



ISSN: 0067-2904

Immunohistochemical Expression of Signal Regulatory Protein Alpha (SIRP α) in Individuals with Colorectal Carcinoma in Baghdad, Iraq

Fatima Omar Abd alkareem¹, Reem Hasan Abdulhussein Al-Oraibi², Hany Akeel Al-hussaniy¹

¹ Al-Nisour University College, Department, of Pharmacy, Baghdad, Iraq

² Al-Yarmouk Teaching Hospital

Received: 16/1/2025

Accepted: 17/ 11/2025

Published: 30/9/2026

Abstract

Bowel cancer is the most frequent cancer type in the gastrointestinal tract and the 4th biggest cause of cancer-related death in the world. The protein (also known as PTPNS1, SHPS1, CD172A, and P84) is a transmembrane glycoprotein that is mostly expressed on neurons and myeloid cells but is especially abundant on macrophages. This study aims to investigate the significant value of SIRP α in colorectal cancer in Iraqi patients in Baghdad and its correlation with clinicopathological features using an immunohistochemistry assay. A total of 45 cases of varied colorectal carcinoma (CRC) samples were gathered from Medical City Teaching Hospital in Baghdad. In contrast, 30 rectum and colon samples from the Forensic Medicine Department showed no discernible abnormalities, were also collected. This study found that high expression of SIRP α in tumor-associated macrophages (TAM) occurred at a rate of 86.66%. However, the results found no significant correlation between the expression of SIRP α and the clinicopathological features of CRC. It concludes that high expression of SIRP α in TAM, and no significant associations between SIRP α and the clinical features of CRC patients.

Keywords: SIRP alpha, Colorectal cancer, Tumor-associated Macrophage, Histological type.

التعبير الكيميائي النسيجي المناعي لبروتين تنظيم الإشارة ألفا (SIRP α) لدى الأفراد المصابين بسرطان القولون و المستقيم في بغداد العراق

فاطمة عمر عبد الكريم¹, ريم حسن عبد الحسين العريبي², هاني عقيل الحسيني¹

¹كلية النسر الجامعة, قسم الصيدلة, بغداد, العراق.

²مستشفى اليرموك التعليمي

الخلاصة :

سرطان الأمعاء هو أكثر نوع سرطان شيوعاً في القناة المعوية المعوية، ويُعد رابع أكبر سبب للوفيات المرتبطة بالسرطان في العالم. يُعتبر بروتين SIRP α (المعروف أيضاً باسم SHPS1، PTPNS1،

*Email : fatma.omar1602@sc.uobaghdad.edu



CD172A وP84) عبارة عن بروتين سكري عبر الغشاء يتم التعبير عنه بشكل أساسي في الخلايا العصبية والخلايا النخوية، ولكنه يتواجد بكثرة خاصة في الخلايا البلعمية الكبيرة. تهدف هذه الدراسة إلى التحقق في القيمة المعنوية لبروتين $SIRP\alpha$ في سرطان القولون والمستقيم في المرضى العراقيين في بغداد، وعلاقته بالسمات المرضية باستخدام فحص الكيمياء المناعية النسيجية. تم جمع 45 عينة من حالات سرطان القولون والمستقيم المختلفة من مستشفى مدينة الطب التعليمي في بغداد. بالإضافة إلى ذلك، تم جمع 30 عينة من الأمعاء والمستقيم التي لا تحتوي على أمراض مرضية ملحوظة من دائرة الطب العدلي لأغراض المقارنة. وجدت الدراسة تعبيراً عالياً $SIRP\alpha$ في الخلايا البلعمية المرتبطة بالورم (TAM) بمعدل 86.66%. كما أظهرت النتائج عدم وجود علاقة معنوية بين تعبير بروتين $SIRP\alpha$ والسمات المرضية CRC. نستنتج من هذه الدراسة أن هناك تعبيراً مرتفعاً لبروتين $SIRP\alpha$ في الخلايا البلعمية المرتبطة بالورم (TAM)، مع عدم وجود ارتباطات معنوية بين تعبير $SIRP\alpha$ والسمات السريرية لمرضى CRC.

