J Appl Biotechnol Rep. 2025 June;12(2):1668-1677

Journal of
Applied Biotechnology Reports

doi 10.30491/jabr.2025.512767.1855

Original Article

# Prognostic Value of Combined SATB2 and Ki67 Expression in Colorectal Cancer Patients: A Retrospective Cohort Study

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**Received** March 16, 2025; **Accepted** May 5, 2025; **Online Published** June 30, 2025

**Abstract**

**Introduction:** Colorectal cancer is the third most prevalent malignancy, with limited prognostic tools due to its heterogeneity. This study examined the simultaneous expression of SATB2 and Ki67 in colorectal cancer patients by immunohistochemistry, with progression-free survival (PFS) and patient demographics.

**Materials and Methods:** The study employed an observational cohort design with a cross-sectional approach, defined as a retrospective-prospective clinicopathological analysis of 128 colorectal cancer patients to examine SATB2/Ki67 immunoreactivity, including variables such as diagnosis duration, progression-free survival (PFS), age, sex, tumor location, grading, histopathological types, and TNM classification. Survival and ROC curve analysis tests were used to determine 46 months as the PFS cutoff and survival criterion.

**Results:** Fifty-six individuals survived PFS, while 72 did not. Patients averaged 54.45 years old, with a 22-67 months PFS, averaging 47 months. Colorectal tubular adenocarcinoma patients had the highest PFS; PFS was lower for rectal cancer patients. SATB2 expression exhibited no significant changes based on gender or patient age; however, female patients showed increased Ki67 expression compared to males. The average expressions of SATB2 and Ki67 were 40.21% ± 29.41% and 25.27% ± 23.16%, respectively. According to TNM staging, 68.9% of patients were categorized in stages I–II, 23.4% in stage III, and 7.8% in stage IV, with survival rates declining as tumor metastasis increased.

**Conclusions:** The study suggested that evaluating SATB2 expression during colorectal cancer treatment could clarify its prognostic importance. SATB2 expression correlates positively with colorectal cancer survival; nevertheless, elevated Ki67 levels negatively impact prognosis, particularly when SATB2 levels are high.

**Keywords:** SATB2, Ki67, Colorectal Cancer, Progression Free Survival, Immunohistochemistry

**Citation:** Kareem. Leelo Al-Obaidy A, A. Kareem H, Jabbar Hasan Y. Prognostic Value of Combined SATB2 and Ki67 Expression in Colorectal Cancer Patients: A Retrospective Cohort Study. J Appl Biotechnol Rep. 2025;12(2):1668-1677. doi:10.30491/jabr.2025.512767.1855

## Introduction

Morbidity and mortality from colorectal cancer (CRC) are significant worldwide. At diagnosis, 70% – 80% of tumors are stage I–III. Patients' prognoses depend on postoperative adjuvant chemotherapy.[1] Ki67 is a nuclear protein exclusively found in proliferating cells, making it an effective cellular marker for assessing the growth fraction of a specific cell population. Special AT-rich sequence-binding protein 2 (SATB2) is a transcription factor associated with the nuclear matrix. This protein, specific to certain tissues, binds to matrix association regions to regulate gene expression. Prior studies indicate that the dysregulation of SATB2 is significant in cancer progression and metastasis. The relationship between Ki67 and SATB2 in colorectal adenocarcinoma cells has been examined through the use of immunohistochemistry markers.[2,3]

The inverse relationship between SATB expression and Ki67, as well as between SATB location and Ki67, further underscores the hypothesis of common biological and clinical importance between SATB and Ki67.[4,5] This study aimed to assess the predictive significance of the DNA-binding protein SATB2 and Ki67 expression in CRC patients who underwent curative surgery. The combined SATB2/Ki67 expressions were compared to other major clinicopathologic markers and their association with postoperative outcomes. Therefore, this subgroup's increased risk of tumor recurrence after surgery necessitates closer surveillance or more aggressive treatment. Together, SATB2 and Ki67 predicted strong proliferation and overall survival better than either marker alone. Ki67 expression was significantly higher in SATB2-positive patients compared to negative ones.[6,7] Thus, SATB2 status may enhance Ki67 prognosis. Patient inclusion based on TNM stage alone may not reliably predict prognosis.

