BULLETIN OF STOMATOLOGY AND MAXILLOFACIAL SURGERY
Volume 21, Issue 9

DOI: 10.58240/1829006X-2025.21.9-260

ORIGINAL ARTICALE

EVALUATION OF SURVIVIN AS A POTENTIAL BIOMARKER IN IRAQI PATIENTS WITH SUPERFICIAL TRANSITIONAL CELL CARCINOMA OF THE BLADDER

Noor M. Abdulkader[1*], Rawaa H. Ali[1], Mohammed B. Ismail[2]
[1] Department of Biochemistry, College of Medicine, University of Baghdad, Baghdad, Iraq.
[2] Department of Surgery, College of Medicine, University of Baghdad, Baghdad, Iraq.
Corresponding author contact:
***Corresponding Author** Noor M. Abdulkader Department of Biochemistry, College of Medicine, University of Baghdad, Baghdad, Iraq. Mobile: 009647700117215 Email: Noor.Abd2400m@comed.uobaghdad.edu.iq
Received: *Aug 7. 2025;* ***Accepted:*** *Aug 28, 2025;* ***Published:*** *Oct. 6, 2025*

Background: Survivin non-invasive tumor marker is an inhibitor of apoptosis protein (IAP) is abundantly expressed in the embryonic tissues and highly expressed in cancer cells, including bladder cancer. Bladder cancer is a prevalent malignancy worldwide, especially in men. Non-muscle invasive bladder cancer (NMIBC) constitutes the majority of newly diagnosed cases and poses challenges due to its high recurrence rate. There is an urgent need for reliable biomarkers that can aid in early detection and monitoring.
Objectives: This study aims to evaluate serum Survivin as a diagnostic biomarker for superficial bladder cancer (SBC).
Materials and Methods: A case-control study was conducted involving 120 participants (60 SBC patients and 60 age- and sex-matched healthy controls). Serum levels of Survivin were measured using ELISA. Statistical analysis included t-tests, Pearson correlation, and ROC curve analysis**.**
Results: Serum levels of Survivin were significantly elevated in SBC patients compared to controls ($p < 0.001$ for most parameters). Survivin showed a strong diagnostic performance at a cut-off value of 588.4 ng/ml with an AUC of 0.901, 85% sensitivity, and 70% specificity. No significant associations were found with age or gender, while higher Survivin levels were observed in non-smokers ($p = 0.03$).
Conclusion: Survivin is a promising non-invasive biomarker for superficial bladder cancer, with strong diagnostic utility. Further multicenter studies are recommended to validate these findings and explore mechanistic links.

Keywords: Biomarker, Bladder cancer, Survivin.

INTRODUCTION

Bladder cancer is one of the most prevalent cancers in the world, especially in men[1]. About 70–80% of initial diagnosis is for non-muscle invasive bladder cancer (NMIBC) [2]. Although often treatable, NMIBC is associated with a high recurrence rate and a significant burden on patients and healthcare systems [3]. Hence, Non-invasive and reliable biomarkers are essential to help in bladder cancer monitoring and early detection [4-5]. Cancer is a leading cause of death worldwide, accounting for over 9.6 million deaths in 2018. Cancer rates are high in countries that are developing [6-7]. Additionally, poor lifestyle choices and political and economic instability are risk factors for cancer [8-9]. Despite the fact that Iraq has had national cancer registries and control programs since 1974, the alarming increase in cancer incidence and fatalities since then is reason for concern [10-11]. According to latest IARC estimates, the top five cancer types that are prevalent in Iraq are colorectal, bladder, lung, breast, and leukaemia [11-12].

Survivin, a member of the inhibitor of apoptosis protein (IAP) family, is undetectable or minimally expressed in normal adult tissues but is highly expressed in embryonic and tumor tissues [13]. Its dual role in inhibiting cell death and regulating mitosis makes it an attractive target for cancer diagnostics and therapeutics [14]. The majority of cancers and embryonic tissues express survivin in high quantities, although normal differentiated cells hardly express it at all. The cell cycle's G2/M phase is when survivin is expressed to support the rapidly dividing cell machinery [15].

During cell division, it facilitates appropriate chromosomal segregation. When survivin is overexpressed in cancer, it may overcome cell cycle checkpoints and allow abnormal transformational cell progression via mitosis [16]. This study aims to evaluate the efficiency of Survivin as a biomarker of bladder cancer.

MATERIALS AND METHODS

120 participants were included in this case-control study: 60 patients with superficial bladder cancer and 60 healthy controls who were matched for age and sex, which conducted at the Biochemistry Department, College of Medicine, University of Baghdad.