Introduction

The colorectal carcinoma (CRC) represents the fourth most lethal solid malignant tumor globally [1]. Therapy for patients with lateral or distant stage CRC has become more diverse and simultaneously more effective due to the various types that can be identified, which exhibit multiple genomic growth sequence forms. However, these developments come with challenges and independent firmness. Immunosuppressive barriers are erected by CRC against antitumor treatment, which limits the performance of the antigrowth immune system. The latest signals have confirmed that using monoclonal antibodies that effectively block the binding of immune control receptors to their natural ligands, thereby stimulating the endogenous immune system, is a valid mechanism for treating many tumors [2]. The major colorectal cancer risk factors are diet, physical inactivity, and obesity [3]. In the first half of the twentieth century, fatality rates from colon and rectal operations frequently approached 20%, with sepsis being the primary cause [4]. The majority of prior immunotherapies tried to boost adaptive immunity, specifically T-cell activity. In the late 2000s, the cluster of differentiation CD47 was a potential focus for cancer treatment, in particular. We scrutinized CD47 as an immune checkpoint molecule to minimize its impact against CRC and explored ways to attract activated antitumor activity through the CD47 blockade. Cancer stem cells (CSCs) are associated with a strong clamping mechanism involving CD47 and excessive CD47 expression. This letter began when my patients with CRC were treated and when models for the disease were examined. Some histocompatibility tissue molecules, known antigens, assist their immune targets in engaging. Our results show that $SIRP\alpha$ identifying CRC is statistically significant and can be used as a model for estimating CRC development. It can also help in prognosis and individual therapeutic choices. It is an immunological checkpoint on the myeloid-specific system that operates in concert with the innate immune system. CD47, which functions as an aposematism signal on cancer cells, reduces macrophage phagocytosis in the immune system [5,6]. A cancer biomarker is a trait that can be tested to predict the risk of developing cancer, the likelihood of cancer recurrence, or patient outcomes. These properties can be molecular, cellular, physiologic, or imaging-related. In response to cancer, cancer cells or normal cells create these biomolecules, which can be discovered in tissues or body fluids. In order to identify changes in DNA, RNA, proteins, or other biomolecules that support cancer diagnosis, prognosis, precision medicine/guided cancer treatment, drug response prediction, or cancer monitoring, biomarker testing for cancer entails profiling tumor or bodily fluids[7].

Signal regulatory protein alpha (SIRP α): structure and function

SIRP is an immunoglobulin superfamily of protein, broadly expressed, that regulates the function of several members of the blood cell types, including macrophages, and T and B

lymphocytes. More specifically, SIRP α inhibits cell activation in myeloid cells by interacting with the myeloid-associated immunoglobulin-like receptors and 2P4 molecules. Activation of macrophages and microglia is limited by the actions of SIRP. SIRP α is the receptor expressed in these cells, recognized by the marker CD172a. The actions of SIRP α are mediated through a phosphorylation-dependent mechanism, by the phosphorylation of tyrosine residues of the cytoplasmic ITIM motif and the presence of cytoplasmic protein tyrosine phosphatases, which recognize this phosphorylated tyrosine for its negative structural properties. In tumor biology, SIRP α signaling of host and immune checkpoint proteins, together with the second-level immunity receptors, enables tumor cells to grow and proliferate in the tissue. In solid and hematological malignancies, SIRP α , through its macrophage-activating properties, facilitates access to tumors by stimulating phagocytosis and clearing them, exhibiting pathogenic properties. Since the expression of SIRP and its association with oncoviruses is unknown among the Iraqi population, the present work aims to assess the IHC expression of SIRP α in patients with colorectal carcinoma, as an indirect consequence of SIRP expression [8].

This protein comprises three external immunoglobulin superfamily (IgSF) domains, two C1-type IgSF (IgC) domains, and one V-type IgSF (IgV) domain, an intracellular tail that may block signaling, and one transmembrane region. Four tyrosine residues in the intracellular tail make up two traditional immunoreceptor tyrosine-based inhibitory motifs (ITIMs). Furthermore, the ligand-binding region of the extracellular IgV-domain allows SIRP to interact with its ligand, CD47 [9]. The binding of CD47, a marker of self-protein, to the SIRP α protein in the macrophage plasma membrane prevents macrophages from engulfing self-cells, making it a crucial checkpoint in our innate immune system. The CD47-SIRP α protein complex has been identified as a promising therapeutic target in cancer and inflammation [10].

