Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2022.119795.2468 Volume 30, Issue 1.2, February 2024, Supplement Issue
Manuscript ID ZUMJ-2202-2468 (R1)
DOI 10.21608/ZUMJ.2022.119795.2468

ORIGINAL ARTICLE

Immunohistochemical Sox2 expression in lung squamous cell carcinoma and adenocarcinoma stage III-IV

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Submit Date 2022-02-02
Revise Date 2022-02-19
Accept Date 2022-02-28

ABSTRACT

Sox2 has been related to cell cycle regulation, stemness and cancer development. It has gained noticeable importance due to its expression in malignancies at different sites including lung cancer. In a trial to improve the unfavorable prognosis of patients suffering from lung cancer especially those with non-small cell lung cancer (NSCLC), this study targets the possible underlying mechanisms of Sox2 in cases of NSCLC using the immunohistochemical expression of Sox2. Forty patients of NSCLC, 18 squamous cell carcinomas (SCC) and 22 adenocarcinomas (AC), were enrolled and evaluated for Sox2 expression. Sox2 was positive in 78% of SCC, and 45.5% of AC. A significant increase of positive Sox2 expression was found in SCC (p=0.04), tumor stage IV (p=0.04) and lower tumor grades (p=0.02). The relation between Sox2 expression and tumor grade and stage in SCC against AC cases showed that positive expression was associated with higher stage and lower grades (p=0.04 for both). The correlation between Sox2 scores and tumor stage and grade among the studied cases showed that Sox2 scores was positively correlated stage (r=0.37, p=0.02) and negatively correlated with tumor grades (r= -0.40, p=0.01). Sox2 positivity points to higher stages and its negativity points to higher grade differentiation, so it could be considered poor prognostic factor. Sox2 has direct role in lung cancer development and its knockdown might be beneficial in overcoming therapeutic resistance.

Keywords: Sox2, Non-small cell lung cancer, squamous cell carcinoma, adenocarcinoma, immunohistochemistry.

INTRODUCTION

Lung cancer constitutes the second cause of cancer for both sexes after prostate for men and breast for women; It is the most common cause of cancer related deaths in men aged above 40 years and women aged above 60 years, causing far more deaths than prostate cancer and breast cancer. It includes broadly two categories; small cell lung cancer (SCLC) comprising 15% and non-small cell lung cancer (NSCLC) which accounts for most cases of lung cancers (85%). [1] Four types of NSCLC can be classified according to their histopathology: adenocarcinoma (AC), squamous cell carcinoma (SCC), the two most common subtypes of NSCLC, large cell carcinoma and undifferentiated carcinoma. Unfortunately, only 15% of cases with NSCLC can achieve 5 years survival.[2] Poor prognosis and limited therapeutic opportunities characterize SCC.[3]

Understanding the corresponding mechanisms for NSCLC evolution and progression beside reaching new therapeutic strategies is the way to improve and overcome the poor outcome and resistant cases of NSCLC for treatment. SCC originates from the basal cells of central airways, while the origin of ACs is the secretory epithelium. [2] Sox2 participates in regulation of cell cycle, DNA repair, and neuronal stem cell renewal. [4,5] Also, it has been associated with carcinogenesis, preservation of stem cell-like cells in cancers, and resistant chemotherapy.[6-8]

Sox2 is abnormally expressed in several cancers, including oesophageal, gastric, and colonic carcinoma. [9,10] Also Sox2 is detected in lung cancer,

either SCLC or NSCLC. [11-13] In lung SCC, Sox2 copy is amplified in 70-80% of the cases. [14-16] Interestingly, it was detected in normal bronchial epithelium and premalignant lesions as starting from squamous dysplasia up to carcinoma in situ. [17] Also amplified Sox2 was reported in high grade lesions in contrast to low grade bronchial lesions. [18] Furthermore, it has not been found in the alveolar lining cells or atypical adenomatous hyperplasia, an adenocarcinoma precursor.[17] Higher expression in SCC was noticed when compared with AC.[19]