Thus, a reliable, customized, and accurate model to predict colorectal cancer prognoses is needed to guide therapeutic practice.[8-10] The study's significance lies in the fact that CRC is one of the most common malignancies. Recently, SATB2, a CRC-specific biomarker, has garnered interest. Low SATB2 expression is a hallmark of liver metastasis and is linked to the molecular evolutionary type

of CRC. Ki67 is a popular proliferative marker. The Ki67 index and SATB2 expression can better assess patient clinical characteristics. Through retrospective and long-term follow-up data on CRC, we developed a joint scoring system and found that immunohistochemistry expression of SATB2 and Ki67 can affect CRC growth and survival.[11,12]

The SATB2 expression is increased during tissue growth, organ development, and some malignancies that increasingly depend on this chromatin remodeling system component. Associated with ribosomal RNA transcription and a regulatory complex, Ki67 governs the cell cycle; however, its exact function is unknown and is employed as an immunohistochemical examination of proliferation.[8,11] SATB2 may be a better prognostic marker for right-sided CRC because previous clinical studies found that positive SATB2 expression in colorectal cancer is more common in the left colon than in the right colon and higher in the prognosis of right-sided CRC than left-sided CRC. Ki67 and SATB2 in CRC have been linked in some cells, although the molecular mechanism and possible linkage are yet unknown.[5,12] The SATB2, a positive marker for colorectal cancer alone, has no predictive significance, but in an earlier study, early-stage tumor survival was linked to the cell proliferation marker Ki67.[7] Colorectal cancer and other malignancies' SATB2 expression and Ki67 connection are uncertain. The key questions are whether SATB2 expression would change in increased Ki67-expressing colorectal cancer patients and whether SATB2 and Ki67 have any predictive value.[5,12]

## Materials and Methods

### *Study Design*

The study utilized an observational cohort design and incorporated a cross-sectional approach, characterized as a retrospective-prospective clinicopathological investigation. The study was carried out at the Al-Jawad Oncology Center (JOC) in Baghdad's Al-Kadimain Medical City using the medical records and Formalin-Fixed Paraffin-Embedded (FFPE) tissue of patients with CRC to examine SATB2 and Ki67 proteins, also known as MKI67 (marker of proliferation Kiel 67), is encoded by the *MKI67* gene in humans and detected using a particular monoclonal antibody against SATB2 and Ki67 as an antigen. Their expression was evaluated by immunohistochemistry, and they were considered independent variables. However, the dependent variable is the Progression-Free Survival (PFS), which measures the interval between the onset of therapy and the progression of the illness or death. Assessing the impact of SATB2 and Ki67 expression on improving progression-free survival (PFS) in patients with colorectal cancer was the aim of this study. Age, sex, smoking history, cancer stage, and the kind and grade of histological tumors were among the basic clinical features and patient demographics that were also determined (Table 1). A systematic randomized sampling was used to choose patients who visited the Al-Jawad Oncology Center for consultation or other private hospital between February 2018 and October 2024.

### *Determinations the Main Predictor Variables*

The combined expression of SATB2 and Ki67 was assessed using immunohistochemistry alongside patient characteristics. Primary information included the patient's progression-free survival (PFS) period, diagnostic time, age, sex, tumor anatomic location, TNM stage, and SATB2 and Ki67 immunoreactivity levels.[13-15]

### *Patient Selection*

To acquire valid research results, the inclusion criteria were initially formulated to create a comprehensive study of colorectal cancer. This study included tissue specimens from patients who had pathologically confirmed colorectal adenocarcinomas. We included 128 cases of colorectal cancer patients between 32 and 90 years old who had not received radiotherapy or chemotherapy before surgery between February 2018 and October 2024, and we used their resected specimens in the study. Thus, the inclusion criteria were as follows: a definite diagnosis of colorectal adenocarcinoma based on pathology and immunohisto chemistry results; no history of chemotherapy, radiotherapy, biotherapy, or other adjuvant treatments before surgery; accurate pathological and follow-up data. The exclusion criteria were as follows: patients who received chemotherapy, radiotherapy, biotherapy, or other adjuvant treatments before surgery; patients with a history of prior malignant or benign tumors. All patients undergoing chemotherapy following surgical tumor excision and participating in this sample provided informed consent. The Ethics Committee of the Al-Jawad Oncology Center authorized this study. We used Formalin-Fixed Paraffin-Embedded (FFPE) tissue alongside surgical report data for enhanced diagnosis. All patients' FFPE tissues were examined by the pathology laboratory of the JOC.[16-18] The eighth edition of the TNM Classification of Malignant Tumors was employed to delineate the stage of colorectal cancer in this study. Furthermore, the middle and lower regions of the material displayed colorectal cancer and anal canal adenocarcinoma, resulting in the classification of patients into four groups: Stage I: T1-2, N0, M0; Stage II: T3-T4, N0, M0; Stage III: T1-4, N1-N2, M0; Stage IV: Any T, any N, M1. Tissue differentiation is classified into three grades: Grade 1: Well-differentiated, Grade 2: Moderately differentiated, and Grade 3: Poorly differentiated or undifferentiated tissue structure. The tumor site is defined as either colon or rectal, and the histological type is determined for all patients with adenocarcinoma, which is categorized as tubular, mucinous, and other forms of adenocarcinoma.[19,20] The required information obtained from the Al-Jawad Oncology Center (JOC), which was utilized to analyze data for immunohistochemistry. We conducted the pertinent