Subjects and methods

Study design

Patient selection depends on many factors, including age, gender, medical history, dietary pattern, and genetics. The selected patients should be representative of the general population; therefore, the main challenge is to obtain a proper selection. The criteria take a long time to accomplish, and this may generate unregulated costs for the center providing these patients. Many factors in patient conditions are multifactorial in nature, and they are also likely to be distorted by patient selection. Several factors can determine and orchestrate these problems, such as aging, smoking, obesity, or aspects of disseminated disease. The therapeutic system should take this condition into consideration. Despite the organ confinement, the adjuvant and preventive aspects of the disease should lead the physician to intervene actively with prevention and therapeutic approaches. Seventy-five cases of colon and rectum biopsies (excisional biopsies and total colectomy) were gathered as paraffin tissue blocks between October 2022 and January 2023 from private labs in Baghdad, Iraq, as well as the Department of Pathology's teaching laboratories at Baghdad Medical City. The distribution of the patient cases was as follows: Before being converted into paraffin blocks, 30 samples of healthy colon biopsies and 45 instances of malignant tumours from Baghdad's Forensic Medicine Institute were preserved in 10% formalin and subjected to a tissue processing procedure. The patient's information reports were also used to gather clinical data, including age, tumour location and size, pathological grade, and stage.

Immunohistochemical staining

The basic concept behind this technique is the particular antibody/antigen binding in tissue. The bound antigen-antibody complex is then seen using a range of spotting techniques.

Immunohistochemical Staining (IHC) uses a range of enzymatic markers, such as peroxidase and alkaline phosphatase, to identify the antigens of interest [11]. The IHC staining procedure was carried out precisely as directed by the instructions provided by the kit manufacturers (PolyExcel, HRP/DAB Detection System, EPR22930-163, ab260039, and Abcam, anti-SIRP alpha antibody). Spleen carcinoma tissue was used as a positive control for SIRP α . Adhering to Magaki, the overall protocol was followed [12]. To de-waxe the tissue sections, the slides were first heated to 60–65°C for 30 minutes, then quickly rinsed in xylene and heated again for 5 minutes. The parts were immersed in progressively lower concentrations of ethyl alcohol to rehydrate them. The slides were placed in a water bath heated to 95 °C and left to boil for 30 minutes after being dipped in the antigen retrieval solution. The slides were then exposed to a peroxidase quencher (H_2O_2) solution for 10 minutes. A diluted (1:2000) SIRP α primary antibody was applied to the tissue sections, and they were subsequently incubated in a humidity chamber at room temperature for 30 minutes. After cleaning the tissue sections, the slides were coated with the PolyExcel Target Binder (Cat# IPS006) and allowed to sit at room temperature for 15 minutes in the humidity chamber. The tissue sections were then covered with PolyExcel PolyHRP (Cat# IPS007) and allowed to sit at room temperature for 15 minutes in the humidity chamber. After applying PolyExcel StunnDAB and its substrate to the slides, they were left at room temperature in a humidity chamber for five minutes, or until the brown stains started to show. The tissue sections were washed twice for 5 minutes each using Tris-Buffer-Saline (TBS). After being counterstained for one to two minutes with drops of Mayer's Hematoxylin, the slides were carefully washed in distilled water (DW) until they were clear. After being dehydrated in progressively higher ethyl alcohol concentrations, the slides were cleaned twice, each for two minutes in xylene. Ultimately, the slides were mounted and cover-slipped using the DPX mounting media. All steps of the study procedures Figure 1. are summarized in