In various studies, the prognostic significance of Sox2 has been considered. High expression was associated with invasiveness and poor outcome. [9,10] Sox2 has been shown to be related to shorter time-to-progression and overall survival in cases of stage I lung ACs suggesting it is a poor prognostic indicator [20], while in SCC, Sox2 overexpression has been related to better outcome. [16,21]

In different studies, a link has been demonstrated between Sox2 expression and treatment resistance in lung cancer. Chou et al found that tumor cells expressing Sox2 showed paclitaxel and cisplatin resistance. [22] Adjuvant treatment with rapamycin, which suppresses the mTOR pathway and blocks the expression of Sox2, increase cisplatin sensitivity in treatment of lung cancer patients. [23] Also, apart from lung cancer, knocking down of Sox2 raised paclitaxel sensitivity and suppressed the invasiveness of cancer stem cells in breast cancer [24], and abolished the resistance to tamoxifen in breast cancer cells with a stem cell-like phenotype. [25]

This work aims to evaluate Sox2 protein expression in cases of NSCLC considering the correlation of its expression with the clinicopathological criteria of the included cases hoping to reach the link between Sox2 and the patients' outcome of NSCLC.

PATIENTS AND METHOD

This cross-sectional study was performed in pathology department, Zagazig university, Egypt in the period (2020-2022). The study group included 40 cases of NSCLC stage III-IV [26], 18 cases of SCC and 22 cases of ACs, those who received neoadjuvant chemotherapy were excluded. Core biopsies were obtained from patients with peripheral tumors using computed tomography-guided transthoracic technique, while those with central lesions underwent bronchoscopy.

Forty core biopsies were prepared for paraffin-blocks. Four to five µm tissue sections were cut from blocks for traditional hematoxylin and eosin stain for setting diagnosis and immunohistochemistry for Sox2 evaluation.

Written informed consents were obtained from all participants. The study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was performed according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for human studies.

Sox2 immunohistochemistry and evaluation

Sections from paraffin-blocks were subjected to xylene and followed by alcohol for dehydration. Blockage of endogenous peroxidase with 0.3% hydrogen peroxide was carried out in absolute methanol. After that, treatment with using Dako target retrieval solution (pH 6.0) were performed for antigen retrieval and incubation for 10 min in microwave was done. The slides were incubated overnight at room temperature using Sox2 antibody (mouse monoclonal antibody; MC0299, dilution 1:50, Medaysis, California, USA), then slides were washed with phosphate buffered saline, followed by using the secondary antibody for 15 min at room temperature, and then rinsed in the buffer again. Usage of 3, 3-diaminobenzidine (DAB, Sigma-Aldrich, MO, USA) as a chromogen was completed and then counterstained with Mayer's hematoxylin.

Four scores was considered for Sox2 evaluation (1-4) according to the extent of nuclear staining of tumor cells, as score 1 for less than <5%; 2 if 5-25% of tumor cells were stained; 3 if 25-50% showed positivity and 4, for more than 50% of positive tumor cells. Score 1 was considered negative, while score 2 or more was positive. [20]

STATISTICAL ANALYSIS

The data were computerized, then SPSS program (Statistical Package for Social Science) version 18.0 was used for statistical analysis. Qualitative data were displayed in frequencies and relative percentages. The difference between qualitative variables were calculated by Chi-square test, and Fisher's exact test was used to calculate the difference when one or more of the studied cells were <5. Quantitative data were expressed as mean ± SD. The significance level was set as p value of >0.05 is non- significant, while p value of < 0.05 is significant, and < 0.01 is considered to indicate highly significant results.

