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## Research Article

# Evaluation of SATB2 Expression and Its Relationship with Cyclin D1 and βHCG in Colorectal Carcinoma

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**Abstract**

***Background***: Different immunostain markers have improved the early diagnosis of cancer, facilitating early-stage treatment. One of these stains was the special AT-rich sequence-binding protein-2 (SATB2), which serves as a diagnostic marker, and its expression may offer prognostic and predictive insights. ***Objectives***: To evaluate the immunohistochemical expression of SATB2 in colorectal carcinoma cases and its relationship with some clinicopathological parameters and its expression with the expression of each β-hCG and Cyclin D1. ***Methods***: This retrospective case series study examined fifty paraffin-embedded blocks of colorectal carcinoma from October 2024 to August 2025 that were collected from Al-Jamhuri Teaching Hospital and some private laboratories in Mosul City, which had already been studied by immunostains of β-hCG and Cyclin D1. Investigation of SATB2 by immunohistochemistry was done. ***Results***: SATB2 was detected in 54% of the cases, mostly in individuals older than 50 years (88.9%). Grade II differentiation is found in 59.2% of these cases, while depth of invasion at the level of T3 and T4 is 85.1%, and lymphovascular invasion constitutes 62.9%. Expression of negative lymph node involvement was observed in 59.3% of cases, with 48.1% of patients at stage II; among the positive cases of SATB2, 85.1% showed high expression of cyclin D1, while 59.2% showed positive β-hCG expression. ***Conclusions***: SATB2 is expressed in 54% of cases in patients over 50 years old, females, and Grade II. SATB2 is strongly associated with the high expression of cyclin D1 and, to a lesser extent, with β-hCG expression.

***Keywords***: β-HCG, Cyclin-D1, colorectal carcinoma, SATB2.

## تقييم تعبير SATB2 وعلاقته بكل من Cyclin D1 و β-hCG في سرطان القولون والمستقيم

**الخلاصة**

**الخلفية**: شهد التشخيص المبكر للسرطان تطورًا ملحوظًا بفضل استخدام واسمات مناعية نسيجية متعددة، مما ساهم في الوصول إلى العلاج في المراحل المبكرة. ويُعد بروتين الارتباط بالتسلسل الغني بالأدينين–الثايمين 2 (SATB2) أحد هذه الواسمات، إذ يعمل كواسم تشخيصي، كما أن تعبيره قد يوفر دلالات إنذارية وتنبؤية. **الأهداف**: تقييم التعبير المناعي النسيجي لـ SATB2 في حالات سرطان القولون والمستقيم، ودراسة علاقته ببعض المعايير السريرية والمرضية، إضافة إلى علاقته بتعبير كل من β-hCG و Cyclin D1. **الطرائق**: أجريت هذه الدراسة الوصفية الاستعادية على خمسين قالبًا من الأنسجة المحفوظة بالبارافين لسرطان القولون والمستقيم، جُمعت خلال الفترة من تشرين الأول 2024 إلى آب 2025 من مستشفى الجمهوري التعليمي وبعض المختبرات الأهلية في مدينة الموصل. وكانت هذه الحالات قد خضعت سابقًا للدراسة باستخدام الصبغات المناعية لـ β-hCG و Cyclin D1، وتم إجراء التحري عن SATB2 باستخدام تقنية الكيمياء المناعية النسيجية. **النتائج**: ظهر تعبير SATB2 في 54% من الحالات، وكان أغلبها لدى المرضى بعمر أكثر من 50 سنة (88.9%). وُجد أن 59.2% من الحالات الإيجابية كانت من الدرجة النسيجية الثانية(Grade II) ، في حين كان عمق الغزو الورمي عند المستوى T3وT4في 85.1% من الحالات، كما وُجد الغزو اللمفاوي الوعائي في 62.9%. لوحظ أن 59.3% من الحالات الإيجابية لـ SATB2 كانت سالبة لانتشار العقد اللمفاوية، وأن 48.1% منها كانت في المرحلة الثانية من المرض. كما أظهر SATB2 الإيجابي ارتباطًا قويًا مع الارتفاع في تعبير Cyclin D1 (85.1%) ، وارتباطًا أقل مع إيجابية تعبير β-hCGبنسبة 59.2%. **الاستنتاجات**: يُعبَّر عن SATB2 في 54% من حالات سرطان القولون والمستقيم، ويكون أكثر شيوعًا لدى المرضى فوق سن الخمسين، والإناث، والحالات ذات الدرجة النسيجية الثانية. ويرتبط SATB2 ارتباطًا قويًا بارتفاع تعبير Cyclin D1، وبدرجة أقل مع تعبيرβ-hCG، مما يدعم دوره كواسم تشخيصي وإنذاري محتمل في سرطان القولون والمستقيم.