analysis on the case material until follow-up of these patients was discontinued.[21-23]

### *Immunohistochemistry*

All samples were serial 4 µm FFPE sections of CRC tissue slices prepared for immunohistochemical examination. The slides were dried at 60 °C for one hour, and then sections were prepared using a five-stage autostainer optimized to achieve the final staining pattern through enzyme digestion, labeling dye, and microwave protocols suitable for FFPE tissue, following the manufacturer's instructions for the IHC kit for SATB2. The product designation is Anti-SATB2, an antibody generated in rabbit, with Product Number HPA029543 from Sigma. The Ki67 Monoclonal Anti-Proliferating Cell Nuclear Antigen Ki67 antibody, generated in mouse, has Product Number P6834 from Sigma. The instructions are provided by Sigma-Aldrich Chemie GmbH, Eschenstrasse 5, D-82024 Taufkirchen.[24,25]

A positive and negative control are essential to validate the specificity and sensitivity of the assay. Normal bone tissue FFPE or bone marrow can be used as a positive control for SATB2 IHC, while lymph node tissue, especially the germinal centers, is suitable as a positive control for Ki67 IHC. Negative control CRC tissue without the addition of the primary antibody (Anti-SATB2 or Anti-Ki67) during the IHC run can be used as a negative control.[23-25] Before examining the results of immunohistochemical staining, it is important to first consider factors that contribute to the reliability of results. First and foremost, it is crucial to optimize the tissue processing and sectioning techniques used for the preparation of the block. Any mishandling or degradation of tissue can lead to the destruction of critical antigenic determinants. Inter-observer agreement was measured and adjusted. The assessments were then converted to digital scores in order to compare the two biomarkers under standardized conditions.[26-30]

SATB2 immunoreactivity was demonstrated in the tumor cell nucleus with different intensities. Two pathologists examined the immunohistochemical slides using microscopy and scored the expression to exclude any potential for inter-observer variation in the scoring system for SATB2 and Ki67. The kappa score for SATB2 was 0.81, while the kappa value for Ki67 was 0.75, indicating a significant agreement between the two pathologists. The scoring system for SATB2 is as follows: Negative (No staining or less than 1% of cells stained), Weak/Focal (1-10% of cells stained, often with weak intensity), Moderate (11-50% of cells stained, with moderate intensity), and Strong/Diffuse (More than 50% of cells stained, with strong intensity).[23,24] The Ki67 IHC scoring system identifies Ki67 as a nuclear protein expressed during all active phases of the cell cycle, including G1, S, G2, and mitosis, excluding resting cells (G0). Ki67 IHC, widely used as a proliferation marker to assess the growth division of a given cell population, is scored as follows: Negative (less than 1% of cells stained), Low (1-10% of cells stained), Moderate (11-30% of cells stained), High (31-50% of cells stained), and Very High (more than 50% of cells stained) (Table 1).[29,30]