RESULTS

Patients' characteristics

The patients' age included in this study ranged from 35 to 77 with mean age 63.4±9.96 ±SD. Male

patients comprised 70% (28/40) of the studied case. The grading of SCC revealed 3 well differentiated, 7 moderately differentiated, and 8 poorly differentiated. The grading of AC revealed 2 well differentiated, 8 moderately differentiated, and 12 poorly differentiated. Staging of NSCLC included 25 stage III, 15 stage IV. Lymphocytic infiltration of tumors was classified into 23 cases with mild infiltrate, 9 cases with moderate infiltrate and 8 cases with severe infiltrate. **(Table 1)**

Interpretation of Sox2 immunohistochemistry:

Sox2 expression was negative (score 1) in 40% of the cases and positive (score 2-4) in 60% of the cases with score 4 the most common positive score (32.5%). It was expressed as a nuclear stain normally in the bronchial epithelium adjacent to the tumors in a patchy appearance **(figure 1)**. Also, Sox2 was expressed with different scores in 14/18 (78%) of SCC, and 10/22 (45.5%) of AC with a statistically significant increase (p=0.04) in SCC **(figure 2)**. Male patients showed positive expression in 60.7% compared with 58.3% in females. Regarding stage, Sox2 was expressed in 12/15 of stage IV (80%), while in 12/25 of stage III (48%) with statistically significant increase (p=0.04). Expression in relation to tumor grade revealed that positive expression was found in all well differentiated tumors, 73% of moderately differentiated tumors and only 40% of poorly differentiated tumors concluding that negative Sox2 expression was significantly associated with higher grades (p=0.02). Positive Sox2 was found in 56.5%, 66.7%, and 62.5% of cases with mild, moderate, and severe tumor lymphocytic infiltrate, respectively. There were no statistically significant associations between Sox2 expression and age, sex, tumor lymphocytic infiltrate (p=0.28, 0.89,0.86, respectively) **(Table 2)**.

Positive Sox2 expression showed no significant increase among AC cases regarding stage (p=0.45) or grade (p=0.20), as 40% and 57.1% were positive in stage III and IV, respectively and 100%, 50% and 33.1% showed Sox2 positivity in well-differentiated, moderately differentiated and poorly differentiated ACs. There was a statistically significant increase in positive Sox2 expression among stage IV SCC (p=0.04). However, negative Sox2 expression was significantly associated with higher grade of SCC cases (p=0.04) **(Table 3)**. A statistically significant positive correlation between Sox2 scores and stages was found among the studied cases (r=0.37, p=0.02). Also, there was a statistically significant negative correlation between Sox2 scores and tumor grades among the studied cases (r= -0.40, p=0.01) **(Table 4)**.

Table (1): Basic characteristic of the studied cases

Variable		**(*n*=40)**	
Age:	*Mean ± SD* *Range*	63.4±9.96 35-77	
		N	**%**
Sex	*Male* *Female*	28 12	70 30
Histopathological type	*Adenocarcinoma* *Squamous cell carcinoma*	22 18	55 45
Tumor Lymphocytic Infiltrate	*Mild* *Moderate* *Severe*	23 9 8	57.5 22.5 20
Stage	*III* *IV*	25 15	62.5 37.5
Grade	*Well differentiated* *Moderately differentiated* *Poorly differentiated*	5 15 20	12.5 37.5 50
Sox2 expression	*Negative* *Positive*	16 24	40 60
Sox2 Scores	*1* *2* *3* *4*	16 6 5 13	40 15 12.5 32.5

Sd: Standard deviation, n: number

Table (2): Relation between Sox2 expression and clinicopathological parameters

Variable		**Sox2 negative (*n*=16)**		**Sox2 positive (n=24)**		**t**	**P**
Age	*Mean ± SD* *Range*	65.5±11.26 40-77		62±8.97 35-75		1.09	0.28 NS
Variable		**N**	**%**	**N**	**%**	**χ^2**	**P**
Sex	*Male* *Female*	5 11	41.7 39.3	7 17	58.3 60.7	0.02	0.89 NS
Histopathological type	*Adenocarcinoma* *Squamous cell carcinoma*	12 4	54.5 22.2	10 14	45.5 77.8	**4.31**	**0.04***
Tumor Lymphocytic Infiltrate	*Mild* *Moderate* *Severe*	10 3 3	43.5 33.3 37.5	13 6 5	56.5 66.7 62.5	0.30	0.86 NS
Stage	*III* *IV*	13 3	52 20	12 12	48 80	**4**	**0.04***
Grade	*Well differentiated* *Moderately differentiated* *Poorly differentiated*	0 4 12	0 26.7 60	5 11 8	100 73.3 40	**7.78**	**0.02***

