



# Clinicopathological Significance of Immunohistochemical Expression of SOX2 Protein in Urothelial Carcinoma of Urinary Bladder in Sample of Iraqi Patients

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## ABSTRACT:

### BACKGROUND:

Bladder carcinoma is the tenth most common carcinoma worldwide. It is one of the most common ten malignancies in Iraq. Sex determining region Y-box 2 (SOX2) is a transcription factor. It plays an essential role in cell fate determination. Aberrant expression of SOX2 has been reported in many types of carcinomas SOX2 expression is said to be associated with tumor progression.

### OBJECTIVE:

To evaluate the prognostic impact of SOX2 immunohistochemical expression in the urothelial carcinoma of the urinary bladder.

### MATERIALS AND METHODS:

This is a retrospective study of fifty patients with urothelial carcinoma of bladder carried out in the Babylon Training Center for Histopathology during the period from December 2022 through December 2023. Two sections from each paraffin embedded tissue block were taken, one for hematoxylin and eosin staining for histopathology revision and the other for immunohistochemistry staining of SOX2.

### RESULTS:

In this study, 78.0% (n=39) showed low SOX2 expression, and 22.0% (n=26) showed 'high' SOX2 expression. A significant association was found between SOX2 expression and tumor stage and muscle invasion status.

### CONCLUSION:

In the current study, we concluded that there was a significant association between SOX2 expression and poor prognostic factors and that SOX2 expression may help detect urothelial carcinoma patients with poor prognostic features.

**KEYWORDS:** SOX2, urothelial carcinoma, immunohistochemistry.

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## INTRODUCTION:

Worldwide, according to the American Institute for Carcinoma Research, bladder carcinoma is the tenth most common carcinoma in the world. It is the sixth most common carcinoma in males and the seventeenth in females. Urothelial carcinoma of the urinary bladder represents 90% of all primary tumours of this organ <sup>(1)</sup>. In Iraq, many cities have suffered from a high incidence of bladder carcinoma, with regional variations among them. This variation has been attributed to many factors, such as societal, economic, and lifestyle differences <sup>(2)</sup>.

Macroscopic findings are variable, ranging from subtle thickening in the bladder wall, to an exophytic growth. Some carcinomas have an endophytic growth pattern <sup>(3,4)</sup>.

Under the microscope, bladder cancer is categorized into two main types: non-invasive and invasive tumours. Non-invasive tumours can be further classified based on their appearance as either flat or papillary. Papillary neoplasms are subdivided into several types including papilloma, inverted papilloma, papillary urothelial neoplasm with low malignant potential, non-invasive low-grade papillary urothelial carcinoma, and non-invasive high-grade papillary urothelial carcinoma. Invasive urothelial carcinoma is categorized into muscle-invasive (MIBC) and non-muscle-invasive (NMIBC). MIBCs are typically aggressive, prone to rapid progression and metastasis, while NMIBCs are less aggressive but have a tendency to recur <sup>(5,6,7,8)</sup>.

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There are different prognostic factors for urothelial carcinoma, like staging, which depends on the depth of spread into the wall and adjacent tissues, whether the carcinoma involves adjacent lymph nodes, and whether the carcinoma has spread to other organs <sup>(9)</sup>. Different types of treatment are available for bladder carcinoma including surgery, along with radiotherapy, chemotherapy, immunotherapy, in addition to Targeted Therapy <sup>(10)</sup>.

The abnormal expression of SOX family transcription factors shows a significant connection with carcinomas. These proteins play crucial roles in embryonic development and are vital for maintaining stem cells in adult tissues. In cancerous conditions, SOX genes frequently experience dysregulation. Consequently, the inappropriate activation of SOX genes becomes a critical factor contributing to the development and advancement of tumours <sup>(11)</sup>.

Abnormal SOX2 expression has been observed in various types of carcinomas. Recent studies indicate that certain anticarcinoma drugs can antagonize bladder carcinoma invasion through the inhibition of SOX2 expression, suggesting an important role of SOX2 in mediating human bladder carcinoma invasion <sup>(12)</sup>.