### *Statistical Analysis*

To identify statistical patterns, the clinical data of 128 eligible patients are continuously examined. The statistical method utilized to evaluate the influence of SATB2 and Ki67 expression on PFS in CRC considered PFS as the dependent variable, with other variables as independent. The study employed Receiver Operating Characteristic (ROC) curve analysis to evaluate PFS, with 56 patients either alive or in the PFS period at the study's conclusion, facilitating the identification of the cutoff value of 46 months for survival statistics. The Kaplan-Meier survival analysis, supplemented by the log-rank test and additional survival analyses, was utilized in the study of time-to-event data, concentrating on the progression-free survival (PFS) period until patient events occur, which may include death, disease recurrence, treatment failure, or other pertinent occurrences.[31,32] The Kaplan-Meier survival analysis, augmented by the log-rank test, facilitates the comparison of survival curves between patient groups with elevated SATB2 or Ki67 production and those with low or nonexistent expression. Cox proportional hazards regression models were utilized to assess the impact of SATB2 or Ki67 expression on progression-free survival periods, both individually and collectively, while controlling for factors such as age, sex, TNM staging, tumor grading, tumor location and continuous variable data shown as means with interquartile ranges. Hazard ratios and odds ratios are calculated using univariable and multivariate analyses. Cox and logistic regression analyses employed Omnibus Tests of Model Coefficients to evaluate the time-dependent effects of parameters associated with progression-free survival and response rate, as established by the Kaplan-Meier survival analysis, Cox Regression, Log Rank (Mantel-Cox), Breslow (Generalized Wilcoxon), and Tarone-Ware tests. The specified durations do not indicate the termination of the PFS period; instead, they denote the cessation of patient follow-up upon the study's completion, as patient follow-up began at different intervals according to case records or the onset of treatment. Approximately half of the patients in the follow-up have not progressed and remain in the progression-free survival (PFS) period; hence, the median survival time of 46 months is utilized as the cutoff value in the survival outcome statistics.[31-33] In total, 56 patients, or 43.8% of the cohort, exhibit a progression-free survival (PFS) period exceeding 46 months and are classified as alive. Conversely, the remaining 72 patients, comprising 56.3%, demonstrate a PFS period of less than 46 months and are categorized as progressed patients (1) or have exited the

PFS period solely for statistical analysis.[34-38] IBM SPSS Statistics V21.0 is employed for statistical calculations.

## Results

The average age of patients was 54.45 years, with a median age of 54 years. The youngest participant was 32 years old, while the oldest was 90 years old. The mean PFS was 47 months with a standard deviation of 11.71 months, spanning from 22 to 67 months, and a standard error of 1.4 months. This demographic analysis indicates that SATB2 and PFS are not influenced by gender or age, although women exhibit higher levels of Ki67 expression. The mean SATB2 expression was 40.21% ± 29.41%, while the mean Ki67 expression was 25.27% ± 23.16%. Elevated SATB2 expression was associated with improved progression-free survival (PFS), whereas increased Ki67 expression correlated with reduced PFS. Additionally, a significant inverse relationship was observed between Ki67 and SATB2 expression, with a p-value of 0.0005 (Table 1 and Figure 1).

The results elucidate the inverse relationship between SATB2 and Ki67, indicating that increased Ki67 expression correlates with a reduced PFS period, while increased SATB2 expression is associated with an extended PFS period and decreased Ki67 levels (Figure 1). Elevated Ki67 expression levels correlate with increased cancer metastasis and reduced differentiation in CRC, impacting patient survival outcomes. Elevated Ki67 levels are associated with decreased survival rates. Elevated SATB2 expression levels correlate with reduced CRC metastasis and enhanced differentiation, which are linked to improved survival outcomes (Table 2).

**Table 1.** Describes the Distribution of Patients based on the Study Variables

| Variables | | Frequency | Percentage (%) |
|---|---|---|---|
| Sex | Male | 62 | 48.4 |
| | Female | 66 | 51.6 |
| TNM Staging | Stage I | 6 | 4.7 |
| | Stage II | 82 | 64.1 |
| | Stage III | 30 | 23.4 |
| | Stage IV | 10 | 7.8 |
| Grading | Well Differentiated | 50 | 39.1 |
| | Moderate Differentiated | 53 | 41.4 |
| | undifferentiated | 25 | 19.5 |
| Site | Colon | 89 | 69.5 |
| | Rectal | 39 | 30.5 |
| Histopathological | Tubular Adenocarcinoma | 90 | 70.3 |
| | Mucinous Adenocarcinoma | 29 | 22.7 |
| | Others types | 9 | 7.0 |
| SATB2 Expression | Negative (> 1%) | 18 | 14.1 |
| | Weak/Focal (1-10%) | 45 | 35.2 |
| | Moderate (11-50%) | 35 | 27.3 |
| | Strong/Diffuse (< 50%) | 30 | 23.4 |
| Ki 67 Expression | Negative (> 1%) | 19 | 14.8 |
| | Low (1-10%) | 32 | 25.0 |
| | Moderate (11-30%) | 34 | 26.6 |
| | High (31-50%) | 29 | 22.7 |
| | Very high (< 50%) | 14 | 10.9 |
| Outcome of PFS according to Median (46 months) | Censored (0) | 56 | 43.8 |
| | Regarded as Progressed (1) | 72 | 56.3 |

