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Immunohistochemical Evaluation of SATB2 Expression in Colorectal Carcinoma in Mosul City, Iraq

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ABSTRACT

Background: Colorectal carcinoma is one of the most common cancer related morbidities and mortality. Only a few clinicopathological parameters give a prediction of the patient's outcome. Therefore, there is a demand for additional prognostic markers, which may also assist in detecting the benefits of treatment.
Objectives: To assess the frequency of SATB2 immunohistochemical expression in colorectal carcinoma, and to assess the relation of SATB2 expression with variable clinicopathological parameters.
Materials and methods: In this retrospective case series study, a study for SATB2 was done by immunohistochemical technique on 50 cases of primary colorectal carcinoma, using mouse monoclonal antibodies (AMAb90635, clone CL0276, Atlas Antibodies AB, Stockholm, Sweden).
Results: The patients' ages ranged from 22-85 years (mean ± SD = 58.6 ± 14.46 years), with a male-to-female ratio of 1:1. Diffuse expression of SATB2 was detected in 70% of cases and a complete absence of expression was seen in 6 cases. A significant association was detected between SATB2 expression and tumor grade and lymph node metastasis (P-value 0.0116 and 0.0218, respectively). While no significant association was detected with patients' age, sex, tumor site, histological subtypes, or stage of the tumor.
Conclusion: SATB2 expression may help in the identification of particularly aggressive colorectal cancer cases and can add additional prognostic information for subgrouping the cases within the same grade and stage.
Keywords: Colorectal carcinoma; SATB2; Expression; Prognosis.

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INTRODUCTION

The malignant tumor of the colon and rectum is the third most common cancer worldwide [1–4], and regarding mortality, it is ranked the second most common cancer [[1, 5]. Although colorectal carcinoma (CRC) is successfully treated when diagnosed at early stages, it shows rapid progression with delayed appearance of clinical symptoms [2, 6]. The diagnosis of the tumor at an early stage, adequate excision of the tumor and proper therapy are important parameters to get a better prognosis [5], but significant prognostic heterogeneity persists within each stage group, especially in CRC stage II and stage III [7].

Therefore, new biomarkers are required to distinguish high-risk cases and classify patients according to their prognosis [8]. Although a lot of studies are being done to identify the markers that help in detecting high risk cases and aid in choosing cases for adjuvant therapy, none of them has been shown to be good markers for routine clinical use [5].

The SATB2 "special AT-rich sequence-binding protein 2", represents a transcription factor [9–12] that attaches to the DNA nuclear matrix attachment region and subsequently directs transcription and chromatin remodeling [3, 4, 11–13]. The SATB2 gene is located on chromosome 2. It includes 11 exons with 191 kilobases in weight and 733 amino acids in length [6, 10, 14]. It was first identified in 2002 in complementary DNA sequencing [7]. SATB2 has a role in osteoblastic and craniofacial differentiation [4, 15, 16], and is also involved in the progression of the central nervous system [4, 11, 13]. Among the epithelial tissue, SATB2 is detected at a high level

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in the epithelium of the lower gastrointestinal tract and in malignant tumors [4, 9, 15]. It shows an expression restricted to colorectal/appendiceal adenocarcinomas, urothelial/renal carcinomas, and tumors that show osteoblastic differentiation [15]. As 71–97% of primary and metastatic CRCs have been reported to stain positively for SATB2 expression [17]. It is widely used as a diagnostic immunohistochemical (IHC) marker for the diagnosis of colorectal adenocarcinomas and differentiates it from other adenocarcinomas [8, 12, 18].

