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The Potential Role of Asprosin and Irisin in Colorectal Cancer Diagnosis in Iraqi Patients

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Abstract

Background: Colorectal cancer (CRC) ranks among the top causes of cancer mortality worldwide, yet early detection remains challenging. Although carcinoembryonic antigen (CEA) is routinely used, the roles of adipocytokines such as Asprosin (ASP) and Irisin (Ir) in CRC diagnosis and prognosis are not well defined. Objective: This study aims to determine the diagnostic and prognostic value of serum ASP and Ir levels in Iraqi CRC patients, with analyses stratified by gender, body mass index (BMI), and age. Materials and Methods: In a nine-month case-control study, 102 individuals (62 histologically confirmed CRC patients and 40 healthy volunteers) were recruited. Serum CEA was quantified by electrochemiluminescence, while Asprosin and Irisin concentrations were measured using ELISA. Statistical comparisons (unpaired *t*-test, ANOVA) and receiver-operating characteristic (ROC) curve analyses were performed to evaluate the biomarker's performance and correlation with BMI, gender, and age. Results: Compared to controls, CRC patients exhibited significantly lower ASP (mean ± SD: 1.85 ± 0.45 vs. 2.32 ± 0.50 pg/mL; $P < 0.001$) and higher Ir levels (3.15 ± 0.70 vs. 2.48 ± 0.60 ng/mL; $P < 0.001$). ASP positively correlated with BMI ($r = 0.42$; $P = 0.002$) and was elevated in males and patients > 60 years. In contrast, Irisin inversely correlated with BMI ($r = –0.35$; $P = 0.008$) and was lower in patients < 50 years. ROC analysis yielded AUCs of 0.7801 for ASP (cut-off 2.098 pg/mL; 83.9% sensitivity and 60.0% specificity) and 0.7571 for Ir (cut-off 2.232 ng/mL; 72.2% sensitivity and 67.7% specificity). Conclusion: Serum ASP and Ir display distinct expression patterns in CRC and demonstrate good diagnostic potential, influenced by BMI, age, and gender. These adipocytokines may complement existing biomarkers to enhance early detection of CRC and risk stratification; larger studies are warranted to validate these findings and explore the underlying mechanisms.

Keywords: Asprosin, Adipokines, Biomarkers, Colorectal Neoplasms, Irisin.

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الدور المحتمل للأسبروسين والإيريسين في تشخيص سرطان القولون والمستقيم لدى المرضى العراقيين

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الخلاصة

الخلفية: يُصنف سرطان القولون والمستقيم من بين الأسباب الرئيسية للوفيات بالسرطان في جميع أنحاء العالم، ومع ذلك لا يزال الكشف المبكر عن هذا المرض يمثل تحدياً. على الرغم من استخدام المستضد الكارسينومبوني (CEA) بشكل روتيني، إلا أن أدوار المستضدات الشحمية مثل الأسبروسين والإيريسين في تشخيص سرطان القولون والمستقيم والتشخيص غير محددة بشكل جيد. الهدف: تهدف هذه الدراسة إلى تحديد القيمة التشخيصية والإنذارية لمستويات الأسبروسين والإيريسين في مصل الدم لدى مرضى سرطان القولون والمستقيم في العراق، مع تحليلات مصنفة حسب الجنس ومؤشر كتلة الجسم والعمر. المواد والطرق: في دراسة حالات وشواهد لمدة تسعة أشهر، تم تجنيد 102 فرد (62 مريضًا مؤكدين نسيجيًا بالسرطان القولون والمستقيم و40 متطوعًا سليمًا). تم قياس كمية CEA في المصل عن طريق (Electrochemiluminescence)، بينما تم قياس تركيزات الأسبروسين والإيريسين باستخدام ELISA. تم إجراء المقارنات الإحصائية (unpaired *t*-test و ANOVA) وتحليلات منحنى خصائص (تحليل ROC) لتقييم أداء المؤشرات الحيوية والارتباط بمؤشر كتلة الجسم والجنس والعمر. النتائج: بالمقارنة مع الضوابط، أظهر مرضى سرطان القولون والمستقيم انخفاضًا ملحوظًا في الأسبروسين (SD±mean: 1.85 ± 0.45 مقابل 2.32 ± 0.50 بيكوغرام/مل؛ P < 0.001) ومستويات أعلى من الأيريسين (3.15 ± 0.70 مقابل 2.48 ± 0.60 نانوغرام/مل؛ P <0.001). ارتبط الأسبروسين ارتباطًا إيجابيًا بمؤشر كتلة الجسم (r = 0.42؛ P = 0.002) وكان مرتفعًا لدى الذكور والمرضى الذين تزيد أعمارهم عن 60 عامًا. وعلى النقيض من ذلك، ارتبط الأيريسين عكسيًا بمؤشر كتلة الجسم (r = −0.35؛ P = 0.008) وكان أقل لدى المرضى الذين تقل أعمارهم عن 50 عامًا. وأسفر تحليل ROC عن معدلات استخدام وسطي للتركيز الكلي تبلغ 0.7801 للأسبروسين (الحد الفاصل 2.098 بيكوغرام/مل؛ حساسية 83.9% وخصوصية 60.0%) و0.7571 للإيريسين (الحد الفاصل 2.232 نانوغرام/مل؛ حساسية 72.2% وخصوصية 67.7%). الاستنتاجات: يُظهر مصل الأسبروسين والإيريسين أنماط تعبير متميزة في سرطان القولون والمستقيم ويظهران إمكانات تشخيصية جيدة، تتأثر بمؤشر كتلة الجسم والعمر والجنس. قد تكمّل هذه الأدييوسيتوكينات الشحمية المؤشرات الحيوية الحالية لتعزيز الكشف المبكر عن سرطان القولون والمستقيم وتصنيف المخاطر؛ وهناك ما يبرر إجراء دراسات أكبر للتحقق من صحة هذه النتائج واستكشاف الآليات الكامنة وراءها.