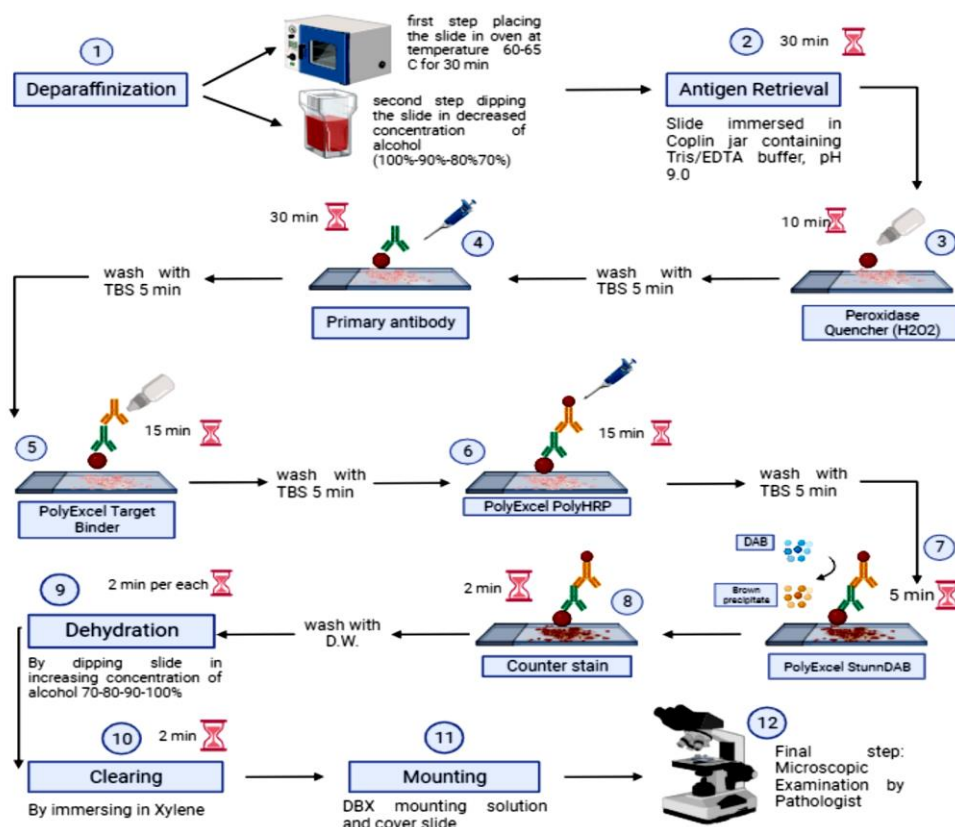


Figure 1: Immunohistochemical staining steps.

Scoring and interpretation of SIRP α expression

The scoring system of SIRP alpha was adopted in agreement with Koga *et al.*, [13]. IHC staining in the membrane and cytoplasm of cancer cells or stromal tumor-infiltrating cells was considered positive. Based on the estimated percentage of positively stained cells in the tumor, as shown in Table 1.

Table 1: Scoring of SIRP α expression

Score	percentage of positively stained cells
0	no staining of tumor or stromal cells
1	Less than one-third of cells are positively stained (weak)
2	One-to two-thirds of cells are positively stained (moderate)
3	More than two-thirds of cells are strongly stained (strong)

Statistical analysis

The data were evaluated by Microsoft Excel and SPSS V28 (Statistical Packages for the Social Sciences, IBM, USA). Simple percentages, frequencies, standard deviations, averages, and ranges were used to display the data. The Chi-square test was used to examine correlations between variables [14], and a P-value of less than 0.05 was considered statistically significant.

Results*IHC expression of SIRP α in colorectal cancer*

SIRP α expression is detected as brown membranous and cytoplasmic staining in tumor-infiltrating cells (macrophages) (Figure 2).