SOX2 overexpression may play a role in prognosis, as it is often found at elevated levels in tumours with lower degrees of differentiation <sup>13</sup>. SOX2 expression is more frequent in MIBC and high-grade NMIBC as compared to low-grade NMIBC. Patients with low SOX2 expression tend to have a higher recurrence-free survival rate than those with high SOX2 expression <sup>(11)</sup>.

The aim of the current study is to evaluate the prognostic impact of SOX2 immunohistochemical expression in urothelial carcinoma of the urinary bladder in a sample of Iraqi patients.

### MATERIALS AND METHODS:

#### Study design and patient characteristics

This retrospective cross-sectional study was carried out in the Babylon Training Center for Histopathology. The study group comprises formalin-fixed paraffin-embedded tissue blocks collected from the archives of Hillah teaching hospital at Hillah city in Iraq during the period from December 2022 through December 2023, including 50 transurethral resection specimens diagnosed with urothelial carcinoma of the bladder. The patient's information, such as age and sex, was retrieved from the archives. Two sections were taken from each block, the first section was stained with hematoxylin and eosin

and the other section was stained immunohistochemistry for SOX2.

#### Histopathological evaluation:

Hematoxylin and eosin-stained sections were prepared and an expert pathologist did the re-evaluation of all the slides to confirm the histopathological diagnosis, tumour staging based on AJCC/UICC TNM, 8<sup>th</sup> edition and tumours grading.

#### SOX2 immunostaining:

Immunohistochemical staining was done according to manufacturer instructions using SOX2 polyclonal antibody by Elabscience/USA. We cut and mount 4-micron formalin-fixed paraffin-embedded tissues on positive charged slides. Antigen Retrieval was done by immersing the sections into Sodium Citrate Antigen Retrieval solution, heating the solution at 95 ° C for about 15 min using microwave oven then cooling the solution to room temperature within 20 minutes then washed the slides with PBS (pH 7.4) for 5 minutes 3 times, after that we eliminate endogenous peroxidase activity by incubating it with (3% H<sub>2</sub>O<sub>2</sub>) for 10 min. Then we added primary antibody (SOX2) with 1:50 dilution ratio, and incubate at 37°C for 1 hour. After which we added (Polyperoxidase-anti-Rabbit IgG), and incubate at 37°C for 20 min. Then incubation of sections with PolyDetector HRP Label for 15 minutes. Later Hematoxylin counterstaining was done by three dip and tissue was dehydrated and mounted with a coverslip. Positive control used was Rat brain as recommended by manufacturer and negative control used was sections treated similarly with the exception of the primary antibody.

#### Immunohistochemical evaluation:

SOX2 immunoreactivity is detected mainly in the nucleus as brown staining and nuclear staining only is considered positive. The staining was evaluated semi-quantitatively for two aspects of parameters including the extent and intensity. Extent was determined as following: 0-1%, 1 – 25 %, 26 – 50 %, 51 – 75%, 76-100 % giving score of 0, 1, 2, 3, 4 correspondingly. The whole slide was scanned and 1000 cell per specimen were counted under 400 power magnification. Percentage expression of SOX2 was evaluated as (number of positive cells/total number of cells (minimum of 1000 cells) in chosen high power fields <sup>(14,15)</sup>. Intensity was subjectively determined as negative, weak, strong and giving score of 0, 1, 2 correspondingly <sup>(16)</sup>. Histological staining score (H-score) was calculated by multiplying the staining intensity score by the proportion score resulting in a number 0-8 but we excluded 5 and 7 because there is no net

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result of number 5 and 7 from multiplying process. In this study we considered  $\geq 4$  as high expression and  $< 4$  as low expression<sup>(16)</sup>. Statistical analysis was carried out using SPSS version 27. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as (Means  $\pm$  SD). Student t-test was used to compare means between two groups. Fisher's Exact Test was used to find the association between categorical variables. P-value  $\leq 0.05$  was considered as significant.

