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ORIGINAL ARTICLE

Assessment of metabolic and inflammatory risk factors in patients with colorectal adenoma and carcinoma

Kolorektal adenoma ve karsinomlu hastalarda metabolik ve inflamatuvar risk faktörlerinin değerlendirilmesi

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Background and Aims: Metabolic syndrome and its related components are thought to be risk factors for developing colorectal neoplasms due to hyperinsulinemia, insulin resistance, and oxidative stress resulting in chronic low-grade inflammation. This study aims to explain the association of colorectal neoplasms (colon adenocarcinoma and colon adenoma) with metabolic syndrome components, non-alcoholic fatty liver disease, and inflammatory markers. **Materials and Methods:** Data of 151 patients diagnosed with colon adenoma and colorectal adenocarcinoma were retrospectively reviewed. Demographic characteristics, routine blood tests, colonoscopic findings, pathology results, tumor-node-metastasis stages of colorectal adenocancer, and hepatic ultrasonography findings were recorded. The Homeostatic Model Assessment for Insulin Resistance scores were calculated. **Results:** The study cohort consisted of 71 patients with adenoma and 80 patients with colorectal adenocancer. The number of patients with diabetes mellitus, hypertension, hypertriglyceridemia, metabolic syndrome, severe liver steatosis was significantly higher in the colorectal adenocancer group compared to the colorectal adenoma group. Additionally, neutrophil-lymphocyte ratio, C-reactive protein, and C-reactive protein to albumin ratio were significantly higher in the colorectal adenocancer group compared to the adenoma group. In univariant analysis, patients with diabetes mellitus, hypertension, hypertriglyceridemia, metabolic syndrome, severe liver steatosis were found to have a shorter duration of survival than those who did not have these risk factors. In multivariate analysis, advanced tumor-node-metastasis stage, severe hepatosteatosis, hypertension, and hypertriglyceridemia were found to be independent risk factors for survival of the patients with colorectal adenocancer. **Conclusions:** Metabolic syndrome, severe liver steatosis, and inflammatory process may be risk factors for the transition from colon adenoma to adenocarcinoma and shorter survival in colorectal cancer patients.

Key words: Colorectal adenoma, colorectal adenocarcinoma, insulin resistance, chronic inflammation

Giriş ve Amaç: Metabolik sendrom ve ilişkili bileşenlerinin, hiperinsülinemi, insülin direnci ve kronik düşük dereceli inflamasyonla sonuçlanan oksidatif strese bağlı kolorektal neoplazmların gelişimi için risk faktörleri olduğu düşünülmektedir. Bu çalışma, kolorektal neoplazmların (kolon adenokarsinom ve kolon adenomu) metabolik sendrom bileşenleri, non-alkolik yağlı karaciğer hastalığı ve inflamatuvar belirteçlerle ilişkisini açıklamayı amaçlamaktadır. **Gereç ve Yöntem:** Kolon adenoma ve kolorektal adenokarsinom tanısı alan 151 hastanın verileri geriye dönük olarak incelendi. Demografik özellikler, rutin kan tetkikleri, kolonoskopik bulgular, patoloji sonuçları, kolorektal kanserin tümör-lenf nodu-metastaz evreleri ve hepatik ultrasonografi bulguları kaydedildi. İnsülin direnç testi skorları hesaplandı. **Bulgular:** Çalışma kohortu, kolorektal adenoma olan 71 hasta ve kolorektal kanseri olan 80 hastadan oluşuyordu. Diabetes mellitus, hipertansiyon, hipertrigliseridemi, metabolik sendrom, şiddetli karaciğer yağlanması olan hasta sayısı adenoma grubuna göre kolorektal kanser grubunda anlamlı olarak daha yüksekti. Ek olarak, nötrofil-lenfosit oranı, C-reaktif protein ve C-reaktif protein/albümin oranı, kolorektal adenoma grubuna göre, kolorektal kanser grubunda anlamlı olarak daha yüksekti. Tek değişkenli analizde diabetes mellitus, hipertansiyon, hipertrigliseridemi, metabolik sendrom, şiddetli karaciğer steatozu olan hastaların, bu risk faktörlerine sahip olmayanlara göre daha kısa sağkalım süresine sahip oldukları bulundu. Çok değişkenli analizde, ileri tümör-lenf nodu-metastaz evresi, şiddetli hepatosteatoz, hipertansiyon ve hipertrigliseridemi, kolorektal adenokanserli hastaların sağkalımı için bağımsız risk faktörleri olarak bulundu. **Sonuç:** Metabolik sendrom, ciddi karaciğer yağlanması ve inflamatuvar süreç, kolorektal kanser hastalarında, kolon adenomundan adenokarsinoma geçiş ve daha kısa sağkalım için risk faktörleri olabilir.