Sd: Standard deviation t: Independent t test χ^2: Chi square test,
NS: non-significant (P>0.05), *: Significant (P<0.05)

Table (3): Relation between Sox2 expression and tumor grade and stage in both AC and SCC

Variable		**AC**				**P**	**SSC**				**P**
		Sox2 negative (*n*=12)		**Sox2 positive (n=10)**			**Sox2 negative (*n*=4)**		**Sox2 positive (n=14)**		
		N	**%**	**N**	**%**		**N**	**%**	**N**	**%**	
Stage	*III* *IV*	9 3	60 42.9	6 4	40 57.1	0.45 NS	4 0	40 0	6 8	60 100	**0.04***
Grade	*Well differentiated* *Moderately differentiated* *Poorly differentiated*	0 4 8	0 50 66.7	2 4 4	100 50 33.3	0.20 NS	0 0 4	0 0 50	3 7 4	100 100 50	**0.04***

AC: Adenocarcinoma, SCC: Squamous cell carcinoma
χ^2: Chi square test NS: non-significant (P>0.05) *: Significant (P<0.05)

Table (4): Correlation between Sox2 scores (score 1-4) and tumor stage and grade among all studied cases (n=40):

Variable	**Sox2 scores (n=40)**	
	r	**P**
Stage	**0.37**	**0.02***
Grade	**-0.40**	**0.01***

r: Spearman's correlation coefficient *: Significant (P<0.05)

