Original article

Investigating the Roles of Metabolic Syndrome and Inflammation as Prognostic Factors in Colorectal Cancer: A Retrospective Study

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Abstract

Aim: Colorectal cancer (CRC) is a leading cause of cancer-related mortality, and there is an increasing amount of evidence suggesting a link between metabolic syndrome (MetS) and the progression of this disease. MetS-related chronic inflammation, oxidative stress, and insulin resistance may contribute to tumor growth and influence patient survival. This study examined the association between MetS, systemic inflammation, and five-year survival among CRC patients.

Methods: A retrospective analysis was conducted on 95 patients treated for CRC at Osijek University Hospital Centre from October 2016 to December 2019. Clinical data, including tumor localization, stage, metabolic parameters, and inflammatory markers (CRP, ESR, and fibrinogen), were collected and analyzed.

Results: Among the 95 patients analyzed, 51.6 % were male, with a median age of 66 years, and 48.4 % were female, with a median age of 63 years. No significant associations were found between MetS, BMI, and five-year survival. However, patients with normal ESR values had significantly higher five-year survival rates ($p = 0.005$). Higher fibrinogen levels were unexpectedly associated with improved survival ($p = 0.03$), whereas elevated CRP levels showed a non-significant trend toward worse outcomes. Tumor localization and stage did not significantly impact survival rates.

Conclusion: These findings emphasize the importance of systemic inflammation in CRC prognosis, suggesting its potential as a prognostic factor independent of MetS. While MetS itself is not directly associated with survival, its pro-inflammatory components may be related. Due to the limited sample size, high variability, and challenges in standardizing the variables, larger multicenter studies are required.

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Introduction

Colorectal cancer is the third most common and the second deadliest malignant disease in the world, characterized by the sequential accumulation of multiple genetic aberrations [1]. Risk factors include dietary habits, reduced physical activity, genetic predisposition, and metabolic disorders. Metabolic syndrome, an increasingly common phenomenon in the modern world, shows a clear association with the incidence of CRC and is, therefore, the focus of numerous studies [2,3,4].

The mechanisms of the association between MetS and CRC include insulin resistance and hyperinsulinemia, chronic inflammation, dyslipidemia, hypertension, and obesity.

Insulin resistance, a key component of MetS, leads to compensatory hyperinsulinemia. Elevated levels of insulin and insulin-like growth factor-1 (IGF-1) promote colonic epithelial cell proliferation and inhibit apoptosis, which may promote carcinogenesis [5], leading to faster disease progression and shorter survival [2]. Elevated levels of IGF-1 may stimulate tumorigenesis through the activation of the PI3K/Akt and MAPK signaling pathways [5,6].

Adipose tissue, particularly visceral fat, secretes proinflammatory cytokines, including TNF-α, IL-6, and CRP, which contribute to chronic low-grade inflammation. Such an environment favors genetic mutations and tumor progression. Systemic inflammation associated with MetS may induce DNA damage and epigenetic changes, which increase the risk of CRC [7]. Inflammation affects all stages of carcinogenesis, including initiation, promotion, and progression [8]. Among the various mediators of inflammation, cytokines play specific but complex roles in promoting or inhibiting malignant transformation. Maintaining the balance between pro-inflammatory and anti- inflammatory factors is essential for maintaining homeostasis, while its disruption in either direction can contribute to the development of CRC [9,10]. Elevated fibrinogen levels are associated with an increased risk of developing CRC. Fibrinogen, a key protein in the coagulation process and a marker of inflammation, can influence the tumor microenvironment, promoting angiogenesis and metastasis. Therefore, measuring serum fibrinogen levels may have clinical value in assessing risk and prognosis for patients with CRC [9,11]. C-reactive protein is an acute-phase protein produced in the liver in response to inflammation, infection, or tissue damage. Elevated CRP levels are often associated with chronic inflammation, which plays a key role in the pathogenesis of CRC. Epidemiological studies and meta-analyses indicate that elevated CRP levels can be a prognostic and predictive biomarker for CRC [11,12]. In patients diagnosed with CRC, elevated CRP levels are associated with a worse prognosis, a higher disease stage, and a higher frequency of metastases [13]. Sedimentation rate (SE), also known as erythrocyte sedimentation rate (ESR), is a non-specific indicator of inflammation that is often used in clinical practice to assess chronic inflammatory conditions, including malignancies. An elevated ESR is associated with CRC, serving as a prognostic and diagnostic marker of this disease [14,15].