Anahtar kelimeler: Kolorektal adenom, kolorektal adenokanser, insulin direnci, kronik inflamasyon

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide and the third leading cause of cancer-related deaths (1). During the development of CRC, there is a progression from benign adenomas to malignant adenocarcinomas. The risk factors for this progression are not crystal clear. However, hypertension, diabetes mellitus (DM), hyperlipidemia, insulin resistance, non-alcoholic fatty liver disease (NAFLD), and obesity are important risk factors that share the occurrence and progression of colon neoplasms (2). Based on the relationship between DM and insulin resistance which are components of metabolic syndrome (MetS), hyperinsulinemia is thought to play a key role in the pathogenesis of cancer by stimulating cell proliferation through the insulin-like growth factor (IGF) system (3). Indeed, MetS harbors other cancer risk factors, such as sedentary life, high-calorie, and fatty diet intake, low fiber intake, and oxidative stress (4). Visceral obesity also causes the production of inflammatory cytokines through adipocytes, resulting in chronic low-grade inflammation (5). Nevertheless, although MetS is associated with a 34% increase in the risk of colorectal neoplasia (colorectal adenoma and CRC) (6), there are also studies with contradictory results (7-10).

In the present study, we aimed to assess the difference between the patients with colorectal adenoma and carcinoma concerning MetS components, the degree of insulin resistance, and liver steatosis. We also scrutinized several serum inflammatory markers such as C-reactive protein (CRP), neutrophil-lymphocyte ratio (NLR), CRP to albumin ratio, and various other demographic data to detect possible risk factors for an adenoma to carcinoma transformation. Finally, we aimed to determine whether these factors affect overall survival in CRC patients.

MATERIALS and METHOD

Overall, 151 patients who had been diagnosed with colonic adenoma and or CRC in our gastroenterology clinics between January 2017 - January 2019 were enrolled in the study. Files of the patients included in the study were retrospectively reviewed from the hospital database, and the data was recorded for analysis. Patients over 18 years old who were diagnosed with colon adenoma or adenocarcinoma in our gastroenterology clinics were included in this study.

Demographic characteristics such as age and gender of the patients, body mass index, waist circumference, systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, triglyceride, fasting blood glucose, fasting insulin level, HbA1c level, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), creatinine, complete blood count (CBC), neutrophil-lymphocyte ratio (NLR), C-reactive protein (CRP), albumin, 25-OH-vitamin D levels were recorded. Those with fasting plasma glucose ≥ 126 mg/dl or HbA1c ≥ 6.5 or those taking oral anti-diabetic drugs and/or insulin were considered to have diabetes mellitus. The Homeostasis Model Assessment-insulin resistance (HOMA-IR) = [Fasting blood glucose (mmol/L) x Fasting insulin (mU/ml)/22.5] was used to detect insulin resistance. According to the anthropometric measurements of the study participants, those with body mass index (BMI) > 30 were classified as obese and those with BMI > 25 as overweight [BMI: square of body weight (kg) / height(m)]. For the diagnosis of hypertension, those with a blood pressure level above 120/80 mmHg or those taking antihypertensive drugs were considered to be hypertensive. MetS was defined according to the revised criteria of the National Cholesterol Education Program/ Adult Treatment Panel III (NCEP /ATP III) published in 2005.