Recent research has shown that SATB2 can guide the expression of genes required for the cell cycle (cell proliferation and division), cell differentiation, migration of the cell [5, 8, 12] and self-renewal of stem cells [5, 8] and it can also take part in DNA replication [16]. Therefore, it may play an important role in cancer initiation, development, and spread [8]. In the CRC, data from limited literature detected that the absence of SATB2 expression is associated with poor outcomes [7, 9, 11, 14, 18]. This suggests that decreased expression of SATB2 may play a role in the progression of CRC [3, 11]. However, the exact role of SATB2 in CRC is not well established [17]. As a result, the current study aimed to determine the frequency of SATB2 IHC expression in CRC and the relationship between SATB2 expression and variable demographic and clinicopathological parameters (such as age of the patients, sex, site, histopathological types, grade, lymph node invasion, and stage).

MATERIALS AND METHODS

In this retrospective case series study, during a period from the first of April 2022 to the first of May 2023, 50 cases of primary CRC (obtained through surgical resection) were collected in the labs of Al Al-Jumhori Teaching Hospital and Al Salam Teaching Hospital in Mosul City/ north of Iraq. The data regarding the patient's age, sex, and site of tumors was obtained from medical records. Sections of 4-micron thickness were cut from the paraffin block of all cases and stained with hematoxylin and eosin (H & E) for reviewing of histological type, tumor grade and re-evaluation regarding the lymph node metastasis and determine the stage of each case. The cases in which the tumor was obtained by surgical resection with the presence of complete information and the availability of paraffin blocks with adequate tissue for H & E-stained slides and IHC studies were included in this study. While the cases with missing information and those diagnosed depending on endoscopic biopsy were excluded.

Immunohistochemical study

One representative block of each case (a paraffin block with a sufficient amount of non-necrotic tumor) was selected, and an IHC study was done after routine antigen retrieval using an automated IHC stainer (Autostainer, Dako Cytomation, Glostrup, Denmark). A mouse monoclonal antibody (AMAb90635, clone CL0276, Atlas Antibodies AB, Stockholm, Sweden) was used as the primary antibody against SATB2 with a dilution of 1:200. The results were assessed manually, and all microscopical interpretations were done without the knowledge of the patients' data. A tissue section treated with buffer solution instead of primary antibody was used as a negative control, while the normal colonic mucosa was used as an internal positive control. Only nuclear staining was regarded as positive and at least 500 tumor cells were assessed to determine the number of positive malignant cells. The expression of SATB2 was scored and divided into three groups according to that described by Schmitt M et al. [19] (Table 1).

Ethical approval

This study was conducted based on the principles of ethics that have their origins in the Declaration of Helsinki, and it was approved by the Medical Research Ethics Committee, College of Medicine, University of Mosul, with a reference number (UOM/COM/MREC/22-23(42) on June -,2023 to get this approval. Furthermore, owing to the retrospective nature of this study, informed consent was waived.

Statistical analysis

The collected data were entered and analyzed using SPSS (Statistical Package for the Social Sciences) version 24. The age of the patients was expressed as mean ± SD, the expression of SATB2 was presented in the figure, and categorical variables were presented in tables as frequencies and percentages. the Chi-square (χ^2) test or Fisher exact test, when indicated, was used to analyze the relationship between SATB2 and variable clinicopathological parameters. The differences were regarded as a significant when the P-value < 0.05.

RESULTS

In this retrospective case series study, 50 cases of primary CRC were enrolled. The age group of the patients ranged from 22-85 years with a mean age ± SD of 58.6 ± 14.46 years, 25 cases (50%) were within 61-80 years of age with a male-to-female ratio of 1:1. The most common site of tumor was the left colon (56%). Regarding the histological type, the majority of cases (94%) were adenocarcinoma (NOS: Not Otherwise Specified). Grade II was the most common (72%). Lymph node metastasis was detected in 25 (50%) cases and the majority of the cases were of stage III (Table 2).