Elevated triglyceride levels and reduced HDL-cholesterol levels are characteristic of MetS and associated with oxidative stress and DNA damage, which may contribute to the development of CRC [16,17]. However, large meta-analyses have concluded that it is not possible to state with certainty that any component of dyslipidemia affects the survival of patients with CRC [18].

Hypertension may indirectly contribute to carcinogenesis through mechanisms related to oxidative stress, endothelial dysfunction, and blood flow disturbances, which may affect the tumor microenvironment [19,20]. Previous studies have suggested that regular preventive blood pressure measurement could identify individuals at increased risk of subsequent CRC [21]. Recent studies confirm the role of beta blockers in reducing postoperative complications of CRC as well as reducing long-term mortality [22].

Overweight and obesity, whose prevalence is increasing in many countries, are associated with a higher risk of CRC [14]. However, many patients with CRC lose weight before being diagnosed, which may lead to an underestimation of this association [23].

Some studies have reported that increased body weight and obesity at the time of colon cancer diagnosis are directly associated with better survival [13,24]. Other large studies have demonstrated that survival is much greater among people with normal body weight compared to those with overweight, obesity, or low body weight [25].

Numerous studies have suggested there is an association between MetS and an increased risk of CRC. A meta-analysis conducted by Esposito et al. [2] found that individuals with MetS have a 34% higher risk of developing CRC compared with individuals without the syndrome. Similarly, studies have shown that individual components of MetS, including obesity and insulin resistance, have an independent impact on the incidence of CRC [20]. Large cohort studies and meta-analyses have shown that individuals with MetS have an increased risk of developing CRC, and this risk is more pronounced among men. In addition, increased waist circumference and impaired glucose homeostasis have been identified as key risk factors [24,27,28].

In this retrospective study, we sought to determine the association between MetS, its individual components, inflammatory markers, and CRC specifically within our center, addressing the increasing prevalence of MetS and the conflicting results of previous studies.

Materials and methods

This retrospective study included 95 patients treated for CRC at Osijek University Hospital Centre between October 2016 and December 2019. The study was approved by the Ethical Committee of our institution (project code: R1-398/2025, date of approval: 17.01.2025). Available patient data were collected from the hospital's electronic database. All patients aged 35 to 78 years old with CRC, who were diagnosed using the International Classification of Diseases, 10th Revision (ICD-10), codes C18.0-C18.9, C19.0, and C20.0, regardless of whether they were treated on an outpatient basis or hospitalized, were included. Patients with colorectal cancer are categorized into those with right-sided and left-sided tumors because these cancers exhibit distinct molecular and genetic profiles, epidemiology, clinical presentations, treatments, and prognoses.The following data were analyzed: gender, age, tumor localization, and tumor stage. Additionally, inflammatory markers, including fibrinogen, ESR, and CRP, were evaluated. The metabolic parameters analyzed included glucose, lipid profile, body mass index, and MetS. A diagnosis of MetS was defined as meeting three or more of the following criteria: high arterial pressure, increased body mass, a blood glucose level (BGL) > 6 mmol/L, and dyslipidemia. All data were anonymized and collected for analysis without being linked to the patients.

Statistical methods: Categorical data were were summarized as counts and percentages (%). Differences in categorical variables were tested using the chi-square test and, when assumptions were not met, Fisher´s exact or Fisher-Freeman-Halton exact test. Numerical data were summarized using measures of central tendency (mean, median) and variability (standard deviation, minimum, maximum, interquartile range). The normality of the distribution of numerical variables was tested using the Shapiro–Wilk test. Differences in continuous variables between two independent groups were assessed using the Student´s test or Mann-Whitney U test, as appropriate. All P-values were two-sided. The significance level was set at $\alpha = 0.05$. Statistical analysis was conducted using IBM SPSS (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp.) and TIBCO Statistica (TIBCO Software Inc. (2020). Data Science Workbench, version 14) statistical software.

Results

This study included 95 participants, of whom 49 (51.6%) were men and 46 (48.4%) were women. The mean age of the male participants was 65.3 years, with median of 66 years, whereas female participans had mean age of 62.years and a median age of the female participants of 63 years (Table 1).