The diagnosis of colonic neoplasm was based on colonoscopic findings and pathology results of samples taken via colonoscopy. We especially paid specific attention to the localization of colonic tumors in detail (the right colon, the left, and the rectum). The diagnosis of NAFLD and the degree of liver steatosis and/or fibrosis was diagnosed by ultrasonography, and/or histopathological examination of the liver biopsy samples.

Liver steatosis was diagnosed and graded by ultrasound-based techniques and grading criteria were as follows: Absent, when the echogenicity of the liver was normal; mild, when there was a slight and diffuse increase of liver echogenicity with normal visualization of the diaphragm and the portal vein wall; moderate, in case of a moderate increase of liver echogenicity with the slightly disrupted appearance of the portal vein wall and the diaphragm; severe, in case of the marked increase of liver echogenicity with poor or no visualization of the portal vein wall and the diaphragm (11). In a pathological examination of the liver biopsy samples, the degree of steatosis between 5 and 33% was classified as mild, 34-66% as moderate, and over 66% as severe steatosis (12). For the diagnosis of NAFLD; alcohol consumption greater than 20 g per day in women or greater than 30 g in men for at least three consecutive months over the past 5 years and chronic hepatitis causes such as viral hepatitis, autoimmune hepatitis, and other potential etiologies were excluded.

Patients with decompensated chronic liver disease, acute, and chronic renal insufficiency, heart failure, extra-colonic malignancies, history of splenectomy, obesity due to endocrine disease, cerebrovascular disease, and postpartum status within the last 6 months were excluded. Those who receive hormone replacement therapy and patients with insufficient clinic files were not enrolled either.

Statistical Analysis

SPSS 21.0 (IBM, Armonk, NY, USA) was used for data analysis. Statistical relationships between categorical data were made using the Chi-Square test. Two independent group t-tests were used for the comparison between groups for the normally distributed variables, and the Mann Whitney U test was used for the non-normally distributed variables. Receiver operating characteristics (ROC)-Analysis was used to find cut-off values for N/L and CRP/lab values. Survival times were given with Kaplan Mayer statistics, and it was decided whether there was a difference between the survival times between groups with the Log-Rank Test. For multivariate analysis, independent factors predicting survival were analyzed using Cox regression analysis.

Ethics Committee

An approval from Zonguldak Bülent Ecevit University, A Non-Interventional Clinical Research Ethics Committee was obtained for the study (Protocol No:2020/22, Approval date:18/11/2020). The study protocol conforms to the ethical guidelines of the 1964 Declaration of Helsinki.

RESULTS

Seventy one patients were diagnosed with colorectal adenoma and 80 patients were diagnosed with CRC. The mean age of the study cohort was 64.68 ± 12.90 years. This was 63.97 ± 12.75 in the adenoma group and it was 65.31 ± 13.09 in the CRC group. There were 44 (62%) men and 27 (38%) women in the adenoma group and 46 (57.5%) men and 34 (42.5%) women in the CRC group. There were no statistically significant differences concerning age and gender in both groups (Table 1). Out of 80 patients diagnosed with colorectal cancer, 11 (7.3%) were classified as stage 1, 18 (11.9%) were classified as stage 2, 17 (11.3%) were classified

Table 1 Demographic features, co-morbidities, and laboratory results of patients.