Transurethral resection of bladder tumors (TURBT) was used to diagnosis the patients, and histological analysis was then performed.

Blood samples were collected and processed for biochemical testing. Serum survivin levels were measured using enzyme-linked immunosorbent assay (ELISA). Kidney function parameters (urea and creatinine) were assessed using standard autoanalyzer methods.

SPSS version 25 was used for statistical analysis. Chi-square and t-tests were used to compare categorical and numerical variables, respectively. Pearson correlation analysis evaluated associations between variables, and ROC curve analysis determined the diagnostic performance of survivin.

RESULTS

The total sample for the current study was 120 participants, 60 as patients and 60 as controls. Figur 1.

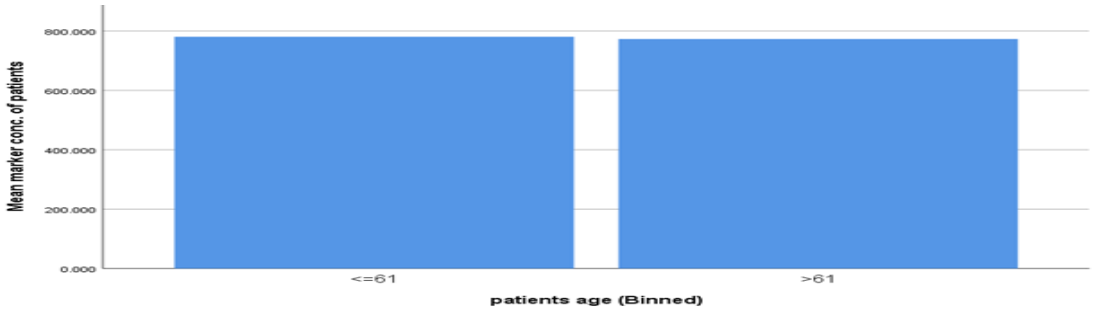

Figure 1. Distribution of Survinin mean according to the patient's age.

Reveals that the most prevalent age was less than or equal (61 years), without any significant statistical difference between patients and controls (p=0.072). Regarding the gender distribution in the studied groups (Figure 2)

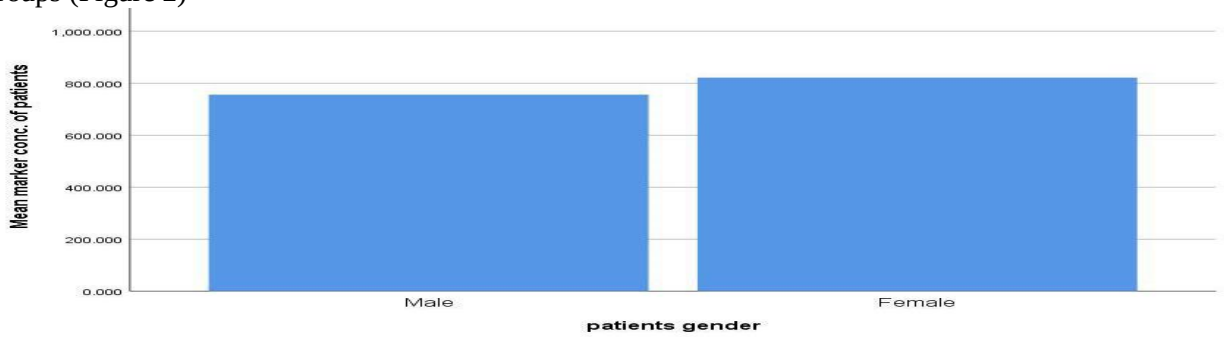

Figure 2. Survivin levels by gender.

Males were more prevalent than females without any significant statistical difference between patients and controls (p=0.556). (45%) of patients and (18%) of controls were smokers without a statistically significant difference (p=0.385), as shown in (Figure 3).

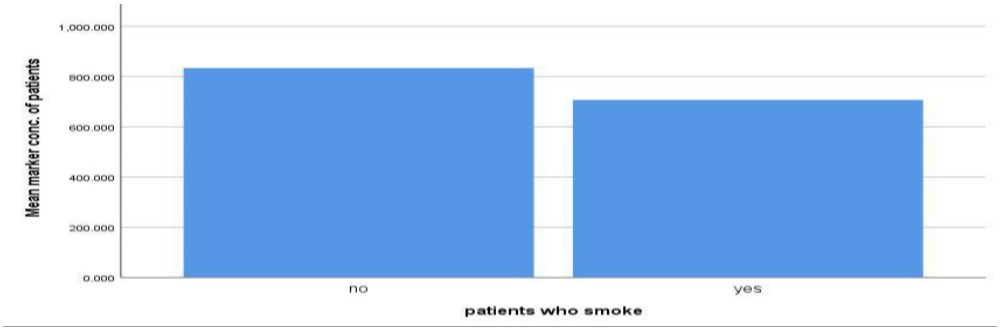

Figure 3. Survivin levels in smokers vs. non-smoker

In regard to Table 1, the mean and (±SD) values of serum creatinine (P<0.001) and blood urea (P=0.018) were significantly different between the patients and controls when the patients' group's values were higher than those of the controls.