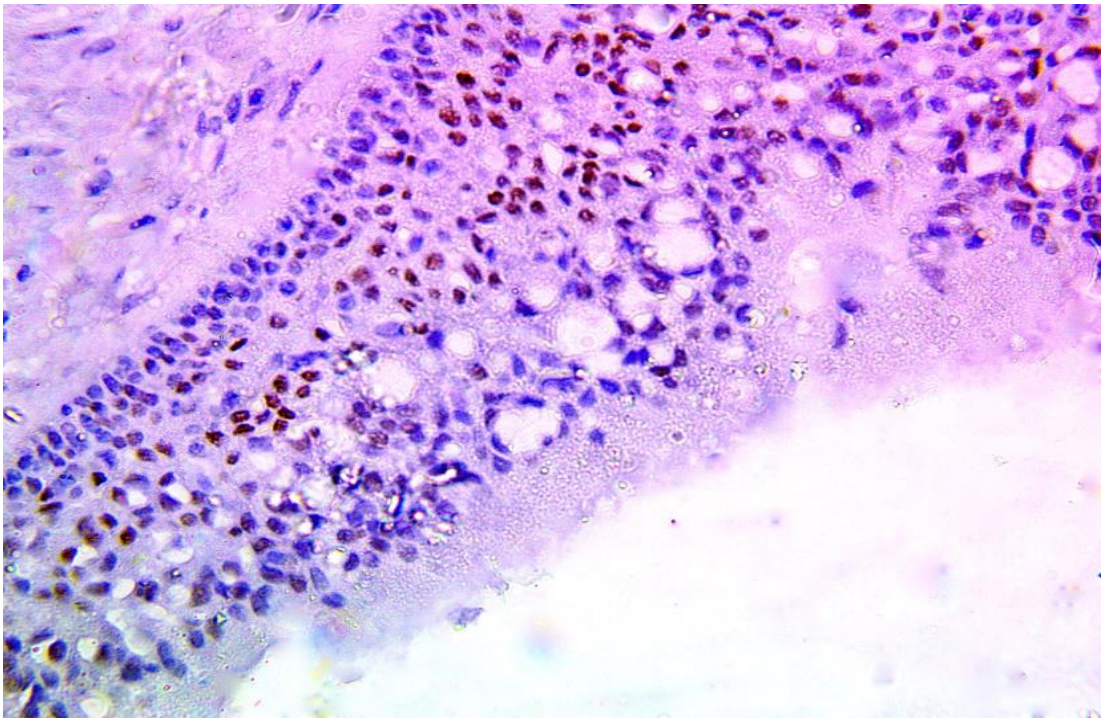

Figure 1: Nuclear Sox2 expression in normal bronchial epithelium (score 2). (IHC, x400).

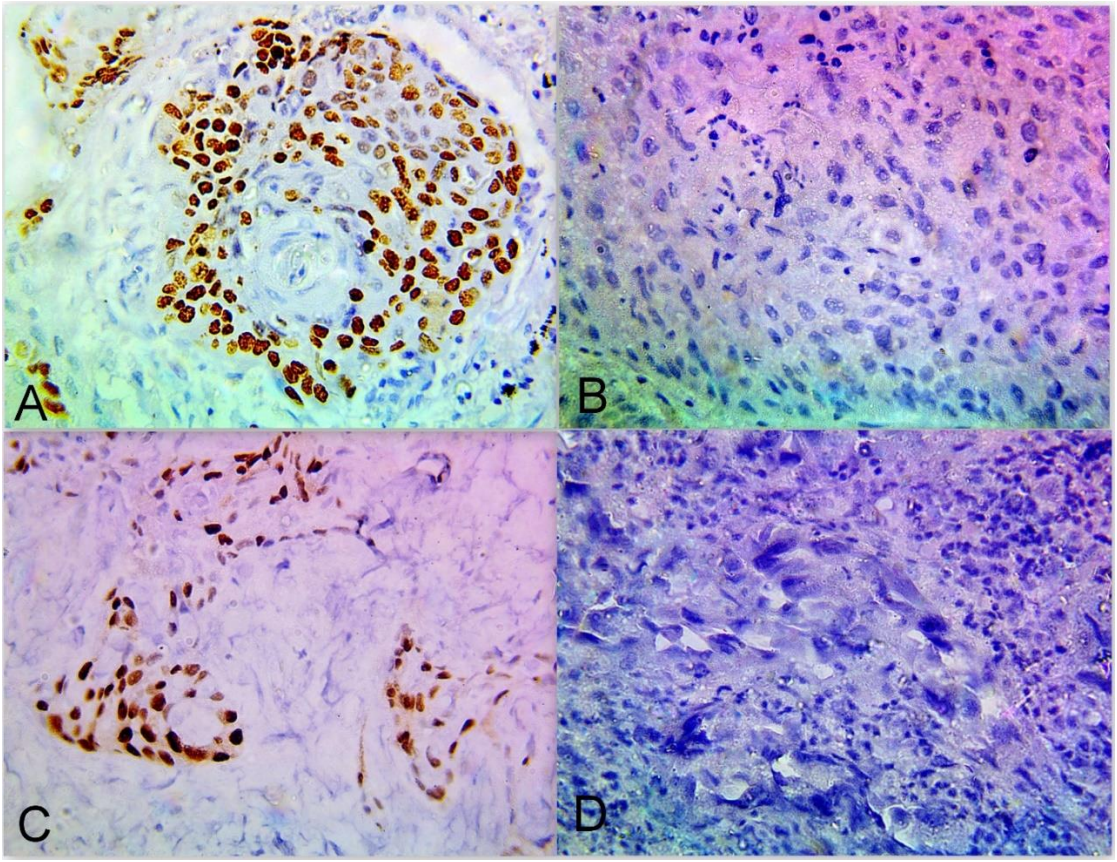

Figure 2: A) and C) Diffuse nuclear Sox2 expression in well- differentiated SCC and moderately differentiated AC, respectively (score 4). B) and D) Negative nuclear Sox2 expression (score 1) in poorly differentiated SCC and AC, respectively. (IHC, x400).