		Adenoma	CRC	p-value
Sex, n (%)	Male	44 (48%)	46 (52%)	0.620
	Female	27 (44%)	34 (56%)	
Age, years [mean (±SD)]		63.97 (± 12.75)	65.31 (± 13.09)	0.413[a]
Body mass index > 30 (kg/m²), n (%)		9 (12.67%)	21 (26.25%)	0.042[b*]
Waist circumference (cm), mean (±SD)		80.85 (± 12.56)	81.96 (±10.41)	0.403[a]
Co-morbidity, n (%)	Diabetes mellitus	31 (43.66%)	49 (61.25%)	0.035[b*]
	Hypertension	43 (60%)	66 (82%)	0.002[b*]
	Metabolic syndrome	17 (23.9%)	32 (40%)	0.026[b*]
	Mild-moderate hepatosteatosis	28 (39%)	32 (40%)	0.046
	Severe hepatosteatosis	4 (5%)	15 (18%)	0.018[b*]
Laboratory, mean (±SD)	Albumin (g/dL)	3.99 (± 0.72)	3.64 (± 0.82)	0.005[a*]
	Total cholesterol (mg/dL)	187.55 (± 52.49)	190.35 (± 50.47)	0.739
	LDL-C (mg/dL)	99.68 (± 34.01)	99.61 (± 37.58)	0.826
	HDL-C (mg/dL)	45.08 (± 16.10)	47.98 (± 24.52)	0.596
	Triglyceride (mg/dL)	91.09 (± 100.06)	116.61 (± 104.03)	0.000 [a*]
	CRP (mg/dL)	17.04 (± 27.15)	41.04 (± 69.55)	0.014 [a*]
	CRP/Albumin	5.19 (± 10.5)	14.06 (± 29.51)	0.006 [a*]
	NLR	2.48 (± 1.76)	4.53 (± 5.517)	0.002 [a*]
	HOMA_IR	4.16 (± 2.74)	5.26 (± 2.66)	0.004[a*]
	Fasting blood glucose (mg/dL)	129.55 (±20.91)	145.30 (± 41.18)	0.006[a*]
	Fasting insulin level (mU/ml)	12.11 (± 7.71)	19.20 (± 9.82)	0.048[a*]
	HbA1c (%)	5.80 (± 0.66)	6.19 (± 0.76)	0.000[a*]

[a]Mann-Whitney U test, [b]Chi-square test, *p < 0.05

CRC: Colorectal cancer; CRP: C-reactive protein; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; NLR: Neutrophil-lymphocyte ratio; HOMA_IR: Homeostasis Model Assessment-insulin resistance.

as stage 3, and 34 (22.5%) were classified as stage 4. The median overall survival duration was 50 months (95% confidence interval, 43-56) for the CRC group.

Our study revealed prominent differences regarding metabolic risk factors between adenoma and CRC groups. For example, fasting blood glucose, fasting insulin level, insulin resistance, and HbA1c levels were significantly higher in patients with CRC than in those with colonic adenomas (p = 0.031, p = 0.048, p = 0.032, p = 0.00, respectively) (Table 1). Moreover, DM was observed in 31 (43.66%) patients with a pathological diagnosis of adenoma, and in 49 (61.25%) people with adenocarcinoma which signified the rate of DM was detected significantly higher in the CRC group than in the adenoma group (p = 0.035). The presence of DM had substantially bad consequences on the survival of patients with CRC since the median survival time in patients with CRC was 75 months whereas it was 48 months in those with CRC and DM (Table 2). We also encountered obesity more in the CRC group than in the adenoma group (26.25% vs 12.67% respectively, p < 0.05). Similarly, the rate of hypertensive patients was significantly higher in the CRC group than in the adenoma group (83% vs 60%, respectively, p = 0.002). Moreover, while the median survival time was 45 months in CRC pa-

tients with hypertension, the median survival time was 87 months in CRC patients without hypertension (Table 2). We also detected more patients with hypertriglyceridemia in the CRC group than in the adenoma group ($p < 0.05$) (Table 1). The cut-off value for the triglyceride level was 159 mg/dl, determined by the receiver operating characteristics (ROC) analysis. It was observed that the median survival time was 47 months in patients with CRC whose triglyceride levels were > 159 mg/dl, while it was 72 months in patients with CRC whose triglyceride levels were ≤ 159 mg/dl (Table 2).

Another important finding in the present study is about MetS and its influences on our patients' survival. Indeed, MetS was detected in less than a quarter of the patients with adenoma and nearly 40% of patients with CRC, and the difference was significant ($p < 0.05$). Particularly, MetS had

Table 2 Results of log-rank univariate analysis for overall survival.