1. Introduction

Colorectal cancer (CRC) counts as the third most prevalent form of cancer and the second most significant contributor to cancer-related mortality on a global basis. In 2018, it was predicted that over 1.8 million new cases of CRC would emerge, resulting in approximately 881,000 deaths worldwide [1]. CRC is the third most often diagnosed cancer among Iraqi patients of both sexes, as GLOBOCAN data discloses. Furthermore, CRC is the second most commonly diagnosed cancer in Iraqi men and fourth in Iraqi women [2]. CRC is characterized

by irregular cell growth (i.e., a disorganized, heterogeneous proliferation of abnormal cells), resistance to cell death, increased proliferative activity, angiogenesis, invasion, and metastasis. It primarily affects the epithelial tissues of the colon and rectum [1, 3].

The rising rates of physical inactivity, obesity, and environmental pollution, such as pollutants from post-conflict areas and emissions from oil refineries, can contribute to an increased risk of CRC in Iraq. Furthermore, in the Iraqi population, many individuals have a significant familial predisposition (e.g., Lynch syndrome and familial adenomatous polyposis), with approximately 50% of patients reporting a family history of CRC. It is believed that this genetic factor accelerates the development of adenomas and the tumorigenesis of CRC [4, 5].

Scholars have proposed that pathological malfunction in adipocytes and the abnormal release of adipocytokines in these intricate tissues could potentially contribute to tumor progression and development [3]. This could occur through various carcinogenic mechanisms, including the facilitation of cell migration and proliferation, as well as the activation of anti-apoptotic pathways [6]. One of the recently identified adipokines is Irisin (Ir), which was discovered by Boström *et al.,* [7]. It is an important exercise-induced peptide that enters the bloodstream following its proteolytic cleavage from a larger transmembrane protein precursor called fibronectin type III domain-containing protein 5 (FNDC5). It has a molecular weight that falls between 20 and 32 kDa and is encoded by the *FNDC5* gene (ACCN: NM_153756.2) [8]. The deglycosylated form of Ir ranges from 12 - 15 kDa. The process of N-glycosylation plays an essential role in determining the biological activity of Ir [8]. The FNDC5 is classified as a transmembrane protein and a prohormone, that is, a precursor protein (inactive hormone) which is enzymatically cleaved to release the active 112-amino acid peptide hormone, Irisin [9]. It attaches to αv integrin receptors to initiate signaling cascades that facilitate muscle contraction and mediate the benefits of physical exercise [10]. Nevertheless, the process through which Ir is released from the prohormone remains unexplained [8]. Initially, it has been reported that Ir contributes to the activation of thermogenesis and the browning of white adipose tissue [7]. Also, it has been demonstrated to be essential in the transformation of white adipose tissue into brown adipose tissue by upregulating Thermogenin (UCP1) expression in Mitochondria. The UCP1 protein plays a vital role in the adaptation of the human body to low temperatures. It inhibits the respiratory chain's ability to produce ATP [7]. Numerous studies demonstrated that the Ir level increases with physical exertion and have shown that it protects against pathological conditions associated with chronic inflammation [8].

For the first time, a scientific study led by Romere *et al*., identified and explained Asprosin (ASP) [11] as a multifunctional adipokine that appears to be a promising factor in the struggle against obesity [12]. ASP is secreted by white adipose tissue and found to be higher in adult obesity and type 2 diabetes mellitus [13]. The *Fibrillin-1* (*FBN1)* gene (ACCN: NM_000138.4) encodes the precursor protein profibrillin-1, which is proteolytically cleaved by furin into two peptide products: mature fibrillin-1, a key extracellular matrix component, and ASP, a 140 amino acid peptide hormone that regulates glucose homeostasis [11]. It has a central effect, and its orexigenic properties can be analogous to the hormone Ghrelin [12, 14]. The circulating ASP has been shown to cross the blood-brain barrier, activate orexigenic AgRPC neurons via the cAMP-dependent pathway, and induce hunger [14]. The mechanisms of ASP action, release factors, and correlations between ASP levels and health conditions or diseases have become the primary fields of scientific investigation. As it serves crucial functions in regulating thermogenesis, total body energy expenditure, and glucose homeostasis, it enhances glucose assimilation and glycogenolysis while reducing lipid deposition, adipogenesis, and gluconeogenesis [12, 15].

Although several studies have measured circulating levels of Ir and, to a lesser extent, ASP in various malignancies, including CRC, the existing literature data remain inconclusive regarding their diagnostic and prognostic utility in clinical settings. In particular, few studies have specifically examined the correlation between these adipocytokines and various demographic and clinicopathological factors in distinct populations. To address the current gaps in understanding, this study investigates the diagnostic and prognostic relevance of the adipocytokines ASP and Ir within a cohort of Iraqi patients diagnosed with CRC. Specifically, it aims to determine whether serum concentrations of these biomarkers differ meaningfully between CRC patients and healthy individuals, and whether such differences may hold clinical significance. In doing so, the study employs a range of statistical analyses to assess diagnostic performance, while also examining the correlation between these adipokines and demographic variables such as sex, age, and body mass index (BMI). This research adopts a multidimensional framework to enhance our understanding of ASP and Ir as potential early indicators of CRC, contributing to the growing field of adipocytokine-based cancer biomarkers.

2. Materials and Methods

2.1 Study design and demographic information

This case-control study recruited a total of 102 participants from an Iraqi cohort between November 2022 and February 2023. CRC cases (n = 62) were diagnosed by certified Histopathologists at Erbil and Rizgari Hospital - Oncology Unit following standard histopathological evaluation. Healthy controls (HC, n = 40) were selected from routine outpatient assessments, with clinical examinations confirming the absence of colorectal pathology. Although the groups were not matched by gender, statistical analysis confirmed that the mean age of CRC cases and HC did not differ significantly ($P > 0.05$), ensuring adequate age matching. The final study population size consisted of 62 cases of CRC and 40 HC.