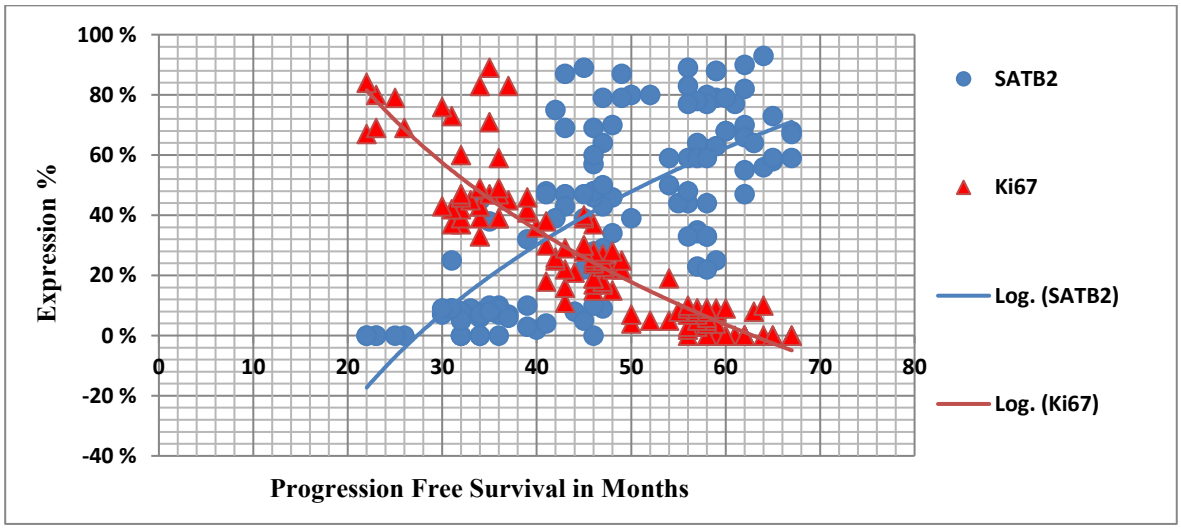


**Figure 1.** Relationship between SATB2/Ki67 Expression and PFS. Depicts the distribution of SATB2 and Ki67 expression percentages in connection to the progression-free survival (PFS) durations in months for colorectal patients.

**Table 2.** Determines the Significant Impact of each Variable on the Progression-free Survival duration of Colorectal Patients by Employing Various Statistical Analyses

| Patients Variables | Kaplan-Meier Test | Chi-Square | D. F | Significance Level for 95% |
|---|---|---|---|---|
| Sex | Log Rank | 0.326 | 1 | 0.568 |
| | Breslow | 0.000 | 1 | 0.984 |
| | Tarone-Ware | 0.082 | 1 | 0.774 |
| TNM Staging | Log Rank | 68.212 | 3 | 0.000 |
| | Breslow | 55.005 | 3 | 0.000 |
| | Tarone-Ware | 61.054 | 3 | 0.000 |
| Tumor Grading | Log Rank | 74.843 | 2 | 0.000 |
| | Breslow | 68.279 | 2 | 0.000 |
| | Tarone-Ware | 71.711 | 2 | 0.000 |
| Neoplasm Location | Log Rank | 7.581 | 1 | 0.006 |
| | Breslow | 7.851 | 1 | 0.005 |
| | Tarone-Ware | 7.867 | 1 | 0.005 |
| Histopathological | Log Rank | 6.460 | 2 | 0.040 |
| | Breslow | 4.879 | 2 | 0.087 |
| | Tarone-Ware | 5.643 | 2 | 0.060 |
| SATB2 Expression | Log Rank | 291.938 | 3 | 0.000 |
| | Breslow | 259.040 | 3 | 0.000 |
| | Tarone-Ware | 274.962 | 3 | 0.000 |
| Ki67 Expression | Log Rank | 185.904 | 4 | 0.000 |
| | Breslow | 153.966 | 4 | 0.000 |
| | Tarone-Ware | 169.204 | 4 | 0.000 |

With decreased tumor tissue differentiation, PFS decreases and colon cancer patients have a higher survival rate than rectal cancer patients and colorectal tubular adenocarcinoma patients have the highest rate of survival than other histopathological types (Table 2).

To examine the impact of SATB2 expression as a variable alongside TNM staging on PFS and identify censored observations, Figure 2 shows a positive correlation between increased SATB2 expression and improved survival period. However, higher tumor stages are associated with lower PFS, with a *p*-value of less than 0.005.