DISCUSSION

The short rate of patients' survival experiencing NSCLC and the high incidence of non-responding cases for therapeutic trials are crucial points that move researchers to find out new explanations for the pathogenesis and advancement of that resistant cancer. This study hypothesized that Sox2 could be in close relation to the initiation and aggressiveness of NSCLC course. So, an applicable easy technique was used to observe this relation, which is Sox2 immunohistochemical expression.

Sox2 was expressed in both SCC and AC, but closely related to squamous differentiation, as we found significant Sox2 expression in SCC compared to AC. Our results agree with Karachaliou et al who concluded that Sox2 has a significant role in lung cancer, being frequently expressed and or amplified in SCC and to lesser extent in SCLC and rarely in AC. [27] It was evidently overexpressed in SCC (91%); however, it was only found in 21% of AC.[28] Also, other studies showed evident Sox2 expression in SCC, as Ying et 2016 reported that 50% of SCC and only 20% of ACs expressed Sox2 showing a significant correlation between Sox2 expression and histological type which agreed also with Sasaki et al [12,19]. Going with previous results, Wilbertz et al concluded that Sox2 expression was significantly correlated with amplified Sox2 in cases of SCC.[21] However, Tenjin et al showed various expression, as they found that Sox2 was markedly expressed with closely results in different types of lung cancers as 90% of SCLC, 80% of SCC and 70% of ACs. [13] The squamous differentiation in organs other than lung, has been closely related to Sox2 as Sox2 gene is amplified and expressed by immunohistochemical staining in some carcinomas of squamous cell origin as in SCC of esophagus and lung, which is emphasized by negative Sox2 in most cases of lung ACs. [14,15]

Relations with other clinicopathological parameters were studied by different studies. Sox2 showed no significant results neither regarding age nor gender in the encountered cases, however, the lower grade of SCC and AC cases was associated with positive Sox2 which goes with Velcheti et al who stated that in ACs, Sox2 was more common in lower grades [29]. This may refer to Sox2 contribution to initiation of tumorigenesis and its fading in higher grades might interpret progression. Sasaki et al found that Sox2 gene copy had significant correlations with male gender and smoking habit and Sholl et al concluded that there were significant correlations with male gender and older, age group, but not with smoking. [19,20]

Different types of lung cancer have been correlated with Sox2 expression with no consensus on its prognostic value. Sox2 was associated with higher stages and lower grades. Our results have been compared with other studies to understand the possible prognostic role of Sox2. Some studies have considered Sox2 as a poor indicator of prognosis in NSCLC [22] as it was correlated with advanced stages and lower overall survival. But also, Sox2 has been identified as a good prognostic factor by Velcheti et al as they found that higher Sox2 expression was significantly related to longer survival in cases of NSCLC [29] and with small sized-tumors, lower lymphovascular involvement and prolonged overall survival in in SCC cases [21]. These controversial results need more work to establish the role and the significance of Sox2 in lung carcinogenesis.

CONCLUSION

Sox2 is expressed in NSCLC, significantly associated with SCC compared to AC. It has significant associations with stage and grade. Further work focusing on Sox2 role in lung carcinogenesis and patients' survival, and its therapeutic importance might contribute to improvement of the clinical outcomes of lung cancer patients, especially NSCLC.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

RECOMMENDATIONS

Performing more research including all types of lung cancer for more accurate monitoring of Sox2 role in lung carcinogenesis and by using different methods of evaluation as molecular tests for Sox2 and experimental studies of Sox2 knockdown to assess its therapeutic role. Also, evaluation of Sox2 relation with overall survival and disease-free survival of NSCLC patients.

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To cite:
said, N. Immunohistochemical Sox2 expression in lung squamous cell carcinoma and adenocarcinoma stage III-IV. *Zagazig University Medical Journal*, 2024; (114-120): -. doi: 10.21608/zumj.2022.119795.2468