### RESULTS:

Fifty cases of bladder urothelial carcinoma were studied (Table1), the expression of SOX2 was mainly in the nucleus of tumour cells.

More than one third of patients (38.0%) presented with age group (60-69 years). Mean age of patients was (63.70  $\pm$  12.79) years with older patient was 100 years and younger patient was 36 years. Regarding distribution of patients according to sex, the majority of patients (N=34, 68.0%) were male patients and only 16 (32.0%) were female patients. Regarding distribution of patients according to muscle invasion, muscle invasion was positive in only 10 patients (20.0%) of total study patient. Majority of patients presented with low grade tumour (N=36, 72 %) and only 16 patients (28 %) presented with high grade tumour. Regarding stage of bladder tumour about two third of patients (66.0%) presented with stage (T1), only ten patients (20.0%) presented with stage (T2) and seven patients (14.0%) presented with stage (Ta). All tumours of stage Ta were of low grade, majority of the T1

stage had low grade (81.81%) and majority of stage T2 had high grade (80.0%). Regarding distribution of patients according to Sex determining region Y-box 2 (SOX2). High expression SOX2  $\geq 4$  represent 11 patients (22.0%) with mean score (5.09  $\pm$  1.64) and Low expression SOX2  $< 4$  represent majority of patients (N=39, 78.0%) with mean score (1.64  $\pm$  1.14). Comparison between two groups of patients including (High expression SOX2  $\geq 4$  and Low expression SOX2  $< 4$ ) according to age and sex of patient (Table2), there was no significant difference in mean age between two groups and there was no significant association between SOX2 and sex of patient. About the comparison according to muscle invasion (Table3), among patients with positive muscle invasion that constitute 20% of all patients, (60 %) had high expression of SOX2 and (40 %) showed low expression of SOX2, while in those with negative muscle invasion, (87.5 %) showed low SOX2 expression and (12.5 %) had high SOX2 expression. Regarding the comparison according to grade and stage of tumour (Table 4), among patients with high grade tumours, 6 cases showed high SOX2 expression and 8 cases showed low SOX2 expression, while in low grade tumour, 5 cases had high SOX2 expression and 31 cases had low SOX2 expression. Regarding stage of tumour, there was 10 cases of stage T2, 6 (60%) showed high SOX2 expression. Stage T1 (N=33 cases), there was 29(87.8%) cases that showed low SOX2 expression. Regarding stage Ta (N= 7), 6 cases showed low SOX2 expression (85.7%).

**Table1: Clinicopathological parameters of patients with Bladder urothelial carcinoma**

Variable	Frequency (%)
<b>Age (years)</b>	
< 40 years	4.0%
40-49 years	8.0%
50-59 years	16.0%
60-69 years	38.0%
70-79 years	24.0%
80-89 years	6.0%
90-100 years	4.0%
<b>Sex of the patients</b>	
Male	32%
Female	68%
<b>Muscle invasion state</b>	
Positive	20%
Negative	80%
<b>Grade of tumour</b>	
High	28 %
Low	72 %
<b>Stage of tumour</b>	
Ta	14.0%
T1	66.0%
T2	20.0%

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**Table 2: The comparison between patients with High expression (SOX2  $\geq$  4) and Low expression (SOX2 < 4) according to age and sex of patient (N=50).**