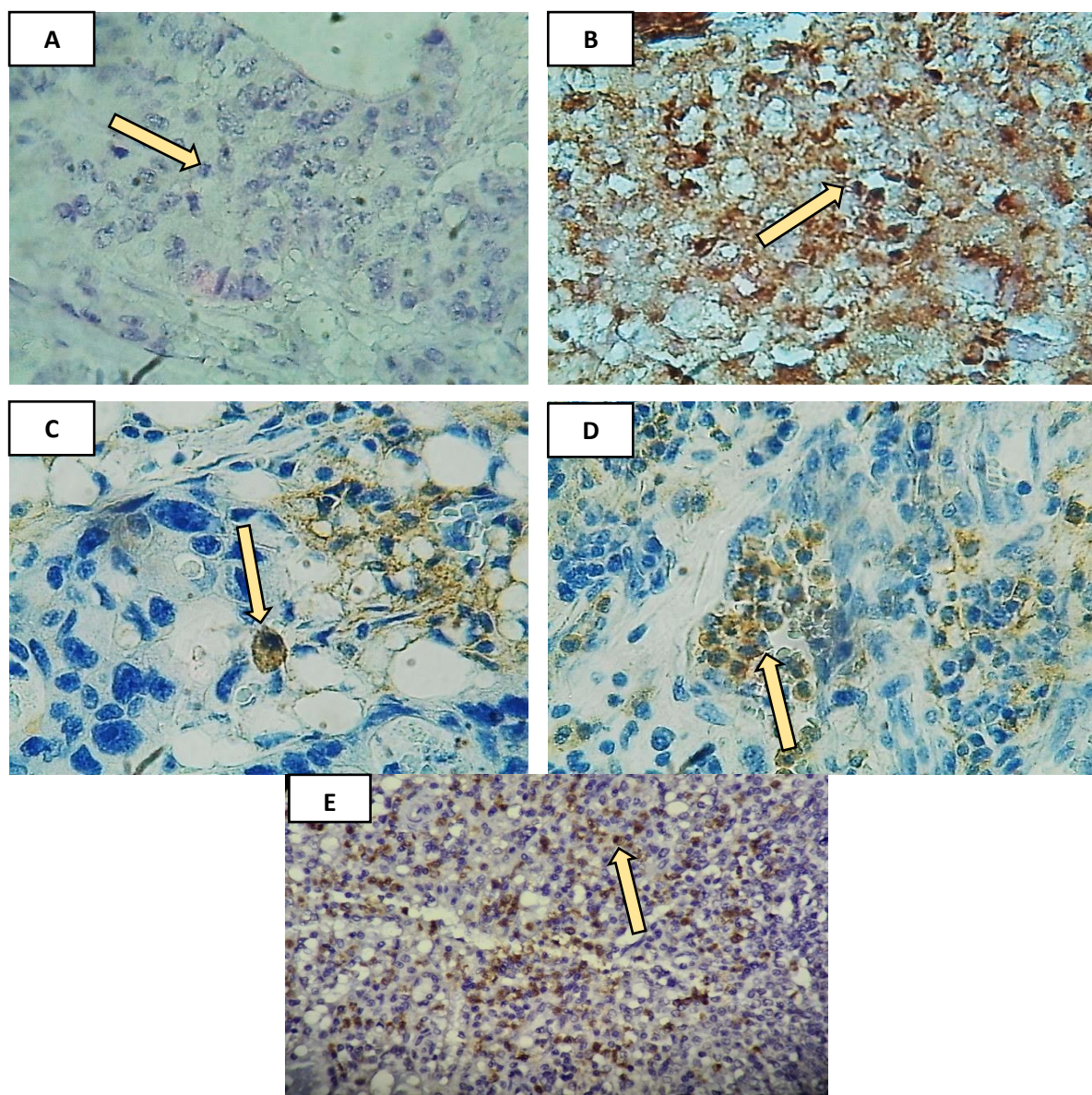


Figure 2: A: Negative cytoplasmic and membranous expression of SIRP α in tumor-infiltrating cell (macrophage). B: Strong cytoplasmic and membranous expression of SIRP α in tumor-infiltrating cells (macrophages). C: Moderately cytoplasmic and membranous expression of SIRP α in tumor-infiltrating cells (macrophages). D: Weak cytoplasmic and membranous expression of SIRP α in tumor-infiltrating cells (macrophages). E: Positive control shows strong positive cytoplasmic and membranous expression of SIRP alpha in normal human spleen carcinoma.

Significantly, SIRP α expression was negative in 100% of normal colon-rectal tissues and positive in 86.66% of malignant cases. (Tables 2 and 3).

Table 2: SIRP α expression in both colon and rectal cancer patients and controls

Expression	SIRP α			
	Malignant		Control	
	No.	(%)	No.	(%)
Positive	39	86.66%	0	0.0%
Negative	6	13.34%	30	100%
P value	0.024*			

Table 3: Associations of SIRP α with clinicopathological features in Iraqi bowel cancer patients

Clinicopathological features		SIRP α		P value
		+	-	
Age groups (years)	<40	6	0	0.140 ^{NS}
	40-49	5	2	
	50-59	12	1	
	>60	16	3	
Gender	Male	17	4	0.349 ^{NS}
	Female	22	2	
Tumor Size	<5 cm	27	3	0.460 ^{NS}
	>5 cm	14	1	
Tumor Site	Left	25	5	0.687 ^{NS}
	Right	14	1	
Tumor Stage	IIA	16	0	0.230 ^{NS}
	IIC	2	0	
	IIIA	2	1	
	IIIB	14	5	
	IIIC	5	0	
Tumor Grade	I	2	0	0.315 ^{NS}
	II	36	6	
		1	0	
Tumor Histological Type	Adenocarcinoma	33	6	0.329 ^{NS}
	Mucinous	4	0	
	Signet ring cell	2	0	
Lymph Node Metastasis	Positive	15	4	0.587 ^{NS}
	Negative	24	2	

Discussion

Predicting the development of the disease and developing novel treatments have been the focus of intensive studies in recent years. Immunotherapy has revolutionized the treatment of cancer. Checkpoint blockage is the basis of these immunotherapy treatments. The CD47/SIRP α pathway is one of these checkpoints [15]. SIRP α is one of the SIRP family members, which was first identified in 1997 [16]. A glycoprotein called SIRP α is present on the plasma membrane of both neuronal cells and myeloid cells, such as macrophages, granulocytes, monocytes, and myeloid dendritic cells [17].