The IHC expression of SATB2 in this study showed 35 (70%) cases with diffuse pattern of expression (Figure 1). No significant association was detected between the SATB2 expression and the age of patients, sex, and site of the tumor (P-value = 0.6736, 0.9095, and 0.4943 respectively). Thirty-four (68%) with adenocarcinoma (NOS) showed a diffuse pattern of expression, the association of SATB2 with the histological type of tumor was statistically not significant (P-value = 1.000). In this study, the pattern of diffuse expression was more detected in cases with grades I and II. This association was statistically significant (P-value = 0.0116). The diffuse expression of SATB2 was more detected in the cases with no lymph node metastasis (P-value = 0.0218). While no significant association (P-value = 0.2852) was detected with the

Table 1. SATB2 expression Patterns.

Diffuse expression	If the tumor tissue either showed a complete expression or few focal areas showed loss of staining in singular cells.
Heterogeneous expression	If focal areas showed loss of staining in a group of cells or there were areas that showed a complete absence of staining.
Absent expression	If all tumor tissue showed a complete lack of staining.

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Table 2. Demographic, Clinical, and pathological characteristics of the 50 cases.

Variable	Number	Percentage
Age in years		
21-30	1	2
31-40	5	10
41-50	8	16
51-60	10	20
61-70	13	26
71-80	12	24
81-90	1	2
Total	50	100
Sex		
Male	25	50
Female	25	50
Total	50	100
Site		
Left colon	28	56
Right colon	12	24
Rectum	9	18
Transvers colon	1	2
Total	50	100
Histological type		
Adenocarcinoma (NOS).	47	94
Adenocarcinoma with neuroendocrine diff.	1	2
Papillary adenocarcinoma.	1	2
Adenocarcinoma with mucinous diff.	1	2
Total	50	100
Grade		
Grade I	7	14
Grade II	36	72
Grade III	7	14
Total	50	100
Lymph node metastasis		
Absent	25	50
Present	25	50
Total	50	100
Stage		
I	6	12
II	18	36
III	21	42
IV	5	10
Total	50	100

pathological stage (Table 3). Figures 2, 3, 4 show representative images of the tumors stained with SATB2.

DISCUSSION

The SATB2 protein shows a specific pattern of expression, with distribution restricted to only a few body tissues [20]. It is highly expressed in the glandular epithelium of the lower gastrointestinal tract [6, 9, 21], and this expression is maintained in cancer of colorectal origin [6, 20]. These findings suggest the use of SATB2 as a diagnostic marker for colorectal differentiation [19, 21]. The specific and high frequency of SATB2 expression in CRC has suggested the hypothesis that SATB2 may have prognostic and predictive effects in this tumor [20]. But still, the exact function of SATB2 as a prognostic factor is not obvious [21]. In this study, the SATB2 expression showed a significant relationship with important prognostic factors, SATB2 may have a prognostic role in CRC.

IHC studies of SATB2 on CRCs revealed that it is a sensi-

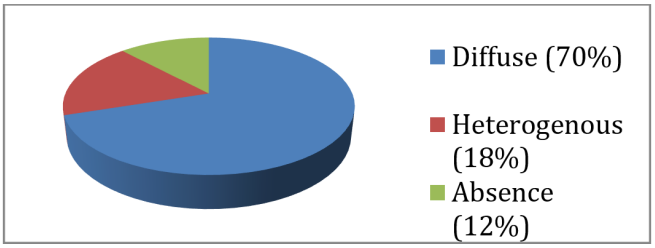

Figure 1. Patterns of SATB2 expression in colorectal carcinoma cases

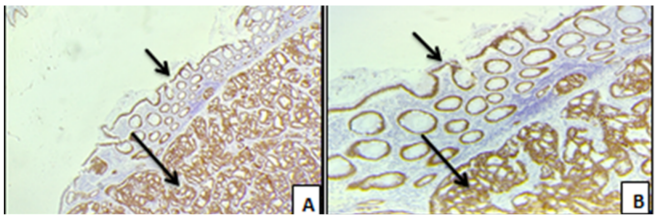

Figure 2. The diffuse pattern of SATB2 immunohistochemical staining in grade I colonic adenocarcinoma (Not otherwise specified, long black arrows) with diffuse nuclear staining of SATB2 in normal colonic mucosa (internal positive control, short black arrows). A: Magnification ×40, B: Magnification ×100.