Peripheral venous serum samples were collected under the supervision of an oncologist from the Oncology Unit at Rizgari Hospital and Nanakali Hospital for Blood Diseases and Cancer in Erbil. CRC diagnosis was confirmed through a combination of colonoscopy findings, abnormal serum Carcinoembryonic antigen (CEA) levels (CEA >10 ng/mL), and subsequent histopathological assessment. A positive colonoscopy was defined as the detection of adenomatous polyps measuring ≥1 cm or the presence of any villous adenoma. Most CRC patients were diagnosed at Tumor, Node, Metastasis (TNM) stages II and III, indicative of localized disease without distant metastasis. Additionally, each participant's BMI was calculated as weight (kg) divided by the square of height (m^2).

2.2 Inclusion and exclusion criteria

Colorectal cancer patients were clinically diagnosed with the disease in its early stages. This diagnosis was confirmed by elevated levels of carcinoembryonic antigen (CEA) exceeding 10 ng/mL, along with a supporting histopathology report. In contrast, the healthy control group had no history of CRC or any other systemic diseases. To minimize potential confounding, we excluded individuals with systemic diseases known to affect metabolic and biochemical profiles (e.g., diabetes, cardiovascular, and autoimmune disorders), as well as those with obesity (defined as a BMI ≥30 kg/m^2) or those on medications that could alter the biochemical markers under study. Additionally, patients with CRC who had received chemotherapy prior to sample collection were excluded. To ensure a homogeneous study population, only early-stage CRC patients (TNM stages II and III) were included, while those with other types of adenocarcinomas were excluded. Furthermore, serum samples that had been hemolyzed or improperly stored were eliminated from biochemical analysis. Participants

with incomplete demographic or clinical data were also eliminated to ensure the dataset's integrity.

2.3 Specimen collection and preparations

Each patient had a venous blood sample of 4-5 milliliters collected and placed into gold-top serum separator tubes. The blood samples were allowed to remain at room temperature for 15 minutes, then centrifuged for 10 minutes at 4000 rpm. To guarantee correct identification and traceability, the samples were immediately moved into uniquely coded and labeled Eppendorf tubes following serum preparation. These samples were stored at -20°C for future analysis, with any hemolyzed samples discarded.

2.4 Serum biochemical analysis

Serum ASP and Ir levels were quantified using enzyme-linked immunosorbent assay (ELISA) kits (Human Asprosin, Human Irisin; SunLong Biotech Company Ltd, China) according to the manufacturer's protocol. All samples and standards were analyzed in duplicate to ensure analytical reliability. Additionally, serum CEA levels were determined using the Cobas E411 immunoassay analyzer, a fully automated system that employs the electrochemiluminescence (ECL) detection method (Elecsys CEA; Roche, Switzerland). The accuracy of the ELISA assay was validated using duplicate sample measurements and standard calibration curves. For the CEA analysis, internal quality control was conducted using manufacturer-provided controls on the Cobas E411 system.

2.5 Statistical analysis

The statistical analysis for this study was conducted using GraphPad Prism version 8.0 and SPSS version 26 software. The Shapiro-Wilk (S-W) and Kolmogorov-Smirnov (K-S) normality tests were employed to assess whether the data followed a normal distribution. Data were analyzed based on their distribution. Comparisons between the CRC and healthy control groups were performed using the Mann-Whitney U test for non-normally distributed variables. For subgroup analyses, patients were stratified based on three demographic variables: gender (male and female), age groups (<35, 35-44, 45-54, and >54 years), and BMI categories (normal weight, overweight, and obese). For subgroup comparisons based on age, gender, and BMI, the Kruskal-Wallis test followed by Dunn's multiple comparisons test was performed. Associations between serum ASP and Ir levels and demographic variables in the patient group were evaluated using Spearman's rank correlation coefficient. These correlation analyses were performed using SPSS version 26 software. Serum concentrations of ASP and Ir were used to generate receiver-operating characteristic (ROC) curves for evaluating their diagnostic performance as biomarkers for CRC. The area under each ROC curve (AUC) ranges from 0.0 (no discrimination) to 1.0 (perfect discrimination), providing a quantitative measure of each adipocytokine’s ability to distinguish CRC patients from HC. Data are expressed as means (standard errors) for normally distributed variables and as medians (interquartile ranges) for non-normally distributed variables. Statistical significance was defined as *P*-values of 0.05 or less.

3. Results

3.1 Demographic Characteristics

A total of 102 participants were recruited for this study, comprising 62 CRC patients and 40 HC. Statistical analysis confirmed that the groups were age-matched, with CRC patients averaging 46.5 ± 1.73 years and HC averaging 41.4 ± 1.48 years ($P > 0.05$), resulting in an overall mean age of 48.2 ± 1.97 years. However, the gender distribution was not equivalent between the groups as the CRC cohort included 30 males and 32 females, whereas the healthy

control group comprised 28 males and 12 females. Detailed characteristics of the study participants are provided in Table 1.

