xu *et al.*, 2023; Zhong *et al.*, 2023).

Nevertheless, more studies to evaluate the role of SOX 9 and SOX 6 in RCC is needed. This study essentially aims at evaluating the immunohistochemical expression of SOX6 and SOX9 in clear RCC cases trying to assess their possible role in tumor progression and prediction of patient's prognosis and survival.

Patient and methods

This retrospective study was carried out on 10 cases of nontumorous renal tissue from nephrectomies conducted for renal failure or pyelonephritis as a normal control and 50 properly selected cases of clear cell renal cell carcinoma. The cases examined in this study comprised archival formalin-fixed, paraffin-embedded nephrectomy tissue blocks, collected between January 2017 and December 2019 at the Pathology Department and Early Cancer Detection Unit, Faculty of Medicine, Benha University. Ethical approval for the study was obtained from the Research Ethics Committee of the Faculty of Medicine, Benha University, Egypt. (RC 3-5-2024)

Exclusion criteria

- Renal cell carcinoma cases of any kind other than the clear cell type.
- Patients with a history of chemotherapy before surgery.
- Situations where paraffin blocks are not accessible.

All collected tissue blocks were sectioned at 4 μ m thickness and stained using the routine hematoxylin and eosin technique. Two independent pathologists, blinded to the clinical data, evaluated the slides. Tumor staging and grading were determined based on the seventh edition of the tumor, nodal, metastasis staging system and the Fuhrman grading system, respectively (Fuhrman *et al.*, 1982; Edge and Compton, 2010). The follow-up period was 36 months.

Immunohistochemical study

Immunohistochemical staining was conducted using the standard streptavidin-biotin method, following the manufacturer's protocol. Details regarding the primary antibodies used are provided in (Table 1). A labeled streptavidin-biotin kit (Neomarker; Labvision, Waltham, USA) was employed for the secondary developing reagents. Sections were developed using 0.02% diaminobenzidine as the chromogen. Negative controls for both markers were prepared by omitting the primary antibody as shown in (Table 1), while a positive control was included in the kit.

Immunohistochemical assessment

SOX9 staining was confined to the nucleus, with intensity classified as follows: 0 (absent), 1 (weak staining), 2 (moderate), and 3 (high). The percentage of immunoreactive tumor cells was visually assessed, and immunohistochemical grading was performed semi-quantitatively, using the methodology established by Wan *et al.* (2017). The scoring method was as follows: 0 (0%), 1 (1–10%), 2 (>10–50%), and 3 (>50%). The final immunoreactivity score (IRS) was determined by multiplying the staining intensity by the proportion of positive cells. Protein expression was then classified into two categories: low (IRS <5.0) and high (IRS \geq 5.0) (Wan *et al.* (2017).

Nuclear staining for SOX6 was assessed using the following scale: 0 (absent staining), 1 (mild yellow staining), 2 (moderate yellow staining), and 3 (intense yellow-brown staining). The proportion of stained cells was evaluated semi-quantitatively as follows: 0 (<5%), 1 (>5–25%), 2 (>25–50%), and 3 (>50%). The total score was derived by multiplying the intensity score by the percentage score. Sections scoring between 0 and 3 were deemed negative, whilst those scoring 4 or above were categorized as positive (Chen *et al.*, 2020).

Table 1 SOX9 and SOX6 antibodies

Markers	Vendor	Clone	Host/ isotope	State	Dilution	Incubation	Positive control	Antigen retrieval
SOX9	Thermo Fisher scientific	Polyclonal	Rabbit/ IgG	Concentrated	1:500	At 4 C overnight	Human prostatic cancer	Citrate buffer (pH 6.0)
SOX6	Thermo Fisher scientific	Polyclonal	Rabbit/ IgG	Concentrated	1:1000	At 4 C overnight	Human breast cancer	Citrate buffer (pH 6.0)

Statistical analysis

Data were analyzed using SPSS version 20 (IBM Corp., New York, USA). The Pearson correlation coefficient was used to assess statistical significance, with a P value less than 0.05 being significant and less than 0.01 regarded as very significant. Survival analysis was conducted using the log-rank test, with findings shown by Kaplan–Meier survival curves.