Several human solid tumors and hematological malignancies have been shown to have increased expression of CD47 [18]. The host's immune system is essential for destroying cancer cells and preventing tumor growth. However, cancerous cells can evade the immune system by expressing immune checkpoint markers, such as CD47 (cluster of differentiation 47) [19]. When immunoreceptor tyrosine-based inhibitory motif regions are activated by binding to CD47, they become phosphorylated, which attracts SHP-1 and SHP-2 protein tyrosine phosphatases. This dephosphorylates downstream molecules, such as myosin IIA, and suppresses phagocytosis [20].

In the present study, forty-five cases of colon and rectal cancer were immunohistochemically examined for SIRP α expression. The results of the current study demonstrated that 86.6% of SIRP α was positively expressed on macrophage-infiltrating cells in the tumor stroma. Koga *et al.*, [13] found that SIRP α expression was significantly linked with the infiltration of macrophages in esophageal squamous cell carcinoma (ESCC). Additionally, Giatromanolaki *et al.*, [21] found that high expression of SIRP α on macrophages associated with tumor cells in Non-Small-Cell Lung Cancer.

A further aspect of this study is the link between SIRP α expression and certain clinicopathological characteristics. Starting with age, aging in the human hematopoietic system is associated with a decrease in bone marrow cellularity, a decline in the adaptive immune response, and an increase in hematological diseases and malignancies. In this study, no significant correlation was found between SIRP α expression and age ($P = 0.140$). Sugimura-Nagata *et al.*, [22] showed that there is no correlation between the expression of SIRP α and age in CRC. On the other hand, this research revealed no association between the expression SIRP α and the site or size of the tumor. The right colon, which includes the cecum as well as the ascending colon, and the left colon, which includes the descending colon, sigmoid colon, and rectum [23]. In contrast, a study by Hu *et al.*, reported that SIRP α expression showed a significant difference with tumor size, but not with the site of the tumor [24].

Regarding gender, another feature in this study, bowel cancer represents one of the most frequent causes of cancer morbidity in men and women [25]. In our study, no significant correlation was found between SIRP α expression and gender in malignant tumors. This outcome corresponds with the finding of Ji *et al.*, [26], who reported no significant correlation between the expression of SIRP α and gender in colorectal cancer. This study revealed no significant association between SIRP α expression and the histological type of malignant cases. Koga *et al.* [13] found no significant correlation between the expression of SIRP α and the histological type of esophageal squamous cell carcinoma. The American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) staging classifications have historically been used to determine the prognosis of colorectal cancer (CRC). In clinical settings, however, variations in survival patterns that are not stage-dependent indicate a complex interplay between stage, pathological characteristics, and biomarkers that influences risk assessment, prognosis, and the direction of treatment [27]. The findings of this research revealed no significant link between SIRP α and stage, grade, and lymph node metastasis. Variations in the histology samples, race, genetic variables, technique, and kits employed could account for the variance between our findings and those of other research. This study is the first to investigate SIRP α in CRC patients in Iraq.

Conclusions

SIRP α is expressed by colorectal carcinoma cells and tumor-associated macrophages, and the pattern of expression shows that SIRP α may play a role in tumor progression. These data provide an additional clue that SIRP α may be an attractive target for controlling the pro-tumorigenic phenotype of TAM, which could lead to a better outcome for TNBC patients. The results support the concept of targeting this pathway for a limited duration. Patients who have undergone surgery to remove primary and metastatic lesions have recovered from lymphopenia and have normal red blood cell levels, which may reduce or, ideally, prevent tumor recurrence. There was no correlation between the expression of SIRP α and the demographic, clinical, and pathological characteristics of CRC patients.