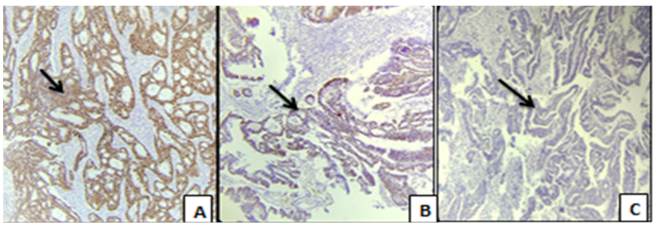

Figure 3. The different patterns of SATB2 expression in colonic adenocarcinoma (black arrows) at low magnification ×100. A: Diffuse pattern, B: Heterogeneous pattern, and C: Absence.

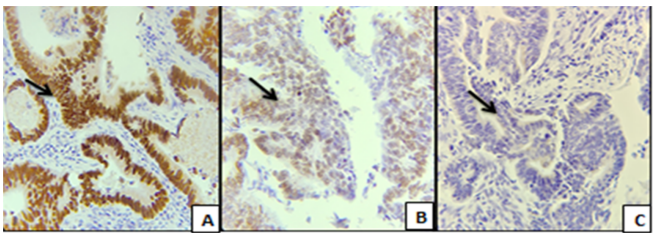

Figure 4. The different patterns of SATB2 expression in colonic carcinoma at higher magnification ×100 (black arrows), showing the nuclear staining A: Diffuse pattern, C: Heterogeneous pattern, and B: Absence.

Table 3. Relation of SATB2 expression with demographic and clinicopathological characteristics of the 50 colorectal carcinoma cases.*

Demographic and clinicopathological characteristics		SATB2 expression			Total NO.(%)	P-value
		Absent NO.(%)	Heterogeneous NO.(%)	Diffuse NO.(%)		
Age in years	21-30	0(0)	1(2)	0(0)	(2)1	0.6736
	31-40	0(0)	1(2)	4(8)	5(10)	
	41-50	1(2)	2(4)	5(10)	8(16)	
	51-60	1(2)	3(6)	6(12)	10(20)	
	61-70	3(6)	1(2)	9(18)	13(26)	
	71-80	1 (2)	1(2)	10(20)	12(24)	
	81-90	0(0)	0(0)	1(2)	1(2)	
	Total	6(12)	9(18)	35(70)	50(100)	
Sex	Male	3(6)	4(8)	18(36)	25(50)	0.9095
	Female	3(6)	5(10)	17(34)	25(50)	
	Total	6(12)	9(18)	35(70)	50(100)	
Site	Left colon	3 (6)	4(8)	21(42)	28(56)	0.4943
	Right colon	2(4)	4(8)	6(12)	12(24)	
	Rectum	1(2)	1(2)	7(14)	9(18)	
	Transvers colon	0(0)	0(0)	1(2)	1(2)	
	Total	6(12)	9(18)	35(70)	50(100)	
Histological type	Adenocarcinoma (NOS)	4(8)	9(18)	34(68)	47(94)	1.000
	Adenocarcinoma with neuroendocrine differentiation	1(2)	0(0)	0(0)	1(2)	
	Micro papillary adenocarcinoma	1(2)	0(0)	0(0)	1(2)	
	Mucinous adenocarcinoma	0(0)	0(0)	1(2)	1(2)	
	Total	6(12)	9(18)	35(70)	50(100)	
Grade	Grade I	1(2)	1(2)	5(10)	7(14)	0.0116*
	Grade II	4(8)	4(8)	28(56)	36(72)	
	Grade III	1(2)	4(8)	2(4)	7(14)	
	Total	6(12)	9(18)	35(70)	50(100)	
Lymph node metastasis	Absent	1(2)	2(4)	22(44)	25(50)	0.0218*
	Present	5(10)	7(14)	13(26)	25(50)	
	Total	6(12)	9(18)	35(70)	50(100)	
Stage	I	0(0)	0(0)	6(12)	6(12)	0.2852
	II	1(2)	2(4)	15(30)	18(36)	
	III	3(6)	6(12)	12(24)	21(42)	
	IV	2(4)	1(2)	2(4)	5(10)	
	Total	6(12)	9(18)	35(70)	50(100)	