Variable		n	Median Survival, Months (95% CI)	p-value
Gender	Women	34	49 (43-54)	0.652
	Men	46	50 (38-61)	
Metabolic syndrome	No	32	60 (49-60)	0,032*
	Yes	48	47 (40 – 55)	
Hepatosteatosis	No	15	75 (68-89)	0.000*
	Mild-moderate	32	56 (41-70)	
	Severe	33	45 (42-47)	
Hypertension	No	14	87 (70-90)	0.000*
	Yes	66	45 (42-47)	
Diabetes	No	31	75 (70-90)	0.031*
	Yes	49	48 (44-51)	
Triglyceride	≤159	35	72 (70-88)	0.000*
	>159	45	47 (44-49)	
TNM stage	Stage 1-2	36	71 (70-90)	0.001*
	Stage 3	19	50 (38-61)	
	Stage 4	25	45 (34-55)	
Tumor site	Right	54	50 (45-54)	0.744
	Left	18	58 (33-58)	
	Rectum	8	47 (40-53)	
CRP	≤10	34	75 (70-89)	0.005*
	>10	46	47 (43-50)	
CRP/Albumin	≤3.89	34	80 (70-89)	0.015*
	>3.89	46	47 (43-50)	
NLR	≤2.52	27	80 (70-95)	0.039*
	>2.52	53	48 (44-51)	
Cigaret	No	34	52 (44-59)	0.558
	Yes	46	48 (41-54)	

*$p < 0.05$

TNM: Tumor, node, metastasis; CRP: C-reactive protein; NLR: Neutrophil-lymphocyte ratio.

terrible effects on the median survival time of our CRC patients. Indeed, the median survival time of the patients with CRC with MetS was found to be thirteen months less than the patients with CRC without MetS (Figure 1), (Table 2). Most of the CRC cases with MetS had tumors located in the right colon (69%) and the rest 17% in the left colon and 14% in the rectum. In our cohort, there were also 8 patients with colorectal adenoma and CRC synchronously and we did not find a higher rate of MetS in these patients compared to the rest of the study cohort (p = 0.301).

It is already known that visceral obesity and MetS have been associated with the vast production of inflammatory cytokines through adipocytes, resulting in chronic low-grade inflammation. Thus, we researched several of the pro-inflammatory markers in our study cohort and we found out that CRP, NLR, CRP/albumin ratio was significantly higher in the CRC group than the adenoma group (p = 0.014, p = 0.002, p = 0.006, respectively). Additionally, we noticed that the median survival was 47 months in CRC patients with CRP ≥ 10mg/dl, and 75 months in CRC patients with CRP < 10 mg/dl (Table 2). Cut-off values were also determined by ROC analysis for NLR and CRP/albumin ratio concerning the survival of patients with CRC. It was determined as 2.52 for NLR and 3.89 for CRP/albumin. The median survival time of CRC patients with a NLR greater than 2.52 was 48 months, while those with a cut-off value of ≤ 2.52 was found to be 80 months (Table 2). Similarly, the median survival time was 47 months in patients with CRC whose CRP/albumin ratio of ≥ 3.89, while it was 80 months in patients with a CRP/albumin ratio of ≤ 3.89 (Table 2).

We also investigated and compared the rate of NAFLD in patients with adenoma and CRC. We found that the rate of severe hepatosteatosis was significantly higher in those with CRC than in the adenoma group (p = 0.018). Additionally, the rate of distant metastasis was noted significantly higher in CRC patients with severe steatosis than in CRC patients with mild-moderate steatosis (p = 0.048). As a result, the median survival time inpatients with severe steatosis was 45 months, while the median survival in CRC patients without steatosis was 75 months (Figure 2), (Table 2). Liver