Table 1. Comparison of biochemical parameters between the study groups

Biochemical Parameters	Study groups		P-Value*
	Patients Mean ± SD (N=60)	Controls Mean ± SD (N=60)	
S. Urea (20-40) mg/dl	32.72±13.92	27.95±6.66	**0.018***
S. Creatinine (0.7–1.2) mg/dl	0.942±0.291	0.782±0.140	<**0.001***

* Students-test indicates a significant difference between independent means at the (P=0.05) level.

The mean and (±SD) values of S. Survinin in bladder cancer patients and healthy individuals are displayed in Table (2) and figure (4). The findings showed a statistically significant difference (P<0.001) between the mean and (±SD) levels of S. Survinin (776.72±219.48 ng/ml) in patients and controls.

Table 2. The study sample was distributed based on the S. Survinin mean and (±SD) values.

Variables	Study groups		P-Value*
	Patients Mean ± SD (N=60)	Controls Mean ± SD (N=60)	
S. Survinin (ng/ml)	776.72±219.48	422.21±73.10	<**0.001***

* Students-test showing a significant difference between independent means at the (P=0.05) level

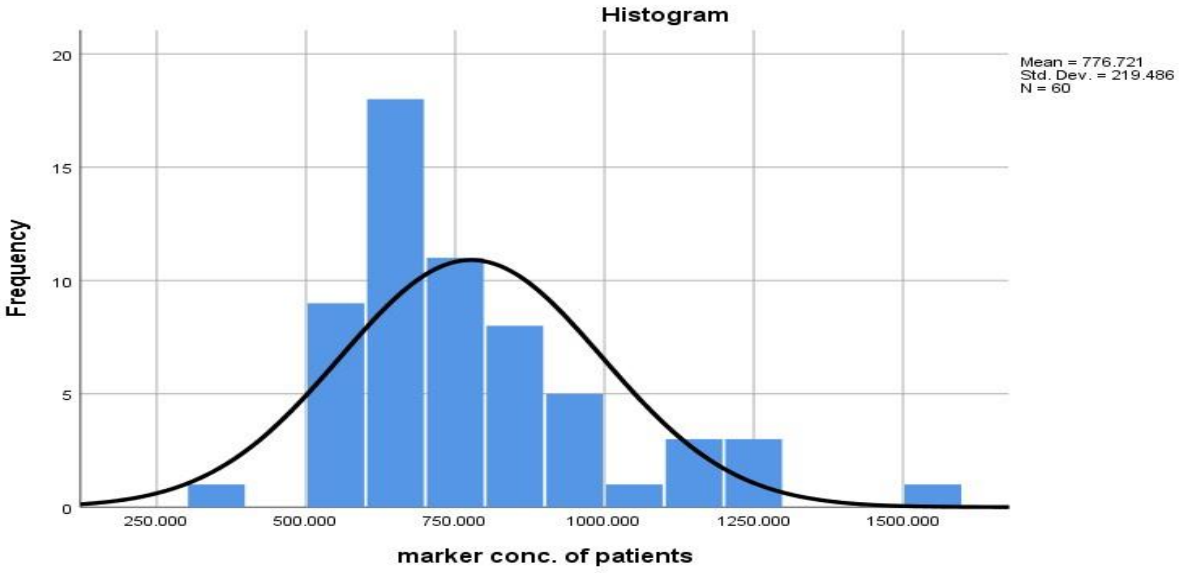

Figure 4. The study sample was distributed based on the mean of Serum Survinin.

The present investigation revealed that patients under the age of 61 had higher mean and (±SD) levels of S. Survinin, with no statistically significant difference (p=0.89). However, there was a significant statistical difference (p=0.03) between the non-smoking patients and smokers in terms of the mean and (±SD) values of S. survinin. according to Table (3).

Table 3. Survivin levels according to age, gender, and smoking status
The mean and Std. Deviation values of survinin in the patients group according to age (<=61,>61), gender (male or female), smoking (Yes, No)

Age	N	Mean ± Std. Deviation	P-value
<=61	31	780.390 ± 177.700	0.89
>61	29	772.798 ± 260.088	
Gender	N	Mean ± Std. Deviation	P-value
Male	45	758.810 ± 195.461	0.27
Female	15	830.452 ± 280.751	
Smoking	N	Mean ± Std. Deviation	P-value
Yes	26	706.877 ± 124.783	**0.03***
No	34	830.130 ± 259.905	

Student's t-test was used to compare the means. A p-value less than 0.05 was considered statistically significant.