Ethical Clearance

This study was ethically approved by the Research Ethics Committee of the College of Science. The Ethics Committee approves the research proposal in its current form. This Ethics committee is working in accordance with the College of Science guidelines on biomedical research.

Conflicts of interest

There is no conflict of interest for the research under construction with any institution, university, company, or other organization.

Reference

- [1] H. Al-Hussaniy and M. Al-Zobaidy, "Effects of Mdm2 Inhibitors on Cellular Viability of Breast Cancer Cell Lines HP100, MCF7," *Bratislava Medical Journal/Bratislavské Lekárske Listy*, vol. 125, pp. 627–634, 2024.
- [2] H. A. Mohammed and N. J. Kandala, "Evaluation of Plasma-microRNA320 level among Colorectal Cancer Iraqi Patients," *Iraqi Journal of Science*, vol. 64, no.3, pp. 1142-1150, 2023.
- [3] H. Sung, R. L. Siegel, M. Laversanne, C. Jiang, E. Morgan, M. Zahwe, Y. Cao, F. Bray, and A. Jemal, "Colorectal cancer incidence trends in younger versus older adults: an analysis of population-based cancer registry data," *The Lancet Oncology*, vol. 26, no. 1, pp. 51-63, 2025.
- [4] W. J. Altaee, "Comparison Between Mechanical and Non Mechanical Bowel Preparation Prior To Elective Colorectal Surgery," *AL-Kindy College Medical Journal*, vol. 7, no. 2, pp. 85-90, 2011.
- [5] Z. Li, Y. Li, J. Gao, Y. Fu, P. Hua, Y. Jing, M. Cai, H. Wang, and T. Tong, "The role of CD47-SIRPα immune checkpoint in tumor immune evasion and innate immunotherapy," *Life Sciences*, vol. 273, p. 119150, 2021.
- [6] P. Economopoulou, R. De Bree, I. Kotsantis, and A. Psyrri, "Diagnostic tumor markers in head and neck squamous cell carcinoma (HNSCC) in the clinical setting," *Frontiers in oncology*, vol. 9, p. 827, 2019.
- [7] V. K. Sarhadi and G. Armengol, "Molecular biomarkers in cancer," *Biomolecules*, vol. 12, no. 8, p. 1021, 2022.
- [8] L. Pan, B. Wang, M. Chen, Y. Ma, B. Cui, Z. Chen, Y. Song, L. Hu, and Z. Jiang, "Lack of SIRP-α reduces lung cancer growth in mice by promoting anti-tumour ability of macrophages and neutrophils," *Cell Proliferation*, vol. 56, no. 2, p. e13361, 2023.
- [9] L. M. Behrens, T. K. van den Berg, and M. van Egmond, "Targeting the CD47-SIRPα innate immune checkpoint to potentiate antibody therapy in cancer by neutrophils," *Cancers*, vol. 14, no. 14, p. 3366, 2022.
- [10] Y. Li, H. Zhou, P. Liu, D. Lv, Y. Shi, B. Tang, J. Xu, T. Zhong, W. Xu, J. Zhang, J. Zhou, K. Ying, Y. Zhao, Y. Sun, Z. Jiang, H. Cheng, X. Zhang, and Y. Ke, "SHP2 deneddylation mediates tumor immunosuppression in colon cancer via the CD47/SIRPα axis," *The Journal of Clinical Investigation*, vol. 133, no. 4, 2023.
- [11] H. M. Hussaini, B. Seo, and A. M. Rich, "Immunohistochemistry and immunofluorescence," in *Oral Biology: Molecular Techniques and Applications*: Springer, 2022, pp. 439-450.
- [12] D. Yigzaw and G. G. Dagnaw, "Review of Immunohistochemistry Techniques: Applications, Current Status, and Future Perspectives," in *Seminars in Diagnostic Pathology*, 2024: Elsevier.
- [13] N. Koga, Q. Hu, A. Sakai, K. Takada, R. Nakanishi, Y. Hisamatsu, K. Ando, Y. Kimura, E. Oki, Y. Oda, and M. Mori, "Clinical significance of signal regulatory protein α (SIRPα) expression in esophageal squamous cell carcinoma," *Cancer science*, vol. 112, no. 8, pp. 3018-3028, 2021.
- [14] J. A. Torres, A. B. C. Brito, V. S. e Silva, I. M. Messias, A. C. Braun, A. P. C. Ruano, M. E. C. Buim, D. M. Carraro, and L. T. D. Chinen, "CD47 Expression in Circulating Tumor Cells and Circulating Tumor Microemboli from Non-Small Cell Lung Cancer Patients Is a Poor Prognosis Factor," *International Journal of Molecular Sciences*, vol. 24, no. 15, p. 11958, 2023.
- [15] Y. Murata, Y. Saito, T. Kotani, and T. Matozaki, "CD 47-signal regulatory protein α signaling system and its application to cancer immunotherapy," *Cancer Science*, vol. 109, no. 8, pp. 2349-2357, 2018.
- [16] S. M. G. Hayat, V. Bianconi, M. Pirro, M. R. Jaafari, M. Hatamipour, and A. Sahebkar, "CD47: role in the immune system and application to cancer therapy," *Cellular Oncology*, vol. 43, pp. 19-30, 2020.
- [17] A. N. Barclay and M. H. Brown, "The SIRP family of receptors and immune regulation," *Nature Reviews Immunology*, vol. 6, no. 6, pp. 457-464, 2006.
- [18] O. Arrieta, A. Aviles-Salas, M. Orozco-Morales, N. Hernández-Pedro, A. F. Cardona, L. Cabrera-Miranda, P. Barrios-Bernal, G. Soca-Chafre, G. Cruz-Rico, M. de L. Peña-Torres, G. Moncada-Claudio, and L. Ramirez-Tirado, "Association between CD47 expression, clinical characteristics and prognosis in patients with advanced non-small cell lung cancer," *Cancer medicine*, vol. 9, no. 7, pp. 2390-2402, 2020.