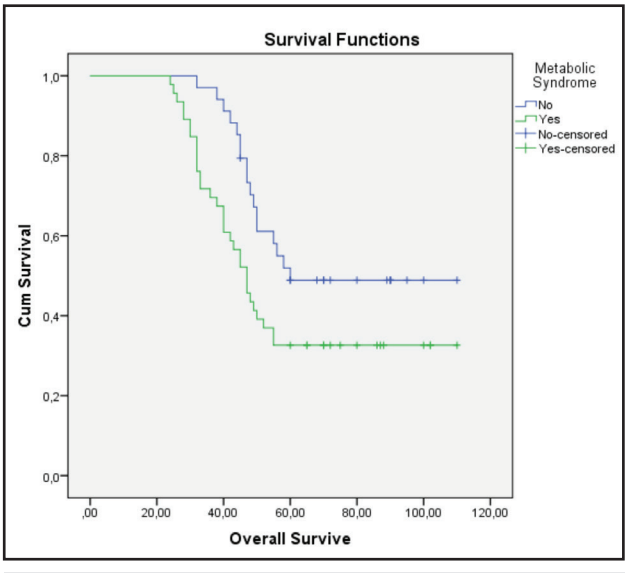

Figure 1 Overall survival in colorectal cancer patients with metabolic syndrome.

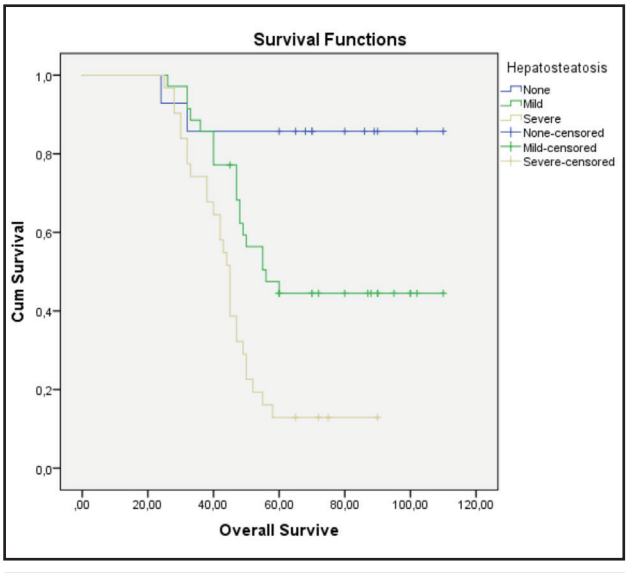

Figure 2 Overall survival in colorectal cancer patients by grades of hepatosteatosis.

Table 3 Results of multivariate analysis for overall survival by the Cox proportional hazard model

Variable		Hazard Ratio (95% CI)	P-value
Metabolic syndrome	No vs. Yes	1.45 (0.7-2.9)	0.303
Hepatosteatosis	No vs. Mild-Moderate	3.42 (0.7-15)	0.10
	No vs. Severe	7.51 (1.3-25)	0.08*
Hypertension	No vs. Yes	2.17 (1.1-4.4)	0.018*
Diabetes Mellitus	No vs. Yes	1.45 (0.7-2.9)	0,306
TNM /Stage	Stage 1-2 vs. Stage 3	1.19 (0.5-2.3)	0.038*
	Stage 1-2 vs. Stage 4	2.24 (1.1-4.5)	0.022*
CRP	≤10 vs. >10	1.26 (0.6-2.5)	0.523
NLR	≤2.52 vs. >2.52	0.31 (0.7-2.9)	0.315
CRP/Albumin	≤3.89 vs. >3.89	1.13 (0.4-2.2)	0.733
Triglyceride	≤159 vs. >159	2.53 (1.2-5.5)	0.010*

*$p < 0.05$

TNM: Tumor, node, metastasis; CRP: C-reactive protein; NLR: Neutrophil-lymphocyte ratio.

cirrhosis was present in 18 out of 80 patients in the CRC group and 10 out of 71 patients in the adenoma group, and these rates were statistically not significant ($p = 0.177$). 13 patients had a liver biopsy with a diagnosis of non-alcoholic steatohepatitis (9 patients had CRC, 4 patients had adenoma).