Results

Clinicopathological results

The studied 50 RCC cases had a mean age of 63.2 ± 11 years (range, 22–71 years). The characteristics of the patients with RCC and tumors are listed in (Table 2).

Immunohistochemical results

SOX6 expression in RCC tissues was markedly reduced in comparison to both normal control tissue and neighboring nontumorous tissue ($P < 0.05$). A significant negative connection was identified between SOX6 expression and many clinicopathological markers (Table 3). Positive SOX6 expression was more often linked to RCC tissues with a lower Fuhrman grade ($P = 0.003$, Figs 1a, 2), reduced tumor size ($P = 0.01$), lower TNM stage ($P = 0.03$), and the lack of lymphovascular invasion (LVI) ($P = 0.014$). No notable

correlations were detected between SOX6 expression and the patient's age or sex.

Conversely, SOX9 expression was markedly increased in RCC tissues relative to normal control and non-tumorous tissues ($P < 0.001$). A significant positive connection was identified between SOX9 expression and the previously described clinicopathological characteristics (Table 3). Elevated SOX9 expression was more often seen in RCC tissues with greater Fuhrman grade ($P = 0.005$, Figs 1b, 3), increased tumor size ($P = 0.006$), advanced TNM stage ($P = 0.04$), and the occurrence of LVI ($P = 0.001$). No substantial changes were seen between SOX9 expression and the patient's age or sex.

Prognostic values of SOX9 and SOX6 expression in clear cell RCC

In the three-year follow-up period, 15 (30%) patients achieved relapse-free survival, 11 (22%) patients suffered recurrence, and 24 (48%) patients succumbed (Table 4). The cohort exhibiting low SOX6 expression had a markedly reduced 3-year relapse-free survival in comparison to the cohort with positive SOX6 expression ($P < 0.05$), as seen in Graph 1. Nonetheless, no substantial connection was seen between SOX9 expression and 3-year relapse-free survival (Graph 2). Graph 3 and Table 5 illustrate the Kaplan–Meier analysis about the correlation between SOX6 and SOX9 expression and disease-free survival. A significant positive correlation was identified between SOX6 expression and 3-year overall survival ($P < 0.05$). In contrast, SOX9 expression exhibited a significant negative connection with 3-year overall survival ($P < 0.05$).

Table 2 Clinico-pathological data of the studied cases

Clinic-pathological parameter	N (%)
Age	
<60 years	21 (42)
≥60 years	29 (58)
Sex	
Male	39 (78)
Female	11 (22%)
Tumor size (T stage)	
<T2 (up to 7 cm)	21 (42)
≥T2 (more than 7 cm)	29 (58)
Fuhrman Grade	
Low grade (I and II)	18 cases (36)
High grade carcinoma (III and IV).	32 cases (64)
TNM Stage	
Low stage (I and II)	22 cases (44)
High stage (III and IV).	28 cases (56)
N stage	
N0	22 cases (44)
N1	28 cases (56)
M stage	
M0	38 cases (76)
M1	12 cases (24)
Vascular invasion	
Negative	20 cases (40)
Positive	30 cases (60)
Total	50

TNM = tumor, nodal, metastasis

Discussion

ccRCC is considered the most common renal malignant tumor with highest mortality rate (70%), its incidence is increasing every year (Chen *et al.*, 2020).