Table 1. Baseline characteristics of subjects participating in this study.

	Gender	
	Male	**Female**
Number (%) of respondents	49 (51.6)	46 (48.4)
Median (Interquartile Range)	66 (61-70)	63 (57-69)

Participants with five-year survival were somewhat more represented in the group with localization C18.0, C18.2, and C18.3 than in the other two groups, yet tumor localization and stage were not significantly associated with five-year mortality status (Table 2.).

Table 2. Differences between localization, cancer stage and five-year survival.

		Number (%) of respondents		
		Five-year survival		Fisher-Freeman-Halton exact test
		No	Yes	
Localization	C18.0, C18.2, C18.3	8 (20.5)	31 (79.5)	p = 0.498
	C18.4, C18.5, C18.6, C18.7	16 (32)	34 (68)	
	C18.9, C19.0, C20.0	2 (33.3)	4 (66.7)	
	Total	26 (27.4)	69 (72.6)	
Cancer stage	T1/T2 with A, B1	1 (10.0)	9 (90)	p = 0.537
	T3 with B2	2 (18.2)	9 (81.8)	
	N1/N2 with B3, C1, C2	9 (25)	27 (75)	
	M with D	13 (22)	46 (78)	
	Total	26 (27.4)	69 (72.6)	

C18.0, caecum cancer; C18.2, ascending colon cancer; C18.3, hepatic flexure cancer; C18.4, transverse colon cancer; C18.5, splenic flexure cancer; C18.6, descending colon cancer; C18.7, sigmoid colon cancer; C18.9, colon, unspecified cancer; C19.0, Malignant neoplasm of rectosigmoid junction; C20.0, malignant neoplasm of rectum; T1, tumor invades submucosa; T2, tumor invades muscularis propria; T3, tumor invades through the muscularis propria into the pericolorectal tissues; N1, metastasis in 1-3 regional lymph nodes; N2, metastasis in 4 or more lymph nodes; A, tumor limited to mucosa; B1, tumor limited to the submucosa, no lymph node invasion; B2, tumors confined to the muscle layer, no lymph node invasion; B3, invading into adjacent organs/structures; nodes not involved C1,the tumor did not exceed the bowel wall, lymph node metastasis; C2, tumor exceeded the intestinal wall and lymph node metastasis; M;D,distant metastatic spread

No association was found between MetS, BMI, and five-year survival. Participants with five-year survival were more represented in the group with normal CRP levels than in the group with elevated CRP levels, but no significant association was found between them. A significant association was observed between ESR and five-year survival, with participants who had normal ESR values being significantly more represented in the five-year survival group than those with elevated ESR values (p=0.005). The proportion of participants with five-year survival was higher in the group with elevated fibrinogen levels than in the group with normal fibrinogen levels (p=0.029) (Table 3.).

Table 3. Differences in levels of C-reactive protein, erythrocyte sedimentation, fibrinogen, body mass index as metabolic syndrome relating to the five-year survival.

		Number (%) of respondents		
		Five-year survival		
		No	Yes	P
Metabolic syndrome	No	8 (29.6)	19 (70.4)	
	Yes	18 (26.5)	50 (73.5)	0.755*
	Total	26 (27.4)	69 (72.6)	
C-reactive protein (ug/L)	Normal	4 (14.8)	23 (85.2)	
	High	21 (34.4)	40 (65.6)	0.060*
	Total	25 (28.4)	63 (71.6)	
Erythrocyte sedimentation (mm/h)	Normal	1 (4.2)	23 (95.8)	
	High	7 (41.2)	10 (58.8)	0.005†
	Total	8 (19.5)	33 (80.5)	
Fibrinogen (g/L)	Normal	7 (43.8)	9 (56.3)	
	High	4 (12.9)	27 (87.1)	0.029†
	Total	11 (23.4)	36 (76.6)	
Body mass index range (kg/m²)	Underweight	2 (100)	0 (0)	
	Normal weight	6 (35.3)	11 (64.7)	
	Overweight	7 (20.6)	27 (79.4)	0.096‡
	Obese	9 (23.1)	30 (76.9)	
	Total	24 (26.1)	68 (73.9)	

*Pearson chi-square test; †Fisher exact test; ‡Fisher-Freeman-Halton exact test.