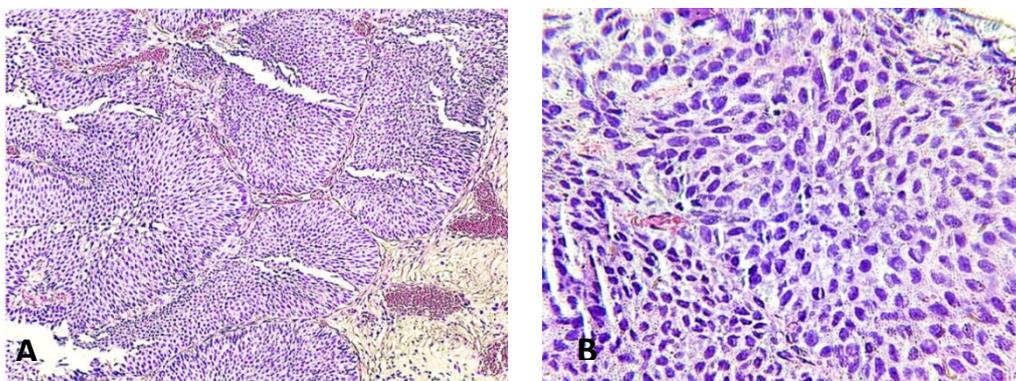
Muscle invasion	Sex determining region Y-box 2 (SOX2)		Total	P-value
	High expression SOX2 $\geq$ 4	Low expression SOX2 < 4		
Positive	6 (60 %)	4 (40 %)	10 (2%)	<b>.001</b>
Negative	5 (12.5 %)	35 (87.5 %)	40 (8%)	
<b>Total</b>	11 (22 %)	39 (78 %)	50 (100%)	

**Table 3: The comparison between patients with High expression (SOX2  $\geq$  4) and Low expression (SOX2 < 4) according to muscle invasion (N=50)**

Study variables	Sex determining region Y-box 2 (SOX2)		Total	P-value
	High expression SOX2 $\geq$ 4	Low expression SOX2 < 4		
Age (years)	(62.27 $\pm$ 11.11)	(64.10 $\pm$ 13.33)	(63.70 $\pm$ 12.79)	<b>0.68</b>
<b>Sex</b>				<b>1.000</b>
Male	8 (23.52 %)	26 (76.47 %)	34 (68 %)	
Female	3 (18.75 %)	13 (81.25 %)	16 (32 %)	
<b>Total</b>	11 (22 %)	39 (78 %)	50 (100 %)	

**Table 4: The comparison between patients with High expression (SOX2  $\geq$  4) and Low expression (SOX2 < 4) according to grade and stage of tumour (N=50).**

Study variables	Sex determining region Y-box 2 (SOX2)		Total	P-value
	High expression SOX2 $\geq$ 4 (N=11)	Low expression SOX2 < 4 (N=39)		
<b>Grade of tumour</b>				<b>0.05</b>
High grade	6 (42.85 %)	8 (57.14 %)	14 (100 %)	
Low grade	5 (13.88 %)	31 (86.11 %)	36 (100 %)	
<b>Total</b>	11 (22 %)	39 (78 %)	50 (100 %)	
<b>Stage of tumour</b>				<b>0.01</b>
Ta	1 (14.28%)	6 (85.71%)	7 (100%)	
T1	4 (12.12%)	29 (87.87%)	33 (100 %)	
T2	6 (60%)	4 (40%)	10 (100 %)	
<b>Total</b>	11 (22%)	39 (78%)	50 (100 %)	



**Figure 1: Urothelial carcinoma, Low grade, Stage T1, H&E stain, A at (100), B at (400) power.**

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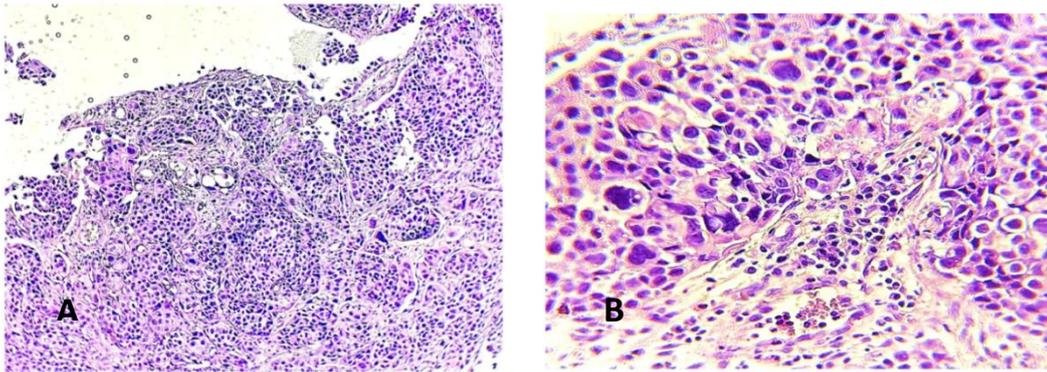


Figure 2 :Urothelial carcinoma, High grade, Stage T1, H&E stain, A at (100) and B at (400) power.