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## INTRODUCTION

Colorectal cancer (CRC) is the second most common cause of cancer-related deaths worldwide and the third most common malignancy in both men and women [1]. The processes behind metastasis and relapses remain poorly understood, although the early events of colorectal carcinoma have been researched quite thoroughly and that early-stage disease treatments have greatly improved over the past few decades [2]. Generally, CRC must be identified using diagnostic panels that include immunohistochemistry (IHC) staining [3]. As a transcription factor, the special AT-rich sequence-binding protein (SATB2) binds to DNA's nuclear matrix attachment region to control transcription and chromatin remodeling [4]. SATB2 exhibits a specific expression pattern, with its distribution limited to a few adult tissue types; in epithelial cells, SATB2

expression is confined to glandular cells in the lower gastrointestinal tract [5]. Additionally, SATB2 is expressed in a subset of neurons in the brain and at lower levels in specific lymphocyte subsets, as well as in testicular and renal tubular cells [6]. SATB2 expression is maintained in CRC and can serve as a diagnostic marker [7]. The idea that SATB2 may offer prognostic and predictive insights stems from the specific and high incidence of SATB2 expression in CRC. SATB2 expression was associated with a positive outcome and the benefit of adjuvant therapy in an incident-case investigation of primary CRC [8]. To evaluate the immunohistochemical expression of SATB2 in colorectal carcinoma cases previously stained by β-hCG and Cyclin D1. This study aims to associate its expression with some clinicopathological parameters (age, gender, degree of differentiation, depth of invasion, lymphovascular invasion, lymph node status, and stage) and assess the relationship between SATB2 and cyclin D1 and β-hCG.

## METHODS

### *Study design and setting*

This retrospective case series study included fifty cases of surgically excised CRC specimens. All cases were previously stained for cyclin D1 and β-hCG and were collected from Al-Jumhori Teaching Hospital and some private laboratories in Mosul City during the period of study from October 2024 to August 2025.

### *Sample selection*

Sections from formalin-fixed paraffin blocks were taken and mounted on slides, then immunostained with SATB2; the expression was evaluated and compared with results of cyclin D1 and β-hCG expression. Some clinicopathological data regarding the age of the patient, gender, grade, depth of invasion, lymphovascular invasion, lymph node status, and pathological stage were retrieved from surgical pathology reports.

### *Sample analysis and scoring*

Immunostaining was performed using the primary antibody against SATB2 (DNA-binding protein, clone EP281, rabbit monoclonal antibody, Vitro Master Diagnostica, Spain). SATB2 expression was evaluated by a NIKON light microscope. Nuclear immunoreactivity was assessed manually and scored in an average of 10 high-power fields of x400 magnification. Only a nuclear staining of SATB2 was considered specific for SATB2 expression patterns, which were categorized into three separate groups: Diffuse: if the tumors either showed a complete expression or only a very focal loss in singular cells. Heterogeneous: if areas with a complete loss of staining were observed. Absent: if the tumors were completely lacking the stain [9]. To minimize the inter-observer variation, all immunostaining slides were evaluated under the microscope, and the expression was scored by two pathologists independently.

### *Ethical considerations*

This study was conducted based on the principles of ethics that have their origin in the Declaration of Helsinki, and it was approved by the Institutional Review Board with a reference number (path 74) on 13/10/2024 to get this approval.

### Data analysis

Statistical analysis was performed by using the Statistical Package for the Social Sciences (SPSS, version 23.0). Descriptive statistics were used to epitomize the data and are represented as frequencies and percentages. The association between SATB2 expression and different clinicopathological parameters was estimated using the chi-square test. and Fisher's exact test was done when appropriate. A *p*-value less than 0.05 was considered statistically significant.