A significant overall difference was found in CRP and ESR values among the analyzed groups (p=0.003 and p=0,005, respectively). The average fibrinogen level was significantly higher in participants who survived five years (p=0.01) (Table 4.).

Table 4. Differences in C-reactive protein, erythrocyte sedimentation, fibrinogen and body mass index relating to the five-year survival.

	Median (Interquartile Range)		
	Five-year survival		
	No	Yes	P
C-reactive protein (ug/L)	36 (12-114)	10 (3-37)	0.003*
Erythrocyte sedimentation (mm/h)	45 (33-68)	14 (9-29)	0.007*
Fibrinogen (g/L)	3 (2-4)	4 (4-5)	0.012†
Body mass index (kg/m²)	28 (24-32)	29 (27-33)	0.127†

* Mann-Whitney U test; †Student t-test.

No significant difference was found in the relationship between gender and five-year survival (Table 5.).

The Mann-Whitney U test showed no significant difference in blood glucosae levels between the two groups according to five-year mortality status (Table 6.).

Table 5. Differences in gender relating to the five-year survival.

Gender	Number (%) of respondents		P
	Five-year survival		
	No	Yes	
Male	12 (24.5)	37 (75.5)	0.516*
Female	14 (30.4)	32 (69.6)	
Total	26 (27.4)	69 (72.6)	

*Pearson chi-square test.

Table 6. Differences in plasma glucose level relating to the five-year survival.

	Median (Interquartile Range)		
	Five-year survival		P
	No	Yes	
Plasma glucose level (mmol/l)	7 (6-8)	6 (5-8)	0.054*

* Mann-Whitney U test.

No significant differences were found in the average values of cholesterol, LDL, triglycerides, and HDL between the two observed groups in relation to five-year survival (Table 7.).

Table 7. Differences in lipid profile level relating to the five-year survival.

Lipid profile level	Median (Interquartile Range)		P
	Five-year survival		
	No	Yes	
Cholesterol (mmol/l)	5 (3-6)	5 (4-5)	0.0522*
Triglycerides (mmol/l)	1 (1-2)	2 (1-2)	0.423‡
High-density lipoprotein (mmol/l)	1 (1-2)	1 (1-1.5)	0.922‡
Low-density lipoprotein (mmol/l)	2 (1-3)	3 (2-3)	0.112*

*Student t-test; ‡Mann-Whitney U test.

Discussion

Colorectal cancer accounts for 10 % of all cancer cases and deaths worldwide, ranking as the second most common cancer in women and the third most common in men. Incidence and mortality rates are 25 % lower among women, suggesting potential sex-related differences in risk factors and disease progression. A concerning trend is the rising incidence and mortality of CRC in individuals under 50, particularly in regard to rectal and left-sided colon cancers. While the exact causes remain unclear, factors such as diet, lifestyle, alterations in gut microbiota, metabolic changes, and chronic inflammation are believed to contribute to the condition [29].

Inflammation is known to play a role in tumorigenesis, though a direct causal link remains unproven. Studies have indicated that elevated baseline CRP levels are associated with an increased risk of cancer, with positive correlations seen for multiple malignancies, including CRC. At the same time, a negative association has been noted for chronic lymphocytic leukemia (CLL) [30]. CRP, a nonspecific inflammatory marker primarily synthesized in the liver, is upregulated in response to cytokine release in various pathological conditions. Evidence suggests that chronic low-grade intestinal inflammation may contribute to CRC development, positioning CRP as a potential biomarker for disease progression [31, 32]. In our study, patients with normal CRP levels (<5 μ g/L) had a higher five-year survival rate than those with elevated CRP levels,

although this association was not statistically significant. This finding aligns with prior research indicating CRP's prognostic value but questioning its independence as a survival predictor [33]. Retrospective case–control studies have reported up to tenfold higher CRP levels among CRC patients compared to healthy controls. This elevation may result from reverse causality, where an advanced malignancy induces a systemic

inflammatory response, leading to increased CRP levels [30,31]. Several studies have reported that elevated CRP levels are more frequently observed in patients with right-sided CRC or tumors exhibiting microsatellite instability (MSI). Moreover, a significant association has been identified between high CRP levels and extensive macrophage infiltration within the tumor microenvironment [11]. Additionally, in the validation cohort, high CRP levels were linked to intraepithelial infiltration of tumors by T cells, particularly T-helper 1 (Th1) cells. However, no significant association was found between CRP levels and an increased systemic cellular immune response [34]. The trend observed in our data reinforces the role of systemic inflammation in CRC progression and highlights the need for further investigation into CRP as a potential risk stratification tool.