The relationship between clinical specificity and sensitivity for each test cut-off is shown graphically by the receiver operator characteristic (ROC) curve. It showed that serum Survinin levels might be used to differentiate between healthy controls and illness patients. Table (4) and Figure (5) list the ideal cut-off values for the diagnosis of disease patients, including AUC, specificity, and sensitivity.

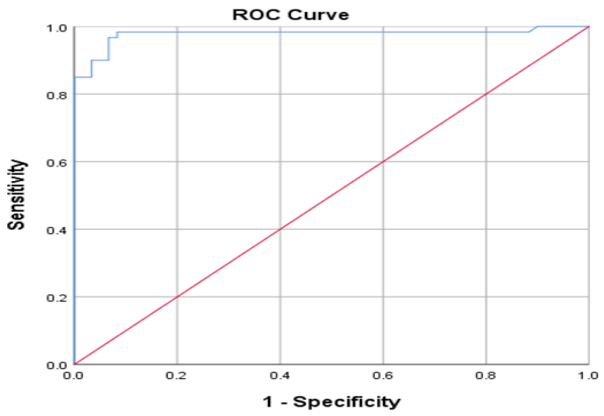

Figure 5. ROC curves for S. Survinin

Table 4. Diagnostic performance of serum survivin in bladder cancer patients
Sensitivity and Specificity, area under the curve (AUC), and Cut-off value for S. Survinin in bladder cancer patients.

Parameter	Sensitivity	Specificity	AUC	Cut-off value
Serum survinin	85%	70%	0.901	588.40

DISCUSSION

The current study evaluated the diagnostic significance of Survivin, an anti-apoptotic protein, in patients with superficial bladder cancer (SBC). Our findings suggest that Survivin holds promise as a sensitive and specific biomarker for early detection of SBC. This aligns with Siragusa et al., 2024 [17] and Albadari & Li, 2023 [14] studies demonstrating that Survivin is overexpressed in various malignancies, including bladder cancer because of its function in encouraging tumor cell mitosis and inhibiting programmed cell death.

In this study, Patients' levels of survivin were noticeably higher than those of healthy controls. With a cutoff value of 588.4 ng/mL, providing 85% sensitivity and 70% specificity. These values underscore its potential as a

clinically useful, non-invasive biomarker for bladder cancer screening and monitoring. The area under the curve (AUC) of 0.901 further confirms its high diagnostic performance. Comparable results have been reported in studies Maas et al., 2023 [18] and Jubber et al., 2023 [19] utilizing urinary and serum Survivin for bladder cancer diagnosis.

Survivin levels were not significantly influenced by age or gender in the patient group [20]. However, non-smokers showed higher Survivin levels compared to smokers, a finding that may initially appear counterintuitive given the well-established link between smoking and bladder cancer. This observation might reflect molecular heterogeneity within bladder tumors or possible compensatory mechanisms among non-smokers that warrant further investigation.

It is important to recognize a number of limitations despite the encouraging outcomes. Generalizability may be impacted by the small sample size and the fact that it was restricted to just one facility in Iraq. Environmental exposures, dietary habits, and genetic predispositions in the studied population could also influence trace element levels and biomarker expression. Furthermore, Survivin's prognostic value and its ability to distinguish between different tumor grades or stages were not addressed in this study and should be investigated in future research.

CONCLUSION

Survivin shows significant elevation in patients with superficial bladder cancer. These biomarkers, particularly survivin, exhibit strong diagnostic potential and may enhance early detection strategies. Integration of these markers into clinical practice could improve diagnosis, prognosis, and treatment monitoring for bladder cancer patients.

DECLARATIONS

Ethical considerations

The research protocol received approval from the Research Ethics Committee at the Department of Biochemistry, College of Medicine, University of Baghdad, Iraq (ethical approval number 100 in 13/11/2024). The research enrolled participants who all provided verbal consent.

Author contributions/CRediT

The research concept and design were contributed by Mohammed B. Ismail and Rawaa H. Ali. Writing the manuscript and collecting the samples: Noor M. Abdulkader. Mohammed B. Ismail and Rawaa H. Ali performed the statistical analysis. All the authors have thoroughly reviewed and given their endorsement to the final version of the manuscript. The authors contributed equally to this work.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Statement on the accessibility of data

The corresponding author can provide the data supporting this study upon reasonable request.

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