The Cox Regression test was employed to analyses the influence of SATB2 and TNM on PFS, as depicted in Figure 2. The results indicate an increase in cumulative survival values and PFS duration in early-stage CRC (stages I and II) associated with high SATB2 expression. Conversely, patients with advanced stages (III and IV) exhibited a decrease in cumulative survival values, highlighting the effects of SATB2 expression and TNM classification on PFS duration. Colorectal patients with negative SATB2 and Ki67 expression exhibited the lowest survival rates, whereas elevated SATB2 expression, even in the presence of high Ki67 levels, was associated with improved survival outcomes (Table 2 and Figure 3).

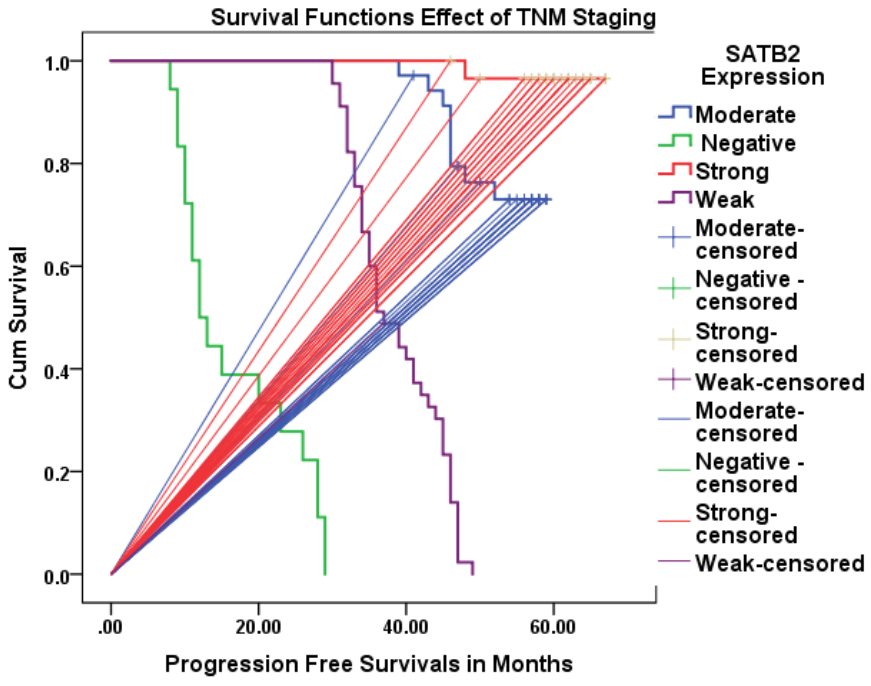


**Figure 2.** Illustrated the impact of SATB2 Expression and TNM Classification on Progression-free Survival (PFS) duration and the Number of Censored Colorectal Cancer Patients.

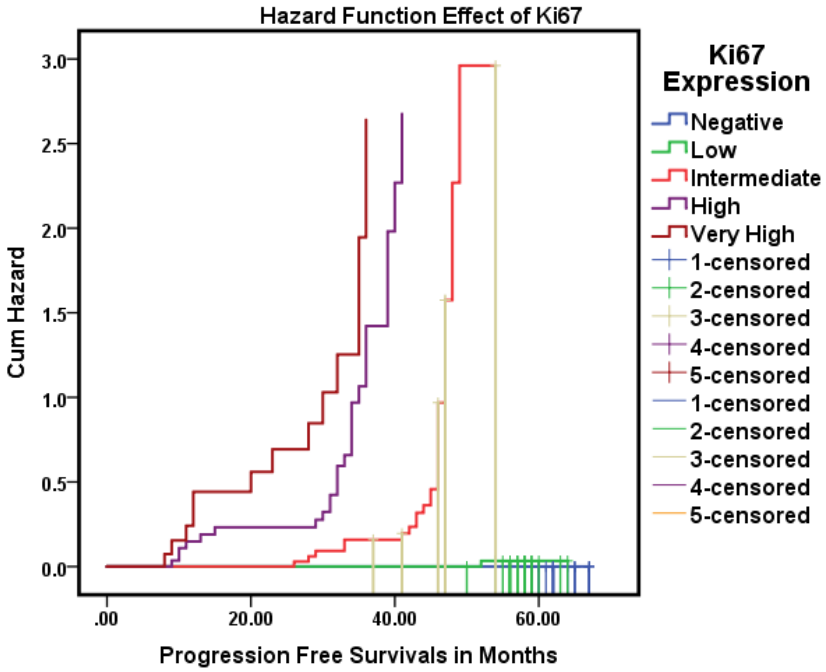


**Figure 3.** Ki67 Expression Affects PFS and Censored Patients. Demonstrated the influence of the hazard function of Ki67, suggesting that elevated Ki67 expression is associated with a decrease in censored patients or progression-free survival (PFS) duration in colorectal patients.