- [19] M. Feng, W. Jiang, B. Y. Kim, C. C. Zhang, Y.-X. Fu, and I. L. Weissman, "Phagocytosis checkpoints as new targets for cancer immunotherapy," *Nature Reviews Cancer*, vol. 19, no. 10, pp. 568-586, 2019.
- [20] N. Dizman and E. I. Buchbinder, "Cancer therapy targeting CD47/SIRP α ," *Cancers*, vol. 13, no. 24, p. 6229, 2021.
- [21] A. Giatromanolaki, A. Mitrakas, I. Anestopoulos, A. Kontosis, I. M. Koukourakis, A. Pappa, M. I. Panayiotidis, and M. I. Koukourakis, "Expression of CD47 and SIRP α macrophage immune-checkpoint pathway in non-small-cell lung cancer," *Cancers*, vol. 14, no. 7, p. 1801, 2022.
- [22] A. Sugimura-Nagata, A. Koshino, S. Inoue, A. Matsuo-Nagano, M. Komura, M. Riku, H. Ito, A. Inoko, H. Murakami, M. Ebi, N. Ogasawara, T. Tsuzuki, S. Takahashi, K. Kasugai, K. Kasai, and S. Inaguma, "Expression and prognostic significance of CD47–SIRP α macrophage checkpoint molecules in colorectal cancer," *International Journal of Molecular Sciences*, vol. 22, no. 5, p. 2690, 2021.
- [23] M. Ahmed, "Colon cancer: a clinician's perspective in 2019," *Gastroenterology research*, vol. 13, no. 1, p. 1, 2020.
- [24] T. Hu, H. Liu, Z. Liang, F. Wang, C. Zhou, X. Zheng, Y. Zhang, Y. Song, J. Hu, X. He, J. Xiao, R. J. King, X. Wu, and P. Lan, "Tumor-intrinsic CD47 signal regulates glycolysis and promotes colorectal cancer cell growth and metastasis," *Theranostics*, vol. 10, no. 9, p. 4056, 2020.
- [25] L. Conti, M. Del Cornò, and S. Gessani, "Revisiting the impact of lifestyle on colorectal cancer risk in a gender perspective," *Critical Reviews in Oncology/Hematology*, vol. 145, p. 102834, 2020.
- [26] K. Ji, Y. Zhang, S. Jiang, L. Sun, B. Zhang, D. Hu, J. Wang, L. Zhao, P. Wang and Z. Tao, "SIRP α blockade improves the antitumor immunity of radiotherapy in colorectal cancer," *Cell Death Discovery*, vol. 9, no. 1, p. 180, 2023.
- [27] K. Chen, G. Collins, H. Wang, and J. W. T. Toh, "Pathological features and prognostication in colorectal cancer," *Current Oncology*, vol. 28, no. 6, pp. 5356-5383, 2021