Table 1: Demographic information of CRC patients and HC

Demographic study		Participants	CRC	HC	*P*-Value
Age		48.2±1.97	46.5± 1.73	41.4±1.48	0.679
Gender	**Male/n (%)**	58 (56.8)	30 (48.4)	28 (70)	
	Female/n (%)	44 (43.2)	32 (51.6)	12 (30)	
BMI	**Male**		25.12±1.65 Kg/m2	22.34±1.98 Kg/m2	0.045*
	Female		26.43±1.15 Kg/m2	23.36±1.02 Kg/m2	0.039*

CRC: Colorectal cancer, HC: Healthy control, BMI: Body mass index

3.2 Serum adipokine levels (Ir and ASP) in CRC patients

In the present study, serum Ir concentrations were significantly higher in CRC patients than in HC, with mean ± SE values of 3.7 ± 1.09 ng/mL versus 2.8 ± 1.07 ng/mL (P= 0.0308) and corresponding medians of 1.099 ng/mL (IQR: 0.81 - 1.33) versus 0.804 ng/mL (IQR: 0.60 - 1.26). In contrast, ASP levels were markedly reduced in the CRC patients (21.13 ± 6.32 ng/mL; median 11.3 ng/mL [IQR: 1.8 - 19.17]) compared to the HC (58.46 ± 17.6 ng/mL; median 19.67 ng/mL [IQR: 8.4 - 38.3]; P = 0.002), highlighting a divergent adipocytokine profile between the two groups (Table 2). These differences are clearly depicted in the bar graph overlays, where Ir levels rise by approximately 32% in CRC patients and ASP levels fall by about 64% relative to controls (Figure 1).

Table 2: Serum concentrations of ASP and Ir in CRC patients and HC.

Study parameters	Groups		*P*-Value
	CRC (n=62)	HC (n=40)	
Irisin			
Mean±SE	3.7±1.09	2.8±1.07	0.0308*
95% CI	(1.5-5.9)	(0.7-5.0)	
Median (25^{th}-75^{th} percentile)	1.099 (0.81-1.33)	0.804 (0.60-1.26)	
Asprosin			
Mean±SE	21.13±6.32	58.46±17.6	0.002*
95% CI	(8.48-33.77)	(22.7-94.17)	
Median (5^{th}-95^{th} percentile)	11.3 (1.8-19.17)	19.67 (8.4-38.3)	

Values are expressed as mean ± standard error (SE) and median (interquartile range, IQR). Statistical comparisons were performed using the Mann-Whitney U test. A P-value < 0.05 was considered statistically significant.

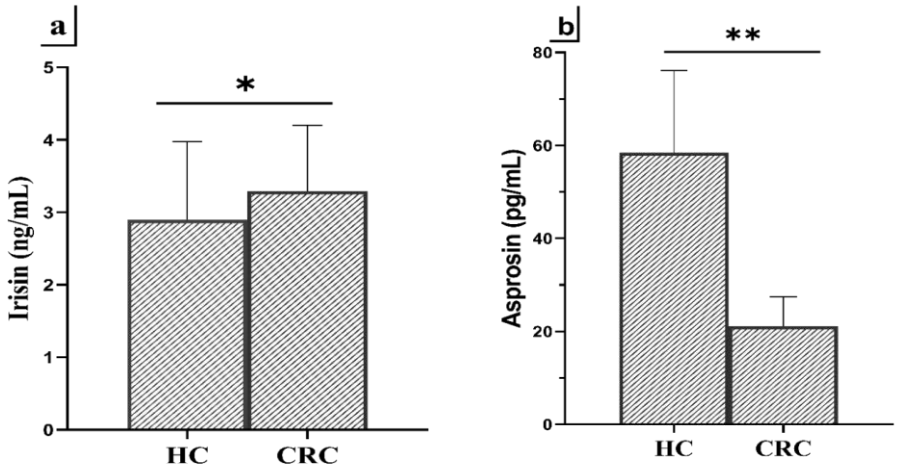

Figure 1. The serum level of Irisin and Asprosin in CRC patients and HC.
The concentration of Irisin and Asprosin was measured in CRC patients and HC; (a) Level of Irisin, (b) Level of Asprosin. The P-value represents significance, denoted as * P < 0.05, **P < 0.01. The data are expressed as mean ± Standard Error of the Mean (M ± SEM).

3.3.1 Gender-Based Differences in ASP and Ir Levels

The present study revealed a notable gender-specific variation in serum ASP levels. In male participants, a statistically significant decrease in ASP was observed in the CRC group compared with the HC (P = 0.028). This indicates potential diagnostic relevance of this adipocytokine in males. Conversely, no significant difference in ASP serum levels was found between female CRC patients and their healthy counterparts. Intriguingly, although not statistically significant, the trend in females was reversed, as CRC patients showed higher ASP levels than HC, suggesting a possible gender-related differential regulation of this adipocytokine hormone (Figure 2a).

Regarding Ir, serum concentrations did not differ significantly between CRC and HC groups in either gender. However, both male and female CRC patients exhibited an upward trend in serum levels of Ir relative to controls, suggesting a potential compensatory or cancer-associated metabolic response, although this trend did not reach statistical significance (Figure 2e).

3.3.2 Age-related differences in serum ASP and Ir Levels

In the present study, age appeared to exert a differential influence on serum ASP levels among individuals with CRC and their healthy counterparts. Among participants over the age of 55, CRC patients exhibited significantly elevated ASP concentrations relative to age-matched HC (P = 0.044), suggesting a possible age-related modulation of ASP expression in malignant states. In contrast, in the 35 - 45 age group, a substantial decline in ASP levels was observed in CRC patients compared to controls (P = 0.0071). While individuals below 35 years did not exhibit statistically significant changes in serum adipocytokine levels, a slight increase in ASP was noted in CRC patients compared to healthy participants (Figure 2b). These findings imply that age may influence the expression of ASP and indicate a potential age-dependent pattern of adipocytokine dysregulation in CRC, although the underlying mechanisms warrant further investigation.

3.3.3 BMI-related differences in serum ASP and Ir Levels

In this study, BMI was found to be a relevant demographic factor influencing adipocytokine levels, particularly ASP concentrations, in patients with CRC. Specifically, CRC individuals classified as overweight exhibited significantly lower ASP levels compared to HC within the same BMI category (P = 0.01). Likewise, normal-weight CRC patients showed a marked reduction in ASP levels, though this difference did not reach statistical significance. In contrast, obese CRC patients had relatively elevated ASP concentrations compared to non-obese CRC individuals, although still lower than their healthy obese counterparts (Figure 2c). These findings suggest that BMI may modulate ASP expression differently in patients with CRC compared to healthy individuals.