## Discussion

Multiple studies associate SATB2 with tumor aggressiveness and enhanced prognosis in colorectal cancer.[39,40] SATB2 serves as a prognostic and predictive biomarker for the differentiation and proliferation of colorectal cancer cells, owing to its clinical significance and immunohistochemistry detectability.[41] The majority of patients sustained progression - free survival after the follow-up period. Female patients had elevated Ki67 expression compared to males, while SATB2 expression remained consistent across gender and age. Age exerted minimal influence on Ki67. The mean expressions of Ki67 and SATB2 were inversely correlated. This study posits that examining SATB2 expression in tumors during or post-treatment will determine if the correlation is positive, negative, or absent. The absence of a correlation between increased SATB2 expression and reduced overall survival may prompt the consideration of alternate treatments for these patient populations.[42-45] Given SATB2's likely correlation with disease development, an additional study explored its function in immunoglobulin-treated basal populations.[46-48] Additional studies may demonstrate SATB2's potential as a biomarker for adjuvant and metastatic therapeutic outcomes.[49,50] SATB2 at 2q33-34, close to BCL2, regulates oncogene transcription and inhibits polarity loss, thereby reducing colorectal cancer incidence. The integration of immunotherapy with anti-PD(L)1 drugs and/or innovative immunoglobulins has emerged as the standard treatment for advanced colorectal cancer, with SATB2 identified as a prognostic marker that may stratify patients according to outcomes and inform targeted therapy. Patients with elevated SATB2 expression demonstrated improved progression-free survival following treatment.[51-53] Ki67, an optimal proliferation marker, is a phosphorylated non-histone nuclear protein situated in the nucleolus, synthesized during resting cell variations in early G1 and translocated from the S phase to the M phase. The expression profile of Ki67 is closely linked to tumor stage, the cell cycle, and treatment response, rendering it a sensitive prognostic marker for malignancies.[54,55] Some researchers have found similar results regarding Ki67 expression, suggesting that overexpression of Ki67 reduces recurrence-free survival. The Ki67 labeling index in colorectal cancer influences tumor aggressiveness and patient survival, with increased nuclear staining linked to decreased patient survival.[56-58] Ki67 expression, especially mitotic activity, is closely linked to tumor growth and survival outcomes. Integrated clinical and scientific approaches are crucial for assessing the significance of Ki67 in the analysis of survival-related anti-proliferative factors.[59] A majority of the 128 colorectal cancer patients (68.9%) were classified as stages I–II without lymph node involvement, 23.4% were in stage III, and 7.8% were in stage IV. A survival study revealed that tumor metastasis markedly diminished survival rates. Censoring was utilized as multiple patients continued to exhibit PFS at the completion of the research. Increased SATB2 expression was associated with extended progression-free survival in our patients; however, advanced TNM stages reduced progression-free survival. The independent prognostic relevance of SATB2 in stage II colon cancer suggests that its expression may vary based on tumor stage. Patients

exhibiting SATB2 expression had diminished disease severity and reduced tumor stages. The findings suggest targeted therapy for colorectal cancer subpopulations exhibiting increased SATB2 expression.[5,38,43,44,53,60] The data support the optimization of SATB2 use with biomarkers. SATB2 and Ki67 were identified as a prognostic combination based on a significant sample size.[40,61,62] While the utility of Ki67 remains contentious, SATB2 seems to be a more dependable marker for therapeutic applications. The data endorse SATB2/Ki67 in prognostic assessments, although with a limited cohort and retrospective design.[6,39,43] Subsequent research should employ next-generation sequencing and sophisticated prognostic indicators to guide early-phase therapy trials. The predictive capacity of SATB2 remains contentious. Certain studies link reduced SATB2 expression to superficial tumor invasion, elevated lymph node ratio, and heightened metastatic risk during surgical procedures. Mortality associated with surgery-related diseases escalates with diminished SATB2 levels. Elevated SATB2 expression may indicate reduced disease-free survival, as suggested by contradictory research findings. The appropriate cut-off values differ; hence this data should be approached with caution.[5,40]