## RESULTS

In this study, 50 cases were collected; regarding the age distribution, it was between 34 and 93 years, with a mean of 60.4 ± 12.7 years. Of them, 40 (80%) cases were over 50 years, and 10 (20%) cases were below 50 years. Females were 30 (60%), and the males were 20 (40%) of the total CRC cases (Table 1). The majority of the cases (32/50), which account for 64%, were Grade II differentiation; Grade I (15/50) was 30%, while Grade III cases (3/50) formed 6% of the total collected cases. Regarding the depth of invasion, T3 was found in the majority of cases, with 34 out of 50 (68%), followed by T4 in 9 out of 50 (18%), T2 in 6 out of 50 (12%), and one case of T1, which accounts for 2% of the total cases. Lymphovascular invasion was positive in 33 cases (66%) and negative in 17 cases (34%). Studying the lymph node involvement, 23 (46% of cases) were positive, while 27 (54% of cases) were negative. Assessing AJCC staging, 6 (12%) cases were on stage I, 21 (42%) cases were on stage II, and 23 (46%) were on stage III. The results of cyclin D1 expression were that 34 (68%) of cases showed high expression and only sixteen cases (32%) showed low expression. About b-hCG expression among 50 cases, 28 of them, accounting for 56%, show positive β-hCG, and 22 of the cases (44%) show negative expression. Fifty cases of CRC stained with SATB2 showed the following results: 27 (54%) were positive, 13 (26%) were negative, and 10 (20%) were heterogeneous. Of the 27 cases with positive SATB2 expression, 24 (88.9%) were equivalent to or older than 50 years, and 3 (11.1%) were younger than 50 years ($p$= 0.13, statistically non-significant). Nineteen cases out of 27 (70.4%) were female with positive expression, 5 (38.5%) were negative, and 6 (60%) were heterogeneous SATB2. Eight of the males (29.6%) were positive, 8 (61.5%)

negative, and 4 (40%) heterogeneous, with $p$= 0.15, which is not statistically significant. In Grade I, Table 1 reveals eleven cases (40.7%) were positive for SATB2, 3 (23.1%) were negative, and 1 (10%) case was heterogeneous.

**Table 1**: Association between the SATB2 Expression and different pathological variables

| Degree of differentiation | SATB2 (+ve) | SATB2 (-ve) | Heterogeneous | *p*-value |
|---|---|---|---|---|
| Grade I | 11(40.7) | 3(23.1) | 1(10) | |
| Grade II | 16 (59.7) | 8(61.5) | 8(80) | 0.15 |
| Grade III | 0(0.0) | 2(15.4) | 1(10) | |
| Total | 27 | 13 | 10 | |
| *Depth of invasion* | | | | |
| T1, T2 | 4(14.8) | 2(15.4) | 1(10) | 0.1 |
| T3, T4 | 23(85.2) | 11(84.6) | 9(90) | |
| Total | 27 | 13 | 10 | |
| *Lymphovascular invasion* | | | | |
| Positive | 17(63) | 8(31.5) | 8(80) | 0.6 |
| Negative | 10(37) | 5(38.5) | 2(20) | |
| Total | 27 | 13 | 10 | |
| *AJCC* | | | | |
| I | 3(11.1) | 2(15.4) | 1(10) | |
| IIA | 12(44.4) | 1(7.7) | 4(40) | |
| IIB | 1(3.7) | 2(15.4) | 1(10) | 0.33 |
| IIIB | 9(33.3) | 7(53.8) | 2(20) | |
| IIIC | 2(7.4) | 1(7.7) | 2(20) | |
| Total | 27 | 13 | 10 | |

Values are presented as frequency and percentage.

In Grade II, 16 (59.2%) cases were positive, 8 (61.5%) cases were negative, and 8 (80%) cases were heterogeneous. In Grade III, 2 (15.4%) cases were negative for SATB2, 1 (10%) was heterogeneous, and there were no cases with positive SATB2 expression ($p$= 0.1). Of the total diffuse SATB2 expression, 4 (14.8%) cases fall in categories T1 and T2, while the remaining 23 (85.1%) cases were within T3 and T4 ($p$= 1.0). Among positive lymphovascular invasion, 17 (62.9%) cases were positive for SATB2 expression, 8 (61.5%) were negative, and 8 (80%) were heterogeneous. In patients with no lymphovascular invasion, 10 (37.07%) cases were positive for SATB2 expression, 5 (38.5%) were negative, and 2 (20%) cases had heterogeneous expression ($p$= 0.6). Among diffuse SATB2 expressions, sixteen cases out of 27 (59.3%) had no lymph node involvement, and 11 out of 27 (40.7%) had N1 or N2 ($p$= 0.4), which is not significant statistically. Among diffuse SATB2 expressions, three cases out of 27 (11.1%) were in stage I, 13 out of 27 (48.1%) were in stage II, and 11 out of 27 (40.7%) were in stage III ($p$= 0.6), which is not significant statistically. Among high cyclin D1 expression, 23 (85.1%) of cases were positive for SATB2 expression, 5 (38.5%) were negative, and 6 (60%) were heterogeneous for SATB2 expression. In patients with low cyclin D1 expression, 4 (14.8%) cases were positive for SATB2 expression, 8 (61.5%) were negative, and 4 (40%) cases were heterogeneous in expression ($p$= 0.01) (Table 2).