In terms of Ir, a pronounced elevation was observed in obese CRC patients in comparison to obese healthy individuals (P = 0.0002), indicating a potentially strong association between obesity and Ir upregulation in CRC carcinogenesis (Figure 2g). While gender differences in Ir levels were noted (with males showing higher levels than females in both CRC and HC groups), this observation was discussed earlier in the gender-based section and is not directly attributable to BMI variation alone.

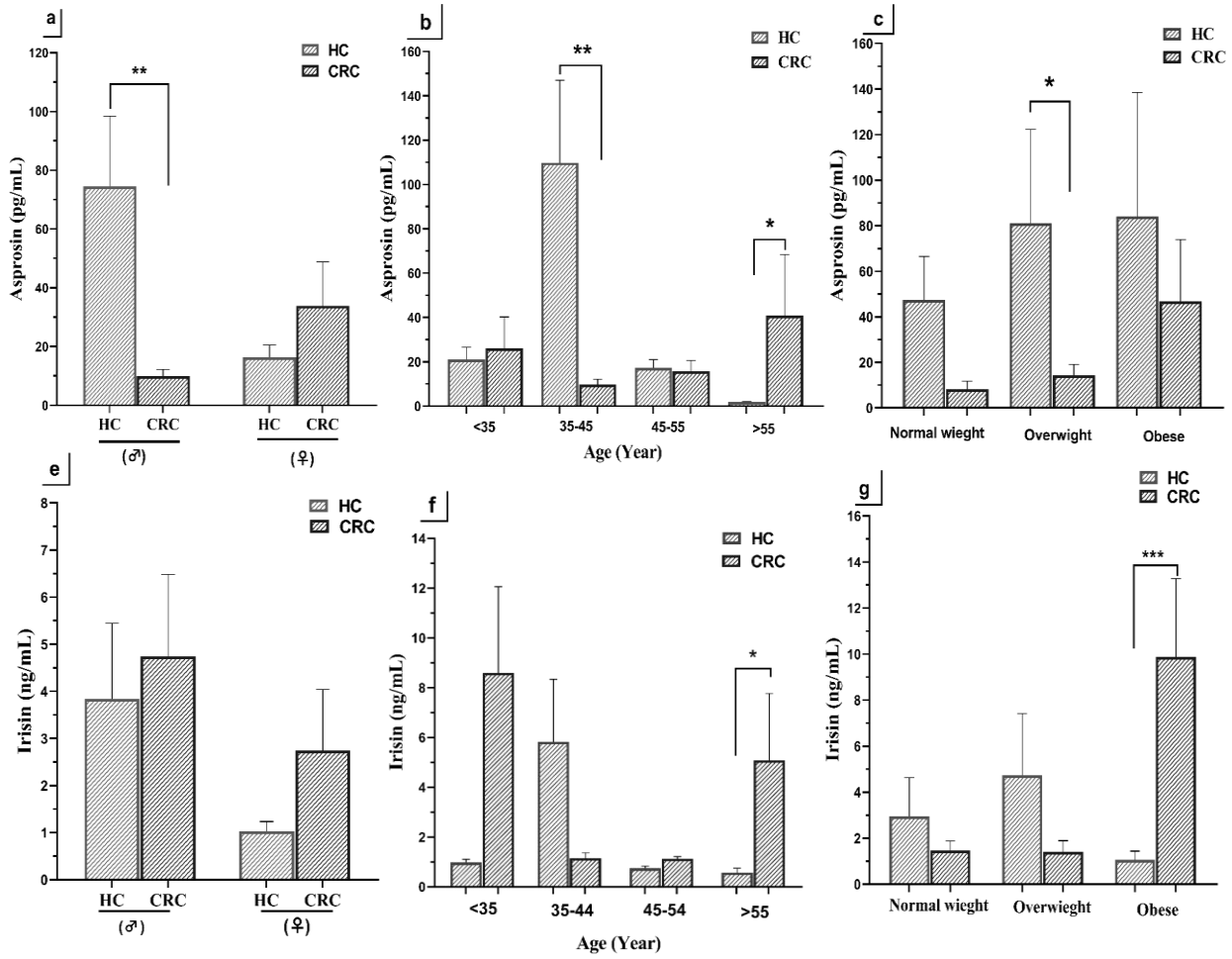

Figure 2. Serum Asprosin and Irisin levels by gender, age, and BMI in CRC patients and HC. Data are expressed as mean ± standard error of the mean (SEM). Comparisons were performed using the nonparametric Kruskal - Wallis test followed by Dunn's multiple comparison post hoc test. Statistically significant differences were observed for Asprosin between CRC and HC groups in males (P = 0.028), in the 35 - 45 and >55 age groups (P = 0.0071 and P = 0.044, respectively), and among overweight individuals (P = 0.01). For Irisin, significant elevations were noted in CRC patients aged >55 years (P = 0.029) and in obese individuals (P = 0.0002) compared to controls. Panels: (a) and (e) show Asprosin and Irisin by gender, (b) and (f) by age group, and (c) and (g) by BMI. P < 0.05 was considered statistically significant

3.4 ROC curve analysis of ASP and Ir

In order to evaluate the potential utility of serum ASP and Ir as supportive indicators for differentiating CRC patients from healthy individuals in clinical settings, receiver operating characteristic (ROC) curve analysis was performed. As shown in Figure 3, ASP exhibited an area under the curve (AUC) of 0.7801 (95% CI: 0.68 - 0.87, $P < 0.0001$), with a sensitivity of 83.93% and specificity of 60.0% at a cut-off value of 2.098 pg/mL (Figure 3a). Irisin showed a slightly lower but still informative AUC of 0.7571 (95% CI: 0.64 - 0.86, $P < 0.0001$), with 72.2% sensitivity and 67.65% specificity at a cut-off value of 2.232 ng/mL (Figure 3b). These findings suggest that both adipomyokine biomarkers, particularly ASP, may aid in the discrimination between CRC patients and healthy individuals, supporting their potential utility in complementary clinical assessment; however, further validation is required.