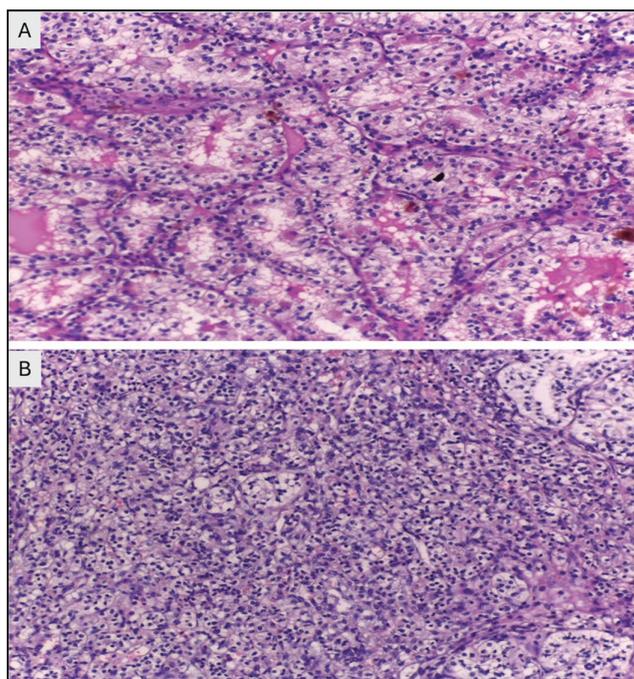
Regarding SOX9 expression, it is significantly upregulated in RCC tissues more than those in normal control ($P < 0.001$). This indicates possible involvement in pathogenesis and progression of renal cell carcinoma. These results were parallel to Kaushik *et al.*, 2021 in their studies on renal cancer. Also, these results are in line with the studies conducted on breast, bladder, pancreas, liver, and nonsmall lung cancer reaching that SOX9 expression was notably increased in malignant compared with its expression in the premalignant lesions suggesting a role in the tumors development and progression (Qin *et al.*, 2014; Sano *et al.*, 2015; Liu *et al.*, 2016; Aguilar-Medina *et al.*, 2019; Grimm *et al.*, 2020).

Majid *et al.* (2012) elucidated that the specific impact of SOX9 overexpression is associated with the

Table 3 Relationship between SOX6 and SOX9 immunohistochemical findings and various clinicopathological data of the studied cases

	Total	SOX expression				P value	
		SOX9-low	SOX9-high	SOX6-negative	SOX6-positive	Sox9	Sox6
		NO	NO	NO	NO		
Age							
<60 years	21	7 (33)	14 (67)	12 (57)	9 (43)	0.423	0.393
≥60 years	29	13 (45)	16 (55)	16 (55)	13 (45)		
Sex, n (%)							
Male	39	17 (44)	22 (56)	21 (54)	18(46)	0.339	0.573
Female	11	3 (27)	8 (73)	7(64)	4 (36)		
Tissue, n (%)							
RCC	50	20 (40)	30 (60)	28 (56)	22 (44)	0.0.2	0.05
Apparently normal	6	5 (80)	1 (20)	2 (30)	4 (70)		
Tumor size, n (%)							
<T2 (up to 7 cm)	21	13 (62)	8 (38)	6 (29)	15 (71)	0.006	0.001
≥T2 (more than 7 cm)	29	7 (24)	22 (76)	22 (76)	7 (24)		
Fuhrman Grade, n (%)							
1–2	18	14 (78)	4 (22)	2 (11)	16 (89)	0.005	0.003
3–4	32	6 (19)	26 (81)	26 (81)	6(19)		
TNM Stage, n (%)							
(I/II)	22	18 (82)	4 (18)	6 (27)	16 (73)	0.04	0.03
(III/IV)	28	10 (35)	18 (65)	21 (75)	7 (25)		
LV Invasion, n (%)							
Negative	20	15 (75)	5 (25)	7 (35)	13 (65)	0.001	0.014
Positive	30	5 (17)	25 (83)	21 (70)	9 (30)		

*HS: Highly significant. *P* value less than 0.01 S: Significant. *P* value less than 0.05.

Figure 1

A) low grade clear cell RCC (H&E; E ×200). B) High grade clear cell RCC (H&E; E ×100).

attenuation of tight junctions. This idea was validated by Capaccione (2014) and Maruno *et al.* (2018) in their investigation of liver and lung cancers, noting the suppression of E-cadherin (CDH). Furthermore,