SATB2 serves as a conserved nuclear matrix-binding protein and transcriptional regulator, playing vital roles in normal development and potentially acting as an oncogenic factor or tumor suppressor in various cancers. In CRC, SATB2 is believed to function as a tumor suppressor. Lowering SATB2 expression in colon cancer cell lines via lentivirus-based shRNA notably increases their invasion capabilities. SATB2 fosters differentiation and hinders stemness in colon cancer cells. High Ki67 expression indicates aggressive, poorly differentiated tumors, with Ki67 positivity linked to a poor prognosis in CRC when assessed with the MIB-1 antibody.[63-65] A significant inverse relationship between SATB2 and Ki67 was noted in primary CRCs, designating Ki67 positivity as an independent risk factor for negative outcomes in patients with elevated SATB2 levels. GSEA analysis revealed stemness as a crucial pathway in patients with high SATB2. This implies that SATB2's role in mitigating Ki67 positivity may arise from its influence on stem-cell-like traits. Proposed mechanisms indicate that SATB2 downregulates stemness-related genes like Bcl2 and SOX2, with loss of SATB2 driving up their expression and Ki67 levels.[66,67] Moreover, combinations of ENPP1 and CCND1 may counteract SATB2's effects, underscoring its significant role in reducing CRC cell stemness through various gene interactions. Further research is needed to examine the degradation processes impacting SATB2 mRNA.[68]

Confirming these findings requires further investigation using a weighted Ki67 score and SATB2 intensity. Bioinformatics can be used to explore multi-genic regulation and its therapeutic implications.[48,57] Kaplan-Meier survival curves indicated that elevated SATB2 expression improved patient outcomes.[40,69,70] Colorectal cancer patients were categorized based on treatment modality and SATB2 expression levels using three Cox models. These results support SATB2 as a predictor of colorectal cancer.[40,63] Further investigation confirmed our survival test results, showing an inverse relationship between SATB2 and Ki67. Factors such as age, sex, TNM stage, tumor grade, and histological tumor types influenced the expression levels of these two biomarkers. This establishes a correlation between SATB2 and Ki67 co-expression with the T and N stages of colorectal cancer.[5-7,49] Additional studies found no correlation between SATB2 and Ki67 expression for clinical-pathological and prognostic variables in colorectal cancer.[30,39,45] The ability of clinical-pathological indicators to predict progression-free survival in these individuals remains uncertain.[43,72]

## Conclusion

The findings revealed that biomarkers may enhance the therapeutic application of SATB2. Ki67 and SATB2 predicted colorectal cancer in many specimens. Reduced SATB2 and elevated Ki67 IHC expression independently correlate with poor colorectal cancer survival, which improves with age, tumor location, and TNM stage. SATB2 can be employed as an auxiliary in colorectal cancer diagnosis alongside Ki67, necessitating enhancements for both. Understanding the roles of SATB2 and Ki67 in colorectal cancer pathobiology is essential. Further location- and stage-specific research is required to validate and apply these findings.

## Authors' Contributions

All authors were involved in the conceptualization and contributed to securing financial support. All study expenses, including the immunohistochemistry test and associated costs, were funded by the researcher rather than the patients. Clinical evaluation of the patient, diagnosis of PFS, and continuous oversight by HAK and YJH, both Senior Oncologists at Al-Emamain Al-Kadimain Medical City, Al-Jawad Oncology Center, Al- Kadhimiya, Baghdad. Immuno histochemical analysis, statistical data analysis, composition, and supervision were conducted in a preliminary manuscript by AKLAO, M.B.Ch.B., Ph.D., is a specialist in clinical immunology.

## Ethical Approval

Ethics were strictly followed in all study methodologies to assure integrity. The Al-Jawad Oncology Centre and other private institutions granted ethical approval. The Al-Jawad Oncology Center Institutional Review Board and Ethical Committee approved the study, which followed the Helsinki Declaration and clinical practice standards. All patients gave

informed consent before enrolling. Hospitalized individuals and their families gave written approval.

## Conflict of Interest Disclosures

The authors declare that they have no conflicts of interest.

## Acknowledgment

We express our gratitude to the Al-Jawad Oncology Center (JOC) in Baghdad's Al-Kadimain Medical City and its laboratory staff for their essential support and collaboration during this study. Their expertise, facilities, and resources were crucial to our research, and we acknowledge the time and effort they dedicated to our project. This study was made possible through the contributions of the Al-Jawad Oncology Center and its laboratory, for which we express our sincere gratitude for their collaboration.

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