According to the univariate analysis, DM ($p = 0.031$), hypertension ($p = 0.00$), hypertriglyceridemia ($p = 0.00$), severe liver steatosis ($p = 0.00$), CRP ($p = 0.005$), CRP to albumin ratio ($p = 0.015$), and NLR ($p = 0.039$) had significant influences on the survival of our CRC patients. Nevertheless, the multivariate analysis indicated advanced tumor, node, metastasis (TNM) stage ($p < 0.05$), severe steatosis ($p < 0.05$), hypertension ($p = 0.018$), and hypertriglyceridemia ($p = 0.01$), to be independent risk factors for shorter CRC survival (Table 3).

DISCUSSION

In the present study, we found that fasting blood sugar, fasting insulin level, insulin resistance, HbA1c levels, the rates of patients with a diagnosis of obesity and or DM are significantly higher in the adenocarcinoma group compared to the adenoma group. In addition, we found that the presence of DM had a significant negative impact on survival in CRC patients in our cohort. Our findings are in line with the current literature indicating that the presence of diabetes in CRC patients worsens the disease prognosis and shortens life expectancy (3,13). The potential mechanisms of interaction between obesity, DM, and colorectal carcinogenesis include marked activation of the inflammatory pathway that develops with insulin resistance, hyperinsulinemia, and insulin-like growth factor (IGF)-I associated with colonic epithelial proliferation (14,15). Furthermore, chronic oxidative stress of hyperglycemia, inhibition of colonic epithelial apoptosis by several mediators such as insulin, adiponectin, leptin resistance, interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), are the important mediators that are believed to play important role in the pathogenesis of CRC (16-19).

We also found that the prevalence of hypertension and MetS were significantly higher in the adenocarcinoma group than in the adenoma group.

Supporting, in a meta-analysis of 13 prospective studies, it was estimated that hypertensive individuals are estimated to have an 11% higher risk for CRC (20). Esposito et al. using both cohort and case-control studies published another meta-analysis that found a 9% increase in the risk of CRC due to hypertension (21). Also, the data supporting the MetS as an independent risk factor for CRC have been obtained from studies investigating the markers of MetS (obesity, abdominal adipose tissue accumulation, and physical inactivity), clinical results of this syndrome (type 2 DM and hypertension), plasma components of metabolic syndrome definition (hypertriglyceridemia, hyperglycemia, and low HDL cholesterol) and the relationship between hyperinsulinemia, underlying MetS, and colonic neoplasms (6,8,10,22). This relationship between MetS and colorectal tumorigenesis was noticed strikingly more in the right colon neoplasms rather than in the left colon neoplasms which were exactly the same as our data (23,24). Kim et al. found that MetS affected right colon adenomas (OR = 1.50, 95% CI = 1.22-1.85), left colon adenomas (OR =1.36, 95% CI = 1.05-1.76), and adenomas in multiple anatomical locations (OR = 1.59, 95% CI = 1.19-2.12), but was not associated with rectum (24) as Bowers et al's study (7). Morita et al. reported that MetS increased the risk of right colon adenoma and large adenomas (> 5 mm in diameter) (25). In our study, we also noticed that MetS affected proximal rather than distal colonic neoplasms. The reason for this association is not clear, but in a rat model, Steinbach et al showed that high-calorie diet intake increased the proliferation of abnormal crypt foci in the entire colon except the distal location (26). The risk carried by the entire syndrome is no more than the sum of the risks carried by its components (21). Thus, it has also been clearly shown that abdominal obesity and abnormal glucose metabolism are responsible for the relationship between MetS and CRC and that MetS does not pose an increased risk beyond these (10,27).

We also observed that serum triglyceride levels were significantly higher in the CRC group compared to the adenoma group. Data regarding the relationship between plasma triglycerides and CRC risk is contradictory. There are large-scale studies in the literature indicating that hypertriglyceridemia increases the risk of both colorectal adenoma (28,29) and cancer (30,31). However, other studies have not been able to show an association between plasma triglyceride levels and CRC risk (32,33). It is emphasized that the level of triglyceride, which is a component of MetS, increases the risk of cancer by increasing free fatty acids (FFA) which are transmitted through the circulation to various organs after being released. Oxidative stress resulting from FFA oxidation has been thought to increase the risk of CRC (34).