Similarly, ESR another key marker of systemic inflammation, showed a statistically significant association with five-year survival. Patients with normal ESR had a significantly higher survival rate than those with elevated ESR, supporting previous studies that have linked elevated ESR to poorer CRC outcomes. This finding suggests that ESR and CRP may be valuable prognostic biomarkers for identifying high-risk CRC patients who may require closer monitoring and more aggressive therapeutic interventions. Some studies have shown that a preoperative ESR elevation (>40 mm/h)

is a predictor of poorer postoperative survival among CRC patients. A recent study found that ESR levels were significantly higher in patients with Dukes stage C or D compared to those with Dukes stage A or B and that patients with elevated ESR had significantly worse outcomes (35). One study also demonstrated an association between an elevated ESR and various clinical and pathological factors, including male sex, decreased hemoglobin levels, an increased platelet count, high preoperative carcinoembryonic antigen (CEA) levels, high preoperative carbohydrate antigen 19-9 (CA19-9) levels, a larger tumor (≥5 cm), a higher T stage, and an advanced TNM stage. Although an elevated ESR was associated with poorer survival, multivariate analysis did not confirm it as an independent prognostic factor. These findings suggest that preoperative ESR elevation in CRC patients may indicate more aggressive tumor behavior and an overall poorer prognosis [36].

Elevated fibrinogen (>3,5g/L) levels are linked to an increased incidence of CRC as well lung cancer [37]. Our results revealed a statistically significant association between fibrinogen levels and five-year survival, with higher fibrinogen levels unexpectedly correlating with improved survival. Although this finding may seem counterintuitive, it underscores the dual role of fibrinogen in cancer progression and immune response. While elevated fibrinogen levels are often linked to an increased tumor burden and systemic inflammation, it may also reflect a heightened inflammatory and coagulation response that, in some cases, enhances antitumor defense mechanisms. These findings

align with the results of previous studies suggesting that fibrinogen's prognostic impact varies based on tumor stage, patient-specific factors, and the overall systemic response [9,38]. Conversely, some studies have reported that elevated preoperative fibrinogen levels are associated with poorer overall and disease-free survival, a reduced response to therapy, larger tumors, and increased tumor invasion, particularly in CRC. A case–cohort study further identified fibrinogen levels ≥4 g/L as an independent risk factor for CRC, emphasizing fibrinogen's potential role as a negative prognostic indicator [9]. Moreover, changes in fibrinogen levels after chemoradiotherapy (CRT) may serve as

an important prognostic marker for rectal cancer. One study found that post-CRT fibrinogen levels significantly correlated with lymphatic and venous invasion, tumor size, depth of invasion, and tumor regression grading. Additionally, patients with higher post- CRT fibrinogen levels exhibited shorter disease-free survival, highlighting fibrinogen's potential relevance in treatment response assessment [11]. A possible explanation for this unexpected direction of association is the presence of unmeasured confounding. In our study, several key determinants of fibrinogen—such as postoperative morbidity, intercurrent infections, residual disease, completion and intensity of oncologic therapy, and detailed comorbidity burden—were not systematically captured in our dataset and therefore could not be adjusted for. These factors may have disproportionately affected patients with lower fibrinogen values, thereby biasing survival estimates. It is also possible that patients with higher fibrinogen values had more favorable baseline characteristics; however, this cannot be verified because these variables were not systematically collected.