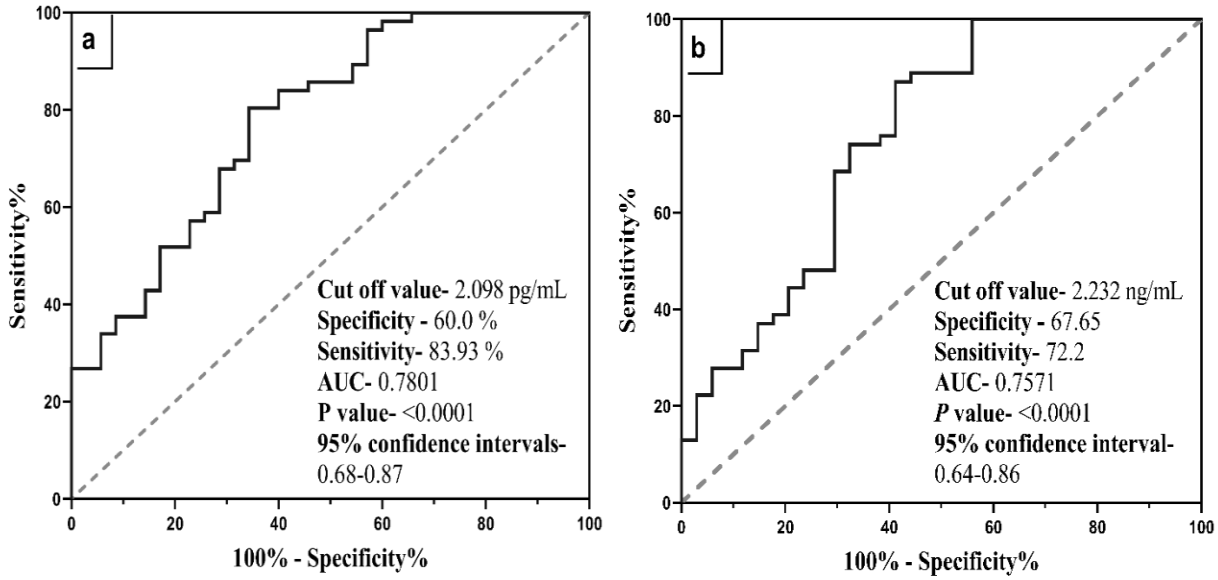

Figure 3: ROC curve analysis of Asprosin and Irisin in colorectal cancer patients.
Panel (a) shows the ROC curve of Asprosin (AUC = 0.7801, 95% CI: 0.68 - 0.87, $P < 0.0001$) with a cut-off value of 2.098 pg/mL (sensitivity = 83.93%, specificity = 60.0%). Panel (b) presents the ROC curve of Irisin (AUC = 0.7571, 95% CI: 0.64 - 0.86, $P < 0.0001$) with a cut-off value of 2.232 ng/mL (sensitivity = 72.2%, specificity = 67.65%).

3.5 Correlation between serum ASP and Ir levels with BMI and CEA in CRC patients

In this study, correlation analyses were performed using SPSS version 26 to assess the relationships between serum ASP and Ir levels, BMI as a major demographic factor, and CEA concentrations among CRC patients. The results are presented in Table 3.

A moderate positive correlation was observed between ASP and BMI in the overall CRC group (r = 0.25, $P = 0.057$), which did not reach statistical significance. However, when analyzed by gender, a stronger positive correlation between ASP and BMI was found in males (r = 0.80, $P = 0.701$) compared to females (r = 0.13, $P = 0.518$), though these associations were also not statistically significant.

Conversely, Ir levels showed a statistically significant inverse correlation with BMI in the overall CRC group (r = –0.23, $P = 0.013$), suggesting that higher BMI is associated with lower Ir levels in CRC patients. This negative correlation was more noticeable in females (r = 0.93, $P = 0.655$) and moderately positive in males (r = 0.34, $P = 0.078$), although neither reached statistical significance individually.

Regarding serum CEA, which was measured for all study participants, ASP showed a strong positive correlation with CEA levels (r = 0.73, $P = 0.455$), while Ir demonstrated a moderate negative correlation (r = –0.52, $P = 0.683$); however, both associations were not statistically significant. These results suggest trends of opposing relationships between the adipocytokines and CEA, but further mechanistic studies are needed for validation.

Table 3: Correlation of serum ASP and Ir levels with BMI and CEA levels in CRC patients.

Study parameter		Asprosin			Irisin		
	Number	CRC/62	Male /30	Female/32	CRC/62	Male/30	Female/32
BMI	r square	0.25	0.80	0.13	-0.23	0.34	0.93
	P-value	0.057	0.701	0.518	0.013*	0.078	0.655
CEA	r square	0.73	-	-	-0.52	-	-
	P-value	0.455	-	-	0.683	-	-

Correlation coefficients (r) and associated *P*-values were calculated using SPSS version 26. A *P*-value < 0.05 was considered statistically significant. Negative and positive r-values indicate the direction of correlation.