* Statistically significant (P-value < 0.5) (Chi-square (χ^2) test and Fisher exact test used when indicated).

tive and highly specific marker to confirm or rule out tumors of colorectal origin [9, 21–23]. SATB2 was expressed in 96% of the primary CRCs in a study done by Zhang et al. [24] and 94.3% in a study done by Elnady et al. [4]. Elaidy et al. [25] found that 86.8% of CRC showed SATB2 expression. In other studies, the positivity of this marker was detected in 85% of CRCs [14, 21, 22]. All these results showed that SATB2 is highly expressed in CRCs, and this high level of expression makes this marker of value in the diagnosis of metastatic adenocarcinomas of colorectal origin [24]. The current study showed a similar result. Ma et al. [7], found that SATB2 was negative in 13% of cases, and Schmitt [19] found that 6% of cases showed a complete absence of SATB2. Mezheyeusk et al. [20] found that 6.8% of cases completely lacked SATB2 immune staining. Possible reasons for these discrepancies include the use of a different SATB2 antibody clone and the variability of the interpretations scoring system or cut-off values used to determine the SATB2 expression and the variability in study populations. The variability in the results of these studies revealed that there is a need for standardized detection methods and a uniform cut-off value. However, all studies done on SATB2 immune staining in CRC, found that the majority of cases showed a diffuse pattern, while the least number of cases showed a complete absence of expression [7].

In this study, no significant association was detected between SATB2 and the age of the patients. This finding was similar to those of Ma et al. [7], Mezheyeusk et al. [20], Eberhard et al. [22], Eldeeb et al. [23], Zhang et al. [24], and Elaidy et al. [25]. This may be attributed to the small sample size and a few numbers of cases of both extremes of age included in this study.

Regarding patients' sex, no significant association was detected,; this result was similar to other studies [7, 20, 22–25]. Although the current study and other studies showed no significant association with sex, future studies with a large number of cases are indicated to confirm this result.

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Suvaitha et al. [5], Ma et al. [7], krudka et al. [8], Schmitt et al. [19], Mezheyeusk et al. [20], and Dum et al. [26] found a significant association of SATB2 with tumor site; the SATB2 loss was more commonly detected in tumors located in the right colon and cecum while SATB2-high tumors were more in left colonic tumors. Although the diffuse pattern of expression in the current study was more detected in the left colon and rectum, no significant association was detected. This result was similar to that of Eberhard et al. [22], Eldeeb et al. [23], Zhang et al. [24], and Elaidy et al. [25]. This may be due to the small sample size of the current study. Additionally, patient heterogeneity and the variation in the selection of SATB2 cutoff may contribute to this discrepancy [24].

In the present study, no significant association was detected between SATB2 expression and tumor histological type. This result is similar to that of Eldeeb et al. [23]. Suvaitha et al. [5], Ma et al. [7], krudka et al. [8], and Schmitt et al. [19] found that mucinous and signet ring cell differentiation were more commonly observed in SATB2-negative tumors compared with SATB2-positive tumors. Further studies with larger sample sizes of these less common subtypes are required to evaluate the pattern of expression of SATB2 in these subtypes.