In recent years, growing evidence has established MetS as a significant risk factor for CRC development and progression. Our study did not find a statistically significant association between MetS and five-year survival. While previous research has linked MetS to worse CRC outcomes, the lack of significance in our cohort may be due to sample size limitations or the heterogeneous presentation of MetS components among patients. The relationship between MetS and CRC is complex, involving multiple interconnected pathways. Each component of metabolic syndrome (MetS) influences cell proliferation. Hyperinsulinemia decreases the production of IGF-binding proteins IGFBP-1 and IGFBP-2, resulting in increased bioavailability of free IGF-1. Additionally, insulin promotes the synthesis of growth hormone (GH), which further stimulates IGF-1 production. Both mechanisms contribute to increases in the levels of free IGF-1. IGF-1 primarily binds to its own receptor (IGF-1R), but it can also interact with insulin receptors. Activation of these receptors triggers phosphorylation cascades that stimulate the PI3K/Akt/mTOR and RAS-MAPK signaling pathways, ultimately promoting anabolic activity and inhibiting apoptosis in cells. Furthermore, hyperglycemia enhances tumorigenic potential by supplying readily available glucose, which is a critical metabolic substrate for the energy-intensive processes of malignant cell proliferation and growth [39]. Under hypoxic conditions, visceral adipose tissue, as a hormonally active organ, regulates the transcription of genes involved in cell proliferation via hypoxia-inducible factor 1 (HIF-1) and the transcription factor NF-κB. The adipokines leptin and resistin act as pro-oncogenic cytokines by activating Janus kinases as well as the MAPK/ERK and PI3K/Akt signaling pathways. Interleukin-6 (IL-6) primarily signals through the STAT pathway, while tumor necrosis factor-alpha (TNF-α) activates the NF-κB pathway. Low-grade chronic inflammation, a hallmark of MetS, promotes the recruitment and activation of inflammatory cells within the tumor microenvironment through various inflammatory

mediators. These include tumor-associated macrophages of the M2 phenotype (TAMs), tumor-associated neutrophils of the N2 phenotype (TANs), and myeloid-derived suppressor cells (MDSCs), all of which contribute to immune tolerance and tumor progression [40,41]. Obesity-induced alterations in gut microbiota composition and bile acid metabolism have also been implicated in colorectal tumorigenesis [39,42]. In individuals with obesity, the gut microbiome undergoes dysbiosis, characterized by a reduced diversity of beneficial microbes (such as Bacteroides and Firmicutes) and an overrepresentation of pro-inflammatory or potentially pathogenic bacteria (e.g., Fusobacterium nucleatum, Escherichia coli with genotoxins). These microbial shifts can lead to chronic mucosal inflammation, disruption of the intestinal barrier, and increased production of bacterial metabolites such as secondary bile acids (e.g., deoxycholic acid), which have been shown to exert carcinogenic effects by promoting DNA damage, oxidative stress, and

epithelial proliferation. Moreover, obesity alters bile acid synthesis and enterohepatic circulation. In excessive quantities, bile acids, particularly hydrophobic secondary bile acids, can act as signaling molecules that activate nuclear receptors such

as FXR and membrane-bound receptors like TGR5, which modulate inflammation, apoptosis, and cellular proliferation in the colon. The cumulative product of these alterations is an environment that supports colorectal tumorigenesis. The reported prevalence of MetS among CRC patients varies significantly depending on the diagnostic criteria used, highlighting inconsistencies across studies. Goulart et al. found that 40.7% of CRC patients met MetS criteria according to the ATPIII definition. In contrast, prevalence rates of 67.5% and 67.0% were observed when applying the AHA and IDF definitions, respectively [43]. MetS is associated not only with increased overall mortality risk but also a significant impact on CRC-specific survival. One meta-analysis reported that MetS was associated with increased all-cause and CRC-specific mortality among CRC patients. Among individual MetS components, diabetes mellitus was linked to higher overall mortality, whereas obesity was associated with increased CRC-specific mortality compared to that for non-MetS patients. Furthermore, the risk of CRC-specific mortality increased with the presence of more metabolic risk factors [42]. Our findings suggest that BMI does not significantly impact survival outcomes among patients with CRC. Despite previous reports linking a higher BMI to increased CRC risk, we did not

observe a clear distinction between patients with shorter survivals and those who survived beyond five years. This raises the question of whether BMI alone is an adequate predictor of prognosis or if other metabolic factors, such as visceral fat distribution or insulin resistance, have a greater impact on CRC outcomes. However, conflicting evidence exists regarding MetS and CRC prognosis. One study suggested that MetS does not significantly influence the surgical outcomes of CRC patients [43].