**Table 2**: Association of SATB2 with Cyclin D1

| Cyclin D1 | SATB2 (+ve) | SATB2 (-ve) | Heterogenous | *p*-value |
|---|---|---|---|---|
| High | 23(85.1) | 5(38.5) | 6(60) | 0.01 |
| Low | 4(14.8) | 8(61.5) | 4(40) | |
| Total | 27 | 13 | 10 | |

Values are presented as frequency and percentage.

Regarding β-hCG among positive cases, 16 (59.2%) cases were positive for SATB2 expression, 6 (46.1%) were negative, and 6 (60%) cases were heterogeneous for expression. Among negative β-hCG cases, 11 (40.7%) were positive for SATB2 expression, 7 (53.8%) were negative, and 4 (40%) cases were heterogeneous ($p$= 0.7), which is not statistically significant (Table 3).

**Table 3**: Association of SATB2 with β-hCG

| β-hCG | SATB2 (+ve) | SATB2 (-ve) | Heterogenous | Total | *p*-value |
|---|---|---|---|---|---|
| Positive | 16(59.2) | 6(46.1) | 6(60) | 28 | 0.7 |
| Negative | 11(40.7) | 7(53.8) | 4(40) | 22 | |
| Total | 27 | 13 | 10 | 50 | |

Values are presented as frequency and percentage.

## DISCUSSION

Colorectal cancer (CRC) is the second most common cause of cancer-related deaths worldwide and the third most common malignancy in both men and women [1]. More research is done for diagnostic and prognostic purposes; one of them is SATB2, which is a transcription factor called special AT-rich sequence-binding protein 2 that interacts with DNA's nuclear matrix attachment region to control transcription and chromatin remodeling [4]. Loss of SATB2 expression in CRC is associated with metastases and a poor prognosis, suggesting that its loss may contribute to tumor growth [10]. In an incident case study of primary colorectal cancer, its expression was linked to a favorable outcome and the benefits of adjuvant therapy [4]. High SATB2 expression was observed in 54% of the cases studied in this study, which agrees with findings by Suvaitha *et al*. in Geneva and Maxime *et al*. in Germany, which showed percentages of 52.3% and 61.3%, respectively [11,9]. These findings concur with those studies conducted in Iraq by Azeez *et*