4. Discussion

Serum analysis of adipocytokines in this study revealed that Ir levels were significantly elevated in CRC patients compared to HC. While this contrasts with several earlier published studies indicating reduced Ir expression in various cancers, including colorectal [16], prostate [17, 18], breast [19], bladder [20], and gastric malignancies [21], which highlights ongoing inconsistencies in the available literature [8, 22]. For instance, Abd Temur *et al.,* reported significantly lower Ir levels in CRC patients, suggesting possible suppression of this adipomyokine during tumor progression [21]. In contrast, other studies have observed increased serum Ir levels and expression in gastrointestinal cancers (e.g., gastric, esophageal, and colon adenocarcinoma), such as those by Shahidi *et al.*, who reported elevated Ir levels in gastric adenocarcinoma [23], and Aydin *et al.*, who documented upregulation of Ir in colon and esophageal cancer [24]. Moreover, in cancer-related conditions, such as obesity, Mai et *al.,* reported an increase in serum Ir levels among individuals with obesity. Their study suggests a crucial relationship between circulating Ir levels, muscular mass, and the metabolic dysfunction associated with adiposity [25].

A plausible explanation for this discrepancy may involve the phenomenon of "Irisin resistance," in which elevated circulating levels occur despite diminished biological effectiveness, similar to Insulin resistance, which is the major cause of type II diabetes [8]. This resistance may result from reduced Irisin receptor sensitivity or downregulation, possibly induced by chronic inflammation or tumor-related metabolic alterations. Moreover, in conditions such as obesity, commonly linked with cancer, serum Ir has been reported to increase, suggesting its elevation may reflect compensatory responses to metabolic stress rather than effective tumor suppression [24, 26]. As the underlying mechanisms remain unclear, further investigation is needed to determine whether Ir acts as a protective adipomyokine or is merely elevated in response to tumor-induced alterations. From the current study perspective, the observed increase in Ir may indicate a reactive rather than regulatory role in CRC pathology, especially in the context of systemic inflammation or metabolic dysfunction [22, 27].

Divergences between the current findings and prior research on serum Ir levels in Iraqi CRC patients may stem from multiple contributing factors. These include variations in demographic profiles, racial and ethnic backgrounds, cancer staging, and the presence of comorbidities, each of which may modulate the biological systemic regulation of Ir under pathological conditions [8, 16]. It is believed that ethnic and regional differences may contribute to variations in Ir expression due to genetic predispositions or environmental exposures, emphasizing the need for further genetic and population-based studies [25]. Moreover, the stage of cancer may significantly affect the expression and circulating Ir levels. For instance, early-stage CRC patients might exhibit different Ir profiles compared to those with advanced or metastatic disease [27]. It is also possible that Ir interacts with other

molecular and metabolic pathways involved in tumor initiation and progression, which could explain the variability in findings across studies [8].

The observed reduction in serum ASP levels in this study aligns with the findings of Du *et al.,* [28], who reported markedly diminished ASP concentrations in cancer patients experiencing anorexia and cachexia syndrome. Nonetheless, despite growing interest in its metabolic and endocrine functions, the role of ASP in oncological contexts remains insufficiently characterized and warrants further investigation. Some studies focusing on metabolic disorders, particularly obesity, have shown that targeting ASP with monoclonal antibodies may reduce circulating levels and suppress appetite, highlighting its potent regulatory function in metabolism [12, 15]. In contrast to the current study results, Kerslake *et al.,* found elevated APS levels, along with increased expression of its receptor, olfactory receptor 4M1 (OR4M1), in both normal and malignant ovarian tissues [29].

Altered ASP expression has also been documented by several studies in conditions characterized by insulin resistance and type 2 diabetes mellitus, which are known to play a significant role in cancer pathophysiology [30, 31]. Precisely, insulin resistance has been implicated in the initiation and progression of colorectal adenocarcinoma, further linking ASP dysregulation with tumor development [28]. Mechanistically, ASP is known to promote hepatic glucose production by activating the G-protein/cAMP/PKA signaling cascade, utilizing cAMP as a secondary messenger [11]. This signaling axis is also involved in oxidative stress responses, and its dysregulation under hypoxic conditions may lead to increased production of reactive oxygen species (ROS) and oxidative damage, as well as the release of inflammatory cytokines and chronic inflammation [32]. Such metabolic disturbances may contribute to tumor progression through several potential pathways, including modulation of G protein-coupled receptor (GPCR) activity, alterations in cellular glucose metabolism, and enhanced inflammatory signaling via proinflammatory cytokines [32, 33]. Additionally, ASP may modulate oncogenic signaling pathways via activating the nuclear factor-κB (NF-κB) cascade, a regulatory axis known to control the transcription of genes implicated in cellular proliferation, survival, and chronic inflammation across a range of pathological states, including malignancies [34].

Taken together, these findings suggest that altered ASP expression may serve not only as a metabolic biomarker but also as a potential prognostic indicator in the early stages of carcinogenesis. This is particularly relevant in the context of the current study on CRC. While both ASP and Ir are closely associated with energy metabolism, the precise molecular mechanisms through which they influence CRC progression remain to be fully elucidated [11]. Based on the present study findings, elevated Ir and suppressed ASP levels may contribute to colorectal adenocarcinoma development through metabolic and inflammatory pathways.

In this study, higher serum Ir levels were observed in male CRC patients and HC compared to their female counterparts. Ir secretion is potently linked to skeletal muscle mass, which tends to be greater in males, partly due to elevated testosterone levels that stimulate FNDC5/Irisin expression through peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1-α)-mediated mitochondrial biogenesis. Supporting this, previous research has demonstrated that testosterone enhances energy expenditure and increases Ir expression in male mice. These findings align with the study by Dokumacıoğlu *et al.,* which reported higher circulating Ir levels in healthy males, emphasising the notion of sex-dependent variation in this important adipomyokine [35].