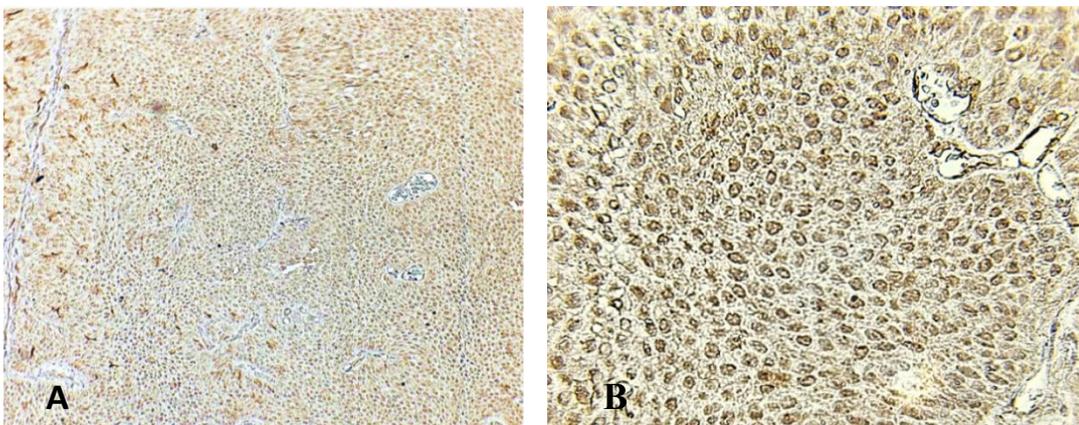


Figure 3 :Urothelial carcinoma, Low grade, Stage T1, showing Low SOX2 expression, A at (100) and B at (400).

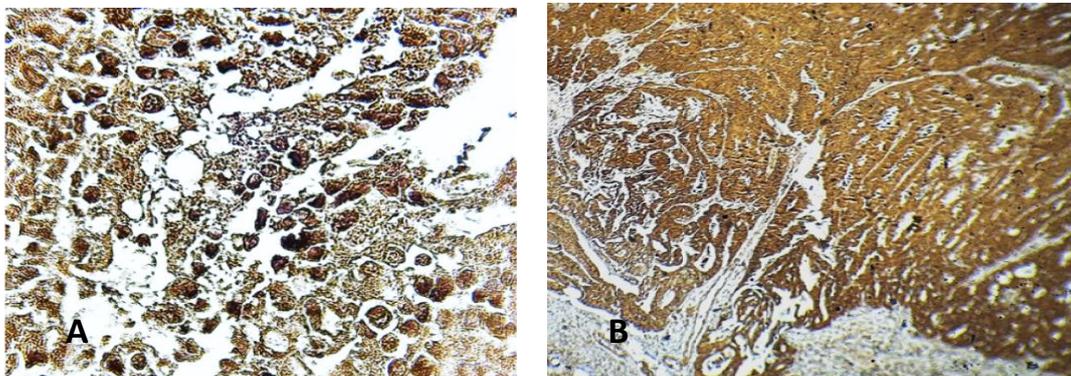


Figure 4 :Urothelial carcinoma, High grade, Stage T1, showing High SOX2 expression A at (40) and B at (400) power.