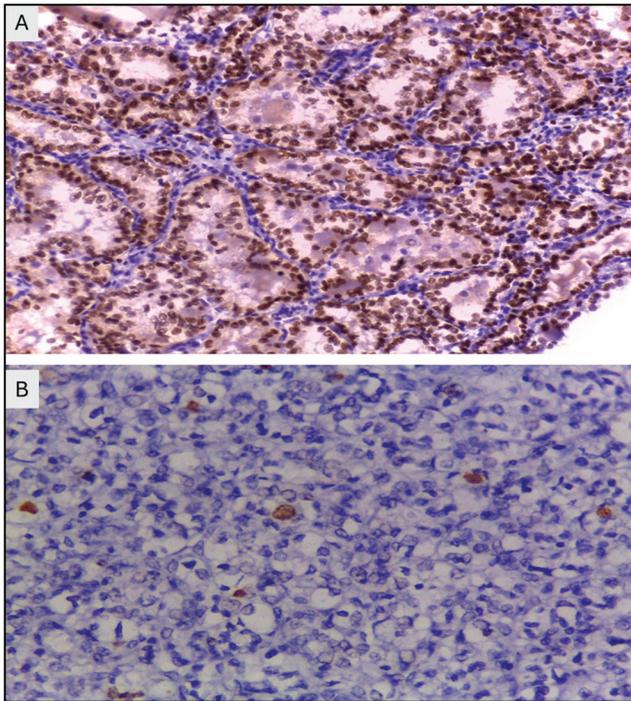
elevated SOX9 expression was correlated with decreased PTK2 expression, which is crucial for cell attachment to the extracellular matrix (Balsas *et al.*, 2017).

The current investigation identified a significant positive relation between SOX9 expression and elevated tumor grade ($P=0.005$). These results align with those documented by Liu *et al.* (2016) and Sano *et al.* (2015) in their investigations of renal cell cancer. Panda *et al.*, 2021 also noted that increased SOX9 expression correlates with higher tumor grade in their study of colorectal and bladder carcinomas.

Another significant association between SOX9 expression and the TNM stage and LVI in ccRCC was reached ($P=0.04$ and 0.001). These results were in alignment with Grimm *et al.* (2020) in their study on renal cell carcinoma in mouse model reporting SOX9 as a key signaling molecule for metastasis (Jo *et al.*, 2014).

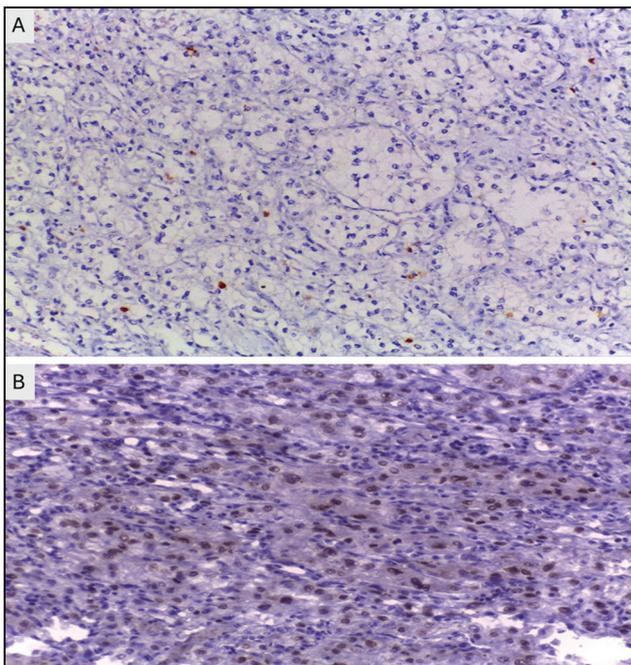
Agreed with these results, Liu *et al.* (2016) in their studies on hepatocellular carcinoma and penile cancer and Qin *et al.* (2011) in their study on esophageal cancer stem cells concluding that inhibition of EGFR/FOXA2/SOX9 axis helps in reduction of cancer invasion and metastasis (Liu *et al.*, 2016; Kaushik *et al.*, 2021). These results can be owed to the positive

Figure 2



A) SOX6 expression: strong and diffuse in the nucleus of low grade ccRCC tumor cells (x200). B) Negative SOX 6 staining in the nucleus of high grade ccRCC tumor cells (x400).