Zhang et al. [24] found no association between SATB2 and tumor grade and stage. Suvaitha et al. [5], Eldeeb et al. [23], and Elaidy et al. [25] found a significant association between SATB2 and the grade and stage of the tumor. The loss of SATB2 expression was more detected in cases with higher grades and higher stages. In the current study, SATB2 heterogenous/absent expression was significantly associated with high grades. Although the diffuse pattern of expression was more detected in patients with a low stage, the association between SATB2 and the stage was not a statistically significant difference. Ma et al. [7] and Mezheyeusk et al. [20] also found a significant association between the SATB2 expression with the grade but no association in their study was detected with the tumor stage. In this study, decreased SATB2 expression was more detected in the cases that showed lymph node metastasis, and diffuse expression was more seen in cases with no lymph node involvement, statistically; this association was significant. This result was similar to that of Eberhard et al. [22], Eldeeb et al. [23], Elaidy et al. [25], and Dum et al. [26] who reported that high SATB2 expression was statistically correlated with negative lymph node involvement. This result may confirm the role of SATB2 in CRC as a tumor suppressor [19].

Tumor differentiation and lymph node metastasis at the time of diagnosis are important factors that predict the patient' prognosis [5]. The decrease in SATB2 expression was more detected in cases with higher grade lymph node metastasis. The current study suggests that loss of SATB2 expression may help detect high-risk CRC cases. This was in agreement with Schmitt et al. [19] in their cohort study of more than one thousand CRC cases, they found that SATB2 low/absent expression was significantly more associated with cases that had high-risk histo-morphological features [19]. Dum et al. [26] found that a high level of SATB2 expression is a strong indicator of the colorectal origin of cancer, and the decreased expression of it reflects the progression of the tumor and poor outcome. Elaidy et al. [25] found that the low expression of SATB2 is more detected in CRC with a higher grade, advanced stage, lymph node involvement, poor disease-free survival, and overall survival rates and concluded that a decrease or loss of SATB2 expression is a sign of aggressive behavior and poor outcome in CRC.

Brocato et al. [6] said that SATB2 is a sensitive immune marker for the diagnosis of CRC differentiation, and its expression is related to a good prognosis, while as CRC progresses, the expression of SATB2 is decreased or lost, thus, it may not be a helpful diagnostic marker for a late-stage CRC. All of these results confirm the result of studies done on SATB2 function in the experimental field, which recognized the tumor-suppressive role of SATB2 in CRC, and identified that SATB2 has a complex function which controls the tumor suppressor genes and suppresses the progression of CRC through interfering with the transcription of SNAIL, "a master regulator of epithelial-mesenchymal transition" [19]. Li et al. [17], also found that SATB2 acts as a tumor suppressor in CRC, and its overexpression prevents the proliferation and migration of CRC cells in vitro through negative regulation of the stemness of CRC cells.

The study's retrospective nature, coupled with the relatively small number of cases, are its two limitations. Future studies with large numbers of cases and longer periods of follow-up would help to get a more statistically significant conclusions and confirm or rule out the results of this study.

CONCLUSION

SATB2 may have a prognostic role in CRC. Therefore, we can use it alongside standard histo-morphological prognostic factors to predict patient outcome, and it can also provide additional prognostic information for subgrouping cases in the same stage of the disease. Given the high expression of SATB2 in CRCs, targeting it therapeutically could aid in patient treatment and disease prevention.

ETHICAL DECLARATIONS

Acknowledgments

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Ethics Approval and Consent to Participate

Ethical approval was obtained from the Medical Research Ethics Committee of the College of Medicine/University of Mosul (Reference number: UOM/COM/MREC/22-23(42) issued on June 6, 2023). Since the study is retrospective and uses data without violating patients' privacy, consent to participate is not applicable.

Consent for Publication

Not applicable (no individual personal data included).

Availability of Data and Material

The data of the current study are available from the corresponding author when requested.

Competing Interests

The authors declare that there is no conflict of interest.

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Authors' Contributions

All of the listed authors significantly, directly, and intellectually contributed to the work and consented to its publication.

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