In addition, we detected higher serum CRP levels, higher NLR, and lower albumin levels which are indicators of ongoing systemic inflammation, in the CRC group compared to the adenoma group. Similarly, a study conducted by Kigawa et al. reported that high plasma CRP levels were positively associated with a higher prevalence of colonic adenoma (OR 1.30; p = 0.031). The authors also noticed a significant relationship between the size (≥ 5 mm) and numbers (≥ 2) of adenomas according to the subgroup analysis (35). Moreover; in a meta-analysis in which a total of 15 studies were included; a high ratio of serum CRP level to albumin before treatment was associated with poor overall survival as our results (36). However, it was stated that this difference was detected only in patients with colon cancer, but not in those with rectal cancer (37). In the present study, the association of MetS with right colon neoplasms suggests that the degree of inflammation can be higher in the right colon rather than in the left colon and or the rectum. NLR has been suggested as a good marker

of systemic low-grade inflammation and was reported as a poor prognostic indicator in colorectal neoplastic disease (38). In the present study, we also noted that CRP, CRP/albumin ratio, and NLR were found to be significantly higher in CRC than in the adenoma group and these inflammatory parameters affect the survival of CRC patients negatively.

Vitamin D also has been proven to have an anti-inflammatory effect, and its deficiency has been shown to increase the risk of CRC through regulation of differentiation of colonic epithelium and inhibition of angiogenesis in the colorectal mucosa (39). In our study, we detected a significant deficiency of serum 25-OH vitamin D levels in the CRC group compared to the adenoma group. A significant inverse relationship between serum 25-OH vitamin D levels and CRC has been observed in several meta-analyses in the literature (40,41).

Severe liver steatosis has been associated with an increased risk of colorectal neoplasia and its recurrence (42). In this study, the rate of severe hepatosteatosis was significantly higher in the CRC group than in the adenoma group. Moreover, the rate of distant metastases was significantly higher and overall survival was lower in patients with severe steatosis than in patients with mild to moderate steatosis. It has been shown in the literature as well as in our study that NAFLD resulting from insulin resistance, is positively correlated with CRC risk, the patients with prior NAFLD have been shown to have a worse prognosis than those CRC patients without NAFLD (43).

In community-based studies, it was observed that being over the age of 50 poses a significant risk for colon adenoma and CRC (44,45). In the present study, the average age is noted to be higher in those with CRC, although it is not statistically significant compared to the adenoma group. Considering the entire group, 80% of the patients with colonic neoplasm are over 50 years old. We also scrutinized the effect of gender on the risk of CRC development. We noted that the number of male patients was higher in both adenoma and CRC groups, but that was not statistically significant. In the literature, it has been shown that the male gender is an independent risk factor for advanced colorectal neoplasm (44,46). In a multi-centric study, it was found that the risk of CRC increases in men compared to women in all components of MetS (47). The possible cause of this condition has been associated with the protective effects of estrogen and progesterone in women receiving postmenopausal hormone replacement therapy.

Our study has several limitations. Other possible confounding factors that may be associated with the risk of colonic neoplasia in patients, such as diet and smoking have not been taken into consideration. Another important limitation can be the relatively small sample size of both groups of patients with colorectal adenoma and CRC.

In a conclusion, frequencies of DM, hypertension, hypertriglyceridemia, and severe liver steatosis were detected significantly higher in the CRC group than in the adenoma group. Thus, MetS was diagnosed substantially more in the CRC group in our study cohort. Inflammatory markers such as CRP, CRP to albumin ratio, and NLR were significantly elevated in the CRC group as well. In univariate analysis, DM, hypertension, hypertriglyceridemia, severe liver steatosis, CRP, CRP to albumin ratio, and NLR had significant influences on the survival of our CRC patients. We determined severe hepatosteatosis, hypertension, hypertriglyceridemia, and advanced TNM stage to be independent risk factors for CRC survival. Nevertheless, further studies are needed to make more clear-cut conclusions on the effects of insulin resistance, severe liver steatosis, hypertriglyceridemia, and serum inflammatory markers in colorectal adenoma and cancer formation.

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