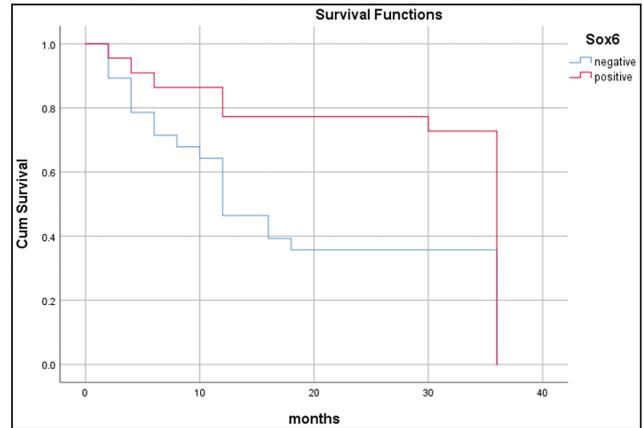
Figure 3



A) SOX9 expression in low grade ccRCC tumor cells, IRS and It;5 (x200). B) Strong SOX9 staining in the nucleus of high grade ccRCC tumor cells IRS and gt;5 (x200).

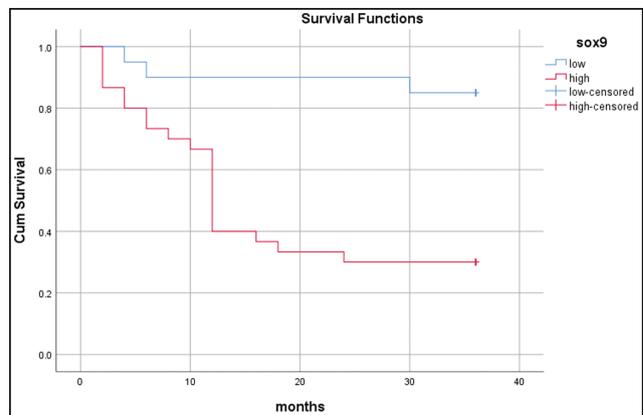
association between SOX9 and Raf/MEK/ERK signaling pathway which is known to have a crucial role in tumor cell dedifferentiation, proliferation, and migration (Li *et al.*, 2015).

Graph 1



Kaplan–Meier survival curves for patients with ccRCC, showing two groups based on SOX6 expression: negative (blue) and positive (red). Cases with positive SOX6 expression exhibited notably better survival rates compared with those with negative SOX6 expression ($P<0.001$).

Graph 2



Kaplan–Meier survival curves for patients with ccRCC, distinguishing two groups based on SOX9 expression levels: low (blue) and high (red). Cases with high SOX9 expression demonstrated considerably worse overall survival rates compared with those with low SOX9 expression ($P<0.001$).

In contrary, another study conducted on prostatic carcinoma reached no statistically significant relation between SOX9 expression and tumor stage (Majid *et al.*, 2012). This may be attributed to different tissues studied with varied cancer biological behavior.

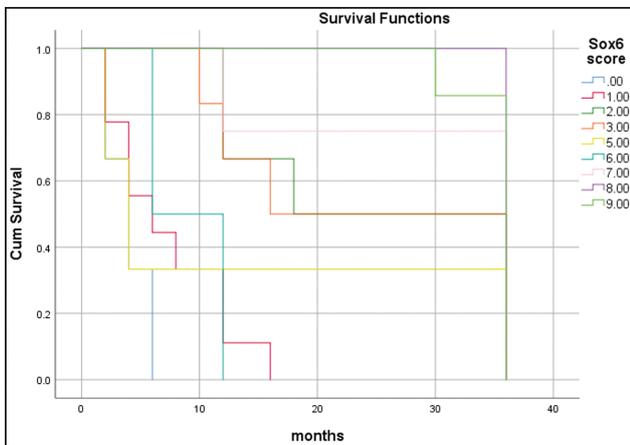
The present study established a strong unfavorable statistical relationship between SOX9 expression and overall survival rates in ccRCC. This aligns with Lü *et al.* (2008) and Zhou *et al.* (2012), who documented favorable statistical associations between SOX9 overexpression and worse survival rates in their investigations of RCC and nonsmall cell lung carcinoma, respectively.

Table 4 Prognostic values of SOX9 and SOX6 expression in clear cell RCC

Prognostic indicator	Result	No.	SOX9 low	SOX9 high	SOX6 negative	SOX6 positive	P value
3-year overall survival (OS)	Died	24	3 (12.5)	21 (87.5)	18 (75)	6 (25)	0.00* 0.009*
	Survived	26	17 (65.4)	9 (34.6)	10 (38.5)	16 (61.5)	
3-year relapse free survival (RFS)	Free	15	12 (80)	3 (20)	3 (20)	12 (80%)	0.072 0.023*
	Relapse	11	5 (45.5%)	6 (54.5%)	7 (63.6%)	4 (36.4%)	

*HS: Highly significant. P value less than 0.01 S: Significant. P value less than 0.05.