*al*. and Al-Omar *et al*., although with higher percentages (78.05% and 70%) [12,13]. Additionally, studies by Zhang *et al*. and Kowalczyk *et al*. conducted in Helsinki revealed values of 80.08% and 96%, respectively [14,4]. These differences in percentages may be due to variations in antibodies or scoring systems [13]. The age distribution in this study was between 34 and 93 years, with a mean of 60 years. However, the majority of cases (88.9%) with positive SATB2 expressions were aged above 50; however, there was no statistically significant relationship between age and high SATB2 expression, which is consistent with Al-Omar *et al*. and Zhang *et al*. [13,14]. Although the older age groups had higher levels of microsatellite, which is opposite to the function of SATB2, because higher MSI indicates more abnormal glandular tissue, which lowers SATB2 levels [15]; however, this explanation is not conclusive, and this high expression may be caused by bias in the data collection regarding the age of the cases in this study. Al-Omar *et al*. [13] and Liu *et al*. in China [16] have shown that there is no relation between the expression and gender; SATB2 was expressed in 70.4% of patients in the current work, with a female predominance and with no significant association. This high expression could be the result of data collection indicating a 2:3 male-to-female ratio. SATB2 was highly expressed in grades I and II, in relation to the degree of differentiation, which is consistent with other studies [4,13,14,17]. Since most of the cases in this study were in grade II, the high positive expressions can be explained by the fact that moderately differentiated CRC still retains normal colonic tissues, and SATB2 is a marker of colorectal differentiation and cell development [5]. Regarding the depth of invasion, a higher percentage of cases (85%) were classified as T3 and T4, which can be explained by the fact that most of the data collected in this study were T3, with only 7 instances classified as T2 and T1 (four of which had positive SATB2 expression). This finding agrees with Zhang *et al*. [14], who found no significant statistical relation, and disagrees with Eldeeb *et al*. [18], who identified a significant association. This discrepancy could be related to differences in the number of cases analyzed and the depth of invasion of the collected data between the studies. Also, not all early stages of CRC showed greater levels of SATB2, which depends on molecular and histological subtypes (whether the tumor has a high MSI level and a mucinous characteristic throughout tumor development) [15]. Although SATB2 positivity is often associated with lower-grade and less aggressive malignancies, it is not limited to tumors without invasion; tumors can express high levels of SATB2 while also showing positive lymphovascular invasion. This phenomenon may be due to tumor heterogeneity; genetic or microenvironmental factors may contribute to vascular invasion in tumor regions that express SATB2 diffusely [19]. SATB2 indicates cellular differentiation rather than invasiveness. Eventually, a well-differentiated tumor may be able to penetrate lymphatic and vascular areas. Hence, it is not necessarily involved in stopping invasion or metastasis, even if it might support the preservation of colorectal cell identity [3]. These results may explain why 60.8% of cases show lymphovascular invasion, which disagrees with a study done by Eldeeb *et al*. in Egypt in 2022 [18] and with Suvaitha *et al*. [11], who show diffuse expression of SATB2 with no lymphovascular invasion and a significant correlation. Lymph node metastasis and tumor differentiation are significant variables that affect a patient's prognosis [20]. In this study, about lymph node involvement, 59.3% of cases show no lymph node invasion, which is consistent with the findings of Eldeeb *et al*. [18] and Al-Omar *et al*. [13], who found a strong relationship between SATB2 and lymph node involvement. This suggests that SATB2 has an inverse relationship with tumor spread and nodal metastases. The expression of β-hCG alone in cases under this study was 56%; 59.2% of them had diffuse expression of SATB2, although β-hCG is considered a poor prognostic immune stain for CRC because it is produced ectopically and shows tumor dedifferentiation and aggressiveness [20]. Even though many studies saw cyclin D1 as a sign of a bad prognosis in patients with colorectal cancer (CRC), mostly because of disruptions in cell cycle control [21,22] 85.1% of positive SATB2 samples had high CNND1 expression; this agrees with the study of Ogino *et al*. in the United States of America (2009) [23]. In colorectal cancer, β-hCG expression was shown to correlate with poor prognosis of patients; it may be a potential marker to predict prognosis, and its expression was positively correlated with the progression of early-stage CRC. Additionally, it can promote the migration and invasion of CRC through epithelial-mesenchymal transition (EMT) [24,25]. Similar expression of two stains may indicate mixed biology that occurs in transitional or heterogeneous tumors when the tumor has started acquiring aggressive potential despite keeping some differentiation (SATB2 positivity) [26]. Also, this agrees with the study of Jun *et al*. in Korea (2023) [27] that shows high expression of cyclin D1 associated with good prognosis. SATB2 indicates that the tumor still resembles the colon epithelial cells, while cyclin D1 indicates the tumor is growing faster; both positive results may indicate the tumor is moderately differentiated but biologically active, as in stage II or III, grade II CRC, as most of the cases in this study were in grade II, which explains that.

## Study Limitations

The study is constrained by the previously collected data and blocks that were stained immunohistochemically by β-hCG and cyclin D1 to find out any relation between them and SATB2. The conflicting results may be attributed to the small sample size, use of old blocks, and the problems associated with the processing.

## Conclusion

SATB2 was expressed in 54% of cases, with higher expression in patients over 50 years old, females, and Grade II patients. It was more prevalent with lymphovascular invasion, T3 and T4 cases, and more in cases with negative lymph node involvement. Additionally, while it was more expressed in cases with positive β-hCG, the results were unfortunately statistically insignificant; diffuse SATB2 expression also had high levels of cyclin D1.

### Conflict of interests

The authors declared no conflict of interest.

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The authors did not receive any source of funds.

### Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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