In contrast, ASP levels showed variation based on BMI, with lower levels in non-obese CRC patients and increased levels in obese individuals. ASP is secreted by adipose tissue and is strongly influenced by fat mass. Thus, individuals with higher adiposity are expected to exhibit elevated ASP concentrations. This finding is consistent with prior studies, which have shown that ASP levels correlate positively with insulin resistance, obesity, and metabolic syndrome [30, 31, 36]. The reduced ASP observed in non-obese individuals may reflect their lower adipose mass and potentially greater insulin sensitivity as well as lower glycemic index. Moradi *et al.,* reported that patients with Neonatal Progeroid Syndrome exhibited markedly low ASP levels, which corresponded with significantly reduced BMI and subcutaneous fat [31]. Correspondingly, in patients with acromegaly, a condition associated with insulin resistance, diabetes, and reduced fat mass, ASP levels were also diminished [37]. These observations, along with the results of the present study, suggest that ASP concentrations may serve as an indicator of both adipose tissue status and metabolic dysfunction in CRC patients.

Serum ASP levels in this study showed a positive correlation with CEA, while Ir levels exhibited a non-significant negative correlation. CEA is a well-established and IVD-confirmed tumor marker used in monitoring CRC progression and is known to increase under chronic inflammatory conditions [21]. The inverse relationship between Ir and CEA levels may reflect the impact of systemic inflammation on muscle-derived adipomyokine dysregulation in patients with CRC. Although not statistically significant, these patterns suggest a divergent role of the two adipocytokines in inflammation-mediated tumor dynamics. Elevated ASP may be linked to proinflammatory responses, while Ir is suppressed in the presence of inflammatory mediators, but further mechanistic studies are warranted to explore this relationship [26, 31, 33, 36].

The correlation analysis also revealed a positive but non-significant association between BMI and ASP levels in CRC patients. This trend is consistent with prior published works, which indicate that ASP concentrations are positively related to BMI and adiposity, particularly in metabolic disorders such as diabetes and obesity [30, 31, 36]. ASP is primarily secreted by white adipose tissue (WAT) and plays a key role in metabolic energy homeostasis and glucose regulation. Elevated adiposity may enhance ASP secretion from adipose tissue, potentially exacerbating the metabolic dysregulation commonly associated with CRC. Moreover, the expansion of adipose tissue is frequently associated with a state of chronic, low-grade inflammation, which can upregulate the production of proinflammatory cytokines, mediators that may in turn amplify ASP expression [32, 33]. These mechanistic insights align with the present findings, offering a plausible explanation for the elevated ASP levels observed among overweight individuals within the Iraqi CRC cohort.

A statistically significant inverse relationship was found between Ir and BMI among CRC participants, suggesting that increased body fat (as indicated by high BMI) is associated with lower circulating Ir levels. This finding aligns with the hypothesis that obesity-induced adipocyte dysfunction negatively affects adipomyokine regulation. As Ir is primarily derived from skeletal muscle fibers, its reduction in individuals with higher BMI may result from reduced muscle mass or impaired FNDC5 signaling in response to metabolic stress. These metabolic changes may not only influence Ir levels but also contribute to the development or progression of CRC through disrupted energy and redox homeostasis [8-10].

Insulin resistance is commonly observed in patients with high BMI and obesity, and ASP has been implicated in this condition due to its role in glucose metabolism and hormonal

regulation [30]. In CRC, insulin resistance may contribute to altered adipocytokine levels, including increased ASP. Therefore, CRC patients who are overweight or obese may exhibit higher ASP concentrations as a result of both their adiposity and insulin resistance [36]. These observations further support the notion that ASP may serve as a link between metabolic dysfunction and cancer progression.

In the present work, gender-specific analysis revealed positive, though non-significant, correlations between ASP and BMI in both males and females. Interestingly, a moderate positive association was observed between Ir and BMI in males, while a similar trend was seen in females with CRC. The relationship between obesity and adipocytokine secretion appears to be modulated by sex-specific hormonal and metabolic factors. In males, increased adiposity may provoke greater ASP release, potentially driven by heightened inflammatory activity within adipose tissue [36]. Conversely, the observed associations between Ir and BMI in female participants may reflect underlying differences in skeletal muscle composition, circulating estrogen levels, or divergent inflammatory signaling pathways. These sex-dependent trends suggest that the regulation of both ASP and Ir in CRC may be influenced by gender-specific physiological mechanisms, underscoring the importance of considering metabolic context in biomarker interpretation.

5. Conclusions

This study presents preliminary evidence supporting the potential utility of Ir and ASP as novel biomarkers in CRC. Their differential expression profiles, modulated by demographic and metabolic factors such as age, sex, and BMI, suggest that these adipocytokines may apprehend cancer-specific physiological changes not fully reflected by conventional markers like CEA. These findings suggest a potential adjunctive role for Ir and ASP in improving early diagnostic accuracy and refining risk stratification in CRC. While caution is warranted given the study's scope and sample size, the observed patterns underscore the need for further investigation. Future studies with broader cohorts and mechanistic analyses will be essential to determine the diagnostic robustness and prognostic value of these biomarkers within diverse clinical contexts.

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7. Ethical Approval and Informed Consent

This study was conducted in accordance with the Declaration of Helsinki and approved by the local ethical committee at Erbil Polytechnic University (EPU) (Approval Code: 11198; Date: 12 December 2023). Written informed consent was obtained from all participants, including both patients and healthy volunteers, prior to their enrollment in the study.

8. Conflict of Interest

The authors report there are no competing interests to declare.

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10. Author contributions

The research paper was written by PJJ and AJM. The theoretical framework was developed by AJM and PJJ, who also carried out the statistical analysis, summarized the article, and proofread it. The manuscript was also proofread, and the language was rectified by HMB and PAI. AJM, SZY, RWH, and SJS completed the experimental works. PJJ, AJM, HMB, and PAI edited the final draft of the manuscript. The study, data analysis, and article were all improved by the authors, who also contributed to discussions on the findings and the final paper version. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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