Graph 3



Kaplan–Meier curves for cases with ccRCC survival. Relation between SOX9 and SOX6 expression and disease-free survival.

Table 5 Relation between SOX9 and SOX6 expression and survival

SOX9	Mean survival	95% C.I	Log rank test	P value
High	16.9.	12.22–21.65	13.536	0.001
Low	32.600	28.525–36.00		
SOX6				
Positive	29.18	24.0–34.47	6.51	0.01
Negative	18.50	13.22–23.6		

Nonetheless, no substantial statistical link was established between SOX9 expression and the 3-year relapse-free survival. This contradicts the findings of Abdelaziz *et al.* (2022), who identified a significant relation between positive SOX-9 expression and reduced 3-year disease-free survival in their breast cancer research. This discrepancy may be attributed to the limited sample size in the present study relative to the extensive breast cancer sample size associated with case availability.

SOX6 expression is considerably downregulated in RCC tissues compared with normal controls ($P=0.05$). These findings suggest that its downregulation may facilitate the onset of renal cell cancer. SOX6 may affect the cell cycle by modulating the transition from the G1 to S phase and exerting an inhibitory impact on the Wnt/ β -catenin signaling pathway, along with its target genes, c-Myc and cyclin D1 (Yazdi *et al.*,

2021). SOX6 tumor-suppressive function is ascribed to its distinct high-mobility group domain (Dang *et al.*, 2020).

These results were parallel to those reported by Casas *et al.* (2011) that used immunohistochemical staining techniques, qRT-PCR, and Western blot analysis proving that Sox6 expression was significantly downregulated in renal cell tissues in vivo and in vitro compared with the adjacent apparently normal tissues (Chen *et al.*, 2020). Also, similar results were reached in studies conducted on prostatic, esophageal, lung and gastric cancers (Qin *et al.*, 2014; Dang *et al.*, 2020; Kambara *et al.*, 2020; Wang *et al.*, 2022).

Conversely, SOX6 expression in some brain tumor types was elevated relative to neighboring normal tissues, suggesting that SOX6 overexpression may serve as a possible diagnostic signal (Chen *et al.*, 2020). These contradictory findings may be ascribed to the possibility that SOX6 expression is tissue-specific.

The present investigation established a significant negative relationship between SOX6 expression and tumor grade, stage, and LVI. The findings corresponded with those of Yazdi *et al.* (2021) and Zhou *et al.* (2020) in their investigations of glioblastoma and hepatocellular carcinoma, respectively. The findings may be attributed to the inhibitory impact of SOX6 overexpression on tumor invasiveness via the suppression of epithelial-mesenchymal transition (Qin *et al.*, 2011).

This research demonstrated that the overexpression of SOX6 correlated with improved overall survival and disease-free survival rates in ccRCC. This aligns with Lyu *et al.* (2021), who identified a substantial statistical association between decreased SOX6 expression and worse survival rates for the same tumor type. These findings align with those of Guo *et al.*, 2013 and Qin *et al.*, 2011. in their investigations of HCC and esophageal cancer, respectively.

In contrast, were the results of Yazdi *et al.*, 2021 who found that there was an insignificant relation between SOX6 expression and the survival rates of glioblastoma. This contradiction may be attributed to the special nature and behavior of glial tumors.

In conclusion, this study suggests that SOX9 may act as promoting gene that participates in the progression and aggressiveness of clear cell RCC. However, SOX6 may act as tumor suppressor gene. Both markers may affect a patient's prognosis and survival. Therefore, combined detection of both markers could have a predictive value of patient's outcome.

Additional large-scale studies are to be recommended to deliver more understanding of SOX9 and SOX6 role in carcinogenesis and clinical management of patients with clear cell RCC. Also, involving more SOX family members in these studies to reveal their possible diagnostic and prognostic significance is recommended.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Abbreviations List

LVI	Lympho-vascular invasion
RCC	Renal cell carcinoma
SOX	Sex-determining region Y box

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