Additionally, Ahmadi et al. reported that CRC patients with MetS had a shorter mean survival time (23 months) compared to those without MetS (27 months). Yet, this study also identified tumor stage, tumor size, and educational level as independent predictors of CRC survival, underscoring the multifactorial nature of CRC prognosis [44].

Recent cancer statistics indicate that between 2015 and 2019, the average annual incidence rate of colorectal cancer was 33 % higher in men, while the overall mortality rate was 43 % higher in men. Furthermore, women demonstrated a slightly higher five-year relative survival rate, suggesting potential sex-related differences in disease progression, response to treatment, or early detection patterns [45,46]. Sexual dimorphism in CRC incidence and prognosis is well-documented, with men generally facing a higher risk than women. Emerging research suggests this disparity may be driven by sex steroid hormones and gut microbiome differences, leading to the concepts of the „microgenderome“ and the „sex hormone–gut microbiome axis“. Studies have indicated that estrogens may promote a healthier gut microbiota composition, potentially reducing CRC risk, while androgens may foster a pro-tumorigenic environment by encouraging the growth of opportunistic pathogens. Additionally, gut microbiota can regulate sex hormone levels through enzyme expression or direct modulation of gonadal function, further influencing CRC susceptibility and progression [47]. At the same time, hyperinsulinemia downregulates the hepatic synthesis of sex hormone-binding globulin (SHBG), leading to elevated levels of bioavailable testosterone. As a potent anabolic hormone, testosterone exerts proliferative, pro-survival, and growth-promoting effects on various cell types, including neoplastic cells [38]. In our study, we investigated sex-related differences in five-year survival and found no statistically significant association between sex and survival. The absence of a statistically significant association in our study may reflect the complex interplay of multiple prognostic factors, including tumor stage, treatment regimens, and comorbidities,

which could attenuate the impact of sex on survival.

The anatomical location of CRC is crucial in disease progression, treatment response, and overall survival. Tumors located in different segments of the colon and rectum exhibit distinct molecular, histopathological, and clinical characteristics that influence prognosis. Right-sided CRC (proximal colon) and left-sided CRC (distal colon and rectum) have been extensively studied for their differences in genetic alterations, immune responses, and microbiome composition. Right-sided CRC (affecting the cecum, ascending colon, and transverse colon) is often associated with microsatellite instability (MSI), BRAF mutations, and a stronger inflammatory response. These tumors tend to present at more advanced stages, with a higher likelihood of peritoneal metastases and a generally poorer prognosis compared to left-sided CRC. Patients with right-sided tumors frequently have a weaker response to anti-EGFR therapy, which further complicates treatment strategies [48,49].

Conversely, left-sided CRC (affecting the descending colon, sigmoid colon, and rectum) is typically characterized by chromosomal instability (CIN), KRAS mutations, and a more favorable prognosis. These tumors are more likely to be symptomatic at an earlier stage, often presenting with obstructive symptoms that prompt earlier detection.

Studies have consistently shown that patients with left-sided CRC, who are RASwt, have better overall and progression-free survival, particularly in cases of metastatic disease, wherein anti-EGFR therapy is more effective [48,49].

Our study examined the relationship between tumor localization and five-year survival, but the findings did not indicate a statistically significant association. Although survival rates varied among tumor locations, the results of the Fisher–Freeman–Halton exact test did not support a clear prognostic distinction based on tumor site. It is most likely that the inclusion of patients from all disease stages and the relatively small sample size resulted in an averaging effect that diluted statistically significant differences attributable to individual stages.

Future studies should incorporate molecular profiling and treatment-specific analyses to better reveal the prognostic implications of tumor localization in CRC. Integrating tumor biology with clinical outcomes may help refine personalized treatment approaches and improve survival predictions for patients based on the tumor site. This study provides real-world insight into the relationship between metabolic syndrome, systemic inflammatory markers, and five-year survival in patients with colorectal cancer treated at a regional referral center. By evaluating routinely collected clinical and laboratory data, it highlights the prognostic relevance of inflammation—particularly ESR—and underscores the complexity of interpreting metabolic and inflammatory profiles in heterogeneous clinical populations. Although no significant associations were observed for metabolic syndrome components or tumor localization, the study highlights relevant patterns that add to the growing understanding of the complex interactions between metabolic health, systemic inflammation, and colorectal cancer prognosis.