### DISCUSSION:

The urothelial carcinoma is considered one of the most common carcinomas in the world and has a significant impact on public health <sup>(17,18)</sup>. Tumour grade and stage, along with the state of the muscle invasion, are among the most important prognostic factors <sup>(13)</sup>. Many previous studies demonstrated a type of cell in tumours that has the properties of stem cells, known as carcinoma

stem cells. These were identified in prostate carcinoma, breast carcinoma, colorectal carcinoma, and others <sup>(19)</sup>. They were considered to play a role in tumour development and its progression, along with its role in treatment failure. Cancer stem cells (CSCs) were found to play an important role in the recurrence and metastasis of urothelial carcinoma. For their

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significant role in tumour behavior, they can be considered as perfect target for therapy<sup>(17)</sup>.

Aberrant SOX2 expression has been reported in many previous studies involving carcinomas in different organs being expressed in CSCs and so associated with their presence. These studies correlated SOX2 expression with tumour progression, some were significantly associated with tumour progression while others were not<sup>(20-25)</sup>.

In our study, we reviewed 50 cases diagnosed with urothelial carcinoma, graded according to WHO classification and staged according to AJCC/ISUP, considering clinical parameters (age and sex) and histopathological (grade, stage, muscle invasion status) parameters and correlating them with SOX2 expression.

In our study, we found a primarily nuclear localization of SOX2 expression. Regarding age of the patients, 38% were in age group 60-69 years. Regarding the sex of patients 68% were male and 32% were females. The current study found that there was no correlation between the age and sex of patients with SOX2 expression with a p value 0.68 and 1.00 respectively. It seems possible that these results are due to the fact that SOX2 expression is correlated with the aggressive behavior of the tumour, which may present at any age or sex, although it is known to be more common in older patients than younger patients and in women than men. These results match those observed in earlier studies by Gayyed et al.<sup>(107)</sup> and Fekry et al.<sup>(17)</sup>.

Regarding tumour grade, 72% (N=36) of neoplasms were low grade neoplasms, and 86.11% (N= 31) out of them showed low SOX2 expression. Among high grade cases (N=14), 8 (57.14%) of them had low SOX2 expression and 6 (42.85%) had high SOX2 expression and the study's results indicate no correlation between SOX2 expression and tumour grade, with a p-value of 0.05. These findings are not in agreement with those obtained by Gayyed et al.<sup>(13)</sup>, Fekry et al.<sup>(17)</sup> and Migita et al.<sup>(26)</sup> in their studies who indicated a relation between high SOX2 expression and loss of differentiation in tumours. However, this is consistent with what Amer et al. found in their study<sup>(27)</sup>.

Regarding the stage of the tumour, an important prognostic factor in UC, 66% were stage T1 invading through lamina propria among which 29 neoplasm (87.87%) had low SOX2 expression. Among stage Ta (N=7) majority had low SOX2 expression (85.71%) and among the stage T2 neoplasms (N=10), 6 of them (60%) had high SOX2 expression. The results of this study did show that there was a significant

association between tumour stage and SOX2 expression with a p-value of 0.01. These results confirm the association between more aggressive tumours and SOX2 expression, and this was consistent with Gayyed et al.<sup>13</sup>, Fekry et al.<sup>(17)</sup>, Migita et al.<sup>(26)</sup> and Basma Amer et al.<sup>(27)</sup>.

Besides tumour stage, considering grouping tumours into MIBC and NMIBC, 40 out of 50 cases did not show muscle invasion (which include as obvious stage Ta and stage T1) and majority of them (N= 35, 87.5%) had low SOX2 expression, with p value of 0.001, indicating a significant association between SOX2 expression and muscle invasion. These results further support the idea of high SOX2 expression association as compared to non-muscle invasive tumours, a finding that was consistent with what Basma Amer et al.<sup>(27)</sup>, Fekry et al.<sup>(17)</sup>, Gayyed et al.<sup>(13)</sup> reported in their studies.

### CONCLUSION:

1. In our study, we concluded that there was a significant association between SOX2 expression and important prognostic factors for urothelial carcinoma. SOX2 high expression was associated a higher stage carcinoma and with muscle invasion.

2. Our results suggest that SOX2 expression may help to detect urothelial carcinoma patients with poor prognostic features.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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