This study has several limitations. Its retrospective design inherently restricts the completeness and accuracy of available clinical information. As previously noted, important prognostic variables—such as postoperative morbidity, intercurrent infections, residual disease, detailed comorbidity profiles, treatment adherence, and the intensity or completion of oncologic therapy—were not consistently documented and therefore could not be incorporated into the analysis. The relatively small sample size limits statistical power and increases the likelihood of type II error, potentially obscuring meaningful associations, particularly those related to metabolic syndrome components and tumor localization. Additionally, key molecular tumor characteristics, including mismatch repair status and KRAS/BRAF mutations, were not available. Finally, the single-center design may limit the generalizability of the findings.

Future studies should address these limitations by including larger, multicenter cohorts with comprehensive clinical and molecular data. Prospective designs with standardized timing of metabolic and inflammatory measurements would allow clearer interpretation of temporal patterns and disease-related changes. Incorporating molecular tumor profiling, immune signatures, and treatment-specific variables may clarify interactions between metabolic factors, inflammation, and tumor biology. Finally, more detailed analyses of tumor localization—integrated with molecular markers and therapeutic regimens—may help refine risk stratification and support the development of personalized treatment strategies.

Conclusion

Our findings contribute to the growing evidence on the prognostic significance of inflammatory, metabolic, sex-related, and anatomical factors in CRC. While some associations reached statistical significance, others demonstrated notable trends, underscoring the need to conduct larger, multicenter studies to better understand the clinical implications of these associations, especially regarding the impact of gut microbiota and bariatric surgery on the incidence and prognosis of these patients. Given

the complex interplay between systemic inflammation, lipid metabolism, tumor location, and sex-related differences, future research should focus on integrating these factors into comprehensive prognostic models. A more refined approach to risk stratification could help identify high-risk patients more effectively, supporting the development of personalized treatment strategies to improve CRC outcomes.

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Istraživanje uloga metaboličkog sindroma i upale kao prognostičkih čimbenika za karcinom debeloga crijeva: retrospektivna studija

Sažetak

Cilj: Kolorektalni karcinom (CRC) jedan je od vodećih uzroka smrtnosti povezane s malignim bolestima, a sve veći broj dokaza ukazuje na povezanost metaboličkog sindroma (MetS) s progresijom ove bolesti. Kronična upala, oksidativni stres i inzulinska rezistencija povezani s MetS-om mogu pridonijeti rastu tumora i utjecati na preživljenje bolesnika. Ovim istraživanjem ispitana je povezanost MetS-a, sistemske upale i petogodišnjeg preživljenja bolesnika s CRC-om.

Metode: Provedena je retrospektivna analiza 95 bolesnika liječenih zbog CRC-a u Kliničkom bolničkom centru Osijek u razdoblju od listopada 2016. do prosinca 2019. Prikupljeni su i analizirani klinički podaci, uključujući lokalizaciju tumora, stadij bolesti, metaboličke parametre i upalne biljege (CRP, SE i fibrinogen).

Rezultati: Od ukupno 95 analiziranih bolesnika, 51,6 % bili su muškarci (medijan dobi 66 godina), a 48,4 % žene (medijan dobi 63 godine). Nije utvrđena značajna povezanost između MetS-a, BMI-a i petogodišnjeg preživljenja. Međutim, bolesnici s normalnim vrijednostima SE imali su značajno više stope petogodišnjeg preživljenja (p=0,005). Više razine fibrinogena bile su neočekivano povezane s boljim preživljenjem (p = 0,03), dok su povišene vrijednosti CRP-a pokazale neznačajan trend prema lošijim ishodima. Lokalizacija i stadij tumora nisu imali značajan utjecaj na stope preživljenja.

Zaključci: Dobiveni rezultati naglašavaju važnost sistemske upale u prognozi CRC-a te ukazuju na njezin potencijal kao prognostičkog čimbenika neovisnog o MetS-u. Iako MetS sam po sebi nije izravno povezan s preživljenjem, njegovi proinflamatorni sastavni dijelovi mogli bi biti od značaja. Zbog malog uzorka ispitanika, nemogućnosti standardiziranja varijabli neophodne su veće, multicentrične studije.

Ključne riječi: metabolički sindrom; novotvorine na debelome crijevu, upala, preživljenje